ABSTRACT

Obesity is the strongest modifiable predictor of type 2 diabetes. The public health concern is due primarily to the dramatic increase in the population burden of obesity and diabetes within the past several decades, which is now predicted to further increase morbidity and premature mortality, possibly decrease life expectancy, and lead to unsustainable health costs in developed and developing nations. The Body Mass Index (BMI: weight in kilograms/height in meter$^2$) is the current metric that characterizes obesity levels and stratifies associated health risk. The BMI, however, is unable to distinguish heterogeneity of risk within obese populations and across ethnic populations. Research has revealed that adipose tissue, which is a function of both adipose cellularity and adipocyte size, is actively involved in energy homeostasis and metabolic regulation, with increasing adipocyte size strongly implicated in obesity-related cellular changes that, if left unaddressed, will eventually lead to the onset of type 2 diabetes. Risk of metabolic disease may depend more on the relative contribution of adipose cellularity and adipocyte size changes than on obesity per se, explaining in part, why heterogeneity of obesity-related diabetes risk occurs within and across populations. The overall objective of this dissertation is to present an alternative obesity-disease paradigm, the Energy Storage Capacity Hypothesis, which may better explain the obesity-disease risk relationship. The specific aims are to highlight the heterogeneity of risk across the BMI continuum and to use The Energy Storage Capacity Hypothesis as the etiologic framework to model diabetes in the US adult population.

In the first study, the 2002 National Hospital Discharge Survey (NHDS) was used to estimate the prevalence of type 2 diabetes among a nationally representative adult morbidly obese (BMI $\geq$ 40) clinical population. We found that 76% of morbidly obese patient discharge
records did not include a diagnosis of type 2 diabetes and that type 2 diabetes diagnosis was reported in only 16% of obesity surgery patient records. The 1999-2002 National Health and Nutrition Examination Survey (NHANES) was the data source for the second study, for which the Energy Storage Capacity Hypothesis was used to model diabetes in the US adult population. Using Asian race as a surrogate for lowest adipose baseline (genetic) cellularity, while largest weight gain in adulthood was treated as a surrogate for increasing adipocyte size, results of this study revealed that despite lower median obesity levels on all anthropometric measures, phenotypically leaner Asians exhibited the highest burden of age-adjusted diabetes (12.3%) compared to Whites (5.4%), Blacks (11.5%), Mexicans (10.7%), and Hispanics (9.5%). The odds of diabetes burden among Asians was 3.9 times higher than Whites [95% CI: 1.4 - 10.8], after controlling for major risk factors of diabetes. Moreover, among those with diabetes, age-adjusted mean hemoglobin A1c levels were higher in Asians, the non-obese, younger adults, and diabetics who did not report having a family history of diabetes. The results of this dissertation support the contention that the BMI may have limited utility for obesity classification and risk stratification. In addition, risk stratification based on classic risk factors for diabetes may be contributing to unintended glycemic exposure in apparently low risk populations. New approaches for identifying high risk obesity exposure in individuals and populations is warranted.
ACKNOWLEDGMENTS

I am profoundly grateful to my doctoral advisor and mentor, Dr. Randall Harris for his wisdom, guidance, knowledge, and support, which made this dissertation possible. I am especially thankful for the many afternoons spent with me discussing clinical and molecular epidemiology, the etiology of chronic diseases, and the role of inflammation. A special thank you goes to Joanne Donk, who added spice, humor, and wit, each and every time I visited the office. I am particularly indebted to Dr. Randi Love who provided the encouragement, support, and guidance I needed to make sound decisions at a critical point in my graduate studies at The Ohio State University. I thank Dr. Judith Schwartzbaum for many insightful discussions on causality and epidemiologic methods and for providing thought-provoking and intellectually stimulating classes. I thank faculty, staff, and fellow students within the College of Public Health for their educational, administrative, and collegial contributions to my academic endeavor at the Ohio State University.

I am very appreciative of the extraordinary assistance given by Dr. Patrick Royston, who provided theoretical and technical support for the multiple imputation procedures and the method of fractional polynomials that were used in this dissertation. A very special thank you to Dr. Felicia Rabito, my professor at the Tulane University School of Public Health and Tropical Medicine, who inspired the Energy Storage Capacity Hypothesis and who has remained involved and supportive of all my research projects throughout my graduate studies. No words can fully express my deep gratitude for her manuscript critiques, enduring commitment, and on-going support. Finally, I am forever grateful to my family, without which, graduate school would not have been possible.
VITA

June 14, 1960...Born - Nurnberg, Germany

2002-present.....Doctoral Candidate, The Ohio State University

2002-2003........Graduate Research Associate, The Ohio State University

2002................MPH, Tulane University School of Public Health and Tropical Medicine

2000.................BS, Exercise Science, Tulane University

PUBLICATIONS


FIELDS OF STUDY

Major Field: Public Health
TABLE OF CONTENTS

ABSTRACT ........................................................................................................ ii

ACKNOWLEDGMENTS .................................................................................... iv

VITA ................................................................................................................... v

LIST OF TABLES .............................................................................................. ix

LIST OF FIGURES ............................................................................................ x

CHAPTER 1. INTRODUCTION ................................................................................. 1
  1.1. Dissertation Overview and Objective .......................................................... 1
  1.2. Type 2 Diabetes ......................................................................................... 4
  1.3. Obesity ..................................................................................................... 8
  1.4. Dissertation Specific Aims ......................................................................... 12

CHAPTER 2. THE ENERGY STORAGE CAPACITY HYPOTHESIS ....................... 14
  2.1. Introduction .............................................................................................. 15
  2.2. The Energy Storage Capacity Hypothesis .................................................. 16
  2.3. Overview of Adipocyte Regulatory Processes ........................................... 17
  2.4. Multidisciplinary Evidence For Energy Storage Capacity as Protective ...... 22
  2.5. Conclusion ............................................................................................... 24
  2.6. A Global Strategy for the Primary Prevention of Weight-Related Chronic
      Diseases ....................................................................................................... 25

CHAPTER 3. COMORBIDITY AMONG THE MORBIDLY OBESE: A
              COMPARATIVE STUDY OF U.S. HOSPITAL PATIENT
              DISCHARGES, NHDS 2002 ................................................................. 27

3.1. Introduction ......................................................................... 28
3.2. Methods ............................................................................. 29
3.3. Results ............................................................................... 31
3.4. Discussion .......................................................................... 36
3.5. Conclusion ......................................................................... 43

CHAPTER 5. CONCLUSION .......................................................... 81

5.1. Discussion .......................................................................... 81
5.2. Public Health Obesity Campaigns: A Call for Change .......... 85

REFERENCES ........................................................................... 87
LIST OF TABLES

1.1 Type 2 Diabetes Pathways .................................................. 6

1.2 Weight and Risk Classification, by BMI ................................................. 9

3.1 Demographic Characteristics of Patient Discharge Records, by Hospital Procedure
   Type and Morbid Obesity Status .................................................... 32

3.2 Age-Specific and Age-Standardized National Prevalence Estimates of Type 2
   Diabetes Among Hospital Discharges of Morbidly Obese Patients, Ages 17-67, by
   Procedure .......................................................... 34

3.3 Age-Specific and Age-Standardized National Prevalence Estimates of Type 2
   Diabetes Among Hospital Discharges of Morbidly Obese Patients, Ages 17-67, by
   Sex and Procedure .................................................... 35

4.1 Characteristics by Race Among US Adults, Ages 20 and Older, National
   Design-Based Estimates .................................................. 62

4.2 Age-Adjusted Characteristics by Race Among US Adults with Self Report Diabetes,
   Ages 20 and Older, National Design-Based Estimates ................................ 64

4.3 Logistic Regression Models of Diabetes Among US Adults, Ages 20 and Older .... 66

4.4 Correlation of A1c with Average Glucose ............................................. 68

4.5 Age-Adjusted Mean A1c Among Diabetics .......................................... 69

5.1 Risk Table for Type 2 Diabetes ...................................................... 83
LIST OF FIGURES

1.1 Risk of Select Obesity-Related Diseases, According to BMI .......................... 2
1.2 Projected Diabetes Burden by Country and Year (in Millions) ...................... 3
1.3 Compartment Model of Body Composition ............................................. 9
2.1 Energy Storage Capacity Hypothesis ....................................................... 17
2.2 Selected Adipocyte Signaling Proteins and Their Actions ............................. 21
3.1 National Prevalence Estimates of Comorbid Conditions Among Morbidly Obese

Patient Discharges, by Procedure .......................................................... 33
4.1 Predicted Probability of Diabetes Per Unit ∆BMI by Race .......................... 67
CHAPTER 1

INTRODUCTION

The linkage between obesity and type 2 diabetes is very strong, in fact so strong that the term diabesity is being frequently used to better describe the current twin epidemic.

1.1. Dissertation Overview and Objective

Public health and clinical approaches to address obesity-related diseases continue to rely on body mass index cutpoints to signal a point for intervention and a call to action. With health care costs threatening the health of our economy and future life expectancy predicted to decrease for the first time in over 100 years, obesity has become the pariah of our time. Despite enormous advances in the biologic understanding of how obesity exerts direct influence on chronic diseases such as type 2 diabetes, the public health message as well as surveillance and screening methods have remained stagnant. As a consequence, the development and burden of type 2 diabetes will continue to go unnoticed, undetected or uncontrolled in apparently low-risk populations. The overall objective of this dissertation is to present an alternative paradigm that better explains the obesity-diabetes risk relationship and apply the etiologic framework to model the burden of diabetes across the BMI continuum.
1.1.1. Background and Significance

The dual global epidemics of obesity and type 2 diabetes are two of the most significant public health threats of the 21st century. Fueled primarily by excess calories and physical inactivity, the dramatic increase in adult overweight and obesity of the past several decades is considered the major cause for the parallel rise in incident and prevalent diabetes (IDF 2006). In addition, a clear dose-response is evident; the greater the level of obesity, the higher the risk of diabetes.

![Figure 1.1. Risk of Select Obesity-Related Diseases, According to BMI](http://www.hsph.harvard.edu/nutritionsource/healthy_weight.html)

During this same time frame, there has also been disturbing rise in the prevalence of childhood and adolescent overweight and obesity, defined as a Body Mass Index (BMI) for Age, at or above the 85th and 95th percentiles, respectively (Ogden, Carroll, & Flegal 2010, 2)
Increasing obesity levels in children have contributed to a much earlier onset of obesity-related diseases; diseases once exclusively seen only in older adults (Freedman et al. 2007). Furthermore, studies have suggested that children who are obese by age 10 are 70% more likely to become obese adults (Serdula et al. 1993).

Since 1999, the trend of increasing obesity prevalence in the United States seems to have abated in children (Ogden, Carroll, & Flegal 2010, 2008) and among some adults (Flegal et al. 2010). Nonetheless, the predicted healthcare burden and profound economic implications for the long-term management of these two intricately related conditions is staggering, as diabetes is projected to affect 438 million people worldwide by the year 2030, at an estimated cost in US dollars of over $490 billion (IDF 2009):

![Prevalence of diabetes](http://www.who.int/diabetes/actionnow/en/mapdiabprev.pdf)

**Figure 1.2. Projected Diabetes Burden by Country and Year (in Millions)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Ranking</th>
<th>Country</th>
<th>People with diabetes (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>India</td>
<td>121.7</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>China</td>
<td>60.4</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>United States of America</td>
<td>77.7</td>
</tr>
</tbody>
</table>

1.2. Type 2 Diabetes

Type 2 diabetes is a metabolic disease marked by high plasma glucose that can be attributed to various underlying etiologies. A diagnosis of type 2 diabetes is made when the fasting plasma glucose level (FPG) is 126 mg/dL or greater (NIDDK 2008). A second confirmatory test is conducted on another day, if results are borderline or otherwise inconclusive (Norris et al. 2008). FPG is currently considered the diagnostic test of choice over hemoglobin A1c and the 2-hour postload plasma glucose test primarily due to the ease, convenience, speed, patient acceptability, cost, reproducibility, and reduced intraindividual variation of the test (Norris et al. 2008). According to the American Diabetes Association (ADA), the FPG is also able to predict microvascular (small vessel) complications to a similar degree than that of the complex and more expensive 2-hour postload plasma glucose test (Norris et al. 2008).

Elevated blood sugar, also known as hyperglycemia, can occur when insulin, which is produced by the beta (β) cells of the pancreas, is no longer able to adequately escort glucose into the cells that use it. In type 1 diabetes, which represents roughly 5-10% of all cases of diabetes, autoimmune destruction of pancreatic β cells leads to no endogenous insulin production and requires exogenous insulin to maintain proper glucose levels in the blood (NIDDK 2008).

With type 2 diabetes, which represents approximately 90-95% of all diabetes cases, pancreatic β cells still produce insulin. Elevated blood glucose may be caused by insulin resistance, which is the inability of insulin to act on a target cell due to reduced or downregulated target cell insulin receptors. It may also be caused by beta cell insufficiency, which results in a mismatch between the amount of insulin that is required to help bring glucose into the cells versus how much is actually produced. For the majority of type 2 diabetes cases, elevated plasma glucose is most likely due to a combination of multiple factors of varying temporal order. In order to better disentangle and differentiate these factors, the following table presents known pathways to type 2 diabetes. This dissertation
focuses on the normal (obesity or lifestyle) pathway to the onset of type 2 diabetes, which we believe is the major contributor for the unprecedented global diabesity epidemic.
Table 1.1. Type 2 Diabetes Pathways

<table>
<thead>
<tr>
<th>Baseline Genetics</th>
<th>Environment</th>
<th>Intermediate Outcome (Acute Response)</th>
<th>Adipocyte-Mediated Continuum</th>
<th>Long-term Compensatory Outcome</th>
<th>Final Outcome</th>
<th>Note(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Modifiable</td>
<td>X</td>
<td>↓ Insulin Secretion [β-Cell Insufficiency]</td>
<td>*</td>
<td>No</td>
<td>*</td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Insulin Resistance [Target Cell Insufficiency]</td>
<td>*</td>
<td>Unlikely</td>
<td>↑ Glucose</td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Insulin Secretion [β-Cell Overproduction]</td>
<td>+</td>
<td>Yes/No</td>
<td>Yes/No</td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>→ Energy Balance</td>
<td>+</td>
<td></td>
<td>Yes</td>
<td>↑ Insulin Resistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>→ Energy Balance</td>
<td>Yes</td>
<td>↑ Insulin Insufficiency</td>
<td>↑ Glucose</td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Not a substantive factor
† Yes – Weight increases are likely, but beta cell insufficiency precedes target cell insulin resistance.
Although diabetes is one of the top ten leading causes of death in the United States, the onset of type 2 diabetes can often go undetected for years before a medical diagnosis is made (Gregg et al. 2004, Harris et al. 1992). This is because hyperglycemia, similarly to hypertension, often lacks clinical signs and symptoms. Undetected or uncontrolled diabetes may result in silent pathology that can do irreparable damage at the microvascular level, causing irreversible quality of life and health consequences such as diabetic retinopathy leading to blindness, diabetic nephropathy to kidney failure, and diabetic neuropathy to amputation (Fowler 2008, Moss, Klein, & Klein 1991).

In addition, the “legacy effect,” originally demonstrated in type 1 diabetics has been confirmed in people with type 2 diabetes. According to Sheehy et al., this phenomenon is the persistent effect of earlier untreated hyperglycemia on large vessels (macrovascular complications) leading to cardiovascular morbidity and mortality, even when blood glucose is later controlled (Sheehy et al. 2010, Holman et al. 2008, Chalmers and Cooper 2008). This may have grave implications for a subset of the population who are not overweight or obese, or who are younger than age 45, and who maybe missed with current screening guidelines (Sheehy et al. 2010).

