Challenges to the diagnosis and treatment of cardiovascular disease posed by the obesity epidemic

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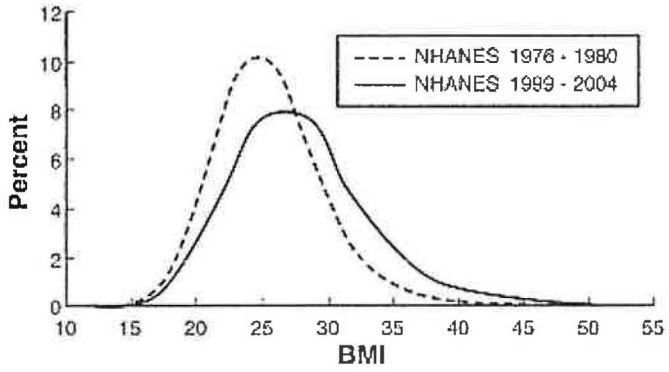
Challenge: How well do we understand the problem?

Obesity Prevalence

Obesity has become a health-care crisis in the United States, affecting one in three US adults[1] and leading to over 100,000 excess deaths[2] and over $100 billion in economic costs[3] annually. The prevalence of obesity (defined as a body mass index (BMI) ≥30 kg/m^2) has doubled over the past three decades. Using data from the National Health and Nutrition Examination Survey (NHANES), the prevalence of obesity at the time of the 1976-1980 survey was 15% overall (13% in men, 17% in women). By the 1999-2004 NHANES survey, this had increased to an overall obesity prevalence of 33% (32% in men, 34% in women).[4] The distribution of BMI in the two NHANES surveys is shown below (**Figure 1**).

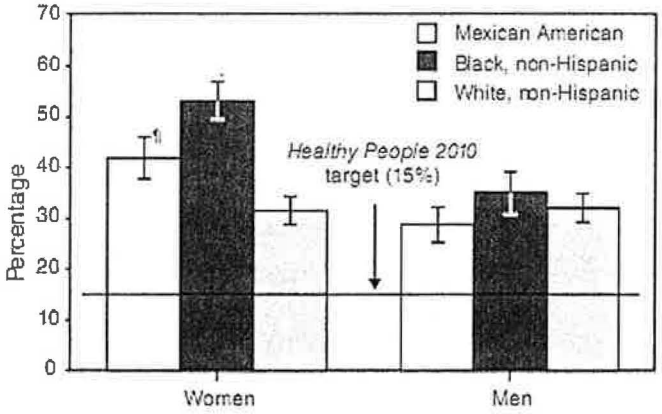
Figure 1. Distribution of BMI for US adults in NHANES 1976-1980 and NHANES 1999-2004[4]



Race/Ethnicity and Gender Differences

Obesity prevalence has steadily increased over time for both genders and all racial/ethnic groups.[5] Among men, obesity prevalence is reasonably similar across racial/ethnic groups. However, among women, African-Americans and Hispanics have markedly higher obesity prevalence compared with whites. In fact, more than half of African-American women were obese by NHLBI criteria (**Figure 2**).[3]

Figure 2. Prevalence of Obesity by Race/Ethnicity and Sex in NHANES 2003–2006


70
60
50
40
30
20
10
0
Percentage
Mexican American
Black, non-Hispanic
White, non-Hispanic
Healthy People 2010
target (15%)
Women
Men

Health Consequences and Costs

Obesity is associated with numerous health consequences, including hepatic and biliary disease, obstructive sleep apnea, degenerative joint disease, infertility and malignancy.[3] But the main cause of increased morbidity and mortality in obese individuals is cardiovascular disease. Obesity is associated with an increased incidence of coronary artery disease and stroke, and with deleterious effects on cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia.[6] The direct effects of obesity on cardiovascular physiology and its impact on cardiovascular disease and outcomes will be covered in more detail later.

As a result of its adverse impact on health, obesity is associated with an enormous cost burden. In fact, medical expenditures for obese workers are twice those for normal weight workers,[3] and per capita spending on medical costs were $1,429 higher annually for obese versus normal weight individuals.[7] Reported health-care costs due to obesity totaled $117 billion in 2000, roughly evenly split between direct costs, such as preventative, diagnostic, and treatment services, and indirect costs, which include wages lost due to illness, disability, or premature death.[8] A more recent report attributes a $40 billion rise in medical spending through 2006 to increased obesity prevalence, including a $7 billion increase in Medicare prescription costs, and goes on to forecast annual spending on obesity of $147 billion in 2008.[7] Projections based on extrapolating the NHANES data collected from the 1970s through 2004 suggest that if current trends continue, over half of US adults, including three out of four African-American women, will be obese by 2030 (**Table 1**).[9] Total health-care costs for overweight and obese patients are predicted to double each decade and by 2030 approach $900 billion annually.[9] This sum would account for approximately 1 in every 6 health care dollars.[9]

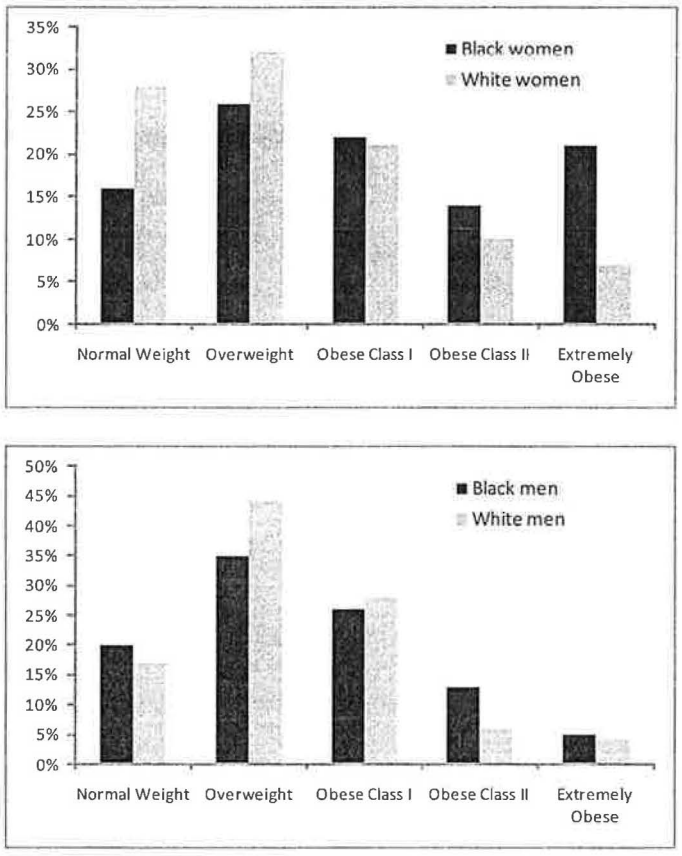
Table 1: Projected prevalence of obesity among US adults[9]

Gender	Ethnicity	Current (1999–2004)	Prevalence projections: prevalence (%) and projection interval		
			2010	2020	2030
Men	Non-Hispanic white	31.1	34.3 (32.3–36.3)	41.5 (38.9–44.0)	48.8 (45.7–51.9)
	Non-Hispanic black	34.0	36.4 (28.7–44.0)	42.7 (33.1–52.3)	49.1 (37.3–60.9)
	Mexican American	31.6	33.3 (29.2–37.4)	39.0 (33.9–43.3)	44.8 (38.5–51.1)
Women	Non-Hispanic white	30.2	35.6 (32.7–38.5)	41.7 (38.0–45.4)	47.9 (43.4–52.4)
	Non-Hispanic black	53.9	58.1 (52.2–64.0)	66.9 (59.6–74.1)	75.6 (66.6–84.6)
	Mexican American	42.3	44.4 (39.9–48.9)	50.1 (44.4–57.8)	55.8 (48.7–62.8)

Extreme obesity as an epidemic within an epidemic

As concerning as the rise in overall obesity prevalence is, a potentially more worrisome issue is apparent in the same data. Over the time period from 1960 to 2004 national estimates of obesity prevalence as a whole increased from 13.3% (10.7% in men, 15.8% in women) to 32.9% (31.7% in men, 34.0% in women), an increase of almost 150%. Over the same time interval, the population prevalence of extreme obesity (defined as a BMI≥40 kg/m^2) increased over 460% from 0.9% (0.3% in men, 1.4% in women) to 5.1% (3.0% in men, 7.3% in women).[4] The prevalence of extreme obesity in the Dallas Heart Study,[10] a multi-ethnic population-based probability sample of Dallas county residents designed to produce unbiased population estimates of cardiovascular disease, was 7.0%. Compared to the 5.0% prevalence of extreme obesity in contemporaneous national data, the higher rate of extreme obesity in this young, urban cohort raises the concern that the importance of the obesity epidemic may in fact be underestimated in high risk populations. In addition, the distribution of extreme obesity in Dallas County residents appeared to have racial and gender specific tendencies that were more pronounced than these tendencies in national surveys (**Figure 3**). Most strikingly, African-American women in Dallas County were more likely to be extremely obese then they were to be normal weight. Further research on the cardiovascular phenotype of extreme obesity and on the impact of extreme obesity on cardiovascular outcomes is ongoing.

Figure 3. The prevalence of BMI groups in Dallas County stratified by sex and race/ethnicity



Challenge: How does obesity affect cardiovascular outcomes?

