EPIDEMIOLOGIC CHARACTERIZATION OF THE RELATIONSHIP OF OBESITY

WITH SUBCLINICAL MYOCARDIAL INJURY AND HEART FAILURE

by
Chiadi E. Ndumele, MD, MHS

A dissertation submitted to Johns Hopkins University in conformity with the requirements for the degree of Doctor of Philosophy

Baltimore, Maryland
November, 2017

Abstract

Obesity is a potent risk factor for heart failure (HF), a cardiovascular condition associated with high morbidity and mortality. However, the relationship between obesity and HF has not been fully characterized. Prior data suggest that obesity may be independently linked to HF. However, there are limited comparisons of the relationship of obesity to various forms of cardiovascular disease (CVD), including HF, coronary heart disease (CHD) and stroke, including the extent to which they are unexplained by traditional mediators of CVD, such as hypertension, dyslipidemia and diabetes. Furthermore, the pathways linking obesity to HF are incompletely understood, with a growing body of laboratory and clinical data suggesting direct toxic effects of obesity on heart muscle. Additionally, the prognostic impact of weight history on HF risk is presently unknown. Therefore, in the following epidemiologic analyses, we compared the associations of obesity with incident HF, CHD and stroke before and after adjusting for traditional CVD mediators (Aim 1); evaluated the cross-sectional association between obesity and a novel biomarker of subclinical myocardial injury, a high sensitivity assay for troponin T (hs-cTnT), and to assess the combined prospective associations of obesity and elevated hs-cTnT with incident HF (Aim 2); assessed the prognostic impact of several weight history metrics on the risk of incident HF (Aim 3); and evaluated the relationship between weight history and myocardial injury, as assessed by hs-cTnT (Aim 4). We demonstrated that: obesity has the strongest association with incident HF among CVD subtypes, and that among CVD subtypes, the association of obesity with HF is uniquely unexplained by traditional risk factors; obesity is independently associated with elevated hs-cTnT and the combination of severe obesity and elevated hs-cTnT is associated with a greater than 9-fold higher risk of incident HF compared to those with normal weight and undetectable hs-cTnT; and that past excess weight and increasing weight over time are

significantly associated with incident HF and elevated hs-cTnT, with perhaps the most useful prognostic information provided by cumulative weight. This work has advanced knowledge regarding the epidemiologic association between obesity and HF and potential pathways underlying this relationship.

Advisor: Josef Coresh, MD, PhD

Readers: Gary Gerstenblith, MD; Elizabeth Selvin, MPH, PhD; John McGready, PhD

Preface

I am grateful to several persons who have influenced and supported my career and the completion of this work. I have had the privilege of working with an outstanding primary mentor for this thesis, Dr. Josef Coresh, a brilliant epidemiologist who has generously provided invaluable teaching, guidance and support at the inception of my investigative career. I am grateful for several other key research mentors and collaborators, who have been gracious in sharing their time and considerable expertise on this work, including Drs. Gary Gerstenblith, Elizabeth Selvin, Roger Blumenthal and Kuni Matsushita. This work would also not be possible without the dedicated staff and participants of the Atherosclerosis Risk in Communities (ARIC) Study. I have had many exceptional didactic experiences during my time at the Bloomberg School of Public Health, and am grateful to the many outstanding course instructors from whom I learned the principles of epidemiology, as well as to the outstanding staff in the Department of Epidemiology. I am also appreciative of the many wonderful teachers I have had throughout my life, who not only taught me academic lessons, but helped me to develop confidence that enabled me to develop and pursue my career goals. None of my work would be possible without the support and love of my friends and family. My amazing brothers are dearest friends and confidants. My loving, wonderful parents devoted so much of their efforts to ensuring that my brothers and I had the best academic opportunities and a clear sense of our potential and purpose. My extended family and friends are a fountain of love and wisdom. My wife Nicole is my best friend and ultimate support, who makes me a better person in so many ways. My beautiful

daughter Faith is my inspiration. And my God is the source of my strength and any talents I have

been blessed with to utilize for this work. I am truly grateful for this learning opportunity.

Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction

Heart Failure – Epidemiology and Clinical Relevance

Heart failure (HF) is a major clinical and public health challenge, affecting approximately 6 million individuals in the United States presently. Principally caused by either impaired contractive function or abnormal relaxation of the myocardium (heart muscle), HF is defined as the inability of the heart to meet the metabolic demands of the body or to only be able to do so at harmfully high filling pressures. Clinically, HF is linked to considerable morbidity and mortality: it is associated with shortness of breath, fatigue and impaired functional capacity; it causes frequent rehospitalizations for HF decompensations; it carries a 50% mortality rate; and it is the leading cause of inpatient Medicare spending in the United States. In contrast with declining rates of premature death due to coronary heart disease (CHD) in recent decades[1, 2], the prevalence of HF, with its associated high morbidity and mortality, is rising rapidly[3-6]. Therefore, there is increasing focus on identifying individuals and populations that are at risk for developing HF, with the long term goal of refining strategies to prevent progression to the clinical syndrome.

The Obesity-Heart Failure Association

Several prospective epidemiologic studies have demonstrated a strong association between obesity and the development of HF[7-10]. While a relationship between obesity has been described for several decades, this association has taken on increased public health importance in

light of the obesity epidemic in the United States and other industrialized nations. The most recent data from the National Health and Nutrition Examination Study demonstrates that obesity is present in 38% of adults and overweight in an additional 32% of adults. Given the potent association between obesity and HF and the high prevalence of obesity, the epidemiologic contribution of excess weight to HF rates is substantial: data from the Framingham study suggests that about 20% of HF cases among men and 28% among women are attributable to overweight and obesity.

The pathways linking obesity and HF are not yet fully defined. Among individuals with obesity, elevated metabolic demand due to excess adipose tissue leads to increased cardiac output and abnormal ventricular remodeling[11]. Conditions closely linked to obesity, such as hypertension[12], diabetes[13], and obstructive sleep apnea[14, 15], are also associated with the development of structural and functional myocardial abnormalities that predispose to heart failure. Additionally, metabolic abnormalities commonly seen in obesity increase the risk of CHD[16], which can lead to ischemic myocardial dysfunction. However, previous epidemiologic analyses demonstrate a strong association between obesity and incident HF independent of CHD and established risk factors[9, 17], indicating that the relationship between obesity and HF is only partially explained by traditional mechanisms.

The relationship of obesity with HF may contrast from the relationship of obesity with other major forms of cardiovascular disease (CVD), such as CHD and stroke. There are divergent mechanisms by which obesity is related to different forms of CVD. The underlying pathophysiology for CHD and stroke is principally related to atherosclerosis and associated thrombosis. In contrast, mechanisms beyond atherosclerotic vascular disease, such as changes in myocardial function and structure due not related to insufficient myocardial blood flow, often

underlie the development of HF. While there has been conflicting data from prospective studies, recent meta-analyses suggest that the relationship of obesity with CHD and stroke may be largely explained by the excess burden of comorbid conditions that are closely linked to atherosclerosis, such as hypertension, dyslipidemia and diabetes. However, there is very limited data comparing the associations of obesity with HF, CHD and stroke, both with regards to their magnitude and the extent to which they remain unexplained after accounting for obesity-associated comorbidities.

Effects of Obesity on the Myocardium

Increasing evidence suggests directs effect of obesity on the myocardium that predisposes to HF. Obesity is independently associated with impaired myocardial contractile function and relaxation[18, 19]. Rodents genetically predisposed to obesity demonstrate increased rates of myocyte DNA damage, myocardial oxidative injury, myocyte apotosis and myocardial fibrosis[20-22]. Laboratory studies suggest that myocardial injury contributes to the myocardial dysfunction associated with excess adiposity[20, 22], and may play a role in the progression from compensatory remodeling to clinical HF[23]. However, clinical data demonstrating a relationship between obesity and myocardial injury are limited. Understanding the relationship of obesity with myocardial injury, and the implications of this association for the development of HF, will significantly advance our understanding of the mechanisms connecting obesity and incident HF.

One reason for the scarcity of clinical evidence for an association between obesity and myocardial injury is the lack of a specific biomarker of low grade myocardial injury. However, this has changed with the emergence of a high sensitivity assay for cardiac troponin T (hs-cTnT).

3

The troponin T enzyme is highly specific to myocardial tissue[24], and elevated circulating levels of troponin T are central to the diagnosis of myocardial infarction in clinical practice[25]. Recently, very high-sensitivity assays for troponin T have been developed that can detect troponin T at 10-fold lower concentrations than current clinical assays (Figure 2)[26, 27]. Several recent studies have demonstrated that minute elevations in hs-cTnT levels, among asymptomatic individuals without known cardiovascular disease, are potent predictors of future HF and mortality, and to a lesser extent CHD[27-32]. Importantly, these small elevations in hs-cTnT levels do not appear to be primarily mediated by macrovascular coronary artery disease[28], but rather appear to correlate with functional and structural myocardial abnormalities that are known to precede the development of HF[28, 30, 33, 34].

Importance of Weight History

An important limitation of most clinical and epidemiologic studies examining the link between obesity and HF is that these studies largely utilize adiposity measures from a single point in time. Adiposity is known to change over time, with increases in fat mass commonly associated with aging. Therefore analyses using weight measures from a single time point likely do not fully reflect the chronic effects of obesity on HF risk. Some population based studies have suggested that weight history may significantly influence the likelihood of myocardial dysfunction and HF. However, most of these studies have relied on retrospective data, which is subject to recall bias and potential misclassification of past obesity status. There are limited prospective analysis using serial assessments of weight status to evaluate the relationship between weight history and HF risk. It is also unclear which aspects of weight history provide

the most prognostic information regarding HF risk. Additionally, the association of weight history with subclinical myocardial injury, as reflected by levels of hs-cTnT, has not yet been explored.

The Obesity Paradox and the Implications of Weight Loss

Despite the increased risk of incident HF associated with obesity, several prior studies have noted an "obesity paradox" among those with existing HF, with obese HF patients having greater survival than HF patients with normal weight[55-57]. In a meta-analysis of 28,000 patients with HF, individuals with obesity had a lower risk of cardiovascular mortality (HR 0.60; 95% CI: 0.53-0.69) and all-cause mortality (HR 0.67; 95% CI: 0.62-0.73) than individuals with normal weight[58]. It is unclear whether this finding reflects a selection bias, given the cachexia associated with HF[59, 60], or if excess adipose tissue is actually protective in the setting of HF[61]. While weight loss is associated improvements in several risk factors for CVD, including the burden of diabetes, hypertension and dyslipidemia, trials of medical weight loss have not demonstrated significant reductions in cardiovascular endpoints. The effects of weight loss on reducing HF risk are therefore unclear. One reason for the lack of positive results from trials of medical weight loss is likely the relatively modest amount of weight reduction achieved. Bariatric surgery, which is associated with large degrees of intentional weight loss, provides an opportunity for elucidating the effect of marked weight reduction on the myocardium. Indeed, several studies have suggested improvements in measures of myocardial structure and function after bariatric surgery. However, the effects of bariatric surgery on myocardial injury; the correlation between longitudinal changes in myocardial injury and changes in myocardial structure and function; and the factors differentiating obese individuals with and without

myocardial injury, and abnormalities in myocardial structure and function are presently unexplored.

I have therefore complemented the epidemiologic analyses in this thesis related to obesity and HF risk with initiating a prospective cohort of nearly 100 bariatric surgery patients assessing changes in myocardial injury, structure and function following bariatric surgery (the BARI-Heart study). This study utilizes the pre-surgical waiting period mandated by insurance studies by employing a pre/post study design. The participants in the study will serve as their own controls, with serial evaluations of myocardial injury, structure and function performed during the pre-surgical waiting period compared to serial myocardial evaluations performed post-operatively. We will additionally perform assays of obesity-associated adipokines, cytokines and measures of insulin resistance that are likely related to the association between excess weight and HF. We anticipate that this study will provide insights regarding mechanisms underlying the link between obesity and HF and the impact of weight loss.

Objectives

In the epidemiologic analyses described in the upcoming text, I aim to answer 4 primary questions: 1) How does the prospective association of obesity with HF compare to those with CHF and stroke, both before and after accounting for the comorbid conditions commonly associated with obesity? 2) What is the association between obesity and hs-cTnT, as a biomarker of myocardial injury, and do obesity and hs-cTnT provide complementary prognostic data regarding heart failure risk? 3) How does weight history impact the risk of HF, and which aspects of weight history provide the most useful prognostic data? 4) How does weight history

influence the likelihood of myocardial injury? To answer these questions, I will utilize data from the Atherosclerosis Risk in Communities (ARIC) study. ARIC is a prospectively, predominantly bi-racial, community based cohort that has been extensively characterized for CVD risk factors; has had continuous follow-up for CVD events for over 20 years; has serial anthropometric assessments from across the adult lifespan; and has assays of hs-cTnT already performed within the cohort. The ARIC cohort is therefore particularly well suited to provide additional insights into the epidemiologic association between obesity and HF.

/

Reference List

(1) Ford ES, Ajani UA, Croft JB et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med* 2007 June 7;356(23):2388-98.

(2) Unal B, Critchley JA, Capewell S. Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000. *Circulation* 2004 March 9;109(9):1101-7.

(3) McCullough PA, Philbin EF, Spertus JA, Kaatz S, Sandberg KR, Weaver WD. Confirmation of a heart failure epidemic: findings from the Resource Utilization Among Congestive Heart Failure (REACH) study. *J Am Coll Cardiol* 2002 January 2;39(1):60-9.

(4) Owan TE, Redfield MM. Epidemiology of diastolic heart failure. *Prog Cardiovasc Dis* 2005 March;47(5):320-32.

(5) Redfield MM, Jacobsen SJ, Burnett JC, Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003 January 8;289(2):194-202.

(6) Roger VL, Weston SA, Redfield MM et al. Trends in heart failure incidence and survival in a community-based population. *JAMA* 2004 July 21;292(3):344-50.

(7) Chen YT, Vaccarino V, Williams CS, Butler J, Berkman LF, Krumholz HM. Risk factors for heart failure in the elderly: a prospective community-based study. *Am J Med* 1999 June;106(6):605-12.

(8) He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. *Arch Intern Med* 2001 April 9;161(7):996-1002.

(9) Kenchaiah S, Evans JC, Levy D et al. Obesity and the risk of heart failure. *N Engl J Med* 2002 August 1;347(5):305-13.

(10) Wilhelmsen L, Rosengren A, Eriksson H, Lappas G. Heart failure in the general population of men--morbidity, risk factors and prognosis. *J Intern Med* 2001 March;249(3):253-61.

(11) Alpert MA. Obesity cardiomyopathy: pathophysiology and evolution of the clinical syndrome. *Am J Med Sci* 2001 April;321(4):225-36.

(12) Lorell BH, Carabello BA. Left ventricular hypertrophy: pathogenesis, detection, and prognosis. *Circulation* 2000 July 25;102(4):470-9.

(13) Guha A, Harmancey R, Taegtmeyer H. Nonischemic heart failure in diabetes mellitus. *Curr Opin Cardiol* 2008 May;23(3):241-8.

(14) Arias MA, Garcia-Rio F, Alonso-Fernandez A, Mediano O, Martinez I, Villamor J. Obstructive sleep apnea syndrome affects left ventricular diastolic function: effects of

nasal continuous positive airway pressure in men. *Circulation* 2005 July 19;112(3):375-83.

(15)   Gottlieb DJ, Yenokyan G, Newman AB et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation* 2010 July 27;122(4):352-60.

(16)   27th Bethesda Conference. Matching the Intensity of Risk Factor Management with the Hazard for Coronary Disease Events. September 14-15, 1995. *J Am Coll Cardiol* 1996 April;27(5):957-1047.

(17)   Ndumele CE, Coresh J, Lazo M et al. Obesity, Subclinical Myocardial Injury and Incident Heart Failure. *Submitted* 2013.

(18)   Peterson LR, Waggoner AD, Schechtman KB et al. Alterations in left ventricular structure and function in young healthy obese women: assessment by echocardiography and tissue Doppler imaging. *J Am Coll Cardiol* 2004 April 21;43(8):1399-404.

(19)   Wong CY, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick TH. Alterations of left ventricular myocardial characteristics associated with obesity. *Circulation* 2004 November 9;110(19):3081-7.

(20)   Barouch LA, Gao D, Chen L et al. Cardiac myocyte apoptosis is associated with increased DNA damage and decreased survival in murine models of obesity. *Circ Res* 2006 January 6;98(1):119-24.

(21) Vincent HK, Powers SK, Dirks AJ, Scarpace PJ. Mechanism for obesity-induced increase in myocardial lipid peroxidation. *Int J Obes Relat Metab Disord* 2001 March;25(3):378-88.

(22) Zhou YT, Grayburn P, Karim A et al. Lipotoxic heart disease in obese rats: implications for human obesity. *Proc Natl Acad Sci U S A* 2000 February 15;97(4):1784-9.

(23) Garg S, Narula J, Chandrashekhar Y. Apoptosis and heart failure: clinical relevance and therapeutic target. *J Mol Cell Cardiol* 2005 January;38(1):73-9.

(24) Ricchiuti V, Voss EM, Ney A, Odland M, Anderson PA, Apple FS. Cardiac troponin T isoforms expressed in renal diseased skeletal muscle will not cause false-positive results by the second generation cardiac troponin T assay by Boehringer Mannheim. *Clin Chem* 1998 September;44(9):1919-24.

(25) Thygesen K, Alpert JS, White HD et al. Universal definition of myocardial infarction. *Circulation* 2007 November 27;116(22):2634-53.

(26) Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clin Chem* 2010 February;56(2):254-61.

(27) Saunders JT, Nambi V, de Lemos JA et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation* 2011 April 5;123(13):1367-76.

(28) de Lemos JA, Drazner MH, Omland T et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA* 2010 December 8;304(22):2503-12.

(29) deFilippi CR, de Lemos JA, Christenson RH et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA* 2010 December 8;304(22):2494-502.

(30) Jungbauer CG, Riedlinger J, Buchner S et al. High-sensitive troponin T in chronic heart failure correlates with severity of symptoms, left ventricular dysfunction and prognosis independently from N-terminal pro-b-type natriuretic peptide. *Clin Chem Lab Med* 2011 November;49(11):1899-906.

(31) Neeland IJ, Drazner MH, Berry JD et al. Biomarkers of chronic cardiac injury and hemodynamic stress identify a malignant phenotype of left ventricular hypertrophy in the general population. *J Am Coll Cardiol* 2013 January 15;61(2):187-95.

(32) Omland T, Pfeffer MA, Solomon SD et al. Prognostic value of cardiac troponin I measured with a highly sensitive assay in patients with stable coronary artery disease. *J Am Coll Cardiol* 2013 March 26;61(12):1240-9.

(33) Martinez-Rumayor AA, de Lemos JA, Rohatgi AK et al. Addition of highly sensitive troponin T and N-terminal pro-B-type natriuretic peptide to electrocardiography for detection of left ventricular hypertrophy: results from the Dallas Heart Study. *Hypertension* 2013 January;61(1):105-11.

(34) Mishra RK, Li Y, DeFilippi C et al. Association of cardiac troponin T with left ventricular structure and function in CKD. *Am J Kidney Dis* 2013 May;61(5):701-9.

(35) Alpert MA, Lambert CR, Panayiotou H et al. Relation of duration of morbid obesity to left ventricular mass, systolic function, and diastolic filling, and effect of weight loss. *Am J Cardiol* 1995 December 1;76(16):1194-7.

(36) Alpert MA, Terry BE, Mulekar M et al. Cardiac morphology and left ventricular function in normotensive morbidly obese patients with and without congestive heart failure, and effect of weight loss. *Am J Cardiol* 1997 September 15;80(6):736-40.

(37) Szczepaniak LS, Dobbins RL, Metzger GJ et al. Myocardial triglycerides and systolic function in humans: in vivo evaluation by localized proton spectroscopy and cardiac imaging. *Magn Reson Med* 2003 March;49(3):417-23.

(38) van der Meer RW, Rijzewijk LJ, Diamant M et al. The ageing male heart: myocardial triglyceride content as independent predictor of diastolic function. *Eur Heart J* 2008 June;29(12):1516-22.

(39) Wende AR, Abel ED. Lipotoxicity in the heart. *Biochim Biophys Acta* 2010 March;1801(3):311-9.

(40) Frankel DS, Vasan RS, D'Agostino RB, Sr. et al. Resistin, adiponectin, and risk of heart failure the Framingham offspring study. *J Am Coll Cardiol* 2009 March 3;53(9):754-62.

(41) Martin SS, Qasim A, Reilly MP. Leptin resistance: a possible interface of inflammation and metabolism in obesity-related cardiovascular disease. *J Am Coll Cardiol* 2008 October 7;52(15):1201-10.

(42) McManus DD. Relations of circulating resistin and adiponectin and cardiac structure and function: the Framingham Offspring Study. 2012 September.

(43) Negi SI, Jeong EM, Shukrullah I, Raicu M, Dudley SC, Jr. Association of low plasma adiponectin with early diastolic dysfunction. *Congest Heart Fail* 2012 July;18(4):187-91.

(44) Paolisso G, Tagliamonte MR, Galderisi M et al. Plasma leptin level is associated with myocardial wall thickness in hypertensive insulin-resistant men. *Hypertension* 1999 November;34(5):1047-52.

(45) Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Obesity and risk of incident heart failure in older men with and without pre-existing coronary heart disease: does leptin have a role? *J Am Coll Cardiol* 2011 October 25;58(18):1870-7.

(46) Yang R, Barouch LA. Leptin signaling and obesity: cardiovascular consequences. *Circ Res* 2007 September 14;101(6):545-59.

(47) Liao Y, Takashima S, Maeda N et al. Exacerbation of heart failure in adiponectin-deficient mice due to impaired regulation of AMPK and glucose metabolism. *Cardiovasc Res* 2005 September 1;67(4):705-13.

(48) Bahrami H, Bluemke DA, Kronmal R et al. Novel metabolic risk factors for incident heart failure and their relationship with obesity: the MESA (Multi-Ethnic Study of Atherosclerosis) study. *J Am Coll Cardiol* 2008 May 6;51(18):1775-83.

(49) Bekwelem W, Lutsey PL, Loehr LR et al. White blood cell count, C-reactive protein, and incident heart failure in the Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol* 2011 October;21(10):739-48.

(50) Choi EY, Yan RT, Fernandes VR et al. High-sensitivity C-reactive protein as an independent predictor of progressive myocardial functional deterioration: the multiethnic study of atherosclerosis. *Am Heart J* 2012 August;164(2):251-8.

(51) Niu J, Kolattukudy PE. Role of MCP-1 in cardiovascular disease: molecular mechanisms and clinical implications. *Clin Sci (Lond)* 2009 August;117(3):95-109.

(52) Zhou L, Azfer A, Niu J et al. Monocyte chemoattractant protein-1 induces a novel transcription factor that causes cardiac myocyte apoptosis and ventricular dysfunction. *Circ Res* 2006 May 12;98(9):1177-85.

(53) Ingelsson E, Sundstrom J, Arnlov J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. *JAMA* 2005 July 20;294(3):334-41.

(54) Shimabukuro M, Higa N, Asahi T et al. Impaired glucose tolerance, but not impaired fasting glucose, underlies left ventricular diastolic dysfunction. *Diabetes Care* 2011 March;34(3):686-90.

(55) Davos CH, Doehner W, Rauchhaus M et al. Body mass and survival in patients with chronic heart failure without cachexia: the importance of obesity. *J Card Fail* 2003 February;9(1):29-35.

(56) Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol* 2001 September;38(3):789-95.

(57) Lavie CJ, Osman AF, Milani RV, Mehra MR. Body composition and prognosis in chronic systolic heart failure: the obesity paradox. *Am J Cardiol* 2003 April 1;91(7):891-4.

(58) Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J* 2008 July;156(1):13-22.

(59) Anker SD, Ponikowski PP, Clark AL et al. Cytokines and neurohormones relating to body composition alterations in the wasting syndrome of chronic heart failure. *Eur Heart J* 1999 May;20(9):683-93.

(60) Anker SD, Sharma R. The syndrome of cardiac cachexia. *Int J Cardiol* 2002 September;85(1):51-66.

(61) Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol* 2009 May 26;53(21):1925-32.

(62) Utz W, Engeli S, Haufe S et al. Moderate dietary weight loss reduces myocardial steatosis in obese and overweight women. *Int J Cardiol* 2012 April 9.

(63) Esposito K, Pontillo A, Di PC et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA* 2003 April 9;289(14):1799-804.

(64) Alpert MA, Lambert CR, Terry BE et al. Effect of weight loss on left ventricular mass in nonhypertensive morbidly obese patients. *Am J Cardiol* 1994 May 1;73(12):918-21.

(65) Karason K, Wallentin I, Larsson B, Sjostrom L. Effects of obesity and weight loss on left ventricular mass and relative wall thickness: survey and intervention study. *BMJ* 1997 October 11;315(7113):912-6.

(66) Owan T, Avelar E, Morley K et al. Favorable changes in cardiac geometry and function following gastric bypass surgery: 2-year follow-up in the Utah obesity study. *J Am Coll Cardiol* 2011 February 8;57(6):732-9.

(67) Masson S, Anand I, Favero C et al. Serial measurement of cardiac troponin T using a highly sensitive assay in patients with chronic heart failure: data from 2 large randomized clinical trials. *Circulation* 2012 January 17;125(2):280-8.

(68) Bottomley PA, Weiss RG. Non-invasive magnetic-resonance detection of creatine depletion in non-viable infarcted myocardium. *Lancet* 1998 March 7;351(9104):714-8.

(69) Gabr RE, Sathyanarayana S, Schar M, Weiss RG, Bottomley PA. On restoring motion-

induced signal loss in single-voxel magnetic resonance spectra. *Magn Reson Med* 2006

October;56(4):754-60.

(70) Weiss RG, Bottomley PA, Hardy CJ, Gerstenblith G. Regional myocardial metabolism of

high-energy phosphates during isometric exercise in patients with coronary artery

disease. *N Engl J Med* 1990 December 6;323(23):1593-600.

(71) Bottomley PA. Spatial localization in NMR spectroscopy in vivo. *Ann N Y Acad Sci*

1987;508:333-48.

Chapter 2 – Aim 1: Obesity and Subtypes of Incident Cardiovascular Disease

Abstract

Background: Obesity is a risk factor for various subtypes of cardiovascular disease (CVD), including coronary heart disease (CHD), heart failure (HF) and stroke. However, there are limited comparisons of the associations of obesity with each of these CVD subtypes, particularly regarding the extent to which they are unexplained by traditional CVD mediators.

Methods and Results: We followed 13,730 ARIC participants with BMI $\geq$18.5 kg/m^2 and no CVD at baseline (Visit 1, 1987-89). We compared the association of higher BMI with incident HF, CHD and stroke before and after adjusting for traditional CVD mediators (including systolic blood pressure, diabetes and lipid measures). Over a median 23 years of follow-up, there were 2,235 HF events, 1,653 CHD events, and 986 strokes. After adjustment for demographics, smoking, physical activity and alcohol intake, higher BMI had the strongest association with incident HF among CVD subtypes, with HRs for severe obesity (BMI $\geq$35 kg/m^2; vs. normal weight) of 3.74 (95% CI: 3.24-4.31) for HF, 2.00 (95% CI: 1.67-2.40) for CHD, and 1.75 (95% CI: 1.40-2.20) for stroke (p values <0.0001 for comparisons of HF versus CHD or stroke). Further adjustment for traditional mediators fully explained the association of higher BMI with CHD and stroke but not with HF (HR 2.27 [95% CI: 1.94-2.64]).

Conclusions: The link between obesity and HF was stronger than those for other CVD subtypes and uniquely unexplained by traditional risk factors. Weight management is likely critical for optimal HF prevention and non-traditional pathways linking obesity to HF need to be elucidated.