The most recent government guidelines by the United States Preventive Services Task Force 2008, recommend screening for type 2 diabetes only for those with uncontrolled hypertension (USPTFS 2008), making prolonged glycemic exposure a near certainty among apparently “low” risk individuals (Sheehy et al. 2010). Extended duration and magnitude of undiagnosed hyperglycemia increases the risk for microvascular as well as macrovascular (large vessel) complications (Fowler 2008, Younis et al. 2003, Stratton et al. 2001), allowing underlying disease processes to unfold unabated. For example, there is a two-fold increase in overall premature mortality, a four-fold increase in deaths due to cardiovascular disease (CVD), and a four-fold increase in stroke deaths among diabetics compared to non-diabetics (USPTFS 2008). In addition, CVD is the primary cause of death among both type 1 and type 2 diabetics, killing one out of every two people (Fowler 2008). After adjusting for age and sex differences, the average US medical expenditure among people with type 1 and type
2 diabetes in 2007 was 2.3 times higher than what expenditures would have been in the absence of diabetes, at a total cost of $174 billion (USPTFS 2008).

The rapid increase in incidence and prevalence of type 2 diabetes is a direct manifestation of contemporary environmental, behavioral, and lifestyle factors that eventually lead to obesity, which is a major predictor of the disease. Although other known risk factors for type 2 diabetes include age, family history, sex, and ethnicity, these factors have not been directly implicated for the increasing burden of the disease. Increasing obesity levels, however, may not be the only reason for the rise in diabetes cases. Other contributors include a change in the diabetes diagnostic cutpoint from 140 mg/dL to 126 mg/dL, adopting the FPG as the diagnostic test of choice, and improved diabetes surveillance, screening, and detection, especially among obese people (Gregg et al. 2004).

1.3. Obesity

The World Health Organization (WHO) defines obesity as excessive bodyfat, which has accumulated to the point where health is negatively affected (WHO 1997). Although the trajectory in the prevalence of obesity may be leveling off in the United States, if global secular trends continue, some researchers have estimated the total burden of obesity to affect 1.2 billion people by the year 2030 (Kelly et al. 2008). The Body Mass Index (BMI) which is a ratio of weight in kilograms to height in meters², is the global metric used for measuring and classifying levels of adiposity and associated obesity-related chronic disease risk.

Although the BMI is considered the standard obesity metric, it is not without limitations, the first being that it does not measure bodyfat. The BMI is a measure of a persons weight, adjusted for their height (Kuczmarski and Flegal 2000). The BMI also does not differentiate two basic components of weight (e.g. the two compartment model of body composition) which are fat mass and fat-free mass as shown in figure 1.3. Thus, people with increased muscle mass, such as bodybuilders, are likely to be misclassified as overweight or obese, whereas fat mass could be underestimated for those who have lost lean mass due to infirmity, sedentary lifestyle, or increasing age (Kuczmarski and Flegal 2000).
The BMI also cannot differentiate the distribution of bodyfat, and it is often visceral abdominal fat rather than peripheral or subcutaneous fat which is implicated in elevated chronic disease risk (Frayn 2000). In addition, using standard BMI cutpoints may not be appropriate for all populations, as studies have shown that diabetes risk varies by ethnicity (Stevens et al. 2002). The observed difference in risk is frequently attributed to ethno-racial

![Figure 1.3. Compartment Model of Body Composition](http://www.formulamedical.com)

Left to right columns represent 2, 3, 4 and 6 compartment models of body composition, respectively.

FFM = fat free mass, M = mineral mass, P = protein, H2O = water, ICF = intracellular fluid, ECF = extracellular fluid, G = glucose + glycogen.

Fat = 25% of weight, Mineral = 4%, Protein = 22% in relevant models.

Adapted from: [http://www.formulamedical.com](http://www.formulamedical.com)

---

<table>
<thead>
<tr>
<th>Weight Classification</th>
<th>Obesity Class</th>
<th>BMI (kg/m²)</th>
<th>Disease Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td></td>
<td>&lt; 18.5</td>
<td>Increased</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td>18.5 ≤ 25</td>
<td>Baseline</td>
</tr>
<tr>
<td>Overweight</td>
<td></td>
<td>25 ≤ 30</td>
<td>Increased</td>
</tr>
<tr>
<td>Obese</td>
<td>I</td>
<td>30 ≤ 35</td>
<td>High</td>
</tr>
<tr>
<td>Obese</td>
<td>II</td>
<td>35 ≤ 40</td>
<td>Very High</td>
</tr>
<tr>
<td>Extreme Obesity</td>
<td>III</td>
<td>≥ 40</td>
<td>Extremely High</td>
</tr>
</tbody>
</table>

differences in the distribution of bodyfat, bodyfat percentage, density of fat free mass, or the relative amount of visceral fat (Stevens 2003b, Hubbard 2000, Werkman et al. 2000, Wagner and Heyward 2000). Still, there are a number of studies that have compared ethnic groups and have found no differences in bodyfat distribution or bodyfat percentage and diabetes risk (Abate et al. 2004, Gower et al. 2002, Gautier et al. 1999, Gallagher et al. 1996).

Inconsistent research results may be at least partially attributed to potential sources of error associated with the methods used to measure visceral fat or bodyfat for a given population under investigation. Moreover, while some measurement error may be random, anthropometric indices such as waist circumference, which is often used as a surrogate for visceral fat, tend to introduce systematic error, with measurement reliability decreasing as bodyfat increases (WHO 1995). In addition, validated methods of body composition analysis for one group may not necessarily be generalizeable to another group (Mattsson and Thomas 2006, Welch and Sowers 2000).

For example, indirect methods of body composition analysis such as hydrodensitometry (under-water or hydrostatic weighing), skin-fold measurements, and bioelectrical impedance all rely on formulas derived from body density constants which frequently do not hold across diverse populations (Deurenberg and Deurenberg-Yap 2003). Criterion methods such as computed tomography (CT), magnetic resonance imaging (MRI) or dual energy X-ray absorptiometry (DXA) to estimate bodyfat percentage are cost prohibitive in most settings (Mattsson and Thomas 2006). Despite a host of methodologic limitations related to obesity metrics, the BMI remains an appealing epidemiologic and clinical measurement tool primarily due to the simplicity, inexpense, ease, the accuracy and reliability of measuring height and weight, and because of the BMI’s positive correlation with bodyfat and obesity-related diseases (Kuczmarski and Flegal 2000).

Because the relation of BMI with type 2 diabetes varies by ethnicity, researchers (Misra 2003, Bei-Fan 2002) have advocated for the development of ethnic-specific BMI cutpoints to address the differences in metabolic disease risk that have been observed. More specifically,
this advocacy is primarily targeted towards Asian subgroups, who paradoxically appear to be at elevated risk for obesity-related chronic diseases at much lower BMI’s than non-Asians (WHO 2004, 2000). Given that the projected diabetes burden among Asians is estimated to affect nearly 200 million people by the year 2025, the WHO introduced (but not without critics - see Stevens 2003) an expanded BMI classification table, which includes lower BMI cutpoints to be used for public health action (WHO 2004).

Lowering BMI cutpoints to signal public health action for particular sub-groups, while potentially useful for primary prevention of obesity-related diseases still does not address the threat of weight gain within BMI categories (one BMI unit ≈3 kgs). This is particularly salient given that secondary prevention efforts to lose weight and keep it off have had limited success (Anderson et al. 2001). In addition, BMI screening at a single point in time does not identify (and therefore exclude public health action towards) people with improved metabolic health due to moderate weight loss (Buchwald et al. 2004, Tremblay et al. 1999). Since a moderate weight loss of 5% to 10% is the current recommendation for those who are overweight or obese (Klein et al. 2004), measuring weight change or BMI over time could be a more informative approach for clinicians, public health educators, and researchers. This is because for many weight-reduced obese persons, restoration of health (including the resolution of diabetes) may occur even though BMI remains in the high risk category (Buchwald et al. 2004). Finally, there are individuals with extremely high BMI’s who, even without weight loss, are metabolically healthy (Scott et al. 2006, Sims 2001). For instance, in a 2006 study of US hospital discharge records, 76% of medical discharge records with the diagnosis of morbid obesity did not include a diagnosis of diabetes (Scott et al. 2006).

The observed differences in obesity levels and risk of type 2 diabetes across various subpopulations continue to challenge public health experts and raise the valid question of pathogenesis. Risk differences might be further clarified if the bio-mechanisms by which obesity causes type 2 diabetes is better understood. The use of etiologic models to help explain how obesity contributes to the onset of type 2 diabetes in populations could help epidemiologists design more informative studies, aid in the development of statistical models.
to better predict type 2 diabetes in diverse ethnic populations, and possibly explain a number of enduring paradoxes that are often attributed to genetic differences.

There are numerous emerging and novel basic science hypotheses regarding obesity-diabetes causal mechanisms. However, there appears to be an increasingly medicalized framework of the evidence, and with it, the development of plausible hypotheses at the exclusion of a public health voice (Scott et al. 2004). This is leading to medical and pharmacologic interests in managing these health problems, while leaving the public health perspective behind. Linking the underlying pathogenesis of obesity related diabetes with behavioral, social, and environmental co-factors may provide additional insight with which to better inform public health policy, develop diabetes screening methods that improve sensitivity, and create programs and interventions that target those at high risk of developing diabetes across the BMI continuum. For this dissertation, we include three independent research reports, the first which presents an alternative obesity-disease pathogenic hypothesis. Collectively, we hope this dissertation provides information for public health professionals that will stimulate new ways of thinking and responding to the continuing problem of obesity and related diseases.

1.4. Dissertation Specific Aims

(1) Chapter one introduces the public health problems of obesity and type 2 diabetes and provides the rationale for proposing an alternative paradigm for how obesity and related diseases are viewed and subsequently addressed in primary and secondary prevention efforts.

(2) The Energy Storage Capacity Hypothesis is presented in chapter two and provides an alternative explanation for obesity-type 2 diabetes patterns that have been observed in diverse populations. Based on the proposed model, BMI cutpoints provide limited utility for risk stratification; instead, controlling relative weight gain across the BMI continuum is recommended as a primary prevention strategy.
(3) In chapter three, national prevalence estimates of selected co-morbid conditions, including type 2 diabetes are derived for a morbidly obese clinical population. Specifically, type 2 diabetes prevalence estimates of morbidly obese patient discharges after obesity surgeries are compared with prevalence estimates of morbidly obese patients after all other hospital procedures. A morbidly obese study population represents one end of the obesity/BMI spectrum.

(4) We use The Energy Storage Capacity Hypothesis presented in chapter two as the etiologic framework to formulate several \textit{a priori} predictions and to statistically model diabetes in a nationally representative US adult population, sampled from the 1999-2002 National Health and Examination Survey (NHANES). In contrast to the study on the morbidly obese, the investigation presented in chapter four focuses on the lean end of the obesity/BMI spectrum.

(5) Chapter five presents an overall discussion of our findings and recommendations for future research.
THE ENERGY STORAGE CAPACITY HYPOTHESIS

We should try to integrate causal pathways at the societal level...with pathogenesis and causality at the molecular level.

Mervyn and Ezra Susser

ABSTRACT

The current obesity-chronic disease risk paradigm attributes excessive fatness to the onset of chronic diseases such as type 2 diabetes. Given the sobering health and economic projections associated with the obesity epidemic, it is essential that the working model which guides prevention and intervention efforts is accurate, and that methods used to measure and quantify obesity’s risk to health are consistent, inexpensive, simple, and effective. The body mass index (BMI) is the metric used clinically, for public health research and surveillance, and for public health campaigns to estimate adiposity and to characterize the obesity-disease risk relationship. Intractable issues with the underlying paradigm, however, limit the utility of BMI cutpoints. We propose an alternative model, The Energy Storage Capacity Hypothesis, which describes the obesity-disease risk relationship, unifies existing obesity-disease theories, and explains several paradoxes observed in the study of obesity and related diseases. Under the proposed model, strategies to reduce diabetes risk exposure do not involve BMI cutpoints.
2.1. Introduction

The current obesity-chronic disease paradigm implicates excessive fatness for the increased risk of chronic disease morbidity and mortality (NHLBI 1998). Obesity-related risk factors, such as hypertension, dyslipidemia, and hyperglycemia if left untreated, lead to the development of cardiovascular diseases, type 2 diabetes, and excess mortality. Given the sobering health and economic projections associated with the obesity epidemic (WHO 1999), it is essential that the working model, which guides prevention and intervention efforts, is accurate, and that the method used to measure and quantify the obesity-chronic disease risk relationship, is consistent across populations, inexpensive, simple, and effective. The body mass index (BMI kg/m$^2$), with specified cutpoints, is the global metric used clinically, for population health research and surveillance, and for public health campaigns to estimate adiposity and to characterize the obesity-chronic disease risk relationship (NHLBI 1998).

Although the BMI provides an acceptable approximation of total bodyfat for the majority of people, it is not without caveats which have been identified and described in the literature (NHLBI 1998). For example, the BMI cannot differentiate between fat and fat free mass. Athletes with increased muscle mass could be misclassified as overweight or obese, whereas bodyfat may be underestimated for those who have lost muscle mass due to infirmity (NHLBI 1998). The BMI does not address risk differences attributed to bodyfat distribution. Studies have shown visceral or belly fat to be independently associated with elevated chronic disease risk (Frayn 2000). Current BMI cutpoints may also not clearly show within-interval variation in morbidity, which could be substantial (Stommel and Schoenborn 2009). Moreover, a low risk adult BMI that increases but stays within the normal range could represent a weight gain of up to 15 kilograms or more. Using BMI cutpoints to signal an appropriate point for intervention could be counterproductive and may impede early intervention efforts for the primary prevention of overweight and obesity. Finally, BMI fails to account for the documented heterogeneity of disease risk across ethnic populations (WHO 2000), and the heterogeneity of prevalent chronic disease within obese populations (Buchwald et al. 2004). These issues coupled with emerging knowledge of energy homeostasis and adipocyte...
regulatory processes point to limitations with the current obesity-chronic disease paradigm, and underscore the need for public health professionals to re-examine the basic obesity-disease assumptions that currently lead public health research and prevention efforts.

Within the past decade, basic science obesity research findings have prompted new obesity-chronic disease hypotheses, many of which are characterized by medicalized terminology such as adipocyte dysfunction or defect (Bays et al. 2004, Poothullil 2001), the ectopic fat storage syndrome (Ravussin and Smith 2002), and defects and failures in adipocyte proliferation (Danforth 2000). Medicalized hypotheses provide a framework for proposing pharmacologic treatment as a strategy to manage obesity-related diseases and may inadvertently undermine primary prevention efforts. Based on our synthesis of multi-disciplinary obesity research results, we offer an alternative obesity-chronic disease paradigm that describes the obesity-chronic disease risk relationship, unifies existing obesity-disease theories, and explains several paradoxes observed in the study of obesity and associated chronic disease. More importantly, we provide an alternative public health strategy for the primary and secondary prevention of obesity-related chronic diseases.