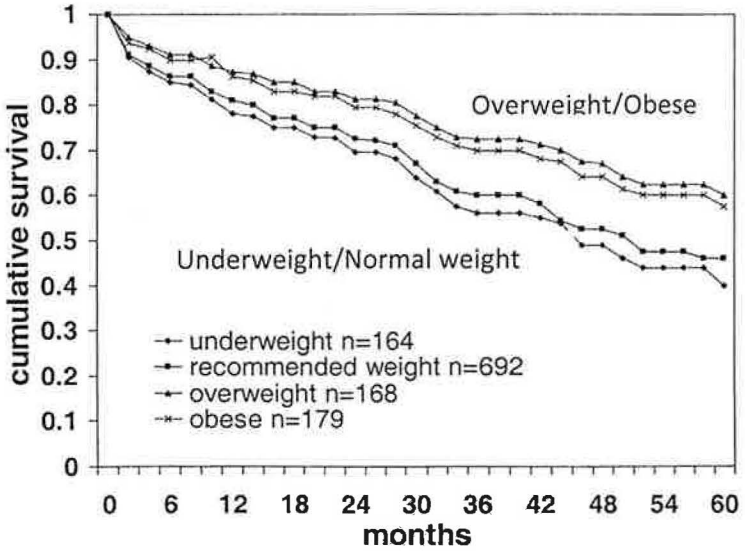
Cardiovascular effects of obesity

Obesity is associated with an increased total body blood volume, higher filling pressures, and increased sympathetic activation, which lead to increased stroke volume and heart rate. The resulting increased cardiac output (CO) is accompanied by decreased systemic vascular resistance (SVR) even though systemic arterial pressure tends to rise with increased weight. Cardiac work is increased. Increased stroke volume and filling pressures can also lead to left atrial or ventricular dilatation increasing the risk of atrial fibrillation and congestive heart failure (CHF). Obesity is associated with increased left ventricular mass, both concentric and eccentric hypertrophy, abnormalities of systolic and diastolic function, increased ventricular arrhythmias, and sudden cardiac death.[11]

Congestive heart failure

Obesity poses an increased risk for the development of heart failure (HF). A study by Kenchaiah and colleagues examined Framingham Heart Study patients over a 14 year period and found the risk of incident HF increased 7% in women and 5% in men with every 1 kg/m^2 increase in BMI.[12] Although a link exists between obesity and incident HF, studies have shown a better HF prognosis in obese patients (**Figure 4**).[13-15] In a meta-analysis by Oreopoulos and colleagues, over 28,000 HF patients were compared to normal weight individuals; obese patients had reduced CV and all-cause mortality.[13] An in-hospital mortality analysis in over 108,000 patients with acute decompensated HF also reported a statistically significant 10% decrease in mortality for every 5 kg/m^2 increase in BMI.[14] Several potential mechanisms of this protective effect have been proposed. Soluble tumor necrosis factor-alpha (TNF-α) receptors are produced by adipose tissue, possibly neutralizing the adverse effects of circulating TNF-α. Decreased levels of natriuretic peptides are present, and the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system are less activated. In advanced HF, increased caloric reserve is thought to counteract the catabolic state, extending life.[11, 13, 14]

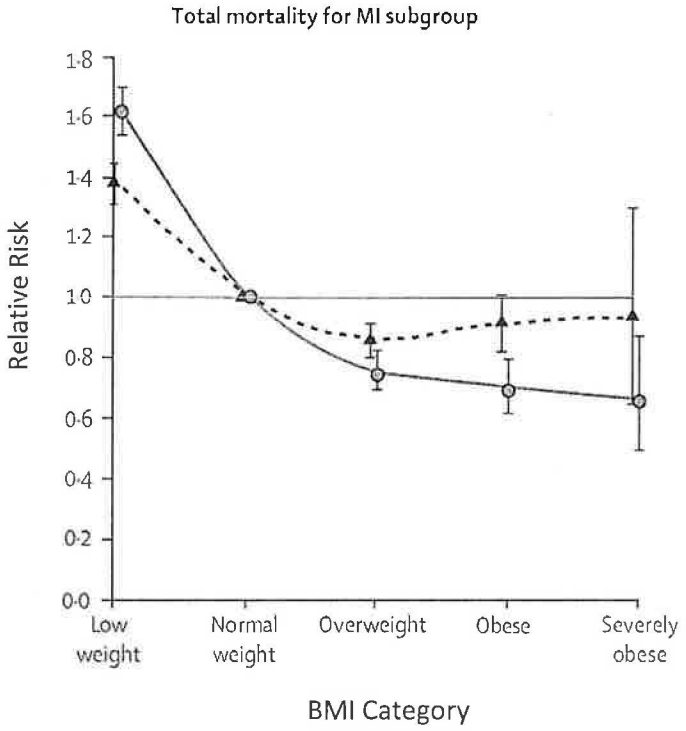
Figure 4. Risk-adjusted transplant-free survival curves for patients with HF stratified by BMI[15]


cumulative survival
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
6
12
18
24
30
36
42
48
54
60
months
Overweight/Obese
Underweight/Normal weight
underweight n=164
recommended weight n=692
overweight n=168
obese n=179

Coronary artery disease

Obesity is strongly associated with atherosclerosis, starting at a young age as fatty streaks in the vessel walls and progressing to frank atherosclerosis.[16] Prospective studies have shown obesity is an independent predictor of incident cardiovascular disease. However, in patients with known cardiovascular disease, after acute myocardial infarction, or after revascularization, overall obesity as assessed by BMI is inversely related to mortality (**Figure 5**).[17, 18] Some of the survival benefit seen with obesity in documented cardiovascular disease may be attributable to patient characteristics, as obese patients, although they have more comorbidities, are younger and more likely to present with single vessel disease.[19] Obesity is not associated with increased mortality after CABG, although it can be associated with wound infections.[20]

Figure 5. Mortality after myocardial infarction as a function of BMI category[17]



Hypertension

Obesity is associated with a higher prevalence for hypertension.[11] Despite this, hypertensive obese patients seem to have a better prognosis versus lean hypertensive patients.[21, 22] A U-shaped relationship between mortality and BMI has been observed, with excess mortality noted at both extremes of the BMI range. Hypertensive obese patients have also been noted to have lower all-cause mortality compared to normal weight patients even if their blood pressure control is worse.[23] This apparent paradox may be attributable to decreased RAAS activation and lower systemic vascular resistance in obese versus lean hypertensive patients.[11]

Atrial fibrillation

The hemodynamic effects of obesity, including elevated filling pressures, predispose to left atrial enlargement and atrial fibrillation.[11] A meta-analysis by Wanahita and colleagues, which included 5 population-based cohort studies and 11 post-cardiac surgery studies evaluated over 123,000 individuals and reported a 49% increased risk of incident AF with increasing BMI.[24] In contrast, post-cardiac surgery studies have generally failed to show an increased risk of post-operative atrial fibrillation in obese patients.[11]

Stroke

Obesity has been identified as an independent risk factor for stroke.[16] This increased risk is multifactorial, with contributing factors including a proinflammatory prothrombotic state, a higher prevalence of hypertension, and a higher prevalence of atrial fibrillation.[11, 16, 24] Result from the Physician's Health Study showed a 4% increase in the risk of ischemic stroke and a 6% increase in hemorrhagic stroke for each 1 kg/m^2 increase in BMI.[11, 25]

Ventricular arrhythmias/Sudden cardiac death

Obesity predisposes to a higher risk for ventricular arrhythmias and sudden cardiac death (SCD), even in the absence of left ventricular dysfunction.[11, 16] In fact, investigators from the Framingham Heart Study reported a 40 times higher annual SCD rate in obese versus non-obese individuals.[26] Several mechanisms associated with obesity are thought to cause this increased risk of SCD: increased electrical irritability, prolonged QTc interval, and the presence of abnormal late potentials. Finally, abnormalities in autonomic function resulting in decreased heart rate variability and an increased heart rate can also increase the risk of SCD in this patient population.[11]

Obesity cardiomyopathy

Obesity cardiomyopathy is thought to be a structural change to the heart attributable to metaplasia. Cords of cells can accumulate between muscle fibers or can cause myocyte degeneration. These pathologic infiltrative changes can lead to conduction system defects and even to the development of a restrictive cardiomyopathy.[16]

Venous disease

A higher intravascular volume and decreased physical activity in obese patients can predispose to edema and venous insufficiency.[11] Venous thrombosis and pulmonary embolism risks are higher.[11, 16] Abnormal endothelial function is also present, caused by increased oxidative stress leading to a decrease in nitric oxide or by proinflammatory cytokines.[16]

Obstructive sleep apnea

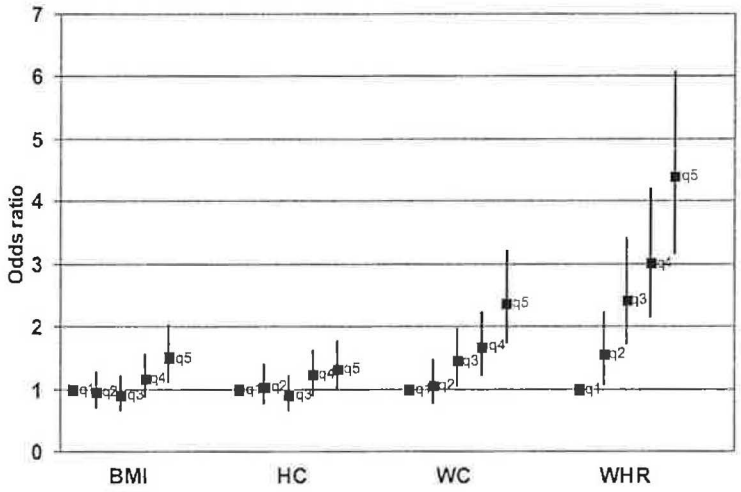
Alveolar hypoventilation due to obesity often leads to obstructive sleep apnea (OSA).[11, 16] This condition is worsened in obese individuals due to their respiratory muscle inefficiency, increased demand for ventilation and breathing workload, and decreased functional reserve capacity and expiratory reserve

volume.[16] Patients with OSA are at increased risk for HF, stroke, arrhythmias, hypertension, myocardial infarction, and overall mortality.[16, 27]

Challenge: How should we define obesity as a cardiac risk factor?