Obesity is a common risk factor for several subtypes of cardiovascular disease (CVD), including coronary heart disease (CHD), stroke, and heart failure (HF).[1-4] However, increasing evidence suggests that obesity leads to various subtypes of CVD through multiple distinct pathways. Some traditional risk factors, including hypertension, diabetes and dyslipidemia, are established as mediators between obesity and atherosclerotic vascular disease. While weight management is a fundamental component of CVD prevention, the majority of individuals with obesity in the general population do not achieve sufficient and sustained weight loss[5-8]. There is therefore great emphasis on controlling the traditional CVD risk factors resulting from obesity as a strategy for reducing cardiovascular risk. However, uniform approaches to the control of cardiovascular risk factors may not have the same impact on the likelihood of developing different subtypes of CVD.

In this context, there are conflicting data regarding whether the relationships of obesity with CHD and stroke are independent of established CVD mediators. Several prospective studies[9-16] and current scientific statements[1] describe obesity as an independent risk factor for CHD and stroke, whereas other studies suggest that the associations are entirely caused by established mediators.[17-24] Nonetheless, a recent meta-analysis indicated that most of the associations of obesity with CHD and stroke may be mediated by hypertension, dyslipidemia and diabetes.[25] Of note, this meta-analysis did not include HF as an outcome and indeed data on an independent association of obesity with incident HF are relatively sparse.[26-29] Most importantly, there are very few prospective analyses comparing the association of obesity with each of these CVD subtypes within the same population after controlling for traditional CVD mediators.

It is possible that mechanisms other than hypertension, dyslipidemia and diabetes, such as excess metabolic demand and direct adverse effects of adiposity on the myocardium, play an

especially important role in the development of HF among individuals with excess weight.[30, 31] If this is the case, traditional CVD risk factor control alone may not lead to optimal prevention of HF. Therefore, in this prospective analysis of white and black middle aged men and women without baseline CVD in the Atherosclerosis Risk in Communities (ARIC) Study, we compared the associations of obesity with incident HF, CHD and stroke, before and after accounting for traditional CVD mediators.

Methods

The ARIC Study is a prospective, predominantly biracial, community-based cohort of 15,792 individuals extensively characterized for cardiovascular risk factors and followed longitudinally for CVD events.[32] Participants were recruited from four U.S. population centers (Washington County, Maryland; Jackson, Mississippi; Forsyth County, North Carolina; and the suburbs of Minneapolis, Minnesota) and examined at a baseline visit in 1987-1989. Participants were subsequently examined at three study visits spaced approximately 3 years apart, and at a 5th visit recently conducted from 2011-2013.

Given the focus on incident CVD events, we excluded those individuals with a prior history of HF, CHD, stroke or peripheral vascular disease at the first ARIC Study visit in 1987-89 (n=1,847). We additionally excluded those individuals with missing data on body-mass index (BMI) (n=25); those participants with a BMI < 18.5 kg/m^2 (n=142); and the small number of participants who were not of black or white race (n=48), leaving a study population of 13,730 individuals. Informed consent was obtained from all study participants, and the IRB affiliated with each ARIC field center and the Coordinating Center approved the study protocol.

Information regarding covariates of interest was collected at Visit 1. The primary

exposure was BMI, calculated from measured weight and height (weight in kilograms divided by meters squared). Smoking status was categorized as current, former or never smoker. Self-reported alcohol use was calculated in grams per week. Occupation was categorized into subtypes of employment. Exercise physical activity was self-reported and assessed via a modified Baecke questionnaire, and each activity was subsequently converted into metabolic equivalents of task (METS) based on the Compendium of Physical Activities. Diabetes mellitus (DM) was defined as the presence of a fasting blood sugar $\geq$ 126 mg/dl, a non-fasting blood sugar $\geq$ 200 mg/dl, a self-reported prior physician diagnosis of diabetes or the use of hypoglycemic medications. Systolic blood pressure was measured three times during the same examination, and the average of the last two measurements was utilized for analysis. Enzymatic assays were used to measure levels of total cholesterol (TC), HDL-cholesterol (HDL-C) and triglycerides, and LDL-cholesterol (LDL-C) was calculated for those with triglycerides $\leq$ 400 mg/dl using the Friedewald's equation[33].

The outcomes of interest were incident HF, CHD and stroke, with follow-up through December 31, 2012. After their baseline visit, ARIC participants were followed continuously for CVD events, receiving annual phone calls to obtain information regarding hospitalizations. For all deaths, vital records were examined, and in the majority of potential CHD cases occurring out of hospital an interview with the decedent's next of kin and a questionnaire completed by the patient's physician were also reviewed. Incident HF was defined as the first hospitalization or death related to HF. HF events were identified via discharge codes from hospitalizations and death certificates (ICD-9 code 428 for hospitalizations and deaths in early years of follow-up, and ICD -10 code I-50 for deaths in later years of follow-up). HF events from 2005 onwards were also adjudicated by an expert panel[34]. Incident CHD was defined as an adjudicated event of

definite or probable non-fatal myocardial infarction or definite fatal CHD. Potential incident strokes were identified via the presence of related discharge codes (ICD-9 codes code 430–437), the mention of a cerebrovascular condition or procedure in a discharge summary, or the presence of stroke findings on a CT or MRI report. If there was disagreement between automated and physician diagnoses, events were then adjudicated from abstracted medical records by a third reviewer. Definite or probable strokes of ischemic or hemorrhagic etiology were included in this analysis.

Statistical Analysis:

We performed univariate comparisons of baseline characteristics across BMI categories (normal weight (18.5 to < 25 kg/m^2), overweight (25.0 to < 30 kg/m^2), obese (30.0 to < 35 kg/m^2) and severely obese ($\geq$ 35.0 kg/m^2)), using ANOVA for continuous variables and the chi-squared test for categorical variables. Using Poisson models, we calculated the adjusted incidence rates for each CVD subtype associated with higher BMI at mean levels of age, sex, race, smoking status, alcohol use, education level, occupation and physical activity within the study population. In addition to the aforementioned categories, BMI was also modeled continuously, by constructing linear spline models with knots at the BMI values of 25, 30, 35, 40 and 45 kg/m^2. We additionally assessed the median onset of incident events for each subtype of CVD.

For each CVD subtype, we constructed Cox proportional hazards models to estimate the hazard ratios and 95% confidence intervals associated with higher BMI, with two levels of adjustment. Model 1 was adjusted for the confounding variables of age sex, race, smoking status, alcohol use, physical activity, education level and occupation. To estimate the associations

between obesity and each CVD subtype after accounting for established mediators, Model 2 was adjusted for the Model 1 variables plus baseline values of traditional mediators of CVD in the setting of obesity: DM, systolic blood pressure, anti-hypertensive medication use, LDL-C, HDL-C, triglycerides, and estimated glomerular filtration rate (eGFR).

In sensitivity analyses, regression models were constructed modeling smoking status, hypertension, diabetes and hypercholesterolemia as time-varying covariates to account for potential changes in these variables after the baseline visit but prior to the onset of CVD events. In creating time-varying covariates, measurements from ARIC Visits 1, 2 (1990-92), 3 (1993-95) and 4 (1996-99) were incorporated in regression analyses if the visit took place before an incident CVD event. Smoking status was categorized as current smoker versus current nonsmoker; hypertension was defined as an SBP $\geq$ 140 mmHg, diastolic BP $\geq$ 90 mmHg or use of anti-hypertensive medications; diabetes was defined as described above; and hypercholesterolemia was defined as an LDL-cholesterol $\geq$ 160 or the use of lipid lowering medications. For the latter three variables, after the onset of the mediator individuals were considered to have that mediator thereafter.

To formally compare the strength of associations for obesity with incident HF, CHD and stroke, we used seemingly unrelated regression. This statistical approach accounts for correlations of the error terms in the risk equations for different outcomes within the same population by estimating the risk equations jointly, thus providing a means for formally comparing the magnitude of the different risk associations[35].

We performed analyses stratified by race, gender and age ($\geq$ 60 or < 60 years) and created product terms to assess for differences in associations across demographic subgroups.

Sensitivity analyses were performed using only adjudicated events of definite or probable incident HF from 2005 onwards. Additional sensitivity analyses were performed adjusting for baseline lung function (forced expiratory volume in one second [FEV-1] and forced vital capacity [FVC]); including coronary revascularization procedures (percutaneous intervention or coronary artery bypass grafting) in the definition of incident CHD; and adding incident CHD to regression models as a time-varying covariate to evaluate the contribution of ischemic events to the association observed between obesity and incident HF. To account for the possibility of death from other causes that may have prevented participants from experiencing one of the outcomes of interest, we additionally performed competing risk regression analyses. We also performed analyses modeling obesity (BMI $\geq$30 kg/m^2) from Visit 1 through Visit 4 as a time-varying covariate, to account for the impact of the development of obesity after the baseline ARIC visit. Additional analyses were performed using waist circumference, divided into sex-specific quartiles, as a secondary metric of adiposity.

All p values presented are 2-sided. Statistical analyses were performed using STATA version 13.1 (StataCorp LP, College Station, Texas).

Results

Baseline characteristics of the study population are displayed in Table 1. Individuals with severe obesity were younger, were most likely to be female and African American, were least likely to be current smokers and had the lowest average levels of exercise physical activity. Higher BMI categories were associated with higher systolic blood pressure, triglycerides and eGFR, lower HDL-C, and a greater prevalence of anti-hypertensive medication use and DM.

25

Over approximately 23 years of follow-up, there were 2,235 HF events, 1,653 CHD events and 986 strokes. For each subtype of CVD, higher BMI was associated with a greater adjusted incidence of events at mean levels of demographic variables, smoking, alcohol use and physical activity (Figure 1). The incidence rate difference for severe obesity vs. normal weight (per 1000 person-years) was 12.1 for HF, 4.0 for CHD and 2.7 for stroke. The median time to incident events for each CVD subtype was 15.7 years for HF, 12.7 years for CHD and 13.7 years for stroke.

In regression models adjusted for confounding variables (Model 1), overweight and obesity were significantly associated with increased hazard ratios for each CVD subtype, however the strongest associations with higher BMI were seen for incident HF (Table 2). For example, severe obesity was associated with a nearly 4-fold higher risk of incident HF (HR 3.74; 95% CI: 3.24-4.31), and an approximately 2-fold higher risk of CHD (HR 2.00, 95% CI: 1.67-2.40) and stroke (HR 1.75; 95% CI: 1.40-2.20), compared to normal weight. In seemingly unrelated regression analyses, the risk coefficient between severe obesity and incident HF was significantly greater than those for incident CHD and stroke (p<0.0001 for both comparisons). In the confounder-adjusted model, with BMI modeled linearly, each 5-units higher BMI was associated with a 46% higher risk of incident HF, compared to 22% and 16% higher risks for incident CHD and stroke, respectively (p<0.0001 for comparisons of risk coefficients).

After further adjustment for traditional CVD mediators (Model 2), a statistically significant association remained between higher BMI and incident HF (HR for severe obesity 2.27; 95% CI: 1.94-2.64), but no significant associations were seen for incident CHD and stroke. Similarly, in the fully adjusted model, every 5-units higher BMI was associated with a 29% higher risk of incident HF, whereas no significant associations were seen for CHD and stroke.

Our findings were analogous when BMI was modeled continuously in linear spline models (Figure 2).

In regression analyses stratified by demographic subgroups using the fully adjusted model, significant associations between higher BMI category and incident HF were seen within each of the pre-specified demographic subgroups (Figure 3). Notably, a trend towards weaker associations between higher BMI and incident HF was seen among African Americans in comparison to Whites (p for interaction = 0.4), although significant associations were seen for both races. In contrast, no significant associations between higher BMI and either incident CHD or stroke were seen in in any of the demographic subgroups after adjustment for both confounders and traditional CVD mediators (data not shown).

Similar findings were also seen when smoking status, hypertension, diabetes and hypercholesterolemia from ARIC Visits 1 through 4 were modeled as time varying covariates (Table 3), with severe obesity having a mildly positive association with incident CHD (HR 1.20; 95% CI: 1.02-1.41) and no significant association with stroke (1.15; 95% CI: 0.90-1.47), compared to a stronger association with incident HF (HR 2.18; 95% CI: 1.87-2.54). Of note, in this time-varying analysis, HF was the only outcome for which significant associations remained for the obese category (BMI 30-34.9 kg/m^2).

Our findings were similar in sensitivity analyses using only adjudicated HF events (N=663), with severe obesity associated with a HR of 2.22 (95% CI: 1.74-2.85) for incident HF compared to normal weight in the fully adjusted model. Findings were also not appreciably different when lung function was included in regression models, when revascularization procedures were included in the definition of incident CHD or when incident CHD was modeled

as a time varying covariate on the outcome of incident HF. Similar findings were also seen in competing risk regression analyses to account for the possibility of non-CVD death precluding the development of the outcomes of interest. Analogous findings were seen when obesity (defined as BMI ≥ 30) was modeled as a time-varying covariate to account for the onset of obesity after the baseline ARIC visit, with significant associations only seen for incident HF after adjustment for traditional CVD mediators (Table 4). In analyses using waist circumference divided into quartiles as a secondary measure of adiposity, higher waist circumference quartiles were only significantly associated with incident HF (HR 1.96 [95% CI: 1.70-2.27] for Q4 vs. Q1) among CVD subtypes in the fully adjusted model (Table 5).

Discussion

In this prospective analysis of a bi-racial community-based cohort of 13,370 adult men and women without baseline CVD, we compared the relationship of higher BMI with incident HF, CHD and stroke. After controlling for confounding variables, we found that overweight and obesity were most strongly associated with incident HF among CVD subtypes. Severe obesity was linked to a nearly 4-fold higher risk of incident HF, compared with approximately 2-fold higher risks for incident CHD and stroke.

In regression analyses adjusting for both confounders and traditional CVD mediators, we found that traditional mediators explained all of the association of higher BMI with incident CHD and stroke. In contrast, the relationship of obesity with incident HF was largely unexplained by traditional mediators. These findings were qualitatively consistent across demographic subgroups. Similar findings were seen when major risk factors and obesity were

modeled as time varying covariates to account for their potential onset after the baseline visit. Our results were also largely unchanged when the analysis was restricted to adjudicated HF events and when CHD was included in regression models as a time varying covariate to account for antecedent MI as a precipitant of HF.

The 2006 AHA Scientific Statement on obesity and cardiovascular disease describes obesity as a risk factor for CHD and stroke independent of established mediators[1], but prior data on this subject have been inconsistent. Some prospective data suggest an association between obesity and CHD and stroke beyond what is explained by traditional CVD mediators[10-12, 14], while other longitudinal studies indicate that extensive adjustment for these mediators fully explains these associations.[17, 18, 21] A meta-analysis indicated that at least half of the association between obesity and CHD, and three quarters of the association between obesity and stroke, is likely explained by hypertension, dyslipidemia and hyperglycemia. The relatively limited prospective data regarding an independent link between obesity and incident HF however, suggest a persistent risk association after accounting for traditional CVD mediators.[26-29]

Most notably, there are very limited analyses comparing the relationship of obesity with HF, CHD and stroke within the same population. A recent analysis of a Norwegian cohort found that "metabolically healthy" obese individuals were at increased risk for HF but not for acute myocardial infarction[28]. Our study, using contemporary follow-up data in a bi-racial community-based cohort, extends prior research by demonstrating a much stronger relationship of obesity with incident HF than with CHD and stroke within the same population, and further, that among major CVD subtypes, the obesity-HF relationship is the only one unexplained by traditional risk factors.

The mechanisms underlying the association between obesity and HF remain incompletely understood. Increased fat mass is associated with expanded blood volume and increased myocardial workload.[31, 36] Obesity is also associated with adverse cardiac remodeling and abnormalities of myocardial structure and function, changes that are known to precede the development of clinical HF.[30, 31, 37] Several adipokines, which are associated in particular with abdominal obesity, are linked to structural and functional myocardial abnormalities and increased HF risk[29, 38-41]. There are increasing laboratory and clinical data suggesting a direct link between obesity and myocardial injury that may predispose to fibrosis, myocardial dysfunction and future HF.[42-44] Several processes are hypothesized to contribute to myocardial injury and dysfunction among individuals with obesity, including increased metabolic demand, the paracrine effects of adipose tissue and increased myocardial triglyceride accumulation leading to myocardial damage and potential apoptosis.[44-46] However, the pathophysiologic links between obesity and HF have not yet been fully elucidated.

Overweight and obesity were associated with higher risks for all forms of CVD, a finding of considerable public health importance given that the majority of the U.S. adult population falls into one of these weight categories. However, this analysis has particularly significant implications for HF prevention. The clinical importance of refining strategies for HF prevention in obesity is reinforced by the finding that the obesity-HF relationship was strongest among the incident CVD subtypes. While weight reduction remains advisable as a first line strategy for CHD and stroke prevention in the setting of obesity, this analysis indicates that controlling the traditional risk factors associated with obesity may address much of the excess risk for these outcomes in this population. In contrast, our findings suggest that controlling traditional risk

factors alone will not be sufficient for addressing the excess risk of HF in association with obesity.

This further indicates that weight management, including the avoidance of weight gain and weight reduction among those who are overweight or obese, is likely critical for optimal HF prevention. However, several prior analyses have documented the challenges of achieving significant and sustained weight loss in the population setting[5-8], indicating the importance of developing additional approaches to reduce the risk of HF associated with obesity. Therefore, these findings also underscore the need for further investigation to elucidate the non-traditional pathways linking obesity to HF, in order to inform novel preventive strategies. Additionally, the later onset of HF relative to CHD and stroke among individuals with obesity may indicate that the processes leading to myocardial dysfunction and HF in this population generally require a cumulative effect over an extended time period prior to the development of clinical disease, which may provide an important window for preventive interventions.

Furthermore, while this analysis highlights the markedly increased risk for incident HF associated with obesity, an obesity paradox has been noted among those with prevalent HF, among whom higher BMI is associated with increased survival[47, 48]. Further investigation is needed to elucidate the mechanisms underlying the obesity paradox, and to understand how the processes leading from obesity to incident HF affect myocardial function, structure and overall prognosis among those who have already developed clinical HF.

This analysis has certain limitations. Although the ARIC population was rigorously assessed with regards to traditional risk factors, the observational nature of this analysis makes the presence of some residual confounding still possible. Additionally, the use of discharge codes

for the diagnosis of HF may have resulted in some misclassification, although analyses restricted to only adjudicated HF events yielded largely unchanged results. This analysis also does not account for therapies administered during follow-up, which may have had variable effects on the risk of developing different subtypes of CVD. Nonetheless, this prospective analysis from an extremely well characterized cohort provides important insights regarding the relative associations of higher BMI with different subtypes of incident CVD, and the extent to which the associations are unexplained by traditional CVD mediators. The community-based design, and the inclusion of a bi-racial population of middle-aged men and women, makes the results broadly generalizable. The large number of events allowed for direct statistical comparisons of the risk associations among obesity and different CVD subtypes, and also permitted assessments of the robustness of the findings across demographic subgroups.

In conclusion, this analysis demonstrates that the associations of overweight and obesity with incident HF are stronger than those for CHD and stroke. Additionally, while traditional CVD mediators explained the associations of obesity with CHD and stroke, the association between higher BMI and incident HF was largely unexplained by adjustment for traditional CVD risk factors and mediators. These findings highlight the importance of weight management for optimal HF prevention, and the need to identify non-traditional pathways linking obesity to incident HF in order to inform the development of additional preventive strategies.

Reference List

(1) Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, Eckel RH. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation.* 2006;113:898-918.

(2) Zalesin KC, Franklin BA, Miller WM, Peterson ED, McCullough PA. Impact of obesity on cardiovascular disease. *Med Clin North Am.* 2011;95:919-37.

(3) Pandey A, Berry JD, Lavie CJ. Cardiometabolic Disease Leading to Heart Failure: Better Fat and Fit Than Lean and Lazy. *Curr Heart Fail Rep.* 2015;12:302-8.

(4) Aune D, Sen A, Norat T, Janszky I, Romundstad P, Tonstad S, Vatten LJ. Body Mass Index, Abdominal Fatness, and Heart Failure Incidence and Mortality: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies. *Circulation.* 2016;133:639-49.

(5) Davis MP, Rhode PC, Dutton GR, Redmann SM, Ryan DH, Brantley PJ. A primary care weight management intervention for low-income African-American women. *Obesity (Silver Spring).* 2006;14:1412-20.

(6) Kraschnewski JL, Boan J, Esposito J, Sherwood NE, Lehman EB, Kephart DK, Sciamanna CN. Long-term weight loss maintenance in the United States. *Int J Obes (Lond).* 2010;34:1644-54.

(7) Martin PD, Dutton GR, Rhode PC, Horswell RL, Ryan DH, Brantley PJ. Weight loss maintenance following a primary care intervention for low-income minority women. *Obesity (Silver Spring).* 2008;16:2462-7.

(8) Ockene IS, Hebert JR, Ockene JK, Saperia GM, Stanek E, Nicolosi R, Merriam PA, Hurley TG. Effect of physician-delivered nutrition counseling training and an office-support program on saturated fat intake, weight, and serum lipid measurements in a hyperlipidemic population: Worcester Area Trial for Counseling in Hyperlipidemia (WATCH). *Arch Intern Med.* 1999;159:725-31.

(9) Bodenant M, Kuulasmaa K, Wagner A, Kee F, Palmieri L, Ferrario MM, Montaye M, Amouyel P, Dallongeville J. Measures of abdominal adiposity and the risk of stroke: the MOnica Risk, Genetics, Archiving and Monograph (MORGAM) study. *Stroke.* 2011;42:2872-7.

(10) Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW, Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med.* 1999;341:1097-105.

(11) Empana JP, Ducimetiere P, Charles MA, Jouven X. Sagittal abdominal diameter and risk of sudden death in asymptomatic middle-aged men: the Paris Prospective Study I. *Circulation.* 2004;110:2781-5.

(12) Garrison RJ, Castelli WP. Weight and thirty-year mortality of men in the Framingham Study. *Ann Intern Med.* 1985;103:1006-9.

(13) Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation.* 1983;67:968-77.

(14) Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE, Hennekens CH, Speizer FE. Body weight and mortality among women. *N Engl J Med.* 1995;333:677-85.

(15) Suk SH, Sacco RL, Boden-Albala B, Cheun JF, Pittman JG, Elkind MS, Paik MC. Abdominal obesity and risk of ischemic stroke: the Northern Manhattan Stroke Study. *Stroke.* 2003;34:1586-92.

(16) Folsom AR, Stevens J, Schreiner PJ, McGovern PG. Body mass index, waist/hip ratio, and coronary heart disease incidence in African Americans and whites. Atherosclerosis Risk in Communities Study Investigators. *Am J Epidemiol.* 1998;148:1187-94.

(17) Jousilahti P, Tuomilehto J, Vartiainen E, Pekkanen J, Puska P. Body weight, cardiovascular risk factors, and coronary mortality. 15-year follow-up of middle-aged men and women in eastern Finland. *Circulation.* 1996;93:1372-9.

(18) Schulte H, Cullen P, Assmann G. Obesity, mortality and cardiovascular disease in the Munster Heart Study (PROCAM). *Atherosclerosis.* 1999;144:199-209.

(19) Tanizaki Y, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Shinohara N, Arima H, Tanaka K, Ibayashi S, Fujishima M. Incidence and risk factors for subtypes of cerebral infarction in a general population: the Hisayama study. *Stroke.* 2000;31:2616-22.

(20) Wang C, Liu Y, Yang Q, Dai X, Wu S, Wang W, Ji X, Li L, Fang X. Body mass index and risk of total and type-specific stroke in Chinese adults: results from a longitudinal study in China. *Int J Stroke.* 2013;8:245-50.

(21) Wormser D, Kaptoge S, Di AE, Wood AM, Pennells L, Thompson A, Sarwar N, Kizer JR, Lawlor DA, Nordestgaard BG, Ridker P, Salomaa V, Stevens J, Woodward M, Sattar N, Collins R, Thompson SG, Whitlock G, Danesh J. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet.* 2011;377:1085-95.

(22) Yatsuya H, Yamagishi K, North KE, Brancati FL, Stevens J, Folsom AR. Associations of obesity measures with subtypes of ischemic stroke in the ARIC Study. *J Epidemiol.* 2010;20:347-54.

(23) Markus HS, Khan U, Birns J, Evans A, Kalra L, Rudd AG, Wolfe CD, Jerrard-Dunne P. Differences in stroke subtypes between black and white patients with stroke: the South London Ethnicity and Stroke Study. *Circulation.* 2007;116:2157-64.

(24) Kurth T, Gaziano JM, Rexrode KM, Kase CS, Cook NR, Manson JE, Buring JE. Prospective study of body mass index and risk of stroke in apparently healthy women. *Circulation.* 2005;111:1992-8.

(25) Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. *Lancet.* 2014;383:970-83.

(26) Del Gobbo LC, Kalantarian S, Imamura F, Lemaitre R, Siscovick DS, Psaty BM, Mozaffarian D. Contribution of Major Lifestyle Risk Factors for Incident Heart Failure in Older Adults: The Cardiovascular Health Study. *JACC Heart Fail.* 2015;3:520-8.

(27) Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. *N Engl J Med.* 2002;347:305-13.

(28) Morkedal B, Vatten LJ, Romundstad PR, Laugsand LE, Janszky I. Risk of myocardial infarction and heart failure among metabolically healthy but obese individuals: HUNT (Nord-Trondelag Health Study), Norway. *J Am Coll Cardiol.* 2014;63:1071-8.

(29) Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Obesity and risk of incident heart failure in older men with and without pre-existing coronary heart disease: does leptin have a role? *J Am Coll Cardiol.* 2011;58:1870-7.

(30) Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. *Physiol Rev.* 2008;88:389-419.

(31) Alpert MA, Omran J, Mehra A, Ardhanari S. Impact of obesity and weight loss on cardiac performance and morphology in adults. *Prog Cardiovasc Dis.* 2014;56:391-400.

(32) The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol.* 1989;129:687-702.

(33) Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* 1972;18:499-502.

(34)   Rosamond WD, Chang PP, Baggett C, Johnson A, Bertoni AG, Shahar E, Deswal A, Heiss G, Chambless LE. Classification of heart failure in the atherosclerosis risk in communities (ARIC) study: a comparison of diagnostic criteria. *Circ Heart Fail.* 2012;5:152-9.

(35)   Zellner A. An Efficient Method of Estimating Seemingly Unrelated Regressions and Tests for Aggregation Bias. *Journal of the American Statistical Association.* 1962;57:348-68.

(36)   Lavie CJ, McAuley PA, Church TS, Milani RV, Blair SN. Obesity and cardiovascular diseases: implications regarding fitness, fatness, and severity in the obesity paradox. *J Am Coll Cardiol.* 2014;63:1345-54.

(37)   Turkbey EB, McClelland RL, Kronmal RA, Burke GL, Bild DE, Tracy RP, Arai AE, Lima JA, Bluemke DA. The impact of obesity on the left ventricle: the Multi-Ethnic Study of Atherosclerosis (MESA). *JACC Cardiovasc Imaging.* 2010;3:266-74.

(38)   Frankel DS, Vasan RS, D'Agostino RB, Sr., Benjamin EJ, Levy D, Wang TJ, Meigs JB. Resistin, adiponectin, and risk of heart failure the Framingham offspring study. *J Am Coll Cardiol.* 2009;53:754-62.

(39)   Karas MG, Benkeser D, Arnold AM, Bartz TM, Djousse L, Mukamal KJ, Ix JH, Zieman SJ, Siscovick DS, Tracy RP, Mantzoros CS, Gottdiener JS, deFilippi CR, Kizer JR. Relations of plasma total and high-molecular-weight adiponectin to new-onset heart failure in adults >/=65 years of age (from the Cardiovascular Health study). *Am J Cardiol.* 2014;113:328-34.

