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Modeling Psychological Factors, Metabolic Syndrome, and Subclinical Atherosclerosis

Author
Ortiz Parada, Manuel Salvador

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Modeling Psychological Factors, Metabolic Syndrome, and Subclinical Atherosclerosis

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in Psychology

by

Manuel Salvador Ortiz Parada

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ABSTRACT OF THE DISSERTATION

Modeling Psychological Factors, Metabolic Syndrome,

and Subclinical Atherosclerosis

by

Manuel Salvador Ortiz Parada

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2014

Professor Christine Dunkel Schetter, co-chair

Professor Hector F. Myers, co-chair

The U.S. Latinos carries a disproportionate burden of Metabolic Syndrome (MetS) and Subclinical Atherosclerosis (ATS), therefore identifying the contribution of psychological factors to both risk for MetS and subclinical ATS is relevant. Two studies were conducted with the U.S. resident Latinos enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA). Study 1 investigated the longitudinal associations of negative affect (i.e. depressive symptoms, anger, and anxiety trait), and psychosocial stress (i.e. chronic stress, and both daily and lifetime experiences of discrimination) with severity of MetS (indexed by the number of MetS criteria), and mediators and moderators of these associations. Study 2 investigated the longitudinal associations between psychological factors, and ATS indexed by coronary calcium calcification, intima-media thickness, artery plaque, common carotid artery-internal carotid artery, and related mechanisms.

Study 1 was conducted with Mexican Americans (n=801), Dominican American (n=175), Puerto Rican American (n=202), and other Central/South Americans (n=213), whereas Study 2 only studied Mexican American participants (n= 801).

Study 1 revealed that Mexican-Americans evidenced greater severity of MetS, the highest levels of fasting glucose and triglycerides, the largest waist size circumference, and the lowest HDL cholesterol levels over time than the other U.S. Latinos. Psychological stress and negative affect were associated with MetS severity in males only, and men evidenced an indirect effect of physical activity on MetS severity via inflammation.

Study 2 demonstrated that neither negative affect nor psychological stresses were related to ATS. Several mediators were significant, with physical activity mediating the effect of chronic stress and negative affect on MetS severity. Furthermore, physical activity and inflammation as a sequence mediated the association of psychological factors and MetS severity.

These studies suggest a different epidemiological health profile for U.S. Latinos, with Mexican-Americans in the region studied having a greater MetS severity across 10 years of follow-up. Furthermore, gender moderated the potential contribution of psychological factors to MetS severity, and physical activity and inflammation mediated the associations of psychological factors with MetS in Mexican-Americans participants. This research adds to our understanding of within group differences in health among Latinos, as well as the contribution of psychological factors to MetS and ATS and related cardio-metabolic mechanisms.

The dissertation of Manuel Salvador Ortiz Parada is approved.

Carlos Grijalva

Hector Betancourt

A. Janet Tomiyama

Christine Dunkel Schetter, Co-Chair

Hector F. Myers, Committee Co-Chair

University of California, Los Angeles

2014

I dedicate this dissertation to my family. I want to express my utmost gratitude to my wife and children who joined me during my graduate studies. Nobody said it would be easy-- and only we know how hard it was, but seeing you, Mateo and Julian growing up gave me the strength to keep going. Lorena, thank you for being such an amazing partner and such a great mom. The way you faced all the problems we had makes me so proud of you-- so this is for you too. Of course I want to say thanks to my parents and sister, who encouraged me to pursue this dream. Thank you for being there, and thanks for waiting for us in Chile!

Le dedico esta tesis doctoral a mi familia. Quiero expresar mi mayor gratitud a mi esposa e hijos que me acompañaron durante mis estudios de doctorado. Nadie dijo que sería fácil y tan sólo nosotros sabemos cuán difícil fue, pero Mateo y Julián verlos crecer me dio la fuerza para continuar. Lorena, gracias por ser una excelente compañera y una gran mamá. La forma en que afrontaste todos los problemas que tuvimos me hace sentir orgulloso de ti, así es que este logro también es para ti. Por supuesto, también quiero agradecer a mis padres y hermana que me alentaron a conseguir este sueño. Gracias por su apoyo y gracias por esperarnos en Chile.

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CURRICULUM VITAE

1999	Bachelor Degree in Psychology, Universidad de Concepción, Chile.
1999	Psychologist, (professional degree equivalent to five years of university education). Universidad de Concepción, Chile.
2000	Scholarship from CONICYT (The National Commission for Scientific & Technological Research of Chile) for graduate Studies (MA).
2003	Master in Social Psychology. Pontificia Universidad Católica de Chile
2003 - 2007	Faculty member at School of Psychology. Universidad Mayor, Temuco, Chile.
2007 - 2014	Faculty member at Department of Psychology, Universidad de La Frontera, Temuco, Chile
2009	FULBRIGHT Scholarship for doctoral Studies
2010 - 2014	Teaching assistant Department of Psychology University of California, Los Angeles
2010 - 2014	Graduate student at Health Psychology program. University of California, Los Angeles

PUBLICATIONS.

Ortiz, M., Chiang, J., & Wiley, J. (2014). How stress gets under the skin, o cómo el estrés psicológico se introduce bajo tu piel. *Revista Médica de Chile* (in press).

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2011. Culture and Diabetes Treatment Adherence in Chile: A Bottom-Up Approach. Presented at symposium: Mixed Methodologies and Multigroup Structural Equation Modeling in Cultural and Health Research. Western Psychological Association (WPA), Los Angeles, California.

2008. Aportes desde la Psicología de la Salud. Paper presented at XVIII Congreso Nacional de Psicología Clínica. Symposium "Aportes desde la Psicología de la Salud". July, 24 -26, 2008. Santiago, Chile.

2008. Adherencia al tratamiento de la diabetes mellitus. Paper presented at XIV Curso de Diabetes y Endocrinología, 29 - 31 de Mayo, Temuco, Chile.

2006. Poster presented at XVII Congreso Chileno de Endocrinología y Diabetes, 9, 10 y 11 de Noviembre 2006, Viña del Mar, Chile.

2006. Paper presented at XVII Congreso Nacional de Psicología Clínica. 20, 21, 22 de Julio, 2006. Santiago

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Introduction

The metabolic syndrome (MetS) is a cluster of interrelated metabolic risk factors that appear to directly promote the development of atherosclerotic cardiovascular disease (ASCVD) and Type 2 diabetes mellitus (T2D) (Grundy et al., 2005). It is well recognized that these metabolic risk factors are atherogenic dyslipidemia, high blood pressure, and elevated plasma glucose (Alberti et al., 2009). However, the underlying pathophysiologic mechanism that leads to MetS remains unclear, with abdominal obesity, (Carr et al., 2004; Park et al., 2003) and insulin resistance (Eckel, Alberti, Grundy, & Zimmet, 2010; Reaven, 1988) as possible leading factors.

Because of this lack of clarity, many definitions for MetS are available. In 1988, Reaven was the first author who talks about MetS, emphasizing the role of insulin resistance as a leading factor for MetS, plus a couple of metabolic abnormalities related (Reaven, 1988). In accordance with Reaven, the World Health Organization (1999) released a new definition for MetS that stressed insulin resistance or diabetes as the key component, plus two or more risk factors. However, in 2001 the National Cholesterol Education Program's Adult Treatment Panel III (NCEP/ATP III) disseminated its own definition, adding central obesity to its list of criteria, and suggesting that insulin resistance per se was not needed for diagnosis (Grundy, et al., 2005).

In 2003, the American College of Endocrinology (ACCE/ACE) modified ATP III definition, suggesting that MetS should be named "Insulin Resistance Syndrome". In 2005, the International Diabetes Federation (IDF) published a new definition, highlighting the role of abdominal obesity as leading factor for MetS. According to the IDF since abdominal obesity is highly related to insulin resistance, it should be included

as the first criteria in order to being diagnosed with MetS. Simultaneously, the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) defined MetS maintaining criteria proposed by the ATP III, but modifying the cut off point for fasting glucose from 110 to 100 mg/dl (Grundy, et al., 2005).

Recently, both the IDF and the AHA/NHLBI (Joint Scientific Statement) agreed a common definition, in which abdominal obesity is no longer a prerequisite for diagnosis but it is 1 of 5 criteria. Thus, the presence of any 3 of 5 following risk factors constitutes a diagnosis of MetS: 1) abdominal obesity as waist circumference ≥ 102 cm (≥ 40 in) for men and ≥ 88 cm (≥ 35 in) for women; 2) elevated triglycerides ≥ 150 mg/dl; 3) low HDL cholesterol < 40 mg/dl men, and <50 mg/dl women; 4) systolic blood pressure ≥ 130, diastolic blood pressure ≥ 85 or being treated for hypertension; and 5) fasting glucose ≥ 100 mg/dl or being treated for diabetes (Alberti, et al., 2009).

Prevalence of MetS

From the data collected in the National Health and Nutrition Examination Survey (NHANES; 1999 – 2002, it was estimated that almost 40% of U.S. adults are classified as having metabolic syndrome under the IDF definitions, and 34% under the ATP III criteria (Ford, 2005). Using the AHA/NHLBI definition, it was estimated a MetS prevalence of 35% among U.S. adults 20 years older (NHANES 1999 – 2004) (Alberti, et al., 2009). In a recent published study using data from the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2010, and the 2009 Joint Scientific Statement for metabolic syndrome reported a 22.9% prevalence of MetS. A decrease in hypertriglyceridemia (from 33.5% to 24.3%) and blood pressure (from 32.2% to 24%) was found, however an elevation on hyperglycemia (12.9% to 19.9%) and waist size

circumference (45.4% to 56.1%) was observed (Beltran-Sanchez, Harhay, Harhay, & McElligott, 2013).

Ethnicity is a powerful predictor of insulin resistance and MetS. Epidemiological studies have demonstrated that MetS occurs in most ethnic groups, including Caucasians, African-Americans, Mexican-Americans, Asian-Indians, and Chinese-Americans, and manifestations of MetS are increased in each group of non-Caucasian ancestry in which comparisons have been made. As stated by Beltran-Sanchez et al. (2013), Mexican-Americans had the highest MetS prevalence rate. Additionally, Ford (2005) reported that in those groups, the highest prevalence was found in Mexican-American men (50.6% ± 2.9) and Mexican-American women (46.2% ± 2.5).

Subclinical Atherosclerosis

Atherosclerosis is a chronic, progressive, inflammatory disease with an asymptomatic phase called subclinical atherosclerosis. When the disease progresses it can eventually lead to cardiovascular disease occurrence (Toth, 2008). Although the association between MetS and subclinical ATS has not been widely studied, the availability of markers for subclinical ATS such as intima-media thickness (IMT) and carotid artery calcification (CAC) allow a better identification and diagnosis of subclinical atherosclerosis. Carotid intima-media thickness (IMT) is a measure of the thickness of the arterial intimal and medial layers, and has been validated as a measure of the risk for cardiovascular disease (Lorenz, Markus, Bots, Rosvall, & Sitzer, 2007). Coronary artery calcification (CAC) is a test that looks for specks of calcium in the walls of the coronary heart arteries. These calcifications in the coronary arteries are an early sign of coronary heart disease (CHD) (Toth, 2008).

The prevalence of subclinical atherosclerosis has been underestimated. However, postmortem evaluation of young men killed during the Vietnam War demonstrated that almost 50% had evidence of coronary ATS (McNamara, Molot, Stremple, & Cutting, 1971). In a recent study conducted with asymptomatic adults under 45 years old without known cardiovascular disease, a prevalence of subclinical coronary atherosclerosis of 9.4% was found (Jin et al., 2012).

In the sections to follow, a narrative literature review of the associations between psychological variables, metabolic syndrome, and subclinical atherosclerosis is conducted. First, evidence for the direct effects that psychological stress, as indexed by chronic stress and perceived discrimination, and negative affect as indexed by depressive symptoms, anger trait, and anxiety trait have on both metabolic syndrome and subclinical atherosclerosis are presented. Second, a series of proposed pathways/mechanisms including unhealthy behaviors and inflammatory response are discussed. Furthermore, evidence for metabolic syndrome predicting subclinical atherosclerosis is offered. Finally, the moderating role that social support and dispositional optimism have on these associations is examined. This literature review is focusing on previous studies conducted with animals and humans, evidence obtained from cross-sectional and longitudinal studies, as well as systematic reviews and meta-analyses.

Psychological Variables, Metabolic Syndrome, and Subclinical Atherosclerosis

The association between psychological factors, metabolic syndrome, and subclinical atherosclerosis has been the object of increasing interest. As depicted in Figure 1, it is thought that psychological factors such as chronic stress, perceived discrimination, depressive symptoms, anger, and anxiety trait may contribute directly or

indirectly through different pathways to the pathogenesis of MetS and subclinical coronary atherosclerosis (Everson-Rose & Lewis, 2005; Goldbacher, Bromberger, & Matthews, 2009; Goldbacher & Matthews, 2007; Kumari et al., 2003; Puustinen, Koponen, Kautiainen, Mantyselka, & Vanhala, 2011; Rozanski, Blumenthal, & Kaplan, 1999; Shively, Register, & Clarkson, 2009; Carderelli et al., 2010; Lewis et al., 2006; Ohira et al., 2012).

Chronic Stress, Perceived Discrimination, MetS and ATS

High chronic psychological stress has been related to an increased likelihood of developing MetS, and subclinical atherosclerosis. In general it has been stated that people who carry high psychological stress burdens are twice as likely to develop MetS as those with low psychological stress burdens (Puustinen, et al., 2011). Cross-sectional and longitudinal evidence obtained from several studies identified that psychological stressors (e.g. demands and control, stress at work, being a caregiver, etc.) are related to MetS and ATS in adolescents, adults, and old people. For instance, evidence obtained from the Whitehall Study II, a large occupational follow-up study conducted with 10,308 British civil servants, suggested that stress at work and the accumulation of stressful events at work were significantly associated with an increased risk of developing MetS. These associations remained significant after adjusting for age, employment grade, health behaviors, and obesity (Chandola, Brunner, & Marmot, 2006). More evidence from the Whitehall Study II, this time with healthy participants at baseline (n= 5,568 white middle-aged men and women), but who where diagnosed with diabetes Type 2 during 18-year follow-up found that these participants were older, had lower employment grade, were more upset with life events not related to work, had higher BMI, higher systolic

blood pressure, higher triglycerides, and lower HDL cholesterol. Among females, job stress was related to a greater risk to develop diabetes Type 2, but only in the obese participants, suggesting an interaction between stress at work and obesity (Heraclides, Chandola, Witte, & Brunner, 2011).

Another study, testing the association between occupational characteristics (professional, sales/office, service, and blue-collar) and psychological job characteristics (job demands and job control) with common carotid artery intima-media thickness was conducted in the Multi-Ethnic Study of Atherosclerosis (MESA) (n= 6,814 adults, free of CVD at baseline). After controlling for multiple confounders (age, sex, race, place of birth and CVD risk factors) results found that common carotid artery IMT was greater for those in blue-collar jobs than in professional jobs. Compared to those in professional jobs, services/sales, service and blue-collar jobs displayed greater common carotid artery IMT, while those with higher levels of control at work had thinner IMT (Fujishiro et al., 2011).

Additional evidence for the link between psychological stress, MetS components, and markers for subclinical ATS are reported in a series of studies (Lambiase, Dorn, & Roemmich, 2012; Roemmich et al., 2011) that confirmed an association between stress-induced cardiovascular reactivity, systolic blood pressure reactivity, and carotid intima-media thickness in adolescents. In these studies, participants were asked to prepare and give a speech, while their heart rate and SBP reactivity were measured. After controlling for demographics variables, a positive association was found between these factors, suggesting that adolescents with greater cardiovascular stress reactivity have greater risk for developing subclinical ATS.

Another series of studies that was conducted with caregivers provide additional support for the association between chronic stress and ATS. For instance, in a study conducted with 152 participants (72 caregivers and 80 non-caregivers) it was found that chronic stress was related with an increased prevalence of coronary artery disease (CHD) among Alzheimer caregivers. A specific pathway linking stress and CHD through MetS was found for men after 30-months of follow-up. Although the association between stress and CHD was not significant for women, a significant path was found between stress and Mets, and between MetS and CHD after 18-months follow-up (Vitaliano et al., 2002). Similarly, a study conducted with 110 Alzheimer caregivers (74-years old), verified an association between the extension of care provided and IMT as measured by ultrasonography. After controlling for independent risk factors such as age, gender, BMI, smoking, sleep quality, hypertension, and caregiving stress, the duration of care was positively related with IMT measured in the internal/bifurcation segments of carotid artery (Roepke et al., 2012).

Two additional studies on healthy participants executed in the Pittsburg Healthy Heart Project (PHHP) confirmed an association between stress and carotid artery intima-media thickness (IMT). In the first study, 337 healthy adults age 50 to 70 reported daily experiences of demands and control, using electronic diaries for two periods of three days each. Additionally, an ambulatory blood pressure, and a carotid IMT exam were performed. From the results obtained it was inferred that high demands were associated with large concurrent carotid artery IMT over and above demographic covariates, and that blood pressure partially mediates this association (Kamarck et al., 2004). In the second study, a later follow-up of this sample was performed demonstrating that the

perception of ongoing psychological demands was associated with 6-years progression in carotid artery IMT, and this association remained significant after adjusting for several risk factors (Kamarck, Shiffman, Sutton-Tyrrell, Muldoon, & Tepper, 2012).

Although chronic stress indexed by job strains, demands and control, caregiving stress, and other indicators has received considerable attention as a possible causal agent for health outcomes, the perception of being discriminated against is another psychological factor that has been related with MetS and subclinical atherosclerosis. The subjective experience of being discriminated against because of one's race/ethnicity has been proposed as a major stressor that may directly or indirectly impact the health of ethnic minorities (Flores et al., 2008) mainly because such experiences are uncontrollable (they are a product of the appearance more than actions) and threaten the social standing of the individual (Zeiders, Doane, & Roosa, 2012).

Evidence obtained from a systematic review and a meta-analysis support this hypothesis. Paradies (2006) conducted a systematic review of 138 population-based studies examining the association between racial/ethnic discrimination and self-reported health. Despite some methodological limitations, perceived racial discrimination was associated with self-reported health. In 26 studies that examined the association between perceived racial discrimination and physical health outcomes (e.g. hypertension, BMI/obesity, birth weight, and mortality), a positive association was found in 44% of the studies (Paradies, 2006). Pascoe and Smart Richman (2009) published a comprehensive meta-analysis of 134 studies reporting the association between perceived discrimination with mental and physical health. In 110 studies that examine the relationship between perceived discrimination and mental health outcome (e.g. depressive symptoms, anxiety,

post-traumatic stress symptoms, well-being, positive and negative affect, etc.), an estimated averaged correlation of -0.2 (95%CI -0.22 to -0.17) was found, suggesting that the experience of perceived discrimination is related to worse mental health outcomes. Similarly, in 36 studies examining the relationship between perceived discrimination and physical health outcomes, including risk factors for CVD (e.g. high blood pressure, heart rate variability, and intima-media thickness), and diseases such as hypertension, CVD, diabetes mellitus, respiratory conditions, etc., a significant negative correlation between perceived discrimination and physical health outcomes was found (r= -0.13; 95%CI = -0.16 to -0.10), suggesting that higher levels of perceived discrimination were associated with worse physical health outcomes (Pascoe & Smart Richman, 2009).

Brondolo et al., 2011, after conducting a search on Medline and PsycInfo during 2009, found 43 studies that examined the relationship between perceived racial/ethnic discrimination and self report-health. Half of these studies informed a strong negative association between perception of being discriminated and self-reported health, 16 reported partial or mixed effects, and only 5 studies showed no significant relationship.

Cross-sectional and longitudinal studies also contribute to the evidence for the link between perceived discrimination and MetS components, and markers of subclinical atherosclerosis. For instance, Lewis and colleagues (2011) reported that the experience of being discriminated against and visceral fat (a key component of MetS) were positively correlated among 402 African-American and Caucasian middle-aged women from Chicago. Specifically, every one-unit increase on the discrimination score predicted an increase of 13 cm^2 of visceral fat, a result that remained significant over and above race, age, total body fat, and depressive symptoms. Interestingly, in a recent study using

MIDUS II data (n= 938) a significant two-way interaction effect between weight discrimination and waist-hip ratio on glycosilated hemoglobin (A1c) was observed, which suggests that weight discrimination is associated with increases in A1c in people with high waist-hip ratio (Tsenkova, Carr, Schoeller, & Ryff, 2011).

A cross-sectional association between perceived discrimination and coronary calcium calcification (CAC) was also reported in the North Texas Healthy Hearth Study. Specifically, 571 participants (54 years and older) free of CHD, self-reported their perception of being discriminated, how they reacted to unfair treatment and a computed tomography scan was performed to assess the presence of CAC. Consistent with expectations, participants who passively responded to unfair treatment had three times greater odds of developing CAC, and this result remained significant after adjusting for age, gender, race, education, BMI, dyslipidemia, smoking, hypertension, diabetes, and having a first degree relative with heart disease (Carderelli, et al., 2010).

Evidence obtained from the SWAN Heart Study also provides further evidence for the association between discrimination and CAC. In a sample of 181 African-American women, the association between perceived discrimination (recent/chronic) and CAC was tested. As hypothesized, chronic discrimination was associated with CAC after adjusting for traditional cardiovascular risk factors and BMI. Although recent discrimination was marginally related to CAC ($p = 0.06$) this result suggests that both recent and chronic exposure to discrimination are associated with atherosclerosis as indexed by CAC (Lewis, et al., 2006).

Not only the effects of chronic perceived discrimination, but also the effects of everyday discrimination on blood pressure trajectories have been described. In a study

conducted with 63 African-American and White participants (aged 18 to 53 years) daily discrimination was associated with steeper trajectories of SBP and DBP during the day and decreased nocturnal heart reactivity. Subjects with high levels of perceived discrimination tend to exhibit steeper positive BP trends when they were awake compared with participants reporting low levels of perceived discrimination (Smart Richman, Pek, Pascoe, & Bauer, 2010).

In summary, the associations of chronic stress and perceived discrimination with MetS and subclinical ATS are evident in multiple cross-sectional and longitudinal studies. According to these studies, both predictors are related to MetS, its individual components, and to subclinical ATS (See Table 1). In the following section, evidence for the associations between depressive symptoms, anxiety, anger trait, MetS, and ATS is presented.

Depressive Symptoms, Anxiety and Anger Trait, MetS and ATS

In the first part of this review, evidence for the link between psychological chronic stress and perceived discrimination with MetS, MetS components, and markers for subclinical ATS was provided. Although the literatures for these links are growing, there are other psychological factors that may play a relevant role in the pathogenesis and progression of physical health outcomes. Specifically, depression, depressive symptoms, anxiety and anger trait are factors regularly linked with MetS and its components and subclinical atherosclerosis. Depressive disorders are related to the incidence of cardiovascular events, re-hospitalization and mortality from cardiovascular diseases, in both patients living with a CDV and in the general population (Jiang & Davidson, 2005).

Table 1: Association between chronic stress, perceived discrimination, and physical health outcomes.

Predictor	Outcome	Authors
Chronic stress at work and the accumulation of stressful events at work	Chronic stress at work is related to greater risk for MetS (OR= 2.25)	Chandola et al. (2006). *BMJ, 332*(7540): 521–525
	Stressful events are associated with risk for DM2 (OR= 1.9)	Heraclides et al. (2009). *Diabetes Care,* 32, 2230 – 2235
	Stress at work is associated with risk for MetS (OR= 1.51)	Chandola et al. (2008). *European Heart Journal, 29*, 640–648
	Stress at work is associated with less physical activity (OR= 1.33)	
Perceived discrimination	Experience of being discriminated against is related to visceral fat ($\beta = 10.34$; $p \leq 0.05$).	Lewis et al. (2011). *American Journal of Epidemiology, 173*, 1223-1231
	Weight discrimination is associated with an increased A1c in participants with high waist hip ratio	Tsenkova et al. (2011). *Annals of Behavioral Medicine, 41*(2), 243-251.
	Experience of racial discrimination is related to physical health outcomes (hypertension, BMI, and obesity).	Paradies (2006). *International Journal of Epidemiology, 35*(4), 888-901.
	Higher levels of perceived discrimination are associated with worse physical health outcomes (r= -0.13; 95%CI = - 0.16 to -0.10)	Pascoe & Smart Richman (2009). *Psychological Bulletin, 135*(4), 531 - 554.

Depression has been linked with Type 2 diabetes and insulin resistance both key components for MetS. A meta-analysis conducted by Knol et al., (2006) that included 9 prospective studies identified that depressive symptoms increased the risk for Type 2 diabetes by 37%. Another meta-analysis identified 13 studies that investigated depressive symptoms as a risk for Type 2 diabetes (n = 6,916 incidents cases), and reported that the risk for incident T2D was 60% greater among depressed participants than non-depressed participants (RR = 1.60; 95%CI 1.37 – 1.88) (Mezuk, Eaton, Albrecht, & Golden, 2008). A new meta-analysis for the association between depression and insulin resistance was published recently. In this study, after reviewing 967 abstracts available on Medline, EMBASE and PsychInfo, the authors identified 18 studies that met inclusion criteria (n=25,847), and estimated a modest but significant pool standardized effect size for the association between depression and IR (0.19; 95% CI 0.11 – 0.27) (Kan et al., 2013).

Additional evidence suggests that MetS is highly prevalent among patients with a history of depression, and current major depression. For instance, in a study with 121depressive patients diagnosed at baseline with the structured clinical interview for DSM III-R, the prevalence of MetS was 36% after 6 years of follow-up (Heiskanen et al., 2006). Moreover, the association between depressive symptoms and MetS as defined by the ATP III was tested in a prospective study with 921 participants. In this study, MetS components were measured at baseline (mean age 12 years) and later in life (mean age 33 years). Depressive symptoms measured at age 24 years predicted MetS in women at age 33 years, such that for each 1 standard deviation increase in depressive symptoms, the risk for MetS is increased by 40% (Pulkki-Råba et al., 2009). Evidence obtained from the Study of Women's Health Across the Nation (SWAN), a prospective study of

menopausal women, confirmed that in women free of MetS at baseline (n= 429) a major lifetime history of depression or current major depressive episode at baseline predicted the onset and presence of MetS during a 7-year follow-up (OR = 1.82; 95%CI 1.06 – 3.14) (Goldbacher, et al., 2009).