Although obesity is an established risk factor for the development of cardiovascular disease (CVD), the most appropriate method of quantifying obesity as a risk factor remains controversial. The most widely used tool for quantifying obesity, BMI, is at best an imperfect proxy for total body fat mass. However, imperfect as it may be, numerous studies have documented an association between increased BMI and incident cardiovascular disease and death.[28, 29] The importance of fat distribution is also the subject of much research interest, and the contention that visceral, rather than subcutaneous, fat is the true driver of the adverse cardiovascular impact of obesity has significant support. Waist circumference (WC), a proxy for abdominal obesity, appears to have a more significant association with metabolic syndrome and abnormalities of glucose or lipid metabolism; in contrast, hip circumference (HC), a proxy for peripheral obesity, has a neutral to inverse association with cardiovascular risk if total fat is appropriately controlled for.[30] Thus, the waist-to-hip ratio is a promising risk marker, reflecting the balance between central and peripheral obesity. As an example, See and colleagues reported the associations between measures of obesity and subclinical atherosclerosis from the Dallas Heart Study (**Figure 6**).[31]

Figure 6. Odds of detectable coronary artery calcium across sex-specific obesity quintiles[31]



WC= waist circumference, HC= hip circumference, WHR= waist-to-hip ratio

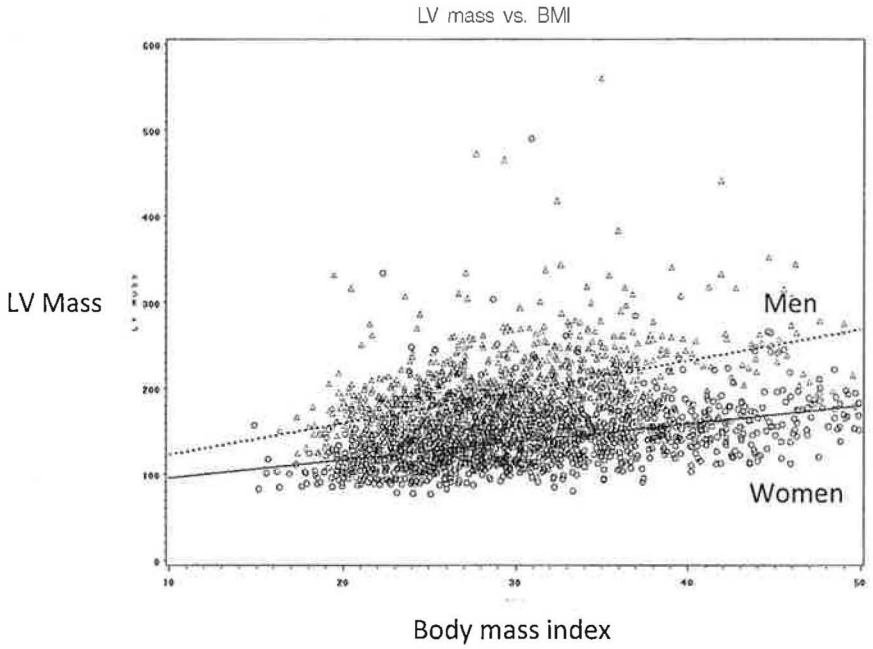
Although measures of visceral adiposity such as waist circumference or even DEXA or MRI-derived body composition analyses offer theoretical advantages, at the population level, this distinction may be less clinically relevant, since waist circumference and BMI correlate closely (Pearson r=0.8 in the DHS). In addition, BMI has several practical advantages in that it is cheap and easy to calculate, and has received widespread acceptance. In the most robust study addressing this issue, Gelber and colleagues used data from the Physician's Health Study[32] and the Women's Health Study[33] which when combined included almost 50,000 patients, 6 or more years of follow up, and a very large number of adjudicated hard end points. They found that BMI, waist circumference, waist-to-hip ratio, and waist-to-height ratio were highly correlated with each other (Pearson r=0.8) and all predicted incident cardiovascular disease with minor differences that were not clinically meaningful.[34]

Challenge: How do we know if obesity-related changes are pathologic?

Obesity and LV mass

The correlation between body size and left ventricular mass is well known (**Figure 7**). However, the most appropriate way to index LV mass for body size is less clear. One commonly used type of indexing uses ratiometric relationships, in this case LV mass/body surface area (BSA), to index for body size. There are two theoretical problems with that approach. First, it assumes a linear relationship between the cardiovascular variable and the body size variable. And second, it scales a three dimensional variable (LV mass) to a two-dimensional one (BSA), creating a mathematical relationship that is incompatible with the physiologic one. An alternative method of indexing uses allometric relationships, where the body size variable is exponentiated and the exponent is allowed to vary to fit observed data. Perhaps the best example, allometric height, indexes LV mass/height$^{2.7}$ with a data-derived exponent approximately what we would expect due to scaling.[35]

Figure 7. Association between LV mass and BMI stratified by sex in the DHS

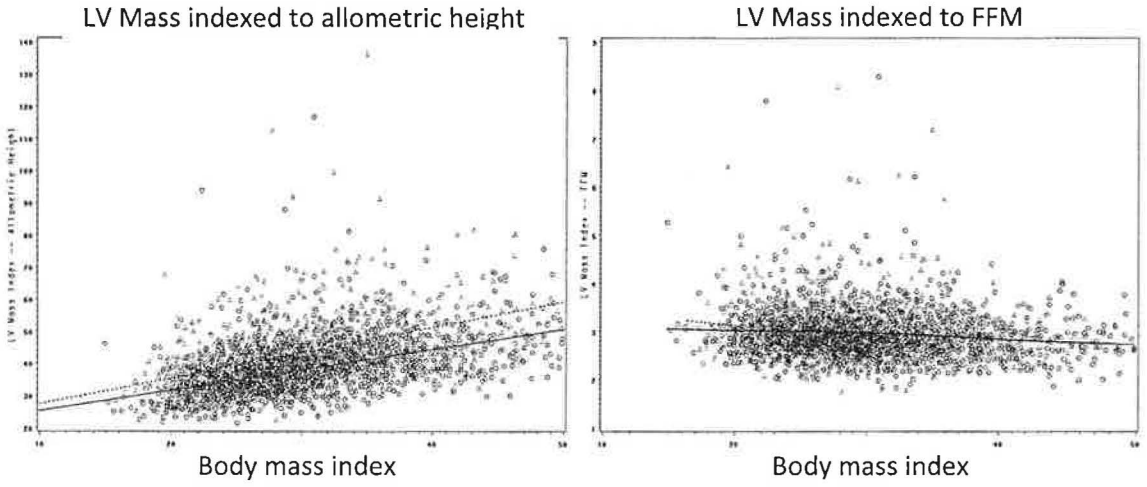


With the emergence of body composition analysis by DEXA into the mainstream, it has now become possible to index LV mass to fat free mass (FFM) which has a strong theoretical advantage in that is scales heart size with that of metabolically active tissues. A large study including almost 1,000 patients with a mean 7 years of follow up showed that both indexing LV mass to BSA and to height$^{2.7}$ predicted similar increases in risk and that subjects classified as having LVH by the allometric height but not body surface area criteria showed no increase in risk, even though these subjects were more likely to be obese.[36] There are no long term outcomes data available for LV mass indexed by FFM.

It is entirely intuitive that someone who is six feet tall and weighs 175 pounds should have a larger heart than someone who is five feet four inches tall and weighs 140 pounds. What is less intuitive is what

should happen if the shorter of the two were to gain an additional 35 pounds of adipose. We know from observation that LV mass will increase with obesity, but it turns out that our decision of how to index LV mass to body size has important implications for whether we associate obesity with LVH. Indexing to allometric height assumes that heart size should not change, regardless of what happens to weight, leading to a very strong correlation between obesity and LVH (**Figure 8**). The opposite occurs with indexing to fat free mass. Fat free mass goes up significantly with increasing obesity. In fact, fat free mass increases to an equal or greater extent than LV mass, leading to a neutral or even inverse relationship between LVH and obesity.[37]

Figure 8. Association between LV mass index and BMI in the DHS



Challenge: Can we study pathophysiology through epidemiology?