(40) McManus DD, Lyass A, Ingelsson E, Massaro JM, Meigs JB, Aragam J, Benjamin EJ, Vasan RS. Relations of circulating resistin and adiponectin and cardiac structure and function: the Framingham Offspring Study. *Obesity (Silver Spring)*. 2012;20:1882-6.

(41) Negi SI, Jeong EM, Shukrullah I, Raicu M, Dudley SC, Jr. Association of low plasma adiponectin with early diastolic dysfunction. *Congest Heart Fail.* 2012;18:187-91.

(42) Garg S, Narula J, Chandrashekhar Y. Apoptosis and heart failure: clinical relevance and therapeutic target. *J Mol Cell Cardiol.* 2005;38:73-9.

(43) Ndumele CE, Coresh J, Lazo M, Hoogeveen RC, Blumenthal RS, Folsom AR, Selvin E, Ballantyne CM, Nambi V. Obesity, subclinical myocardial injury, and incident heart failure. *JACC Heart Fail.* 2014;2:600-7.

(44) Zhou YT, Grayburn P, Karim A, Shimabukuro M, Higa M, Baetens D, Orci L, Unger RH. Lipotoxic heart disease in obese rats: implications for human obesity. *Proc Natl Acad Sci U S A.* 2000;97:1784-9.

(45) Barouch LA, Gao D, Chen L, Miller KL, Xu W, Phan AC, Kittleson MM, Minhas KM, Berkowitz DE, Wei C, Hare JM. Cardiac myocyte apoptosis is associated with increased DNA damage and decreased survival in murine models of obesity. *Circ Res.* 2006;98:119-24.

(46) Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. *JACC Heart Fail.* 2013;1:93-102.

(47) Clark AL, Fonarow GC, Horwich TB. Obesity and the obesity paradox in heart failure. *Prog Cardiovasc Dis.* 2014;56:409-14.

(48) Lavie CJ, Sharma A, Alpert MA, De SA, Lopez-Jimenez F, Milani RV, Ventura HO. Update on Obesity and Obesity Paradox in Heart Failure. *Prog Cardiovasc Dis.* 2016;58:393-400.

Table 1. Baseline Characteristics of Study Population, Stratified by BMI Category

	Normal Weight N=4,602	Overweight N=5,480	Obese N=2,471	Severely Obese N=1,177	p value
Mean Age, in years (SD)	53.8 (5.8)	54.0 (5.7)	54.0 (5.7)	53.1 (5.6)	<0.001
Female – %	63.8	44.8	55.4	77.5	<0.001
African American – %	16.9	25.3	35.1	48.5	<0.001
Current Smokers – %	31.7	23.6	20.3	14.9	<0.001
Mean exercise physical activity, in (met*min)/ week (SD)	736.6 (855.9)	669.8 (777.7)	511.9 (686.8)	352.2 (567.8)	<0.001
Mean systolic blood pressure, in mmHg (SD)	116.0 (18.1)	121.1 (17.9)	125.1 (17.8)	129.9 (19.0)	<0.001
Use of anti-hypertensive medication – %	12.2	20.8	30.7	42.1	<0.001
Diabetes – %	4.2	9.0	17.3	26.6	<0.001
Mean LDL-C, in mg/dl (SD)	130.7 (38.6)	140.3 (38.9)	142.3 (39.1)	136.0 (36.6)	<0.001

Mean HDL-C, in mg/dl (SD)	58.9 (18.4)	49.6 (15.6)	47.0 (14.5)	48.2 (13.7)	<0.001
Median triglycerides, in mg/dl (IQR)	91 (68-126)	112 (80-160)	128 (92-179)	124 (90-170)	<0.001
Mean eGFR, in ml/min/ 1.73 m2 (IQR)	104.0 (96.5-111.1)	102.3 (94.4-110.5)	103.0 (93.8-112.7)	108.0 (98.4-118.5)	<0.001
Mean waist circumference, in cm (SD)	84.5 (7.5)	96.8 (7.0)	107.1 (7.6)	122.0 (11.6)	<0.001

Table 2: Association of Higher BMI Categories With Adjusted HRs (and 95% CIs) for CVD Subtypes

	Normal Weight (BMI 18.5-24.9) N=4,602	Overweight (BMI 25-29.9) N=5,480	Obese (BMI 30-34.9) N=2,471	Severely Obese (BMI>35) N=1,177
Model 1[*]				
Incident HF	Ref	1.38 (1.23-1.54)	2.10 (1.85-2.38)	3.74 (3.24-4.31)
Incident CHD	Ref	1.26 (1.11-1.43)	1.53 (1.33-1.77)	2.00 (1.67-2.40)
Incident stroke	Ref	1.17 (1.00-1.37)	1.32 (1.10-1.60)	1.75 (1.40-2.20)
Model 2†				
Incident HF	Ref	1.12 (0.99-1.26)	1.50 (1.32-1.72)	2.27 (1.94-2.64)
Incident CHD	Ref	0.96 (0.84-1.09)	0.95 (0.81-1.11)	1.06 (0.87-1.29)
Incident stroke	Ref	0.99 (0.84-1.17)	0.97 (0.80-1.19)	1.13 (0.88-1.44)

[*]Model 1: Adjusted for age, race, sex, alcohol use, smoking status, physical activity, occupation and education level

†Model 2: Adjusted for Model 1 variables + diabetes, systolic blood pressure, anti-hypertensive medication use, HDL-C, LDL-C, triglycerides and estimated GFR

Table 3: Association of Higher BMI Categories with Incident CVD Subtypes with Adjustment for Major Risk Factors* as Time Varying Covariates

	Normal Weight (BMI 18.5-24.9) N=4,602	Overweight (BMI 25-29.9) N=5,480	Obese (BMI 30-34.9) N=2,471	Severely Obese (BMI>35) N=1,177
Incident HF	1.0 (Ref)	1.11 (0.99-1.25)	1.40 (1.22-1.60)	2.18 (1.87-2.54)
Incident CHD	1.0 (Ref)	0.98 (0.88-1.09)	0.97 (0.86-1.11)	1.20 (1.02-1.41)
Incident stroke	1.0 (Ref)	0.98 (0.83-1.16)	0.94 (0.77-1.15)	1.15 (0.90-1.47)

*The following risk factors were modeled as time varying covariates from ARIC Visits 1 through 4 to account for their potential onset after the baseline visit: smoking status (current smoker vs current non-smoker); hypertension (defined as systolic blood pressure $\geq$ 140, diastolic blood pressure $\geq$ 90 or use of anti-hypertensive medications); diabetes (defined as fasting blood sugar $\geq$ 126, non-fasting blood sugar $\geq$ 200, self-reported prior physician diagnosis or use of hypoglycemic medications); and hypercholesterolemia (LDL cholesterol $\geq$ 160 mg/dl or use of lipid lowering medications). Measurements from study visits occurring before incident CVD events were incorporated in regression analyses. For hypertension, diabetes and hypercholesterolemia, after their onset those risk factors were considered to be present thereafter. Regression models were additionally adjusted for age, race, sex, alcohol use, occupation, education level, physical activity, HDL-C, triglycerides and estimated GFR.

Table 4: Association of Obesity (BMI ≥ 30), Modeled as a Time Varying Covariate*, with Incident CVD Subtypes

	Non-Obese (BMI 18.5-29.9)	Obese (BMI ≥ 30)
Incident HF	1.0 (Ref)	1.44 (1.32-1.58)
Incident CHD	1.0 (Ref)	1.00 (0.92-1.10)
Incident stroke	1.0 (Ref)	1.05 (0.91-1.20)

*Obesity, defined as a BMI ≥ 30, was modeled as a time varying covariate from ARIC Visits 1 through 4 to account for its potential onset after the baseline visit. The reference group was non-obese (BMI < 30). Measurements from study visits occurring before incident CVD events were incorporated in regression analyses. After the onset of obesity, obesity was considered to be present thereafter. Regression models were adjusted for age, race, sex, alcohol use, smoking status, occupation, education level, physical activity, diabetes, systolic blood pressure, anti-hypertensive medication use, HDL-C, LDL-C, triglycerides and estimated GFR.

Table 5: Association of Sex-Specific Waist Circumference Quartiles[*] With Adjusted HRs (and 95% CIs) for CVD Subtypes

	Quartile 1 N=3,286	Quartile 2 N=3,299	Quartile 3 N=3,534	Quartile 4 N=3,605
Model 1†				
Incident HF	1.0 (Ref)	1.43 (1.23-1.67)	1.74 (1.50-2.00)	3.01 (2.63-3.44)
Incident CHD	1.0 (Ref)	1.25 (1.06-1.46)	1.42 (1.22-1.66)	1.87 (1.61-2.16)
Incident stroke	1.0 (Ref)	1.13 (0.92-1.38)	1.33 (1.09-1.61)	1.67 (1.38-2.01)
Model 2‡				
Incident HF	Ref	1.25 (1.07-1.46)	1.33 (1.15-1.55)	1.96 (1.70-2.27)
Incident CHD	Ref	1.01 (0.86-1.18)	0.97 (0.83-1.14)	1.04 (0.89-1.22)
Incident stroke	Ref	0.99 (0.80-1.22)	1.04 (0.85-1.28)	1.14 (0.92-1.39)

[*]Waist circumference quartile ranges – quartile 1: women 52-83 cm, men 52-91 cm; quartile 2: women 84-92, men 92-97 cm; quartile 3: women 93-103 cm, men 98-104 cm; quartile 4: women 105-178 cm, men 104-178 cm

†Model 1: Adjusted for age, race, sex, alcohol use, smoking status, physical activity, occupation and education level

‡Model 2: Adjusted for Model 1 variables + diabetes, systolic blood pressure, anti-hypertensive

medication use, HDL-C, LDL-C, triglycerides and estimated GFR

Figure 1. Association of BMI Categories with Adjusted Incident Rates for Different CVD Subtypes
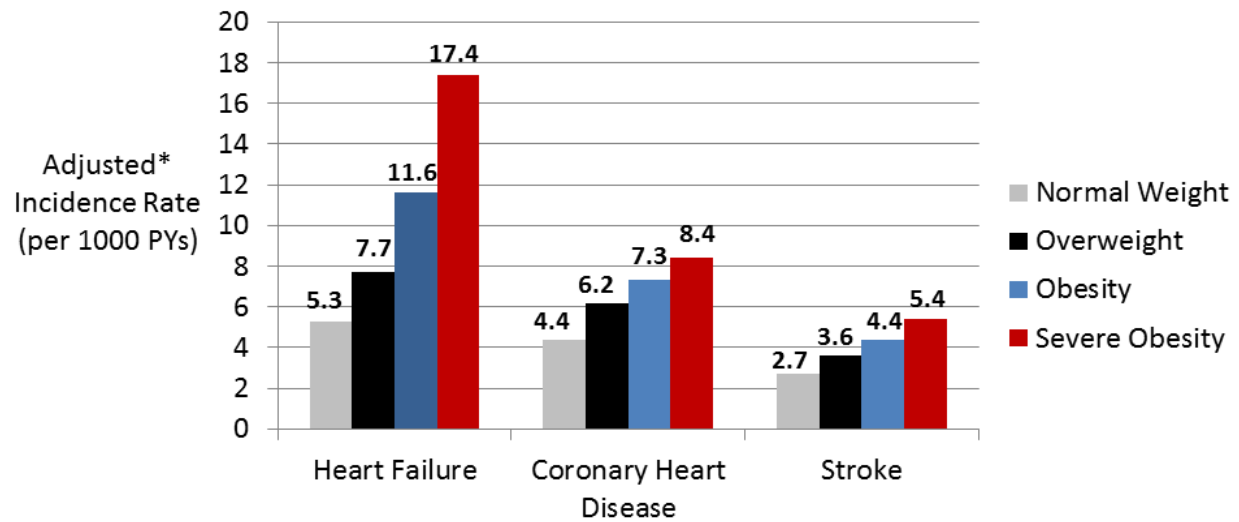
*At mean levels of age, sex, race, smoking status, alcohol use, education level, occupation and physical activity

Incidence rates calculated at mean levels of age, sex, race, smoking status, alcohol use, education level, occupation and physical activity within the study population.

Figure 2: Relationship of Continuous BMI with Incident CVD Subtypes in Linear Spline Models After Multivariable Adjustment
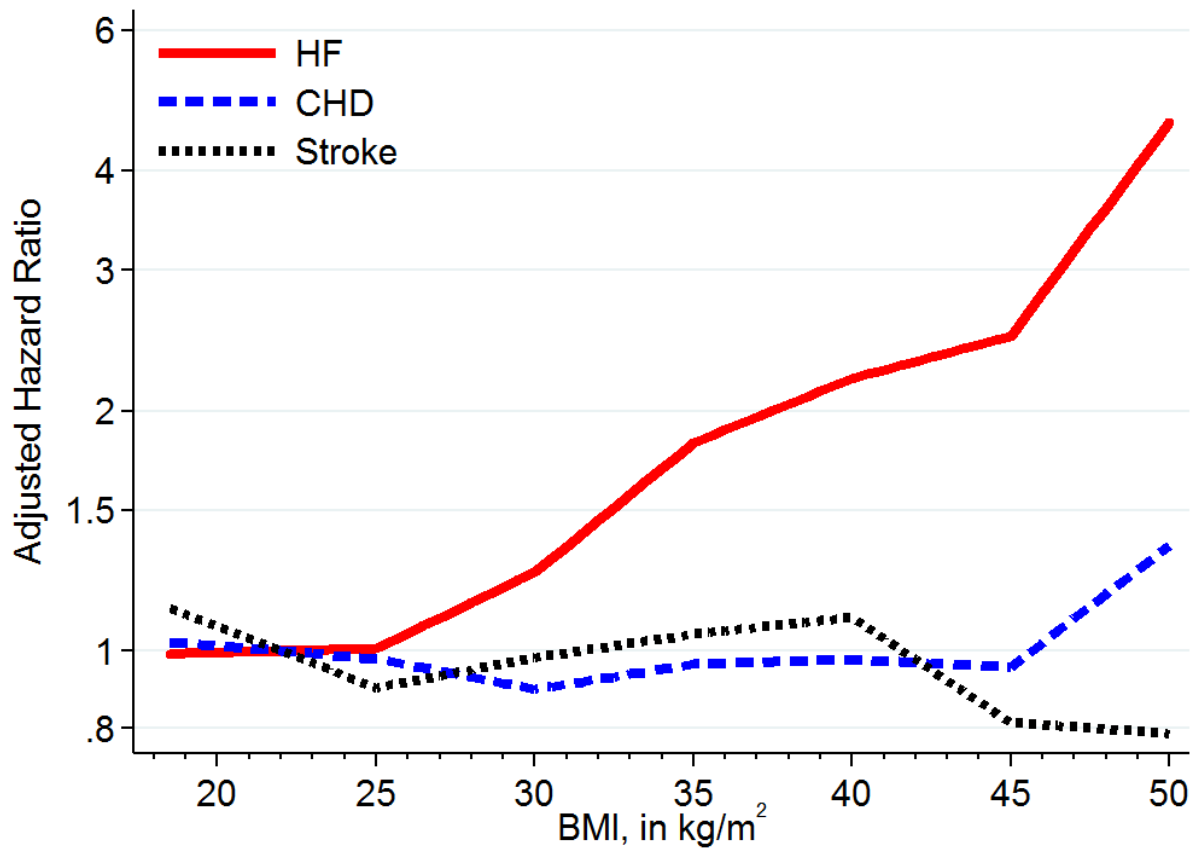
Linear spline with knots at the BMI values of 25, 30, 35, 40 and 45 kg/m² and reference at BMI of 22 kg/m².

Adjusted for age, race, sex, alcohol use, smoking status, occupation, education level, physical activity, diabetes, systolic blood pressure, anti-hypertensive medication use, HDL-C, LDL-C, triglycerides and estimated GFR

Figure 3. Association of Higher BMI Categories with Incident HF After Multivariable Adjustment, Within Demographic Subgroups

Subgroup	HR	(95%CI)
Men (N=6,057)		
Normal Weight	(Ref)	
Overweight	1.08	(0.91-1.28)
Obese	1.44	(1.18-1.76)
Severely Obese	2.27	(1.73-2.98)
Women (N=7,673)		
Normal Weight	(Ref)	
Overweight	1.14	(0.96-1.34)
Obese	1.52	(1.26-1.82)
Severely Obese	2.25	(1.85-2.74)
Whites (N=10,128)		
Normal Weight	(Ref)	
Overweight	1.22	(1.06-1.40)
Obese	1.69	(1.43-1.99)
Severely Obese	2.67	(2.18-3.27)
Blacks (N=3,602)		
Normal Weight	(Ref)	
Overweight	0.89	(0.71-1.12)
Obese	1.14	(0.89-1.45)
Severely Obese	1.63	(1.26-2.10)
Age < 60 (N=10,851)		
Normal Weight	(Ref)	
Overweight	1.17	(1.01-1.36)
Obese	1.57	(1.33-1.86)
Severely Obese	2.30	(1.91-2.78)
Age ≥ 60 (N=2,879)		
Normal Weight	(Ref)	
Overweight	1.03	(0.85-1.25)
Obese	1.37	(1.09-1.71)
Severely Obese	2.00	(1.49-2.68)

Hazard Ratio (95% CI)

— Overweight — Obese — Severely Obese

Adjusted for age, race, sex, alcohol use, smoking status, occupation, education level, physical activity, diabetes, systolic blood pressure, anti-hypertensive medication use, HDL-C, LDL-C, triglycerides and estimated GFR

*Please note that a manuscript detailing the work in Aim 1 has been published in the Journal of the American Heart Association

Chapter 3 – Aim 2: Obesity, Subclinical Myocardial Injury and Incident Heart Failure

Abstract

Objectives: To evaluate the association of obesity with a novel biomarker of subclinical myocardial injury, cardiac troponin T measured with a new high sensitivity assay (hs-cTnT), among adults without clinical cardiovascular disease (CVD).

Background: Laboratory evidence suggests a relationship between obesity and myocardial injury that may play a role in the development of heart failure (HF), but there is limited clinical data regarding this association.

Methods: We evaluated 9,507 participants in the Atherosclerosis Risk in Communities Study without baseline CVD (Visit 4, 1996-1999). We assessed the cross sectional association of body-mass index (BMI) with high ($\geq$14 ng/L) and measurable ($\geq$3 ng/L) hs-cTnT levels after multivariable regression. We further evaluated the independent and combined associations of BMI and hs-cTnT with incident HF.

Results: Higher BMI was independently associated with a positive, linear increase in the likelihood of high hs-cTnT, with severe obesity (BMI >35 kg/m^2) associated with an odds ratio of 2.20 (95% CI: 1.59-3.06) for high hs-cTnT after adjustment. Over 12 years of follow-up, there were 869 incident HF events. Obesity and hs-cTnT were both independently associated with incident HF, and individuals with severe obesity and high hs-cTnT had a greater than 9-fold higher risk of incident HF (HR 9.20 [95% CI: 5.67-14.93]) than individuals with normal weight and undetectable hs-cTnT.

Conclusions: Among individuals without CVD, higher BMI has an independent, linear association with subclinical myocardial injury, as assessed by hs-cTnT levels. Obesity and hs-cTnT provide independent and complementary prognostic information regarding the risk of incident HF.

Key Words: obesity; heart failure; epidemiology; troponin

Introduction:

Obesity is a known risk factor for the development of heart failure (HF)(1, 2), but the mechanisms underlying the relationship between obesity and HF are incompletely understood(3). Conditions closely linked to obesity, such as hypertension (HTN) and diabetes mellitus (DM), only partially explain the association between obesity and incident HF(4). Obesity is independently associated with abnormalities of myocardial contractile function and relaxation and abnormal cardiac remodeling(5, 6), changes which precede clinical HF(1). Laboratory studies suggest that myocardial injury, related to the endocrine and inflammatory effects of adipose tissue, may be one pathway by which obesity leads to myocardial dysfunction and subsequent HF(5, 7, 8).

A novel biomarker of subclinical myocardial injury that may provide further insight into the relationship between obesity and HF is cardiac troponin T measured via a new high sensitivity assay (hs-cTnT)(9). Novel high sensitivity assays can detect troponin in the circulation at levels far below the detection limits of conventional assays used in clinical practice. Previous studies among asymptomatic individuals have found that minute elevations in troponin detected with these high sensitivity assays are robust predictors of future HF and mortality, and to a lesser extent, incident coronary heart disease (CHD)(10, 11). Despite increasing evidence regarding the adverse effects of excess adiposity on the myocardium, the relationship between obesity and hs-cTnT among asymptomatic individuals, and the implications of this relationship for the development of HF, has not yet been investigated.

The objective of this study was to test the hypothesis that obesity is independently associated with subclinical myocardial injury, as assessed by hs-cTnT, in a population-based study

of individuals free of clinical cardiovascular disease (CVD) at baseline. We further evaluated the independent and combined associations of obesity and hs-cTnT with incident HF, to assess whether these variables provided complementary prognostic information regarding HF risk.

Methods:

The Atherosclerosis Risk in Communities (ARIC) Study is a prospective, population-based cohort of 15,792 individuals enrolled from four U.S. communities: Washington County, Maryland; Jackson, Mississippi; Forsyth County, North Carolina; and the suburbs of Minneapolis, Minnesota. The study protocol has been described previously(12). Participants were recruited between 1987 and 1989, and examined at baseline and at three subsequent visits, at approximately 3 year intervals. A fifth study visit is presently ongoing. ARIC Visit 4 (1996-1998), at which hs-cTnT measurements were available for all participants, was the baseline for this analysis.

Of the 11,492 participants who attended ARIC Visit 4, we excluded individuals with a history of self-reported CVD at Visit 1 or a CVD event (including prior hospitalization related to HF, validated non-fatal myocardial infarction or coronary revascularization, or silent myocardial infarction by ECG criteria) at or prior to Visit 4 (N=1,572), a small number of individuals not of black or white race (N=31), and those participants with body-mass index (BMI) < 18.5 kg/m^2 (N=74). We also excluded participants missing data on prior CVD (N=214), hs-cTnT (N=242) or anthropometric measurements (N =16), for a final study population of 9,507 individuals. All participants provided informed consent, and the study protocol was approved by the institutional review boards associated with each ARIC field center.

Information on BMI and all covariates of interest were obtained by history, physical and laboratory examination at Visit 4. BMI was calculated from measured height and weight and categorized as normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), obese (30-34.9 kg/m^2) or severely obese ($\geq$ 35 kg/m^2). Smoking status was categorized as current, former or never smoker and self-reported alcohol intake was calculated in grams per week. HTN was defined as having a prior physician diagnosis of HTN, using anti-hypertensive medications, or having a systolic blood pressure of $\geq$ 140 mmHg or a diastolic blood pressure $\geq$ 90 mmHg on examination. Individuals were classified as having DM if they had a self-reported history of DM, used hypoglycemic medications, had a fasting blood glucose of $\geq$ 126 mg/dl or had a non-fasting blood glucose of $\geq$ 200 mg/dl. Total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and triglycerides were measured using enzymatic assays, and LDL-C was calculated using the Friedewald equation (TC − HDL-C − [triglycerides/5]) for participants with triglycerides $\leq$ 400 mg/dl.

Hs-cTnT was measured in 2010 from thawed plasma samples initially obtained at Visit 4 and stored at -80 degrees Celsius, using the Elecsys Troponin T high-sensitivity assay (Roche Diagnostics, Indianapolis, IN) on an automated Cobas e411 analyzer. The primary outcome in cross-sectional analyses was high hs-cTnT levels, defined as $\geq$14 ng/L, corresponding to the 99th percentile for hs-cTnT in a healthy reference population as provided by the assay manufacturer, a cutpoint used in prior analyses(11, 13). The secondary outcome was measurable hs-cTnT, which reflected levels of hs-cTnT greater than the assay measurement limit of 3 ng/L. The between assay coefficients of variation for control materials with mean hs-cTnT concentrations of 2,378 ng/L and 29 ng/L were 2.6% and 6.9%, respectively.

In prospective analyses, the outcome of interest was incident HF, defined as the first hospitalization or death related to HF occurring after Visit 4, with follow-up through January 2009. Participants were called on a yearly basis to obtain information regarding hospitalizations, and vital records were examined for all deaths. Hospitalizations and deaths due to incident HF were defined by HF discharge codes (ICD-9 code 428 for hospitalizations and deaths early during follow-up and ICD-10 code I50 for later deaths). HF events after 2004 were additionally adjudicated by an expert panel.

Statistical analysis:

Differences in demographic, clinical and laboratory characteristics among individuals in different BMI categories were assessed using the chi-squared test for categorical variables and analysis of variance for continuous variables.

In cross-sectional analyses, we evaluated the association of BMI with elevated hs-cTnT levels at Visit 4. We used multivariable logistic regression to assess the relationship of higher BMI categories with high ($\geq$14 ng/L) and measurable ($\geq$3 ng/L) hs-cTnT levels, with normal weight (18.5-24.9 kg/m^2) as the reference. Using logistic regression, we also evaluated the continuous association of BMI (per kg/m^2) with high hs-cTnT levels using restricted cubic splines, centered at the median BMI. Model 1 was adjusted for age; Model 2 was adjusted for the variable in Model 1 plus sex, race, and smoking status; Model 3 was adjusted for all variables in Model 2 plus DM, HTN, LDL-C, HDL-C, triglycerides, alcohol intake, N-terminal pro-brain natriuretic peptide (NT-proBNP) and estimated GFR. We conducted additional analyses stratified by age (older or younger than 65 years), gender and race, and tested for interactions of these demographic variables with BMI on the outcome of high hs-cTnT.

In prospective analyses, we examined the associations of obesity and hs-cTnT with incident HF. We used Cox proportional hazards models to estimate the adjusted hazard ratios and corresponding 95% confidence intervals for the prospective association between BMI categories at baseline and risk of HF after adjustment for baseline risk factors, utilizing the same modeling approach used for the cross-sectional analyses. To examine the combined effects of BMI and hs-cTnT on incident HF, we conducted analyses stratified by hs-cTnT levels at baseline (undetectable (<3 ng/L), measurable (3-13 ng/L) and high ($\geq$14 ng/L)). We tested for statistical interactions on the multiplicative scale between BMI category and hs-cTnT level on the outcome of incident HF. For analyses modeling hs-cTnT as a continuous variable, spline models were constructed with the value of 1.5 ng/L imputed for those with undetectable hs-cTnT as has been done in prior analyses (10). We performed sensitivity analyses limited to those individuals with adjudicated HF events. We conducted additional sensitivity analyses substituting waist circumference (WC), in quartiles, for BMI as the metric for adiposity.

Statistical analyses were performed with Stata version 10.1. All reported p values are 2-sided.

Results:

Individuals in higher BMI categories were slightly younger, and more likely to be female and African-American (Table 1). Mean alcohol intake and the proportion of current smokers was lower in higher BMI categories. As expected, higher BMI category was also associated with a significantly higher prevalence of HTN and DM, as well as with higher triglycerides and lower HDL-C. Severely obese individuals had a slightly higher mean estimated GFR. Higher BMI was also associated with lower levels of NT-proBNP.

Measurable hs-cTnT was found in the majority of study participants (65.9%) (Figure 1). The prevalence of measurable hs-cTnT was higher among individuals with severe obesity than those with normal weight (69.9 vs 60.4%, p < 0.001). The prevalence of high hs-cTnT levels increased with higher BMI category, being found in 4.5% of individuals with normal weight, 6.7% of individuals with overweight, 9.0% of those with obesity and 9.5% of those with severe obesity (p for trend <0.001).

Higher BMI categories were associated with an increased likelihood of having high hs-cTnT levels, even after adjustment for traditional HF risk factors (Table 2). After adjusting for all HF risk factors, severe obesity was associated with an odds ratio of 2.20 (95% CI: 1.59-3.06) for high hs-cTnT, compared with normal BMI (Model 3). An independent, linear relationship between BMI and high hs-cTnT levels was seen when BMI was modeled continuously using a restricted cubic spline (Figure 2). Each 5 kg/m^2 higher increment in BMI was independently associated with a 26% higher odds of high hs-cTnT levels. Significant positive associations were also seen between obesity and measurable hs-cTnT levels (Table 2).