Supplementary support for the link between depression, MetS, and MetS components has been reported in several studies. As example, depressed women may have increased visceral fat accumulations, accompanied by decreased insulin sensitivity and elevation of inflammatory cytokines (Kahl et al., 2005). In another population-based study the association between mental health symptoms and MetS was tested in 223 participants classified with high or low mental health symptoms. The prevalence of MetS for men was 49% and 21% for women. Participants reporting high depressive symptoms indexed with the Hamilton Rating Scale for depression had a 30% increased risk for MetS compared with those participants scoring low in depressive symptoms. Noteworthy, these associations were statistically significant only in men (Viinamaki et al., 2009). Similarly, in a cross-sectional study with 1,024 outpatients with stable coronary heart disease it was found that depressive symptoms, anger expression, hostility and pessimism were related to the prevalence of MetS (Cohen, Panguluri, Na, & Whooley, 2010). Evidence obtained with 541 participants enrolled in the Healthy Women Study, a 15-years follow-up study demonstrated that depressive symptoms and severity of stressful life events were related to the prevalence of MetS, as defined by WHO, ATP III and IDF clinical criteria (Raikkonen, Matthews, & Kuller, 2007).

The association between depression and MetS, and whether MetS mediated the association between depression and cardiovascular disease was tested with 652 women

that had a previous diagnosis of depression and/or elevated depressive symptoms. After 5.9-years of follow-up, it was informed that women who had both depression and high depressive symptoms had an increased risk of developing MetS (OR =1.6) compared with women with no depression, and 2.6 times greater risk of developing cardiovascular disease (Vaccarino et al., 2008).

The longitudinal association between depressive symptoms, and anxiety symptoms with dyslipidemia and waist size circumference was tested during a 2-year follow-up period among a sample of 2,126 participants in the Netherlands, and confirmed previous findings that baseline symptoms of depression and anxiety predicted a decrease in HDL cholesterol and an increase in waist size circumference (van Reedt Dortland, Giltay, van Veen, Zitman, & Penninx, 2013). Similarly, a psychological risk index composed by perceived stress, depressive symptoms, anger-in, and cynicism predicted a greater CAC progression over time in a 3-year follow-up study in a sample of 149 participants from the Healthy Women Study who participated in the Pittsburg Mind-Body Center study (Low, Matthews, Kuller, & Edmundowicz, 2011). Similar results were found with baseline anger trait scores predicted the risk for developing MetS, and MetS in turn predicted an increase in the intima-media thickness (IMT) over 3 years in a sample of 209 postmenopausal women (Raikkonen, Matthews, Sutton-Tyrrell, & Kuller, 2004). Supplementary evidence for a cross-sectional association between trait anger and IMT was identified in the Multi-Ethnic Study of Atherosclerosis (Ohira, et al., 2012). In this study, 6,561 men and women (Whites, African American, Hispanics, and Chinese) participating at baseline exam completed measures for anger, anxiety trait and depressive symptoms. Common carotid artery (CCA) and internal carotid artery (ICA) IMT exams

were used as markers for atherosclerosis. Results indicated that only trait anger was directly associated with both markers of ATS and carotid plaque. These associations were stronger for men than women, and in Whites than in the other ethnic groups.

Similarly to chronic stress and perceived discrimination, negative affective states specifically depressive symptoms, anger, and anxiety trait have each been associated with MetS and subclinical ATS (See Table 2). Evidence obtained from several studies demonstrated that these predictors increase the risk for being diagnosed with Type 2 diabetes, MetS, and its individual components as well as for subclinical ATS.

Table 2: Association between negative affectivity variables and physical health outcomes

Predictor	Outcome	Authors
Depressive symptoms/depression	Significant standardized effect size for the association between depression and insulin resistance (*r* = 0.19).	Kan et al. (2013). *Diabetes Care, 36*, 480 - 486.
	Depressive symptoms increased the risk for Type 2 diabetes (OR = 1.37)	Knol et al. (2006). *Diabetologia, 49*, 837 - 845
	Risk for incident T2D is greater among depressed participants than non-depressed participants (OR = 1.60).	Mezuk at al. (2008). *Diabetes Care, 31*(12), 2383-2390
Trait anger	Predicted risk for MetS, and MetS in turn predicted an increase risk for IMT. 3-years follow-up	Raikkonen et al. (2004). *Psychosomatic Medicine, 66*(6), 903-908.

Psychological Factors, MetS and Subclinical ATS: What are the Mechanisms?

In the previous sections, evidence from several literatures for the association between psychological variables, metabolic syndrome, and subclinical atherosclerosis was presented. From these cross-sectional and longitudinal studies, together with results obtained in systematic reviews and meta-analyses, there is strong evidence that psychological variables are related to physical health outcomes, however the underlying mechanisms through which they exert their effects on these physical health outcomes have yet to be demonstrated. In the following section, several mechanisms, specifically dysregulation of physiological systems and unhealthy behaviors, are proposed as linking psychological variables, MetS, MetS components, and subclinical ATS.

Psychological Stress Mechanisms. One of the most extensively studied mechanisms linking psychological variables and physical health outcomes is the hormonal response system to psychological stress. The hypothalamic pituitary adrenal (HPA) axis known as one of the major stress response systems (Zeiders, et al., 2012), works in close connection with the nervous system providing an integrated response to psychological stress. In response to psychological stress, the body responds activating a cascade of physiological events that includes a coordinated response involving the hypothalamus, the anterior pituitary gland, and the adrenal cortex. Specifically, neurons from the medial paraventricular nucleus of the hypothalamus (PVN) liberates corticotropine releasing hormone (CRH) into the anterior pituitary gland via the hyphophyseal portal vessel to stimulate the production of adrenocorticotropic hormone (ACTH), which in turn stimulates the adrenal cortex to produce glucocorticoids. In addition, catecholamines regulate the function of the PVN neurons and CRH production

(Sapolsky, Romero, & Munck, 2000). In parallel, CRH stimulates the sympathetic adrenal-medullary axis (SAM) to produce norepinephrine and epinephrine from the adrenal medulla (Black, 2006; Perez-Tejada et al., 2013). The renin-angiotensin system (RAS) also participates in the stress response. The sympathetic innervation of the kidney initiates a cascade of physiological reactions, where angiotensinogen is converted into angiotensin II (angio II), which is involved in vasoconstriction, elevation of blood pressure, and increase in heart rate (Black, 2006).

The immune system, and the inflammatory response are sensitive to the effects of psychological stress as well. Glucorticoids production will enhance the release of catecholamines, which in turn can alter lymphocyte functioning. Furthermore, chronic stress can diminish the production of antibodies as a consequence of the impaired CD4, and B-cell functioning or the decreased of dentritic cells' presentation capability (Rabin, 1999). Importantly, the acute inflammatory response can be altered by stress. According to Rabin (1999), the hormonal response to stress can influence the production of pro-inflammatory cytokines, decreasing the ability of the innate defense system to fight bacteria. Sapolsky (2004) postulated that glucocorticoid production, as part of the hormonal response to stress, will halt the formation of new lymphocytes, inhibit the release of pro-inflammatory cytokines (e.g., interleukins, interferon), diminish the responsiveness of lymphocytes, and cause lymphocytes to be removed from circulation and returned to storage in immune tissues.

According to Black (Black, 2003; 2006), all of these articulated physiological events have a concomitant impact on visceral fat, insulin resistance, blood pressure, and dyslipidemia. For example, evidence obtained from animal models have shown that

social stress subordination of the cytomologus monkey leads to insulin resistance with hyperglycemia, increased visceral fat, dyslipidemia, and raised blood pressure, all of which constitute MetS components (Black, 2006).

Animal models using the chronic social defeat stress (CSDS) protocol, an experimental paradigm in which mice facing repeated social aggression tend to exhibit behavioral deficits similar to human sick behavior, including social isolation and diminish preference for rewards, have provided valuable evidence for the link between psychological stress and lipid synthesis dysregulation. Thus, an experiment conducted with the C57BL/6 mouse line, a mouse well known for it's vulnerability to chronic social stress, demonstrated that after 10-day of CSDS exposure, the mice spent more time interacting with an inanimate object than with an unfamiliar mouse, which was considered a measure of depression-like behavior. After this stage, mice were randomly assigned to two groups, one receiving a low fat standard rodent chow, and the other a high fat and high cholesterol diet (HFD). The results of the second phase demonstrated that the combination of CSDS and HFD produced a significant increase in both total cholesterol and non-HDL cholesterol levels. In addition, CSDS was associated with an elevated fasting glucose levels, and raised insulin levels for both diets (Chuang et al., 2010).

From humans' studies, it has been established that psychological stress is related to the pathogenesis of MetS. Experimental studies inducing psychological stress by manipulating mental arithmetic task, color-words conflict test or giving a public speech, have been shown to be able to elicit a release of CRH with the consequence of an increase in cortisol, and catecholamine production (Black, 2006). Noteworthy, under

acute or chronic psychological stress a state of insulin resistance is developed. Insulin resistance will be manifested by glucose intolerance with hyperglycemia, accompanied by a compensatory increase of plasma insulin, high triglycerides, and low HDL cholesterol concentration. Additionally, insulin resistance may produce a blood pressure elevation and obesity (Black, 2003; Bjorntorp, 1999; Bjorntorp & Rosmond, 1999a, 1999b). Pro-inflammatory cytokines (IL-6 and TNF α) released as part of the stress response may induce insulin resistance by dysregulating the insulin signaling. These cytokines are involved in a process called serine phosphorilate that affect the insulin receptor impeding insulin binding and signaling (Ross, 1999).

Moreover, psychological stress has been associated with visceral fat accumulation (Raikkonen, Keltikangas-Jarvinen, Adlercreutz, & Hautanen, 1996). The mechanisms linking psychological stress and visceral fat have been well described by Bjorntorp (1991). Visceral fat is a unique kind of fat rich in blood vessels, nerve supplies, and beta-adrenergic receptors. Compared with other types of fat such as total body fat or subcutaneous fat, abdominal fat is the most metabolically active, and the most atherogenic component of fat, contributing to the formation of fatty plaques in arteries (Lewis, Kravitz, Janssen & Powell, 2011). In addition, it has a high concentration of glucocorticoids receptors, and is less responsive to antilipolytic action of insulin, the mechanism that explains the elevated triglyceride concentrations common in diabetic patients. These fat cells are an important source of pro-inflammatory cytokines, especially IL-6, which is released from visceral and subcutaneous fat after SNS activation (e.g. with stress) (Pradhan, Manson, Rifai, Buring, & Ridker, 2001).

Psychological stress has been linked with an impaired functioning of the endothelium. Black and Garbutt, (2002) proposed that psychological stress is correlated with structural changes in arteries, and that atherosclerotic blood vessel are extremely sensitive to sympathetic stimulation, which if this becomes chronic could lead to an additional endothelium damage. Activation of the sympathetic nervous system (e.g. with stress) will also activate the renin-angiotensin system (RAS) that liberates angio II, a powerful mediator for hypertension. Furthermore, increased pro-inflammatory cytokines such as IL-6 are centrally involved in the pathogenesis of atherosclerosis, and their association with psychological factors including stress and negative emotional states has been well demonstrated (Everson-Rose & Lewis, 2005; Lu, Zhao, Zhang, & Jiang, 2013).

Depressive symptoms mechanisms. The mechanisms linking depressive symptoms/depression with MetS and subclinical ATS are similar to those proposed for chronic stress; that is, the physiological dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, and the inflammatory response. Hyperactivity of the HPA axis in depressed patients has been considered another possible mechanism linking depression and physical health outcomes. Evidence obtained from several meta-analyses confirmed an association between depression and HPA-axis dysregulation. In Knorr, Vinberg, Kessing, & Wetterslev (2010) meta-analysis, high levels of awakening and evening cortisol levels in depressed patients (n= 1,357) were reported. Further, in another meta-analysis large cortisol levels among depressed patients (d = 0.60), in addition to high levels of ACTH (d = 0.28) were reported (Stetler & Miller, 2011).

A large body of studies indicates that depression is associated with a dysregulated inflammatory response. As previously stated inflammatory cytokines (IL-6 and TNF-α)

and anti-inflammatory cytokines (IL-10) are essentially involved in the pathogenesis of MetS and ATS. There is evidence suggesting that depression is accompanied by an increased production of cytokines (IL-6 and TNF-α) and an acute phase reactive protein (CRP), which in turn is related to the onset of cardiovascular disease and diabetes (Kaptoge et al., 2010).

In summary, there is strong suggestive evidence that psychological stress and depression are centrally involved in the pathogenesis of MetS and subclinical atherosclerosis. The role of pro-inflammatory cytokines, a common hypothesized underlying mechanism is discussed further in the next section.

Physiological Pathway: The Role of Pro-Inflammatory Cytokines

Psychological stress, and depression/depressive symptoms induce pro-inflammatory cytokines. Three recent meta-analyses reported high levels of inflammatory cytokines in depressed participants (Dowlati et al., 2010; Howren, Lamkin, & Suls, 2009; Liu, Ho, & Mak, 2012). In these meta-analyses, several inflammatory markers were associated with a major depression diagnosis or with depressive symptoms. For instance, Dowlati et al (2010) reported high levels of IL-6 and TNF-α among MDD patients, and Howren et al (2009) confirmed this association in large population samples. Furthermore, in a meta-analysis conducted by Steptoe, Hamer, & Chida, (2007), the evidence found in 30 studies that met inclusion criteria (n = 1,749) suggested that acute psychological stress, manipulated under laboratory conditions elicited production of pro-inflammatory markers. Specifically, a robust effect for increased IL-6 and IL-1b were reported, and a marginal effect for CRP as well. Furthermore, a recent systematic review identified 41 studies linking psychological stress and CRP. In particular, the studies analyzed included

employment and unemployment stress, burnout and vital exhaustion, caregivers stress, interpersonal stress, socioeconomic status, and perceived discrimination. In all these studies, a positive association between chronic stress and elevated circulating CRP was found (Johnson, Abbasi, & Master, 2013).

Furthermore, animal studies confirm these effects. For instance, rodent exposed to an unpredictable chronic mild stress (UCMS) challenge, exhibit depression-like behaviors such as agitation, anhedonia, and learned helplessness, which in turn generates vascular inflammation evidenced by an increased of multiple pro-inflammatory markers including CRP, and IL-6. Furthermore, UCMS has been able to produce an upregulated expression of TNF-α, CRP, and other markers of inflammation in the rabbit aorta (Lu, et al., 2013).

Moreover, evidence from human studies, also confirmed the association between chronic stress and pro-inflammatory cytokines. For instance, people rating themselves lower in subjective social status (SSS), often must face stressful experiences and in general they report more stressful events than people rating themselves high in SSS. Taking this into consideration the association between SSS and IL-6 was tested in a sample of 138 healthy students who completed the Trier Social Stress Test (TSST) and provide a measure for IL-6. Confirming the hypothesis, students who placed themselves low in the ladder had greater IL-6 responses from the baseline to 45 minutes post-stressor, and from baseline to 2 hours post-stressor (Derry et al., 2013).

Pro-inflammatory cytokines are essentially involved in the underlying mechanism linking psychological factors, and subclinical atherosclerosis. Thus, it is thought that the pro-inflammatory cytokines induced by psychological stress stimulates the expression of

adhesion molecules on the injured endothelium, thereby producing a local inflammation reaction in the vascular walls (Gu, Tang, & Yang, 2013). In the lesions zones, activated endothelial cells, macrophages, and T-lymph secrete pro-inflammatory cytokines including TNF-α, IL-1, IL-6, interferon, and other markers, that consequently perpetuate atherogenesis by maintaining an aggressive environment inside the blood vessels (Lu, et al., 2013).

In sum, there is evidence suggesting that psychological stress and depression/depressive symptoms stimulate the production of pro-inflammatory cytokines, which are essentially related to the pathogenesis of MetS and subclinical ATS. Therefore, it is thought that psychological factors may increase the risk for MetS and ATS indirectly by promoting pro-inflammatory cytokines production.

Unhealthy Behaviors as Mechanisms

Unhealthy behaviors namely physical inactivity, unhealthy diet, smoking and drinking behavior, have all been independently associated with an increased risk for MetS and subclinical ATS, however, in this section they will be presented as potential mechanisms linking stress/depression with physical health outcomes. Specifically, an inverse association between stress/depression and health behaviors is proposed, leading to an increased risk to develop MetS and ATS.

Physical Activity. Chronic stress and depression are associated with an increased risk of CVD, and physical activity has emerged as a possible underlying behavioral mechanism. According to Hamer (2012) physical activity explains up to 30% of the association between stress/depression and CVD, and participants categorized as stressed/depressed report lower levels of physical activity.

Studies examining the relationship between physical activity, blood pressure, and cardiac response have provided consistent evidence about the potential buffering effect that a single bout of exercise may have on blood pressure and cardiac functioning in response to standardized behavioral stress tasks (Hamer, Taylor, & Steptoe, 2006) suggesting a protective role for physical activity. For example, exercise has been associated with stress-buffering effects in offspring of hypertensive families compared to low risk population (Hamer, Jones, & Boutcher, 2006). A proposed mechanism for this protective effect is a reduction in the stress-induced inflammatory response (Hamer, 2006). As previously mentioned, pro-inflammatory cytokines has been linked with atherosclerotic disease (Black & Garbutt, 2002; Lu, et al., 2013), obesity (Black & Garbutt, 2002), and insulin resistance (Ross, 1999), however it is argued that exercise-induced IL-6 is acting as a strong anti-inflammatory agent. According to Pedersen (Pedersen, 2011) an increase in IL-6 levels are expected after an acute bout of physical activity, promoting an anti-inflammatory environment by increasing IL-1 receptor agonist and inhibiting TNF-α synthesis. This proposed mechanism was tested in a study conducted by Hamer and Steptoe (2007) with 207 participants drawn from the Whitehall study II epidemiological cohort. In this study, subjects were exposed to two mental stressors consisting of a 5-minute Stoop task and a 5-minute mirror tracking. Blood sample test and heart rate variability were measured during baseline, stress, and 45 minutes afterward. The results indicated a significant increase in IL-6 and IL-1 receptor agonist after 45-minute post-stress. Physical fitness indexed by lower exercise heart rate was related to smaller IL-6 and TNF-α response to stress, after controlling for demographics and behavioral risk factors.

Eating Behavior/Diet. Eating behavior/diet is another proposed underlying mechanism linking stress/depression with MetS/ATS. It is widely recognized than high exposure to psychological stressors is associated with impulsive eating behavior (Groesz et al., 2011.), and high intake and preference for high fat and sugary foods (Torres & Nowson, 2007). Therefore, Groesz et al. (2011) tested the hypothesis that greater life stress is related to greater drive to eat, and greater intake of food high in fat and sugar. This study was conducted with a sample of 561 Northern California women, who self-reported levels of perceived stress, chronic stressor exposure, restraint, desinhibition, hunger, binge eating, and intake of palatable non-nutritious food and nutritious food. The results obtained confirmed that perceived stress was directly related to intake of palatable non-nutritious food, and indirectly associated with nutritious food. Perceived stress was also related to lack of control, binge eating, and hunger. In the same direction, chronic stress was related to intake of non-nutritious food, lack of control over eating, hunger, and binge eating. Similarly, another study conducted with 442 participants evaluated the association between psychological stress due to interpersonal stress and work daily hassles, and eating behaviors such as snacking, fruit and vegetable consumption, and perceived variations in daily food intake. After a 7-day daily dairy register, results indicate that a greater consumption of high fat and sugar, and lower intake of vegetables and fruit were related to ego-threatening, and interpersonal and work-related hassles (O'Connor, Jones, Conner, McMillan, & Ferguson, 2008).

Evidence obtained from animal studies demonstrated a link between high fat diet, body weight, and insulin resistance. For instance, a series of experiments conducted with male Wistar rats exposed to different diets: standard laboratory chow; high

fat/carbohydrates; or cafeteria diet (containing bread, cheese, pizza, chocolate, cake, etc), different housing conditions (individual/group), and different physical activity levels (swimming in a water basin/control) demonstrated effects on food intake, visceral fat, and insulin resistance. Rats exposed to double housing had higher food, and higher water intake per day, although no body weight difference was found. Rats exposed to physical activity gained less weight that rats in the control group, however no differences were found in food and water intake per day. Consistent with body weight, the total amount of fat (visceral plus subcutaneous) was lower for rats under the exercise condition. Rats with unlimited access to high fat/carbohydrates diet gained more weight than those rats with unlimited access to standard laboratory chow. Subcutaneous and visceral fat were higher under high fat/carbohydrate condition. Rats with free access to cafeteria diet gained more body weight that those under unlimited standard laboratory chow. In addition they showed higher plasma insulin baseline levels than control rats, and an increased visceral and subcutaneous fat (Kretschmer et al., 2005).

Smoking/Drinking Behavior. Not only physical activity and eating behavior/diet have been linked to MetS and subclinical ATS, but also smoking and drinking behavior have also been identified as another contributing factor (Honda, Goodwin, & Neugut, 2012). The direct and indirect effects of psychological stress and smoking behavior were examined in a community sample of 291 men and women. Subjects participating in this study completed a measure of cumulative stress that included items for recent life events, major life events, life traumas, and chronic stress, as well as a measure for impulsivity and smoking history. The results indicated a direct effect of cumulative stress on smoking status, together with an indirect effect through impulsivity. The finding suggests that for

each point increase in cumulative stress, the odds for being a smoker increased by 16%. Remarkably, all of the measures of cumulative stress were positively associated with smoking status, and all of these associations were mediated by impulsivity (Ansell, Gu, Tuit, & Sinha, 2012). In addition, a qualitative study was conducted using a community-based approach with focus groups with 56 participants from South Bronx, New York, a low-income community characterized by poor health outcomes. The study investigated the effects of perceived stress, its relationship with health, and potential mechanisms. As expected, smoking behavior, violence and aggression, uncontrolled eating, sleep deprivation, and physical inactivity were factors linking stress and health outcomes in this sample (Kaplan, Madden, Mijanovich, & Purcaro, 2013).

The link between smoking behavior and metabolic syndrome has been reported in a recent meta-analysis that involved 13 studies (n = 56,691 participants). As expected, a positive association between active smoking and MetS was estimated (RR = 1.26, 95% CI: 1.10 – 1.40). A dose-response analysis shown that the risk for MetS was greater for active male smokers (RR = 1.34, 95%CI: 1.20 – 1.50) than former smoker (RR = 1.19, 95% CI: 1.00 – 1.42). Furthermore, heavy smokers had a stronger risk for MetS (RR = 1.42, 95%CI: 1.27 – 1.59) compared with light smokers (RR = 1.10, 95%CI: 0.9 – 1.35) (Sun, Liu, & Ning, 2012). Similarly, a narrative review conducted by (Athyros, Katsiki, Doumas, Karagiannis, & Mikhailidis, 2013) stated the role that smoking and smoking cessation have on several cardio-metabolic risk factors. Thus, smoking has been associated with an increase in LDL cholesterol, plasma triglycerides, and very low-density lipoprotein levels, as well as a diminish HDL cholesterol levels. Besides these effects, smoking has been linked with vascular endothelium dysfunction, which in turn

plays an important role in the pathogenesis of hypertension and myocardial ischemia. According to Athyros et al., (2013) it is thought that smoking induces endothelium dysfunction by increasing the production of free radical components and pro-oxidant molecules. Endothelium dysfunction is associated with an impaired release of endothelium-derived relaxing factors such as nitric oxide (NO), endothelium-derived contracting factors such as endothelium 1 and angiotensin, as well as pro-inflammatory pro-thrombolytic, and growth factors, all of whom have been implicated in the underlying mechanisms of several CVD.

Further, the acute effect that smoking has on insulin resistance, and several MetS components were compared between smokers (n=119) and non-smoker controls (n=59) (mean age 32 years). In this study, smokers had higher HOMA-IR (a marker for insulin resistance), and total nitrite/nitrate levels (a marker for nitric oxide) than non-smokers. Within group comparisons indicates an increase in HOMA-IR index, total nitrite/nitrate, heart rate, and high sensitivity CRP one hour after smoking (Seet et al., 2012).

In sum, the link between chronic stress/depression and MetS and ATS seems to be mediated in part by unhealthy behaviors. Although these behaviors are independent risk factors for these physical health outcomes, it is expected that chronic stress and depressive symptoms will be positively related to these risk factors, increasing in turn the likelihood of developing and/or being diagnosed with MetS and subclinical ATS.

Does the Metabolic Syndrome Predict Subclinical Atherosclerosis?

Several undisputed risk factors for subclinical ATS have been identified, and many of these risk factors are also MetS component. Thus, MetS is thought to be related to several metabolic risk factors including insulin resistance, obesity, dyslipidemia,

hypertension, and systemic inflammation, all of which have been linked with subclinical ATS (Stevenson, Wright, & Boydstun, 2012; Toth, 2008). Therefore several studies suggest that MetS can predict the occurrence of subclinical ATS. For instance, evidence obtained from the Spokane Heart Study (SHS), a prospective longitudinal study conducted between 1994 and 2006, demonstrated a longitudinal association between MetS and coronary artery calcification (CAC) in a sample of 434 non-clinical healthy volunteers, asymptomatic for coronary artery disease at enrollment (Stevenson, et al., 2012). In a different study, a cross-sectional association between MetS and carotid IMT was reported in a non-diabetic Korean sample (Won et al., 2013).

Interestingly, a study predicting coronary artery calcification (CAC), demonstrated a significant association between MetS as defined by ATP III, AHA/NHLBI, and IDF criteria, and CAC. Thus, in a sample of 458 asymptomatic Brazilian men free of diabetes (mean age = 46 years) MetS was diagnosed in 28% of the sample under ATP III criteria, 29% according to AHA/NHLBI criteria, and 34% under IDF definition. Furthermore, participants diagnosed with MetS according to ATP III criteria had higher systolic and diastolic blood pressure, higher BMI, higher fasting glucose, higher triglycerides, and were more likely to have CAC than men without MetS. Moreover, the odds for CAC in patients with MetS compared with those without MetS according to ATP III, AHA/NHLBI, and IDF definition were 1.59 (95%CI= 1.05 - 2.39), 1.63 (95%CI= 1.09 – 2.45) and 1.64 (95%CI= 1.11 – 2.42) respectively (Narla et al., 2009). Similarly, another study testing the association of available MetS definition and carotid intima-media thickness (IMT) in a sample of 1,782 subjects, demonstrated an association between MetS, and IMT. Furthermore, 52%, 60.5%, and 63.5% of the

participants were diagnosed with MetS under ATP III, IDF, and AHA/NHLBI criteria, respectively. The odds for IMT for men diagnosed with MetS compared with those without MetS were 1.46 (95%CI= 1.15 – 1.85), 1.53 (95%CI= 1.20 – 1.95), and 1.56 (95%CI= 1.22 – 2.01) according to ATP III, IDF, and AHA/NHLBI definition, respectively. For women with MetS compared with women without MetS the odds for IMT was 1.30 (95%CI= 0.96 – 1.76), 1.78 (95%CI= 1.31 – 2.43), and 1.46 (95%CI= 1.07 – 1.99) according to ATP III, IDF, and AHA/NHLBI criteria, correspondingly (Skilton, Moulin, Serusclat, Nony, & Bonnet, 2007) (See Table 3).