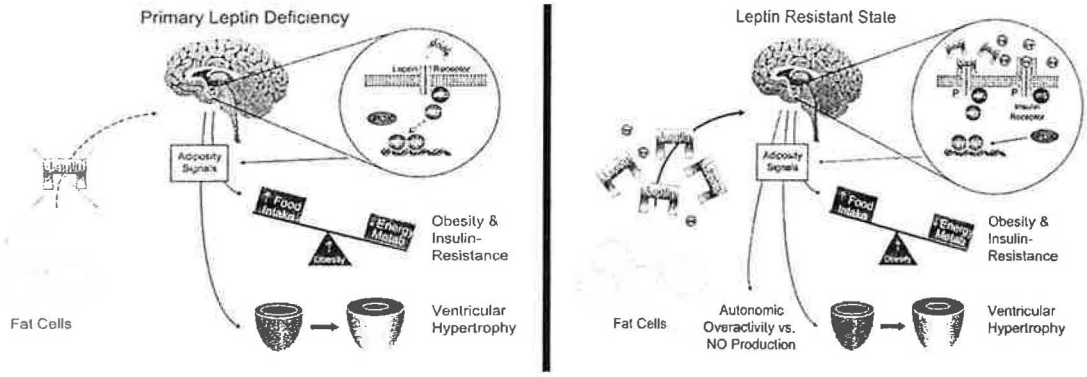
Leptin and LV hypertrophy

A detailed explanation of the pathophysiologic effects of obesity on the heart is still under investigation. One of the major correlates of obesity is increased serum concentrations of leptin, a peptide hormone produced by adipocytes. The product of the obesity (ob) gene, leptin acts on hypothalamic receptors to decrease food intake and increase energy expenditure. It also has been shown to act on tissue receptors expressed in the heart, although the phenotypic effects of leptin on the heart have not been well characterized. The physiologic role of leptin has not been fully elucidated, but is believed to include protecting non-adipose tissue from lipid-induced trauma from overnutrition by directly limiting the level of overnutrition and by upregulating fatty acid oxidative capacity. Low leptin levels redistribute mass centrally in times of caloric shortfall.[38]

There are murine knockout models of leptin deficiency and leptin resistance. Both of these knockout models lead to the phenotype of hyperphagia and decreased energy expenditure.[39] In primary leptin deficiency, the leptin receptor is unoccupied, leading to adiposity signals and ventricular hypertrophy that is correctable with leptin infusion (**Figure 9**). Leptin resistance is the mechanism believed to occur in human obesity.[40] In the setting of caloric excess, phosphorylation of the leptin receptor leads to decreased leptin signaling resulting in relative leptin deficiency. This also leads to obesity and ventricular hypertrophy.[40, 41] Leptin has direct antihypertrophic effect on cultured neonatal rat

myocytes. In adult mice, leptin deficiency leads to LVH that can be reversed by leptin administration; caloric restriction reverses the obesity but does not reverse the LVH.[42]

Figure 9. Leptin deficiency and Leptin resistance[41]



Human studies of the association between leptin and LV mass or LV wall thickness have been inconclusive.[43] Using data from the Dallas Heart Study, including precise measurements of fat and lean mass by DEXA and detailed cardiac phenotyping by MRI, we were able to demonstrate the relationship between serum leptin concentration and LV geometry from an epidemiology perspective. Increasing leptin was associated with decreasing LV mass decreasing LV mass, LV end diastolic volume (EDV), and LV wall thickness (WT) (**Table 2**). These results remained significant after multivariable modeling in women, but not men, likely due to lower leptin levels in men. However we cannot exclude a true gender difference in the relationship between leptin and LV geometry.

Table 2. Models showing the relationship between leptin and LV geometry

Women			**Men**		
	Unadjusted			**Unadjusted**	
Outcome	beta ± SE	P	Outcome	beta ± SE	P
LV Mass	-10.2 ± 1.7	<0.001	LV Mass	-1.7 ± 1.0	0.087
LV EDV	-8.4 ± 1.1	<0.001	LV EDV	-2.0 ± 0.6	0.002
LV WT	-0.2 ± 0.1	0.005	LV WT	0.01 ± 0.04	1
	Adjusted*			**Adjusted***	
LV Mass	-4.2 ± 1.3	0.001	LV Mass	-0.5 ± 0.8	0.5
LV EDV	-2.8 ± 1.1	0.009	LV EDV	-0.8 ± 0.6	0.2
LV WT	-0.2 ± 0.1	0.033	LV WT	0.01 ± 0.03	0.7

*Multivariable models are adjusted for fat and lean mass, race/ethnicity, HTN, CHF, CAC>10, and smoking status

Challenge: Are our tools good enough?

Obesity and detecting LVH by ECG

The presence of left ventricular hypertrophy (LVH) is associated with adverse cardiovascular outcomes including heart failure and cardiovascular death.[44-47] This association is particularly robust among women[44] and African-Americans.[47, 48] In addition to offering prognostic information, successful identification of LVH in asymptomatic patients at risk for adverse cardiovascular events can help guide therapy.[49] Electrocardiography (ECG) is the most common means of screening for LVH because it is inexpensive, rapidly performed, and readily available. However, the low sensitivity of commonly used ECG criteria for LVH can lead to a high rate of false negative results, especially in populations where the prevalence of LVH is high.[50-52] Obesity is particularly problematic because it is associated with increased LVH,[53-55] yet has effects on the morphology of the ECG that decrease sensitivity for detecting LVH.[56-58]

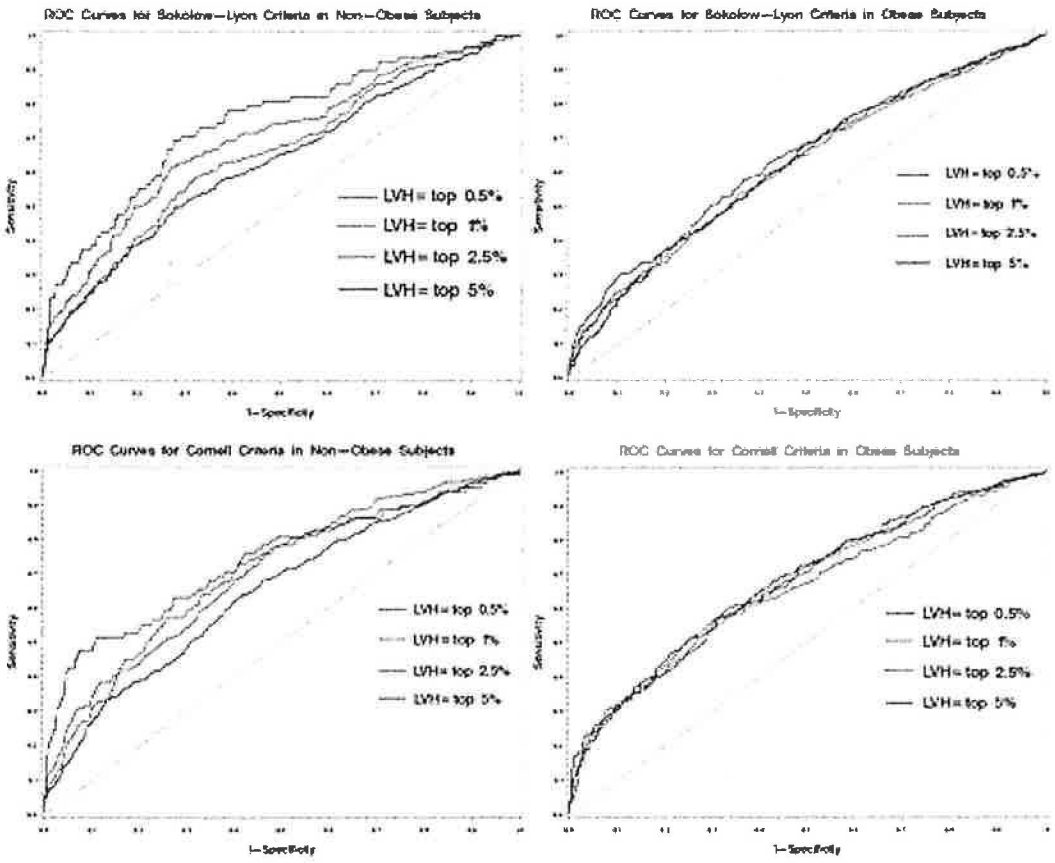
Using data from the Dallas heart Study including precise measurement of LV mass by cardiac MRI, we were able to precisely quantify the effects of obesity on the ECG diagnosis of LVH in the largest multi-ethnic population based cohort examined to date. MRI derived left ventricular mass (LVM) was indexed to allometric height (height$^{2.7}$), and LVH was defined as an LVM index (LVMI) greater than the gender-specific 97.5th percentile of a healthy, normotensive, normal-weight subpopulation of the DHS.[48] Sensitivity analysis was performed to investigate the effect of LVH severity on test performance using additional definitions of LVH: 95th, 99th percentile, and 99.5th percentile. The 99.5th percentile values most closely approximate echo-derived values that previously have been identified as optimal thresholds to predict clinical cardiovascular events.[59] LVMi $\geq$ 99.5th percentile will be further denoted as moderate to severe LVH.

There were 55% women and 49% African-American subjects in the study sample. Mean age was 44 and mean BMI was 30 kg/m^2; the prevalence of hypertension and diabetes were 32% and 10%, respectively. The prevalence of LVH was 31% and of moderate to severe LVH was 14%. Obese subjects were more often women and African-American ($p<0.0001$ for each) and had significantly higher rates of hypertension and LVH ($p<0.0001$ for each). The mean LVM and LVMI were significantly higher among obese subjects ($p<0.0001$ for each). Overall test sensitivity for LVH using published voltage partitions was low (9-17%) and specificity was high (95-97%) for all ECG methods. Sensitivity increased for all criteria when the definition for LVH was restricted to moderate to severe LVH.