2.2. The Energy Storage Capacity Hypothesis

We propose that genetically determined (high baseline) adiposity relating to white fat cell number (cellularity) is protective against obesity-related chronic disease processes by providing greater absolute energy storage capacity, henceforth called The Energy Storage Capacity Hypothesis. Obesity-related metabolic risk increases only when energy storage nears a threshold of energy storage capacity - independent of how obesity is currently measured, such as through BMI-defined adiposity cutpoints, body fat percentage, or anthropometric measures. Factors which limit energy storage capacity include the size limit of individual adipocytes, the number of adipocytes, and the proliferative potential for new adipocytes. Holding proliferation constant Figure 2.1 depicts the Energy Storage Capacity Hypothesis:
2.3. Overview of Adipocyte Regulatory Processes

Adiposity encompasses fat cell number and fat cell size. Adipose tissue, which includes adipocytes (fat cells) within a connective tissue matrix, serves important physiologic functions that include protecting vital organs and helping to preserve heat through insulation. The individual fat cell, however, is primarily a repository or storage-type vesicle for excess energy in the form of triglyceride that acts to buffer energy imbalances when energy intake is not equal to energy output. Fat cells thus provide a normal dynamic physiologic storage space for excess energy in long-term generally isocaloric environments (Faust and Miller 1983). For example, when chronic energy intake exceeds short term energy requirements and exceeds glycogen storage capacity (the storage form of glucose) of the liver and muscle tissue, excess fuel (energy) is converted to fat by the liver, in the form of triglyceride. Triglycerides are

![Figure 2.1. Energy Storage Capacity Hypothesis](image-url)
then transported in the blood, and are stored within the fat cells of the body. In other words, adipose cellularity represents the capacity to store excess energy, with more fat cells equating to more storage availability.

As excess energy in the form of triglyceride is stored in adipocytes, each individual fat cell increases in both diameter and in volume, with the ability to expand twenty-fold in diameter and over one thousand-fold in volume (Bjornheden 2004, Hewitt 1997). Likewise, when energy intake does not meet energy requirements, stored fat is mobilized from the fat cell, used for energy, and fat cells subsequently become smaller. Fat cell size, therefore directly represents energy status - or how much excess energy is being stored at any given time. In observational studies of an apparently healthy general adult population, weight changes in adulthood then, could reasonably act as a surrogate for fat cell size changes—either increasing or decreasing.

Basic science research has revealed that adipocytes are more than a simple repository for energy and that they are actively involved in energy homeostasis and metabolic regulation by synthesizing, secreting, or downregulating a multitude of autocrine, paracrine, and endocrine signaling products such as hormones, complement components, growth factors, and cytokines (Bays et al. 2004, Ravussin and Smith 2002, Fruhbeck et al. 2001). These metabolic regulatory activities are in direct response to the energy storage status the fat cell itself, independent of the actual number of fat cells (Fruhbeck et al. 2001, Kim 2000).

For example, the autocrine effect demonstrated by grossly enlarged adipocytes includes downregulation of insulin receptors, decreased GLUT-4 translocation to the cellular membrane, inhibition of lipoprotein lipase activity, increased hormone sensitive lipase, and increased lipolytic activity (Fruhbeck et al. 2001). Reduction of local blood flow represents a paracrine response, while there is an endocrine response via the synthesis and secretion of leptin, which acts on the hypothalamic-pituitary axis to decrease food intake and increase energy expenditure (Fruhbeck et al. 2001). Collectively, the overall regulatory response reduces adipocyte sensitivity to store energy, reroutes energy to other more sensitive cells, and distally, helps modify the metabolic environment. In addition, adipose tissue secretion of
inflammatory products such as tumor necrosis factor alpha (TNF-α) could point to physical stress or strain on the grossly enlarged adipocyte plasma membrane, as plasma membrane wounding is considered the principal mechanosensing event that initiates the inflammatory response (Vlahakis and Hubmayr 2005, Zeghari 2000). This may help explain why enlarged fat cells elicit the inflammatory response, while increased numbers of fat cells do not. TNF-α triggers synthesis of interleukin-6 (IL-6) (Yudkin et al. 1999), which is the prime inducer of C-reactive protein, a risk marker for cardiovascular disease and type 2 diabetes (Yudkin et al. 1999). Collectively, these regulatory proteins coupled with a possible unfavorable surface area to volume ratio caused by the grossly enlarged adipocyte, directly implicate adipocyte size as the pathogenic precursor to obesity related diseases.

If excess energy intake continues and the critical limit of energy storage capacity of an individual mature adipocyte is reached, fibroblast-like precursor cells are stimulated to differentiate into new adipocytes, thereby expanding energy storage capacity (Hausman et al. 2001, Fruhbeck et al. 2001, Hube and Hauner 2000, Marques, Hauman, & Martin 1998, Rosenbaum and Leibel 1998). Creating a moderate energy deficit through physical activity and diet reduces the size, but not the number of fat cells. Once the size of adipocytes is reduced to the point that signaling products are normalized, adipose sensitivity and function is restored (Dixon et al. 2008, Buchwald et al. 2004).

The implication is that given the same level of excess energy over time - with all else being equal, an individual with lower adipose cellularity (lower fat cell number) would reach a fat cell size expansion maximum or ”critical threshold” before an individual with a greater number of fat cells, and as a result, adipocyte signaling would occur sooner, adverse metabolic markers would manifest earlier, and progression to type 2 diabetes would occur sooner - all at a lower absolute weight gain than an individual with greater adipose cellularity. This was partially shown as early as 1972, when Leonhardt and colleagues isolated adipocytes from humans and rats via incubation by collagenase and measured adipocyte size distributions with the pulse counter ZG 2. Their results revealed that obese ”maturity” onset-diabetics had lower adipocyte numbers with greater cell volumes than obese non-diabetics (Leonhardt
et al 1972). From an epidemiologic perspective, if there were differences in baseline adipose cellularity among certain groups, then groups with lower overall cellularity would exhibit similar signs, symptoms, risk markers, and metabolic disease patterns as hypothesized in individuals.

We believe that obesity-related chronic disease is not due to innate dysfunctions or defects of the adipocyte, but rather that pathology develops as a result of chronic excess energy intake reaching and eventually exceeding the threshold of physiologic energy storage capacity. Enlarged fat cells become increasingly insensitive in order to constrain energy uptake. Resistant adipose storage activity in an environment of a chronic positive energy balance results in hyperinsulinemia, hyperglycemia, dyslipidemia, and eventual lipotoxicity and glucotoxicity of non-adipose tissue, including the $\beta$ cells of the pancreas (Unger 2003). Pancreatic $\beta$ cell functional deterioration leading to eventual insulin insufficiency is a plausible factor in the development of type 2 diabetes (Wajchenberg 2007), but it is more likely to be secondary to resistant fat cells. In addition, chronic overexpression of adipocyte inflammatory products may themselves contribute to thromboembolic complications and vascular damage (Yasojima et al. 2001).

Because an energy deficit reduces the size, but not the number of fat cells, there is a potential limit to the magnitude of intentional weight loss among individuals with high levels of adipose cellularity (Spalding et al. 2008, Löfgren et al. 2005, Kral et al. 1977, Leonhardt et al. 1972). This is because, if weight loss efforts continue and adipocytes are reduced to a critical minimum threshold, a minimum size is probably defended by opposing action. For example, leptin concentrations increase as fat cell size increases and decrease as fat cell size decreases (Löfgren et al. 2005). Adiponectin, on the other hand, is an insulin sensitizing adipocyte-derived hormone with anti-inflammatory properties and high levels are associated with reduced heart attack (Kadowaki and Yamauchi 2005). Adiponectin levels are reduced in obesity and increase with weight loss (Fruhbeck et al. 2001). In this manner, adipocyte signaling proteins appear to work in concert, contributing to energy homeostasis and metabolic regulation both locally and distally. An adipocyte signaling model in Figure
2.2 shows selected adipocyte-derived proteins and their purported metabolic regulatory actions.

Figure 2.2. Selected Adipocyte Signaling Proteins and Their Actions
2.4. Multidisciplinary Evidence For Energy Storage Capacity as Protective

2.4.1. The transgenic mouse model

Transgenic fatless mice present with classic symptoms of obesity-related conditions such as the metabolic syndrome and type 2 diabetes. Surgical transplantation of fat tissue to the mice reverses diabetes, normalizes glycemia and insulinemia, and improves blood lipids (Gavrilova et al. 2000). Because intracellular liver and muscle energy storage capacity is limited, these cells will respond similarly to the fat cell, inhibiting further energy uptake once an energy storage threshold is reached. This is consistent with research findings that are supportive of Reavens Muscle Insulin Resistance Theory (Reaven 1998). With available fat cells provided through surgical transplantation, excess energy can be stored. With no fat cells to store excess energy, the fatless mice present clinically as if they were obese.

In another rodent model, Bains et al. described a line of transgenic rats (autosomal dominant late-onset obesity phenotype) who gradually accumulated large amounts of fat viscerally, but not peripherally, despite a normal low fat diet (Bains et al. 2004). These rats presented with normal fasting blood glucose, insulin, and cortisol levels, and increased insulin sensitivity in glucose tolerance tests. The increase in visceral adiposity specifically reflected an increase in adipocyte number, not size. These researchers noted that “the consequence of excess visceral fat was not related to the absolute fat load, but rather, to the number of adipocytes to carry it.”

2.4.2. Pharmacotherapy induces adipogenesis and increases insulin sensitivity

Okuna and colleagues identified the molecular mechanism of Troglitazone, a thiazolidinedione (TZD), which is a class of oral antidiabetic drug that increases target tissue sensitivity to insulin in vivo without additional insulin output by the pancreas. Using obese Zucker rats, Okuna showed that Troglitazone increased fat cell number in white adipose tissue, without affecting the total mass or total triglyceride content of adipose tissue. Energy counterbalance occurred because of a concomitant decrease in the number of large adipose cells – the loss
primarily through apoptosis. The differentiation of fibroblasts into new, small adipocytes and the reduction of grossly enlarged adipocytes alleviated insulin resistance. Research has subsequently shown that TZDs decrease insulin resistance in humans by increasing adipocyte differentiation through the high affinity ligand activation of the nuclear hormone receptor, peroxisome proliferator activated receptor-gamma (PPAR-γ) (Larsen et al. 2003). PPAR-γ is expressed primarily by adipocytes and is a key regulator in adipogenesis (Larsen et al. 2003).

2.4.3. Bariatric surgery vs. liposuction: negative energy balance vs. adipose tissue removal

Bariatric surgery for morbid obesity is the only treatment proven to produce sustained weight loss (Buchwald et al. 2004). This is accomplished by reducing the gastric reservoir, which results in a significant decrease in energy intake and creates a large energy deficit, which reduces adipocyte size. For a majority of patients, bariatric surgery improves blood pressure, lipid and insulin levels, and resolves type 2 diabetes (Buchwald et al. 2004). These results occur even though most patients remain heavy. In contrast, in a study of liposuction (Klein et al. 2004), which surgically removes fat cells (reduces fat cell number), weight loss occurred, but there were no improvements in other health parameters.

2.4.4. Visceral fat hypothesis

The correlation between visceral fat and insulin resistance has long been recognized. However, there are compelling lines of reasoning (see Bains 2004 and Frayn 2000), as well as numerous studies, that call into question a causal relationship. For example, Gower in 2002 showed that the benefits of a weight loss of 13 kg in white and black premenopausal women were comparable, despite white women losing significantly more visceral fat than black women. Improvements in insulin sensitivity and lipid concentrations were similar across groups and could not be attributed to any particular body fat depot (Gower et al. 2002). Studies on Pima Indians further challenge the belief that visceral fat is responsible for metabolic
dysregulation. Gautier and colleagues compared the visceral and subcutaneous adipose tissue of Pima Indians to age, sex, and BMI-matched Caucasians and found that insulin resistance and hyperinsulinemia found in the Pima Indians could not be explained by fat deposition (Gautier et al. 1999). Weyer et al. showed that enlarged subcutaneous abdominal adipocyte size and not BMI-defined obesity, predicted type 2 diabetes in Pima Indians (Weyer et al. 2000).

2.4.5. Reconciliation of classic obesity-disease hypotheses

Studies supporting the Fetal Origins Hypothesis (Hales and Barker 1992) have shown that low birth weight babies have the highest adult metabolic risk profile at every level of adult obesity (Barker et al. 2002, Wright et al. 2001) However, when excessive postnatal weight gain is controlled, there is no increase in risk of diabetes for small size at birth (Hypponen, Power, & Smith 2003). Other theories, such as the Thrifty Genotype (Neel 1962) implicate hyperinsulinemia as antecedent or causal to obesity, either through the apparent overproduction of insulin in modern times, by metabolic programming shown in both animal and human studies (Patel, Srinivasan, & Aalinkeel 2000), or by the maternal-fetal intrauterine environment, as reflected in gestational diabetes (Silverman et al. 1998). Sub-groups affected by these circumstances may be particularly vulnerable in obesigenic environments as either genetic propensity or biologic mechanisms altered in early life could augment or accelerate energy storage. This would exert strong independent and gene-environment effects on obesity-related chronic disease risk, as is commonly seen in high-risk populations such as the Pima Indians (Knowler et al. 1978).

2.5. Conclusion

Although the global obesity epidemic is the result of a complex interplay of multiple factors which will require broad multi-level strategic approaches to effectively address, our synthesis of cross-disciplinary obesity research reveals what is mechanistically occurring at the cellular level when energy intake exceeds energy expenditure beyond innate energy
storage capacity, and how that manifests and influences what is observed, often paradoxically in diverse populations. In view of emerging evidence, it is clear that the current obesity-disease paradigm, which implicates excessive fatness for the increased risk of obesity-related chronic diseases, is becoming increasingly obsolete. Consequently, the BMI has arrived at a public health cross-road, whereby its usefulness in characterizing obesity-disease risk and its convenient role in epidemiologic obesity research and surveillance are no longer indistinguishable. Weight-related chronic disease is skyrocketing in countries such as China, India, and Japan (Misra 2003, Deurenberg and Deurenberg-Yap 2003, Bei-Fan 2002, Weisell 2002, WHO 2000) and these populations are at-risk for chronic diseases at much lower BMIs compared with those of European or African ancestry (Pan et al. 2004, Enas et al. 1996).

While the BMI could continue to serve as a global adiposity index for epidemiologic obesity surveillance, continued reliance on BMI cutpoints for risk stratification is a serious setback to primary prevention of weight-related chronic diseases and will result in unnecessary delay towards a meaningful and timely early response. The global obesity crisis, unfortunately, does not allow public health professionals the luxury of waiting for quality evidence-based research, such as randomized controlled trials to inform public health action and guide public health policymakers on best practices for preventing obesity-related chronic disease. In the absence of such evidence, however, the obesity prevention evidence framework discussed by Swinburn and colleagues (2005) allows for selecting interventions based on best available evidence, without excluding untried but promising new strategies. Based on emerging scientific knowledge, new strategies could include primary and secondary prevention efforts across the BMI continuum, completely independent of an obesity-disease risk classification.

2.6. A Global Strategy for the Primary Prevention of Weight-Related Chronic Diseases

The Energy Storage Capacity Hypothesis provides a biologic basis for the public health recommendation of preventing a 10% weight gain among healthy sedentary adults at all levels
of adiposity (Truesdale, Stevens, & Cai 2005, Klein 2001, Willet, Dietz, & Colditz 1999, Tremblay et al. 1999, NHLBI 1998, Colditz et al. 1995). Although this recommendation may be conservative for a portion of a healthy population for whom greater energy storage capacity would provide protection beyond a 10% weight gain in adulthood (severely obese healthy people), we believe this approach is the best population-based primary prevention strategy against weight-related chronic diseases for healthy adults. Monitoring adult weight gain is inexpensive, easy to administer, of low risk and minimal discomfort, impervious to stigma or misclassification, and most importantly, may arrest silent pathologic processes in all populations, across all levels of adiposity.