Table 3: Association between MetS and subclinical atherosclerosis markers

Predictor	Outcome	Authors
MetS defined by ATP III MetS defined by AHA/NHLBI MetS defined by IDF	Predicted CAC (OR = 1.59) Predicted CAC (OR = 1.63) Predicted CAC (OR = 1.64)	Narla et al. (2009). *Journal of the Cardiometabolic Syndrome, 4*(1), 33-39.
MetS defined by ATP III MetS defined by AHA/NHLBI MetS defined by IDF MetS defined by ATP III MetS defined by AHA/NHLBI MetS defined by IDF	Predicted IMT in men (OR = 1.46) Predicted IMT in men (OR = 1.56) Predicted IMT in men (OR = 1.53) Predicted IMT in women (OR = 1.30) Predicted IMT in women (OR = 1.07) Predicted IMT in women (OR = 1.78)	Skilton et al. (2007). *Atherosclerosis, 190*(2), 416-422.

In sum, many of the risk factors associated with MetS are risk factors for subclinical atherosclerosis as well. Furthermore, the evidence presented suggests that MetS can predict subclinical atherosclerosis, no matter what criteria is used, and they appear to share a similar underlying pathogenesis. Both psychological stress and negative affect are considered as direct contributors in the onset and progression of these health outcomes, and their effects are influenced indirectly through physiological deregulation and changes in health behavior. Nevertheless, several moderators of these associations such as social support and dispositional optimism have also been the object of study. Therefore, in the next sections, evidence for the moderating role that these variables have will be discussed.

Psychological Factors, MetS, and Subclinical ATS: What are the Moderators?

Social support and trait optimism have been identified as possible moderators of the association between psychological variables, MetS, and ATS. For instance, low social support is associated with an increased mortality from CVD (Berkman et al., 2003). MetS and central obesity were found more frequently in people self-reporting high loneliness than low loneliness (considered a proxy for social support) in a sample of 3,211 English adults 50 to 79 years old. These results remained significant after controlling for age and smoking status (Whisman, 2010; Whisman, Uebelacker, & Settles, 2010). Similarly, in a study conducted with 783 participants, social isolation was independently associated with CAC, after controlling for demographics and physiological measures (Kop et al., 2005).

The association between intima-media thickness (IMT) and pessimism/optimism as a continuous score was evaluated in a study conducted with 209 middle-aged healthy premenopausal women enrolled in the Healthy Women Study (HWS). In this study

women (90% Whites) completed a self-reported measure for optimism/pessimism at entry, and IMT measures by ultrasound scans. The results of a multiple linear regression demonstrated that higher pessimism at entry was associated with greater IMT increase over 3-years. Most optimistic participants had less IMT progression than the more pessimistic, suggesting than optimistic women have a slower progression of IMT in their middle life (Matthews, Raikkonen, Sutton-Tyrrell, & Kuller, 2004). Further, Cohen et al. (2010) compared outpatients with stable coronary disease with and without MetS, and found higher levels of depression, anger expression, hostility and pessimism in those with MetS.

Social support and dispositional optimism have been linked with the pro-inflammatory response as well. For instance, low social support has also been associated with elevated inflammatory cytokines, including IL-6, TNF-α, CRP, and fibrinogen (Seeman, Berkman, Blazer, & Rowe, 1994). Further, a cross-sectional association between several inflammatory markers and optimism/pessimism was reported in a sample of 6,814 participants enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA). In these participants free of clinical history of cardiovascular disease, a higher level of optimism correlated with lower concentrations of IL-6, fibrinogen and homocysteine. However, after adjusting for demographics only pessimism remained statistically associated with these inflammatory markers (Roy et al., 2010). Interestingly, a cross-sectional association between dispositional optimism and cardiometabolic risk factors was found in a sample of 529 non-Hispanic White and 421 non-Hispanic black (mean age = 15 years) from Cincinnati. After conducting a multivariate regression analysis controlling for age, gender, parent education, BMI, smoking and pubertal stage, sum

dispositional optimism was inversely associated with IL-6 and insulin, but only among the black participants. Similarly, optimism was related to higher concentration of high-density lipoprotein in the entire sample. Pessimism, on the other hand, was associated with high glucose levels, but only in the white subsample (Oreskovic & Goodman, 2013).

In addition social support and optimism have also been related to health behaviors. For instance, in a sample of 640 adults (mean age 48 years) social support was positively associated with three specific diet quality indexes: Alternate Healthy Eating Index (AHEI), Dietary Approaches to Stopping Hypertension (DASH), and the Mediterranean Diet Score (Ferranti et al., 2013). In another study conducted with 131 Latino smokers who were parents of a child with asthma (mean age = 37 years), high perceived partner support were associated with greater rates of quitting smoking (43.5%) compared with those with lower partner social support (17.4%) (Brothers & Borrelli, 2011). Similarly, dispositional optimism was related to several health behaviors in a sample of 773 Dutch elderly men. Specifically, high levels of optimism were associated with high fruit and vegetable consumption, high physical activity, non-smoking and surprisingly with higher alcohol intake (Giltay, Geleijnse, Zitman, Buijsse, & Kromhout, 2007). In a similar community sample of 128 older adults (mean age 70.5 years) recruited from two general practices in London, self-reported their levels optimism and health behaviors. The results confirmed the association between optimism and no smoking behavior, higher levels of physical activity (walking and vigorous), moderate alcohol intake, and better self-reported health (Steptoe, Wright, Kunz-Ebrecht, & Iliffe, 2006).

Thus, social support and dispositional optimism should be studied in order to achieve a better understanding of their moderating role in the relationship between psychological variables and health outcomes.

Proposed Studies

Although the literatures reviewed permit us to state that psychological variables are involved directly and indirectly to the relevant physical health outcomes (e.g. MetS, and subclinical ATS), the majority of the studies were conducted testing for individual pathways, for instance, the direct effect of chronic stress on risk for MetS, or the indirect effect of psychological stress on ATS through pro-inflammatory responses. However, few studies have tried to test simultaneously the direct effect of psychological variables on MetS and subclinical ATS, and those studies that have tried, conducted short-term follow-ups. In addition, studies testing mechanisms have considered MetS as an endpoint or outcome, but few treated MetS as another possible mediator between psychological variables and subclinical ATS. Finally, the majority of the studies testing the role of psychological variables on MetS and ATS have been conducted with White, and African-American populations, and little or no research has been conducted with U.S. Latino population.

Therefore, the proposed studies are taking advantage of the robustness of the psychological and physiological measures included in MESA, the large sample of Latino enrolled, the long term follow-up conducted (10 years), to test the possibility that psychological variables have both direct and indirect effects on MetS and subclinical ATS, as well as considering MetS as a mediator in the relationship between psychological variables and ATS. These pathways can be tested individually and simultaneously.

Proposed Studies, purpose, and Hypotheses

Study 1: Longitudinal Association of Psychological Variables and Metabolic Syndrome in U.S. Latino Group: Evidence From the Multi-Ethnic Study of Atherosclerosis (MESA)

Purpose and Hypotheses

The primary goal for Study 1 is to test the longitudinal associations between psychological variables (negative affect, and psychological stress) and the number of MetS components met by the sample of Latinos enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA), and to determine whether these associations are mediated by unhealthy behaviors and physiological variables, and moderated by psychological resources (optimism and social support).

Hypotheses

1) Negative affect and psychological stress at Exam 1 will predict risk for MetS at Exam 3.
2) Psychological resources of optimism and social support at Exams1 and 2 will moderate these associations.
3) The associations between psychological variables and MetS at Exam 1 will be mediated by inflammatory markers (e.g. IL-6, CRP, and fibrinogen), and unhealthy behaviors (e.g. diet, physical activity, smoking, and alcohol consumption) at Exam 2.

Study 2: Longitudinal Association of Psychological Variables and Subclinical Atherosclerosis in U.S. Latino Group: Evidence From the Multi-Ethnic Study of Atherosclerosis (MESA).

Purpose and Hypotheses

To test the longitudinal associations between psychological factors, and the progression of atherosclerosis indexed by coronary calcium calcification (CAC), intima-media thickness (IMT), artery plaque (plaque) and common carotid artery-internal carotid artery (CCA-ICA), as mediated by unhealthy behaviors, physiological variables and MetS.

Hypotheses

4) Negative affect and psychological stress at Exam 1 will predict subclinical ATS progression measured by coronary calcium calcification (CAC), intima-media thickness (IMT), artery plaque (plaque) and common carotid artery-internal carotid artery (CCA-ICA) at Exam 5.
5) The association between negative affect, psychological stress, and subclinical ATS progression at Exam 5 will be mediated by unhealthy behaviors and inflammatory markers at Exam 2, and MetS at Exam 3.

Method

The Multi-Ethnic Study of Atherosclerosis (MESA) is a population-based prospective cohort study of 6,814 U.S. adults from different racial/ethnic groups. Data were collected from several university study centers, including: Wake Forest, Columbia, John Hopkins (city and county tracts), Minnesota, Northwestern, and UCLA. Five examination time-points were conducted: Baseline/Exam 1 (July 2000 – July 2002); Exam 2 (July 2002 – January 2004); Exam 3 (January 2004 – July 2005); Exam 4 (July 2005 – July 2007); and Exam 5 (April 2010 – February 2012).

The institutional review boards at all participating study centers approved the protocol, and all participants gave informed written consent. Details about the study have been previously published (Bild, 2002).

Participants

Analyses were conducted only on the Latino sample (n = 1,391), which was oversampled in MESA. This sample includes: Mexican Americans (n = 801), Dominican Americans (n = 175), Puerto Rican Americans (n = 202), and other Central/South Americans (n = 213). Participants with known cardiovascular disease were excluded at baseline.

Measures

Depressive Symptoms were measured with the Center for Epidemiologic Studies Depression scale (CES-D) (Radloff, 1977), which is a 20-item self-report depression symptoms measure that was rated on a 0 to 3 point scale (0 = "rarely"; 3 = "most"). The CES-D assesses depressed mood ("*past week, I felt sad*"), feelings of worthlessness ("*past week, I felt I was not as good as other people*"), feelings of hopelessness ("*past*

week I felt hopeful about the future"), poor concentration ("*past week, I had trouble keeping my mind on what I am doing*"), loss of appetite ("*past week, I had poor appetite*"), and sleep disturbance ("*past week, sleep was restless*"). High scores are indicative of greater depression. In this study, a reliable sum score (Cronbach $\alpha = 0.88$) was calculated and used in the analyses.

Anxiety Trait, and Anger Trait were assessed with the State-Trait personality inventory (Spielberg, 1980). Participants answered 10 anger trait item ("*I have a fiery temper"; "I get angry when slowed by others' mistakes*"), and 10 anxiety trait items ("*I feel nervous and restless"; "I lack self-confidence*"). Answers were scored from 1 ("*almost never")* to 4 *("almost always*"). Two reliable sum scores were calculated (Cronbach $\alpha = 0.82$ and Cronbach $\alpha = 0.77$ respectively) and used in the analyses.

Chronic Stress was assessed with the Chronic Stress Burden Scale that was developed for the Healthy Women's Study (Bromberger & Matthews, 1996). Participants were asked to identify 5 ongoing difficulties ("*health problem*", "*health problem in someone close to them*", "*job difficulties*", "*financial strains*", and "*difficulties in a relationship with someone close*"). Items were dichotomous (0 = "no", 1 = "yes") and, the total score was calculated by summing the total number of items to which a "yes" response was given (range 0 to 5).

Perceived Life Discrimination was measured with a questionnaire based on Krieger and Sidney's (Krieger & Sidney, 1996), and Williams' (Williams, 1997) work. Participants answered 6 questions related to lifetime discrimination experience ("*Unfairly fired or denied a promotion"; "unfairly discouraged by a teacher from continuing education")*. Items were dichotomous (0 = "no", 1 = "yes") and, the total score was

calculated by summing the total number of items to which a "yes" response was given (range 0 to 6).

Daily Life Discrimination was measured with "The everyday discrimination scale" (Williams, Yu, Jackson & Anderson, 1997). Participants were asked to answer 9 questions related to daily life discrimination experience ("*people act as if you are dishonest"; "you are called names or insulted"*). The answers are scored on a 6-point range (1= almost everyday; 6= never) and a reliable sum score (Alpha = 0.87) was calculated and used in the analyses.

Social Support was assessed with the ENRICHD Social Support Inventory (ESSI) (ENRICHD, 2000). The original scale is a 7-item self-report measure that assesses structural, instrumental, and emotional support ("*someone is available to help with daily chores*", or "*someone is available to provide emotional support*") was administered in Exam 1. The ESSI is scored on a five-point scale (1 = "none of the time"; 5 = "all of the time"), except for the seventh item, which has a yes/no response. MESA participants responded only to the first 6 items, and a reliable sum score (Alpha= 0.88) was calculated and used in the analyses.

Dispositional Optimism was measured with the Life Orientation Test (LOT) (Scheier & Carver, 1985) at Exam 2. Participants answered 6 questions ("*In uncertain times, I usually expect the best*"; "*I'm always optimistic about my future*"). Answers were scored on a 5-point scale from 1 *(I agree a lot)* to 5 *(I disagree a lot).* A reliable sum score (Alpha= 0.73) was calculated and used in the analyses.

Unhealthy Behaviors: Diet, smoking, alcohol consumption, and physical activity were assessed at Exam 2 with standard questionnaires. Cigarette smoking was measured

as never (0), former (1), and current (2) smokers. Never smoking was defined as lifetime consumption of less than 100 cigarettes; and former smoking as quit smoking ≥ 1 year earlier. Alcohol use was screened with the questions *"have you ever consumed alcoholic beverages?"* and *"do you presently drink alcoholic beverages?"* and participants were classified as never (0), former (1), and current (2) drinkers (Bertoni et al., 2010). Physical activity was measured with the intentional exercise variable from the Typical Week Physical Activity Survey (Bild, 2002) and defined as the sum of moderate and vigorous physical activity.

Physiological Variables

Inflammatory Markers Interleukin 6 (IL-6), CRP (C reactive protein) and fibrinogen were collected at Exam 1 and assayed using standard procedures. IL-6 level was measured by an ultrasensitive enzyme-linked immuno absorbent assay (R&D Systems Minneapolis, Minnesota); CRP and fibrinogen antigen levels were measured using the BNII nephelometer (N high sensitity to CRP and N antiserum to human fibrinogen; Dade-Behring, San Mateo, CA) (Ranjit et al., 2007).

Metabolic Syndrome (MetS) Severity. Metabolic syndrome was defined according to the criteria proposed by ATP III (Grundy, Brewer, Cleeman, Smith, & Lenfant, 2004), including waist size circumference, HDL cholesterol, triglycerides, raised blood pressure, and fasting glucose and diagnosed at Exam 3. In this study, the number of MetS criteria met (range from 0 to 5) was used as a proxy for severity of MetS.

Subclinical Atherosclerosis Markers. Several markers for subclinical atherosclerosis were assessed at Exam 5, including:

a) *Left distal Common Coronary Artery (CCA) Coronary Intima-Media Thickness (CIMT)*, and b) *Left Internal Coronary Artery (ICA) Coronary Intima-Media Thickness (CIMT)* were measured by carotid ultrasomnography, capturing images of the right and left common carotid and internal carotid arteries, as well as images of the near and far wall, using a high-resolution B-mode ultrasound (O'Leary et al., 1999).

c) *Total Carotid plaque*. Ultrasound images were obtained from a matrix array probe (M12L; GE Medical Systems, Milwaukee, WI) with the frequency set at 13 MHz for the common carotid artery and 9 MHz for the ICA and with two focal zones at a frame rate of 32 frames/sec. Images of the internal carotid artery and the videotaped transverse sweep were further reviewed to determine the presence and severity of any lesion (plaque) in the ICA, on either the near or far walls (Polack et at. 2013).

d) *Coronary Calcium Calcification (CAC)*. CAC was assessed by chest-computed tomography with either a cardiac-gated electron-beam CT scanner or a multi-detector CT system (Carr, Nelson, Wong, & al., 2005).

Covariates Variables:

Demographic Characteristics: Several potential covariates were assessed at Exam 1 and considered as possible covariates including: nationality, socioeconomic position index (educational attainment and income), age and sex. Language spoken at home, and years lived in the U.S. were used as a proxy for level of acculturation.

Data Analysis

A series of analyses, all of which were organized according to the following scheme, were conducted:

1) Descriptive analysis and MANOVAS with Bonferroni correction to test for

differences between the 4 national groups and within-sample patterns on study variables (e.g. MetS components, psychological variables, inflammatory markers, etc).

2) Growth curve modeling (Singer & Willet, 2003) was conducted to examine the trajectory of the overall MetS criteria over time, as well as the trajectory of each individual MetS components over time (e.g. waist size circumference, HDL cholesterol).

Growth models allow for flexible handling of time and account for non-independence from repeated measures on each participant. In addition to typical linear regression parameters (intercept and slope), these models can have a random intercept, capturing individual differences in baseline measures (e.g. individual differences in baseline systolic blood pressure), and random slope capturing differences in the change across examinations (e.g. trajectory of MetS components). For this analyses time was coded as 0, 1, 2, 3, and 4 (with 0 representing the baseline examination (Exam 1), and 1 to 4 representing Exams 2 to 5). Since the aim of these analyses was purely descriptive, no explanatory variables (e.g. psychological variables) were included as predictors. The overall trajectory of MetS criteria was tested including gender and nationalities as explanatory variables. In addition, the trajectories of the MetS components were tested for each national group.

3) The longitudinal associations between psychological variables and MetS (hypotheses 1 & 2) were tested with hierarchical multiple regression.

Separate analyses were conducted with different set of variables. The first set of analyses was conducted with baseline negative affect variables (depressive symptoms,

anger and anxiety trait) predicting number of MetS criteria at exam 3. The second set of analyses was performed with baseline chronic stress variables (chronic burden, life discrimination, and daily discrimination) predicting the same outcome. Both sets of analyses were conducted in the following steps in invariant order:

Step 1: Tested a crude model including only predictors, without adjusting for any covariate.

Step 2: Adjusted by control variables (demographics and behaviors).

Step 2b: Added the interaction terms of negative affect variables and moderators (e.g. depressive symptoms X social support), and the interaction terms between chronic burden variables and moderators (e.g. life discrimination X social support).

Step 3: Added inflammatory markers.

4) Additionally, to test role of physical activity and inflammation as mediators of the association between psychological factors and MetS (hypotheses 3), as well as the role of gender as moderator of this association, a multi-group SEM was conducted with gender as a grouping variables.

The maximum likelihood (ML) method of estimation was used. Several goodness-of-fit indices were used, including chi-square (χ^2), a Comparative Fit Index (CFI equal to or greater than 0.95), a Tucker-Lewis Index (TLI equal or greater than 0.90), and a Root Mean Square Error Approximation (RMSEA equal to or less than 0.05). In addition to theoretical considerations, the Lagrange Multiplier (LM) test was performed in order to improve the overall model fit, if needed.

The algorithms implied for testing a multi-group SEM are as follow (Byrne, 2008):

4.1) *Test of baseline model*: This step start by testing the hypothesized model for each group separately. These base models establish the number of factors, items or indicators, and postulated correlations between them. Ideally these models will be well fitted, although some differences across groups might be present (Bentler, 2005). Once the baseline model has been established for each group separately, the next step is to test the configural model.

4.2) *Test of configural equivalence*. This step requires that the same number of factors and their loadings to be equal across groups, therefore no constraints are imposed on any parameter. Testing the configural invariance will test the same parameters that were tested in baseline models for each group, but this time as a multi-group model. A well-fitted model will provide evidence that the structure across groups is similar, since what is being tested in this step is the multi-group representation of the baseline model. Parameters obtained from this step as well as fit statistics will be the reference baseline values against the posteriors model that will be contrasted.

4.3) *Test of measurement equivalence*. Measurement equivalence is usually referred to as metric equivalence, since what is often tested in this step is the extent to which the content of the factors indicators (items) have the same meaning across groups. This step involves first the constraint in factors loading to be equal across males and females, and second the comparison of fit of this model (loadings constraints) with the configural model. Because these two models are nested, they can be compared in pairs by computing the chi-square difference and degrees of freedom (Likelihood ratio chi-square test). The decision is based on χ^2 difference. If the difference is statistically significant, then the models compared are not equivalent across groups (the constraints imposed do

not hold). On the other hand, if the difference is not statistically significant, then the equality constraints are supportable.

In looking for possible problematic or non-equivalent parameters across groups, the Lagrange Multiplier Test provides evidence for non-equivalent parameters across groups (LMtest $p \leq 0.05$). Thus, the next step consists in releasing the constraint in the problematic parameter, re-test the model, and compare his fit with the configural model. This additional step is usually coined as a *Partial measurement invariance* (Byrne, Shavelson, & Muthen, 1989).

4.4) *Test of structural invariance*. Once measurement equivalence or partial measurement equivalence has been achieved, the next step consists in adding constraints in the structural paths (relationships between factors or variables), while maintaining the factor loadings equality across groups. The fit of this model will be contrasted with the configural model, and the decision to hold the structural invariance is based on the Likelihood ratio χ^2 difference. If this test is not statistically significant, it is concluded that the structural model is equivalent across groups. On the other hand, if the difference is statistically significant, then it can be inferred that there is a moderating effect on the relationships in the model. Furthermore, the LMtest may be useful in the identification of problematic structural paths, if needed.

5) The longitudinal association between baseline psychological variables and subclinical atherosclerosis markers at Exam 5 (Study 2, hypotheses 4 & 5) was tested with Structural equation modeling.

The analysis was conducted using structural equation modeling (SEM) with the full information maximum likelihood (FIML) method of estimation. FIML is a modern

approach to handling missing data, which was used in this analysis because the subclinical atherosclerosis examination was performed on only the 50% of the sample that was available at Exam 5. Thus missing data was considered missed at random (MAR) or in other word missing for a knowable reason (Little, 2013).

All the analyses were conducted with STATA 13.1. It was considered a nominal alpha equivalent to 0.05.

Study 1: Results

Participant characteristics at baseline exam

Table 4 shows the sociodemographic characteristics at baseline for each of the four Latino groups, and the total sample of 1443 participants. Fifty-five percent were Mexican American (n=799), 12.13% were Dominican American (n=175), 13.9% were Puerto Rican American (n=200), and 18.6% were Central/South American (n=269). Fifty-two percent of the sample was female; the mean age of the sample was 60.85 years (SD = 10.2); the Mexican Americans were the oldest group (M = 61.47; SD = 10.3); and the Dominican Americans had lived the longest in the United States (M = 41.29; SD = 13.1). Sixty-eight percent of the sample was born outside of the United States. Ninety-five percent of the Central/South Americans were born outside the Unites States (16.9% from El Salvador, 14.1% from Ecuador, 11.3% from Colombia, 10.8% from Guatemala, and 7.5% from Peru). Sixty-percent of the sample was married, and 67.2% spoke Spanish at home. Thirty four percent completed grade 8 or less of education, and 48.9% had an income equal to or less than $24,999 per annum (See Table 4).

Group differences on MetS components, at baseline

As shown in Table 5, group difference tests indicated that there were significant differences on several MetS components. Mexican Americans had the highest means on BMI ($F_{(3,1439)}$= 7.98; $p\leq$ 0.0001), waist circumference ($F_{(3,1439)}$= 7.89; $p\leq$ 0.0001), fasting glucose ($F_{(3,1437)}$= 7.24; $p\leq$ 0.05), triglycerides ($F_{(3,1438)}$= 16.01; $p\leq$ 0.0001), and the lowest mean HDL cholesterol ($F_{(3,1295)}$= 8.83; $p\leq$ 0.0001) levels. Dominican Americans had the highest mean diastolic blood pressure ($F_{(3,1439)}$= 7.24; $p\leq$ 0.001). However, there were no significant group differences on systolic blood pressure ($F_{(3,1439)}$= 1.29; p= 0.27),

LDL cholesterol ($F_{(3,1407)}$= 1.57; p= 0.19), or total cholesterol ($F_{(3,1438)}$= 0.77; p= 0.52) (See table 5).

Group differences on psychological variables and inflammatory markers

Table 6 presents the means and standard deviations for the psychosocial variables and inflammatory markers at baseline for each U.S. Latino group. Group difference tests indicated that there were significant differences on chronic stress, depressive symptoms, and inflammatory markers. Puerto Rican Americans had the highest scores on both chronic stress ($F_{(3,1414)}$= 3.92; $p\leq$ 0.01) and depressive symptoms ($F_{(3,1439)}$= 5.28; $p\leq$ 0.05), Mexican Americans had the lowest score on both chronic stress and depressive symptoms, but there were no significant group differences on social support ($F_{(3,1437)}$= 1.97; p= 0.12).

Mexican Americans had the higher IL-6 concentration ($F_{(3,1399)}$= 9.59; $p\leq$ 0.001), and Dominican Americans had higher levels on Fibrinogen ($F_{(3,1433)}$= 6.12; $p\leq$ 0.001). No difference was observed on Fibrinogen ($F_{(3,1432)}$= 1.36; p= 0.25).

Changes in the number of metabolic syndrome components across exams

As shown in Table 7, the number of MetS components observed in participants increased from baseline examination (Exam 1) to Exam 4, and then decreases from Exam 4 to 5, possibly due to attrition or improvement in one of the individual criteria (see Figure 1). In order to test the significance of the overall trajectory of number of metabolic syndrome components obtained, a growth curve modeling was performed, considering the exam as a discrete variable. As shown in Table 8, the increase from one exam to the next was statistically significant as was the decrease from exam 4 to 5 (see table 8).

Subsequent analyses tested for possible gender and nationality differences. The number of MetS criteria met by males and females respectively at each exam are shown in Tables 9 and 10. Similar to what was found with the overall sample, there was an increase in the number of MetS criteria met from baseline examination to Exam 4, and then a decrease from Exam 4 to 5. The growth curve modeling analysis revealed a significant main effect of gender (F=24.07, $p \leq 0.0001$). Further analyses indicated that the pattern of changes among the women over the 5 time-points was significantly different overall from that found in the men ($\beta = 0.35$, $p \leq 0.0001$) (see Table 11 & Figure 2). For women, the change from Exam 1 to Exam 2 was statistically significant ($p \leq 0.05$), but the changes from exam 2 to 3, 3 to 4 and, 4 to 5 were all marginally significant. For men, the only statistically significant change occurred from Exam 3 to 4 ($p \leq 0.05$). The gender X Exam interaction was not statistically significant (F= 2.14, p= 0.71).