Over a median of 12.1 years of follow-up, 869 incident HF events occurred within the study sample. Higher BMI category at baseline was associated with a progressive increase in the risk of incident HF, with severe obesity associated with a hazard ratio of 3.39 (95% CI: 2.74-4.19) in age-adjusted analysis (Figure 3). After adjustment for established HF risk factors and other confounders, higher baseline BMI continued to be significantly associated with incident HF (HR for severe obesity 2.39 [95% CI: 1.89-3.01]). After multivariable adjustment, each 5 kg/m^2 higher baseline BMI was independently associated with a 32% higher risk of incident HF.

Figure 4 displays the results of Cox regression analyses on the outcome of incident HF with stratification by both BMI category and hs-cTnT level (as undetectable, measurable or high hs-cTnT). At each level of hs-cTnT, higher BMI was significantly associated with an increased risk of incident HF (Table 3). Similarly, within each BMI category, greater values of hs-cTnT were associated with increased HF risk. BMI and hs-cTnT provided complementary prognostic information, with individuals with severe obesity and high-hs-cTnT levels having a greater than 9 fold higher risk of incident HF than individuals with normal weight and undetectable hs-cTnT (HR 9.20; 95% CI: 5.67-14.93). While the combined presence of obesity and high hs-cTnT was associated with markedly increased risk, no statistically significant interaction was seen between BMI and hs-cTnT levels on the outcome of incident HF (p for interaction = 0.10).

Analogous results were seen when using WC rather than BMI as the measure for adiposity. In the full regression model, the top quartile of WC was associated with an odds ratio of 2.08 (95% CI: 1.53-2.82) for high hs-cTnT, compared to the bottom quartile. Furthermore, individuals in the top quartile of WC with high hs-cTnT had a hazard ratio of 8.33 (95% CI: 5.37-12.92) for incident HF relative to those in the lowest waist circumference quartile with undetectable hs-cTnT. Interestingly, when WC was added to models assessing the association between BMI and high hs-cTnT, the association for BMI became nonsignificant (p=0.19) while that for WC remained significant (p<0.001), suggesting that abdominal obesity may be most relevant to the development of myocardial injury.

Positive associations between obesity and hs-cTnT, and between hs-cTnT and HF, were also seen when hs-cTnT was modeled as a continuous variable (Figures 5 and 6). Analyses limited to those individuals with adjudicated HF events (N=427 events) demonstrated similar findings. Adjustments for baseline use of anti-hypertensive and cholesterol-lowering medications did not

alter the results appreciably. The results were also generally similar across subgroups by age, race and sex, with no statistically significant interactions of these variables with hs-cTnT, although the association between BMI and hs-cTnT tended to be weaker among women compared with men (p for interaction = 0.24), and among African-Americans compared with white participants (p for interaction = 0.30).

Discussion:

In this population-based study of 9,507 men and women without CVD at baseline, we found an independent association between higher BMI and subclinical myocardial injury, as reflected by high hs-cTnT levels, that persisted after adjustment for traditional cardiovascular risk factors. This association had significant clinical implications, as obesity and hs-cTnT were both independently associated with an increased risk of hospitalization or death for incident HF over 12 years of follow-up. Even after adjustment for HF risk factors, individuals with severe obesity and high hs-cTnT levels had a greater than 9-fold higher risk of incident HF than individuals with normal weight and undetectable hs-cTnT levels.

Previous studies have demonstrated an association between obesity and incident HF. However, the mechanisms underlying the relationship between obesity and HF have not yet been fully elucidated, with the association being only partially explained by traditional risk factors. Within the Framingham Heart Study, obesity was associated with a 2-fold increased risk of incident HF among men and women after adjustment for HTN, DM, prior myocardial infarction and other risk factors(4). Similar findings have been seen in other cohorts(14-16). Past work from our group has also demonstrated the utility of elevated hs-cTnT, beyond traditional risk factors, for predicting

future HF. The present analysis extends prior research by revealing an independent, linear association between BMI and high hs-cTnT levels, and demonstrating the prognostic implications of elevations in both BMI and hs-cTnT for incident HF risk. Our findings also suggest that abdominal obesity may be most important for the development of myocardial injury. Notably, the relationship between BMI and hs-cTnT contrasts with the known inverse relationship between obesity and levels of NT-proBNP, another marker of future HF risk.

This study also adds to the growing body of literature examining the correlates and consequences of hs-cTnT levels among individuals in ambulatory populations(10, 11, 13, 17).. Hs-cTnT levels are strongly associated with incident cardiovascular events, and the available evidence suggests that the association between hs-cTnT and cardiovascular risk is not primarily mediated by macrovascular coronary atherosclerosis. In multiple studies, hs-cTnT is more strongly associated with the risk of incident HF than with CHD events(10, 11). In addition, past research has not shown an independent association between hs-cTnT and coronary artery calcium, a surrogate for subclinical atherosclerosis(13). In contrast, hs-cTnT has been independently associated with abnormalities of myocardial structure and function that commonly precede the development of HF(13).

While there are limited past studies regarding the relationship between obesity and hs-cTnT(18), there is increasing laboratory evidence linking obesity to subclinical myocardial injury. Obesity is associated with abnormal cardiac remodeling and with impaired myocardial contractile function and relaxation, independent of coronary heart disease and traditional obesity-associated risk factors such as HTN and DM(5, 19). Studies of animal models of obesity suggest that chronic myocardial injury may contribute to the myocardial dysfunction associated with excess adiposity. Rodents genetically predisposed to obesity demonstrate increased rates of myocyte DNA damage,

myocardial oxidative injury, myocyte apotosis, myocardial fibrosis, and impaired contractile function compared to leaner, wild-type rats(20-22).. It has been suggested that myocardial injury and resultant apoptosis may play a role in the progression from compensatory ventricular remodeling to clinical HF(23). With the emergence of hs-cTnT as a novel marker of subclinical myocardial damage, evaluations of the relationship between obesity and myocardial injury can now be extended from animal models to clinical studies.

Clinical Implications:

This analysis highlights the prognostic valueof obesity and elevated hs-cTnT for HF risk. Obesity was independently associated with incident HF at each level of hs-cTnT, and higher hs-cTnT levels were similarly associated with increased HF risk within each BMI category. Those individuals with severe obesity and high hs-cTnT had the greatest risk of HF. These findings suggest that in addition to its relationship with subclinical myocardial injury, obesity likely contributes to HF risk via additional mechanisms. Furthermore, obesity and hs-cTnT levels each provide independent and complementary prognostic information, beyond traditional risk factors, regarding HF risk. Individuals without clinical CVD and with high BMI and high hs-cTnT levels appear to represent a group at markedly increased risk for the development of HF.

Limitations:

This analysis has certain limitations. Although the study participants were rigorously evaluated for risk factors and there was extensive adjustment for covariates associated with HF, there remains the possibility of residual confounding in this observational analysis. The diagnosis of incident HF was based on hospital discharge and death certificate codes, which may have resulted in some misclassification. This analysis does not account for the potential impact of medical therapies

during the follow-up period. Additionally, cardiac imaging was not available to determine the structural and functional myocardial abnormalities leading to HF among individuals with obesity and elevated hs-cTnT. Nonetheless, this is an analysis within a large, biracial and extremely well characterized prospective cohort with long-term follow-up for incident HF events. The large number of HF events provided power to stratify by both BMI category and hs-cTnT levels, in order to fully examine the contributions of both of these variables to incident HF risk. We were also able to exclude individuals with baseline clinical CVD using data on prior adjudicated events.

In conclusion, in this analysis of men and women without baseline CVD, we found an independent, linear association between BMI and subclinical myocardial injury, as indexed by high hs-cTnT levels. Additionally, higher BMI and hs-cTnT levels were both independently associated with incident HF, with individuals with both severe obesity and high hs-cTnT having markedly increased risk. Further investigation is needed to elucidate the mechanisms linking obesity to elevated hs-cTnT, and to understand the interplay of obesity and subclinical myocardial injury in the development of HF.

Reference List

1. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009; 119:1977-2016.

2. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. JACC Heart Fail 2013; 1:93-102.

3. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2006; 113:898-918.

4. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. N Engl J Med 2002; 347:305-13.

5. Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. Physiol Rev 2008; 88:389-419.

6. Zalesin KC, Franklin BA, Miller WM, Peterson ED, McCullough PA. Impact of obesity on cardiovascular disease. Med Clin North Am 2011; 95:919-37.

7. Choi EY, Yan RT, Fernandes VR, et al. High-sensitivity C-reactive protein as an independent predictor of progressive myocardial functional deterioration: the multiethnic study of atherosclerosis. Am Heart J 2012; 164:251-8.

8. Martin SS, Qasim A, Reilly MP. Leptin resistance: a possible interface of inflammation and metabolism in obesity-related cardiovascular disease. J Am Coll Cardiol 2008; 52:1201-10.

9. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem 2010; 56:254-61.

10. deFilippi CR, de Lemos JA, Christenson RH, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA 2010; 304:2494-502.

11. Saunders JT, Nambi V, de Lemos JA, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation 2011; 123:1367-76.

12. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol 1989; 129:687-702.

13. de Lemos JA, Drazner MH, Omland T, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA 2010; 304:2503-12.

14. Chen YT, Vaccarino V, Williams CS, Butler J, Berkman LF, Krumholz HM. Risk factors for heart failure in the elderly: a prospective community-based study. Am J Med 1999; 106:605-12.

15. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med 2001; 161:996-1002.

16. Wilhelmsen L, Rosengren A, Eriksson H, Lappas G. Heart failure in the general population of men--morbidity, risk factors and prognosis. J Intern Med 2001; 249:253-61.

17. Rubin J, Matsushita K, Ballantyne CM, Hoogeveen R, Coresh J, Selvin E. Chronic hyperglycemia and subclinical myocardial injury. J Am Coll Cardiol 2012; 59:484-9.

18. Pervanidou P, Akalestos A, Bastaki D, Apostolakou F, Papassotiriou I, Chrousos G. Increased circulating High-Sensitivity Troponin T concentrations in children and adolescents with obesity and the metabolic syndrome: A marker for early cardiac damage? Metabolism 2012.

19. Turkbey EB, McClelland RL, Kronmal RA, et al. The impact of obesity on the left ventricle: the Multi-Ethnic Study of Atherosclerosis (MESA). JACC Cardiovasc Imaging 2010; 3:266-74.

20. Barouch LA, Gao D, Chen L, et al. Cardiac myocyte apoptosis is associated with increased DNA damage and decreased survival in murine models of obesity. Circ Res 2006; 98:119-24.

21. Zhou YT, Grayburn P, Karim A, et al. Lipotoxic heart disease in obese rats: implications for human obesity. Proc Natl Acad Sci U S A 2000; 97:1784-9.

22. Vincent HK, Powers SK, Dirks AJ, Scarpace PJ. Mechanism for obesity-induced increase in myocardial lipid peroxidation. Int J Obes Relat Metab Disord 2001; 25:378-88.

23. Garg S, Narula J, Chandrashekhar Y. Apoptosis and heart failure: clinical relevance and therapeutic target. J Mol Cell Cardiol 2005; 38:73-9.

Table 1: Baseline Characteristics of the ARIC Study Population at Visit 4 (1996-1999), Stratified by BMI Category

	Normal Weight N=2,448	Overweight N=3,800	Obese N=2,118	Severely Obese N=1,141	p value
Mean Age, in years (SE)	62.9 (0.1)	62.7 (0.1)	62.4 (0.1)	61.6 (0.2)	<0.0001
Female – %	64.6	51.0	55.0	74.2	0.003
African American – %	13.5	20.2	27.2	33.4	<0.001
Current Smokers – %	21.5	14.1	9.8	8.7	<0.001
Mean alcohol Intake, in grams/week (SE)	39.2 (1.7)	36.9 (1.4)	28.8 (1.8)	15.8 (1.5)	<0.0001
Mean systolic blood pressure, in mmHg (SE)	123.1 (0.4)	126.8 (0.3)	129.5 (0.4)	132.4 (0.5)	<0.0001
Hypertension – %	31.5	42.1	51.7	62.7	<0.001
Diabetes – %	6.0	12.8	20.4	29.6	<0.001

Mean LDL-C, in mg/dl (SE)	119.4 (0.7)	124.4 (0.5)	125.3 (0.8)	122.6 (1.0)	<0.0001
Mean HDL-C, in mg/dl (SE)	57.8 (0.4)	49.4 (0.3)	46.7 (0.3)	46.5 (0.4)	<0.0001
Median triglycerides, in mg/dl (IQR)	103 (75-143)	123 (90-174)	134 (98-190)	132 (98-184)	<0.0001
Median NT-proBNP, in pg.ml (IQR)	80.6 (42.7-139.3)	58.0 (29.1-111.0)	52.8 (25.1-104.1)	59.6 (30.8-117)	<0.01
Mean eGFR, in ml/min/ 1.73 m2 (SE)	82.8 (0.4)	82.5 (0.3)	82.4 (0.4)	84.7 (0.6)	0.0001

Table 2: Adjusted Odds Ratios for the Cross-Sectional Association of Body Mass Index Categories with Elevated Cardiac Troponin T Detected with a Highly Sensitive Assay (hs-cTnT) in Adults without Clinical CVD

	Normal Weight (BMI 18.5-24.9 kg/m²) N=2,448	**Overweight (BMI 25-29.9 kg/m²) N=3,800**	**Obese (BMI 30-34.9 kg/m²) N=2,118**	**Severely Obese (BMI ≥ 35 kg/m²) N=1,141**
Odds Ratios (95% CI) for High hs-cTnT (≥14 ng/L)*				
Model 1	1.0 (Ref)	1.56 (1.24-1.96)	2.24 (1.76-2.87)	2.69 (2.03-3.56)
Model 2	1.0 (Ref)	1.28 (1.01-1.63)	1.89 (1.47-2.44)	3.14 (2.33-4.22)
Model 3	1.0 (Ref)	1.17 (0.91-1.52)	1.60 (1.21-2.12)	2.20 (1.59-3.06)

Odds Ratios (95% CI) for Measurable hs-cTnT (≥3 ng/L)†				
Model 1	1.0 (Ref)	1.32 (1.19-1.48)	1.67 (1.47-1.90)	1.79 (1.52-2.10)
Model 2	1.0 (Ref)	1.04 (0.93-1.17)	1.37 (1.19-1.57)	1.86 (1.57-2.21)
Model 3	1.0 (Ref)	1.03 (0.91-1.17)	1.29 (1.11-1.49)	1.66 (1.39-1.99)

Model 1: Adjusted for age

Model 2: Adjusted for Model 1 variable plus sex, race, and smoking status

Model 3: Adjusted for all variables in Model 2 variables plus DM, HTN, LDL-C, HDL-C, triglycerides, alcohol intake, NT-proBNP and estimated GFR

*Reference for high hs-cTnT = not high hs-cTnT

†Reference for measurable hs-cTnT = undetectable hs-cTnT

Table 3: Incidence Rates and Hazard Ratios for Incident HF Associated with Higher BMI and hs-cTnT Categories

		Normal Weight (N=2,448)	Overweight (N=3,800)	Obese (N=2,118)	Severely Obese (N=1,141)	p value per 5-point higher BMI
Undetectable hs-cTnT	Incidence Rate*	3.14	3.16	4.96	7.26	<0.001
	HR† (95% CI)	1.00 Reference	0.99 (0.64-1.53)	1.58 (0.99-2.52)	2.19 (1.33-3.62)	
	Incidence Rate*	5.99	7.12	8.61	17.12	

						<0.001
Measurable hs-cTnT	HR† (95% CI)	1.69 (1.14-2.52)	1.97 (1.36-2.87)	2.30 (1.56-3.39)	4.16 (2.82-6.15)	
High hs-cTnT	Incidence Rate*	26.57	29.20	32.70	40.55	<0.05
	HR† (95% CI)	6.10 (3.61-10.32)	5.58 (3.58-8.70)	6.76 (4.29-10.65)	9.20 (5.67-14.93)	

Crude incidence rates and adjusted hazard ratios for incident HF associated with higher BMI within each hs-cTnT category. Note that each 5-point higher increment of BMI was associated with increased HF risk among individuals with undetectable (p<0.001), measurable (p<0.001) and high hs-cTnT (p<0.05).

*Incident HF events per 1,000 person-years

†Adjusted for age, sex, race, smoking status, diabetes mellitus, hypertension, LDL-C, HDL-C,

triglycerides, alcohol intake, NT-proBNP and estimated GFR

Figure 1. Distribution of Cardiac Troponin T Detected with a Highly Sensitive Assay (hs-cTnT) in the ARIC Population without Clinical CVD, Stratified by BMI Category
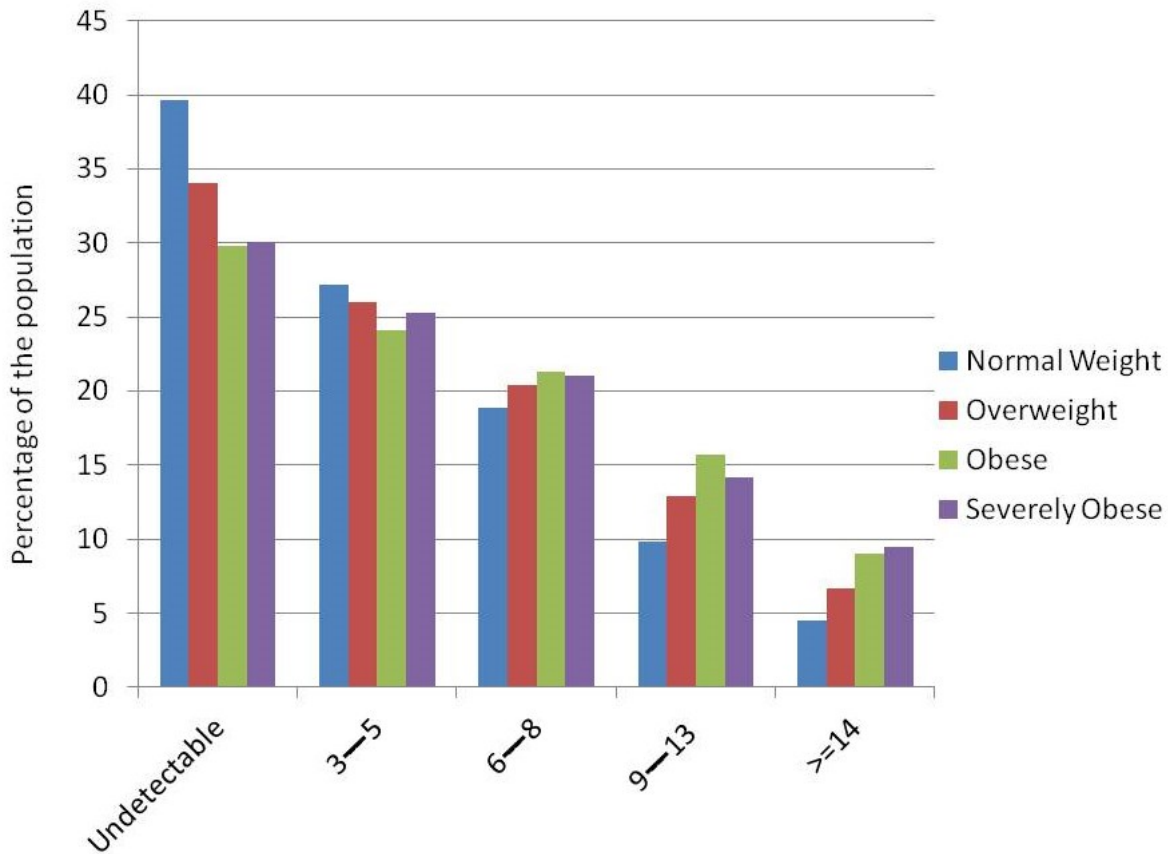
Hs-cTnT levels are reported in ng/L

Figure 2. Cross-Sectional Association of BMI with High hs-cTnT Levels in Restricted Cubic Spline Model

Adjusted for age, sex, race, smoking status, DM, HTN, LDL-C, HDL-C, triglycerides, alcohol intake, NT-proBNP and estimated GFR. Restricted cubic spline centered at the median BMI.

Figure 3. Adjusted Hazard Ratios for Incident HF Associated With Higher BMI Categories
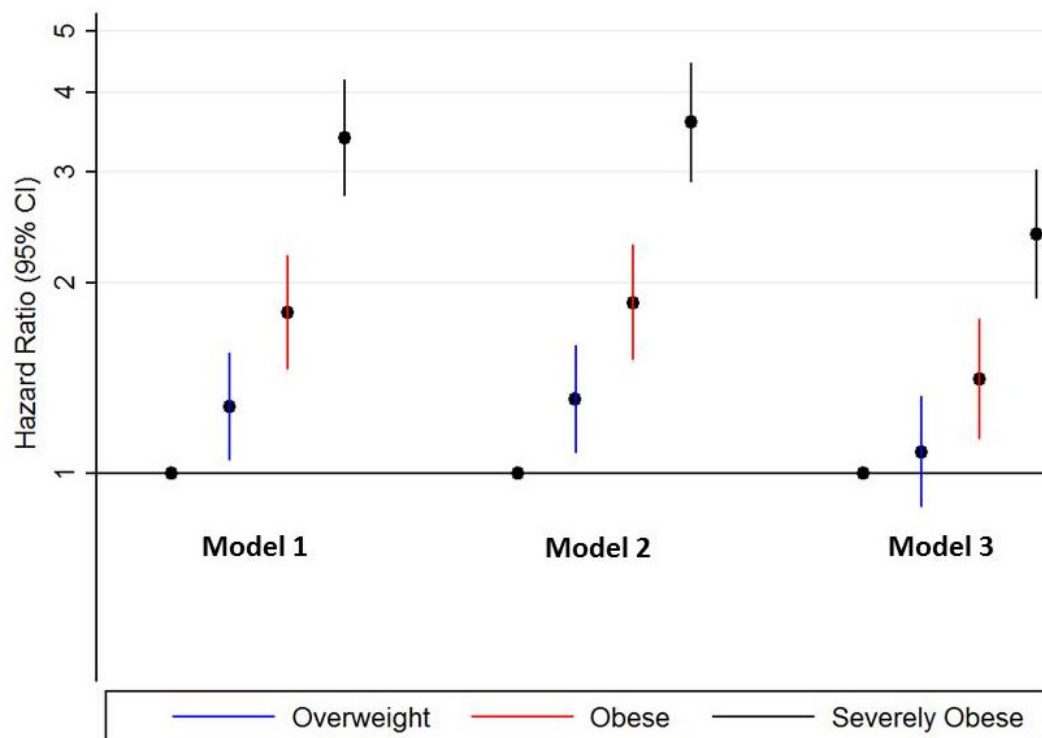
Model 1: Adjusted for age

Model 2: Adjusted for Model 1 variable plus sex, race, and smoking status

Model 3: Adjusted for all variables in Model 2 variables plus DM, HTN, LDL-C, HDL-C, triglycerides, alcohol intake, NT-proBNP and estimated GFR

Figure 4. Combined Associations of BMI Categories and Hs-cTnT Levels with Risk of Incident HF
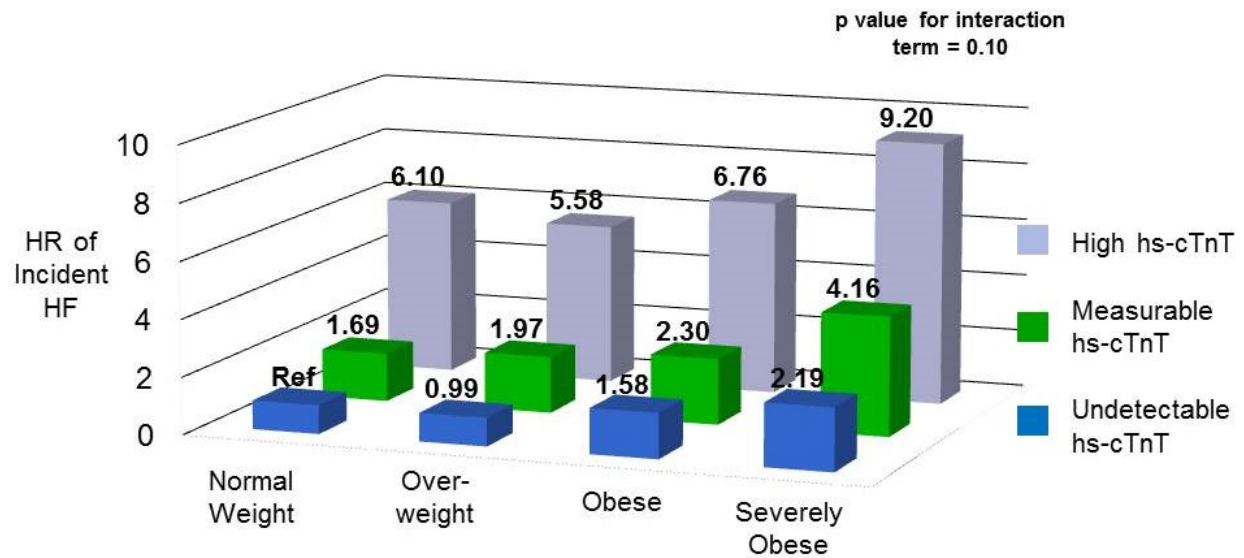
Adjusted for age, sex, race, smoking status, DM, HTN, LDL-C, HDL-C, triglycerides, alcohol intake, NT-proBNP and estimated GFR

Figure 5: Cross-Sectional Association of BMI with Continuous hs-cTnT Levels in Linear Spline Model
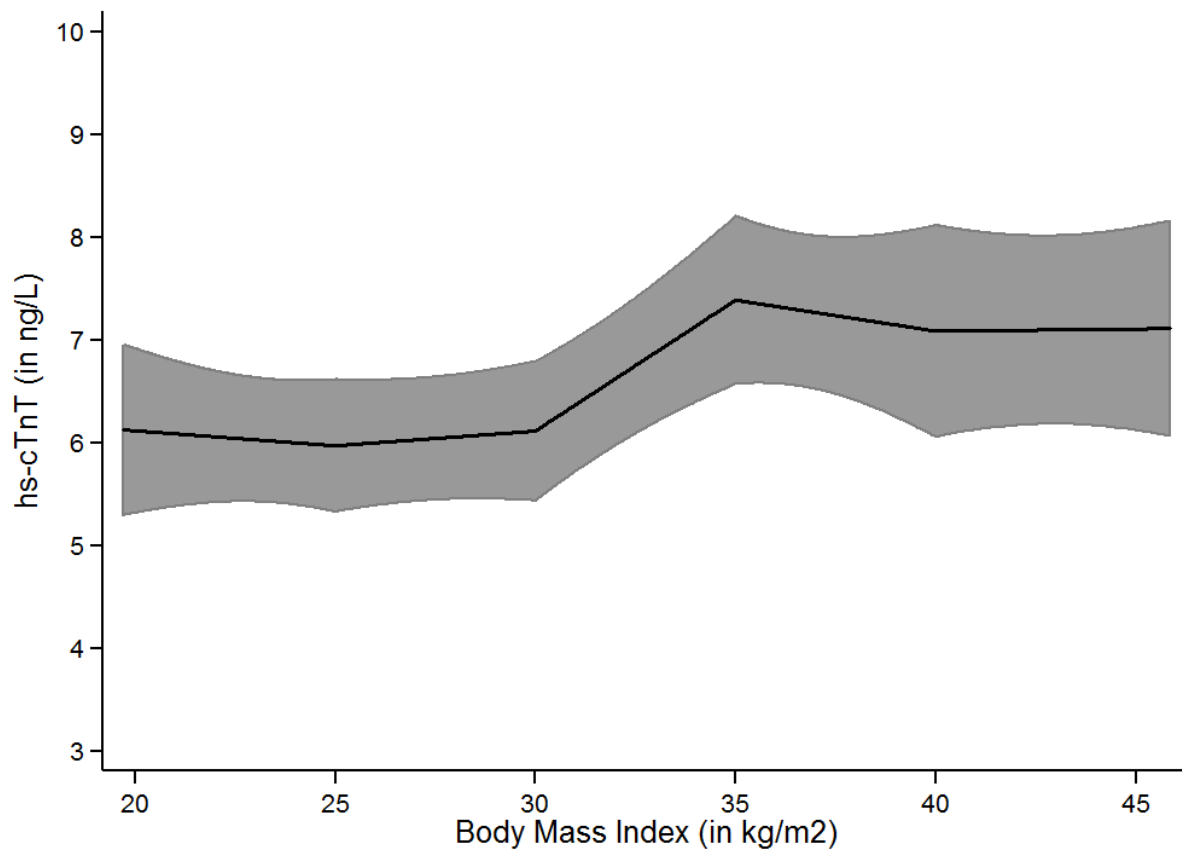
Adjusted for age, sex, race, smoking status, diabetes mellitus, hypertension, LDL-C, HDL-C, triglycerides, alcohol intake, NT-proBNP and estimated GFR