Epidemiologic research has unequivocally identified most chronic diseases as diseases of lifestyle. Eliminating the stigma of size and how one looks and instead refocusing attention on behavior and how one "lives" is an important and necessary step towards primary prevention of chronic disease. The Energy Storage Capacity Model is a novel obesity-disease prevention paradigm, which provides a different framework for launching new obesity research such as developing an obesity metric that more accurately characterizes or predicts chronic disease risk for the global community. The Energy Storage Capacity Model also provides a new perspective for addressing a serious public health problem, which may lead to innovative strategies for the prevention and attenuation of weight-related chronic diseases.
CHAPTER 3

COMORBIDITY AMONG THE MORBIDLY OBESE: A COMPARATIVE STUDY OF U.S. HOSPITAL PATIENT DISCHARGES, NHDS 2002

Falstaff: Sirrah, you giant, what says the doctor to my water? Page: He said, sir, the water itself was a good, healthy water...

King Henry IV, PI, AI, S2, L1-4
William Shakespeare

ABSTRACT

Background: Increasing severity of obesity is associated with increasing morbidity. However, among morbidly obese patients defined by a Body Mass Index (BMI [kg/m$^2$] \(\geq 40\)), comorbid prevalence has been reported primarily in case series reports of the bariatric surgical literature. To derive national prevalence estimates, we used a nationally representative sample of hospital discharge records to compare demographic characteristics and selected comorbid conditions commonly experienced by morbidly obese patients. Specifically, surgical obesity procedure discharge records are compared with discharge records of morbidly obese patients for all other hospital procedures. Methods: The 2002 National Hospital Discharge Survey and the International Classification of Diseases, 9th Revision, Clinical Modification were used to identify and describe all morbidly obese patient discharge records (n=3,473) and to
quantify the prevalence of selected obesity-related comorbid conditions. **Results:** Compared with morbidly obese patient discharge records for all other hospital procedures, the obesity surgery discharge records (n=833) revealed patients who were younger (median, 42 vs 48 years; range, 17 to 67) predominately female (82.3% vs. 63.7%), and with a higher prevalence of sleep apnea (24.0% vs. 11.8%), osteoarthritis (22.9% vs. 11.8%), and gastroesophageal reflux disease (27.7% vs. 11.7%); (all P < .001). The prevalence of type 2 diabetes was lower in the obesity surgery patients (16.1% vs. 24.3%; P < .003), whereas hypertension (45.9% vs. 41.0%; P = 0.13) and asthma (9.6% vs. 12.0%; P = 0.26) were similar in the two groups. **Conclusions:** Demographic characteristics and comorbid prevalence of morbidly obese patients discharged after obesity surgery are consistent with reports in the bariatric surgical literature. Although obesity surgery discharge records represented younger patients, a higher percentage of several comorbid conditions were revealed. Possible explanations for this include preferential diagnosis with the obesity surgery group, differential diagnostic coding, or increased severity of morbid obesity. Advancing surgical and insurance guidelines for bariatric surgery will require quality patient level clinical data that accurately describe and quantify the demographic distribution of obesity and the associated burden of disease.

### 3.1. Introduction

Although adult obesity is a growing epidemic that affected 30.6% of the US population between 1999-2002 (Hedley et al. 2004), the prevalence of morbid obesity (defined as a body mass index [BMI] $\geq 40$ kg/m$^2$) increased at twice the rate of obesity (BMI $\geq 30$ kg/m$^2$) (Freedman et al. 2002). During this time period, one in 20 people were classified as morbidly obese (Hedley et al. 2004, Flegal et al. 2002), although the prevalence was disproportionately higher in women of non-Hispanic black (13.5%) and Mexican (5.7%) ethnicity (Hedley et al. 2004). Severity of obesity, both then and now, is associated with a substantial increase in health care utilization, morbidity, and mortality (Arterburn, Maciejewski & Tsevat 2005).

Despite the public health implications associated with the rise in morbid obesity, there are only limited data on the prevalence of common obesity-related comorbid conditions.
among the morbidly obese. Most research on morbid obesity has been on patients undergoing bariatric surgery at academic institutions (Buchwald et al. 2004). However, comorbidity among the morbidly obese reported in the bariatric literature may not represent bariatric surgical patients nationally. In addition, due to the selective nature of this patient population, bariatric surgical patients may have different characteristics than other morbidly obese patients. Although this is a reasonable assumption, it has not yet been investigated.

Therefore, the overall objective of this study is to provide further insight into the prevalence of selected comorbid conditions among the morbidly obese clinical population by examining a nationally representative sample of inpatient hospital medical discharge records using the 2002 National Hospital Discharge Survey (NHDS). The specific aims are to describe demographic characteristics and quantify the prevalence of selected comorbid conditions for morbidly obese patients discharged after surgical obesity procedures, and to compare this information with that obtained for morbidly obese patients discharged after all other hospital procedures.

3.2. Methods

3.2.1. Data source and sample design

The National Hospital Discharge Survey (NHDS) is the longest continuously running nationally representative survey on inpatient care in the United States (Defrances and Hall 2004). The NHDS collects discharge record data from non-federal short-stay hospitals (< 30 days) that are selected through a complex three-stage survey design. The hospital sampling frame and sample are updated every 3 years. For the year 2002, the sample comprised 445 hospitals and 327,254 discharge records. The records are weighted against the 2000 U.S. Census to derive nationally representative estimates of hospital discharge data in the United States. For our analysis, we excluded newborns, leaving us with a sample size of 292,059 patient discharge records.
3.2.2. Demographic, diagnosis, and hospital procedure data

Patient characteristics for these analyses include sex, race/ethnicity, and age. Up to seven diagnoses are collected by the NHDS. The first-listed, or principal, diagnosis is usually the primary cause of hospital admission, with the remaining diagnoses as secondary or existing conditions. Up to four hospital procedures per discharge record (the primary procedure and three other procedures) are included in the NHDS. Only procedures related to the hospital admission are reported, including surgical operations, medical procedures, diagnostic procedures, or any special treatment. The diagnosis-related group (DRG) version 18.0 is used to group similar surgical/clinical primary procedures. One DRG code is listed per discharge record. All medical coding is done according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

3.2.3. Morbid obesity diagnosis and procedure inclusion

To identify morbid obesity, all diagnoses (1-7) coded 278.01 were selected. DRG 288 comprises operating room obesity procedures, of which 10 are gastric surgical procedures for weight loss and two are related to adipose or skin removal. Only one nongastric procedure, 86.83 (adipose surgical operations), was coded under DRG 288 among morbidly obese patient discharges in this sample; which represented < 1% (186/84,735) of all estimated obesity surgery procedures. Therefore, we included all operating room obesity procedures for our analysis. We dichotomized morbidly obese patient discharges according to the DRG. DRG 288 represents surgical obesity procedures, whereas all other DRGs include all other hospital procedures.

3.2.4. Comorbid diagnosis and inclusion

We selected all diagnoses (1-7) recorded for six comorbid conditions related to morbid obesity. These diagnoses, along with their ICD-9-CM diagnosis codes, are as follows: type 2 diabetes; controlled or uncontrolled but without complications (250.00, 250.02); hypertension; benign or malignant, essential, heart, renal, or secondary, but without complications (401.00,
401.10, 401.90, 402.00, 402.10, 402.90, 403.00, 430.10, 403.90, 404.00, 404.10, 404.90, 405.00, 405.10, 405.90); sleep apnea (780.57); osteoarthritis: degenerative joint disease, specific, or unspecified (715.00–716.99); gastroesophageal reflux disease (GERD) (530.81); and asthma: all specified (493.00-493.99). We selected these comorbid conditions because they are the most commonly reported comorbidities in the bariatric surgical literature and have been shown to improve or resolve as a result of surgery (Buchwald et al. 2004).

3.2.5. Statistical analysis

All statistical analyses were conducted using Stata software, v. 9 (Statacorp 2005). To derive national discharge estimates, data were analyzed and weighted using the methodology recommended by the NHDS (NHDS 2002). Categorical variables are reported as counts and proportions, while continuous variables are presented as as means or medians along with their ranges, standard errors (SE’s) or interquartile ranges (IQR). Standard errors and 95% confidence intervals were obtained by applying the methods and formulas outlined in the NHDS 2002 public-use data file documentation (NHDS 2002). Exact two-tailed P values are provided. Statistical differences are noted for P < .05.

3.3. Results

Table 3.1 describes the demographic characteristics of US hospital patient discharges. The first column represents operating room obesity procedure discharges of morbidly obese patients (mean age, 41.3 years; range, 17 to 67 years). The second column reflects all other hospital procedure discharges for morbidly obese patients truncated from age 17 to 67 years, to provide a direct comparison with the obesity surgery group. The third column includes all hospital discharges of morbidly obese patients of all ages (1 to 92 years). The fourth column lists all hospital discharges for patients not coded as morbidly obese. The final column gives the entire 2002 sample of patient discharges for the entire age range (1 to 99 years).

Patients coded as morbidly obese represented 1.2% of US hospital discharges in 2002 while 21.6% of all hospital procedures among morbidly obese patient discharges were surgical obesity
Table 3.1. Demographic characteristics of patient discharge records, by hospital procedure type and morbid obesity status, NHDS 2002

<table>
<thead>
<tr>
<th>Variables</th>
<th>Morbid Obese (BMI 40+)</th>
<th>Morbid Obese (BMI 40+)</th>
<th>Morbid Obese (BMI &gt;40)</th>
<th>Not Morbid Obese (BMI &lt;40)</th>
<th>All Patients (All BMI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Estimate (N)*</td>
<td>84,735</td>
<td>260,527</td>
<td>393,108</td>
<td>33,333,503</td>
<td>33,726,611</td>
</tr>
<tr>
<td>Procedures (% of all BMI)</td>
<td>91.4</td>
<td>1.3</td>
<td>1.2</td>
<td>98.8</td>
<td>100</td>
</tr>
<tr>
<td>Female (%)</td>
<td>82.3</td>
<td>63.7</td>
<td>68.7</td>
<td>60.2</td>
<td>60.3</td>
</tr>
<tr>
<td>Mean Age (SE)*</td>
<td>41.3 (0.04)</td>
<td>47.8 (0.02)</td>
<td>49.0 (0.02)</td>
<td>52.1 (0.004)</td>
<td>52.1 (0.004)</td>
</tr>
<tr>
<td>Median Age (IQR)**</td>
<td>42 (18)</td>
<td>48 (18)</td>
<td>49 (20)</td>
<td>54 (42)</td>
<td>50 (42)</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>62.3</td>
<td>61.9</td>
<td>62.6</td>
<td>61.7</td>
<td>61.7</td>
</tr>
<tr>
<td>Female</td>
<td>82.9</td>
<td>61.6</td>
<td>67.4</td>
<td>59.7</td>
<td>59.8</td>
</tr>
<tr>
<td>Black</td>
<td>8.7</td>
<td>15.6</td>
<td>13.6</td>
<td>11.8</td>
<td>11.8</td>
</tr>
<tr>
<td>Female</td>
<td>83.0</td>
<td>74.9</td>
<td>75.8</td>
<td>61.4</td>
<td>61.6</td>
</tr>
<tr>
<td>Other†</td>
<td>1.7</td>
<td>2.4</td>
<td>2.3</td>
<td>3.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Female</td>
<td>92.2</td>
<td>53.4</td>
<td>60.3</td>
<td>59.0</td>
<td>59.0</td>
</tr>
<tr>
<td>Not Stated</td>
<td>27.3</td>
<td>20.1</td>
<td>21.5</td>
<td>22.6</td>
<td>22.6</td>
</tr>
<tr>
<td>Female</td>
<td>80.2</td>
<td>63.0</td>
<td>68.6</td>
<td>61.0</td>
<td>61.1</td>
</tr>
</tbody>
</table>

† Obesity procedures are discharges coded as Diagnostic Related Group (DRG) = 288 (Operating Room Obesity Procedures). All Other Hospital Procedures include every procedure coded under the ICD-9 CM except obesity procedures classified under DRG = 288. All analyses exclude newborn discharges.

* Means, medians, and frequencies are national estimates derived by using the NHDS 2002 frequency weighting variable, as recommended.

** SE = standard error; IQR = interquartile range

† Other races include American Indian / Alaskan Native; Asian; Native Hawaiian / Pacific Islander; Multiple Race; and Other (some categories are not represented by certain sub-race groupings. For example, there are no Asians reported as morbidly obese under the Obesity Procedures heading).

Females represented 82.3% of all obesity procedure discharges. Specifically, white women accounted for 51.6% (43,741/84,735) of obesity procedure discharges while black women represented only 7.2% (6,125/84,735). Comparing the median age of morbidly obese patients, age range (17 to 67 years), those discharged for obesity procedures were, on average, 6 years younger than patients discharged for all other hospital procedures (42 vs 48; IQR each, 18).
The prevalence of selected comorbid conditions among morbidly obese patient discharges is shown in Figure 3.1. Although younger and predominantly female, the group discharged for obesity procedures had a significantly higher proportion of gastroesophageal reflux disease (GERD), sleep apnea, and osteoarthritis than the group discharged for all other hospital procedures. The proportion of type 2 diabetes was lower in those discharged for obesity procedures, whereas the proportion of hypertension and asthma was similar in the two groups. We also investigated comorbidity in patients age 17 to 67 who were coded as obese (ICD-9-CM 278.00) (n=4,412) in the group discharged for all other procedures (data not shown). Compared with those coded as morbidly obese, discharges coded as obese reported similar proportions with respect to type 2 diabetes (24.6%), hypertension (45.3%), osteoarthritis (10.4%), asthma (11.1%), and GERD (10.5%); only sleep apnea was lower (5.3%).
In Table 3.2 we show the unadjusted weighted prevalence of type 2 diabetes among morbidly obese patient discharges by procedure type, while Table 3.3 shows the age-specific and age-standardized weighted prevalence of type 2 diabetes, by sex and procedure type. In general, morbidly obese males tended to have a higher prevalence of type 2 diabetes than females and type 2 diabetes was more prevalent among the all other hospital procedures discharges.

Table 3.2. Age-specific and age-standardized national prevalence estimates† of type 2 diabetes among hospital discharges of morbidly obese patients, ages 17–67, by procedure, NHDS 2002

<table>
<thead>
<tr>
<th>Age Interval</th>
<th>Obesity Procedures</th>
<th>All Other Hospital Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diabetes Diagnosis</td>
<td>Population (N)</td>
</tr>
<tr>
<td>17–27</td>
<td>732</td>
<td>10,076</td>
</tr>
<tr>
<td>28–37</td>
<td>2,218</td>
<td>20,723</td>
</tr>
<tr>
<td>38–47</td>
<td>3,304</td>
<td>27,166</td>
</tr>
<tr>
<td>48–57</td>
<td>6,548</td>
<td>22,529</td>
</tr>
<tr>
<td>58–67</td>
<td>798</td>
<td>4,241</td>
</tr>
<tr>
<td>Unadjusted Total</td>
<td>13,600</td>
<td>84,735</td>
</tr>
</tbody>
</table>

Standardized‡ Prevalence Estimates

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>[95 % CI]</td>
<td>[18.1 ; 18.4]</td>
</tr>
<tr>
<td>[23.7]</td>
<td>[23.5 ; 23.8]</td>
</tr>
</tbody>
</table>

†National estimates derived by frequency weighting of the NHDS 2000 weight variable. Estimates derived from frequency weighted sample sizes over 2,000 are considered unbiased. Estimates derived from frequency weighted sample sizes under 2,000 are considered unreliable.