Table 12 displays the mean of MetS criteria by each Latino group across the five time-points. The results of the analysis revealed a significant main effect of nationalities (F= 9.25, $p \leq 0.0001$), such that Dominican-Americans (β= -0.46, $p \leq 0.001$), Puerto Rican Americans (β= -0.4, $p \leq 0.001$), and Central/South Americans (β= -0.26, $p \leq 0.01$) met significantly fewer MetS criteria than the Mexican Americans. As depicted in Figure 3, a significant interaction between nationalities and Exam was observed (F= 2.41; $p \leq 0.001$). There was a marginally significant difference between the Puerto Ricans and Mexican-Americans at Exam 3 (p = 0.07), which was no longer significant at Exam 4 (p = 0.13).

Analyses of the changes in each MetS component over time

Changes in triglyceride levels

Figure 4 is depicting the changes in triglyceride levels for the overall Latino sample, and in each national group. After conducting a growth curve modeling analysis it was possible to estimate a main effect of Exam (F= 43.36, $p\leq$ 0.0001), meaning that the changes in triglycerides levels across exams was statistically significant. A test of the simple slope for exam revealed that the change in triglyceride level from Exam 3 to 4 was marginally significant (p= 0.09), and that the only significant change occurred from Exam 4 to 5 (see Table 13). Further, a significant main effect of nationality was observed (F= 20.07, p≤ 0.0001). Post-hoc tests indicated that the Mexican-Americans had a higher triglyceride level in comparison with the Dominican-Americans (β= 47.18, $p\leq$ 0.0001), Puerto Rican-Americans (β= 37.86, $p\leq$ 0.0001), and the Central/South-Americans (β= 23.15, $p\leq$ 0.0001).

Furthermore, a significant interaction between Exam and nationalities was found (F= 3.03, $p\leq$ 0.0001). The test of simple slope for Mexican-Americans revealed a significant change from Exam 3 to 4 ($p\leq$ 0.01), and from Exam 4 to 5 ($p\leq$ 0.0001). Furthermore, a significant change from Exam 4 to 5 was observed for Dominican-Americans ($p\leq$ 0.05), and Central/South Americans ($p \leq$ 0.0001) (see table 14).

Changes in fasting glucose

The overall trajectory of fasting glucose as well as the specific trajectory for each national group is depicted in Figure 5. The growth curve modeling analysis showed a main effect for Exam (F= 22.64, $p\leq$ 0.0001) such that the change from Exam 1 to 2, 2 to 3, 3 to 4, and 4 to 5 were all statistically significant (see Table 15). A main effect for

nationalities was estimated (F= 3.02, $p\leq$ 0.05), such that Mexican-Americans have a higher fasting glucose than Dominicans-Americans (β= 9.14, $p\leq$ 0.001), however, Mexican-Americans did not differ from Puerto Rican-Americans (β= 3.3, p= 0.283), and Central/South-Americans (β= 4.35, p= 0.112). The interaction tested between Exam and nationalities was not statistically significant (F= 0.63, p= 0.81). Secondary analyses indicated that all changes overtime in the Mexican-Americans were statistically significant (all $p\leq$ 0.001). For Dominican-Americans, Puerto Rican-Americans, and Central/South-Americans, the changes in fasting glucose from exam 3 to 4 ($p\leq$ 0.01), and from Exam 4 to 5 were statistically significant ($p\leq$ 0.001) (see Table 16).

Changes in systolic blood pressure

A growth curve modeling analysis was performed testing the overall trajectory of systolic blood pressure as well as the trajectory for each national group (see Figure 6). A main effect of Exam was found (F= 4.51; $p\leq$ 0.01), such that the change between SBP between Exam 1 and 2 ($p\leq$ 0.05), and between Exam 4 and 5 ($p\leq$ 0.05) were statistically significant. No main effect for nationalities was found (F= 1.31, p= 0.26), although a marginal difference was found between Mexican-Americans and Puerto-Ricans (β= 3.32, p= 0.052). In addition, analysis testing the interaction between Exam and nationalities was significant (F= 4.37, $p\leq$ 0.0001). A simple slope analysis shows that there was a significant change in SBP between Exam 1 and 2 ($p\leq$ 0.01) for Mexican-Americans, as well as significant changes for Dominican-Americans and Puerto Rican-American between Exams 2 and 3 (Dominicans $p\leq$ 0.05, Puerto Ricans $p\leq$ 0.0001), and between Exams 4 and 5 ($p\leq$ 0.01) (see Table 17 & 18).

Changes in diastolic blood pressure

Mean DBP at each exam for the overall Latino sample as well as for each national group respectively are shown in Tables 19 & 20. As shown in Figure 7, a main effect for Exam was found (F= 44.72, $p\leq$ 0.0001) with all exams being statistically different from baseline (all $p\leq$ 0.0001), as well as between Exam 1 and 2 ($p\leq$ 0.0001), and between Exam 4 and 5 ($p\leq$ 0.0001).

A significant main effect of nationalities was found (F= 7.28, $p\leq$ 0.0001), with Dominican-Americans having higher diastolic blood pressure than Mexican-Americans (β= 3.83, $p\leq$ 0.0001), Puerto Rican-Americans (β= 2.54, $p\leq$ 0.05), and than Central/South Americans (β= 3.38, $p\leq$ 0.001) (see Figure 7). In addition, a significant interaction between Exam and nationalities was obtained (F= 3.22, $p\leq$ 0.0001), with all exams significantly different from baseline (all $ps\leq$ 0.0001) in the Mexican-Americans and Central/South-Americans (see Table 20).

Changes in waist circumference

Mean waist circumference for the overall sample, as well as comparisons between all exams and baseline, and comparisons between adjacent exams are shown in Table 21. Growth curve modeling analysis found a significant main effect of Exam (F= 25.09, $p\leq$ 0.0001), and a main effect of nationality (F= 7.64, $p\leq$ 0.0001). The overall trajectory changed marginally from Exam 1 to 2 (p = 0.068), and changes from Exam 2 to 3, 3 to 4 and 4 to 5 were all statistically significant (all $ps\leq$ 0.0001). Mexican-Americans had higher mean waist circumferences changes compared with Dominican-Americans (β= 5.17, $p\leq$ 0.0001) and with Central/South-Americans (β= 1.95, $p\leq$ 0.05), but were not significantly different than Puerto Rican-Americans. There was also a significant

interaction between exam and nationalities (F= 3.08, $p\leq$ 0.0001) (see Table 22, and Figure 8).

Changes in HDL cholesterol

A growth curve modeling analysis was conducted testing the effects of Exam, nationalities and the interaction between Exam and nationalities (see Tables 23 & 24). As shown in Figure 9, a significant main effect for Exam (F= 18.01, $p\leq$ 0.0001), nationalities (F= 7.26, $p\leq$ 0.0001), and the interaction term (F= 2.43, $p\leq$ 0.0001) were found. As shown in Figure 9, the overall trajectory for HDL cholesterol revealed that the successive changes from baseline examination to Exam 5, were all statistically significant. Furthermore Mexican-Americans have lower HDL cholesterol level in comparison with Dominican-Americans (β = 2.43, $p\leq$ 0.05), Puerto Rican-Americans (β = 2.96, $p\leq$ 0.001), and Central/South-Americans (β = 3.81, $p\leq$ 0.0001).

Test of hypotheses 1 to 3.

Before testing the longitudinal association between psychological variables and MetS, several variables were covaried with MetS in a regression model. Results indicated that age (β= 0.021, $p\leq$ 0.001), socioeconomic position (β= -0.084, $p\leq$ 0.05), and male gender (β= -0. 426; $p\leq$ 0.001) were associated with number of MetS criteria, and in the direction expected. Dominican-Americans (β= -0.32; p= 0.052), Puerto-Rican Americans (β= -0.299; p= 0.081), and Central/South Americans (β= -0.329; $p\leq$ 0.05) have lower number of MetS criteria than Mexican Americans, although some of these associations were only marginally significant. Furthermore, neither smoking (β= 0.157, p= 0.184) nor physical activity (β= -0.00001; p= 0.195) were related to MetS, and a marginally significant, but counterintuitive finding was obtained with alcohol consumption, with

drinkers reporting lower number of MetS criteria than non-drinkers (β= -0.232; p = 0.055). None of the variables used as proxy for acculturation (language spoken at home, and years lived in the U.S.) were related to the number of MetS criteria. Giving these results, subsequent analyses included only the covariates that were related to MetS.

Bivariate associations between psychological variables and MetS score

In Table 25, a matrix of Pearson correlation coefficients calculated between psychological variables and MetS score is presented. Consistent with expectations, all the psychological variables were related to each other in the expected direction; however, only daily discrimination (r= -0.07; $p\leq$ 0.05) and optimism (r= -0.06; $p\leq$ 0.06) were modestly associated with MetS score, and they were small in magnitude.

Longitudinal association between baseline negative affect variables and MetS criteria (Hypothesis 1)

Step 1: Crude model

The first analysis was conducted with negative affect variables measured at baseline (Exam 1) predicting the number of MetS criteria at exam 3. In this crude model a significant association between anger trait and number of MetS criteria (β= -0.027; p= 0.009) was found, a marginal effect for depressive symptoms predicting number of MetS criteria (β= 0.011; p= 0.071), but Anxiety trait was not related to number of MetS criteria (β= -0.005; p= 0.628).

Step 2: Covariates adjustment

In the next step, when age, socioeconomic position, gender and nationality were added, the association between the negative affect variables and MetS was no longer

significant. Adding inflammatory markers in the next step (Step 3) did not change these results (see Table 26).

Longitudinal association between baseline chronic stress variables and MetS criteria (Hypothesis 1)

Step 1: Crude model.

In the first step, chronic stress variables measured at baseline (Exam 1) predicting the number of MetS criteria at Exam 3. The results obtained revealed only a marginal effect for daily discrimination (β= -0.014; p= 0.07); neither chronic burden (β= 0.026; p= 0.48), nor life discrimination (β= 0.048; p= 0.28) were related to the number of MetS criteria at Exam 3.

Step 2: Covariates adjustment.

In a second step, all the significant covariates were added, and a significant main effect for life discrimination (β= 0.087; $p \leq 0.05$) predicting number of MetS criteria at Exam 3 was found. Chronic burden remained non-significant (β= 0.0326; p= 0.362), and daily discrimination became non-significant (β= 0.001; p= 0.844). Adding the inflammatory markers in Step 3 (IL-6, CRP, and fibrinogen) resulted in life discrimination becoming marginally significant (β= 0.082; p= 0.054) (see Table 27).

Moderation analyses (Hypothesis 2)

Does social support and optimism moderate the association between negative affect and MetS?

As shown in Table 28, a first set of analyses were conducted with optimism and social support as moderators of the association between negative affect variables and

number of MetS criteria at Exam 3, adjusting for covariates. Although a main effect for optimism and social support was expected, neither optimism (β= -0.006; p= 0.809) nor social support (β = 0.009; p= 0.963) were related to MetS. Of all the interaction terms tested, only a marginal effect was found for optimism X anxiety trait (β= -0.0192; p= 0.085), such that participants low in optimism but high in anxiety have higher number of MetS criteria than participants high in optimism and high in anxiety (see Figure 10). The other interactions terms tested were not statistically significant.

Does social support and optimism moderate the association between chronic stress and MetS? (Hypothesis 2)

In a separate set of analyses and adjusting for covariates, optimism and social support were tested as moderators of the association between chronic stress variables and number of MetS criteria, however neither a main effect nor an interaction effect were found to be significant, dismissing the role of these variables as moderators or the association between chronic stress variables and MetS (see Table 29).

Does nationality moderate the association between psychological variables and number of MetS Criteria?

Two sets of analyses were conducted testing the role of nationality as a moderator of the association between chronic stress variables and MetS, and negative affect variables and MetS (see Table 30). Several interaction terms were created (e.g. Mexican X depressive symptoms, Mexican X life discrimination, and Mexican X anxiety trait) and entered into the analysis along with covariates. For the model including negative affect variables predicting number of MetS components, the interaction term between nationality and depressive symptoms was statistically significant (F= 2.8; p< 0.05). The

simple slope analysis revealed a counterintuitive finding for Dominicans, such that participants scoring low (i.e. 1SD below the mean) in depressive symptoms have higher numbers of MetS criteria than those participants scoring high (i.e. 1SE above the mean) in depressive symptoms (β= -0.718, $p\leq$ 0.05). Additionally a marginal but consistent with theory, interaction effect was found for Puerto Ricans, such that participants scoring 1SD above the mean in depressive symptoms have higher number of MetS criteria than those participants scoring 1SD below the mean in depressive symptoms (β= 0.539, p= 0.056) (see Figure 11).

Although the overall interaction term between nationalities and anger trait was not statistically significant (F= 1.95, p= 0.119), a simple slope analysis for Puerto Ricans revealed a counter-intuitive finding, such that participants scoring low in anger trait (1SD below the mean) have higher number of MetS criteria than participants scoring high in anger trait (1SD over the mean) (β= -0.063, $p\leq$ 0.05) (see Figure 11).

Analyses with nationality as a moderator of the relationship between chronic stress variables and number of MetS criteria was not statistically significant.

Multi-group structural equation modeling

A multi-group SEM was conducted to test the possible role of gender as a moderator of the associations between baseline negative affect, baseline chronic burden and MetS criteria at Exam 3, as well as if these associations were mediated by physical activity, and inflammatory markers as proposed in hypothesis 3 (see Figure 12). The analysis was conducted using structural equation modeling (SEM) with the maximum likelihood (ML) method of estimation. All the analyses controlled for socioeconomic position and age.

Several steps were conducted prior to testing the structural model invariance, including testing the configural invariance, the measurement model equivalence, and the partial measurement invariance. These steps are needed to ensure that possible differences between males and females are not due to measurement artifact.

Test of baseline model

First, a separate analysis was conducted with males and females. As shown in Table 31, the goodness-of-fit for each model are excellent for both males ($\chi^2_{(31)}$= 51.21; $p \leq 0.05$; CFI= 0.98; TLI= 0.97; RSMEA= 0.036), and females $\chi^2_{(35)}$= 51.8; $p \leq 0.05$; CFI= 0.99; TLI= 0.98; RMSEA = 0.029). Although, the overall model supports the factor structure for both males and females, some differences emerged in the pattern of association between factors, differences that will be tested in the following steps.

Test of configural invariance

In this step, a model that imposes an equivalent form on the relationships between factors but any equality constraints on factor loading was fitted. Configural invariance requests an equivalent form solution with the same indicators loadings on the latent factor for males and females, but the loading need not be the same condition that is satisfied according to the fit indices obtained ($\chi^2_{(100)}$= 168.44; $p \leq 0.001$; CFI = 0.98; TLI= 0.96; RMSEA = 0.036) (see Table 31, Model 1). These results support a similar factor structure for males and females.

Test of measurement equivalence.

A separate analysis was performed testing for invariant loadings between males and females; in other words, the factors loading were constrained to be equal across

groups, making them invariant between males and females. As shown in Table 31 (Model 2), the fit for this model was good ($\chi^2_{(92)}$= 200.07; $p \leq 0.0001$; CFI = 0.96; TLI= 0.94; RMSEA= 0.047), however the difference between this model and the configural invariance model was statistically significant (LR $\chi^2_{(8)}$= 31.68; $p \leq 0.0001$), implying that measurement invariance cannot be completely supported. Additionally, the Lagrange Multiplier test indicated that the loading of depressive symptoms (LM$\chi^2_{(1)}$= 18.80; $p \leq$ 0.001) on the latent factor negative affect was different for men and women. Therefore, this loading was released in the next step that tested for partial measurement invariance.

Test of partial measurement invariance.

After releasing the equality constraint for depressive symptoms across gender, an improvement in the fit of this model was observed ($\chi^2_{(91)}$= 180.64; $p \leq 0.0001$; CFI = 0.98; TLI= 0.96; RMSEA = 0.039) (see Table 31, Model 3). The overall chi-squared difference between this model and the baseline model (Model 1) was not statistically significant (LR $\chi^2_{(9)}$= 12.2; $p = 0.2$), which led us to decide favorably for this measurement model as the more plausible for each gender.

Test of structural invariance.

In order to test for differences in the structural paths (associations between factors and variables), constrains were added on all these paths. Although the fit indices for this model are good ($\chi^2_{(106)}$= 206.28; $p \leq 0.0001$; CFI = 0.97; TLI= 0.95; RMSEA = 0.042), this model in terms of chi-square was worse. Furthermore, the chi-square difference with the previous model (Table 31, model 3) (LR $\chi^2_{(15)}$= 25.64; $p \leq 0.05$) provides statistical evidence for rejecting this model. Based on these results, it can be concluded that the

structural paths are different between males and females in this sample, in other words gender is moderating the association between psychological variables and number of MetS criteria.

Interpretation of the final multiple-group model

After this first round of analyses, evidence for the role of gender as a moderator of the association between baseline psychological variables and number of MetS criteria was obtained. Thus, for females, neither chronic stress factors nor negative affect factors were associated with severity of MetS (number of MetS criteria). On the other hand, the opposite was found for males, specifically a direct association between chronic stress and number of MetS criteria was observed (β= 0.42, $p\leq$ 0.05). Furthermore, negative affect was related to MetS severity (β= -0.35, $p\leq$ 0.05).

Contrary to what was hypothesized, neither inflammation nor physical activity mediates the association between psychological factors and MetS severity, although a main effect of inflammation over MetS was found for both females (β= 0.34, $p\leq$ 0.001) and males (β= 0.28, $p\leq$ 0.001). Additionally, gender moderated the association between physical activity and MetS severity, such that this association was significant for females (β= -0.09, $p\leq$ 0.05), but not for males (β= 0.007, p= 0.83) (see Figure 13 & 14).

Overall, trait anger and life discrimination were associated with the number MetS components in participants, although with further adjustment, the association between trait anger and MetS scores became nonsignificant. Gender moderated the association between psychological variables and MetS, such that these associations were statistically significant for males but not for females. Physical activity and inflammatory markers did not mediate these associations, although a direct effect of inflammation on our outcome

variables was observed. In addition, the evidence did not support the hypothesis that social support or optimism would moderate the association between psychological variables and MetS scores.

Transitioning from Study 1 toStudy 2

Given that Mexican-Americans evidenced greater severity of MetS than any other Latino group, specifically, showing the highest levels of fasting glucose and triglycerides levels, the largest waist size circumference, and the lowest HDL cholesterol levels, a new SEM analysis testing the model proposed in Study 1 was performed, but this time with Mexican-Americans only. This sets the stage for the analyses in Study 2 of Mexican Americans only.

Because Study 1 results showed that gender moderated the patterns of associations between psychological variables and MetS score, a multi-group SEM was initially planned. However, the test of baseline model did not fit well for Mexican-Americans women ($\chi^2_{(46)}$= 167.66; $p \leq 0.01$; CFI = 0.88; TLI= 0.79; RMSEA = 0.082), making unadvisable or impossible to perform this analysis (Byrne, 2008). Alternatively, a new SEM analysis was performed with only the Mexican Americans participants, including a dummy code for gender (0/1), which allowed a test of the fit of the model while simultaneously estimating mean gender differences in all the variables included in the model. The result of this SEM analysis is depicted in Figure 15. As expected, negative affectivity (β= -0.42, $p\leq 0.05$) and chronic stress (β= 0.53, $p\leq 0.01$) both significantly predicted physical activity, which in turn significantly predicted less systemic inflammation (β= -0.13, $p\leq 0.05$), and lower MetS scores (β= -0.11, $p\leq 0.05$).

Furthermore, systemic inflammation significantly predicted higher MetS scores (β= 0.31, $p \leq 0.001$). Although a direct association between negative affectivity and chronic stress with MetS severity was expected, the direct effect was not significant. Nevertheless, the overall fit for this model with the indirect effect was good $\chi^2_{(33)}$= 95.6; $p \leq 0.0001$; CFI = 0.97; TLI= 0.93; RMSEA = 0.049.

Gender differences emerged in several variables tested in this model. Female Mexican Americans had significantly greater chronic burden, depressive symptoms, trait anxiety, IL-6, CRP and fibrinogen (all $p \leq 0001$). Male Mexican Americans showed significantly greater life discrimination, social support, and more moderate and vigorous physical activity (all $p \leq 0.001$). As in bivariate effects, female Mexican Americans also had greater MetS scores than males ($p \leq 0.001$). No differences were observed by gender in these multivariate tests other variables in the model in daily discrimination, anger, and optimism (see Table 32).

Study 1: Discussion

The rapid growth of the Latino population in the U.S. represents one of the most important demographic trends affecting the Unites States. To a well-established population of Mexican, Puerto Rican and Cuban origin, other Latinos such the Dominicans, Salvadorans, Guatemalans, and Colombians have been added which increased both the overall size and rate of growth of the U.S. Latino population. According to the last U.S. Census, the Latino population living in U.S. in 2012 was about 53 million, and it is projected to reach 132 million by 2050.

This demographic expansion poses many challenges in terms of understanding Latino health and its determinants. The available information suggests that health status

differs across different national groups, although the lack of detailed data for all the subgroups of Latinos living in the U.S. makes it difficult to estimate the true incidence and prevalence of important diseases such as diabetes mellitus and cardiovascular disease. Furthermore, past methodological approaches that treat Latinos as a single group and compares them with non-Latino whites and/or African-Americans have concealed possible within-group differences in their health profile. Taking this into consideration, we studied the four Latino sub-groups: Mexicans, Puerto Ricans, Dominicans, and Central/South Americans - that were enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA). The main aim of this study was to determine the longitudinal associations of negative affect (i.e. depressive symptoms, anger, and anxiety trait), and psychosocial stress (i.e. chronic stress, and both daily and lifetime experiences of discrimination) measured at baseline examination with severity of MetS (indexed by the number of MetS criteria) at exam 3, as well as possible mediators and moderators of these associations.

Our first set of findings in this study identified a number of differences in the risks factors for MetS between the four groups compared, including that Mexican-Americans evidenced greater severity of MetS than the other Latino groups. Specifically, Mexican-Americans had the highest levels of fasting glucose and triglyceride levels, the largest waist size circumference, and the lowest HDL cholesterol levels. These results are consistent with previous studies conducted on the MESA sample, (Ortiz et al, under review) including different cardiovascular risk profiles in the four Latino sub-groups enrolled in MESA (Allison et al., 2008). In addition, and consistent with other evidence reported by Daviglus et al., (2012), Latinas evidence more severe MetS criteria and more

risk factors for cardiovascular diseases than Latino males. Our results are an important addition to this profile because they identify gender and Latino group differences in CVD risk profiles that persist over 10 years of follow-up, and therefore this is valuable information that better characterizes the epidemiologic health profiles of the Latino populations living in the United States.

Two sets of regression analyses were conducted to test the contributions of psychosocial variables on severity of MetS. First, depressive symptoms, anger, and anxiety trait were regressed on severity of MetS, then the contributions of chronic stress, lifetime discrimination, and daily discrimination were estimated. Consistent with expectation, we found a positive association between trait anger and the number of MetS components, as was a trend for depressive symptoms. However, the strength of these associations were no longer significant after controlling for age and socioeconomic status, result that may be explained by the fact that anger expression tends to vary with age, decreasing in elderly people (Baeg, Wang, Chee, Kim, & Kim, 2011; Barefott, Beckman, Haney, Siegler, & Lipkus, 1993), in addition to a well demonstrated health-compromising effects of anger, which may be greater among low socioeconomic people (Beatty, & Matthews, 2009; Boylan, & Ryff, 2013; Merjonen et al., 2008). Nevertheless, this is somewhat surprising given that an association between anger trait and MetS was found in a study of women (Raikkonen, Matthews, Sutton-Tyrrell, & Kuller, 2004), and is consistent with the results of a meta-analysis of 25 prospective studies that found a strong association of anger/hostility with coronary heart disease (Chida & Steptoe, 2009). The lack of significant association between depressive symptoms and severity of MetS is also surprising since several studies support this link. However, it is important to note

that the distribution of depressive symptoms in this sample was negatively skewed, which suggest a restriction of range. Therefore, the relationships between anger trait, depressive symptoms and MetS in U.S. resident Latinos merits further study.

Results of tests of the longitudinal association between chronic stress, life discrimination and daily discrimination with the number of MetS components indicated that only burden of lifetime experiences of discrimination was related to severity of MetS. Our finding is consistent with previous studies (Lewis et al., 2006; Lewis et al., 2011; Smart Richman, Pek, Pascoe, & Bauer, 2010) and with two meta-analyses (Paradies, 2006; Pascoe & Smart Richman, 2009) that were conducted with African Americans and Whites. However, ours is one of a small number of studies that tested this association with U.S.-resident Latinos. For example in the Paradies (2006) meta-analysis that reported a positive association between lifetime discrimination and physical health, only 19% of the 138 studies included in this meta-analysis were conducted with Latinos.

Although we were expecting that chronic stress would be longitudinally associated with severity of MetS, a null finding was obtained for the overall sample. However, when a multi-group structural equation modeling analysis was performed with gender as a moderator, a significant longitudinal association between the latent factor of chronic stress and severity of MetS was observed, but only for males, suggesting that gender moderates these associations.

A possible explanation for this finding is greater stress reactivity to experiences of discrimination among Latino males than in females. The physiological response to psychological stress has been characterized as “fight of flight” in men, whereas in females the response as been described as “tend and befriend” (Taylor et al., 2000),

suggesting greater reactivity of the hypothalamic-pituitary-adrenal axis (HPA), and the sympathetic neural activity (SAM) (Kudielka and Kirschbaum, 2005; Kajantie and Phillips, 2006), but in women this response may be related to oxytocin release, a hormone that is believed to buffer the effects of psychological stress on physical health. In addition, Wang et al., (2007) identified gender differences in neural responses to psychological stress by experimentally demonstrating greater prefrontal cortex (RPFC) activity in males than females, and greater limbic system activation in females. This physiologic asymmetry was also evident in greater cortisol levels in men but not in women. This link is relevant since it has been demonstrated that both the HPA axis activity and sympathetic neural activity are related to visceral fat and insulin resistance (Bjorntorp, 1999), both key players in the pathogenesis of MetS.