Figure 6. Prospective Association of Continuous hs-cTnT with Incident HF in Restricted Cubic Spline Model
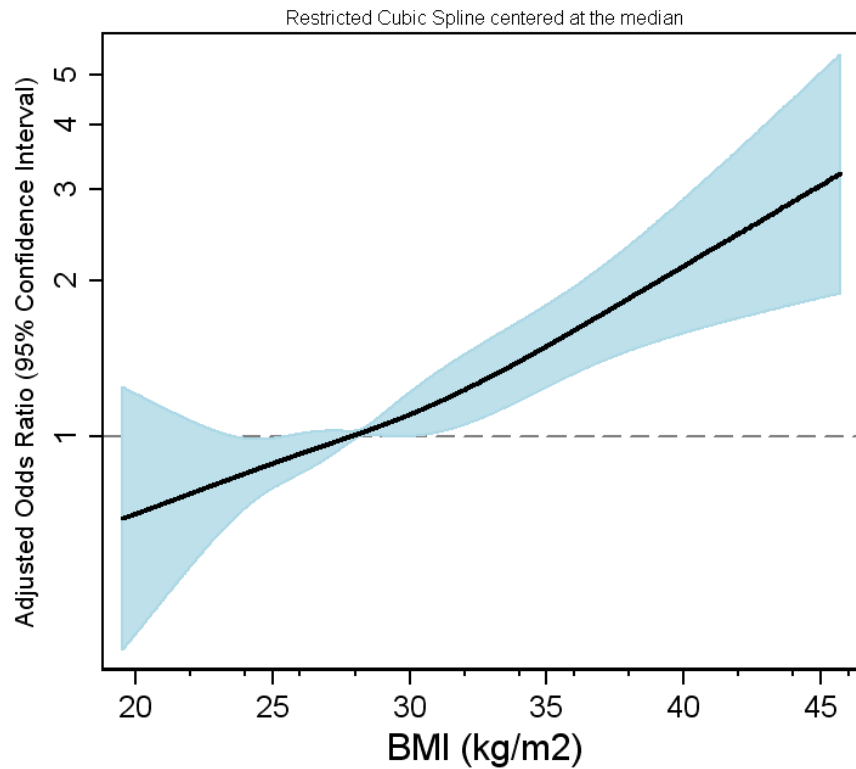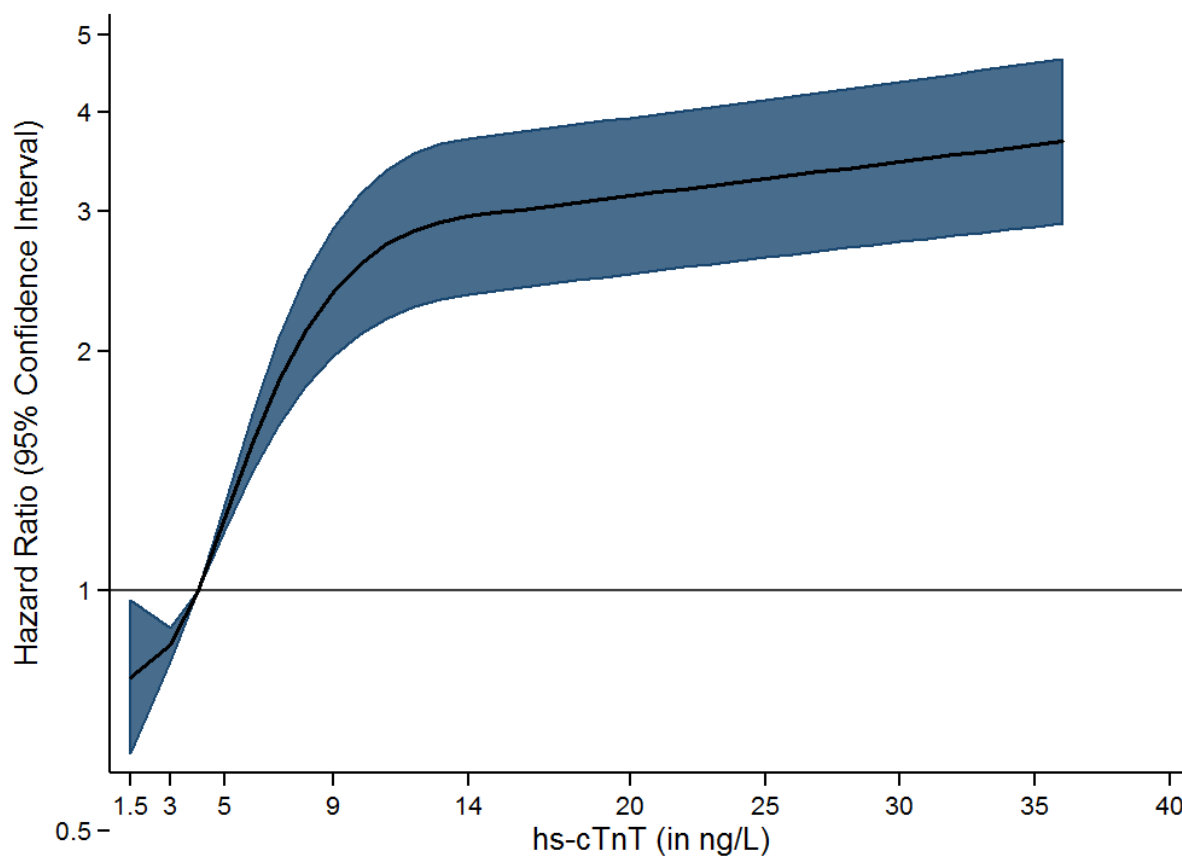

Adjusted for age, sex, race, smoking status, diabetes mellitus, hypertension, LDL-C, HDL-C, triglycerides, alcohol intake, NT-proBNP and estimated GFR

*Please note that a manuscript detailing the work in Aim 2 has been published in the Journal of the American College of Cardiology (JACC): Heart Failure

Chapter 4 – Aim 3: Weight History and Incident Heart Failure Risk

Abstract

Background: Current obesity is a potent risk factor for incident HF. However, there are limited data regarding whether weight history influences HF risk, and if so, what aspects of weight history provide the most prognostic information regarding HF risk beyond current weight.

Methods: We analyzed 9,284 participants at Visit 4 (1996-98) of the Atherosclerosis Risk in Communities (ARIC) study, with BMI $\geq$18.5 kg/m^2, no history of CHD or HF and weight history data from ARIC Visits 1 (1987-89) through 4. We additionally utilized self-reported weight at age 25. BMI at each time point was categorized as normal weight (18.5-<25 kg/m^2), overweight (25-<30 kg/m^2) or obese ($\geq$30 kg/m^2). We cross-tabulated BMI categories at Visit 4 ("current BMI") and Visit 1, and at Visit 4 and age 25, and constructed Cox regression models to assess associations with incident HF occurring after Visit 4 through December 31, 2013. We additionally compared the model quality associated with various weight history metrics, including past BMI measures, duration of obesity and cumulative BMI, when added to a regression model including current BMI.

Results: Over a median 16 years of follow-up, there were 1,229 incident HF events. Higher HF risk was seen with increases in BMI category from Visit 1 to Visit 4 (HR 1.20 [1.03-1.40]) and from age 25 to Visit 4 (HR 1.43 [1.24-1.65]) relative to a stable weight category, with no significant associations for decreases in BMI category. Within each current BMI category, a higher past BMI category (at Visit 1 or age 25) was associated with increased HF risk, with those

with obesity at both time points having the highest risk (HRs 2.48 [2.08-2.96] for obesity at Visit 1 and Visit 4 and 3.60 [2.74-4.74] for obesity at age 25 and Visit 4. Among weight history metrics, cumulative BMI from age 25 to Visit 4 improved model quality for risk of incident HF the most.

Conclusions and Relevance: Weight history provides important prognostic information beyond current weight regarding HF risk, with cumulative weight from young adulthood to late middle age providing particularly useful prognostic information. Weight control across the adult life span should be emphasized for optimal HF prevention.

Current obesity is a potent and well-established risk factor for the development of heart failure (HF)[1-4]. Obesity likely has a stronger association with incident HF than with other major forms of cardiovascular disease (CVD), such as CHD and stroke[5]. Additionally, prospective studies demonstrate that among the major forms of CVD, the link between obesity and HF may be the only one unexplained by the traditional risk factors associated with obesity such as hypertension, diabetes and dyslipidemia, suggesting an association that is partially independent of these risk factors[5;6]. However, in evaluating the link between obesity and HF, most analyses have utilized anthropometric measurements from a single time point, which does not fully account for the effects of long-term obesity and weight changes on HF risk. There is presently limited knowledge about how weight history influences the likelihood of developing future HF.

Primarily retrospective analyses among adults with obesity suggest associations of the duration of morbid obesity with abnormal cardiac remodeling, systolic and diastolic dysfunction and the probability of prevalent HF[7;8]. However, such retrospective data are subject to the potential for recall bias[9], which could lead to the misclassification of obesity status. In contrast, there are very few prospective analyses evaluating the relationship between adult weight history and the development of HF. Furthermore, it is currently unknown which aspects of weight history provide the most prognostic information regarding HF risk beyond current weight. Characterizing the association between weight history and incident HF could inform risk

assessments and help refine recommendations for weight management to reduce the likelihood of developing HF.

We therefore evaluated the relationship between adult weight history and incident HF within the community-based, prospective, predominately bi-racial Atherosclerosis Risk in Communities (ARIC) Study. With serial anthropometric measurements across the adult life span, detailed risk factor characterization and extended follow-up for HF events, the ARIC study data provides an excellent opportunity to understand whether, and if so how, weight history influences HF risk.

Methods:

ARIC is a prospective cohort of 15,792 individuals recruited from 4 U.S. population centers in 1987-89: Washington County, MD; Forsyth County, NC; Jackson, MS; and the suburbs of Minneapolis, MN. The design of ARIC has previously been fully described[10]. Participants were aged 45-64 years at the time of recruitment. Following the baseline visit, participants were examined at 3 subsequent study visits spaced approximately three years apart: Visit 2 (1990-92), Visit 3 (1993-95) and Visit 4 (1996-98). An additional 5th study visit was completed in 2011-2013. Participants underwent a history and examination, including anthropometric measurements, at each of the ARIC study visits. Continuous active surveillance for incident cardiovascular events was performed for all participants from the baseline visit until December 30, 2013. All ARIC participants provided informed consent and the institutional review boards associated with each ARIC site approved the study protocol.

To leverage the full weight history data within ARIC in evaluating the association between weight history and incident HF, this analysis included participants at ARIC Visit 4 who had attended each of the prior study visits and had anthropometric measurements performed at each time point (Figure 1). We then assessed the relationship of weight history from ARIC Visit 1 through Visit 4 (a 9-year span in middle age) with the risk of incident HF occurring after Visit 4. We additionally calculated BMI from participants' self-reported weight at age 25, a variable that was obtained by questionnaire at Visit 1, and utilized this variable to evaluate the association of weight history from age 25 through Visit 4 (at which time the mean age was 63 years) with incident HF occurring after Visit 4.

Of 11,656 Visit 4 participants, we excluded individuals with HF or CHD at or prior to Visit 4 (self-reported HF or CHD at Visit 1; or HF-related hospitalization or death, adjudicated non-fatal myocardial infarction or coronary revascularization event, or silent myocardial infarction by ECG criteria at or prior to Visit 4; n = 1,572). We additionally excluded individuals missing data on prior HF or CHD at Visit 1 (n=214); those missing BMI data at Visits 1, 2, 3 or 4 (n=417); those persons with BMI < 18.5 at any of the study visits (n = 138); and the limited number of individuals not of black or white race (n = 31), yielding a study population of 9,284 individuals.

The primary exposure variable was body-mass index (BMI), based on measured weight and height at each study visit and calculated in kg/m^2. BMI was categorized as normal weight (18.5 to < 25 kg/m^2), overweight (25.0 to < 30 kg/m^2) and obese ($\geq$ 30.0 kg/m^2). The BMI at Visit 4, the baseline for the prospective analyses of incident HF events, was defined as the "current BMI". BMI measurements from each of the prior ARIC study visits and self-reported BMI at age 25 were used as "past BMIs" for assessing weight history. Information regarding

covariates was obtained at Visit 4. Smoking status was categorized as current, former or never smoker. Alcohol use was calculated in grams per week. Systolic blood pressure was measured three times and the mean of the last two measures was used for analysis. Diabetes was defined as a prior diagnosis of diabetes, the use of hypoglycemic medications, a fasting blood glucose ≥ 126 mg/dl or a non-fasting blood glucose ≥ 200 mg/dl. Enzymatic assays were used to measure total cholesterol (TC), HDL cholesterol (HDL-C) and triglycerides, and LDL cholesterol was calculated by using the Friedewald equation for participants with triglycerides < 400 mg/dl (TC – HDL-C – (triglycerides/5)).

Incident HF was defined as the first hospitalization or death related to HF, identified using discharge codes[11]. In early follow-up, ICD-9 code 428 was used to identify both hospitalizations and deaths related to HF, whereas in later follow-up ICD-10 code I50 was used to identify HF deaths. After 2004, HF events were additionally adjudicated by an expert panel. Follow-up for incident HF events was available through December 31, 2013.

Statistical Analysis

We performed univariate comparisons of participant characteristics across BMI categories at Visit 4, using the chi-squared test for categorical variables and ANOVA for continuous variables.

We constructed Cox proportional hazards models to estimate hazard ratios and 95% confidence intervals for the association of various aspects of weight history with incident HF. Regression models were adjusted for the potential confounders age, race, sex, smoking status, alcohol use, education level and occupation. In sensitivity analyses, we additionally adjusted for

Visit 4 measures of traditional risk factors potentially along the causal pathway between obesity and HF, including systolic blood pressure, anti-hypertensive medications, diabetes, LDL-C, HDL-C, triglycerides and estimated GFR.

We evaluated the association of changes across BMI categories from Visit 1 to Visit 4 with the risk of incident HF after Visit 4. We compared those individuals who transitioned from normal weight to overweight or obese or from overweight to obese from Visit 1 to Visit 4 (those who increased in BMI category) to those who remained in the normal weight or overweight categories at both time points. We similarly compared those who transitioned from obese to overweight or normal weight or from overweight to normal weight from Visit 1 to Visit 4 (those who decreased in BMI category)to those who remained in the obese or overweight categories at both time points. We performed identical analyses assessing the associations of increases or decreases in BMI category from Age 25 to Visit 4 with incident HF after Visit 4.

To assess the association of past BMI category with HF risk within each current BMI category, we performed cross-tabulations of BMI categories at Visit 4 and Visit 1 and estimated the risk of incident HF occurring after Visit 4 for each subgroup, with those individuals with normal weight at both time points serving as the reference group. We performed the same analysis using cross tabulations of BMI categories at age 25 and Visit 4. We also performed similar cross-tabulations using waist circumference tertiles at Visit 1 and Visit 4 as an alternative measure of adiposity. In sensitivity analyses, to assess the combined associations of past and present BMI categories with incident HF independent of obesity-associated risk factors, we additionally adjusted regression models for diabetes, systolic blood pressure, anti-hypertensive medication use, LDL-C, HDL-C, triglycerides and estimated GFR.

We tested for multiplicative interactions of the above associations with race, gender and age group ($\geq$ or < 65 at Visit 4).

We then evaluated and compared the prognostic value associated with several different weight history metrics: BMI at Visit 1 (mean age 54 years); BMI at age 25; absolute BMI change from Visit 1 to Visit 4; absolute BMI change from age 25 to Visit 4; cumulative BMI from Visit 1 to Visit 4 (approximation of the area under the curve for BMI, using the equation: [$\frac{1}{2}BMI_{V1}$ $+BMI_{V2} +BMI_{V3} + \frac{1}{2}BMI_{V4}$] x [total # of years]); cumulative BMI from age 25 to Visit 4 (approximating the area under the curve for BMI using the equation: [$(BMI_{T1} +BMI_{T2})/2$ x [duration in years between T_1 and T_2], for every 2 consecutive timepoints from age 25 through Visit 4, and summing the values for each of the intervals); and duration of obesity (obesity at each time point coded as a dichotomous variable (0 or 1) and the presence of obesity at each time point multiplied by the duration of obesity in years between visits). Each weight history metric was scaled by its standard deviation for comparability. We then added each weight history metric separately to a regression model that included current BMI as a covariate, with the outcome being incident HF after Visit 4. We estimated hazard ratios and 95% confidence intervals for the HF risk associations for current weight and each weight history metric (per 1-SD) when both variables were simultaneously included in the regression model. For each weight history metric we additionally assessed model quality, as reflected by Aikake's Information Criteria (AIC: -2logL + 2*(# of variables in the model)), which takes into account both model fit and the complexity of the regression model[12]. A lower AIC value indicates better model quality.

To further evaluate the association between incident HF and cumulative weight, we created a variable of "BMI years". The BMI variable was centered at 25 kg/m^2 (the upper limit of normal weight) and the average BMI over all of the study time points was multiplied by the

time interval from the first available BMI assessment (at age 25) to age at Visit 4. For example, an individual with an average BMI of 30 kg/m^2 for 20 years would have 100 BMI years (5 BMI units above 25 kg/m^2 x 20 years = 100). We evaluated the HF risk associated with each 100 higher BMI years and constructed restricted cubic spline models (using Harrel's method, with 4 knots at -143.1, -3.3, 111.7 and 372.8 kg/m^2*years) to further characterize the continuous association between BMI years and incident HF.

All p values presented are 2-sided. Statistical analyses were performed using Stata 13.1 (StataCorp, College Station, TX). Dr. Ndumele had full access to all of the data in the study and takes responsibility for data integrity and the data analysis.

Results

Characteristics of the study population, stratified by BMI category at Visit 4, are displayed in Table 1. Individuals with obesity were more likely to be African American, to have diabetes and use anti-hypertensive medications, were less likely to be current smokers, and had higher mean systolic blood pressure and lower average levels of HDL-C.

During a median 15.8 years of follow-up, there were 1,229 incident HF events. Over the 9-year interval from Visit 1 to Visit 4, 72% of individuals remained in a stable BMI category, whereas 23% of individuals increased in BMI category over time and 5% decreased (Figure 2a). Relative to those with a stable BMI category over time, those who increased in BMI category from Visit 1 to Visit 4 had a HR of 1.20 for incident HF (95% CI: 1.03-1.40), whereas no significant risk association was seen for those who decreased in BMI category (HR 0.95; 95% CI: 0.75-1.21).

During the longer interval from Age 25 to Visit 4 (given the mean age of 63 at Visit 4, approximately a 38 year interval), we saw less weight stability: 33% remained in a stable BMI category, whereas 65% increased and 2% decreased (Figure 2b). Those who increased in BMI category from age 25 to Visit 4 had a HR of 1.43 (1.24-1.65) for incident HF relative those in a stable BMI category. For the small number of individuals who decreased in BMI category over that time period, there was a non-significant trend towards lower HF risk (HR 0.75; 95% CI 0.49-1.14).

When evaluating cross-tabulations of the current BMI category (Visit 4) and BMI category at Visit 1 (Table 2), we found that within each current BMI category, having a higher past BMI category was associated with a greater risk of incident HF. Overall, those individuals with obesity at both time points had the highest risk for HF (HR 2.48; 95% CI: 2.08-2.96). We found a similar pattern, but stronger associations, when examining cross tabulations of current BMI category and BMI category at age 25 (Figure 3 and Table 2). Among those individuals with current obesity, progressively higher HF risk was seen for those with prior normal weight (HR 1.89; 95% CI: 1.56-2.29), prior overweight (HR 2.28; 95% CI: 1.83-2.83) and prior obesity (HR 3.60; 95% CI: 2.74-4.74) at age 25. Similar patterns, although with attenuated associations, were seen in sensitivity analyses additionally adjusting for Visit 4 measures of traditional risk factors along the causal pathway between obesity and HF, including blood pressure, diabetes and lipid measures (Table 3), with higher past BMI category continuing to be associated with greater HF risk within each current BMI category.

These findings were similar across subgroups defined by race, gender and age, with no significant interactions seen between changes in weight category over time and these demographic variables on the outcome of incident HF. We saw findings analgous to those using

91

BMI categories when we examined cross-tabulations of waist circumference (divided into tertiles) at Visit 1 and Visit 4, with those in the top tertile of waist circumference at both time points having the highest risk of HF (HR 2.56; 95% CI: 2.16-3.04) (Table 4).

The prognostic information associated with various weight history metrics (per 1-SD) when separately added to a regression model that included current BMI is displayed in Table 5. In the model including current BMI alone, each 1-SD higher increment in current BMI was associated with a 47% increased risk in HF and this base model had an AIC of 20,956 (measure of model quality with only current weight and covariates in model). Each of the weight history metrics demonstrated significant associations with incident HF when added to a regression model that included current BMI. The greatest improvement in model quality was associated with adding cumulative BMI from age 25 to Visit 4 to current BMI and other covariates in the regression model, with an AIC of 20,664 (the lowest A1C reflecting the best model quality). The next greatest improvement in model quality was seen with the addition of BMI at age 25 to current BMI and other covariates in the regression model, with an AIC of 20,670.

We further examined the association of cumulative weight from age 25 to V4 with HF risk by estimating the association between BMI years and incident HF. The distribution of BMI years within the study population ranged from -274 to 1,205 (kg/m^2) * years, with individuals with negative values being those who had BMI measurements less than 25 kg/m^2 at one or more of the study time points. We found a strong positive association between higher BMI years and incident HF risk, as displayed in the restricted cubic spline in Figure 4. On average, every 100 higher BMI years was associated with a 22% higher risk of developing HF (95% CI: 1.18-1.25).

Discussion

In this prospective analysis of 9,284 participants in a community-based cohort with serial measurements of weight over time, we found that weight history provided significant prognostic information beyond current weight regarding HF risk. Increasing BMI category over time was associated with greater HF risk. Additionally, at each level of current weight, a higher past weight was associated with increased risk, with those individuals with obesity at both current and past time points having the greatest HF risk. These findings persisted after additional adjustment for several obesity-associated risk factors, including hypertension, diabetes and dyslipidemia. Among various weight history metrics added to a regression model including current BMI, cumulative weight from young adulthood to late middle age was linked to the greatest improvements in model quality, and may thereby provide the best prognostic information beyond current weight regarding HF risk.

There have been few prospective investigations regarding the impact of weight history on HF risk. One prospective analysis from the CARDIA study demonstrated that a longer duration of obesity from young adulthood to early middle age was associated with concentric LV remodeling and trends towards decreased systolic function[13]. Another analysis from CARDIA suggested that cumulative weight provides prognostic information regarding HF risk[14]. However, that analysis incorporated adiposity measurements primarily from young adults and included only 33 HF cases. The current analysis utilizes data on weights from across the adult lifespan (from age 25 to age 75 for the oldest participants) and over 1,200 incident HF events to evaluate the prognostic information associated with various weight history metrics. Evaluating weights from young adulthood through late middle age and elderly years, with subsequent extended follow-up for HF events, allowed for a more complete assessment of the chronic effects of

excess weight on the likelihood of developing HF over the life course. Additionally, the large number of events allowed us to evaluate the consistency of our findings across key demographic subgroups, which was not possible in prior analyses.

The associations of past obesity and greater cumulative weight with incident HF in this analysis suggest that chronic effects of excess weight on the myocardium over time increase the risk of future HF. The additional finding that the association between weight history and future HF persisted after adjustment for obesity-associated risk factors such as hypertension, diabetes and dyslipidemia, suggests effects of long term obesity on myocardial dysfunction and HF risk that are independent of these comorbid conditions. Obesity is independently linked to abnormalities of cardiac structure and function that predispose to the development of clinical HF[15-17]. Several processes have been hypothesized to contribute to the relationship between obesity and myocardial dysfunction, including increased metabolic demand and expanded blood volume[16;18], low-grade myocardial injury[19-21], the effects of adipokines and cytokines associated with obesity[22-28] and the toxic effects of fat accumulation within the myocardium and other ectopic foci[21;28-32]. Defining the precise pathophysiologic mechanisms by which weight history predisposes to the development of HF will help to better delineate at-risk populations and to inform additional strategies for HF prevention.

In terms of clinical implications, this analysis highlights the importance of maintaining a healthy weight to reduce HF risk. Those remaining in a stable BMI category had significantly less HF risk than those who experienced an increase in BMI category over time, with those individuals maintaining a normal weight having the lowest overall risk of incident HF. Additionally, while any history of excess weight was associated with HF risk within each current weight category, the delay of weight gain was associated with less HF risk. For example, among

those with current obesity, prior overweight and obesity at age 25 were associated with greater

HF risk than prior overweight and obesity at Visit 1 in middle-age (mean age 54 years). In

addition, there was an almost 2-fold difference in risk between participants with current obesity

who were also obese at age 25 (HR 3.60; 95% CI: 2.74-4.74) and those who had normal weight

at age 25 but developed obesity later in life (HR 1.89; 95% CI: 1.56-2.29). This indicates that

weight control even from young adulthood likely significantly impacts the risk of HF later in life.

Additionally, cumulative weight, an integrated measure of prior weights from each time point,

provided the most useful prognostic information beyond current weight regarding HF risk, and

cumulative weight expressed in BMI years had a potent relationship with incident HF. The

concept of BMI years may be particularly useful for describing the importance of long term

weight control for reducing HF risk to younger adults. This metric will need to be assessed in

additional cohorts and settings to evaluate its potential utility as a clinical tool for

prognosticating and communicating HF risk related to excess weight.

Given that this is an observational cohort study, with the majority of the individuals

gaining weight over time and unclear precipitants for the limited amount of weight loss that was

observed, this analysis is not well equipped to evaluate the effects of intentional weight loss on

HF risk. Nonetheless, we observed a trend towards decreased risk among the small number of

participants whose BMI category decreased from young adulthood to late middle age. Weight

loss has been associated with improvements in myocardial function and structure, particularly in

the context of bariatric surgery[33;34], and is recommended in current guidelines as a component of

strategies to prevent HF[35]. However, there is a dearth and urgent need for interventional studies

of weight loss to validate the benefits of weight reduction on decreasing HF risk among those

with obesity.

This study has certain limitations that should be considered. Residual confounding is always a concern in observational studies. The etiology and intentionality of weight changes over time is unknown, but this would be of greatest concern with weight loss, which was uncommon in this cohort study. While the majority of the analysis utilized weight measurements obtained during serial ARIC examinations, weight at age 25 was self-reported, and there were no available measurements between age 25 and the first ARIC examination. This study does not account for medical treatments administered during follow-up that may have affected the development of heart failure. Additionally, the use of discharge codes for HF diagnosis may have led to case misclassification. However, the findings from this large, biracial community-based cohort are broadly representative, and repeated measures of weight over time in addition to extended follow-up for HF events have allowed for a detailed prospective assessment of the relationship between weight history and incident HF.