‡The sum of age-specific denominators (population column) were used as weights within each age interval to calculate the standardized summary prevalence estimates (Rothman KJ and Greenland S. Modern Epidemiology, 2nd ed, 1998. Estimates derived using Episheet ©)
Table 3.3. Age-specific and age-standardized national prevalence estimates† of type 2 diabetes among hospital discharges of morbidly obese patients, ages 17–67, by sex and procedure, NHDS 2002

<table>
<thead>
<tr>
<th>Male</th>
<th>Age Interval</th>
<th>Diabetes Diagnosis</th>
<th>Population (n)</th>
<th>Prevalence (%)</th>
<th>Diabetes Diagnosis</th>
<th>Population (n)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Obesity Procedures</td>
<td></td>
<td></td>
<td>All Other Hospital Procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17–27</td>
<td></td>
<td></td>
<td>23</td>
<td>1,002</td>
<td>2.3</td>
<td>134</td>
<td>2,856</td>
</tr>
<tr>
<td>28–37</td>
<td></td>
<td></td>
<td>165</td>
<td>3,977</td>
<td>4.1</td>
<td>1,727</td>
<td>10,662</td>
</tr>
<tr>
<td>38–47</td>
<td></td>
<td></td>
<td>991</td>
<td>3,333</td>
<td>29.7</td>
<td>6,034</td>
<td>25,960</td>
</tr>
<tr>
<td>48–57</td>
<td></td>
<td></td>
<td>2,211</td>
<td>6,425</td>
<td>34.4</td>
<td>9,074</td>
<td>29,717</td>
</tr>
<tr>
<td>58–67</td>
<td></td>
<td></td>
<td>53</td>
<td>240</td>
<td>22.1</td>
<td>8,749</td>
<td>25,281</td>
</tr>
</tbody>
</table>

Unadjusted Total

<table>
<thead>
<tr>
<th>Male</th>
<th>Diabetes Diagnosis</th>
<th>Population (n)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obesity Procedures</td>
<td>3,443</td>
<td>14,977</td>
</tr>
<tr>
<td></td>
<td>All Other Hospital Procedures</td>
<td>25,718</td>
<td>94,476</td>
</tr>
</tbody>
</table>

Standardized‡ Prevalence Estimates

<table>
<thead>
<tr>
<th>Male</th>
<th>Diabetes Diagnosis</th>
<th>Population (n)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obesity Procedures</td>
<td></td>
<td>[95 % CI]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25.1</td>
<td>[23.8 ; 26.5]</td>
</tr>
<tr>
<td></td>
<td>All Other Hospital Procedures</td>
<td>26.7</td>
<td>[26.4 ; 27.0]</td>
</tr>
</tbody>
</table>

Female

<table>
<thead>
<tr>
<th>Age Interval</th>
<th>Diabetes Diagnosis</th>
<th>Population (n)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17–27</td>
<td>709</td>
<td>9,074</td>
<td>7.8</td>
</tr>
<tr>
<td>28–37</td>
<td>2,053</td>
<td>16,746</td>
<td>12.3</td>
</tr>
<tr>
<td>38–47</td>
<td>2,313</td>
<td>23,833</td>
<td>9.7</td>
</tr>
<tr>
<td>48–57</td>
<td>4,337</td>
<td>16,104</td>
<td>26.9</td>
</tr>
<tr>
<td>58–67</td>
<td>745</td>
<td>4,001</td>
<td>18.6</td>
</tr>
</tbody>
</table>

Unadjusted Total

<table>
<thead>
<tr>
<th>Female</th>
<th>Diabetes Diagnosis</th>
<th>Population (n)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obesity Procedures</td>
<td>10,157</td>
<td>69,758</td>
</tr>
<tr>
<td></td>
<td>All Other Hospital Procedures</td>
<td>37,661</td>
<td>166,051</td>
</tr>
</tbody>
</table>

Standardized‡ Prevalence Estimates

<table>
<thead>
<tr>
<th>Female</th>
<th>Diabetes Diagnosis</th>
<th>Population (n)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obesity Procedures</td>
<td></td>
<td>[95 % CI]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16.4</td>
<td>[16.1 ; 16.7]</td>
</tr>
<tr>
<td></td>
<td>All Other Hospital Procedures</td>
<td>21.6</td>
<td>[21.4 ; 21.8]</td>
</tr>
</tbody>
</table>

† National estimates derived by frequency weighting of the NHDS 2000 weight variable. Estimates derived from frequency weighted sample sizes over 2,000 are considered unbiased. Estimates derived from frequency weighted sample sizes under 2,000 are considered unreliable.

‡ The sum of age-specific denominators (population column) were used as weights within each age interval to calculate the standardized summary prevalence estimates (Rothman KJ and Greenland S. Modern Epidemiology, 2nd ed, 1998. Estimates derived using Episheet ©)
3.4. Discussion

To the best of our knowledge, this was the first study to describe demographic characteristics and common comorbid conditions among morbidly obese patients in a nationally representative sample of US hospital discharges. Compared with morbidly obese patients discharged for all other procedures, morbidly obese patients discharged for surgical obesity procedures were more likely to be younger white females. The demographic characteristics of the obesity surgery group is consistent with that reported in the bariatric surgical literature (Buchwald et al. 2004, Livingston and Ko 2004, Carbonell et al. 2004, Choban, Lu & Flanbaum 2000). Previous studies have implicated disparities in health care access and utilization, insurance status, sociocultural influences, and socioeconomics as contributing factors for the demographic discordance observed between those who are medically eligible for bariatric surgery and those who actually receive it (Livingston and Ko 2004, Carbonell et al. 2004, Zizza et al. 2003). According to the National Health and Nutrition Examination Survey (NHANES) 1999-2002, which includes the same survey year as this study, the age-adjusted self reported diabetes prevalence among measured morbidly obese adults, ages 20 and older was estimated at 20.3% with a 95% confidence interval of 16.4% to 24.1% (unadjusted estimates were similar). These data (unpublished) suggest that underdiagnosis of diabetes may not be a serious problem among severely obese people.

A higher prevalence of GERD, sleep apnea, and osteoarthritis was found in the younger, mostly female surgical obesity procedures group. This was an unexpected finding, because both groups were coded as morbidly obese, and the all other hospital procedures group was on average older, with a greater representation of men and minorities. Older age, male sex, and ethnicity are associated with increased comorbidity in morbidly obese bariatric patients (Carbonell et al. 2004). There are a number of possible explanations for the differential rates of these comorbid conditions. Obesity is associated with GERD, sleep apnea, and osteoarthritis. One proposed mechanism for the obesity-GERD relationship is that obesity increases intra-abdominal pressure, displacing the lower esophageal sphincter (LES) and increasing the gastroesophageal pressure gradient, leading to increased esophageal acid
reflux (Hampel, Abraham & El-Serag 2005). However, this mechanism does not adequately explain why the younger, mostly female obesity surgery group was diagnosed with higher rates of GERD, given that both groups were coded as morbidly obese. Another possible biologic explanation may be the hypothesized role of estrogens in the etiology of GERD. Nilsson et al. found a stronger relationship between BMI and GERD among young, severely obese premenopausal women (odds ratio [OR]6.8; 95% confidence interval [CI] 4.7 to 9.7) compared with men (OR 3.3; 95% CI 2.4 to 4.7) and postmenopausal women (OR 4.2; 95% CI 3.2 to 5.5) at the same BMI level (Nilsson et al. 2003). These authors theorized that the association between estrogen and GERD is a nitric oxide mediated reduction in smooth muscle tone at the LES. Obese women have increased fatty tissue estrone production, lower concentrations of sex hormone binding globulin, and thus a larger proportion of unbound active estradiol. Excess estrogen increases nitric oxide synthesis (the primary relaxing transmitter substance of the LES), which leads to reduced LES tone and increased acid reflux (Hampel, Abraham & El-Serag 2005).

GERD and sleep apnea often coexist in morbidly obese patients (Orr et al. 2004), but the prevalence of sleep apnea is two to three times higher in men than in women (Gibson 2005). We also found this sex difference in our study. Elevated rates of sleep apnea among obesity surgery discharges was due to a higher prevalence of sleep apnea overall for both men (47.3% vs 17.2%) and women (19% vs 8.7%) compared with all other hospital procedure discharges of morbidly obese patients. Elevated rates of GERD, sleep apnea, and osteoarthritis could occur due to increased severity of obesity in the obesity surgery group. The possibility that persons who elect to undergo obesity surgery are heavier within the morbidly obese range could account for the higher prevalence of sleep apnea. Greater obesity levels also might affect intra-abdominal pressure in the obesity surgery group, which could lead to an increased frequency of GERD. Increased severity of morbid obesity might also explain the higher rate of osteoarthritis, which is positively correlated with weight and is a strong predictor of bilateral knee osteoarthritis, especially in obese women (Hart and Spector 1993).
Unfortunately, we were unable to evaluate the severity of obesity, because the NHDS does not collect data on weight and height.

It is also possible that because clinical and insurance-driven criteria for bariatric surgery approval requires the presence of comorbid conditions, morbidly obese patients who elect to undergo obesity surgeries could be sicker than other morbidly obese patients. On the other hand, there are limited diagnostic coding slots in the discharge record. If patient hospitalizations for the all other procedures group were disproportionately complicated compared with those for the obesity surgery group, then medical coders might report diagnoses specifically related to the complication, thus undercoding existing or otherwise controlled health conditions. This could underestimate the prevalence of the selected comorbid conditions among the all other procedures group, making these patients appear less sick. This form of undercoding bias has been reported previously (Jencks, Williams & Kay 1988).

There could also be preferential diagnosis for persons seeking elective surgical obesity treatment. The majority of insurers who provide and approve bariatric surgery have strict eligibility criteria that include a minimum BMI of 40 with the presence of comorbid conditions (Hall 2003). Thus, bariatric surgical centers are proactive diagnostically and administratively in helping potential surgical candidates obtain insurance approval. Diagnostic tests, such as sleep studies to assess sleep apnea, are often performed to identify previously undetected conditions. This may result in a more thorough accounting of obesity associated comorbidities for those undergoing obesity surgeries. However, for all other hospital procedures, subclinical or vaguely symptomatic diseases could remain undetected (Gibson 2005). Differential coding may also be related to optimizing hospital reimbursement and minimizing denial or audit of hospital procedures (Miller and Lineberry 2004).

Other biases could include nondifferential medical coding errors or random miscoding of diagnoses, bias caused by missing data, or bias caused by systematic comorbid undercoding for patients discharged for all other hospital procedures. Overall, the prevalence of morbid obesity for all procedures among adults 20 yrs and older was 1.28%. The 2001-2002 national
adult population estimate of morbid obesity was 5.1% (Hedley et al. 2004). This finding implies that either morbidly obese individuals do not representatively use inpatient hospital services or that morbid obesity is an undercoded diagnosis for procedures not specifically related to obesity surgery. The latter is more likely, as undercoding of obesity and morbid obesity is a long-recognized source of bias in administrative datasets and medical records (Fitch et al. 2004, Einbinder 2002, Stafford et al. 2000). For example, using BMI as the criterion standard, researchers (Einbinder 2002) evaluated morbid obesity coding accuracy and found that morbid obesity had a sensitivity of 0.19 and a specificity of 0.99, meaning that many patients do not get properly coded as morbidly obese, but those who do get coded as such are likely to be morbidly obese.

Recent validation studies (Rector et al. 2004, Wilchesky, Tabblyn, & Huang 2004, Einbinder 2002, Quan, Parsons & Ghali 2002) of comorbidity coding derived from administrative datasets have revealed a general undercounting of comorbidities, a wide range of sensitivity, and consistently high specificity. Quan et al. reported the prevalence of comorbidity by data source (1200 randomly selected administrative discharge records from April 1, 1996 to March 31, 1997 and the corresponding patient medical records for an urban region in Calgary, Canada) and evaluated measures of agreement for 17 comorbidities that constitute the Charlson index (Quan, Parsons & Ghali 2002). Using the patient medical records as the criterion standard, they found that sensitivity varied widely by comorbid condition (range, 24.6% to 87.8%), and specificity exceeded 96% for all comorbidities. For uncomplicated diabetes (similar to the definition used in our study), the prevalence percentage difference between the administrative data (9.9%) and the chart data (8.7%) was 1.2%; in addition, the Kappa ($K$) score was 0.74, sensitivity was 81.7%, specificity was 96.9%, the positive predictive value was 71.4%, and the negative predictive value was 98.2%. Other studies have also shown substantial agreement and accuracy for diabetes and other potentially life-threatening comorbidities (Rector et al. 2004, Wilchesky, Tabblyn, & Huang 2004). Assuming that the criterion standard (the patient medical record) is error–free and accurately classifies patient comorbidity, these results suggest that administrative datasets
are, in general, coding diabetes and other comorbid conditions that either require inpatient medical management or may be risk factors for the primary diagnosis (Kokotailllo and Hill 2005, Quan, Parsons & Ghali 2002).

Confounding by reimbursement pricing could also influence demographic characteristics and comorbid prevalence among the obesity surgery group. Angus et al. revealed that for Roux-en-Y gastric bypass coded under DRG 288, there is a financial disincentive for surgeons to treat publicly insured patients ($931 ± $73) compared with privately insured patients ($2,356±$822), while hospital reimbursement is higher for public insurance ($11,773±$4,462) than for private insurance ($4,435 ± $3,106) (Angus et al. 2003).

In this study, patient discharges coded as obese compared with morbidly obese had similar rates for many of the selected comorbid conditions among the all other procedures group. This finding may also be the result of coding biases. Nevertheless, Fobi and colleagues evaluated gastric by-pass outcomes in patients with BMI > 32 and < 40 and reported that obese patients and morbidly obese patients had similar reasons for pursuing surgical weight loss. Obese patients also had comparable underlying comorbidities and fewer postoperative complications. In this group the percent excess weight loss averaged 95% at 27 months follow-up, and these patients were considered the most motivated and compliant patients in the practice (Fobi et al. 2002). To date, no studies have evaluated the BMI indications for bariatric surgery, which have been established by consensus (NIH 1991). More research is needed in this area to better inform U.S. clinical and insurance guidelines on the obesity levels most appropriate for bariatric surgery.

3.4.1. Study Limitations

The results of our study should be evaluated in light of the limitations. First, the NHDS 2002 is a cross-sectional survey of hospital discharges for a single year. Cross-sectional studies focus on the characteristics of interest for a defined population during a specified time period or on the differences observed between subgroups within the studied population, without assuming a hypothesis. This study design captures a snapshot in time and is ideally
used to identify the burden of disease in a population, for the purposes of health resource planning and allocation, or generating hypotheses. Cross-sectional studies conducted to estimate disease prevalence are also known as prevalence studies.

If cross-sectional studies are used for etiologic inference, then a number of potential limitations must be recognized. For example, cases with long duration or better survival are more likely to be represented in a cross-sectional study, which can bias results if the duration of disease is associated with the exposure under investigation. Because data on exposures and outcomes are collected at the same time, cross-sectional studies are unable to answer questions of etiology if the temporal sequence of the exposure and outcome is ambiguous. This is because reverse causality cannot be ruled out (eg, is obesity causing low back pain or is low back pain leading to an inactive lifestyle, which then contributes to obesity?) In addition, because cross-sectional studies are observational designs, they are prone to biases that are often avoided in experiments or randomized controlled trials. For instance, lack of randomization may reduce the comparability between the exposed and unexposed groups. Although confounding may be controlled in the design or analysis stage, this is possible only for known or measured confounders.