C-statistics for moderate to severe LVH were significantly higher in the non-obese compared to the obese group, comparisons between obese and non-obese groups for less severe LVH did not reach statistical significance. To further illustrate the differences in test performance for varying degrees of LVH, ROC curves were generated for additional cutoffs of LVMI (**Figure 10**). ECG sensitivity and overall test performance improve as the severity of LVH increases in non-obese subjects. In contrast, ECG sensitivity remains uniformly poor even for severe LVH in obese subjects. For obese subjects, the ROC curves for LVH definitions ranging from very inclusive (95th percentile) to very strict (99.5th percentile) are only slightly above the line of unity and are indistinguishable. In contrast, for normal weight participants, we observed a progressive increase in the c-statistic with increasing LVH severity. Subdivided further by BMI, obese subjects have low sensitivity for all LVH definitions, showing the ECG performs poorly among the obese for all severities of LVH. The increase in c-statistic for normal weight

participants does not become noticeable until above the 97.5th percentile cutoff, suggesting that the ECG performs poorly for detecting mild LVH regardless of the presence of obesity.

Figure 10. ROC curves for LVH stratified by obesity, LVH severity, and LVH definition



In order to highlight the importance of obesity, sex, and race upon ECG performance, we produced a model to predict false negative classification by the ECG (**Table 3**). We included the above characteristics and current smoking, the only other simple clinical predictor that consistently predicted false negative status in logistic regression models. These factors may allow physicians to quickly identify patients who are less suitable for LVH screening with the ECG and to better interpret test results. Notably, obesity had the strongest association with false negative classification, regardless of LVH severity. False negative rates in normal weight subjects are generally low for moderate to severe LVH and high for less severe LVH, which reiterates our finding that the ECG poorly identifies mild LVH in all groups.

Table 3. Predictors of false negative classification for LVH by ECG

Odds of False Negative Classification			
Risk Predictor	Odds Ratio	95% Confidence Limits	
Age	0.99	0.98	1.005
African-American	1.62	1.32	1.98
Hypertension	2.19	1.74	2.75
Obesity	6.46	5.23	7.98
Female Sex	3.09	2.51	3.81
Diabetes	1.16	0.86	1.58
Current Smoking	1.32	1.05	1.65

In summary, our findings are threefold: 1) all ECG criteria perform very poorly for detecting mild LVH, 2) sensitivity for detecting more severe LVH is improved among non-obese subjects, but remains poor in obese subjects, regardless of the criterion used, and 3) false negative evaluations for LVH can be predicted using simple clinical criteria, of which obesity is the most important. The high false negative rate among obese subjects suggests that appropriate skepticism be applied to a negative ECG result for LVH in obese patients or those with multiple other risk predictors. In the context of the growing obesity epidemic, we will continue to see a decline in the value of the ECG alone as a screening tool for LVH which may lead to increased reliance on more expensive imaging modalities to confirm suspected LVH, an as yet unappreciated economic consequence of the obesity epidemic.

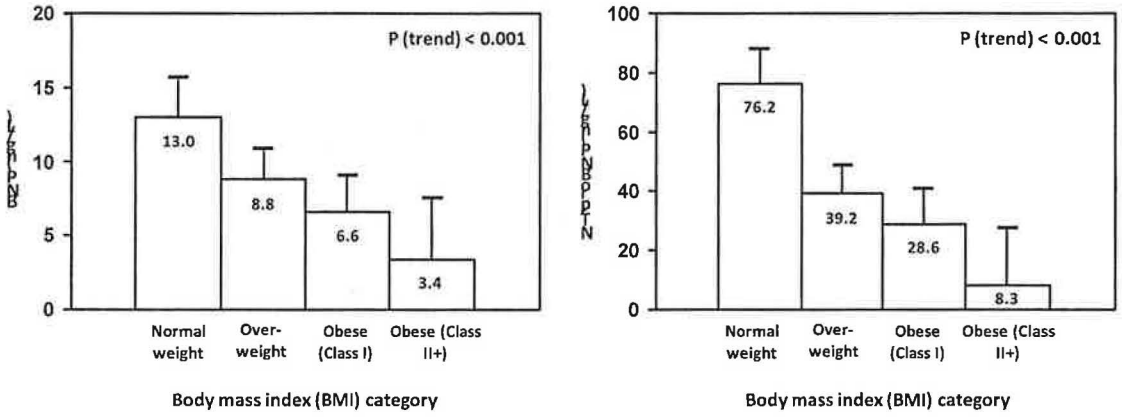
Challenge: How does obesity affect biomarker metabolism?

The effect of obesity on natriuretic peptide concentrations

The natriuretic peptide (NP) system consists of a family of three peptides with potent natriuretic and vasodilatory properties. B-type natriuretic peptide (BNP) is secreted as a pro-hormone and then cleaved into the active BNP and the inactive NT-proBNP. The effects of BNP include increased vascular endothelial permeability, suppression of the renin angiotensin aldosterone axis, and natriuresis. Transgenic mice overexpressing BNP have BNP concentrations 10x normal and SBP 20-30 mmHg lower than controls, while inactivation of the natriuretic peptide system leads to salt-sensitive hypertension. Wang and colleagues from the Framingham Heart Study showed that higher BMI was associated with lower BNP levels. They postulated that this inverse relationship may be due to increased expression of the NPR-C clearance receptor by adipose tissue resulting in increased clearance of BNP in obese subjects, and suggested that this may help explain the cause of obesity-related hypertension.[60, 61] In order to further elucidate the role of NPR-C in mediating the relationship between obesity and BNP, we examined two hypotheses. First, that the concentration of amino-terminal (NT)-proBNP, which is not believed to bind NPR-C,[62] would be unrelated to measures of obesity, and second, that BNP would be inversely related to fat mass, but not lean mass. Using data from the Dallas Heart Study we confirmed

the previously described association between higher BMI and lower BNP (**Figure 11**) and demonstrated for the first time a similar inverse relationship between higher BMI and lower NT-proBNP.[63]

Figure 11. Natriuretic peptide concentrations across categories of BMI[63]



To further elucidate this relationship, we performed detailed multivariable modeling (**Table 4**). When BMI was replaced in the models by direct measurements of fat and lean mass from DEXA body composition analysis, only lean mass retained the independent inverse association with both BNP and NT-proBNP; fat mass was not associated with either BNP or NT-proBNP.

Table 4. Natriuretic peptide levels and body composition [63]

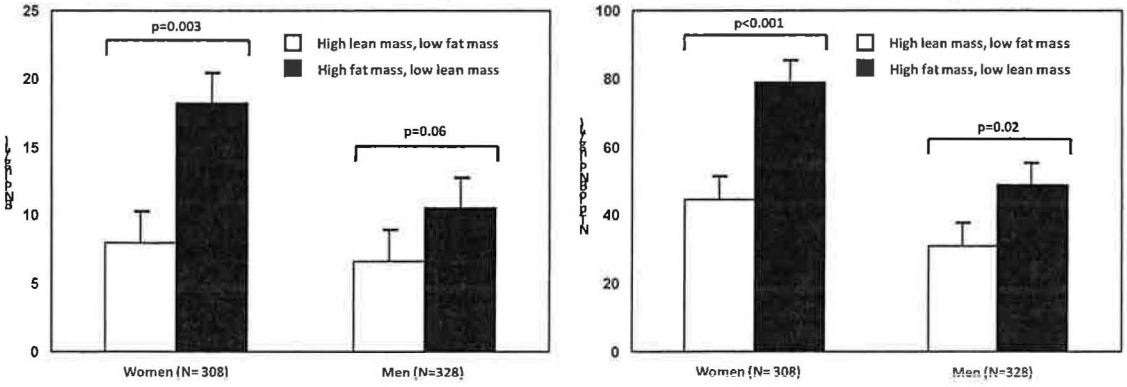
Logistic regression models for low BNP and N-terminal-proBNP	Men Odds Ratio (95% CI)	Women Odds Ratio (95% CI)
Odds of low BNP		
Model 1:		
Body mass index (per 5 kg/m^2)	1.34 (1.16-1.55)	1.11 (1.02-1.21)
Model 2:		
Total body fat mass (per 10 kg)	0.94 (0.79-1.14)	0.97 (0.84-1.12)
Total body lean mass (per 10 kg)	1.62 (1.32-2.00)	1.44 (1.12-1.84)
Odds of low N-terminal pro-BNP		
Model 1:		
Body mass index (per 5 kg/m^2)	1.42 (1.20-1.68)	1.19 (1.08-1.31)
Model 2:		
Total body fat mass (per 10 kg)	1.05 (0.85-1.32)	0.94 (0.79-1.11)
Total body lean mass (per 10 kg)	1.55 (1.21-1.99)	1.63 (1.20-2.20)

Multivariable logistic regression models are stratified by sex and adjusted for age, race/ethnicity,

diabetes, hypertension, prior myocardial infarction, left ventricular mass and end diastolic volume; low BNP is defined as <4 ng/L, low NT-proBNP is defined as in the lowest sex-specific quartile (<7.6 ng/L for men, < 20.4 ng/L for women).