In conclusion, weight history adds significant prognostic information beyond current weight, with both prior elevated weight and increasing weight over time associated with increased HF risk. Among various weight history metrics, cumulative weight from young adulthood onwards may provide the best prognostic information beyond current weight regarding the risk of incident HF. Strategies to promote weight management across the adult life span should be developed and emphasized in order to facilitate optimal HF prevention.

Reference List

(1) Aune D, Sen A, Norat T et al. Body Mass Index, Abdominal Fatness, and Heart Failure Incidence and Mortality: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies. *Circulation* 2016;133:639-649.

(2) Del Gobbo LC, Kalantarian S, Imamura F et al. Contribution of Major Lifestyle Risk Factors for Incident Heart Failure in Older Adults: The Cardiovascular Health Study. *JACC Heart Fail* 2015;3:520-528.

(3) Kenchaiah S, Evans JC, Levy D et al. Obesity and the risk of heart failure. *N Engl J Med* 2002;347:305-313.

(4) Poirier P, Giles TD, Bray GA et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2006;113:898-918.

(5) Ndumele CE, Matsushita K, Lazo M et al. Obesity and Subtypes of Incident Cardiovascular Disease. *J Am Heart Assoc* 2016;5.

(6) Morkedal B, Vatten LJ, Romundstad PR, Laugsand LE, Janszky I. Risk of myocardial infarction and heart failure among metabolically healthy but obese individuals: HUNT (Nord-Trondelag Health Study), Norway. *J Am Coll Cardiol* 2014;63:1071-1078.

(7) Alpert MA, Lambert CR, Panayiotou H et al. Relation of duration of morbid obesity to left ventricular mass, systolic function, and diastolic filling, and effect of weight loss. *Am J Cardiol* 1995;76:1194-1197.

(8) Alpert MA, Terry BE, Mulekar M et al. Cardiac morphology and left ventricular function in normotensive morbidly obese patients with and without congestive heart failure, and effect of weight loss. *Am J Cardiol* 1997;80:736-740.

(9) Raphael K. Recall bias: a proposal for assessment and control. *Int J Epidemiol* 1987;16:167-170.

(10) The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol* 1989;129:687-702.

(11) Rosamond WD, Chang PP, Baggett C et al. Classification of heart failure in the atherosclerosis risk in communities (ARIC) study: a comparison of diagnostic criteria. *Circ Heart Fail* 2012;5:152-159.

(12) Akaike H. A new look at the statistical model identification. IEEE Transactions on Automatic Control 19[6], 716-723. 12-6-1974.

(13) Reis JP, Allen N, Gibbs BB et al. Association of the degree of adiposity and duration of obesity with measures of cardiac structure and function: the CARDIA study. *Obesity (Silver Spring)* 2014;22:2434-2440.

(14) Reis JP, Allen N, Gunderson EP et al. Excess body mass index- and waist circumference-years and incident cardiovascular disease: the CARDIA study. *Obesity (Silver Spring)* 2015;23:879-885.

(15) Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. *Physiol Rev* 2008;88:389-419.

(16) Alpert MA. Obesity cardiomyopathy: pathophysiology and evolution of the clinical syndrome. *Am J Med Sci* 2001;321:225-236.

(17) Bello NA, Cheng S, Claggett B et al. Association of Weight and Body Composition on Cardiac Structure and Function in the ARIC Study (Atherosclerosis Risk in Communities). *Circ Heart Fail* 2016;9.

(18) Lavie CJ, Sharma A, Alpert MA et al. Update on Obesity and Obesity Paradox in Heart Failure. *Prog Cardiovasc Dis* 2016;58:393-400.

(19) Barouch LA, Gao D, Chen L et al. Cardiac myocyte apoptosis is associated with increased DNA damage and decreased survival in murine models of obesity. *Circ Res* 2006;98:119-124.

(20) Ndumele CE, Coresh J, Lazo M et al. Obesity, subclinical myocardial injury, and incident heart failure. *JACC Heart Fail* 2014;2:600-607.

(21) Zhou YT, Grayburn P, Karim A et al. Lipotoxic heart disease in obese rats: implications for human obesity. *Proc Natl Acad Sci U S A* 2000;97:1784-1789.

(22) Frankel DS, Vasan RS, D'Agostino RB, Sr. et al. Resistin, adiponectin, and risk of heart failure the Framingham offspring study. *J Am Coll Cardiol* 2009;53:754-762.

(23) Karas MG, Benkeser D, Arnold AM et al. Relations of plasma total and high-molecular-weight adiponectin to new-onset heart failure in adults >/=65 years of age (from the Cardiovascular Health study). *Am J Cardiol* 2014;113:328-334.

(24) McManus DD, Lyass A, Ingelsson E et al. Relations of circulating resistin and adiponectin and cardiac structure and function: the Framingham Offspring Study. *Obesity (Silver Spring)* 2012;20:1882-1886.

(25) Negi SI, Jeong EM, Shukrullah I, Raicu M, Dudley SC, Jr. Association of low plasma adiponectin with early diastolic dysfunction. *Congest Heart Fail* 2012;18:187-191.

(26) Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Obesity and risk of incident heart failure in older men with and without pre-existing coronary heart disease: does leptin have a role? *J Am Coll Cardiol* 2011;58:1870-1877.

(27) Choi EY, Yan RT, Fernandes VR et al. High-sensitivity C-reactive protein as an independent predictor of progressive myocardial functional deterioration: the multiethnic study of atherosclerosis. *Am Heart J* 2012;164:251-258.

(28) Bekwelem W, Lutsey PL, Loehr LR et al. White blood cell count, C-reactive protein, and incident heart failure in the Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol* 2011;21:739-748.

(29) Szczepaniak LS, Dobbins RL, Metzger GJ et al. Myocardial triglycerides and systolic function in humans: in vivo evaluation by localized proton spectroscopy and cardiac imaging. *Magn Reson Med* 2003;49:417-423.

(30) van der Meer RW, Rijzewijk LJ, Diamant M et al. The ageing male heart: myocardial triglyceride content as independent predictor of diastolic function. *Eur Heart J* 2008;29:1516-1522.

(31) Vincent HK, Powers SK, Dirks AJ, Scarpace PJ. Mechanism for obesity-induced increase in myocardial lipid peroxidation. *Int J Obes Relat Metab Disord* 2001;25:378-388.

(32) Wende AR, Abel ED. Lipotoxicity in the heart. *Biochim Biophys Acta* 2010;1801:311-319.

(33) Aggarwal R, Harling L, Efthimiou E, Darzi A, Athanasiou T, Ashrafian H. The Effects of Bariatric Surgery on Cardiac Structure and Function: a Systematic Review of Cardiac Imaging Outcomes. *Obes Surg* 2015.

(34) Owan T, Avelar E, Morley K et al. Favorable changes in cardiac geometry and function following gastric bypass surgery: 2-year follow-up in the Utah obesity study. *J Am Coll Cardiol* 2011;57:732-739.

(35) Yancy CW, Jessup M, Bozkurt B et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013;128:e240-e327.

Table 1: Baseline Characteristics of Study Population, Stratified by BMI Category at Visit 4

	Normal Weight N=2,352	Overweight N=3,748	Obese N=3,184	p value
Mean Age, in years (SD)	62.9 (5.8)	62.8 (5.7)	62.1 (5.5)	<0.001
Female – %	64.8	50.5	61.2	<0.001
African American – %	12.5	19.0	28.7	<0.001
Current Smokers – %	20.8	13.6	9.2	<0.001
Mean systolic blood pressure, in mmHg (SD)	122.7 (19.2)	126.7 (18.1)	130.3 (17.8)	<0.001
Use of anti-hypertensive medication – %	19.6	30.0	44.2	<0.001
Diabetes – %	5.8	12.4	23.3	<0.001
Mean LDL-C, in mg/dl (SD)	119.2 (33.6)	124.4 (32.8)	124.0 (33.8)	<0.001
Mean HDL-C, in mg/dl (SD)	57.9 (18.0)	49.3 (15.5)	46.7 (14.5)	<0.001

Median triglycerides, in mg/dl (IQR)	91 (68-126)	112 (80-160)	128 (92-179)	<0.001
Mean eGFR, in ml/min/ 1.73 m2 (IQR)	80.8 (70.8-93.0)	81.0 (71.0-93.0)	81.3 (70.5-94.4)	0.07
Mean waist circumference, in cm (SD)	87.3 (7.6)	99.2 (7.0)	115.3 (11.3)	<0.001

Table 2. Hazard Ratios (95% CIs) for Associations of Cross-Tabulations of BMI Categories at Visit 4 and at an Earlier Time Point (Visit 1 or Age 25) With Incident HF

BMI Categories at Visit 1 and Visit 4 (9 years apart)				BMI Categories at age 25 (self-reported) and Visit 4			
	Normal Weight at Visit 1	Overweight at Visit 1	Obesity at Visit 1		Normal Weight at age 25	Overweight at age 25	Obesity at age 25
Normal Weight at Visit 4	n=2,123 Ref (1.0)	n=222 1.35 (0.94-1.95)	n=7 n/a	Normal Weight at Visit 4	n=1,953 Ref (1.0)	n=109 1.26 (0.75-2.10)	n=6 n/a
Over-weight at Visit 4	n=1,080 1.10 (0.87-1.40)	n=2,453 **1.33** **(1.11-1.58)**	n=215 **2.18** **(1.58-3.00)**	Over-weight at Visit 4	n=2,883 **1.22** **(1.02-1.45)**	n=615 **1.54** **(1.19-1.99)**	n=64 **2.15** **(1.14-4.06)**
Obesity at Visit 4	n=48 n/a	n=1,050 **1.50** **(1.21-1.87)**	n=2,086 **2.47** **(2.08-2.93)**	Obesity at Visit 4	n=1,868 **1.87** **(1.55-2.24)**	n=924 **2.18** **(1.76-2.70)**	n=292 **3.42** **(2.60-4.48)**

n/a = associations cannot be estimated due to the high imprecision resulting from the small

sample size (< 50 individuals) in this group

Adjusted for age, sex, race, cigarette smoking, alcohol use, educational level and occupation

Table 3. Hazard Ratios (95% CIs) for Associations of Cross-Tabulations of BMI Categories at Visit 4 and at an Earlier Time Point (Visit 1 or Age 25) With Incident HF in Regression Model Adjusted for Traditional Risk Factors Associated with Obesity

BMI Categories at Visit 1 and Visit 4 (9 years apart)				BMI Categories at age 25 (self-reported) and Visit 4			
	Normal Weight at Visit 1	Overweight at Visit 1	Obesity at Visit 1		Normal Weight at age 25	Overweight at age 25	Obesity at age 25
Normal Weight at Visit 4	n=2,123 Ref (1.0)	n=222 1.22 (0.85-1.76)	n=7 n/a	Normal Weight at Visit 4	n=1,953 Ref (1.0)	n=109 1.22 (0.73-2.04)	n=6 n/a
Over-weight at Visit 4	n=1,080 1.00 (0.78-1.27)	n=2,453 1.10 (0.92-1.32)	n=215 **1.65** **(1.19-2.28)**	Over-weight at Visit 4	n=2,883 1.04 (0.87-1.25)	n=615 1.25 (0.96-1.62)	n=64 1.79 (0.91-3.50)
Obesity at Visit 4	n=48 n/a	n=1,050 **1.17** **(0.94-1.47)**	n=2,086 **1.78** **(1.48-2.13)**	Obesity at Visit 4	n=1,868 **1.41** **(1.17-1.71)**	n=924 **1.56** **(1.25-1.95)**	n=292 **2.26** **(1.71-3.00)**

n/a = associations cannot be estimated due to the high imprecision resulting from the small sample size (< 50 individuals) in this group

Adjusted for age, sex, race, cigarette smoking, alcohol use, educational level, occupation, LDL-C, HDL-C, triglycerides, systolic blood pressure, anti-hypertensive medication use, diabetes and estimated GFR (Visit 4 assessments of all variables except occupation and educational level)

Table 4. Hazard Ratios (95% CIs) for Associations of Cross-Tabulations of Waist Circumference Tertiles at Visit 1 and Visit 4 With Incident HF

	1st Waist Circumference Tertile at Visit 1	2nd Waist Circumference Tertile at Visit 1	3rd Waist Circumference Tertile at Visit 1
1st Waist Circumference Tertile at Visit 4	n=2,259 Ref (1.0)	n=627 1.12 (0.85-1.48)	n=28 n/a
2nd Waist Circumference Tertile at Visit 4	n=651 1.14 (0.86-1.52)	n=1,849 **1.43** **(1.18-1.73)**	n=576 **1.81** **(1.41-2.32)**
3rd Waist Circumference Tertile at Visit 4	n=102 1.44 (0.76-2.72)	n=688 **1.45** **(1.12-1.87)**	n=2,500 **2.50** **(2.11-2.95)**

n/a = associations cannot be estimated due to the high imprecision resulting from the small sample size (< 50 individuals) in this group

Adjusted for age, sex, race, cigarette smoking, alcohol use, educational level and occupation

Table 5: Association of Weight History Metrics (per 1-SD) with Incident HF in Regression

Models Including Current BMI

Weight History Metric	HR (95% CI) for V4 BMI	HR (95% CI) for Weight History Metric	AIC for Model
Unadjusted	**1.41** (1.34-1.49)	n/a	20,956
Cumulative BMI from Age 25-V4	**1.20** (1.08-1.34)	**1.26** (1.10-1.45)	20,664
BMI at Age 25	**1.37** (1.29-1.46)	**1.06** (1.00-1.13)	20,671
BMI at Visit 1	1.07 (0.95-1.21)	**1.36** (1.20-1.53)	20,934
Cumulative BMI from V1-4	1.11 (0.95-1.30)	**1.29** (1.11-1.50)	20,948
Obesity Duration (from V1-V4)	**1.29** (1.18-1.40)	**1.13** (1.04-1.23)	20,949

Obesity Duration (from age25-V4)	**1.33** **(1.25-1.42)**	**1.09** **(1.03-1.14)**	20,949

*Regression models including weight history metrics adjusted for "current" (Visit 4) BMI and age, sex, race, cigarette smoking, alcohol use, educational level and occupation

Figure 1: Description of Study Population
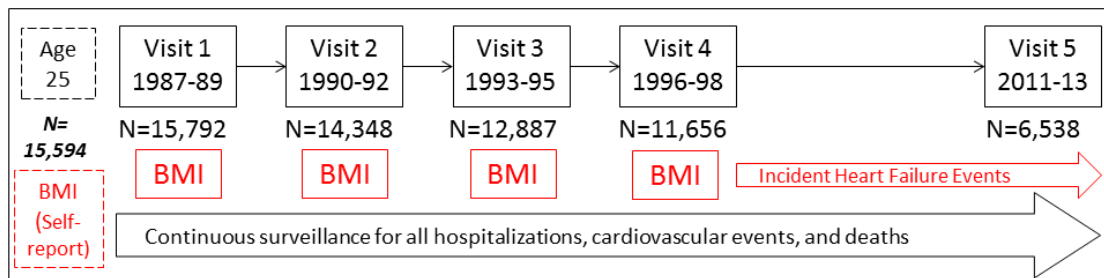
Of 11,656 Visit 4 participants, excluded:
- 1,572 individuals with HF or CHD at or prior to Visit 4
- 214 individuals missing data on prevalent HF or CHD at Visit 1
- 422 individuals missing data on BMI at Visits 1, 2, 3 or 4
- 133 individuals with BMI < 18.5 at any study visit
- 31 individuals not of black or white race

Yielding a study population of **9,284 Visit 4 participants** with available BMI data from Visits 1-4, with follow-up for HF events from Visit 4 through December 31, 2013

Figure 2: Proportion of Study Participants with Stable, Increasing or Decreasing BMI Category Over Time

From Visit 1 to 4
(9 years apart)

- Stable (Ref): 72
- Increase: 23
- Decrease: 5

From Age 25 to Visit 4
(mean age 63 at V4)

- Stable (Ref): 33
- Increase: 65
- Decrease: 2
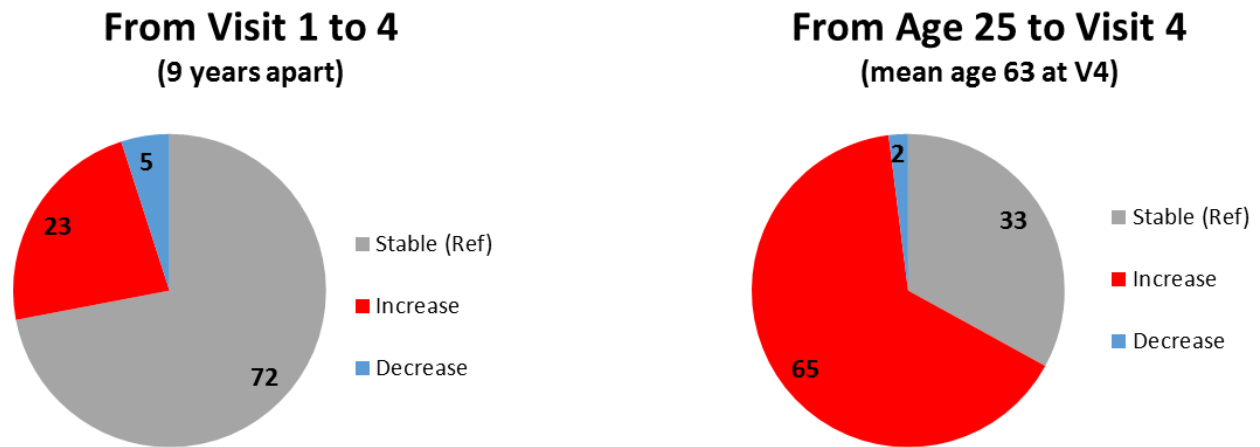
BMI categories are defined as normal weight (BMI 18.5 to <25 kg/m^2), overweight (BMI 25 to <30 kg/m^2) and obese (BMI 25 to <30 kg/m^2). Changes in BMI category over time are shown from Visit 1 to Visit 4 and from Age 25 to Visit 4.

Figure 3. Hazard Ratios for Incident HF Associations of Cross-Tabulations of BMI Categories at Visit 1 and Visit 4 (Panel A) and Age 25 and Visit 4 (Panel B)
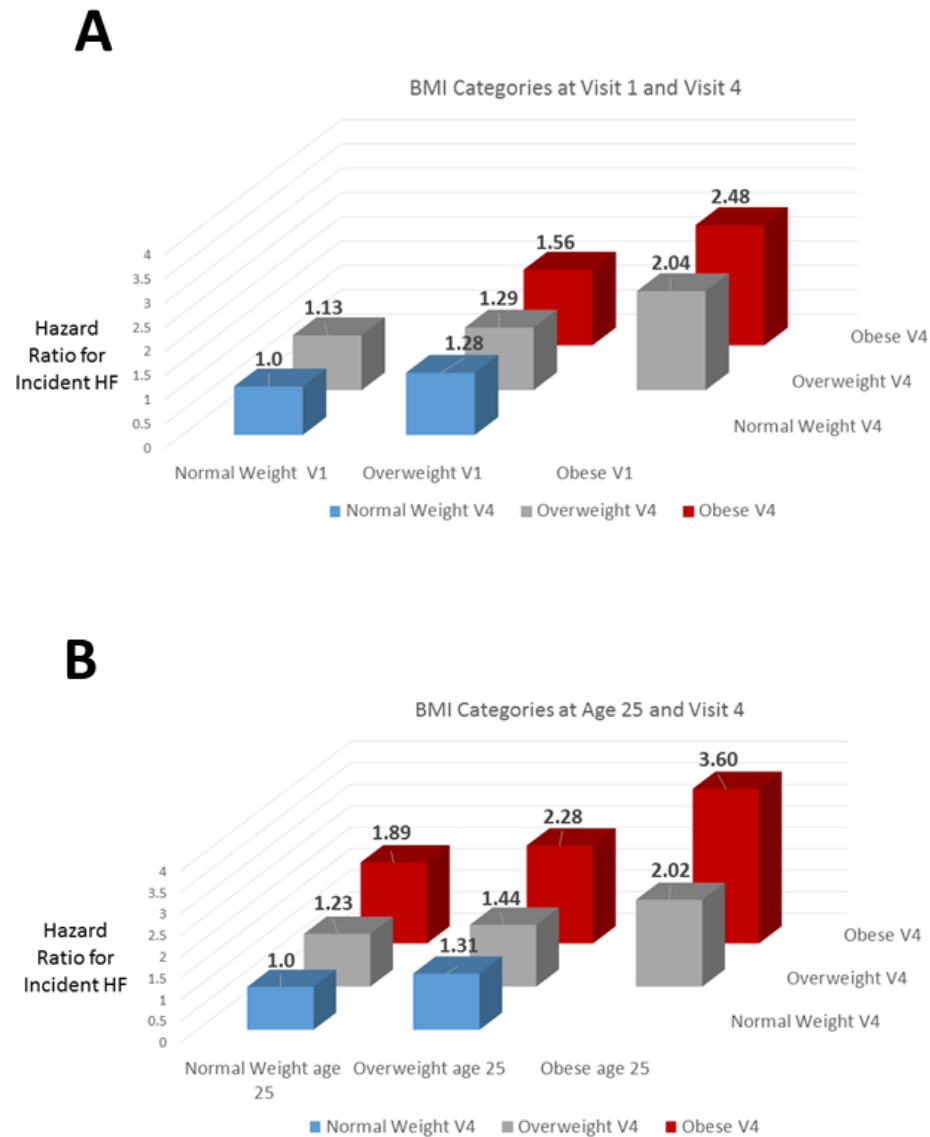
Adjusted for age, sex, race, cigarette smoking, alcohol use, educational level and occupation

* Missing bars are for subgroups with less than 50 individuals, for whom associations cannot be estimated due to the high imprecision resulting from the small sample size

Figure 4: Restricted Cubic Spline for the Association Between BMI Years and Incident HF
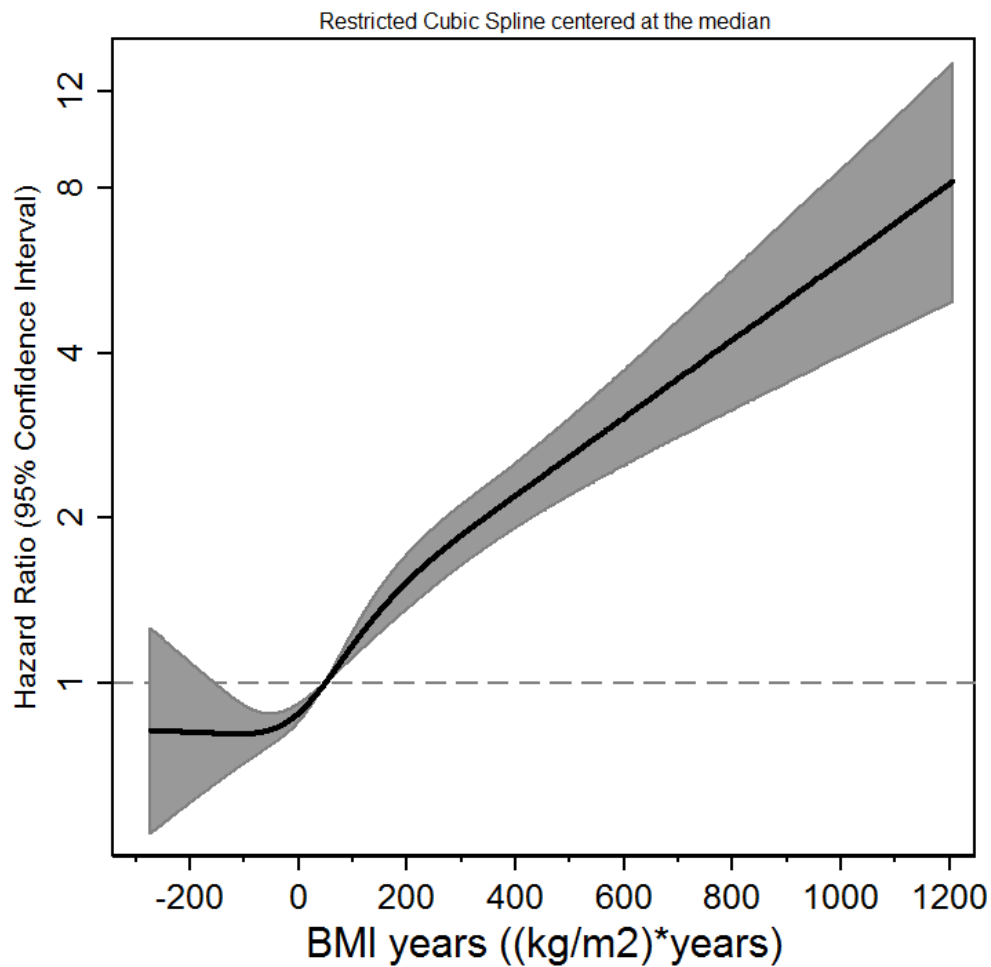
Cubic spline centered at the median. Regression model adjusted for age, sex, race, cigarette smoking, alcohol use, educational level and occupation

Chapter 5 – Aim 4: Weight History and Subclinical Myocardial Injury

Abstract

Introduction: Excess weight is associated with subclinical myocardial damage, as reflected by high sensitivity cardiac troponin-T (hs-cTnT) concentrations, which portends high heart failure risk. However, the association between weight history and myocardial damage is unknown.

Methods: We evaluated 9,062 ARIC Visit 4 (1996-99) participants with body-mass index (BMI) ≥ 18.5 kg/m^2 and no prior cardiovascular disease. We cross-tabulated Visit 4 ("current") BMI categories of normal weight, overweight and obese with those at Visit 1 (1987-89) and with BMI categories calculated from self-reported weight at age 25. Duration of obesity was calculated in years. A cumulative weight measure of "excess BMI years" was also calculated (product of mean BMI [centered at 25 kg/m^2] over all ARIC time points x follow-up duration). We used logistic regression to estimate associations of weight history metrics with increased hs-cTnT ($\geq$14 ng/L) at Visit 4.

Results: Overall, 623 individuals (7%) had increased hs-cTnT at Visit 4. Within each current BMI category, prior excess weight was associated with increased hs-cTnT, with the strongest associations for those with past and current obesity (OR 3.85 [2.51-5.90] for obesity at age 25 and Visit 4). Each 10-years longer obesity duration was associated with increased hs-cTnT (OR 1.26; 1.17-1.35). Each 100 higher excess BMI years was also progressively associated with increased hs-cTnT (OR 1.21; 1.14-1.27).

Conclusion: Prior obesity and greater cumulative weight from young adulthood increase the likelihood of myocardial damage, indicating chronic toxic effects of adiposity on the myocardium and the need for weight maintenance strategies targeting the entire lifespan.

Introduction

Obesity is a well-established risk factor for several types of cardiovascular disease (CVD), but the pathways underlying these associations are incompletely understood(1;2). This is particularly true for the relationship between obesity and heart failure (HF), where several large epidemiologic studies demonstrate a risk association independent of traditional mediators of the relationship between obesity and CVD, such as hypertension, diabetes and dyslipidemia(3-6). A growing body of laboratory data suggest direct toxic effects of obesity on the myocardium that predispose to the development of heart failure(7;8). Similarly, clinical studies demonstrate a strong association between obesity and high sensitivity cardiac troponin-T (hs-cTcT), a biomarker of subclinical myocardial damage, (9;10), and that the combination of obesity and increased hs-cTnT is linked to a markedly increased risk for future HF(10).