For this study, a probability sample of discharge records eliminated the possibility of systematic differences between discharge records that were eligible to be sampled and those that were selected, thus allowing generalization of results to the U.S. national population of hospital discharges. We described morbidly obese patient discharges and the differences observed between those discharged for obesity surgery and those discharged for all other hospital procedures. We provided possible biologic explanations for our findings and also discussed the potential influences of selection bias (obesity surgery patients are a self-selected population), information bias (diagnostic coding errors), detection bias (differential detection of comorbidities), and confounding (differential reimbursement pricing and/or other uncontrolled extraneous variables).

A second potential limitation is the use of an administrative dataset to investigate comorbid prevalence. Nationally representative administrative datasets such as the NHDS
are a rich source of demographic, diagnostic, procedural, and comorbidity information and are commonly used in clinical research (Livingston and Ko 2004, Carbonell et al. 2004). Population-based datasets avoid the selection bias associated with single-center studies or academic and referral centers (Rosenberg, Greenfield & Dimick 2006). In addition, probability samples of these data sources increase statistical power and allow generalization of results to a larger population, usually at the state, regional, or national level (Rosenberg, Greenfield & Dimick 2006). Nevertheless, datasets of this type may introduce bias into a study due to both differential and nondifferential diagnostic coding errors, missing data, nonuniformity in choice of diagnostic codes, coding for reimbursement optimization, and limited slots for diagnostic coding (Rosenberg, Greenfield & Dimick 2006). Not adjusting for confounding may also lead to inappropriate conclusions.

A third limitation is that the NHDS 2002 is a probability sample of hospital discharge records, similar to the Nationwide Inpatient Sample and many other administrative datasets; therefore, the unit of analysis is discharge records. The results obtained (eg, mean age, percentage of males) from the weighted sample of discharge records represents unbiased estimates of US national hospital discharges—not patients. Proper interpretation of results is important, because multiple hospital discharge records could exist for a single patient and the NHDS does not account for multiple records per patient in the probability sampling scheme. The implication is that national patient estimates could be biased. For example, if 20 out of 100 obesity surgery discharge records are coded as male, then the percentage of male obesity surgery discharges for the year would correctly be 20%. If four males had two obesity surgeries each within the year (4 x 2 = 8 discharges), and 12 males had one surgery each (12 x 1 = 12 discharges) for a total of 20 discharge records (8 + 12 = 20 male discharges), then 16 male patients (4 + 12 = 16 males), or 16%, underwent obesity surgery within the year.

Generalization from a representative sample of hospital discharge records to the national morbidly obese patient population can be inferred to the extent that national discharge estimates obtained from the weighted sample of discharge records reflect the demographic
characteristics and comorbid prevalence estimates of the morbidly obese national hospital patient population. There are currently no quality nationally representative patient-level data with which to compare our results. One approach that can be used to evaluate representativeness for the obesity surgery group is by evaluating the consistency of the overall body of bariatric surgical literature.

### 3.5. Conclusion

Obesity has been the subject of intensive research, surveillance, and intervention efforts, yet remarkably little is known about the health status of morbidly obese persons. Comorbid prevalence is one measure of health status, and administrative datasets are increasingly being used to answer clinical questions of this nature. However, correct assessment of comorbid frequency in morbidly obese patients depends on obtaining valid diagnostic information from these data sources.

Although primary prevention is the best approach to attenuating the obesity epidemic and associated comorbidities, bariatric surgery is currently the only successful treatment of obesity-related diseases for which primary and secondary obesity prevention efforts have failed (Maggard et al. 2005, Buchwald et al. 2004, Carbonell et al. 2004, Livingston and Ko 2004, Sjöstrom et al. 2004, Choban et al. 2002). Indications for surgical weight loss procedures include specified cutpoints of obesity levels and obesity-related comorbidity. Thus, advancing surgical and insurance guidelines for bariatric surgery will require quality patient-level clinical data that accurately describe and quantify the demographic distribution of obesity and the associated burden of disease. Ideally, and in accordance with National Institutes of Health guidelines (NIH 1991), bariatric surgery should be available for those patients at greatest risk for obesity-related morbidity and mortality.
ABSTRACT

Background: Obesity and risk of related chronic diseases is currently defined and classified by the body mass index (BMI), calculated as weight in kilograms (kgs) divided by height in meter squared (m²). Although obesity is one of the strongest predictors of diabetes, heterogeneity of risk persists across ethnic groups and within obesity levels. Understanding the underlying mechanism by which obesity causes diabetes may help to clarify paradoxical findings and introduce new perspectives in primary and secondary prevention of type 2 diabetes. The Energy Hypothesis Capacity Hypothesis was used as the etiologic framework to model diabetes in the US adult population. Methods: The 1999-2002 National Health and Nutrition Examination Survey (NHANES) was used to describe diabetes burden and greatest weight gain in adulthood by race, among nationally representative adults, ages
20 and older. Logistic regression was used to model the dependent variable, DIABETES, using the risk factors of AGE, RACE, Family History of Diabetes (FHDM), lowest BMI in adulthood (LowBMI) and greatest BMI gain in adulthood (∆BMI) as predictors. Multiple imputation (MI) was used to address missing data while the potential interaction of RACE and ∆BMI was assessed graphically. Post Hoc analysis evaluated mean A1c among diabetics by RACE, BMI categories, AGE, and FHDM. Results: Operationally defined Asian RACE exhibited the highest burden of diabetes despite lowest crude and age adjusted current BMI and lowest ∆BMI among all racial subgroups. The adjusted odds of diabetes among Asians was 3.9 times higher than Whites; odds ratio and 95% confidence interval [OR 3.9 ; 95% CI 1.4 - 10.8]. MI did not substantively modify the results [OR 4.3 ; 95% CI 2.4 - 7.5]. Despite significantly lower crude and age-adjusted current BMI and lower ∆BMI compared to Blacks, Mexican and Hispanics, the burden of diabetes was highest among Asians, although this did not reach statistical significance. Within racial groups, obesity levels, both current and ∆BMI, were positively associated with diabetes burden. The predicted probability of diabetes was generally highest among Asians per unit ∆BMI, even after accounting for all major risk factors of DIABETES. Among diabetics, mean A1c levels were higher in normal and overweight people compared to those measured as obese and severely obese and also higher among Asians, young adults, and diabetics who did not report having a family history of diabetes. Conclusions: Results of this study are consistent with the Energy Storage Capacity Hypothesis. Subgroups considered low risk for either the development of diabetes or diabetic glycemic control appear to be at high risk for glycemic exposure and possible future health complications related to diabetes.
4.1. Introduction

Although recent data suggest that the rise in the prevalence of adult obesity in the United States may be leveling off, almost 70% of people ages 20 and older are overweight and obese (defined by the body mass index - BMI: kg/m² ≥ 25), with nearly 34% classified as obese (BMI ≥ 30) (Flegal et al. 2010). While obesity prevalence does vary by age, sex, and ethnicity, it disproportionately affects African Americans (44.1%) and Hispanics (38.7%) (Flegal et al. 2010).

The public health problem with obesity is the strong association with numerous health conditions, particularly type 2 diabetes (Norris et al. 2008). For most of the decade and beyond, the steep and steady rise in obesity, for example, an 85% increase from 1993 to 2008 (Flegal et al. 2010), has been paralleled by a similar rise in the prevalence of type 2 diabetes (Sheehy et al. 2010), a serious metabolic health condition medically defined by the presence of excess glucose in the blood (fasting plasma glucose of 126 mg/dL or more) (Norris et al. 2008). More importantly, even though obesity trends may be abating, the prevalence of diagnosed diabetes continues to rise (Sheehy et al. 2010). Although other known risk factors for type 2 diabetes include family history, age, ethnicity, and sex, obesity is considered one of the strongest predictors of the disease, and only obesity is modifiable, and therefore a target for public health intervention.

Despite years of obesity research, surveillance, screening, and intervention, public health approaches to preventing chronic diseases through attenuating obesity have been abysmal. So much so, that the decreases achieved in coronary heart disease (CHD) mortality due to successful medical advances along with decreases in smoking incidence and prevalence, may be offset by a decrease in future life expectancy, secondary to type 2 diabetes (Olshansky et al. 2005). Further complicating the public health challenge of targeting obesity for intervention, certain subgroups, such as people of Asian ancestry appear to be at elevated risk for obesity-related chronic diseases at much lower BMI’s than non-Asians (WHO 2004, 2000).
Indeed, international research has unequivocally shown that obesity related chronic diseases are gaining a significant foothold in poor developing countries, known more often for problems of hunger and infectious diseases (IDF 2009). Recent studies conducted in the United States, however, have also shown that American Asians have high risk for developing type 2 diabetes at lower BMI’s compared to other ethnic groups. For example, Shai and colleagues (2006) used the Nurses Health Study to evaluate BMI, BMI change, and risk of incident type 2 diabetes in a multi-ethnic US cohort that included Whites, Asians, Blacks, and Hispanics. They conducted a retrospective cohort analysis of 78,419 apparently healthy middle-aged women who were followed for 20 years [1980-2000]. Multivariable analysis revealed that although Asian women had the lowest mean BMI and lowest mean BMI change, their risk of incident type 2 diabetes was highest, relative to Whites (RR: 1.99; 95% CI [1.50-2.60]). Asian women also had the highest relative risk of type 2 diabetes per 5 unit change in BMI. Controlling for the additional factors of dietary scores (including energy intake and alcohol), exercise, and smoking status did not appreciably alter the relative risks. Although this cohort represented a homogeneous group of educated middle-aged women in the nursing profession, and researchers did not control for place of birth, education, or income level, these findings are consistent with reports that Asian risk of diabetes occurs at much lower BMIs than other ethno-racial groups (Deurenberg-Yap and Deurenberg 2003, Misra 2003, Bei-Fan 2002).

Another multi-ethnic study reported similar results to the Nurses Health Study. In this US population based cross-sectional 2001 survey of diabetes prevalence among multi-ethnic adults (McNeely and Boyko 2004), researchers found that after adjustment for BMI, age, and sex, the odds of diabetes was 1.6 times higher in Asian Americans compared to Whites, despite reporting the lowest mean BMI among the studied groups. These data, from the Behavioral Risk Factor Surveillance System (BRFSS), while similar to the Nurses Health Study in the overall conclusions, excluded younger adults. In addition, current self report BMI was evaluated instead of measured BMI, change in BMI was not investigated, the
response rate was low (51.1%), missing data (7.5%) were ignored, and family history of diabetes, which is a major risk factor for diabetes, was not controlled.

Why Asians are at elevated risk for type 2 diabetes at a lower BMI has been a source of continuing investigation. Many researchers have long implicated excess visceral fat as a plausible explanation. The visceral fat-type 2 diabetes risk hypothesis, however, has produced equivocal results, with some experimental studies even showing a protective effect (Bains et al. 2004, Okuna et al. 1998). Similarly, epidemiologic results have also been inconclusive. For instance, in a cross-sectional study assessing insulin-producing pancreatic beta (\(\beta\))-cell function and insulin sensitivity among 77 healthy glucose tolerant, normotensive young adults, Asian American participants were the leanest group, as defined by the waist-to-hip ratio (WHR), yet exhibited higher levels of insulin resistance compared to Caucasians, African Americans, and Mexican Americans (Chiu et al. 2000). In addition, the difference in WHR in the Asian group could not explain the observed differences in insulin sensitivity after accounting for family history of diabetes. Chiu and co-workers also sought to disentangle the relationship between insulin sensitivity and pancreatic beta \(\beta\)-cell function and found that ethnicity was primarily associated with insulin sensitivity and that the observed ethnic differences in pancreatic \(\beta\)-cell function were secondary to differences in insulin sensitivity. These findings rule out a potential independent genetic risk pathway to type 2 diabetes via \(\beta\)-cell degradation, at least in this sample. Although these results point to target tissue insulin resistance as antecedent to \(\beta\)-cell changes, they are not supportive of obesity-disease theories that directly implicate visceral fat as the causal mechanism. The visceral fat hypothesis, though appealing, is far from conclusive. For example, several studies have shown greater levels of visceral fat among white women relative to black women, with black women having greater total bodyfat, but also exhibiting greater insulin resistance (Shai et al. 2006).

Given that the projected worldwide diabetes burden among Asians is estimated to affect nearly 200 million people by the year 2025, the WHO introduced an expanded international BMI classification table which includes lower BMI cutpoints to be used for public health
action for Asians (WHO 2004). Lowering BMI cutpoints to signal public health action for particular sub-groups does not aid in etiologic understanding and does not address the threat of weight gain within BMI categories (one BMI unit ≈ 3 kgs). A 6-9 kg increase in weight to trigger intervention efforts may simply be too late. Once adults have gained weight, losing the excess weight and keeping it off long-term is extremely difficult (Anderson et al. 2001).

Moreover, a single BMI screening does not identify heavy people with improved metabolic health due to intentional weight loss (Buchwald et al. 2004, Tremblay et al. 1999), nor does a single screening identify unhealthy people who may have gained weight within the normal BMI range. A moderate weight loss of 5% to 10% has been shown to significantly improve metabolic markers among people who are overweight or obese (Klein et al. 2004, DPPRG 2002, Goldstein 1992). These observations suggest that measuring weight change or BMI over time may be a better approach for accurately predicting diabetes risk. For many weight-reduced obese persons, resolution of type 2 diabetes occurs even when maintenance BMI remains in the obese category (Buchwald et al. 2004). This is most clearly exemplified in bariatric patients who have undergone a surgical weight loss procedure. In a randomized controlled trial which compared adjustable gastric banding and conventional therapy for type 2 diabetes remission, Dixon and colleagues revealed that the degree of weight loss, not the method of weight loss, was the major factor for diabetes remission among obese participants, even though the average post-intervention BMI remained high (Dixon et al. 2008).

Independent of weight loss efforts however, is the observation that a large majority of individuals who are severely obese, are metabolically healthy, at least defined by the absence of type 2 diabetes (Brochu et al. 2001). Substantiating Brochu’s research, a representative sample of US hospital discharge records for year 2002, showed that 76% of medical discharge records with a recorded diagnosis of morbid obesity did not include a diagnosis of diabetes (Scott et al. 2006).
The elevated diabetes risk shown in relatively lean Asian subgroups and the observation that a large majority of severely obese people are metabolically healthy might be further clarified if the underlying bio-mechanism by which obesity causes type 2 diabetes is better understood. The use of explicit etiologic hypotheses could help epidemiologists design more informative studies, aid in the development of statistical models to better predict type 2 diabetes in diverse ethnic populations, and possibly explain a number of enduring obesity-disease paradoxes.

William Stehbens, in his article on causality in medical science, stated that the most effective management, treatment, and prevention of any illness must be based on the causa vera or specific cause (Stehbens 1992). Developing a comprehensive obesity-type 2 diabetes model which is anchored by the causa vera along with secondary behavioral, cultural, social, psycho-social, and environmental co-factors is vitally important from a public health perspective as globalization is leading to increasingly diverse societies. Group-specific obesity metrics to improve disease prediction or risk classification for various subpopulations may be a necessary stop-gap, but identifying underlying disease etiology and clearly differentiating it from the secondary role of contributing or influential factors (Stehbens 1992) will ultimately provide the best evidence for improving the public’s health (Duell 2006, Stehbens 1992), in this case, through the prevention, detection, and resolution of type 2 diabetes.