Although gender differences in stress reactivity and concomitant physiological consequences has received empirical support, our study did not include measures of HPA axis output nor SAM activity, thus making untestable this mechanisms as a plausible explanation for our results. Furthermore, we observed greater prevalence of MetS in women than in men, which suggests that other variables or mechanisms may be implicated in the pathogenesis of MetS, such as the inflammatory response and physical activity in response to psychological stress. In fact, Latinas in our study scored higher in all the inflammatory markers (IL-6, CRP, and fibrinogen), and engaged in less moderate and vigorous physical activity compared with Latino males, possibly explaining difference in MetS prevalence.

Although it was hypothesized that these variables might mediate the association between chronic stress, negative affect and severity of MetS, neither baseline chronic

stress, nor baseline negative affect were related to inflammation or to physical activity, thus precluding the possibility of a mediation effect. Despite this, however, the inflammatory markers did predict severity of MetS at Exam 3 for both men and women, which is consistent with prior studies that identified systemic inflammation as a precursor of insulin resistance (Ross, 1999), atherosclerosis (Everson-Rose & Lewis, 2005; Lu, Zhao, Zhang, & Jiang, 2013), diabetes and cardiovascular diseases (Kaptoge et al., 2010).

In addition, physical activity was directly associated with the number of MetS components at Exam 3 but only for women, whereas for men, physical activity was indirectly associated with severity of MetS via inflammation. These results are consistent with Pedersen's (2011) hypothesis, which suggested that exercise-induced IL-6 promotes an anti-inflammatory environment by increasing IL-1 receptor agonist, therefore reducing systemic inflammation and risk for MetS. Nevertheless, this finding suggests a protective role of physical activity, a role that seems to operate differently in Latino men and women.

Additional analyses were conducted testing the role of optimism and social support as moderators of the association of negative affect, chronic stress and severity of MetS. However these variables did not moderate the associations, possibly due to restriction in the range on social support and optimism measures. Most of the Latino sample reported high levels of social support and optimism, suggesting that these variables may moderate these associations when comparing Latinos to other groups but not within this one group. Thus it may be worthwhile for future studies to identify other psychological resources that might moderate burdens of stress such as cultural resources.

Finally, although we did not hypothesize sub-group differences in the association

between negative affect, chronic stress, and severity of MetS, our results revealed that Puerto Ricans who had higher depressive symptoms also had higher severity of MetS, and the opposite was true for the Dominicans. Furthermore, Puerto Ricans reporting high trait anger had less severe MetS than those scoring low. The association between depressive symptoms and severity of MetS is consistent with theory and with previous studies reporting that Puerto Ricans living in the U.S. are more prone to experience psychiatric disorders compared with other Latinos, possibly due to lower socioeconomic status and higher rates of unemployment (Alegria et al., 2007). The other effects were counter to hypotheses, and deserve more study.

The MESA dataset provided an excellent opportunity to test these hypotheses due to the large sample of Latinos and the strength of the constructs measured. Furthermore, having multiple assessments over long time spans and low sample attrition allowed us to test the longitudinal associations between the variables of interest. Scoring MetS markers as a continuous variable permitted us to estimate the severity of MetS, and the use of advanced analytical techniques, growth curve modeling and structural equation modeling, allowed us to analyze the trajectory of changes in the overall number of MetS components, to test changes over time in each MetS component separately, to test the association between variables of interest, as well as to test complex models of mediation and moderation. All of these strengths add to our knowledge of MetS in the United States today.

Despite these strengths, there are limitations worth noting. Initially, we aimed to test the role of unhealthy behavior as a latent factor, indexed by smoking, drinking behavior, and physical activity, however this latent factor did not fit well and when it did,

the fit indices were poor (results not reported). Therefore, only physical activity was included in the analyses as it was the only continuous variable available that was assessed with a well-validated measure. Similarly, a measure for diet was considered for inclusion in the analyses, however the measure used in MESA at baseline did not allow us to calculate a total healthy or unhealthy diet score, thus eliminating this variable from possible consideration. Another limitation is related to the life discrimination measure. In MESA, participants answered questions related to lifetime discrimination, however they did not reported the reasons why they believed they were targets of discriminated, making impossible to identify if they attributed that discrimination to race, gender, socioeconomic status, nationality, appearance such as weight, or other reasons. The original measure developed by Krieger and Sidney (1997) does include questions for this purpose but they were not used in MESA.

Also, MESA does not allow further disaggregation of the Central/South Americans group, which is a heterogeneous cluster that includes people from different national origins and different sociodemographic profiles. This heterogeneity makes conclusions drawn from these results difficult to interpret for Latinos from some countries in Latin America.

Given that the mean age at baseline was 61 years, it will be helpful to follow a younger sample to disentangle the effects of cumulative exposure to psychological stressors from the effects of different sources and types of psychological stressors (e.g. stresses at work, financial stresses) on severity of MetS, and MetS components, at different developmental stages. Similarly, the inclusion of daily dairy methodologies might provide valuable information regarding critical or acute episodes of stress, and the

ways people cope might help to better understand the Latino population living in the U.S. Furthermore, the study of a more heterogeneous sample in terms of income and other indicators of SES such as wealth will allow us to better estimate the role of socioeconomic position as a protective factor for the development of MetS.

Finally, for a future study we proposed to explore how psychological variables measured at baseline might predict different trajectories in the overall severity of MetS, as well as in each MetS component.

Table 4: Socio-demographic characteristics at baseline for each of the four Latino groups

	Mexican American (n=801)	Dominican American (n=175)	Puerto Rican American (n=203)	Central/South American (n=213)	Total (n=1388)	p
Age (Mean, SD)	61.47 (10.3)	59.05 (10.2)	59.65 (10.1)	61.09 (10.2)	60.85 (10.2)	.011
Years lived in USA (Mean, SD)	28.02 (16.9)	25.83 (10.7)	41.29 (13.1)	25.42 (12.6)	29.43 (15.4)	.001
MetS women%	57	44.3	42.2	44.3	50.9	.001
MetS men%	43.4	23.1	34.8	38.5	39.2	.001
Male %	50.4	44.6	45.8	42.7	47.8	.099
US born %	50.4	0	16.9	5.2	32.2	.001
Foreign born %	49.6	100	83.1	94.8	67.7	.001
Marital Status %						
Married	60.6	61.7	55.7	61	60.1	.95
Widowed	14.3	8.6	13.9	10.8	13	.48
Divorced	13.8	16	15.9	11.7	14	.79
Separated	4.9	7.4	7.5	7	5.9	.76
Never married	5.5	5.7	14	7.5	6.1	.87
Education %						
Grade 8 or less	37.5	40	17.9	31	34	.01
Grades 9 – 11	9.6	9.7	18.4	8.9	10.8	.18
Complete high school/GED	19.6	13.7	25.9	23	20.3	.24
Technical school, some college	25.9	25.7	26.9	22.5	25.5	.92
Bachelor degree	4.4	4.6	8	7.5	5.4	.46
Graduate or professional	2.9	6.3	3	7.5	4	.18
Income %						
< $12000	18.8	25	20	21.1	20.1	.69
$12000 – 24999	30.3	26.7	20.5	32.5	28.8	.27
$ 25000 - 49999	32.9	33.7	38.5	29.6	33.4	.88
$50000 – 74999	9.8	9.9	14.5	8.6	10.3	.61
$75000 – 99999	5.3	4.7	4.5	4.8	5	.97
≥ $100000	2.8	0	2	3.3	2.4	.19

Table 5: Mean comparison of risk factors for metabolic syndrome for U.S. Latino

	Mexican American Mean (SD)	Dominican American Mean (SD)	Puerto Rican American Mean (SD)	Central South American Mean (SD)	Total Mean (SD)	p	Post-hoc
BMI (kg)/(m^2)	29.91 (5.2)	28.06 (4.4)	29.74 (5.3)	28.80 (4.6)	29.48 (5.1)	.001	a>b; a>d; c>b
Waist circumference (cm)	101.8 (13.08)	96.63 (12.3)	100.77 (14.3)	98.91 (12.5)	100.56 (13.2)	.001	a>b; a>d; c>b
Waist criteria >102cm (male) %	43.2	30.8	45.7	35.2	41	.099	
Waist criteria >88cm (female) %	84.1	66	77.1	79.5	79.8	.001	a>b; d>b
SBP (mmHg)	127.15 (22.9)	127.16 (21.2)	123.78 (20.2)	126.06 (20.5)	126.50 (21.9)	.74	
% ≥ 130 mmHg	40.3	42.3	33.8	42.4	39.9	.24	
DBP (mmHg)	70.8 (10.4)	74.63 (9.2)	72.10 (9.3)	71.19 (10.06)	71.53 (10.1)	.001	b>a; b>d
% ≥ 85 mmHg	9.6	15.4	9.5	10.3	10.4	.53	
% on hypertensive medication	25.2	42.3	30.8	27.7	28.5	.001	b>a; b>c; b>d
Fasting glucose (mg/dl)†	106.07 (40.6)	96.95 (27.6)	102.6 (37.3)	103.04 (44.9)	103.95 (39.5)	.021	a>b
%≥110 mg/dl	33.2	22.9	28.9	27.7	30.4	.032	a>b
LDL cholesterol (mg/dl)	118.90 (32.4)	124.68 (35.7)	118.53 (32.1)	119.18 (34.2)	119.63 (33.1)	.41	
HDL cholesterol (mg/dl)	46.11 (12.4)	48.54 (11.7)	49.12 (13.4)	49.75 (13.9)	47.41 (12.8)	.001	c>a; d>a
% HDL < 40 mg/dl (men)	49.6	32.1	33.7	41.8	44.3	.003	a>b; a>c; d>c
% HDL < 50 mg/dl (female)	52.8	49.5	39.4	41	48.3	.026	a>c; a>d

Total cholesterol (mg/dl)	198.76 (±38.1)	198.2 (±37.8)	194.44 (±34.6)	198.11 (±38.07)	197.96 (±37.1)	0.16	
Triglycerides (mg/dl)	170.86 (±88.09)	125.90 (±65.17)	134.91 (±69.21)	144.69 (±77.61)	155.96 (±83.26)	.001	a>b; a>b; a>c; d>b
% ≥150 mg/dl	51.4	26.3	31.3	35.7	42.9	.001	a>b; a>c; a>d; d>b

a = Mexican-American; b = Dominican-American; c = Puerto Rican; d = Central/South American

For blood pressures, *Wilks' Lambda* = 0.018; $F = 37279.16$; $p \leq 0.01$.

For lipids, *Wilks' Lambda* = .952; $F = 5.615$; $p \leq 0.01$.

For Inflammatory markers (IL-6, Fibrinogen, and CRP) *Wilks' Lambda* = 0.967; $F = 5.023$; $p \leq 0.01$

Bonferroni correction was applied controlling for alpha inflation.

Table 6: Mean comparison in psychosocial variables and inflammatory markers at baseline among U.S. Latino.

	Mexican American[a] Mean (SD)	Dominican American[b] Mean (SD)	Puerto Rican American[c] Mean (SD)	Central/South American[d] Mean (SD)	Total Mean (SD)	p	Post-hoc
Chronic Stress †	1.17 (1.1)	1.31 (1.2)	1.49 (1.3)	1.42 (1.2)	1.27 (1.2)	.002	c>a
Depressive symptoms †	8.78 (8.5)	9.00 (8.6)	11.4 (9.5)	10.06 (8.9)	9.38 (8.7)	.002	c>a
Social support †	24.54 (5.4)	24.42 (5.2)	23.63(6.01)	23.75 (6.3)	24.27 (5.6)	.099	
IL-6 log (pg/mL)	0.17 (0.27)	0.05 (0.27)	0.13 (0.26)	0.13 (0.28)	0.15 (0.27)	.001	a>b
Fibrinogen antigen log (mg/dl)	2.54 (0.08)	2.55 (0.08)	2.55 (0.08)	2.54 (0.08)	2.54 (0.08)	.25	
CRP log (mg/L)	0.39 (0.45)	0.24 (0.51)	0.43 (0.44)	0.35 (0.46)	0.37 (0.46)	.001	c>b

a = Mexican-American; b = Dominican-American; c = Puerto Rican; d = Central/South American
Wilk's Lambda = 0.982; F= 2.72; $p \leq 0.01$ † Homogeneity of variance was not accomplished. Brown-Forsythe test and Games-Howell post-hoc comparison were performed. Bonferroni correction was applied controlling for alpha inflation.

Table 7: Percent of MetS component met by participants at each exam

# MetS	Exam1%	Exam2 %	Exam3 %	Exam4 %	Exam5 %
0	8.86	8.6	8.07	7.31	6.93
1	18.89	18.36	17.55	16.55	19.03
2	26.02	24.35	22.98	22.94	23.37
3	22.49	24.19	26.69	25.71	29.06
4	17.44	17.20	17.46	18.82	15.31
5	6.3	7.3	7.25	8.66	6.31
MetS	Yes: 46.33%	Yes: 48.69%	Yes: 51.4%	Yes: 53.2%	Yes: 50.67%
n	1445	1302	1214	1190	967

Exam 1: July 2000 – July 2002; Exam 2: July 2002 – January 2004; Exam 3: January 2004 – July 2005; Exam 4: July 2005 – July 2007; Exam 5: April 2010 – February 2012

Table 8 Means and Standard Deviation for MetS total score at each exam, and changes from baseline and adjacent exam

Exam	Mean	Standard error	95%CI	Δ with baseline exam	Δ with previous exam
Exam 1	2.39	0.03	2.32 - 2.46	---	---
Exam 2	2.46	0.03	2.39 - 2.53	0.067*	0.067*
Exam 3	2.52	0.03	2.45 - 2.59	0.129**	0.062*
Exam 4	2.61	0.03	2.53 - 2.68	0.215**	0.085**
Exam 5	2.54	0.03	2.47 - 2.62	0.152**	0.063*

* $p \leq 0.05$; ** $p \leq 0.01$

Table 9: Percent of MetS component met by Male participants at each exam

# MetS	Exam1 %	Exam2 %	Exam3 %	Exam4 %	Exam5 %
0	11.83	11.72	11.15	9.25	7.98
1	20.78	21.03	21.6	18.68	22.84
2	27.13	23.43	21.6	24.73	24.39
3	20.06	23.92	25.61	24.73	26.39
4	15.15	15.25	14.98	17.08	14.41
5	5.05	4.65	5.05	5.52	3.00
MetS	Yes: 40.26%	Yes: 43.82%	Yes: 45.64%	Yes: 47.33%	Yes: 43.8%
n=	693	623	573	562	451

Exam 1: July 2000 – July 2002; Exam 2: July 2002 – January 2004; Exam 3: January 2004 – July 2005; Exam 4: July 2005 – July 2007; Exam 5: April 2010 – February 2012

Table 10: Percent of MetS component met by female participants at each exam

# MetS	Exam1 %	Exam2 %	Exam3 %	Exam4 %	Exam5 %
0	6.12	5.74	5.31	5.57	6.01
1	17.15	15.91	13.91	14.65	15.7
2	25	25.18	24.22	21.34	22.48
3	24.73	24.45	27.66	26.59	31.4
4	19.55	19	19.69	20.38	16.09
5	5.6	9.72	9.22	11.46	8.33
MetS	Yes: 51.73%	Yes: 53.17%	Yes: 56.57%	Yes: 58.43%	Yes: 55.82%
n=	752	679	640	628	516

Exam 1: July 2000 – July 2002; Exam 2: July 2002 – January 2004; Exam 3: January 2004 – July 2005; Exam 4: July 2005 – July 2007; Exam 5: April 2010 – February 2012

Table 11: Female and Male mean of MetS component met at each exam, and differences with baseline examination

Exam	Mean Female	Mean Male	Mean Difference	Δ with baseline Female	Δ with baseline Male
Exam 1	2.56	2.21	0.35***	---	---
Exam 2	2.65	2.25	0.41***	0.09*	0.04
Exam 3	2.72	2.3	0.42***	0.07†	0.05
Exam 4	2.79	2.4	0.39***	0.07†	0.1*
Exam 5	2.71	2.36	0.35***	0.08†	0.04

$^{\dagger}p \leq 0.10$; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.0001$.
Mean differences represent absolute values

Table 12: Mean of MetS components met across exams by nationalities, and differences with previous exam

Nationality	Exam 1 (Mean)	Exam 2 (Mean)	Δ 2-1	Exam 3 (Mean)	Δ3-2	Exam 4 (Mean)	Δ4-3	Exam 5 (Mean)	Δ5-4
Mexicans	2.55	2.59	-0.03	2.69	-0.1*	2.7	-0.01	2.64	0.05
Dominicans	2.08	2.12	-0.04	2.21	-0.08	2.45	-0.23**	2.4	0.05
Puerto Rican	2.16	2.28	-0.12†	2.22	0.06	2.5	-0.27***	2.47	0.03
Central/South	2.29	2.42	0.13*	2.44	0.15*	2.49	0.21**	2.37	0.08

$^{\dagger}p \leq 0.1$; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$

Table 13: Means and Standard Deviation for Triglycerides at each exam, and changes from baseline and adjacent exam

Exam	Triglycerides (Mean)	Standard error	Δ with baseline (reference)	Δ with previous exam
Exam 1	157.79	2.39	---	---
Exam 2	155.59	2.47	2.2	2.2
Exam 3	154.17	2.52	3.62	1.42
Exam 4	147.88	2.54	9.91***	6.29†
Exam 5	127.79	2.69	30***	20.08***

Exam 1 = Reference group. Δ = difference in absolute value; $^{\dagger}p \leq 0.10$; ***$p \leq 0.0001$

Table 14: Means and Standard Deviation for Triglycerides at each exam, and changes from baseline and adjacent exam by nationalities

Triglycerides	Mexicans (Mean)	Standard error	Dominicans (Mean)	Standard error	Puerto Ricans (Mean)	Standard error	Central/South (Mean)	Standard error
Exam 1	173.09	3.17	125.9	6.77	135.22	6.33	149.93	5.46
Exam 2	170.07	3.2	125.35	6.91	133.44	6.57	149.02	5.6
Exam 3	167.94	3.36	137.08	6.98	132.24	6.73	140.75	5.73
Exam 4	157.53	3.39	130.84	6.99	129.64	6.71	143.63	5.87
Exam5	133.60	3.63	114.56	7.19	123.16	7.1	120.63	6.23
Δ 1-2	3.01	3.04	0.54	6.37	1.77	6.07	0.91	5.19
Δ 2-3	2.13	3.17	11.72†	6.53	1.21	6.35	8.26†	5.37
Δ 3-4	10.41**	3.26	6.23	6.58	2.59	6.44	2.88	5.58
Δ 4-5	23.92***	3.51	16.27*	6.79	6.48	6.82	23***	6.02
Δ 1-2	3.01	3.04	0.54	6.37	1.77	6.07	0.91	5.19
Δ 1-3	5.14†	3.12	11.17†	6.44	2.98	6.25	9.18†	5.31
Δ 1-4	15.56***	3.15	4.93	6.46	5.57	6.22	6.29	5.46
Δ 1-5	39.49***	3.41	11.33*	6.67	12.06	6.65	29.29***	5.84

Exam 1 = Reference group. Δ = difference in absolute value; $^{\dagger}p \leq 0.10$; $*p \leq 0.05$; $**p \leq 0.01$; $***p \leq 0.0001$

Table 15: Means and Standard Deviation for fasting glucose, and changes from baseline and adjacent exam

Exam	Fasting glucose (Mean)	Standard error	Δ with baseline (reference)	Δ with previous exam
Exam 1	103.66	1.02	---	---
Exam 2	107.41	1.05	3.75***	3.75***
Exam 3	105.83	1.07	1.58†	2.17*
Exam 4	109.25	1.08	3.42**	5.59***
Exam 5	112.44	1.14	3.18***	8.78***

Exam 1 = Reference group. Δ = difference in absolute value; $^{\dagger}p \leq 0.10$; ***$p \leq 0.0001$

Table 16: Means and Standard Deviation for fasting glucose at each exam, and changes from baseline and adjacent exam by nationalities

Fasting glucose	Mexicans (Mean)	Standard error	Dominicans (Mean)	Standard error	Puerto Ricans (Mean)	Standard error	Central/South (Mean)	Standard error
Exam 1	106.04	1.37	96.89	2.94	102.73	2.75	101.68	2.37
Exam 2	110.29	1.42	100.81	2.99	107.33	2.84	103.35	2.43
Exam 3	109.36	1.45	98.97	3.02	103.58	2.90	101.67	2.47
Exam 4	110.77	1.46	104.85	3.02	109.2	2.89	107.57	2.52
Exam 5	115.35	1.55	106.61	3.09	111.92	3.03	108.10	2.66
Δ 1-2	4.25***	1.21	3.91	2.54	4.59†	2.41	1.66	2.06
Δ 2-3	0.92***	1.26	1.84	2.59	3.74	2.52	1.68	2.13
Δ 3-4	1.41***	1.29	5.88**	2.61	5.61**	2.56	5.90**	2.21
Δ 4-5	4.58***	1.39	1.75***	2.7	2.72***	2.70	0.53**	2.39
Δ 1-2	4.24***	1.21	3.91	2.54	4.59†	2.41	1.66	2.06
Δ 1-3	3.32**	1.24	2.07	2.56	0.85	2.48	0.01	2.11
Δ 1-4	4.73***	1.25	7.95**	2.57	6.46**	2.47	5.88**	2.17
Δ 1-5	9.31***	1.35	9.71**	2.65	9.18***	2.64	6.42**	2.32

Exam 1 = Reference group. Δ = difference in absolute value; $^{\dagger}p \leq 0.10$; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.0001$

Table 17: Means and Standard Deviation for systolic blood pressure, and changes from baseline and adjacent exam

Exam	SBP (Mean)	Standard error	Δ with baseline (reference)	Δ with previous exam
Exam 1	126.63	0.57	---	---
Exam 2	125.49	0.58	1.14*	1.14*
Exam 3	124.78	0.60	1.85***	0.7
Exam 4	125.21	0.60	1.42**	0.43
Exam 5	126.58	0.63	0.05	1.37*

*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.0001$

Table 18: Means and Standard Deviation for systolic blood pressure at each exam, and changes from baseline and adjacent exam by nationalities

SBP	Mexicans (Mean)	Standard error	Dominicans (Mean)	Standard error	Puerto Ricans (Mean)	Standard error	Central/South (Mean)	Standard error
Exam 1	127.15	0.76	127.16	1.63	123.82	1.53	126.85	1.32
Exam 2	125.33	0.79	125.69	1.67	124.89	1.58	126.29	1.35
Exam 3	126.31	0.81	122.35	1.68	121.13	1.61	124.68	1.38
Exam 4	127.47	0.81	121.04	1.67	121.56	1.61	124.34	1.41
Exam 5	126.09	0.86	127.62	1.72	127.7	1.68	125.9	1.49
Δ 1-2	1.82**	0.69	1.52	1.46	1.06	1.39	0.56	1.19
Δ 2-3	0.98	0.73	3.57*	1.5	3.76**	1.45	1.61	0.74
Δ 3-4	1.16	0.74	1.31	1. 5	0.43	1.47	0.33	1.28
Δ 4-5	1.37†	0.80	6.58***	1.55	6.14**	1.54	1.55	1.38
Δ 1-2	1.82**	0.69	1.52	1.46	1.06	1.39	0.56	1.19
Δ 1-3	0.84	0.71	4.8	1.48	2.69	1.43	2.17	1.22
Δ 1-4	0.32	0.72	6.12	1.45	2.26	1.42	2.51	1.25
Δ 1-5	1.05	0.78	0.46	1.52	3.87	1.5	0.95	1.34

Exam 1 = Reference group. Δ = difference in absolute value; $^{\dagger}p \leq 0.10$; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.0$

Table 19: Means and Standard Deviation for diastolic blood pressure, and changes from baseline and adjacent exam

Exam	DBP (Mean)	Standard error	Δ with baseline (reference)	Δ with previous exam
Exam 1	71.52	0.26	---	---
Exam 2	70.20	0.27	1.32***	1.32***
Exam 3	69.83	0.28	1.69***	0.36
Exam 4	69.65	0.28	1.87***	1.82
Exam 5	68.02	0.30	3.49***	1.62***

***$p \leq 0.0001$

Table 20: Means and Standard Deviation for diastolic blood pressure at each exam, and changes from baseline and adjacent exam by nationalities

DBP	Mexicans (Mean)	Standard error	Dominicans (Mean)	Standard error	Puerto Ricans (Mean)	Standard error	Central/South (Mean)	Standard error
Exam 1	70.8	0.35	74.63	0.75	72.09	0.71	71.24	0.61
Exam 2	69.25	0.36	73.35	0.77	71.82	0.73	69.71	0.62
Exam 3	69.53	0.37	71.92	0.77	69.82	0.74	69.33	0.64
Exam 4	69.62	0.37	71.18	0.77	69.41	0.74	69.01	0.65
Exam 5	66.84	0.4	71.72	0.79	69.6	0.77	67.58	0.69
Δ 1-2	1.54***	0.32	1.27†	0.67	0.26	0.64	1.53**	0.55
Δ 2-3	0.27	0.33	1.49*	0.69	1.95**	0.67	0.38	0.57
Δ 3-4	0.08	0.34	0.73	0.69	0.47	0.68	0.32	0.59
Δ 4-5	2.78***	0.37	0.53	0.71	0.18	0.71	1.42*	0.64
Δ 1-2	1.54***	0.32	1.27†	0.67	0.26	0.64	1.53**	0.55
Δ 1-3	1.17***	0.33	2.7***	0.68	2.19***	0.66	1.91***	0.56
Δ 1-4	1.17***	0.33	3.33***	0.68	2.67***	0.65	2.23***	0.57
Δ 1-5	3.95***	0.36	2.9***	0.71	2.48***	0.69	3.66***	0.62

Exam 1 = Reference group. Δ = difference in absolute value; $^{\dagger}p \leq 0.10$; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.0001$

Table 21: Means and Standard Deviation for waist size circumference, and changes from baseline and adjacent exam

Exam	WSC (Mean)	Standard error	Δ with baseline (reference)	Δ with previous exam
Exam 1	100.65	0.35	---	---
Exam 2	100.95	0.37	0.29†	0.29†
Exam 3	101.63	0.36	0.99***	0.68***
Exam 4	102.26	0.36	1.61***	0.62***
Exam 5	101.62	0.36	0.98***	0.64***

†p≤ 0.1; ***$p \leq 0.0001$

Table 22: Means and Standard Deviation for waist size circumference at each exam, and changes from baseline and adjacent exam by nationalities

WSC	Mexicans (Mean)	Standard error	Dominicans (Mean)	Standard error	Puerto Ricans (Mean)	Standard error	Central/South (Mean)	Standard error
Exam 1	101.8	0.47	96.63	1.00	100.65	0.94	99.84	0.81
Exam 2	102.07	0.47	97.49	1.01	100.51	0.95	100.17	0.82
Exam 3	103.19	0.47	97.7	1.01	100.42	0.95	100.5	0.82
Exam 4	103.5	0.48	98.88	1.01	102.00	0.95	100.96	0.83
Exam 5	102.91	0.49	99.32	1.02	101.14	0.97	99.48	0.84
Δ 1-2	0.27	0.23	0.85†	0.48	0.14	0.47	0.32	0.39
Δ 2-3	1.12***	0.24	0.21	0.49	0.09	0.47	0.33	0.41
Δ 3-4	0.3	0.24	1.18*	0.49	1.58**	0.48	0.46	0.42
Δ 4-5	0.59*	0.26	0.43	0.51	0.85†	0.51	1.48***	0.46
Δ 1-2	0.27	0.23	0.85†	0.48	0.14	0.46	0.32	0.39
Δ 1-3	1.39***	0.23	1.06*	0.48	0.24	0.47	0.65	0.40
Δ 1-4	1.69***	0.23	2.24***	0.49	1.34**	0.47	1.12**	0.41
Δ 1-5	1.1***	0.25	2.68***	0.5	0.48	0.49	0.35	0.44

Exam 1 = Reference group. Δ = difference in absolute value; $^{\dagger}p \leq 0.10$; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.000$

Table 23: Means and Standard Deviation for HDL cholesterol, and changes from baseline and adjacent exam

Exam	HDL (Mean)	Standard error	Δ with baseline (reference)	Δ with previous exam
Exam 1	47.52	0.35	---	---
Exam 2	48.28	0.36	0.76***	0.76***
Exam 3	47.7	0.36	0.17	0.58*
Exam 4	48.54	0.36	1.02***	0.84***
Exam 5	50.97	0.37	3.44***	2.42***

*p≤ 0.5; ***$p \leq 0.0001$

Table 24: Means and Standard Deviation for HDL cholesterol at each exam, and changes from baseline and adjacent exam by nationalities

HDL	Mexicans (Mean)	Standard error	Dominicans (Mean)	Standard error	Puerto Ricans (Mean)	Standard error	Central/South (Mean)	Standard error
Exam 1	46.10	0.46	48.53	1.00	49.07	0.93	49.92	0.81
Exam 2	46.57	0.47	49.53	1.01	50.17	0.95	51.01	0.81
Exam 3	46.12	0.48	48.74	1.01	49.80	0.96	50.13	0.82
Exam 4	47.28	0.48	48.67	1.01	50.12	0.96	51.12	0.83
Exam 5	48.59	0.50	53.11	1.02	53.83	0.90	54.18	0.86
Δ 1-2	0.46	0.29	1.19†	0.62	1.09†	0.59	1.08*	0.51
Δ 2-3	0.44	0.31	0.98	0.64	0.36	0.62	0.87†	0.52
Δ 3-4	1.15***	0.32	0.07	0.65	0.31	0.63	0.98†	0.54
Δ 4-5	1.31***	0.34	4.43***	0.66	3.71***	0.66	3.06***	0.59
Δ 1-2	0.46	0.29	1.19†	0.62	1.09†	0.59	1.08†	0.51
Δ 1-3	0.02	0.31	0.21	0.63	0.73	0.62	0.21	0.52
Δ 1-4	1.17***	0.31	1.05	0.61	1.05†	0.61	1.19*	0.53
Δ 1-5	2.49***	0.33	4.57***	0.65	4.76***	0.65	4.26***	0.57

Exam 1 = Reference group. Δ = difference in absolute value; $^{\dagger}p \leq 0.10$; $*p \leq 0.05$; $**p \leq 0.01$; $***p \leq 0.0001$

Table 25: Bivariate associations between study variables.