While most studies evaluating the relationship between excess weight and cardiovascular disease risk utilize anthropometric measures from one time point, a growing body of data demonstrates that weight history may significantly influence the likelihood of developing cardiovascular events. In past studies, both a longer duration of obesity and higher measures of cumulative weight were linked to increased risk for incident HF(11;12). While the mechanisms for this association are not yet known, imaging studies indicate that a history of excess weight is linked to several abnormalities of myocardial structure and function(13;14). However, it is

presently unknown how weight history impacts the likelihood of subclinical myocardial damage, as indexed by hs-cTnT. Understanding the relationship between weight history and hs-cTnT will both elucidate the timing of myocardial damage related to obesity and inform recommendations for weight maintenance to promote optimal cardiovascular prevention. Additionally, given the strong association of minute increases in hs-cTnT among those without clinical CVD with future cardiovascular events and mortality(15;16), the association between past weight patterns and subclinical myocardial damage is of considerable clinical significance.

Therefore, in the present analysis, we examined the relationship between various weight history metrics and increased hs-cTnT in the predominately bi-racial, community-based Atherosclerosis Risk in Communities (ARIC) study. With repeated measures of weight across the adult life span, detailed risk factor characterization, and continuous cardiovascular event ascertainment allowing for the exclusion of individuals with clinical CVD, the ARIC study is well-suited to evaluate the link between weight history and subclinical myocardial damage.

Materials and Methods

The ARIC study was originally designed to investigate the etiology of CVD and initially recruited 15,792 participants from four U.S. population centers: Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and suburbs of Minneapolis, Minnesota. ARIC participants aged 45-64 years were recruited in 1987-89 (Visit 1) and subsequently examined at visits in 1990-92 (Visit 2), 1993-95 (Visit 3), 1996-98 (Visit 4) and, most recently, from 2011-13 (Visit 5). In addition to undergoing detailed history and examinations, including anthropometry, at each study visit, participants have been followed continuously for cardiovascular events since baseline at Visit 1. Previous papers described the design of ARIC in

detail([17](#)). The institutional review boards associated with each ARIC site approved the study protocol and all ARIC participants provided informed consent.

This analysis included participants who attended ARIC Visit 4 and who had available data on body mass index (BMI) from each of the prior ARIC visits. Of 11,656 participants at Visit 4, we excluded: 1,572 participants with a history of HF or CHD at, or prior to, Visit 4 (self-reported HF or CHD at Visit 1; or HF-related hospitalization or death, adjudicated non-fatal myocardial infarction or coronary revascularization event, or silent myocardial infarction by ECG criteria at or prior to Visit 4); 214 participants missing data on prevalent HF or CHD; 417 participants missing data on BMI at one of the study visits; 222 participants missing data on hs-cTnT at Visit 4; 138 participants with BMI values less than 18.5 kg/m^2 at one or more of the study visits (due to the confounding associated with underweight); and 31 not of black or white race, for a final study population of 9,062 individuals.

The primary exposure was BMI, based on measured weight and height at each visit and calculated in kg/m^2. BMI was categorized as normal weight (18.5 to <25 kg/m^2), overweight (25 to < 30 kg/m^2) and obese ($\geq$ 30 kg/m^2). BMI measured at Visit 4, the time point of hs-cTnT measurement, was defined as "current BMI", while BMI measures from the past ARIC study visits were defined as "past BMIs". We additionally calculated BMI from self-reported weight at age 25, a variable that was collected at ARIC Visit 1. We used these data to evaluate the associations of weight history from ARIC Visits 1 through 4 (a 9-year span in middle age) and from age 25 through Visit 4 (from young adulthood to late middle age) with the likelihood of subclinical myocardial damage at Visit 4.

Information regarding demographics, health behaviors and cardiovascular risk factors was obtained at ARIC Visit 4. Smoking status was categorized as current, former, and never smoker. Alcohol intake was self-reported and calculated in grams per week. Diabetes was defined as meeting one of more of the following criteria: a prior diagnosis of diabetes, the use of hypoglycemic medications, a fasting blood glucose $\geq$ 126 mg/dl or a non-fasting blood glucose $\geq$ 200 mg/dl. Systolic BP was measured twice at the study visit using standardized techniques, and the mean of the measurements was used for analysis. Total cholesterol, HDL-cholesterol (HDL-C) and triglycerides were measured using enzymatic assays. LDL-C was subsequently calculated using the Friedewald equation [TC – HDL-C – (triglycerides/5)] for those with triglycerides less than 400 mg/dL. Estimated glomerular filtration rate (eGFR) was calculated using the MDRD equation. NT-proBNP was measured using the Elecsys proBNP II immunoassay (Roche Diagnostics).

hs-cTnT was measured in 2010 from thawed Visit 4 plasma samples. Between Visit 4 and 2010, the samples were stored at -80 degrees C. hs-cTnT measurements were performed using the Elecsys Troponin T high-sensitivity assay (Roche Diagnostics) on an automated Cobas e411 analyzer. The between assay coefficients of variation for control materials with mean hs-cTnT concentrations of 2,378 ng/L and 29 ng/L were 2.6% and 6.9%, respectively. The primary outcome in the present study was increased hs-cTnT, defined as $\geq$14 ng/L, a cutpoint that has been used in several prior analyses relating hs-cTnT to cardiovascular endpoints and mortality(15;16).

Statistical Analysis

We performed univariate comparisons of demographic and clinical variables across BMI categories at Visit 4, using chi-square tests for categorical variables and ANOVA for continuous variables.

Logistic regression was used to assess the associations of different weight history patterns with increased hs-cTnT concentrations at Visit 4. We used two regression models: Model 1 was adjusted for the potential confounders of age, sex, race, smoking status and alcohol intake. Model 2 was adjusted for the Model 1 variables plus additional variables potentially on the causal pathway between obesity and myocardial damage, including diabetes, systolic blood pressure, anti-hypertensive medication use, LDL-C, HDL-C, triglycerides, eGFR, and NT-proBNP.

We assessed how changes across the BMI categories of normal weight, overweight and obese from Visit 1 to Visit 4 were associated with the likelihood of increased hs-cTnT at Visit 4. We compared the likelihood of increased hs-cTnT between those individuals with stable normal weight or overweight from Visit 1 to Visit 4 and those who transitioned from normal weight to overweight or obesity, or from overweight to obesity (those whose BMI category increased). Similarly, we compared those individuals with stable overweight or obesity from Visit 1 to Visit 4 to those who transitioned from overweight to normal weight, or from obesity to overweight or normal weight (those whose BMI category decreased). We performed identical analyses using the time points of age 25 and Visit 4. We assessed the improvements in model quality associated with separately adding BMI category at Visit 1 and BMI category at age 25 to regression models including BMI category at Visit 4 using likelihood ratio tests.

We created cross-tabulations of BMI categories at Visits 1 and 4, with those individuals with normal weight at both time-points serving as the reference, and estimated each subgroup's likelihood of increased hs-cTnT. We performed the same analysis using cross-tabulations of BMI categories at age 25 and Visit 4. We similarly cross-tabulated tertiles of waist circumference at Visits 1 and 4 as an additional measure of adiposity, and estimated each subgroup's odds of increased hs-cTnT (with those in the lowest waist circumference tertile at both time points serving as the reference). We tested for interactions between the weight change patterns above and race, sex and age ($\geq$ or < 65 years at Visit 4) on the outcome of increased hs-cTnT.

To further evaluate the effects of chronic excess weight on the likelihood of myocardial damage, we assessed the associations of duration of obesity and cumulative weight, expressed in "excess BMI years" with increased hs-cTnT. Duration of obesity was calculated by coding obesity at each time point from age 25 to Visit 4 as 0 or 1 (for absent or present, respectively), and then multiplying the product of the obesity variable at two consecutive time points by the duration in years between those time points and summing each of the products. For those with obesity at Visit 1 but not at age 25, we assumed obesity onset starting at age 40. We then evaluated the association between each 10 years longer duration of obesity and the odds of increased hs-cTnT. This was performed for the entire population, and in subgroups stratified by race, sex, age ($>=$ or < 65 years), hypertension status, diabetes status and presence of chronic kidney disease (CKD; eGFR < 60 ml/min/1.73 m^2). Excess BMI years was calculated by centering the BMI variable at 25 kg/m^2 (the upper limit of normal weight), averaging BMI across the time points and multiplying the average of centered BMI by the duration in years of observation (from age 25 to age at Visit 4). Using this calculation, an average BMI of 30 kg/m^2

(5 units above 25 kg/m^2) for 20 years would equate to 100 excess BMI years. Analyses were performed assessing the odds of myocardial damage associated with each 100 units higher excess BMI years. A restricted cubic spline model (using Harrell's method) was also constructed to assess the continuous association between excess BMI years and increased hs-cTnT.

In sensitivity analyses, we evaluated the associations of duration of obesity and excess BMI years with increased hs-cTnT using only BMI calculated from measurements from ARIC Visits 1 through 4. In additional sensitivity analyses, we evaluated the associations of weight and height separately with increased hs-cTnT, to assess how these two components of the BMI calculation were associated with myocardial damage.

All analyses were performed using Stata 13.1 (StataCorp). All *P* values presented are 2-sided.

Results

The mean age of the study population at Visit 4 was 63 years, with 58% women and 21% African American. Those individuals in higher BMI categories were slightly younger, more likely to be African American, and less likely to be current smokers (**Table 1**). Individuals with obesity also had higher mean systolic blood pressures, a higher prevalence of anti-hypertensive medication use and diabetes, generally more abnormal lipid values and lower NT-proBNP concentrations.

Overall, 23% of individuals increased in BMI category from Visit 1 to Visit 4, while 72% remained in a stable BMI category, and 5% decreased in BMI category. At Visit 4, 7% of individuals (n=623) had increased hs-cTnT concentrations. Those individuals whose BMI category increased from Visit 1 to Visit 4 had an OR of 1.54 (95% CI: 1.20-1.97) for increased

hs-cTnT, relative to those with stable normal weight or overweight. For those whose BMI category decreased from Visit 1 to Visit 4, there was no significant association with increased hs-cTnT (OR 1.12; 95% CI: 0.78-1.61) relative to those with stable overweight or obesity. From age 25 to Visit 4, 65% increased, 2% decreased and 33% remained in a stable BMI category. A BMI category increase from age 25 to Visit 4 was associated with an OR for increased hs-cTnT of 1.27 (95% CI: 1.02-1.59), whereas a BMI category decrease over the same time frame had no significant association with increased hs-cTnT (OR 1.06; 95% CI: 0.60-1.87). Overall, adding Visit 1 BMI category to a model including Visit 4 BMI category improved the model fit (likelihood ratio test *P*<0.01), as did adding BMI category at age 25 to Visit 4 BMI category (likelihood ratio test *P*<0.001).

In evaluating the multivariate associations of cross-tabulations of BMI at Visit 1 and Visit 4 with myocardial damage (**Table 2**), we generally found that within each current BMI category a history of excess weight was associated with a greater likelihood of increased hs-cTnT. Those with both current and past obesity had a tendency towards greater odds of increased hs-cTnT (OR 2.15; 95% CI: 1.57-2.92) than those with current obesity and past overweight at Visit 1 (OR 1.55; 95% CI: 1.07-2.22). Those with current overweight and past obesity also had a high likelihood of increased hs-cTnT (OR 2.05; 95% CI: 1.25-3.38). Interestingly, the odds of increased hs-cTnT (OR 1.57; 95% CI: 1.07-2.32) were significantly increased in those who transitioned from normal weight to overweight from Visit 1 to Visit 4, whereas no association was seen for those with persistent overweight over the same time period (OR 1.07; 95% CI: 0.79-1.45).

In the multivariate cross-tabulations of BMI at age 25 and Visit 4 (**Table 2**), we similarly found that within each current weight category, a higher past weight category in young

adulthood was associated with an increased likelihood of increased hs-cTnT. For example, among those individuals with current obesity, a progressive increase in the odds of increased hs-cTnT was seen for those with past normal weight (OR 1.71; 95% CI: 1.22-2.39), past overweight (OR 2.04; 95% CI: 1.44-2.90) and past obesity (OR 3.85; 95% CI: 2.51-5.90) at age 25. Overall, when considering cross-tabulations of BMI at Visit 1 and Visit 4 or at age 25 and Visit 4, those individuals with both past and current obesity had the greatest likelihood of increased hs-cTnT.

We found similar patterns across subgroups defined by race, gender, and age, with no significant interactions between these demographic variables and changes in weight categories on the outcome of increased hs-cTnT. Similar patterns were also seen when we evaluated cross-tertiles of waist circumference at Visits 1 and 4 (**Table 3**), with those in the highest waist circumference tertile at both time points having the greatest likelihood of increased hs-cTnT (OR 2.67; 95% CI: 1.91-3.72).

The duration of obesity within the study population ranged from 0 to 50.1 years. On average, each 10 years longer duration of obesity was associated with an OR of 1.26 (95% CI: 1.17-1.35) for increased hs-cTnT. Significant associations between duration of obesity and increased hs-cTnT were seen in all demographic subgroups and among those participants with and without hypertension, diabetes and CKD at Visit 4 (**Figure 1**), with no statistically significant interactions between obesity duration and each of these subgroups (all $P > 0.05$). The association between obesity duration and increased hs-cTnT remained significant after adjustment for current BMI ($P<0.001$).

The range of excess BMI years above 25 kg/m^2 in the study population was from -274 to 1,205 kg/m^2 * years. Individuals with negative values were those who had BMI values of less

than 25 kg/m^2 at one or more of the study time points. There was a strong, positive continuous association between excess BMI years and the likelihood of increased hs-cTnT, as shown in the restricted cubic spline in **Figure 2**. On average, each 100 higher excess BMI years was associated with a 21% higher odds of increased hs-cTnT (95% CI: 1.14-1.27). This association remained significant and was slightly stronger after additional adjustment for current BMI at Visit 4 (HR 1.38: 95% CI: 1.18-1.62).

We also found significant associations for duration of obesity and excess BMI years with increased hs-cTnT in sensitivity analyses using only measured BMI from ARIC Visits 1 through 4. In additional sensitivity analyses, we found that higher tertiles of weight at Visit 1 and Visit 4 and cross-categories of weight tertiles at both time points were significantly associated with increased hs-cTnT, whereas height tertiles were not independently associated with increased hs-cTnT at either time point.

Discussion

In this analysis of 9,062 individuals in the ARIC study, we demonstrated that weight history influences the likelihood of subclinical myocardial damage. After adjustment for demographics and comorbid conditions, increases in BMI category during middle age, and from young adulthood through late middle age, relative to stable normal weight or overweight, were associated with increased hs-cTnT. Additionally, within each category of current weight, a history of obesity was associated with increased hs-cTnT, with those individuals who were obese in both young adulthood and late middle age having the greatest overall likelihood of having increased hs-cTnT. The impact of chronic excess weight on the likelihood of myocardial damage

126

was further demonstrated by strong associations of both obesity duration and cumulative BMI, expressed in excess BMI years, with increased odds of increased hs-c-TnT. These findings, which remained consistent across various demographic subgroups, illustrate the importance of long term weight maintenance for minimizing the likelihood of future myocardial damage.

Obesity is a potent risk factor for several forms of cardiovascular disease, but the pathways underlying these risk associations are divergent and incompletely understood(1;2;18). While the associations of obesity with coronary heart disease and stroke are largely explained by traditional mediators of cardiovascular disease, such hypertension, dyslipidemia and diabetes(19;20), the link between obesity and HF is uniquely unexplained by these traditional CVD mediators(3-6). A growing body of evidence suggests direct effects of obesity on the myocardium, which may explain the potent association between obesity and HF that is independent of comorbid conditions. Clinical studies demonstrate that obesity is independently linked to several abnormalities of myocardial structure and function that predispose to the development of HF(21-23). Laboratory studies have shown that rodents genetically predisposed to obesity demonstrate evidence of increased myocyte damage relative to wild-type mice(7;8). Clinical studies within ARIC and other cohorts demonstrate a strong and independent association between obesity and hs-cTnT among individuals without clinical cardiovascular disease(9;10). Increased hs-cTnT has been linked to increased CVD risk in prospective studies, particularly HF(15;16). Furthermore, prior work within this cohort demonstrates that the combination of severe obesity and increased hs-cTnT is associated with 9-fold higher risk of incident HF over a decade compared to those with normal weight and undetectable hs-cTnT(10). This analysis expands on prior work by demonstrating the cumulative effects of long-term obesity and increasing weight over time on the likelihood of subclinical myocardial damage.

The precise mechanisms by which obesity leads to myocardial damage have not yet been elucidated. We demonstrated a similar association between the duration of obesity and increased hs-cTnT among individuals with and without hypertension, diabetes and CKD, demonstrating that the link between a history of excess weight and myocardial damage is not entirely explained by these comorbid conditions. Several factors have been proposed as potential contributors, including increased myocardial demand due to hemodynamic stress(21;22;24), the effects of obesity-associated adipokines and cytokines on the myocardium(6;25-28), and the toxic effects of adipose tissue accumulation in myocardial tissues(29-32).

In this analysis, we saw high odds of increased hs-cTnT for those who transitioned from obese to overweight from Visit 1 to 4, and from overweight to normal weight from Age 25 to Visit 4. The implications of this finding are uncertain, as the intentionality of weight loss within a cohort study is unknown. While speculative, it is possible that this association reflects reverse causality due to weight loss from undetected clinical comorbidities. On the other hand, prior research suggests that marked intentional weight loss occurring after bariatric surgery is associated with reduced myocardial damage, as assessed by high sensitivity cardiac troponin I concentrations(33). Further research is needed to elucidate the effects of intentional weight loss through lifestyle modification on myocardial damage. However, the rates of significant and sustained intentional weight loss remain relatively low in the general population (34;35). Therefore, understanding the pathways linking chronic obesity and increased hs-cTnT may inform novel strategies to reduce myocardial damage and the likelihood of future CVD events among those with obesity.

From a clinical standpoint, this analysis underscores the importance of long-term weight control for optimizing cardiovascular prevention. A history of excess weight was linked to a

greater likelihood of myocardial damage at each level of current weight, and those individuals with both past and present obesity had the highest odds of increased hs-cTnT. These findings were even more pronounced when considering weight at age 25. Furthermore, the finding that the duration of obesity was linked to a similar likelihood of subclinical myocardial damage among individuals with and without diabetes, hypertension and chronic kidney disease indicates the limitations of traditional risk factor control alone for addressing the toxic effects of chronic obesity on the myocardium. These results indicate the importance of defining and implementing strategies to promote weight management, even from young adulthood, for reducing the likelihood of developing myocardial damage. Cumulative weight measured in excess BMI years demonstrated a strong association with increased hs-cTnT. A metric such as excess BMI years could prove useful for communicating to young and middle aged adults the risks of excess weight from early in life and the importance of maintaining a normal weight for decreasing long-term cardiovascular risk.

This analysis has some limitations. As an observational study, it is susceptible to residual confounding. Additionally, while most of the BMI values were based on measured weight and height, BMI at age 25 was based on self-report, which is subject to recall bias. Additionally, being a cohort study in which most individuals gained weight over time and the intentionality of any weight loss is uncertain, this study is poorly equipped to assess the impact of weight loss on the likelihood of myocardial damage. In addition, some survival bias is introduced by only including individuals who survived and were without CVD by Visit 4. An important consideration regarding the excess BMI years construct is its heavy dependence on age, as an older individual with the same obesity status as a younger person would have a greater number of excess BMI years. However the strong risk association between excess BMI years and

myocardial damage, after adjustment for age and other confounders, also underscores the importance of maintaining a healthy weight in the context of aging. Additionally, unlike excess BMI years, the duration of obesity variable doesn't reflect the risk associated with BMI values in the high overweight range (e.g., BMI 29 kg/m^2). Nonetheless, this analysis from an extremely well-characterized cohort with repeated measures of weight across the adult lifespan provides important insights about the association between weight history and subclinical myocardial damage. Furthermore, the use of a community-based bi-racial cohort of men and women makes the results broadly generalizable.

In conclusion, we found that a past history of excess weight and increasing weight over time are associated with a greater likelihood of future myocardial damage. These findings are also seen when considering past weights from young adulthood, which underscores the importance of weight management across the entire adult lifespan for the lowest likelihood of myocardial damage and related cardiovascular events.

Reference List

1. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, Eckel RH. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2006;113:898-918.

2. Zalesin KC, Franklin BA, Miller WM, Peterson ED, McCullough PA. Impact of obesity on cardiovascular disease. Med Clin North Am 2011;95:919-37.

3. Del Gobbo LC, Kalantarian S, Imamura F, Lemaitre R, Siscovick DS, Psaty BM, Mozaffarian D. Contribution of Major Lifestyle Risk Factors for Incident Heart Failure in Older Adults: The Cardiovascular Health Study. JACC Heart Fail 2015;3:520-8.

4. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG et al. Obesity and the risk of heart failure. N Engl J Med 2002;347:305-13.

5. Morkedal B, Vatten LJ, Romundstad PR, Laugsand LE, Janszky I. Risk of myocardial infarction and heart failure among metabolically healthy but obese individuals: HUNT (Nord-Trondelag Health Study), Norway. J Am Coll Cardiol 2014;63:1071-8.

6. Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Obesity and risk of incident heart failure in older men with and without pre-existing coronary heart disease: does leptin have a role? J Am Coll Cardiol 2011;58:1870-7.

7. Barouch LA, Gao D, Chen L, Miller KL, Xu W, Phan AC et al. Cardiac myocyte apoptosis is associated with increased DNA damage and decreased survival in murine models of obesity. Circ Res 2006;98:119-24.

8. Zhou YT, Grayburn P, Karim A, Shimabukuro M, Higa M, Baetens D et al. Lipotoxic heart disease in obese rats: implications for human obesity. Proc Natl Acad Sci U S A 2000;97:1784-9.

9. McEvoy JW, Lazo M, Chen Y, Shen L, Nambi V, Hoogeveen RC et al. Patterns and determinants of temporal change in high-sensitivity cardiac troponin-T: The Atherosclerosis Risk in Communities Cohort Study. Int J Cardiol 2015;187:651-7.

10. Ndumele CE, Coresh J, Lazo M, Hoogeveen RC, Blumenthal RS, Folsom AR et al. Obesity, subclinical myocardial injury, and incident heart failure. JACC Heart Fail 2014;2:600-7.

11. Alpert MA, Terry BE, Mulekar M, Cohen MV, Massey CV, Fan TM et al. Cardiac morphology and left ventricular function in normotensive morbidly obese patients with and without congestive heart failure, and effect of weight loss. Am J Cardiol 1997;80:736-40.

12. Reis JP, Allen N, Gunderson EP, Lee JM, Lewis CE, Loria CM et al. Excess body mass index- and waist circumference-years and incident cardiovascular disease: the CARDIA study. Obesity (Silver Spring) 2015;23:879-85.

13. Alpert MA, Lambert CR, Panayiotou H, Terry BE, Cohen MV, Massey CV et al. Relation of duration of morbid obesity to left ventricular mass, systolic function, and diastolic filling, and effect of weight loss. Am J Cardiol 1995;76:1194-7.

14. Reis JP, Allen N, Gibbs BB, Gidding SS, Lee JM, Lewis CE et al. Association of the degree of adiposity and duration of obesity with measures of cardiac structure and function: the CARDIA study. Obesity (Silver Spring) 2014;22:2434-40.

15. deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, Seliger SL. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA 2010;304:2494-502.

16. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation 2011;123:1367-76.

17. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol 1989;129:687-702.

18. Aune D, Sen A, Norat T, Janszky I, Romundstad P, Tonstad S, Vatten LJ. Body Mass Index, Abdominal Fatness, and Heart Failure Incidence and Mortality: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies. Circulation 2016;133:639-49.

19. Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. Lancet 2014;383:970-83.

20. Ndumele CE, Matsushita K, Lazo M, Bello N, Blumenthal RS, Gerstenblith G et al. Obesity and Subtypes of Incident Cardiovascular Disease. J Am Heart Assoc 2016;5.

21. Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. Physiol Rev 2008;88:389-419.

22. Alpert MA. Obesity cardiomyopathy: pathophysiology and evolution of the clinical syndrome. Am J Med Sci 2001;321:225-36.

23. Turkbey EB, McClelland RL, Kronmal RA, Burke GL, Bild DE, Tracy RP et al. The impact of obesity on the left ventricle: the Multi-Ethnic Study of Atherosclerosis (MESA). JACC Cardiovasc Imaging 2010;3:266-74.

24. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. JACC Heart Fail 2013;1:93-102.

25. Frankel DS, Vasan RS, D'Agostino RB, Sr., Benjamin EJ, Levy D, Wang TJ, Meigs JB. Resistin, adiponectin, and risk of heart failure the Framingham offspring study. J Am Coll Cardiol 2009;53:754-62.

26. Karas MG, Benkeser D, Arnold AM, Bartz TM, Djousse L, Mukamal KJ et al. Relations of plasma total and high-molecular-weight adiponectin to new-onset heart failure in adults >/=65 years of age (from the Cardiovascular Health study). Am J Cardiol 2014;113:328-34.

27. McManus DD, Lyass A, Ingelsson E, Massaro JM, Meigs JB, Aragam J et al. Relations of circulating resistin and adiponectin and cardiac structure and function: the Framingham Offspring Study. Obesity (Silver Spring) 2012;20:1882-6.

28. Negi SI, Jeong EM, Shukrullah I, Raicu M, Dudley SC, Jr. Association of low plasma adiponectin with early diastolic dysfunction. Congest Heart Fail 2012;18:187-91.

29. Szczepaniak LS, Dobbins RL, Metzger GJ, Sartoni-D'Ambrosia G, Arbique D, Vongpatanasin W et al. Myocardial triglycerides and systolic function in humans: in vivo evaluation by localized proton spectroscopy and cardiac imaging. Magn Reson Med 2003;49:417-23.

30. van der Meer RW, Rijzewijk LJ, Diamant M, Hammer S, Schar M, Bax JJ et al. The ageing male heart: myocardial triglyceride content as independent predictor of diastolic function. Eur Heart J 2008;29:1516-22.

31. Wende AR, Abel ED. Lipotoxicity in the heart. Biochim Biophys Acta 2010;1801:311-9.

32. Zhou YT, Grayburn P, Karim A, Shimabukuro M, Higa M, Baetens D et al. Lipotoxic heart disease in obese rats: implications for human obesity. Proc Natl Acad Sci U S A 2000;97:1784-9.

33. Lyngbakken MN, Omland T, Nordstrand N, Norseth J, Hjelmesaeth J, Hofso D. Effect of weight loss on subclinical myocardial injury: A clinical trial comparing gastric bypass surgery and intensive lifestyle intervention. Eur J Prev Cardiol 2016;23:874-80.

34. Kraschnewski JL, Boan J, Esposito J, Sherwood NE, Lehman EB, Kephart DK, Sciamanna CN. Long-term weight loss maintenance in the United States. Int J Obes (Lond) 2010;34:1644-54.

35. MacLean PS, Wing RR, Davidson T, Epstein L, Goodpaster B, Hall KD et al. NIH working group report: Innovative research to improve maintenance of weight loss. Obesity (Silver Spring) 2015;23:7-15.