For this study, we investigated the relation of race and weight gain with diabetes using the Energy Storage Capacity Hypothesis (Scott et al. 2004) as the underlying etiologic framework. Briefly, this hypothesis (Chapter two) proposes that adiposity related to high baseline white adipose cellularity (more fat cells) is protective against obesity-related chronic diseases such as type 2 diabetes, by providing greater absolute energy storage capacity with which to store excess energy. Obesity-related health risks increase only when energy storage nears the threshold of energy storage capacity, as each individual fat cell has a size limit beyond which adipocyte regulatory proteins reduce the capacity to store additional energy, in part, by inducing insulin resistance. The implication is that less fat cells, which imply less storage capacity would result in the onset of obesity-related diseases at a lower level of frank
excess energy (less weight gain). We explored this hypothesis in adults, ages 20 and older, by using the 1999-2002 National Health and Nutrition Examination Survey (NHANES), a cross-sectional representative sample of the US population. We used race/ethnicity and self report greatest BMI gain in adulthood as risk markers and phenotypic surrogates for fat cell number and fat cell size, respectively. Asians were assumed in our model, to possess the least number of fat cells relative to Whites, African Americans, Mexicans, or other Hispanics, while greatest BMI gain represented greatest weight gain, and by extension, a positively correlated fat cell size. The specific aims were threefold:

1. Examine the association of race/ethnicity and diabetes, while controlling for the major known risk factors of type 2 diabetes
2. Examine current BMI and greatest BMI gain among diabetics, stratified by race
3. Examine the association of greatest BMI gain among diabetics, within race

The predictions made based on The Energy Storage Capacity Hypothesis were the following:

1. A higher odds of diabetes will be observed among Asians, relative to Whites, Blacks, Mexicans, or Hispanics, even after accounting for the major risk factors of diabetes.
2. Asian diabetics will exhibit a lower current BMI and lower greatest BMI gain relative to Whites, Blacks, Mexicans, and other Hispanics.
3. Within race categories, current BMI and greatest BMI gain will be positively associated with diabetes.

Although the use of race as a biologic category is controversial (Wolf 2006, Winker 2006, Winker (2006) and Issa et al. (2006) both concluded that in observational studies, race could serve as an investigative or exploratory proxy for a biologic category under a narrow hypothesis-driven rationale (in this case, adipose cellularity). We believe this study meets that criterion.
4.2. Methods

4.2.1. Data source, sample frame, and sample design

4.2.1.1. Data source. The National Health and Nutrition Examination Survey (NHANES) is arguably one the best known population health surveys in the United States. NHANES uses a complex multistage probability survey design to efficiently obtain nationally representative estimates of health and nutrition parameters of the non-institutionalized civilian population ages two months and older (NHANES 2002). Specifically, NHANES selects survey participants using a four stage probability sampling design. The sampling plan has been broadly described by Dohrmann and colleagues (Dohrmann et al. 2004) as follows:

Stage 1 - Counties: The entire United States is divided into geographic areas or clusters, which are known as primary sampling units (PSUs). These are counties or small groups of contiguous counties. PSUs are combined to form strata, usually based on PSU size, geographic region, and demographic characteristics.

Stage 2 - Census Blocks: Within each of the PSUs, approximately 24 census blocks or groups of census blocks are selected. These are called segments or secondary sampling units (SSUs).

Stage 3 - Households: Households from the selected census blocks are subsampled at random and screened.

Stage 4 - Individuals: Person(s) of a particular race-sex-age subdomain within a screened household are interviewed and selected with pre-specified probabilities, while the remainder of the household is excluded.

NHANES 1999-2002 survey years were used as the data source for this study.

4.2.1.2. Sample frame. The sample frame for the NHANES 1999-2001 survey originated from 358 PSUs selected out of a total of 1,995 for the design of the 1995-2004 National Health Interview Survey (NHIS) (Botman et al. 2000). These 358 PSUs were divided into four panels, each forming a nationally representative sample of the US population. In forming the four panels, large PSUs were split, while the remaining PSUs were stratified according to
geographic region, race, and income level. NHANES 1999-2001 used two of the four panels (the other two panels were used by the National Medical Expenditure Survey). Because the large PSUs were split, approximately 200 PSUs were available for sample selection. Thus, the PSUs from the two panels of the NHIS were used as the sample frame for NHANES 1999-2001 (Dohrmann et al. 2002).

Out of 200 PSUs, 120 PSUs were originally selected for six NHANES annual surveys (1999-2004) using a measure of size related to 1990 Census county-specific information on the percent Mexican American, percent Black, and the NHIS PSU-selection probability. Twenty PSUs were randomly assigned to each of the six data years (NHANES 2002). For NHANES survey years 1999-2001, sample selection of PSUs was based on this linked design with the NHIS. A subset of 15 PSUs were then selected to be used for each survey year, with the additional five held in reserve. In 1999, only 12 PSUs were selected due to a delay in data collection, for a total of 27 PSUs for the years 1999-2000. However, because one large PSU was included in both survey years, the 1999-2000 survey used 26 PSUs for variance estimation. Of 22,839 households screened during years 1999-2000, 6,005 households had at least one eligible person identified to be interviewed. In total, 12,160 persons were identified as eligible to participate, 9,965 were interviewed and 9,282 were medically examined, for response rates of 81.9% and 76.3%, respectively for the survey year 1999-2000 (NHANES 2005). An independent set of PSUs were selected for the 2002-2006 survey years. These PSUs were selected from a different sample frame of over 3,000 PSUs completely unlinked to the NHIS. The subsequent sampling design, survey content, and response rates however, were similar to the 1999-2000 NHANES (NHANES 2005). For NHANES 2001-2002, a total of 11,039 people were interviewed and 10,477 medically examined. Among all eligible participants for the survey years 1999-2002, 83% were interviewed and 78% were medically examined (Cowie et al. 2006).

4.2.1.3. Complex survey design. The complex survey design of NHANES 1999-2002 used multi-stage weighting to account for the unequal probabilities of selection, adjustment due to unit non-response, and poststratification of the sample weights to Census population
estimates. Subgroups that were oversampled included Mexican Americans, Non-Hispanic blacks, adolescents, the elderly, and for the year 2000, low-income whites and pregnant women (Carroll and Curtin 2000). Because NHANES collects data at multiple levels ( screener, interviewer, examiner), non-response and poststratification adjustments also occur at each level of data collection. For NHANES 1999-2002, poststratification of sample weights to Census population estimates were changed to account for the 2000 Census. In other words, for the survey years 1999-2000, sample weights were based on population estimates using the 1990 Census, while the sample weights in the 2001-2002 surveys were based on the 2000 Census. To accommodate the change, NHANES derived special 4-year sample weights for the interview and examination subsamples of both sample surveys to account for the differences in census years. Based on NHANES recommendation, we concatenated the two survey years, NHANES 1999-2000 and 2001-2002, and analyzed these as a single survey for a total interview sample size of 21,004 and examination sample size of 19,759 (NHANES 2005). For this study, we analyzed selected data on all adults ages 20 and older, excluding pregnant women for a total interview sample size of 9,591.

4.2.2. Operational definitions of study variables

4.2.2.1. Dependent variable. The outcome or dependent variable for this study was DIABETES. The question on diabetes that interviewers posed ( face-to-face) to participants in NHANES for survey years 1999-2002 was as follows, [Other than during pregnancy, ( for women)], have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes? We recoded and categorized diabetes as a dichotomous [0=No; 1=Yes] variable. Only 1.42% of responses were Borderline, Refused, and Don’t Know and were dropped and excluded from the analyses. Their exclusion did not modify the results. NHANES does not differentiate types of diabetes, however, approximately 90-95% of all cases of diabetes are classified as type 2 (CDC 2008), which means that the body is still producing insulin. In addition, the classification of type 2 diabetics does not rule out the possibility of taking
exogenous insulin.

4.2.2.2. Primary exposures. Three BMI variables were the major obesity exposure variables under investigation. BMI rather than weight alone was chosen to control for height. Current BMI was defined as weight in kilograms divided by height in meters$^2$. NHANES interviewers measured each survey participant for weight and height using standardized protocols to derive current BMI, which was kept as a continuous variable. We created two additional continuous BMI measures which were calculated based on current measured height, self report least weight (kgs) since age 18, and self report greatest weight (kgs) in adulthood. These were used to derive the additional BMI metrics for this study, which we defined as low BMI (using least weight since age 18) and ΔBMI or greatest BMI gain, which was calculated using the difference between lowest reported weight and greatest reported weight and current measured height. We included lowest BMI primarily to control for BMI status before adulthood, which is the recommended strategy when assessing BMI change or weight gain (Hu 2008). ΔBMI was used as the proxy measure to describe excess energy, which when stored, increases fat cell size and invariably results in weight gain. WAIST circumference was the final obesity metric, which was measured in centimeters and treated as a continuous variable.

RACE was the other major exposure variable under investigation. The NHANES 1999-2002 survey years included a question on RACE, which offered self-selection from 5 categories during the time of this analysis: 1 = Non-Hispanic White; 2 = Non-Hispanic Black; 3 = Mexican; 4 = Other; 5 = Other Hispanic. There was no explicit Asian Race. "Other" included all Asians, Eskimos, Pacific Islanders and mixed races. In analyzing this subgroup with Census data, the following was revealed: Alaskan Eskimo Indian and Pacific Islander populations were and are not increasing in the US population; these subgroups make up a very small proportion of the total population (<.01%), and primarily reside in Alaska and Hawaii, respectively. For the 1999-2002 survey years, NHANES did not sample from Alaska, Hawaii, or Indian reservations. The mixed race group for the 2000 Census represented a very
small percentage of the total population and was predominately reported among children in year 2000. In addition, according to the Census website, Asians were the fastest growing group during this time. The 2000 Census for the proportion of Asians ages 20 and over was 3.6%. The 1999-2002 NHANES estimates for "Other" in this study was 3.8% and the 2004 Census estimates for Asians was 4.2%. For this study, we operationally defined the "Other" race category as Asian. As of September 2009, the NHANES questionnaires were greatly expanded, and now include much greater specificity across and within race/ethnic/ancestral categories.

4.2.2.3. Other risk factors for diabetes. Other major known risk factors for diabetes were controlled for in this study and included self reported: AGE, Family History of Diabetes (FHDM), and SEX. These data were obtained through face-to-face interviews. The AGE question asked the current age of the participant and AGE in years was treated as a continuous variable. The FHDM question asked "Do any of your blood relatives have diabetes?" FHDM was treated as a dichotomous variable in this study [0=No ; 1= Yes] with Don’t Know and Refused responses (2.1%) excluded from the analyses. SEX was coded as a dichotomous variable [0=Female ; 1 = Male].

4.2.2.4. Secondary potential influential variables. EDUCATION, INCOME, and BIRTH were treated as secondary co-factors that were introduced and investigated in multivariable analyses. These were included primarily to consider their contribution as potential substantive confounders and fell out of the final model. EDUCATION was categorized and coded as 1=less than high school, 2=high school, or 3= greater than high school. For INCOME, we used the Current Population Survey (CPS) Family Poverty Index Ratio (PIR) as a continuous variable (Range 0-5). The PIR is the ratio of family income to the appropriate poverty threshold. If the total family income is less than the family threshold value, then everyone in the family is considered poor. PIR’s below one are below the poverty threshold, while PIR’s above 1 indicate income above the poverty level. Poverty thresholds
are adjusted annually for inflation and poverty definitions include income before taxes and non-cash benefits such as food stamps. The variable BIRTH represented Country of Birth and were coded and categorized as 1=Born in 50 US States or Washington; 2=Born in Mexico; 3=Born in any other location or foreign country.

4.2.3. Statistical analyses

4.2.3.1. Descriptive analysis. Data were analyzed using Stata, v. 9 Statacorp (2005). Diabetes cases are presented as counts and proportions, stratified by race. Continuous variables are described as means with standard errors (SE) along with medians and interquartile ranges (IQR). Categorical variables are shown as proportions or percentages with their 95% confidence intervals (95% CI). Because the age distribution strongly differs with race, and diabetes is associated with both race and age, we show the crude and age-adjusted diabetes proportion with 95% CI, along with the age-adjusted characteristics of self report diabetes, stratified by race. Estimates were age adjusted to the 2000 US Census population using direct standardization, distribution #12 (Klein and Schoenborn 2001). Design-based analysis, which accounts for the complex survey design of NHANES, was used to generate descriptive statistics. The relevant sampling weight was accounted for in the calculations of all medians and IQR’s. Four year interview weights were applied for interview questions and anthropometric measures, while four year examination weights were applied to medical examination derived data and logistic regression analysis. Exact two-tailed p-values are reported when relevant and p values < 0.05 are regarded as statistically significant.

4.2.3.2. Logistic regression analysis. Because the dependent variable, DIABETES was coded dichotomously, binary logistic regression was used to develop a design-based main effects model, which accounts for unequal probability sampling, clustering, and stratification. Likelihood ratio tests were used to identify the best fitting/most parsimonious main effects logistic regression risk model with diabetes as the dependent variable. The primary risk factors of AGE, FAMILY HISTORY, RACE, Low BMI, and ∆BMI were retained as
independent variables in the final main effects model. We initially used a backward selection approach to identify the major covariates to remain in the model. We then singly introduced the secondary influential covariates into the model to identify whether their addition added substantive information. Based on likelihood ratio tests, current BMI, SEX, WAIST, EDUCATION, INCOME, and BIRTH did not substantively contribute to a final, efficient model and they were dropped.

Once the main effects design-based model was developed, the continuous variables in the model were evaluated for linearity in the logit using the method of fractional polynomials on the model-based logistic regression model (Royston and Sauerbrei 2005). The method of fractional polynomials identifies the best model by comparing the fit with the straight line model using the deviance difference (Royston, Ambler & Sauerbrei 1999). The Fracpoly package in Stata (Statacorp 2005) was used to identify the following transformations of the following continuous variables: AGE was transformed as a 2 degree fractional polynomial, powers (2 3), adjusted for covariates in the model. Low BMI was modeled as a first degree fractional polynomial power (3) adjusted for the same covariates, and ΔBMI was modeled as a quadratic term.

To evaluate the stability and reliability of the point estimates and standard errors obtained from the final main effects logistic model, we re-analyzed the logistic regression final main effects risk model with various statistical approaches: Ignoring the complex survey design entirely (a model-based analysis), accounting for the complex survey design of NHANES (design-based analysis), applying probability weights with robust standard errors, conducting a bootstrap analysis with bias corrected standard errors using 1200 replications, and applying a second bootstrap analysis that included EDUCATION and INCOME. These extra steps were undertaken to evaluate the stability and reliability of point estimates and variance due to small sample sizes during analysis of subgroups.

4.2.3.3. Logistic regression assessment and diagnostics. We conducted a series of logistic regression assessments and diagnostics on our final main effects logistic regression
model. To evaluate whether our model was properly specified, that no relevant variables were excluded, and that no extraneous variables remained in the model, we conducted the linktest which uses the linear predicted values to rebuild the logistic regression model. The linktest revealed no specification errors (Hat $p=0.000$; Hat $^2p=0.330$). To assess the fit of our model, the Hosmer-Lemeshow goodness-of-fit test statistic was used, which showed no significant difference overall between the observed and expected counts of reported diabetes, suggesting that the main effects logistic model reasonably fit the data ($\chi^2 = 0.55$, df(4); $p = .968$).

Collinearity among the obesity variables was also investigated. Both the tolerance and the variance inflation factors fell within normal parameters, showing that collinearity was not a concern (mean VIF = 5.18; mean Tolerance $<1.0$). The area under the curve (AUC) Receiver Operating Characteristic (ROC) analysis, which provides information on the discriminatory power of the model, that is, the ability to discriminate between subjects who experience the outcome and those who do not, revealed excellent discrimination (AUC=.8645) as classified by Hosmer and Lemeshow (2000). The overall rate of correct classification based on a .50 cutpoint was 90.1% with 98.65% specificity and 16.62% sensitivity.