	1	2	3	4	5	6	7	8	9	10	11	12
1) Sep	-											
2) Age	-0.30*	-										
3) Physical activity	0.26*	-0.33*	-									
4) Chronic stress	0.09*	-0.15	0.04	-								
5) Depressive symptoms	-0.15*	-0.06*	-0.06*	0.37*	-							
6) Life discrimination	0.16*	-0.13*	0.10*	0.26*	0.13*	-						
7) Daily discrimination	0.24*	-0.25*	0.15*	0.30*	0.28*	0.40*	-					
8) Anger	0.03	-0.22*	0.05	0.25*	0.37*	0.19*	0.27*	-				
9) Anxiety	-0.07*	-0.10*	-0.03	0.35*	0.66*	0.14*	0.28*	0.45*	-			
10) Optimism	0.002	-0.009	-0.02	-0.14*	-0.27*	-0.12*	-0.19*	-0.15*	-0.31*	-		
11) S. Support	0.08*	0.02	0.04	-0.22*	-0.41*	-0.14*	-0.25*	-0.22*	-0.39*	0.17*	-	
12) MetS score	-0.20*	0.18*	-0.15*	0.01	0.03	0.01	-0.04	-0.07*	-0.01	-0.06*	-0.03	-

$p \leq 0.05$

Table 26: Crude and adjusted model for the association between baseline negative affect variables and number of MetS criteria at exam 3

	β	*95%CI*	*p*
Model 1			
Depressive symptoms	0.011	-0.0009, 0.0225	0.071
Trait anger	-0.027	-0.0474, -0.0067	0.009
Trait anxiety	-0.006	-0.0279, 0.0168	0.628
Model 2			
Depressive symptoms	0.006	-0.0061, 0.0174	0.349
Trait anger	-0.013	-0.0334, 0.0072	0.206
Trait anxiety	-0.009	-0.0305, 0.0133	0.442
Model 3			
Depressive symptoms	0.004	-0.0065, 0.0163	0.4
Trait anger	-0.013	-0.0333, 0.0065	0.188
Trait anxiety	-0.006	-0.0268, 0.0156	0.607

Model 1: Crude model. Model 2: Adjusted by age, gender, socioeconomic status, and nationalities. Model 3: Fully adjusted model added inflammatory markers.

Table 27: Crude and adjusted model for the association between baseline chronic stress variables and number of MetS criteria at exam 3

	β	*95%CI*	*p*
Model 1			
Chronic burden	0.025	-0.0461, 0.0977	0.482
Life discrimination	0.048	-0.0389, 0.1356	0.278
Daily discrimination	-0.013	-0.0285, 0.0011	0.070
Model 2			
Chronic burden	0.032	-0.0376, 0.1028	0.362
Life discrimination	0.087	0.0021, 0.1732	0.045
Daily discrimination	0.001	-0.0132, 0.0162	0.844
Model 3			
Chronic burden	0.032	-0.0365, 0.0998	0.363
Life discrimination	0.082	-0.0012, 0.1661	0.054
Daily discrimination	0.0007	-0.0137, 0.0153	0.914

Model 1: Crude model. Model 2: Adjusted by age, gender, socioeconomic status, and nationalities. Model 3: Fully adjusted model added inflammatory markers.

Table 28: Moderators for the association between baselines negative affect variables and number of MetS criteria at exam 3

	β	*95%CI*	*p*
Optimism	0.009	-0.3583, 0.3754	0.963
Depressive symptoms X Optimism	0.0051	-0.0065, 0.0167	0.391
Trait anger X Optimism	0.0076	-0.0123, 0.0276	0.451
Trait anxiety X Optimism	-0.019	-0.0411, 0.0026	0.085
Social support	-0.006	-0.0554, 0.0432	0.809
Depressive symptoms X Social support	-0.0006	-0.0022, 0.0011	0.497
Trait anger X Social support	-0.0016	-0.0044, 0.0010	0.224
Trait anxiety X Social support	0.0022	-0.0008, 0.0052	0.155

Table 29: Moderators for the association between baselines negative affect variables and number of MetS criteria at exam 3

	β	*95%CI*	*p*
Optimism	0.029	-0.2100, 0.2688	0.810
Chronic burden X Optimism	0.0199	-0.0566, 0.0965	0.610
Life discrimination X Optimism	0.0047	-0.0897, 0.0992	0.922
Daily discrimination X Optimism	-0.0111	-0.0267, 0.0044	0.160
Social support	-0.0172	-0.0487, 0.0142	0.283
Chronic burden X Social support	-0.0013	-0.012, 0.0094	0.808
Life discrimination X Social support	0.0028	-0.0099, 0.0156	0.663
Daily discrimination X Social support	0.0015	-0.0005, 0.0036	0.152

Table 30: Nationalities as moderator for the association between baselines negative affect variables and number of MetS criteria at exam 3

	β	*95%CI*	*p*
Mexicans X Depressive symptoms	0.236	-0.115, 0.5883	0.188
Dominicans X Depressive symptoms	-0.718	-1.4134, -0.0231	0.043
Puerto Ricans X Depressive symptoms	0.539	-0.0138, 1.0923	0.056
Central/South X Depressive symptoms	0.017	-0.5008, 0.5366	0.946
Mexicans X Trait anger	-.0111	-0.0395, 0.0172	0.442
Dominicans X Trait anger	0.026	-0.0326, 0.0847	0.384
Puerto Ricans X Trait anger	-0.063	-0.1134, -0.0142	0.012
Central/South X Trait anger	-0.007	-0.0478, 0.0331	0.722
Mexicans X Trait anxiety	-0.009	-0.0344, 0.0157	0.465
Dominicans X Trait anxiety	0.004	-0.0513, 0.0600	0.878
Puerto Ricans X Trait anxiety	0.001	-0.0465, 0.0476	0.981
Central/South X Trait anxiety	0.011	-0.0272, 0.0496	0.568

Table 31: Test of configural, measurement, and structural invariance across gender

Model	χ^2	*df*	*CFI*	*TLI*	*RSMEA*	*90%CI*	$\Delta\chi^2$	*Δ df*
Model 1: Configural invariance	168.44	100	0.98	0.96	0.036	0.026 – 0.045	_	_
Model 2: Measurement invariance	200.07	92	0.96	0.94	0.047	0.038 – 0.056	31.68***	8
Model 3: Partial measurement invariance	180.64	91	0.97	0.95	0.034	0.034 – 0.052	12.2	9
Model 4: Structural invariance	206.28	106	0.97	0.95	0.042	0.033 – 0.050	25.64*	9

*** $p \leq 0.0001$. CFI = Comparative Fit Index; TLI= Tucker Lewis Index; RMSEA= Root Mean Square Error Approximation; $\Delta\chi^2$= Chi-square difference; Δ *df*= Degrees of freedom difference. Model 1 has no constraints across gender. Model 2: Factors loadings across gender are constrained. Model 3: Releases depressive symptoms loading constraint across gender. Model 4: Structural paths are constrained across gender.

Table 32: Gender differences on study variables

	Female		Male		
	Mean	SE	Mean	SE	p
Chronic burden	1.18	0.04	1.01	0.04	***
Depressive symptoms	10.9	0.35	7.88	0.29	***
Life discrimination	0.53	0.03	0.83	0.04	***
Daily discrimination	13.1	0.21	13.6	0.23	ns
Anger	15.1	0.15	14.8	0.16	ns
Anxiety	16.6	0.17	15.6	0.18	***
Optimism	3.29	0.02	3.33	0.02	ns
Social Support	23.7	0.21	24.9	0.21	***
Physical Activity	7.82	0.04	8.22	0.04	***
IL-6	0.39	0.02	0.29	0.02	***
CRP	1.05	0.03	0.66	0.03	***
Fibrinogen	5.89	0.01	5.82	0.01	***
MetS score	2.69	0.05	2.26	0.06	***

*** $p \leq 0.001$; $^{\dagger}p \leq 0.07$, ns = non-significant difference

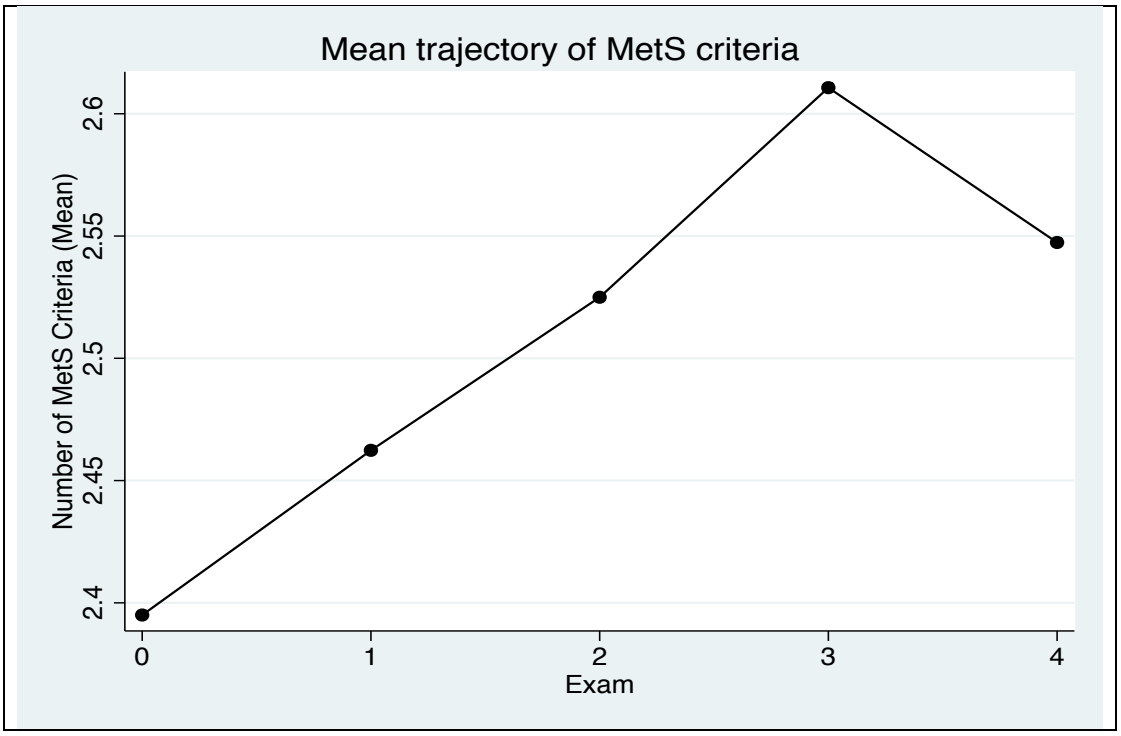

Figure 1: Trajectory of MetS criteria from exam 1 to 5.

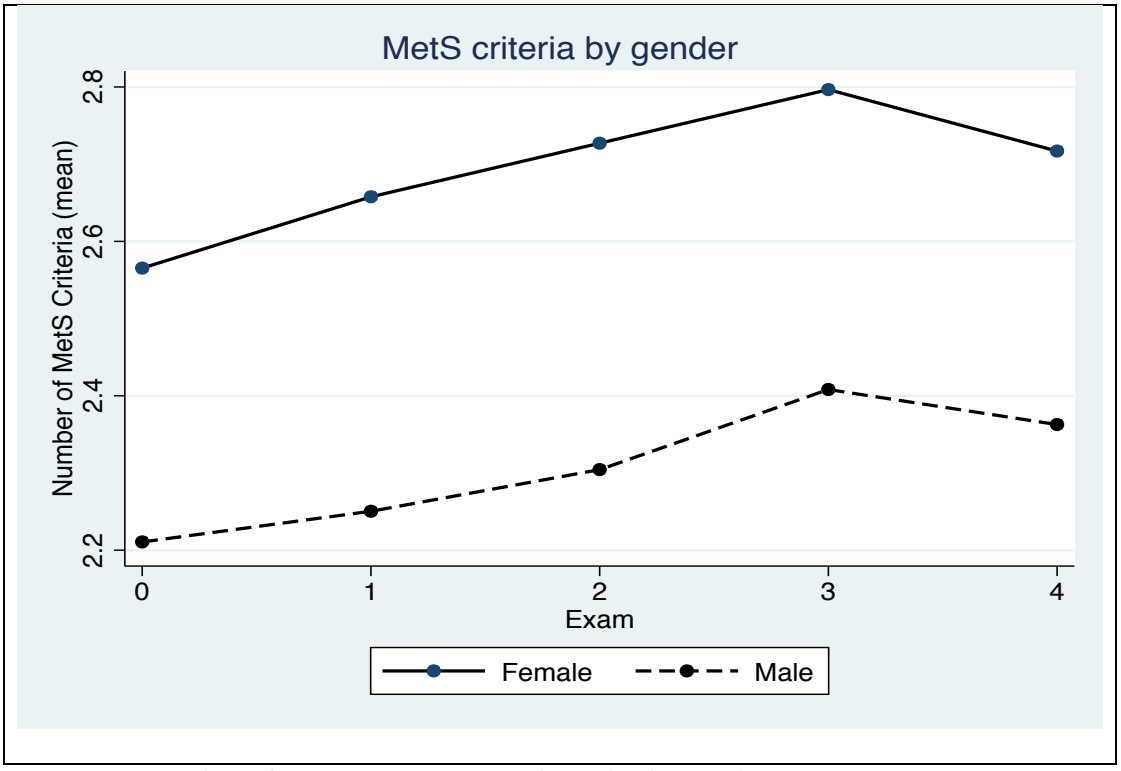

Figure 2: Number of MetS components trajectories by gender

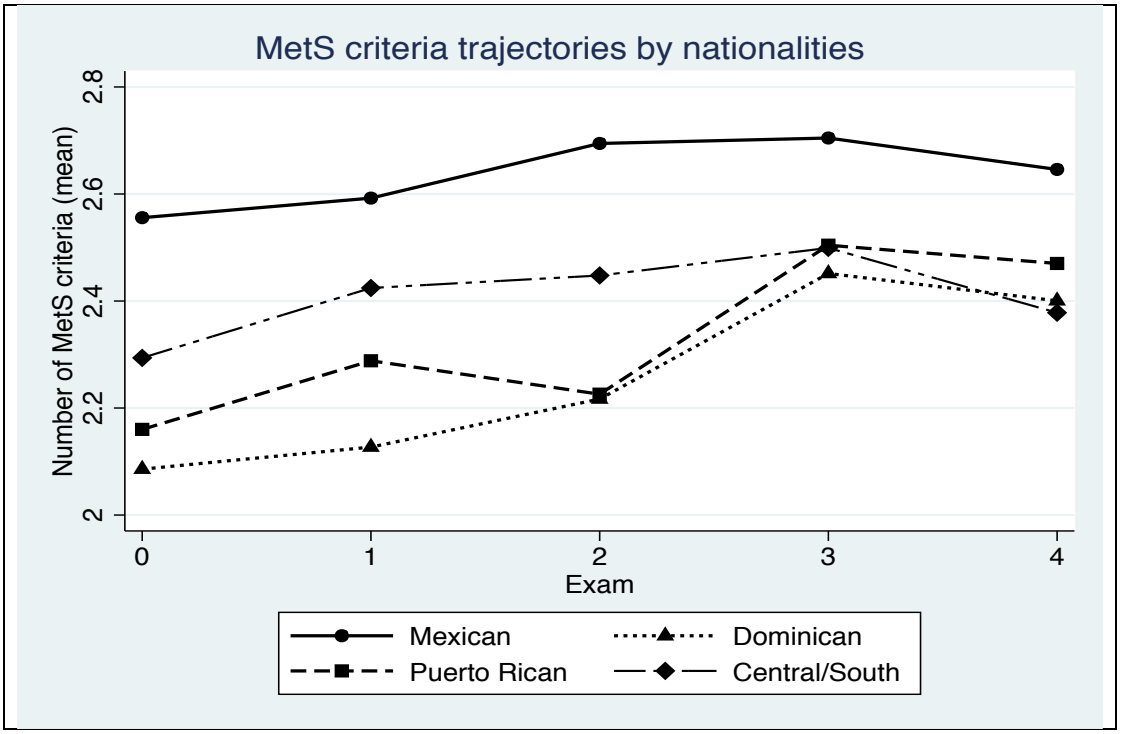

Figure 3: Number of MetS components trajectories by nationalities

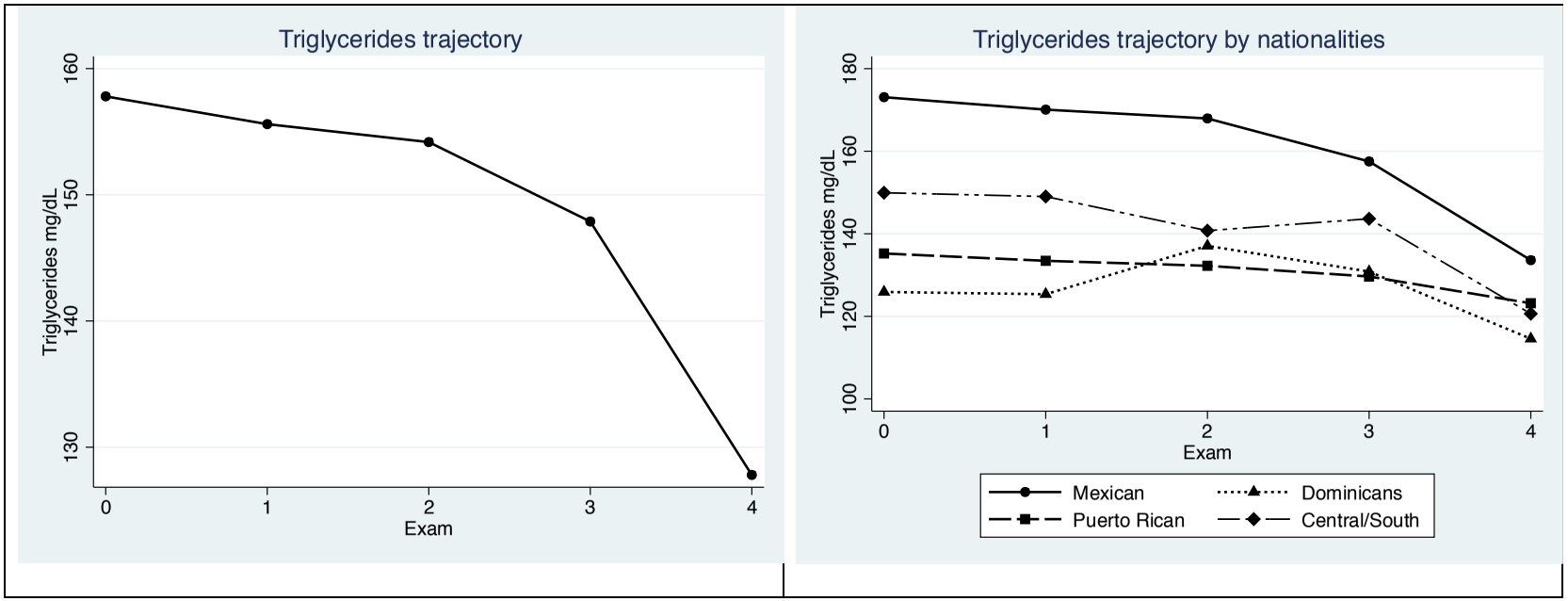

Figure 4: Triglycerides trajectory. Left figure depicts the trajectory for the overall Latino sample. Right figure depicts the trajectory for each national group

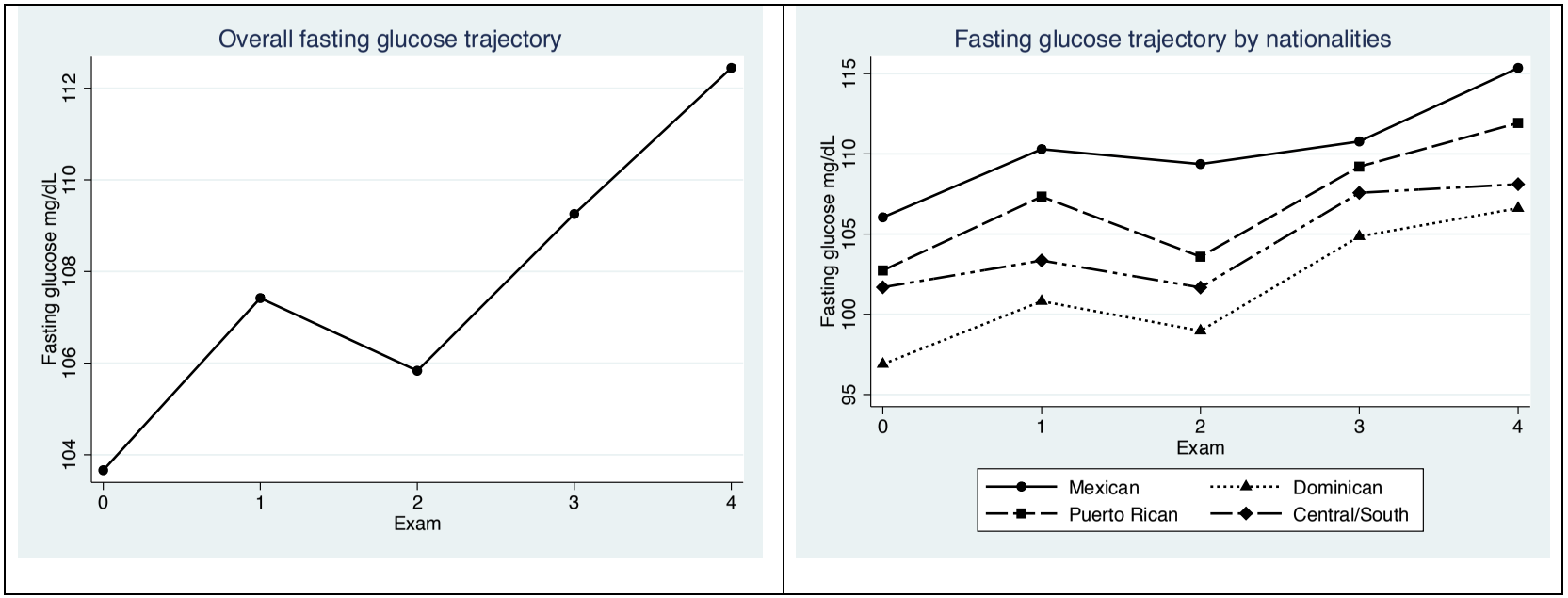

Figure 5: Fasting glucose trajectory. Left figure depicts the trajectory for the overall Latino sample. Right figure depicts the trajectory for each national group