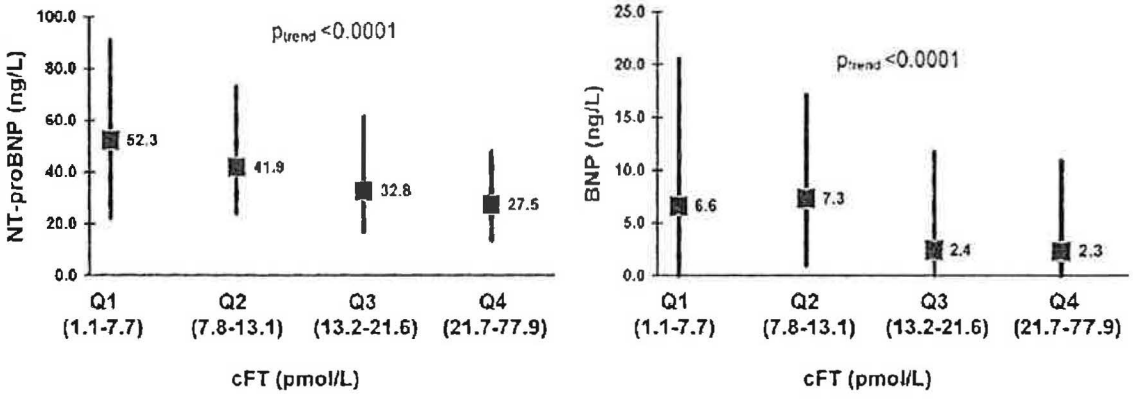
Confirmatory stratified analyses comparing subjects with discordant lean mass and fat mass values showed the same result (**Figure 12**). BNP and NT-proBNP levels were significantly lower among subjects with below-median fat mass and above-median lean mass versus those with above median fat mass and below-median lean mass. We concluded that the association between higher BMI and lower NT-proBNP showed that non-clearance mechanisms are likely to be important, and postulated, since the association was similar for BNP and NT-proBNP, this effect could be mediated by sex steroid hormones that coordinately influence natriuretic peptide synthesis as well as body composition.[63]

Figure 12. Natriuretic peptide levels stratified by sex and fat and lean mass[63]



In a follow up study using data from the Reynolds Women's Study,[64] we demonstrated an inverse association between natriuretic peptide levels and measures of free testosterone status (**Figure 13**). After adjusting for measures of free testosterone, BMI and lean mass were no longer significantly associated with BNP or NT-proBNP, highlighting the significance of lean mass and suggesting that eternal factors such as free testosterone may be very important in understanding the relationship between BMI and cardiovascular disease.

Figure 13. Natriuretic peptide levels across quartiles of calculated free testosterone (cFT)[64]



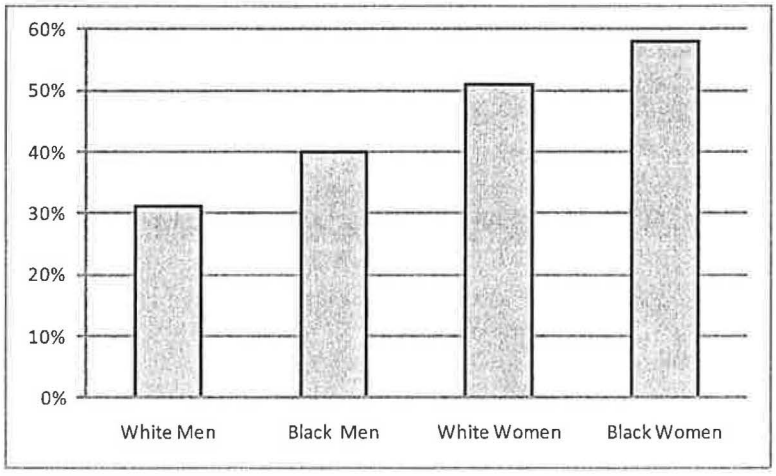
Challenge: How do gender and racial differences impact obesity and cardiovascular disease?

C-reactive protein (CRP), Sex, Race/Ethnicity, and Obesity

Measures of obesity are among the strongest correlates of CRP levels, and suggest inflammation may help explain the greater burden of cardiovascular disease among obese individuals. Prospective studies have demonstrated a clear association between higher levels of C-reactive protein (CRP) and adverse cardiovascular events.[65] AHA guidelines have defined the high-risk threshold for CV events as >3 mg/l. In order to assess the implications of this threshold in women and African-Americans we once again went to the Dallas Heart Study.[66] The proportion of subjects who would be considered high-risk for CV events based on CRP levels was estimated for each race and sex group (**Figure 14**). Black women, black men, and white women were significantly more likely to have CRP values in the high-risk range compared with white men.

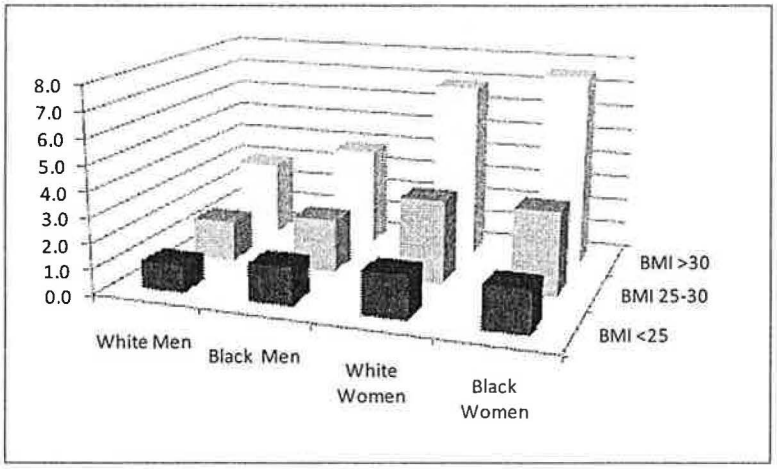
With respect to ethnicity, higher CRP levels in African-Americans may reflect a higher risk factor burden or racial differences in inflammation. However, it is also possible that CRP may overestimate the risk for cardiac and vascular events in African-Americans. The prognostic implications of the racial differences in CRP distributions cannot be determined from these cross-sectional data. Long-term outcome studies in African-American subjects are needed to determine the implications of these findings and to determine whether the CDC/AHA risk thresholds are appropriate. Although the association between elevated CRP levels and adverse CV outcomes in women is clear, the utility of a threshold that identifies over half of all women in Dallas between the ages of 30 and 65 as at high risk is not clear.

Figure 14. Proportion above a CRP threshold of 3 mg/l stratified by race and sex



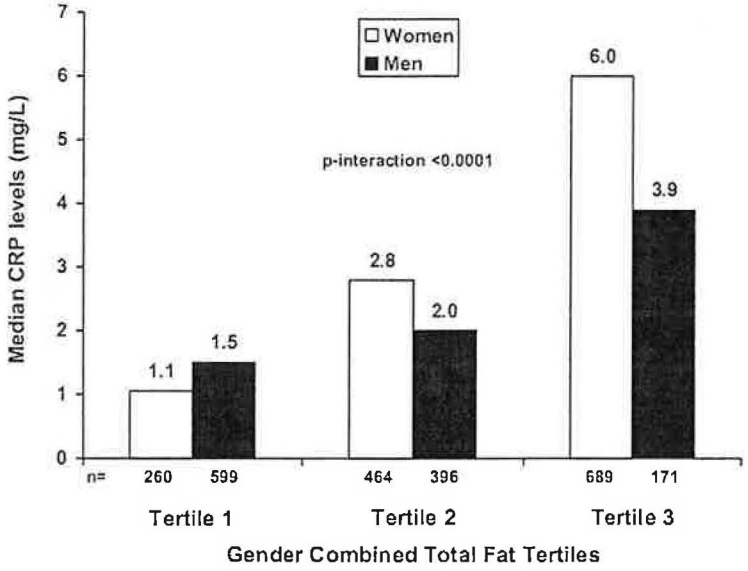
These differences appear to be mediated in large part by gender differences in the relationship between obesity and CRP; CRP levels increase to a greater degree with increasing adiposity in women than in men (**Figure 15**).

Figure 15. Relationship between CRP and BMI by race and sex



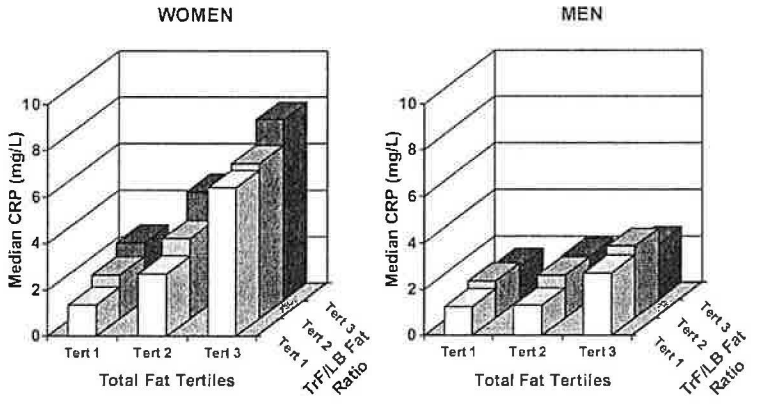
Using DEXA-derived determinations of total body fat mass, we were able to show that fat mass is driving the relationship between BMI and CRP as well as the gender interaction.[67] We demonstrated that women and men in the lowest tertile of total fat mass had comparable CRP levels, but median CRP increased to a much greater degree with increasing total fat mass in women compared with men (adjusted P-interaction<0.0001) (**Figure 16**).

Figure 16. Sex differences in the association between total fat and CRP[67]



Differences in body fat distribution as determined by MRI appear to contribute modestly to the gender difference in the association between CRP levels in and fat mass. CRP levels were positively correlated with increases in truncal fat in women but not men in models adjusted for total body fat mass (**Figure 17**).