Table 1: Characteristics of Study Population at Visit 4, Stratified by BMI Category

	Normal Weight N=2,352	Overweight N=3,748	Obese N=3,184	*P* value
Mean Age, in years (SD)	62.9 (5.8)	62.8 (5.7)	62.1 (5.5)	<0.001
Female – %	64.8	50.7	61.3	<0.001
African American – %	12.5	19.2	28.7	<0.001
Current Smokers – %	20.6	13.6	9.2	<0.001
Mean systolic blood pressure, in mmHg (SD)	122.8 (19.3)	126.7 (18.1)	130.3 (17.9)	<0.001
Use of anti-hypertensive medication – %	19.5	29.9	44.1	<0.001
Diabetes – %	5.9	12.5	23.2	<0.001
Mean LDL-C, in mg/dL (SD)*	119.0 (33.5)	124.5 (32.8)	124.0 (33.8)	<0.001
Mean HDL-C, in mg/dL (SD)*	57.9 (18.0)	49.3 (15.5)	46.7 (14.5)	<0.001

Median triglycerides, in mg/dL (Interquartile interval)*	103 (75-143)	123 (90-175)	134 (99-187)	<0.001
Median eGFR, in ml/min/ 1.73 m2 (Interquartile interval))	80.8 (70.8-93.0)	81.0 (71.0-93.0)	81.3 (70.3-94.4)	0.11
Median NT-proBNP, in pg/ml (Interquartile interval)	80.6 (42.5-138.4)	58.1 (29.4-111.3)	55.9 (26.7-108.1)	<0.001
Mean waist circumference, in cm (SD)	87.3 (7.6)	99.2 (6.9)	115.3 (11.4)	<0.001

To convert mg/dL to mmol/L multiply by 0.2586 for cholesterol, by 0.01129 for triglycerides

Table 2. Odds Ratios (95% CIs) for Associations of Cross-Tabulations of BMI Categories at Visit 4 and at an Earlier Time Point (Visit 1 or Age 25) With Increased hs-cTnT

BMI Categories at Visit 1 and Visit 4 (9 years apart)				BMI Categories at age 25 (self-reported) and Visit 4			
	Normal Weight at Visit 1	Overweight at Visit 1	Obesity at Visit 1		Normal Weight at age 25	Overweight at age 25	Obesity at age 25
Normal Weight at Visit 4	n=83/2,086 [4.0%] Ref = 1	n=18/215 [8.4%] 1.31 (0.73-2.34)	n=6 n/a	**Normal Weight at Visit 4**	n=78/1,916 [4.1%] Ref = 1	n=16/105 [15.2%] **2.34** **(1.23-4.44)**	n=6 n/a
Over-weight at Visit 4	n=51/1,047 [4.9%] **1.57** **(1.07-2.32)**	n=152/2,400 [6.3%] 1.07 (0.79-1.45)	n=35/207= [16.9%] **2.05** **(1.25-3.38)**	**Over-weight at Visit 4**	n=156/2,808 [5.6%] 1.23 (0.90-1.68)	n=63/601 [10.5%] **1.51** **(1.03-2.21)**	n=8/62 [12.9%] 1.69 (0.69-4.13)
Obesity at Visit 4	n=47 n/a	n=77/1,021 [7.5%] **1.55**	n=205/2,033 [10.1%] **2.15**	**Obesity at Visit 4**	n=120/1,815 [6.6%] **1.71**	n=101/899 [11.2%] **2.04**	n=57/288 [19.8] **3.85**

		(1.07-2.22)	(1.57-2.92)		(1.22-2.39)	(1.44-2.90)	(2.51-5.90)

n = number with increased hs-cTnT within subgroup [proportion with increased hs-cTnT]

n/a = associations cannot be estimated due to the high imprecision resulting from the small sample size (< 50 individuals) in this group

Adjusted for age, sex, race, cigarette smoking, alcohol use, LDL-C, HDL-C, triglycerides, systolic blood pressure, anti-hypertensive medication use, diabetes, NT-proBNP and estimated GFR

Table 3. Hazard Ratios (95% CIs) for Associations of Cross-Tabulations of Waist Circumference Tertiles at Visit 1 and Visit 4 With Increased hs-cTnT

	1st Waist Circumference Tertile at Visit 1	2nd Waist Circumference Tertile at Visit 1	3rd Waist Circumference Tertile at Visit 1
1st Waist Circumference Tertile at Visit 4	n=57/2,212 [2.6%] Ref = 1	n=55/614 [9.0%] **1.92** **(1.26-2.94)**	n=28 n/a
2nd Waist Circumference Tertile at Visit 4	n=20/633 [3.2%] 1.36 (0.77-2.40)	n=118/1,807 [6.5] **1.53** **(1.07-2.18)**	n=53/555 [9.6%] **1.66** **(1.08-2.55)**
3rd Waist Circumference Tertile at Visit 4	n=2/98 [2.0%] 2.04 (0.47-8.75)	n=38/670 [5.7%] **1.91** **(1.21-3.04)**	n=278/2,441 [11.4%] **2.67** **(1.91-3.73)**

n = number with increased hs-cTnT within subgroup [proportion with increased hs-cTnT]

n/a = associations cannot be estimated due to the high imprecision resulting from the small sample size (< 50 individuals) in this group

Adjusted for age, sex, race, cigarette smoking, alcohol use, LDL-C, HDL-C, triglycerides, systolic blood pressure, anti-hypertensive medication use, diabetes, NT-proBNP and estimated GFR

Figure 1. Association Between Each 10 years Longer Duration of Obesity and Odds of Increased hs-cTnT (≥14 ng/L) Within Demographic and Clinical Subgroups
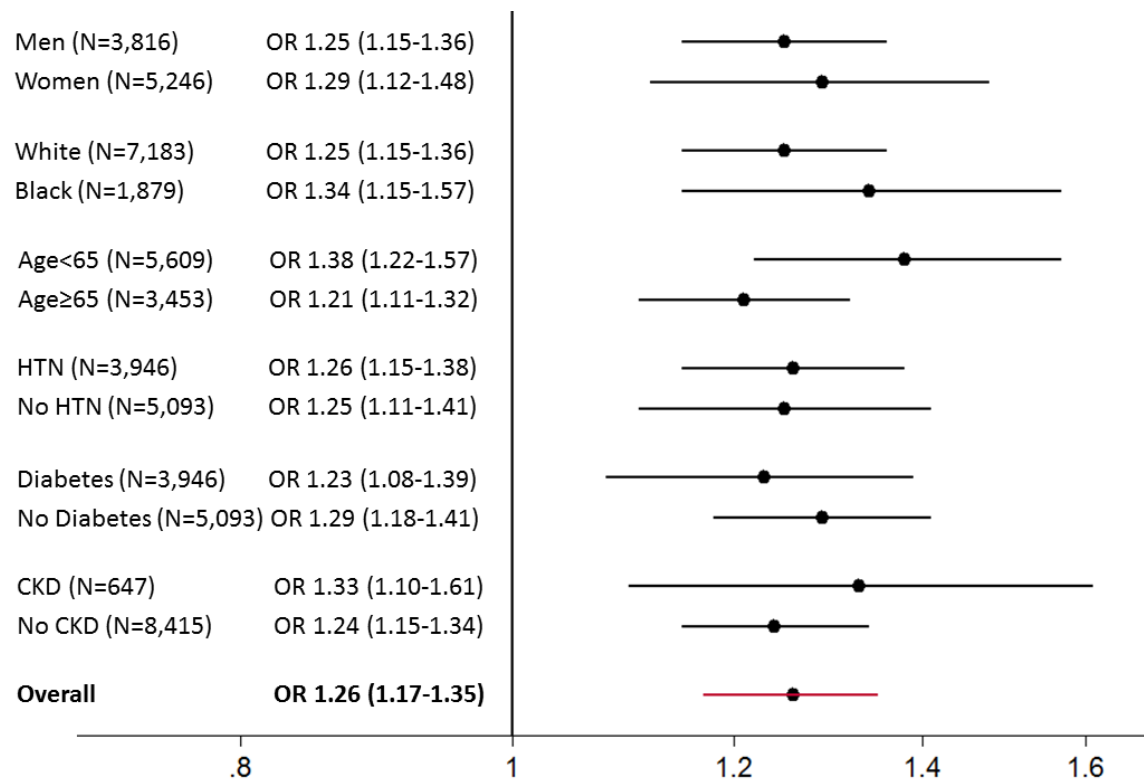
Men (N=3,816)	OR 1.25 (1.15-1.36)
Women (N=5,246)	OR 1.29 (1.12-1.48)
White (N=7,183)	OR 1.25 (1.15-1.36)
Black (N=1,879)	OR 1.34 (1.15-1.57)
Age<65 (N=5,609)	OR 1.38 (1.22-1.57)
Age≥65 (N=3,453)	OR 1.21 (1.11-1.32)
HTN (N=3,946)	OR 1.26 (1.15-1.38)
No HTN (N=5,093)	OR 1.25 (1.11-1.41)
Diabetes (N=3,946)	OR 1.23 (1.08-1.39)
No Diabetes (N=5,093)	OR 1.29 (1.18-1.41)
CKD (N=647)	OR 1.33 (1.10-1.61)
No CKD (N=8,415)	OR 1.24 (1.15-1.34)
Overall	**OR 1.26 (1.17-1.35)**

Adjusted for age, sex, race, cigarette smoking, alcohol use, LDL-C, HDL-C, triglycerides, systolic blood pressure, anti-hypertensive medication use, diabetes, NT-proBNP and estimated GFR. When stratified by a given subgroup, the covariate defining the subgroup [e.g., sex for sex-stratified analyses or estimated GFR for analyses stratified by CKD] was removed from the regression model with the exception of age modeled continuously, which was kept in all models. All *P* values for interactions across subgroups > 0.05.

Figure 2. Restricted Cubic Spline for the Association between Excess BMI years and OR of Increased hs-cTnT (≥14 ng/L)

Adjusted for age, sex, race, cigarette smoking, alcohol use, LDL-C, HDL-C, triglycerides, systolic blood pressure, anti-hypertensive medication use, diabetes, NT-proBNP and estimated GFR. Restricted cubic spline centered at median value for excess BMI years.
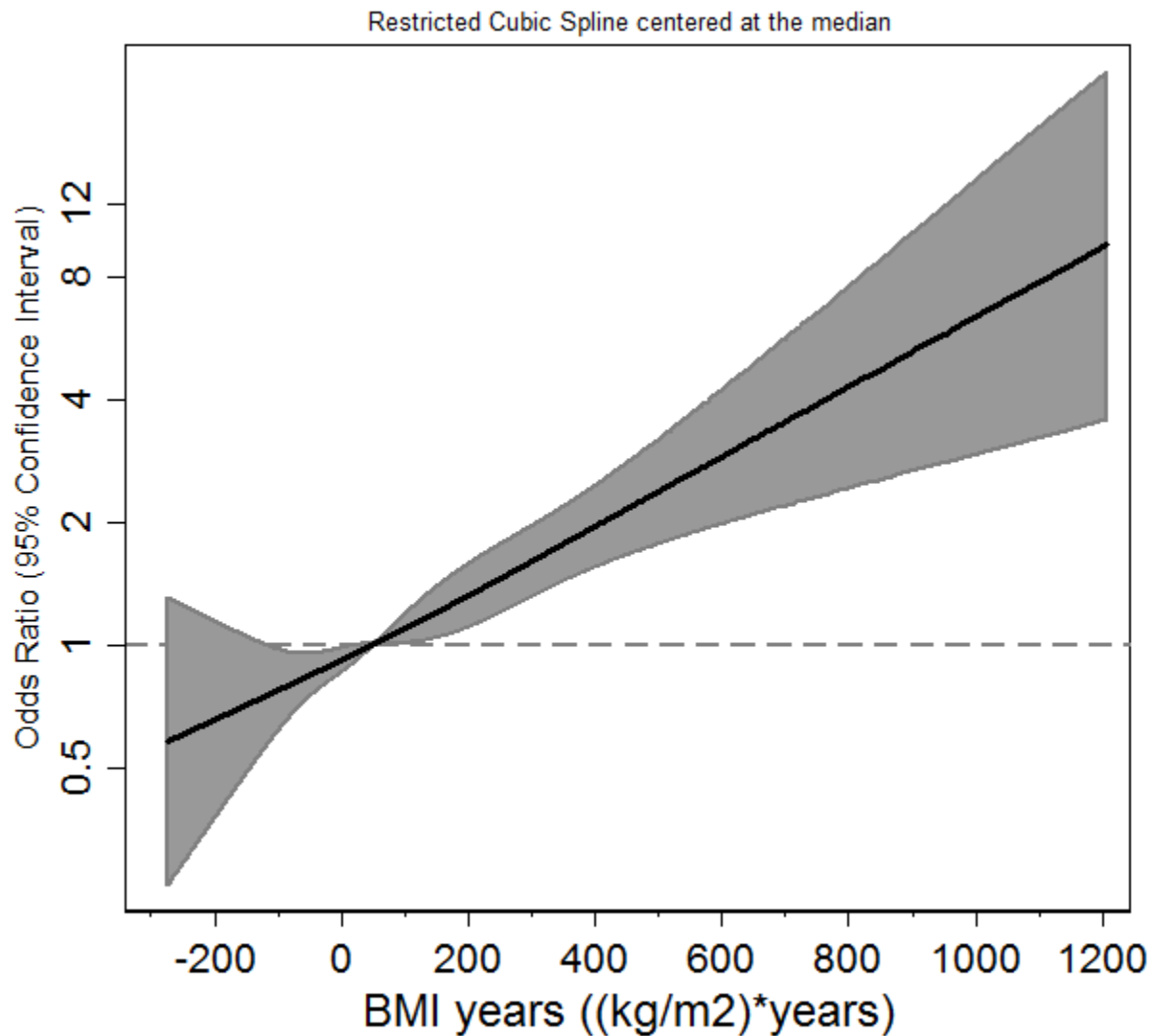
*Please note that a manuscript detailing the work in Aim 4 is in press at the journal Clinical Chemistry.

Chapter 6: Conclusions

Given the emergence of a global obesity epidemic, there is a public health imperative to fully characterize the epidemiologic association between obesity and CVD. The research projects described in this dissertation further our understanding about the link between obesity and HF. In addition to advancing this knowledge, our work has the potential to support efforts to refine strategies to predict and prevent HF associated with obesity.

Several forms of CVD are known to be linked to obesity[1, 2]. The preceding work demonstrated that the association between obesity and HF was stronger than the associations of obesity with other major forms of CVD, such as CHD and stroke. Additionally, while the associations of obesity with CHD and stroke were explained by traditional risk factors associated with obesity, such as HTN, DM and dyslipidemia, the link between obesity and HF was largely unexplained after accounting for these risk factors. These findings have several clinical and public health implications. First, it demonstrates that risk for HF should be a foremost clinical concern among those with obesity. With the emergence of the obesity epidemic, HF is therefore likely to represent a major public health challenge in coming years. This is particularly important given the high morbidity and mortality associated with HF, with a 50% 5-year mortality rate among those newly diagnosed with HF[3]. Secondly, these findings suggest that controlling traditional risk factors may be sufficient for preventing CHD and stroke associated with obesity. However, given the residual association between obesity and HF after controlling for comorbid conditions, it is likely that the strategy of risk factor control is likely to be insufficient for addressing HF risk among those with obesity. Third, this analysis indicates that non-traditional pathways are particularly relevant to the link between obesity and HF. While maintaining a

healthy weight, or achieving substantial and sustained weight loss among those with obesity, are likely the optimal strategies for reducing HF risk associated with obesity, data demonstrates that these are frequently unsuccessful in real-world settings[4, 5]. Therefore, there is an urgent need to elucidate the non-traditional pathways linking obesity and HF as a means of facilitating the development of novel preventive strategies.

To that end, we also evaluated the link between excess weight and subclinical myocardial injury. Several prior studies suggest toxic effects of adiposity on the myocardium. Obesity is associated with adverse cardiac remodeling, several abnormalities of myocardial structure and function that predispose to the development of HF[6, 7]. In laboratory studies, rodents genetically predisposed to obesity have shown evidence of myocardial injury, with evidence of DNA damage, increased myocyte apotosis, myocardial fibrosis and abnormal cardiac remodeling[8, 9]. However, clinical studies had not yet demonstrated an association between obesity and myocardial injury, due in large part to the absence of a suitable biomarker of subclinical myocardial injury.

The emergence of high-sensitivity cardiac troponin T (hs-cTnT) as a highly sensitive and specific marker of subclinical myocardial injury[10] has enabled clinical assessments of the link between excess weight and myocardial injury in the general population. We found a potent association between obesity and hs-cTnT among adults without clinical CVD, that was unexplained by traditional risk factors associated with obesity. Furthermore, the combination of severe obesity (a BMI $\geq$ 35) and high hs-cTnT was associated with an approximate 9-fold higher risk of HF over a decade than normal weight and undetectable hs-cTnT. This analysis provides clinical confirmation of an association between obesity and myocardial injury, however the pathways underlying this association are yet to be elucidated. It is interesting to consider

whether hs-cTnT will be a viable surrogate outcome to test the cardioprotective impact of interventions on obesity in a shorter time period and smaller sample size than it would take compared to incidence of heart failure itself. It is possible that hs-cTnT could provide an individual level measure of whether interventions are resulting in cardioprotection. This may not mark all pathways equally but might provide a new risk factor that is closer to the organ of interest than traditional risk factors such as blood pressure and serum cholesterol and importantly, it might monitor pathways with direct cardiac toxicity less directly linked to traditional atherosclerosis risk factors.

Most studies evaluating the link between obesity and HF utilize single anthropometric measurements to estimate risk associations. However, this likely underestimates the effects of chronic obesity on the likelihood of HF. In the preceding work, we assessed the associations between incident HF and various aspects of weight history, including prior weights, duration of obesity and cumulative weight. Using ARIC Visit 4 as the time point for "current" weight assessments and as the baseline for incident HF events, we found that at each level of current weight, a higher past weight was associated with greater HF risk. Those individuals with both past and current obesity were at the highest risk of incident HF.

Importantly, these findings were most pronounced when considering past weight from age 25, indicating the importance of weight management from young adulthood (or earlier) for influencing HF risk. Additionally, when comparing various weight history metrics in regression models including current weight on the outcome of incident HF, we saw the greatest improvements in model quality when including cumulative weight from age 25 to Visit 4. Cumulative weight measured in BMI years had a potent association with incident HF and could

serve as a useful tool for communicating the HF risk related to obesity to young and middle-aged adults.

While we have demonstrated the importance of weight history for assessing the HF risk related to obesity, the mechanisms by which prior obesity promotes increased HF risk are uncertain. Given the link we found between obesity and myocardial injury, as reflected by hs-cTnT, we examined the association between weight history and hs-cTnT among adults without known CVD. We found that prior elevated weight and increasing weight over time were associated with an increased likelihood of myocardial injury. Additionally, cumulative weight and the duration of obesity were both significantly associated with elevated hs-cTnT. These associations were consistent across demographic and clinical subgroups. These findings further underscore the importance of long term weight control for optimizing HF prevention.

Ongoing work and Future Directions

The work in this thesis sets the stage for several future investigative projects. As mentioned above, there is an urgent need to elucidate the non-traditional pathways linking obesity to incident HF. Several factors have been hypothesized to be contributors to HF risk among those with obesity, including: high blood volume and metabolic demand[11, 12]; ectopic fat deposition within the myocardium (termed myocardial steatosis), with associated myocyte injury[13-15]; and the paracrine effects of adipose tissue on the myocardium[16-18]. However, there is limited clinical data regarding the effects of these factors on myocardial injury, myocardial dysfunction and future HF risk among those with obesity. Developments in magnetic resonance imaging (MRI) now allow the non-invasive quantification of myocardial steatosis[19]. Several

adipokines and cytokines associated with obesity have been identified as potential mediators of the link between obesity and HF. In future work, we will perform assessments of myocardial steatosis and measurements of adipokines and cytokines associated with obesity to assess their links with myocardial injury, myocardial dysfunction and HF, and to assess whether these measures differ among obese individuals with and without clinical HF.

There is considerable interest in defining strategies for preventing HF among individuals with obesity. The optimal approach for preventing HF related to obesity is likely weight management. In the preceding work, those with consistently normal weight were at the lowest risk of myocardial injury or future HF. However, maintenance of a normal weight is increasingly uncommon in the midst of the current obesity epidemic. In the preceding work, we found that 65% of individuals increased in BMI category from age 25 to ARIC visit 4 (mean age 63). Furthermore, less than a quarter of the study population maintained a normal weight from young adulthood to late middle age. Additionally, several studies have demonstrated that after obesity has developed, efforts to achieve and maintain significant weight loss in the outpatient setting are frequently unsuccessful[4, 5]. Therefore, there is an urgent need to develop alternate strategies for HF prevention among individuals with obesity. Understanding the processes linking obesity and HF has the potential to significantly aid this process. For example, if myocardial steatosis is key factor in the development of HF associated with obesity, therapies to reduce myocardial steatosis may help to reduce HF risk. I anticipate using observational studies regarding the obesity-HF relationship to inform future interventional studies.

The preceding work illustrates the importance of maintaining a healthy weight from young adulthood onwards for all HF prevention. However, there is a lack of well-defined strategies to promote and motivate long-term weight maintenance within younger populations.

For young adults, one challenge may be communicating the HF risks in middle age or late adulthood that are associated with obesity in young adulthood. In the preceding work, we demonstrated that cumulative weight from young adulthood, described in BMI years, had strong associations with myocardial injury and future HF. Such a metric could be useful in helping to communicate the importance of healthy weights from an early age. The clinical implications of using the BMI years to aid risk communication deserves further study. Future studies may estimate the years of life lost (YLL), years of life with disability (DALY) and years free of heart failure lost per BMI year. Such average time lost may help individualize the information.

Finally, despite the known potent association between obesity and HF risk, the impact of weight loss on HF outcomes is presently unknown. In fact, several studies have documented an "obesity paradox", where among individuals with existing HF, those with obesity have better survival than those in lower weight categories[20-22]. It remains unknown whether this finding represents reverse causation due to the cachexia (wasting and weight loss) associated with HF, or if there is truly a protective effect of excess weight in the setting of prevalent HF. There is considerable interest in understanding the impact of intentional weight loss on HF related risks. To this end, I initiated the BARI-Heart study, a prospective cohort study of bariatric surgery patients designed to examine the effects of marked intentional weight loss on myocardial injury structure and function. We have designed a pre-post study, taking advantage of the insurance-mandated pre-surgical waiting period in which pre-surgical assessments of adiposity, cardiac biomarkers and echocardiographic measures (assessed at 2 pre-surgical time visits) will be compared to identical assessments performed post-operatively (at 6 and 12 months post-operatively). The BARI-Heart study has recruited 98 participants (of a planned 100) who are now undergoing follow-up assessments. We anticipate this study will provide additional insights

regarding the effects of weight loss on the myocardium and stored specimen will inform future work.

In conclusion, we have demonstrated that obesity has a potent risk association with incident HF that is uniquely unexplained by the traditional risk factors associated with obesity. Additionally, weight history measures provide prognostic information regarding HF risk beyond current weight, with cumulative weight from young adulthood onwards providing perhaps the most useful additional information regarding risk. We have also found that obesity and weight history have strong associations with measures of subclinical myocardial injury. Furthermore, the combined presence of severe obesity and elevated myocardial injury markers is associated with a markedly increased risk of future HF. This work has provided additional insights regarding the association between obesity and HF, a major clinical and public health challenge.

Reference List

(1) Poirier P, Giles TD, Bray GA et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2006 February 14;113(6):898-918.

(2) Zalesin KC, Franklin BA, Miller WM, Peterson ED, McCullough PA. Impact of obesity on cardiovascular disease. *Med Clin North Am* 2011 September;95(5):919-37.

(3) Roger VL, Weston SA, Redfield MM et al. Trends in heart failure incidence and survival in a community-based population. *JAMA* 2004 July 21;292(3):344-50.

(4) Kraschnewski JL, Boan J, Esposito J et al. Long-term weight loss maintenance in the United States. *Int J Obes (Lond)* 2010 November;34(11):1644-54.

(5) MacLean PS, Wing RR, Davidson T et al. NIH working group report: Innovative research to improve maintenance of weight loss. *Obesity (Silver Spring)* 2015 January;23(1):7-15.

(6) Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. *Physiol Rev* 2008 April;88(2):389-419.

(7) Alpert MA. Obesity cardiomyopathy: pathophysiology and evolution of the clinical syndrome. *Am J Med Sci* 2001 April;321(4):225-36.

(8)   Barouch LA, Gao D, Chen L et al. Cardiac myocyte apoptosis is associated with increased DNA damage and decreased survival in murine models of obesity. *Circ Res* 2006 January 6;98(1):119-24.

(9)   Zhou YT, Grayburn P, Karim A et al. Lipotoxic heart disease in obese rats: implications for human obesity. *Proc Natl Acad Sci U S A* 2000 February 15;97(4):1784-9.

(10)   Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clin Chem* 2010 February;56(2):254-61.

(11)   Alpert MA. Obesity cardiomyopathy: pathophysiology and evolution of the clinical syndrome. *Am J Med Sci* 2001 April;321(4):225-36.

(12)   Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol* 2009 May 26;53(21):1925-32.

(13)   Vincent HK, Powers SK, Dirks AJ, Scarpace PJ. Mechanism for obesity-induced increase in myocardial lipid peroxidation. *Int J Obes Relat Metab Disord* 2001 March;25(3):378-88.

(14)   Wende AR, Abel ED. Lipotoxicity in the heart. *Biochim Biophys Acta* 2010 March;1801(3):311-9.

(15)   Zhou YT, Grayburn P, Karim A et al. Lipotoxic heart disease in obese rats: implications for human obesity. *Proc Natl Acad Sci U S A* 2000 February 15;97(4):1784-9.

(16) Frankel DS, Vasan RS, D'Agostino RB, Sr. et al. Resistin, adiponectin, and risk of heart failure the Framingham offspring study. *J Am Coll Cardiol* 2009 March 3;53(9):754-62.

(17) Karas MG, Benkeser D, Arnold AM et al. Relations of plasma total and high-molecular-weight adiponectin to new-onset heart failure in adults >/=65 years of age (from the Cardiovascular Health study). *Am J Cardiol* 2014 January 15;113(2):328-34.

(18) Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Obesity and risk of incident heart failure in older men with and without pre-existing coronary heart disease: does leptin have a role? *J Am Coll Cardiol* 2011 October 25;58(18):1870-7.

(19) Szczepaniak LS, Dobbins RL, Metzger GJ et al. Myocardial triglycerides and systolic function in humans: in vivo evaluation by localized proton spectroscopy and cardiac imaging. *Magn Reson Med* 2003 March;49(3):417-23.

(20) Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol* 2009 May 26;53(21):1925-32.

(21) Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J* 2008 July;156(1):13-22.

(22) Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol* 2001 September;38(3):789-95.

Curriculum Vitae

Chiadi Ericson Ndumele was born on August 20, 1976 at Jacoby Hospital in Bronx, New York. He is the first of three sons to Eric and Patience Ndumele, immigrants from Nigeria. After graduating from Montclair High School, he attended Johns Hopkins University for his undergraduate training, where he received a B.A. with honors in Natural Science in 1998. He subsequently completed medical school at Harvard University, where he graduated *cum laude* in 2003. From 2003-2006, he completed residency training in Internal Medicine at Brigham and Women's Hospital, where he returned to serve as Chief Medical Resident during the 2008-2009 academic year. He began his Cardiology Fellowship at Johns Hopkins in 2006, completing two years of clinical training prior to taking a hiatus to serve as Chief Medical Resident. From 2009-2011, during the final two years of his Cardiology Fellowship, he completed a Masters of Health Science Degree in Epidemiology at Johns Hopkins' Bloomberg School of Public Health within the T32 Cardiovascular Epidemiology Training Program. For his academic performance, he was inducted into the Delta Omega Public Health Honor Society. During the final year of his Cardiology Fellowship (2010-2011), he also served as Chief Cardiology Fellow. He joined the faculty in the Division of Cardiology at Johns Hopkins as an Assistant Professor in 2011, devoting the majority of his time to clinical and population research related to adiposity and cardiovascular disease, while also serving as an attending physician in the Coronary Care Unit and the Outpatient Cardiology Clinic. In 2011, he also began his Doctorate of Philosophy in Epidemiology at Johns Hopkins' Bloomberg School of Public Health. In 2012, he was named the Robert E. Meyerhoff Assistant Professor at Johns Hopkins, awarded every five years to two minority faculty members in the School of Medicine demonstrating excellence in their field of study. He is married to Nicole Lee Ndumele and has a daughter, Faith Ngozi Lee Ndumele.