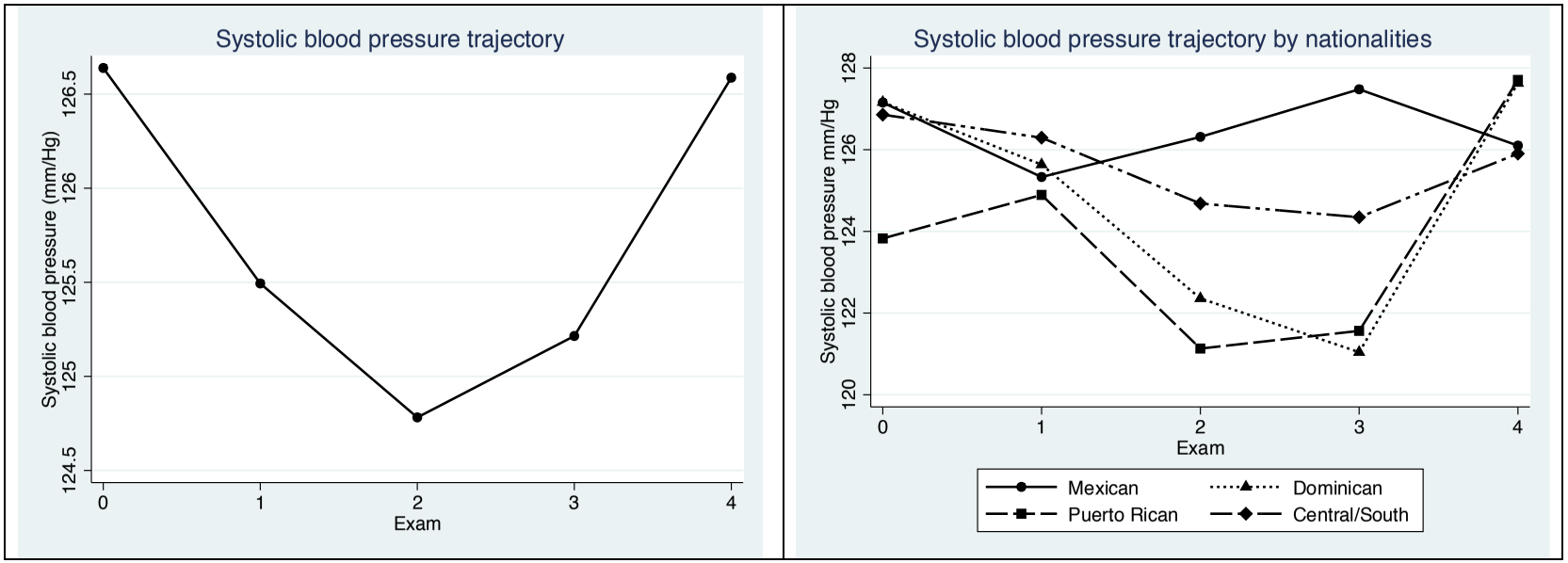

Figure 6. Systolic blood pressure trajectory. Left graph represents SBP trajectory for the overall Latino sample. Right figure depicts SBP trajectory by nationalities

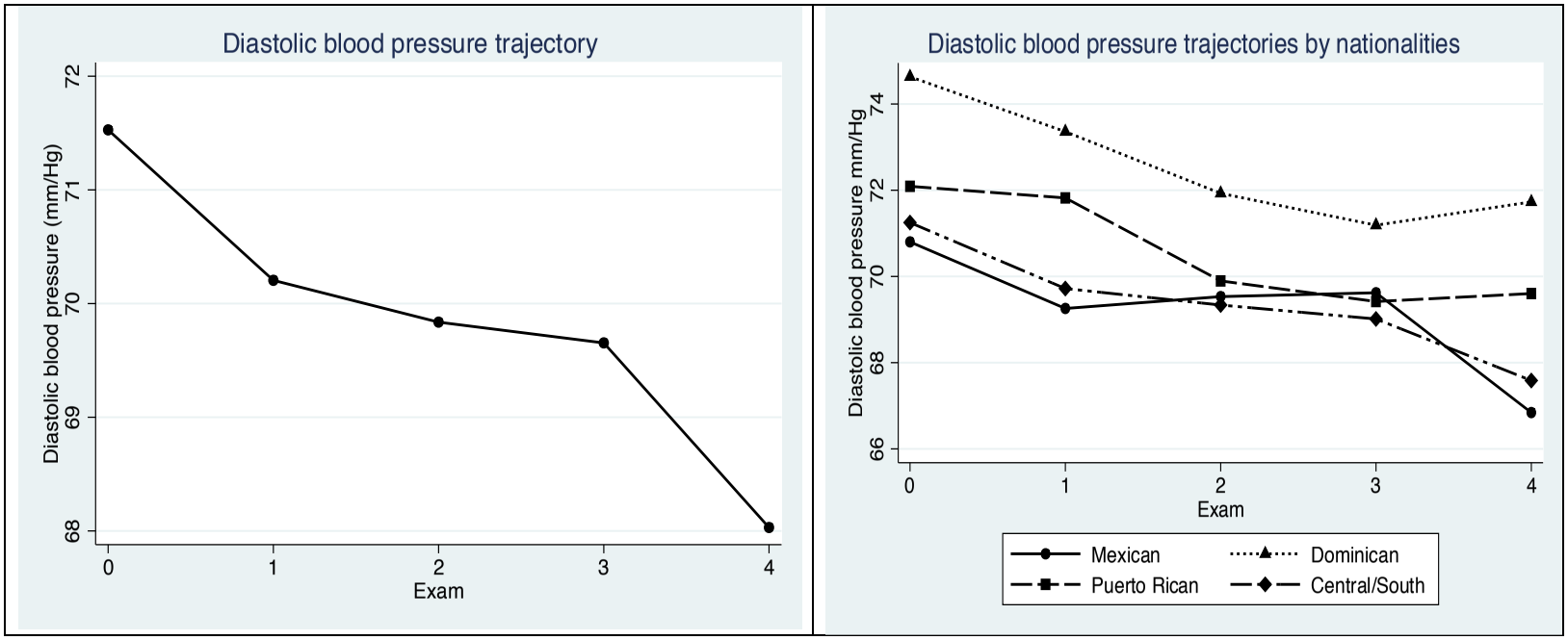

Figure 7. Diastolic blood pressure trajectory. Left graph represents DBP trajectory for the overall Latino sample. Right figure depicts DBP trajectory by nationalities

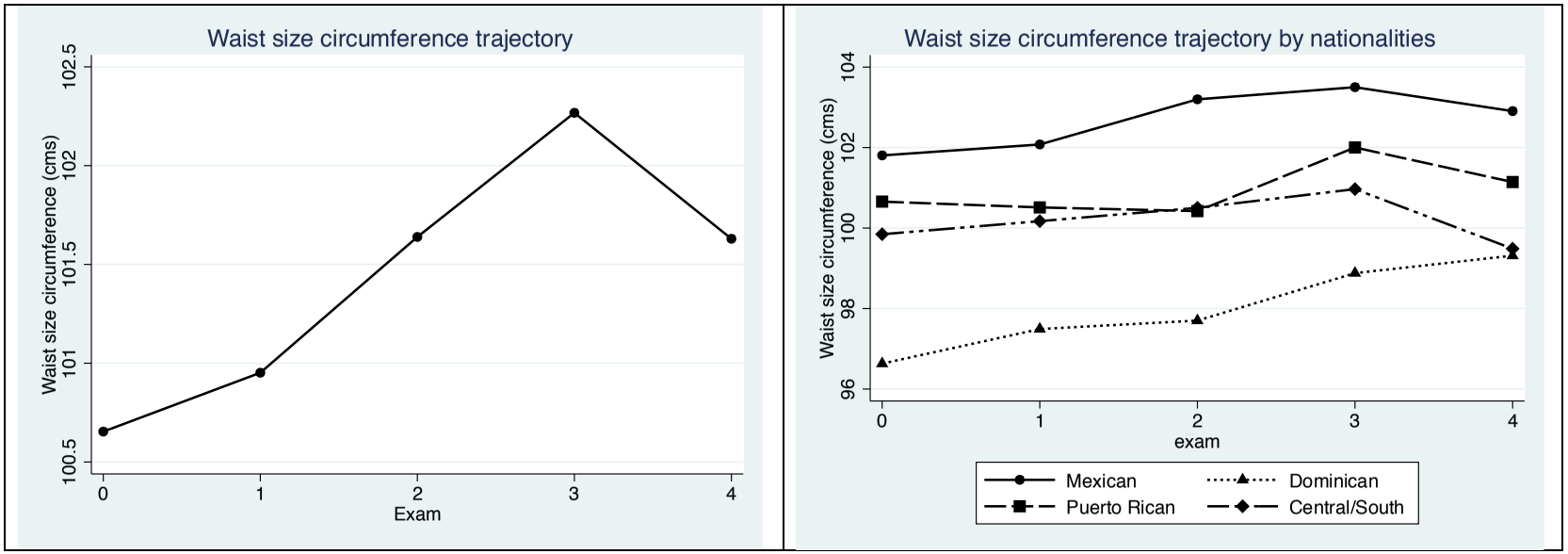

Figure 8: Waist size circumference trajectory. Left figure depicts the overall waist size circumference trajectory. Right figure shows the trajectories for each national group.

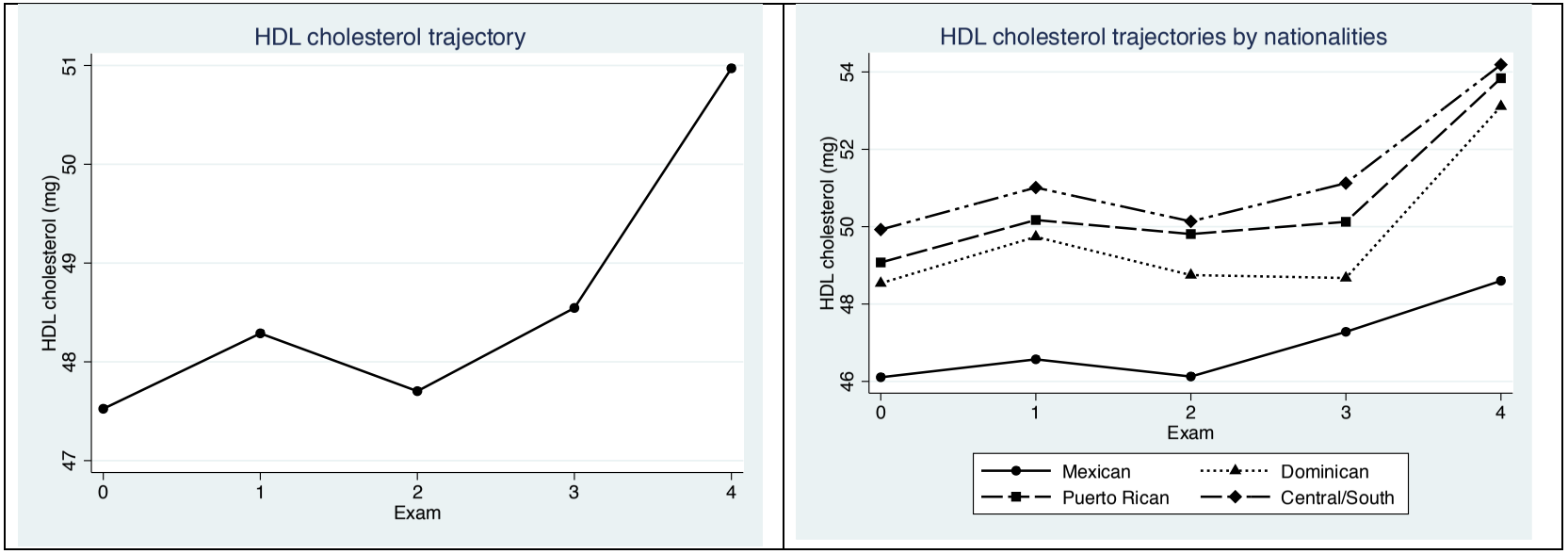

Figure 9: HDL cholesterol trajectory. Left graph depicts the overall HDL cholesterol trajectory. Right graph displays HDL cholesterol by nationalities.

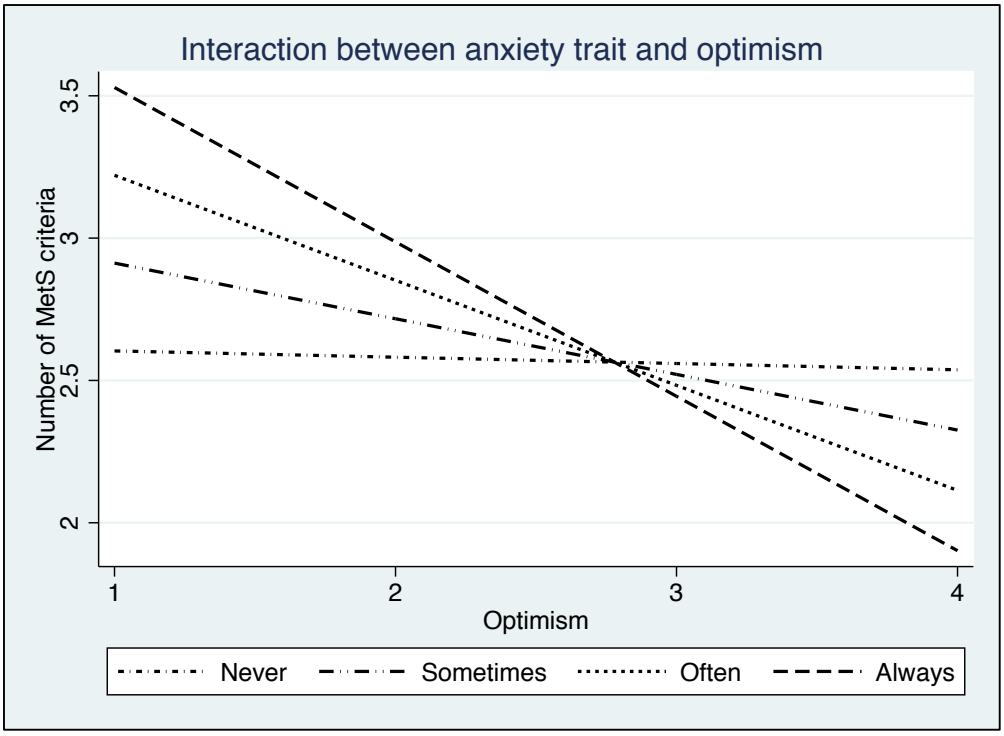

Figure 10: The marginal interaction between optimism and anxiety trait. Participants reporting high level of optimism (score 4) and high level of anxiety (always) have lower number of MetS criteria than participants reporting low optimism (score 1) and lower anxiety (never)

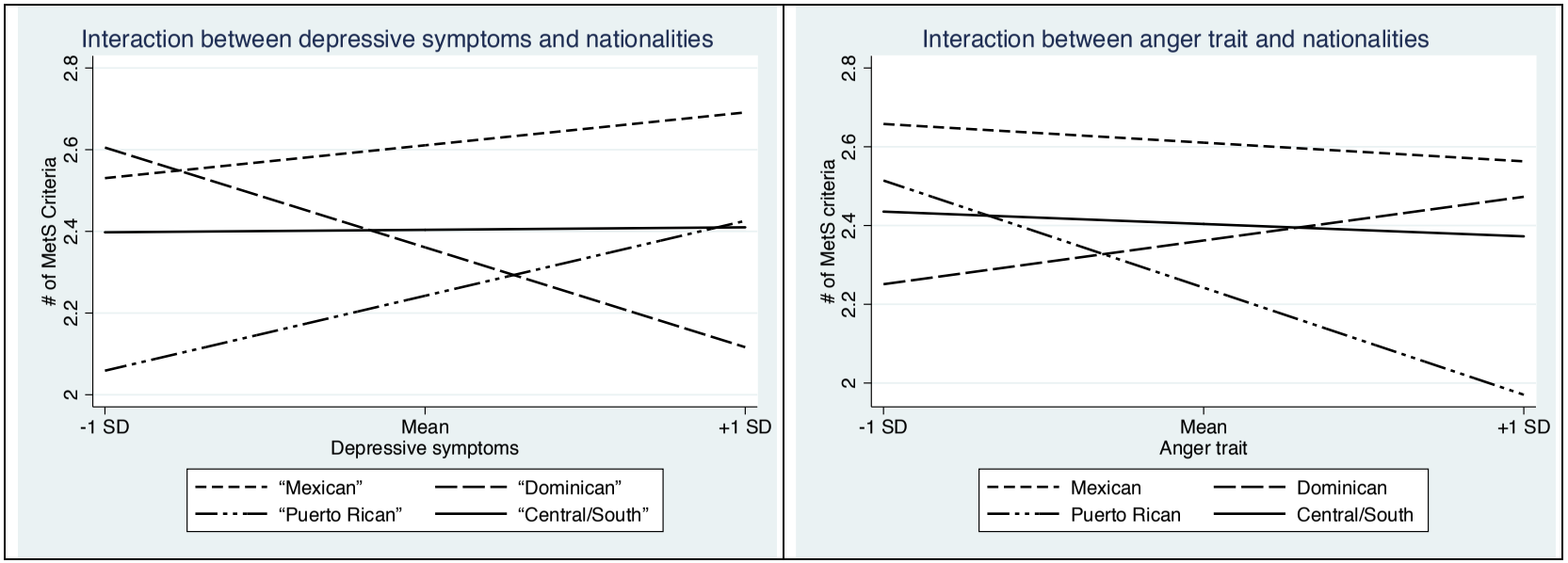

Figure 11: Interaction between nationalities and negative affect variables. Left graph depicts the interaction between the nationalities and depressive symptoms. Right graph shows the interaction between nationalities and anger trait.

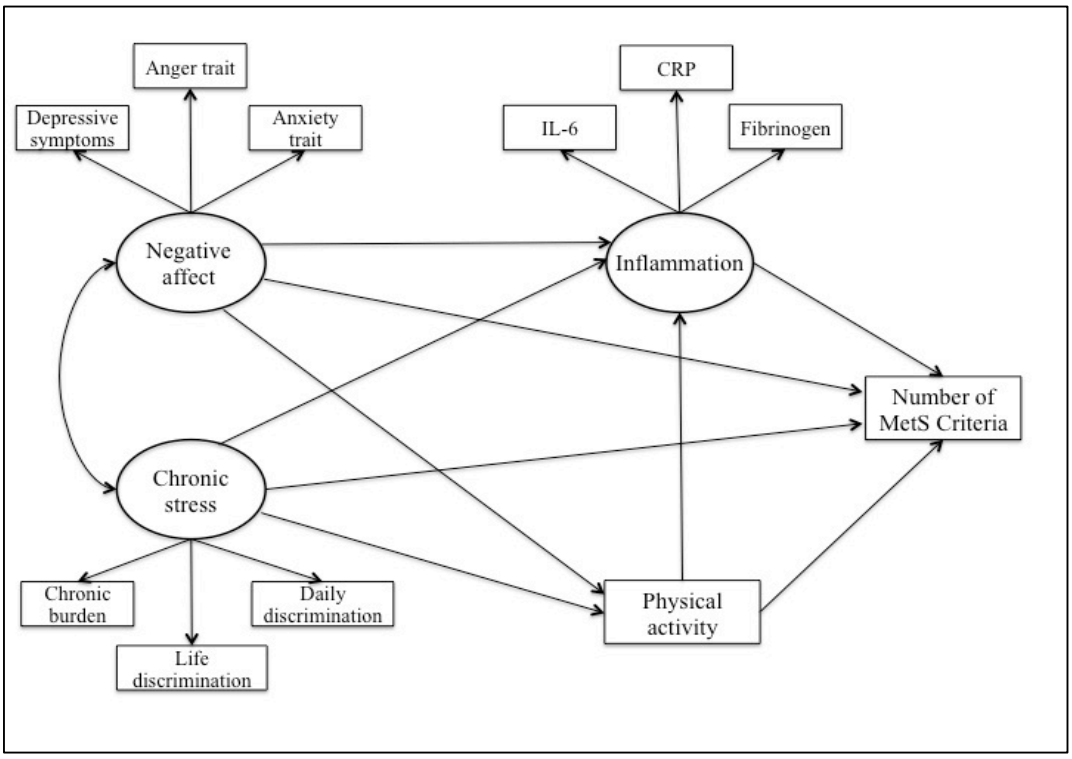

Figure 12: Theoretical model with negative affect and chronic stress predicting MetS

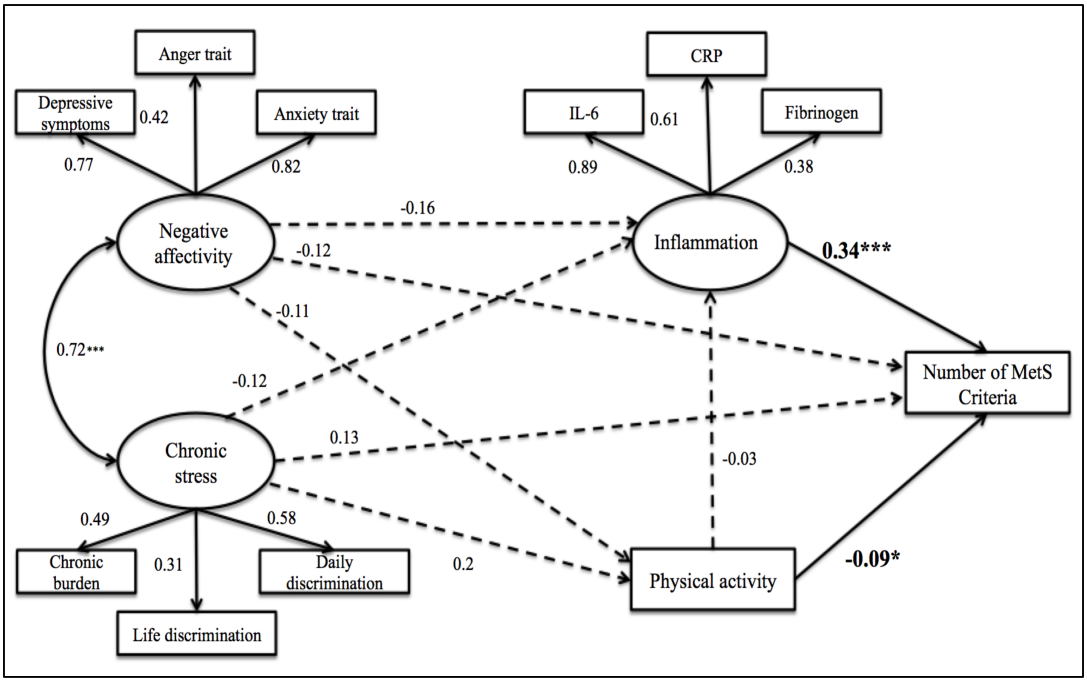

Figure 13: Multi-group SEM for female. $\chi^2_{(91)}$= 180.6; $p \leq 0.0001$; CFI = 0.97; TLI= 0.95; RMSEA = 0.043. Factor loadings and structural paths coefficients are presented as standardized coefficients solution. Solid lines represent significant paths. Dash lines represent non-significant paths.

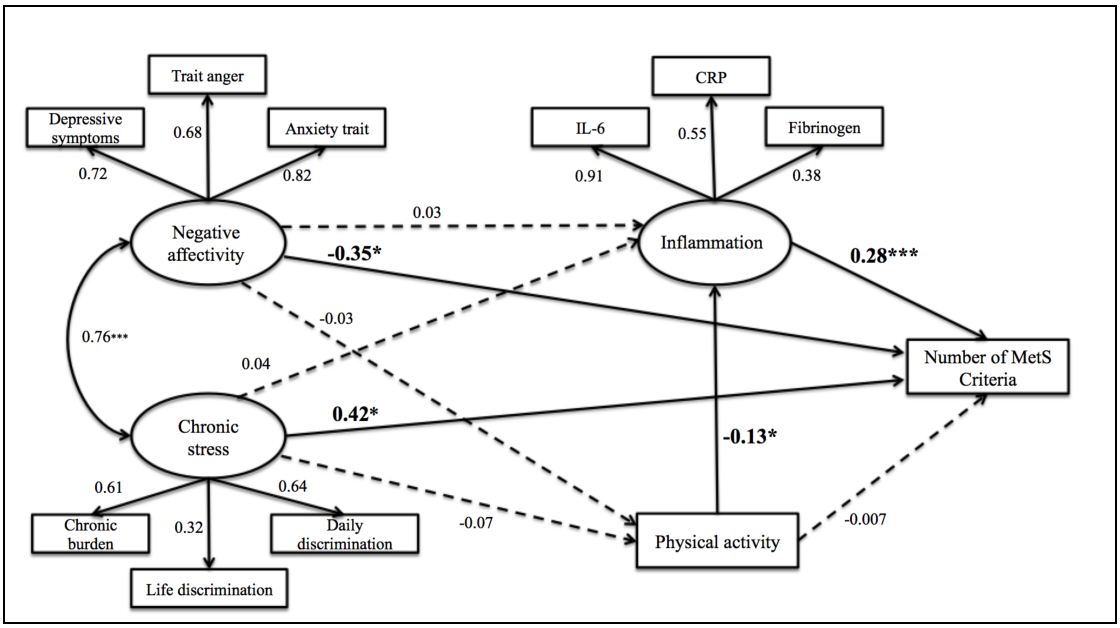

Figure 14: Multi-group SEM for male. $\chi^2_{(91)}$= 180.6; $p \leq 0.0001$; CFI = 0.97; TLI= 0.95; RMSEA = 0.043. Factor loadings and structural paths coefficients are presented as standardized coefficients solution. Solid lines represent significant paths. Dash lines represent non-significant paths.

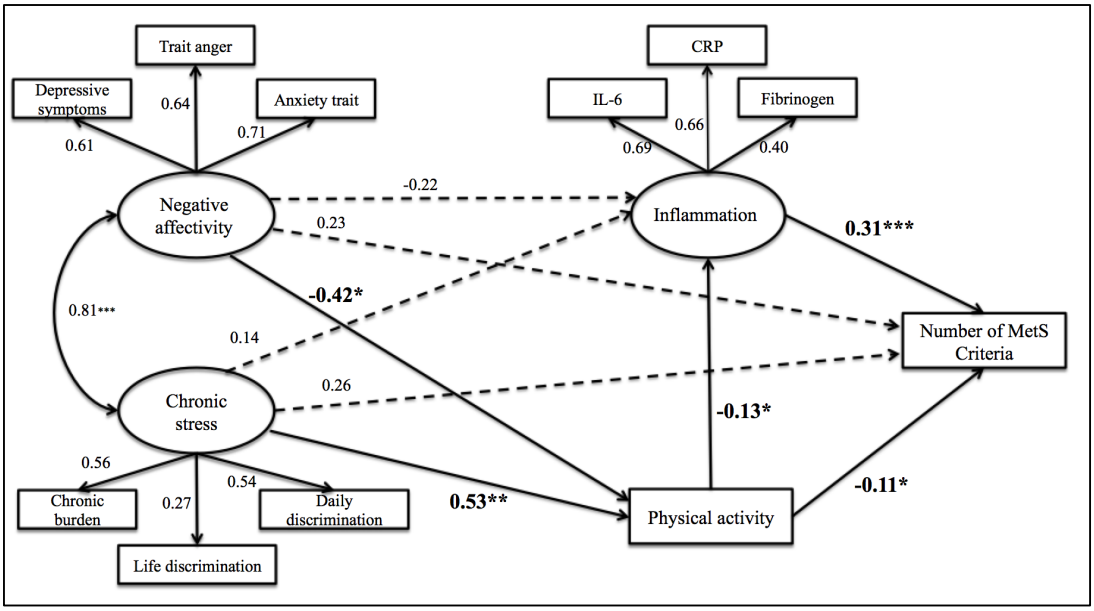

Figure 15: Study 1 model tested with Mexican-Americans participants.
$\chi^2_{(33)}$= 95.6; $p \leq 0.0001$; CFI = 0.97; TLI= 0.93; RMSEA = 0.049. Factor loadings and structural paths coefficients are presented as standardized coefficients solution.
Solid lines represent significant paths. Dash lines represent non-significant paths.