Figure 17. Truncal (TrF) to lower body fat (LBF) ratio and CRP levels stratified by sex[67]



In the largest study to date evaluating the association between leptin and CRP, we found a strong association between plasma leptin and CRP levels in women, but not in men, independent of measures of adiposity. This suggests there may be sex-related differences in the inflammatory response to obesity that is in part mediated by leptin. The mechanisms behind these findings are unknown, but they may reflect direct stimulation of CRP release from the liver by leptin or an indirect mechanism such as leptin mediated increased production of IL-6.[68]

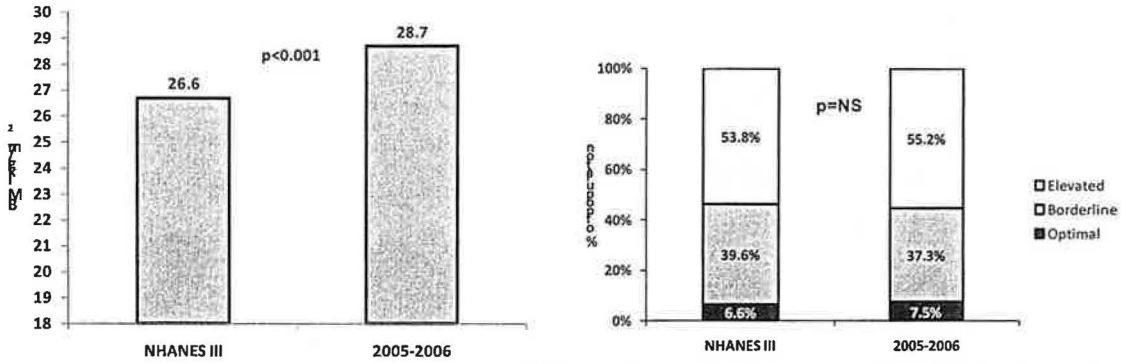
The implications of this sex interaction are unclear. It is possible that inflammation may disproportionately affect women as they become more obese, and contribute to the development of cardiovascular risk factors and adverse cardiovascular events. Alternatively, the strong association between adiposity and CRP may lessen the predictive power of CRP for cardiovascular events in obese populations, particularly women. Given the increasing interest in using CRP for cardiovascular disease risk stratification, it is important to consider whether CRP risk as defined in the AHA statement may not properly apply to a contemporary, multiethnic population with high rates of obesity.

Challenge: How is obesity affecting cardiovascular risk over time?

Understanding how risk factor profiles change over time may provide insight into how to modify cardiovascular disease rates in the US population. Using data from the National Health and Nutrition Examination Survey (NHANES), a population instrument designed to assess the health and nutritional status of the entire US population, we assessed changes in risk factor profiles over the past two decades.

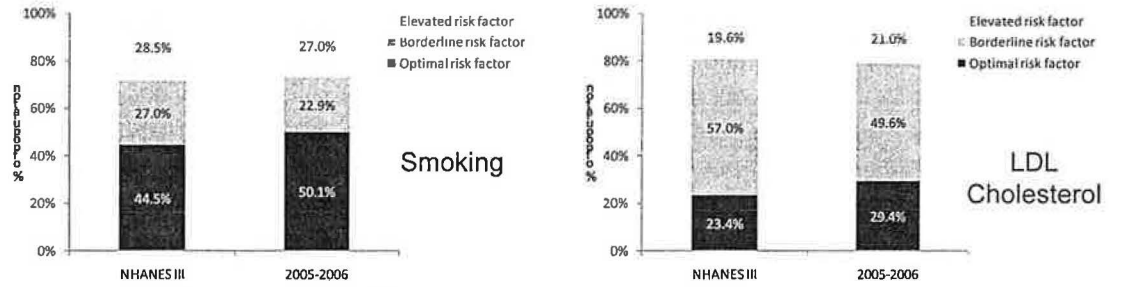
Our early comparison group data came from NHANES III (1988-1994) and the late comparison group data were drawn from the NHANES 2005-2006. Prevalence data from each time point were age-standardized to the 2000 census to allow between-group comparisons. Each individual was risk stratified based on four factors, fasting glucose, blood pressure, LDL cholesterol, and smoking status into one of three groups: optimal (all optimal risk factors), borderline (one or more borderline, but no elevated risk factors), or elevated (one or more elevated risk factors). Over the twenty year interval, mean BMI increased significantly (**Figure 21**).

Figure 21. BMI and cardiac risk factor profile in NHANES III (1988-1994) and NHANES 2005-2006



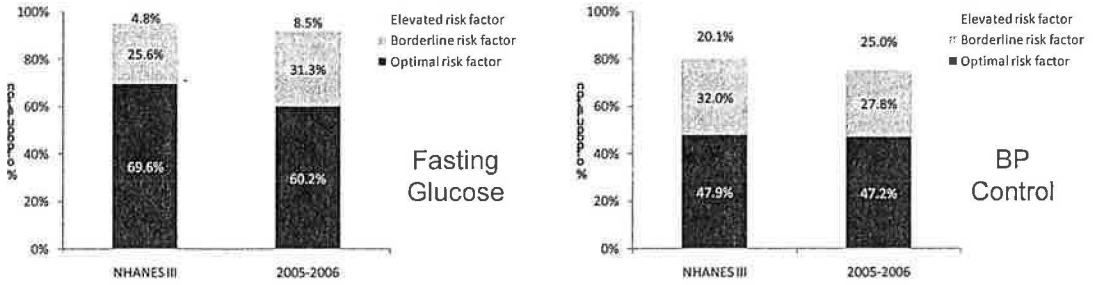
Over the same time period, there was essentially no change in the population distribution of cardiovascular risk. The prevalence of an optimal risk factor profile remained low and over half the population continued to have an elevated risk factor profile. In order to try to understand why the overall risk profile remains unaffected despite a massive public health effort aimed at improving cardiovascular risk, and to uncover any hidden deleterious effects of the rise in obesity, we further examined the component risk factors that comprise the overall profile (**Figure 22**).

Figure 22. Improvement in smoking status and LDL cholesterol from 1988-1994 to 2005-2006



Examining smoking status and LDL cholesterol levels offers some positive signs. The increase in "optimal risk" for smoking reflects a drop in the rate of new smokers entering the adult population, and the increase in "optimal risk" for LDL cholesterol reflects better attainment of more stringent LDL targets. However, the other component risk factors offer cause for concern. The proportion of people in the worst risk factor category for fasting glucose has risen dramatically; blood pressure control has worsened as well. (**Figure 23**).

Figure 23. Worsening in fasting glucose and blood pressure control from 1988-1994 to 2005-2006



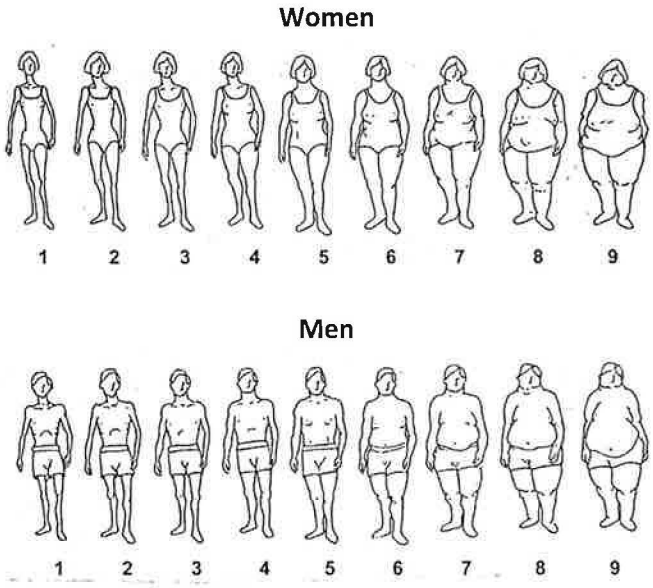
Thus it appears that improvements in smoking status and LDL cholesterol control over the past 20 years were entirely offset by worsening in fasting glucose and blood pressure control. While the current study is limited in its ability to draw causal inferences, it seems likely that the steady rise in obesity over the same time period may help explain our failure to improve in the latter categories. Failure to appropriately address the obesity epidemic may halt the decline in CV morbidity and mortality rates we are currently enjoying.

Challenge: Why do we fail at obesity prevention?