Study 2: Results

Longitudinal associations between psychological factors and subclinical atherosclerosis (ATS) markers (Hypotheses 4 & 5)

To test the longitudinal associations between psychological factors measured at baseline examination with the progression of atherosclerosis, and whether these associations are mediated by unhealthy behaviors, inflammatory markers and MetS severity, a structural equation modeling was conducted. The proposed theoretical model is presented in Figure 16. Thus, a direct effect of negative affect and chronic stress on subclinical atherosclerosis was hypothesized. Furthermore, these effects were expected to be mediated by physical activity, inflammatory markers, and MetS severity. Because Mexican-American participants are the larger sample in the study, and they have the highest MetS prevalence, this final analysis was conducted only with them. Furthermore, because females have higher MetS scores than males, a dummy code for gender was included into the model. Thus, gender differences in all the study variables were estimated.

Figure 17 depicts the direct and indirect effects for the variables of interest on subclinical ATS. As expected, higher levels of inflammation were related to higher number of MetS criteria (β= 0.31, $p\leq$ 0.001) and with greater subclinical atherosclerosis (β= 0.15, $p\leq$ 0.05). Higher levels of physical activity were related to lower levels of inflammation (β= -0.16, $p\leq$ 0.001), and lower number of MetS criteria (β= -0.11, $p\leq$ 0.05), and most important, evidence for MetS severity predicting subclinical atherosclerosis was found (β= 0.18, $p\leq$ 0.05). Although the hypothesized direct effect of negative affect and chronic burden on subclinical ATS were not significant, the overall fit

of this model was excellent $\chi^2_{(78)}$= 120.99; $p \leq 0.001$; CFI = 0.98; TLI= 0.97; RMSEA = 0.026 (90%CI= 0.017 – 0.035). Furthermore, these latent factors were not associated with either inflammatory markers or with MetS severity, although both negative affect (β= -0.37, $p \leq 0.01$), and chronic burden (β= 0.44, $p \leq 0.001$) were related to physical activity.

Test for the indirect effects were conducted using the algorithms proposed by Sobel, and revealed that baseline negative affect predicted indirectly the severity of MetS at Exam 3 via physical activity and inflammation ($\beta_{indirect}$= 0.018, $p \leq 0.05$) (see Figure 16). Similarly, baseline chronic stress indirectly predicted MetS severity at Exam 3 through physical activity and inflammation ($\beta_{indirect}$= -0.021, $p \leq 0.05$). Furthermore, a marginal indirect effect for physical activity, inflammation and MetS mediating the association between negative affect and subclinical ATS was found ($\beta_{indirect}$= 0.003, p= 0.095). Further, this result is almost identical to the effect for chronic stress ($\beta_{indirect}$= 0.004, p= 0.1) (see Table 33).

The dummy code for gender allowed us to identify gender differences that emerged in several variables tested in this model. Thus, female Mexican Americans, similar to the models following Study 1, had greater chronic burden, depressive symptoms, trait anxiety, IL-6, CRP and fibrinogen (all $p \leq 0001$). Male Mexican Americans experienced greater life discrimination, social support, and reported greater moderate and vigorous physical activity (all $p \leq 0.001$). As in Study 1, females have greater MetS scores than males ($p \leq 0.001$), but males scored higher on several subclinical atherosclerosis markers, such as left distal CCA – CIMT, left ICA-CIMT, and CCA (all $p \leq 0.001$).

Thus, hypothesis 4 regarding psychological factors and ATS was not supported. However, some evidence for physical activity, inflammation, and MetS as mediators of the association between psychological factors and subclinical ATS was found, thus providing partial support for hypothesis 5.

Study 2: Discussion

Mexican-Americans are the largest Latino population living in the U.S. representing about two-third (50 millions) of the Latinos living in U.S. Previous studies (Ford, Giles & Dietz, 2002; Park et al., 2003) have reported that they carry a disproportionate burden of cardio-metabolic risk factors such as obesity, hypercholesterolemia, and insulin resistance, in comparison with non-Latino whites, and even with other U.S. Latinos. The prevalence of MetS among Mexican-Americans is the highest of any other racial or ethnic group. In 2002, the age-adjusted MetS prevalence for Mexican-Americans has been estimates in 31.9%, and by 2008 the estimated prevalence of MetS increased to 44.5% for men and 44.1% for women (Allison et al., 2008). Thus, these data are consistent with the results we obtained in Study 1, which demonstrated that Mexican-Americans enrolled at baseline examination (2000 – 2002) met a higher number of MetS components over time (2010 – 2012), including triglycerides and fasting glucose levels, waist size circumference, and lower HDL cholesterol over time.

Although several studies, including ours, document greater risk for developing MetS among Mexican-Americans, as well as greater risk for diabetes mellitus and atherosclerotic cardiovascular disease, additional evidence that link MetS and subclinical ATS is still needed. Such evidence would indicate whether MetS is a leading contributor to risk for subclinical ATS, and help to estimate the predictive validity of MetS. It is also

important to determine the relative contribution of psychological variables such as negative affect and chronic stress, which a few previous studies have reported significant associations between these factors and both MetS and subclinical ATS. Therefore, we conducted structural equation modeling to estimate the direct effects of two latent factors, that is, negative affect and chronic stress, on subclinical ATS, and the indirect effects of physical activity, inflammation and number of MetS components.

The specific aims of this second study were to test a model of pathways in the Mexican-Americans sample enrolled in MESA. Specifically, we tested whether negative affect and psychological stress at Exam 1 predicted subclinical ATS measured by coronary calcium calcification (CAC), intima-media thickness (IMT), artery plaque (plaque), and common carotid artery-internal carotid artery (CCA-ICA) at Exam 5. In addition, we tested whether these associations were mediated by unhealthy behaviors and inflammation at Exam 2, and number of MetS components at Exam 3.

Although previous studies reported a direct effect of psychological variables on subclinical ATS (Black and Garbutt, 2002; Ohira, et al., 2012), our results did not confirm this finding. Neither baseline negative affect nor chronic stress were directly associated with markers of subclinical atherosclerosis measured 10 years later. However, our results revealed that these latent factors were indirectly related to ATS through their association with physical activity, which in turn was related to less inflammation and greater number of MetS components. Thus, Mexican-American participants reporting greater chronic stress also reported higher levels of physical activity, which is consistent with previous studies demonstrating the potential role of physical activity as a mediator of relations between psychological stress and physical health outcomes. Furthermore,

negative affect was negatively associated with physical activity, and physical activity predicted better outcomes.

Physical activity was related to less systemic inflammation, consistent with previous evidence of way that physical activity can protect against cardiovascular disease risk. For example, Pedersen (2011) proposed that physical activity reduces systemic inflammation by promoting an anti-inflammatory environment that increases inflammatory agonist receptors. Hammer and Steptoe (2007) demonstrated experimentally this anti-inflammatory effect, in addition to smaller IL-6 and TNF-α response to psychological stress; and evidence obtained form the Whitehall Study II suggests that the practice of regular physical activity was related to lower levels of CRP and IL-6 (Hamer et al., 2012).

In our study, systemic inflammation was directly associated with both MetS and subclinical ATS, result that supports the idea that systemic inflammation is a similar underlying mechanism that contributes to MetS and subclinical ATS pathogenesis. Moreover, this result is congruent with studies that identified systemic inflammation as an independent risk factor for MetS, subclinical ATS and coronary heart disease (Ross, 1999; Lowe et al., 2004; Luc et al., 2003; Langenberg et al., 2006; Lu et al, 2013; Gu et al., 2013). Furthermore, we found evidence for a link between MetS and subclinical ATS, with number of MetS components serving as a precursor of subclinical ATS. This is consistent with the results from Stevenson et al. (2011) which showed that MetS as a latent factor indexed by its components predicted coronary artery calcification. Our finding also adds to this evidence by demonstrating that severity of MetS as indexed by the number of MetS components met by participants predicted subclinical ATS as a latent

factor indexed by four markers of ATS, including coronary artery calcification (CAC), artery plaque, carotid intima-media thickness (CIMT), and common carotid artery-internal carotid artery (CCA-ICA). Further, this finding has predictive validity by suggesting that the more severe MetS is, the greater the probability of developing subclinical ATS. Thus the early detection, prevention, screening of MetS may help to identify people who are high risk for ATS, and tailored interventions aimed to reduce the severity of MetS may contribute to the slower the progression of subclinical ATS.

As in Study 1, differences in study variables emerged between males and females participants. Females scored higher on chronic burden, depressive symptoms, and trait anxiety than males. Furthermore, their levels of inflammatory markers, and MetS score were higher than males. On the other hand, males scored higher on life discrimination, social support, and moderate and vigorous physical activity. Further, comparison on subclinical atherosclerosis markers revealed that males have greater coronary artery calcification, left distal coronary intima-media thickness, and greater left common coronary artery - internal coronary artery, than females. This finding is harder to interpret. Since females have higher levels of inflammation, and higher MetS score than males, it may have been expected that they also would score higher on subclinical ATS, but the opposite was found, suggesting that other independently confounding factors such as smoking might be contributing to this differences. Post-hoc comparisons on smoking, indexed by pack years cigarette consumed, revealed that males in this sample smoked more than females by large the amount of cigarette (M males = 11.3; M females = 3.3), making this a likely explanation. In further analyses and future studies, cigarette smoking

should be included , since smoking has been identified as an independent risk factor for subclinical ATS.

This study also had several strengths. First, the use of SEM to test our hypotheses permitted us to test direct, indirect, and total effects in our model. Second, the large sample of Mexican-American participants allowed us to test our model in the largest U.S. Latino group. Third, the availability of several markers of subclinical ATS allowed us to conceptualize it as a latent factor. Finally, and perhaps the main strength of this study is that it takes advantage of the longitudinal design of MESA, allowing us to test the longitudinal association between the variables of interest.

Study 2 also had limitations. The reduced and unbalanced sample of the other U.S. Latino group studies in MESA did not allowed us to run a multi-group SEM looking for possible differences in the patterns of association revealed in this study. The use of MetS as a continuous variable allowed us to have an indicator of MetS severity, which allowed us to show that the more MetS components met by participants, the greater the risk for developing a cardiovascular disease. However this strategy did not allow us to identify which of these factors is the leading contributor to risk, or the specific association between the individual components of MetS and ATS. Therefore, future studies may be able to address this, perhaps by conceptualizing MetS as a latent factor. Although we included a dummy variable for gender, which allowed tests of gender differences in study variables, we were not able to determine if the patterns of association between factors and variables were moderated by gender using SEM. Therefore, it will be beneficial for future studies to further examine gender moderation.

Overall, although we did not find evidence for psychological variables measured at baseline predicting subclinical ATS after 10 years of follow-up, our study contributes by providing evidence about the role that physical activity has on physical health, as well as regarding the predictive validity of MetS. That is, we expanded on previous studies by demonstrating a longitudinal association between severity of MetS and subclinical atherosclerosis, as indexed by four markers of ATS.

Table 33: Direct and indirect effect for longitudinal association between negative affect, chronic stress and subclinical ATS

Direct effect	*β*	*Indirect effect*	*β*
Negative affect–>Physical activity	-0.36**	Negative affect–>Physical activity–>MetS	0.041†
Negative affect–>Inflammation	-0.03	Negative affect–>Physical activity–>MetS–>ATS	0.008
Negative affect–>MetS	-0.12	Negative affect–>Physical activity–>Inflammation–>MetS	0.018*
Negative affect–>ATS	0.009	Negative affect–>Physical activity–>Inflammation–>ATS	0.008
Chronic stress–>Physical activity	0.44***	Negative affect–>Physical activity–>Inflammation–>MetS–>ATS	0.003†
Chronic stress–>Inflammation	-0.03	Chronic stress–>Physical activity–>MetS	-0.049†
Chronic stress–>MetS	0.18	Chronic stress–>Physical activity–>MetS–>ATS	-0.009
Chronic stress–>ATS	-0.17	Chronic stress–>Physical activity–>Inflammation–>MetS	-0.021*
Physical activity–>Inflammation	-0.16**	Chronic stress–>Physical activity–>Inflammation–>ATS	-0.011
Physical activity–>MetS	-0.11*	Chronic stress–>Physical activity–>Inflammation–>MetS–>ATS	0.004†
Physical activity–>ATS	-0.03		
Inflammation–>MetS severity	0.31**		
Inflammation –>ATS	0.15*		
MetS Severity–>ATS	0.18*		

†$p \leq 0.1$; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$

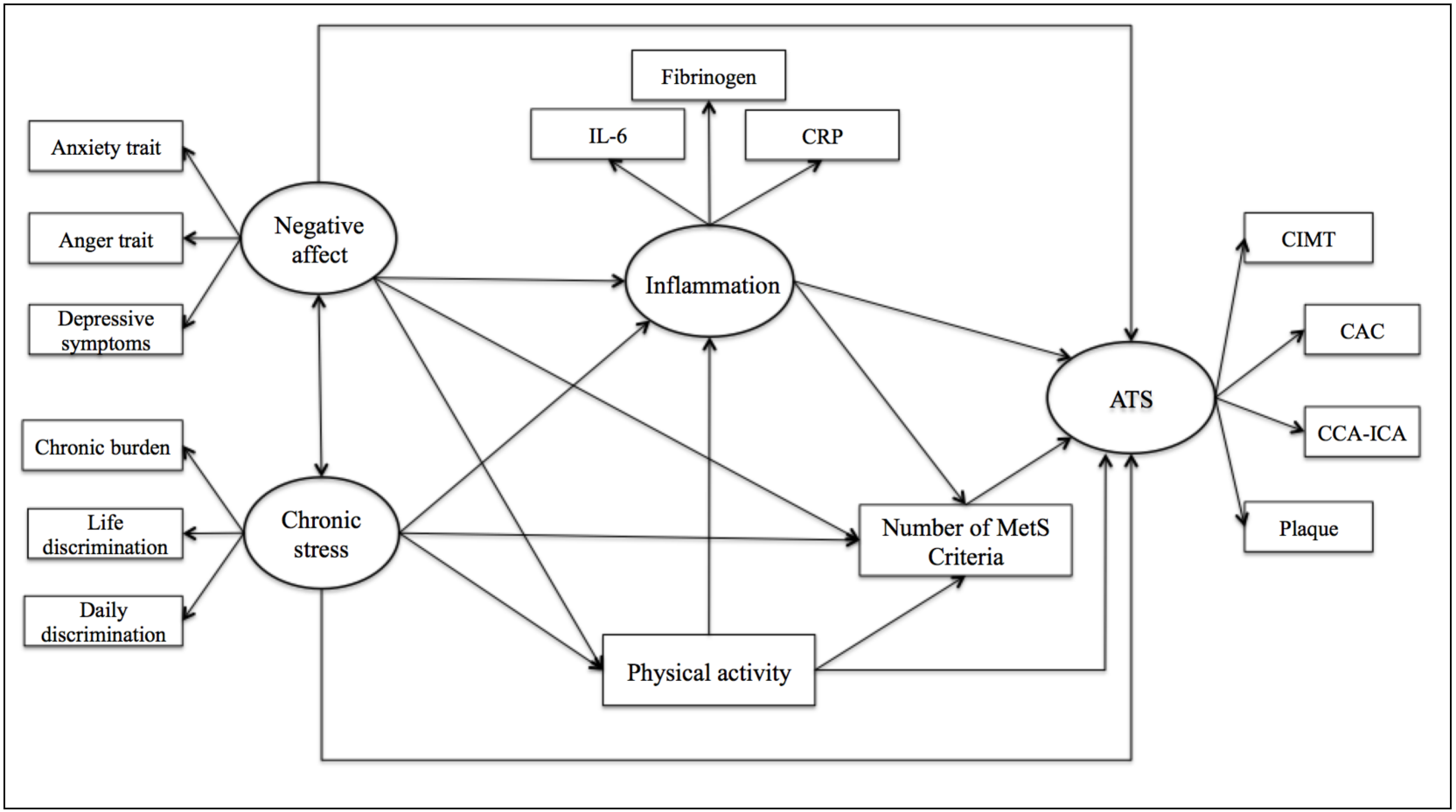

Figure 16: Theoretical model for the longitudinal association between negative affect, chronic stress and subclinical ATS

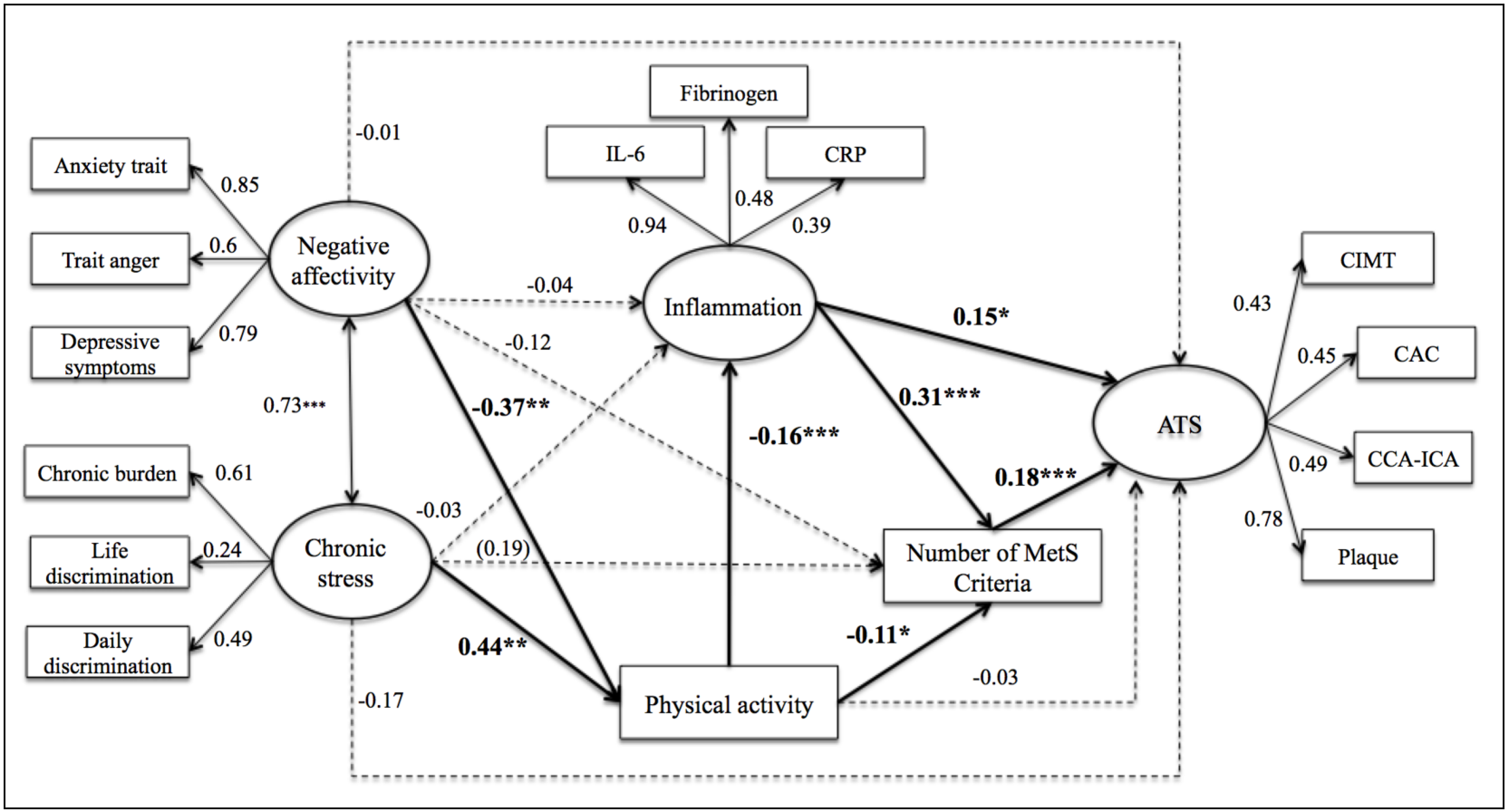

Figure 17: Fitted solution for the longitudinal association between psychological factors and subclinical ATS in Mexican-American participants. $\chi^2_{(78)}$= 120.99; $p \leq 0.001$; CFI = 0.98; TLI= 0.97; RMSEA = 0.026. Factor loadings and structural paths coefficients are presented as standardized coefficients solution. All factor loadings were statistically significant ($p \leq 0.01$). Solid lines represent significant paths. Dash lines presents non-significant paths.

Conclusion

This dissertation involved two studies with the MESA dataset. The purpose of the first study was to test longitudinal associations between psychological variables (negative affect, and psychological stress) and the number of MetS components met by the U.S. Latino participants enrolled in MESA. Additionally, the goal was to determine whether these associations were mediated by unhealthy behaviors and physiological variables, as well as moderated by psychological resources (optimism and social support). The second study aimed to test the longitudinal associations between psychological factors, and the progression of atherosclerosis indexed by coronary calcium calcification (CAC), intima-media thickness (IMT), artery plaque (plaque) and common carotid artery-internal carotid artery (CCA-ICA)—this, too mediated by unhealthy behaviors, physiological variables and MetS.

Together these results indicated that Mexican-Americans evidenced greater severity of MetS than any other Latino group. Specifically, they showed the highest levels of fasting glucose and triglycerides levels, the largest waist size circumference, and the lowest HDL cholesterol levels. Latinas evidenced more severe MetS and more risk factors for cardiovascular disease than Latino males, a difference that persisted over 10 years of follow-up. Furthermore, psychological stress and negative affect were associated with MetS severity in males only, and men showed an indirect effect of physical activity on MetS severity via inflammation. Inflammatory markers, in turn, predicted MetS severity and subclinical ATS over time. Physical activity was related to inflammation and MetS severity. Finally, psychological stress and negative affect did not predict subclinical ATS, although, they were indirectly related to MetS severity via physical activity and

MetS.

Although the current set of findings adds to our understanding of within group differences in health among Latinos, as well as the contribution of psychological factors to MetS and subclinical ATS and related mechanisms, continued investigation on Latino health outcomes and its determinants is necessary. Thus, this study sets the stage for further research with a more heterogeneous sample in terms of age, income and education, as well as the inclusion of other stressors (e.g. financial stress, stress at work) and ways of coping.

Overall we identified gender and Latino group differences in cardiovascular risk profiles, and therefore we better characterized the epidemiologic health profile of the Latino populations living in the U.S. Thus, we believe that these findings in addition to our methodological approach that looks for within group differences in the U.S. Latino group have useful implications for policy makers and researchers.

Appendices

Preliminary Research and Results

Previous studies with the U.S. Hispanic sample enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA) were conducted using data collected at baseline.

First Preliminary Study: Predictors of Metabolic Syndrome in U.S. Latino Groups in The Multi-Ethnic Study of Atherosclerosis (MESA)

The purpose of the first study was to investigate within-group differences in the prevalence of MetS in the subsample of Latinos enrolled in MESA, as well as the cross-sectional association between psychological factors and MetS and related mechanism. In order to test this objective, analyses at baseline were conducted with the U.S. Hispanic sample (n= 1,388) that included Mexican Americans, Dominican Americans, Puerto Rican Americans and Central/South Americans. MANCOVAS and hierarchical logistic regression were conducted to test the effects of psychosocial variables (chronic stress, depressive symptoms, and social support) and their interaction terms, as well as inflammatory markers (IL-6, CRP, Fibrinogen), and lifestyle behaviors (exercise, smoking and drinking status) after controlling for demographics (i.e. nationality, age, gender, socioeconomic position, and language spoken at home). Results indicated that Mexican American men (43%) and women (57%) evidenced the greatest prevalence of MetS. The best predictors of risk for obtaining a MetS diagnosis were being Mexican American, older age, female gender, high chronic stress, and high levels of inflammatory markers, lower socioeconomic position, and alcohol consumption. Tests of interaction terms were not statistically significant. These results identified group differences in risk for MetS among the U.S. Hispanic groups. However, within this all Latino sample,

several socio-demographic, psychosocial, and inflammatory variables were associated with greater risk of being diagnosed with Mets. Since depressive symptoms, and social support was not found to be associated with risk for MetS, additional research is needed to explore their relative contribution for risk for and/or protection from MetS.

Second Preliminary Study: Factorial Structure of Metabolic Syndrome Among Latino Population Enrolled in The Multi-Ethnic Study of Atherosclerosis (MESA)

The purpose of the second study was to test the factorial structure of MetS in the Latino sample enrolled in MESA, using data collected at baseline. To test a hierarchical four-factor structure with obesity, insulin resistance, lipids, and blood pressure as first order factors, and MetS as a second order factor, a confirmatory factor analysis (CFA) was conducted. Because Mardia's normality assumption was violated, robust fit indexes are reported. The findings obtained show that the proposed hierarchical structure for MetS was well supported (SB $\chi^2_{(14)}$= 96.1, $p < 0.001$); CFI = 0.974; SRMS = 0.031; RSMEA = 0.065 (0.053, 0.077) (see Figure 2), with all the paths being statistically significant. However, a subsequent structure tested with insulin resistance as an underlying common factor for obesity, lipids, and blood pressure provides a similar goodness of fit (SB $\chi^2_{(16)} = 98.57$, $p < 0.001$); CFI = 0.973; SRMS = 0.032; and a RMSEA = 0.06 (0.05, 0.073) (see Figure 3). Thus, this factorial structured was in accordance with the WHO definition for MetS; insulin resistance appears as the unique underlying factor for obesity, dyslipidemia and blood pressure, and offers a parsimonious solution for MetS among the Latino population living in the U.S.

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