Body Size Misperception

One obstacle to attempted weight loss and potential target for intervention is misperception of body size. Among obese individuals (BMI ≥ 30 kg/m^2), misperception is defined as the desire to maintain or even gain weight. In order to further elucidate the extent and significance of body size misperception, and its potential impact on cardiovascular disease prevention, we examined over 2,000 obese subjects from the Dallas Heart Study.[10] Study participants were shown the Stunkard scale, a well-validated gender-specific visual scale of nine figures representing increasing body sizes from very thin (1) to very large (9) (**Figure 18**).[69]

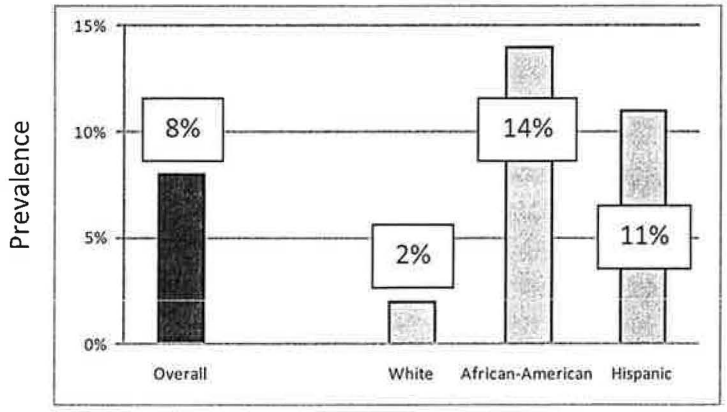
Figure 18. Stunkard figure rating scale[69]



The Stunkard scale has been used previously in multi-ethnic populations[70] and has been correlated to increasing BMI across scale figures in Caucasian populations.[71] Participants were asked to choose from the body size figures to answer the following questions about themselves: (1) "Choose your ideal figure" (ideal body size) and (2) "Choose the figure that reflects how you think you look" (actual body size). Among obese individuals, body size misperception was defined as a self-perceived ideal body size larger than their self-perceived actual body size, representing a desire to maintain or gain weight. Questions to assess beliefs about general health perceptions and health care access were obtained from the 1999 Behavioral Risk Factor Surveillance System Questionnaire.[72]

We determined the sample-weight adjusted distribution of body size misperception in the obese Dallas County population in 2000, overall and stratified by race/ethnicity (**Figure 19**). Almost 1 in 10 obese Dallas County adults had body size misperception, meaning they wished to maintain or gain weight. This belief was held predominantly among African Americans and Hispanics, as compared to Caucasians.

Figure 19. Body size misperception in Dallas County overall and Stratified by Race/Ethnicity



Subjects with body size misperception (**Table 5**) were younger and more likely to be male. Little difference existed in baseline lipids and fasting glucose and the prevalence of hypercholesterolemia or diabetes was similar. There was a lower prevalence of hypertension among those with misperception, but negligible differences in mean systolic and diastolic blood pressure. Despite a larger BMI in the population without misperception, both groups had similar lean body mass and waist to hip ratios, suggesting that those with misperception did not have a more athletic or muscular body habitus. Importantly, those with misperception were much less likely to exercise. Overall, individuals with misperception were not healthier than those without misperception.

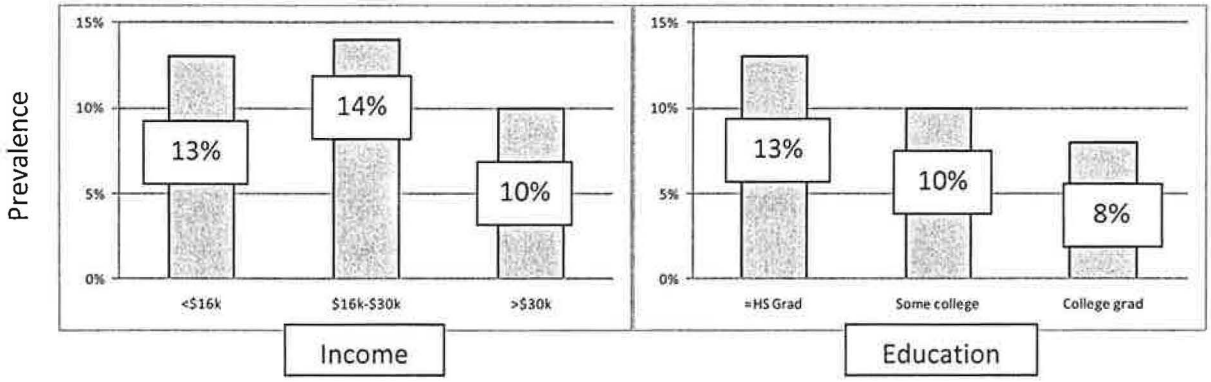
Table 5. Characteristics of obese (BMI ≥ 30 kg/m2) DHS subjects stratified by Body Size Misperception

Characteristics of Obese DHS Population Stratified by Body Size Misperception			
Characteristic	**Body Size Misperception (N=266)**	**No Misperception (N=1790)**	**P-value**
Age* (yrs)	39.5 ± 12.5	41.6 ± 11.8	0.009
Men	121 (45%)	649 (36%)	0.004
BMI* (kg/m^2)	34.6 ± 4.6	36.6 ± 6.0	<0.0001
Lean Body Mass* (kg)	62.5 ± 11.2	60.6 ± 11.9	NS
Waist Circumference* (cm)	110.8 ± 12.1	113.6 ± 14.3	0.020
Waist-Hip Ratio*	0.9 ± 0.1	0.9 ± 0.1	NS
SBP* (mmHg)	131.5 ± 18.4	131.3 ± 19.5	NS
DBP* (mmHg)	80.7 ± 10.4	80.9 ± 10.2	NS
Total Cholesterol* (mg/dl)	183.7 ± 39.1	182.2 ± 39.3	NS
LDL* (mg/dl)	113.1 ± 35.4	108.5 ± 34.7	NS
HDL* (mg/dl)	47.2 ± 11.6	46.5 ± 11.9	NS
Triglycerides* (mg/dl)	121.5 ± 114.5	142.8 ± 128.1	0.070
Fasting Glucose*(mg/dl)	109.2 ± 53.4	112.2 ± 50.0	NS
History of Hypertension	92 (35%)	752 (43%)	0.020
History of High Cholesterol	21 (15%)	183 (15%)	NS
History of Diabetes	20 (14%)	251 (20%)	NS
Family History of Premature MI	24 (9%)	206 (12%)	NS
Current Smoker	73 (27%)	414 (23%)	NS
Exercise Dose** (METS*min/wk)	0 (0, 319)	60 (0, 479)	<0.0001

Results shown are mean ± SD, median(IQR), or N (%) as appropriate

Comparison of socioeconomic status did not fully explain body size misperception. Study subjects with higher income or attained education did have a non-statistically significant trend toward lower prevalence of body size misperception. The unweighted prevalence rates are shown below (**Figure 20**). Unweighted data are reported here. The prevalence of body size misperception remained substantial in the higher income or education strata, demonstrating that lack of income or education alone were not the primary determinants of body size misperception.

Figure 20. Prevalence of Body Size Misperception stratified by socioeconomic factors



People with body size misperception were much more likely to rate their health as "excellent" or "very good" and to report feeling healthier than people of the same age (**Table 6**). They also perceived little lifetime risk of disease, with more than half endorsing a low lifetime risk of myocardial infarction, diabetes, or hypertension, and a shocking 2 out of 3 of these already obese individuals estimating they were at low lifetime risk of developing obesity.

Table 6. Beliefs of obese (BMI ≥ 30 kg/m2) DHS subjects stratified by Body Size Misperception

Beliefs of Obese DHS Population Stratified by Body Size Misperception			
	Body Size Misperception (N=266)	**No Misperception (N=1790)**	**P-value**
Health Belief			
Health Excellent or Very Good	140 (52%)	551 (31%)	<0.0001
Health Better than Most Your Age	130 (50%)	567 (32%)	<0.0001
Perceived Lifetime Risk			
Low Risk of MI	151 (61%)	789 (46%)	<0.0001
Low Risk of Diabetes	156 (63%)	814 (47%)	<0.0001
Low Risk of HTN	129 (52%)	590 (34%)	<0.0001
Low Risk of Obesity	166 (66%)	594 (34%)	<0.0001
Disease awareness			
Hypertension	54/92 (59%)	533/752 (71%)	0.02
Diabetes	8/20 (40%)	176/251 (70%)	0.01

Finally, we attempted to differentiate health behaviors that may relate to these beliefs (**Table 7**). Those with body size misperception visited physicians much less often and, when they did visit physicians, were less likely to report discussing weight loss, dietary changes, or exercise. There were no differences in availability of health insurance or levels of trust in physicians to explain disparities in physician visits.

In fact, those with misperception were more trusting of doctors compared to those without (data not shown).

Table 7. Behaviors of obese (BMI ≥ 30 kg/m2) DHS subjects stratified by Body Size Misperception

Behaviors of Obese DHS Population Stratified by Body Size Misperception			
	Body Size Misperception (N=266)	**No Misperception (N=1790)**	**P-value**
No MD visit in past year	117 (44%)	472 (26%)	<0.0001
Talk to Health Care Provider			
Losing Weight	57/149 (38%)	896/1318 (68%)	<0.0001
Diet	57/149 (38%)	844/1318 (64%)	<0.0001
Exercise	67/149(45%)	870/1318 (66%)	<0.0001

In conclusion, we have identified a significant obese population in Dallas County comprised primarily of African-Americans and Hispanics that feel they need to maintain or even gain weight, and represent an important target population for obesity treatment programs. This population appears comfortable with their weight and unaware of the detrimental effects of obesity, as evidenced by their lack of physical activity, regular medical care, and discussion of lifestyle changes when seen by health care providers. It is likely that current obesity treatment strategies do not adequately target this population, underscoring a need for physicians to devise new methods, both in the clinical setting and through community-based participatory programs, for obesity treatment in cardiovascular disease prevention.

Challenges to the diagnosis and treatment of cardiovascular disease posed by the obesity epidemic

How well do we understand the problem?
How does obesity affect cardiovascular outcomes?
How should we define obesity as a cardiac risk factor?
How do we know if obesity-related changes are pathologic?
Can we study pathophysiology through epidemiology?
Are our tools good enough?
How does obesity affect biomarker metabolism?
How do gender and racial differences impact obesity and cardiovascular disease?
How is obesity affecting cardiovascular risk over time?
Why do we fail at obesity prevention?

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