4.2.3.4. Missing data and use of multiple imputation. Missing data was a factor in this dataset which was addressed through the use of multiple imputation (MI). Missing data, if it is not missing completely at random (MCAR), can introduce bias if the incomplete dataset results in coefficients that are different than would have been obtained if data were not missing. Missing data can also increase variance due to loss of information. Missing at Random (MAR) is a necessary condition for the principled use of MI (Rubin 1987). The MAR assumption requires that the probability of missingness can depend on other observed variables in the dataset but should be independent of the value of the missing data itself (Wayman 2003).

Based on our analysis, the majority of missing data points were located within two variables: least weight (kgs) since age 18 (5237/9591; 54.6% missing), which partly derived
the calculation of Low BMI, and self report greatest weight (kgs) in adulthood (267/9591; 0.03%), which partly derived ΔBMI. Further inquiry revealed that the missing data for Low BMI and ΔBMI was associated with survey year. The first question, was in fact, not included in the 2001-2002 survey years and therefore, the large majority of missing data met the MAR assumption, with Low BMI and ΔBMI representing nearly 80% of all missing values in this study. Other missing values (mv) included: [DMCAT (n=139); FHDM (n=206); current ht (n=976); and current wt (n=998)].

MI methods aim to recapture the nature of the relation between variables of the complete dataset and to simultaneously address the increased variance caused by the loss of information and account for variance due to the uncertainty caused by the missing data method itself (Schafer 1999). In addition to being a valid and user-friendly missing data method, simulation studies have shown that MI is robust against departures from the MAR assumption and MI is seemingly forgiving with the selection and number of auxiliary variables used to predict the imputed values (Schafer and Olsen 1998). We used the MI regression-based methods developed by Patrick Royston (Royston 2005, Raghunathan et al. 2001) for Stata software and conducted M=20 imputations to derive the averaged estimated coefficients and standard errors for the final complete logistic regression model, which we also present.

4.2.3.5. Graphical interpretation of possible interaction. Because the study was not powered sufficiently to detect significant differences in diabetes burden between ethnic subgroups in our main effects logistic model, we graphically assessed the possibility of interaction by showing the predicted probabilities of DIABETES per one unit increase in ΔBMI by race categories, adjusting for all other covariates in the model.

4.2.3.6. Post hoc analysis. To further investigate the implication of the Energy Storage Capacity Hypothesis, we evaluated age-adjusted mean A1c (%) among diabetics by BMI.
categories, AGE, RACE, and FHDM, which have all been shown to be independent predictors of A1c among people with impaired glucose tolerance (IGT) (Herman et al. 2007). Percentage A1c among diagnosed diabetics reveals information about glucose management over a two to 3 month window. It can be an indicator of treatment effectiveness and/or treatment compliance among diabetics.

4.3. Results

4.3.1. Description of the study population

Table 4.1 describes the characteristics of the study population including demographic information, anthropometric measures and DIABETES burden. The RACE subgroup, which was operationally defined as Asian, exhibited the highest estimated burden of DIABETES among all studied racial groups, despite lower crude and age adjusted (data not shown) mean obesity measures, including age-adjusted WAIST circumference (White: p=.015; Black: p=.007; Mexican: p=.016; Hispanic: p=.079) current BMI (White: p=.023; Black: p=.000; Mexican: p=.003; Hispanic: p=.018) and ΔBMI (White: p=.150, Black: p=.000, Mexican: p=.041, Hispanic: p=.171). Although all obesity measures were significantly lower among Asians compared to Blacks and Mexicans, there was no statistically significant differences in age adjusted diabetes burden. The only obesity measure which was similar across all race categories was unadjusted Low BMI in adulthood.
Table 4.1. Characteristics by race among US adults, ages 20 and older, national design-based estimates, NHANES 1999–2002

<table>
<thead>
<tr>
<th>Variables</th>
<th>White (N=4706)</th>
<th>Black (N=1821)</th>
<th>Mexican (N=2189)</th>
<th>Asian (N=238)</th>
<th>Hispanic (N=498)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DM = Diabetes (n)</strong></td>
<td>368</td>
<td>247</td>
<td>275</td>
<td>30</td>
<td>58</td>
</tr>
<tr>
<td>DM Unadjusted (%)</td>
<td>5.8 (95% CI: [5.2–6.6])</td>
<td>10.3 (95% CI: [8.7–11.9])</td>
<td>6.8 (95% CI: [5.6–8.0])</td>
<td>10.9 (95% CI: [5.8–16.0])</td>
<td>8.2 (95% CI: [4.4–11.9])</td>
</tr>
<tr>
<td>DM Age-Adjusted* (%)</td>
<td>5.4 (95% CI: [4.7–6.1])</td>
<td>11.5 (95% CI: [10.0–13.0])</td>
<td>10.7 (95% CI: [9.6–11.8])</td>
<td>12.3 (95% CI: [7.1–17.5])</td>
<td>8.2 (95% CI: [5.7–13.3])</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean(SE)</td>
<td>48.2 (.35)</td>
<td>43.9 (.45)</td>
<td>38.5 (.66)</td>
<td>44.4 (.95)</td>
<td>43.3 (1.25)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>46.0 (25)</td>
<td>42.0 (22)</td>
<td>36.0 (19)</td>
<td>44.0 (22)</td>
<td>40.0 (24)</td>
</tr>
<tr>
<td><strong>Female Sex (%)</strong></td>
<td>50.2</td>
<td>53.9</td>
<td>44.9</td>
<td>52.7</td>
<td>54</td>
</tr>
<tr>
<td><strong>Family History DM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (%)</td>
<td>48.4</td>
<td>55.1</td>
<td>50.00</td>
<td>46.5</td>
<td>48.6</td>
</tr>
</tbody>
</table>

**Anthropometric Measures**

<table>
<thead>
<tr>
<th>Measures</th>
<th>Mean (SE)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Wt (kg)</td>
<td>80.8 (.43)</td>
<td>75.9 (.51)</td>
</tr>
<tr>
<td>Current Ht (cm)</td>
<td>170.1 (.16)</td>
<td>164.0 (.24)</td>
</tr>
<tr>
<td>Current Waist (cm)</td>
<td>96.2 (.41)</td>
<td>94.7 (.43)</td>
</tr>
<tr>
<td>Current BMI (kg/m²)</td>
<td>27.9 (.17)</td>
<td>28.2 (.19)</td>
</tr>
<tr>
<td>Lowest Adult Wt (kg)</td>
<td>62.1 (.34)</td>
<td>59.2 (.51)</td>
</tr>
<tr>
<td>Lowest BMI</td>
<td>21.5 (.14)</td>
<td>22.0 (.17)</td>
</tr>
<tr>
<td>Greatest Wt (kg)</td>
<td>86.1 (.46)</td>
<td>80.7 (.58)</td>
</tr>
<tr>
<td>Greatest BMI</td>
<td>29.7 (.17)</td>
<td>29.9 (.23)</td>
</tr>
<tr>
<td>Greatest ∆ Wt (kg)</td>
<td>24.1 (.71)</td>
<td>22.0 (.74)</td>
</tr>
<tr>
<td>Greatest ∆ BMI</td>
<td>8.1 (.24)</td>
<td>8.0 (.24)</td>
</tr>
</tbody>
</table>

Abbreviations: CI(confidence interval); SE(standard error); IQR(interquartile range); kg(kilogram); cm(centimeter); BMI(body mass index = weight in kg/height in meter²); ∆(change)

* Age-adjusted to the 2000 census population using the recommended age distribution and age adjustment weights for NHANES 1999–2002 (20–39 yrs- wt: .396579; 40–59yrs- wt: .371795; 60+yrs- wt: .231626)

b Denominators may differ due to missing data; 4 year interview weights are applied

c Current height is measured and used for all BMI metrics
Age adjusted characteristics by RACE among those who reported DIABETES is shown in Table 4.2. After standardizing by age, Asian diabetics were the youngest of racial groups [mean age(yrs) = 45.6; SE(.62)]. Sex differences were observed among diabetics with Black (70.8%) and Mexican (67.4%) diabetics being predominately female. Race stratified diabetics exhibited higher obesity levels than the estimated overall adult population (diabetics and nondiabetics), and also self reported a higher frequency of FHDM. Asian diabetics, however, had significantly lower crude (crude data among diabetics not shown) and age adjusted ΔBMI than any other racial group. The crude difference between mean ΔBMI among Asians, according to diabetes status was small; approximately a 1 unit difference and was not statistically significant [not diabetic: 7.0 SE(.78) vs. diabetic: 8.1 SE(.76); p=.455]. Among all other racial groups, however, crude ΔBMI’s were significantly higher among diabetics (all p < .001).

One reason for the much smaller difference in ΔBMI among Asians was a significant difference in crude self report Low BMI according to diabetes status [non-diabetic: 21.4 SE(.64) vs. diabetic: 24.1 SE(1.3); p=.008]. All other ethnic racial groups reported almost identical Low BMI’s regardless of diabetes status (all p< .001), with only Whites also showing a crude mean significant difference [non-diabetic: 21.3 SE(.11) vs. diabetic: 23.9 SE(.81); p=.004]. After age-adjustment, Low BMI’s among all racial groups increased with the highest mean value reported in Asians [26.2 SE(.82)] followed by Whites [25.5 SE(1.6)].

To identify if the magnitude of the increased Low BMI observed among Asians modified the overall substantive results observed in logistic regression, we conducted a logistic regression analysis disassociating least and greatest weight by dropping Low BMI and ΔBMI from the model and added least weight in adulthood and greatest weight in adulthood along with current height as separate independent variables. These results showed no substantive difference between this model and all other logistic regressions performed. After accounting for all other covariates in the model, the odds of diabetes burden among Asians were 3.6 times that of Whites [OR 3.6; 95% CI 1.3 - 9.7], which was consistent with logistic regression models that included Low BMI and ΔBMI.
Table 4.2. Age-adjusted\(^a\) characteristics by race among US adults with self report diabetes, ages 20 and older, design-based estimates, NHANES 1999–2002

<table>
<thead>
<tr>
<th>Variables</th>
<th>White N=4706</th>
<th>Black N=1821</th>
<th>Mexican N=2189</th>
<th>Asian N=238</th>
<th>Hispanic N=498</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM = Diabetes (n)</td>
<td>368</td>
<td>247</td>
<td>275</td>
<td>30</td>
<td>58</td>
</tr>
<tr>
<td>DM (%)</td>
<td>5.4</td>
<td>11.5</td>
<td>10.7</td>
<td>12.3</td>
<td>9.5</td>
</tr>
<tr>
<td>[95 % CI]</td>
<td>[4.7–6.1]</td>
<td>[10.0–13.0]</td>
<td>[9.6–11.8]</td>
<td>[7.1–17.5]</td>
<td>[5.7–13.3]</td>
</tr>
<tr>
<td>Age (yrs) Mean (SE)</td>
<td>49.0 (.43)</td>
<td>48.0 (.51)</td>
<td>47.0 (.62)</td>
<td>45.6 (.62)</td>
<td>49.2 (1.3)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>63.0 (21)</td>
<td>56.0 (21)</td>
<td>54.0 (19)</td>
<td>53.0 (16)</td>
<td>56.0 (14)</td>
</tr>
<tr>
<td>Female Sex (%)</td>
<td>40.2</td>
<td>70.8</td>
<td>67.4</td>
<td>45.7</td>
<td>59.0</td>
</tr>
<tr>
<td>Family History DM Yes (%)</td>
<td>76.4</td>
<td>87.5</td>
<td>74.2</td>
<td>94.3</td>
<td>86.4</td>
</tr>
<tr>
<td>Anthropometric Measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Wt (kg)</td>
<td>94.8 (2.9)</td>
<td>91.1 (2.0)</td>
<td>86.1 (1.6)</td>
<td>82.1 (6.1)</td>
<td>91.7 (10.24)</td>
</tr>
<tr>
<td></td>
<td>88.8 (28.2)</td>
<td>90.5 (27.9)</td>
<td>79.1 (21.3)</td>
<td>70.9 (21.7)</td>
<td>74.3 (22.6)</td>
</tr>
<tr>
<td>Current Ht (cm)(^b)</td>
<td>170.0 (.92)</td>
<td>166.5 (.84)</td>
<td>161.2 (1.25)</td>
<td>166.6 (2.6)</td>
<td>164.6 (.79)</td>
</tr>
<tr>
<td></td>
<td>168.2 (14.6)</td>
<td>167.5 (14.9)</td>
<td>160.7 (14.5)</td>
<td>166.0 (11.4)</td>
<td>163.8 (12.9)</td>
</tr>
<tr>
<td>Current Waist (cm)</td>
<td>109.9 (2.5)</td>
<td>107.2 (1.7)</td>
<td>107.3 (1.9)</td>
<td>100.3 (4.4)</td>
<td>106.3 (7.9)</td>
</tr>
<tr>
<td></td>
<td>108.5 (22.3)</td>
<td>107 (20.6)</td>
<td>103.7 (17.8)</td>
<td>93.2 (14.4)</td>
<td>94.8 (14.2)</td>
</tr>
<tr>
<td>Current BMI (kg/m(^2))</td>
<td>32.7 (.88)</td>
<td>32.9 (.86)</td>
<td>33.3 (.99)</td>
<td>29.0 (1.4)</td>
<td>33.6 (3.8)</td>
</tr>
<tr>
<td></td>
<td>31.3 (9.7)</td>
<td>31.5 (9.7)</td>
<td>29.7 (8.5)</td>
<td>26.2 (3.5)</td>
<td>27.5 (6.9)</td>
</tr>
<tr>
<td>Lowest Adult Wt (kg)</td>
<td>73.6 (4.0)</td>
<td>67.6 (2.5)</td>
<td>59.9 (.48)</td>
<td>77.1 (4.4)</td>
<td>61.4 (1.2)</td>
</tr>
<tr>
<td></td>
<td>63.6 (19.1)</td>
<td>59.1 (15.9)</td>
<td>59.1 (13.6)</td>
<td>61.4 (7.3)</td>
<td>56.8 (13.6)</td>
</tr>
<tr>
<td>Lowest BMI (kg/m(^2))</td>
<td>25.5 (1.6)</td>
<td>24.1 (1.2)</td>
<td>23.5 (.52)</td>
<td>26.2 (.82)</td>
<td>22.5 (.41)</td>
</tr>
<tr>
<td></td>
<td>22.5 (5.7)</td>
<td>21.7 (4.8)</td>
<td>22.5 (4.8)</td>
<td>21.7 (3.3)</td>
<td>22.2 (2.7)</td>
</tr>
<tr>
<td>Greatest Wt (kg)</td>
<td>106.3 (3.6)</td>
<td>102.3 (3.2)</td>
<td>94.9 (1.0)</td>
<td>92.5 (5.6)</td>
<td>102.7 (9.1)</td>
</tr>
<tr>
<td></td>
<td>100.0 (29.5)</td>
<td>100.0 (28.2)</td>
<td>90.5 (24.1)</td>
<td>79.5 (20.9)</td>
<td>85.5 (34.1)</td>
</tr>
<tr>
<td>Greatest BMI (kg/m(^2))</td>
<td>37.0 (1.1)</td>
<td>35.9 (.86)</td>
<td>36.6 (.90)</td>
<td>32.8 (1.2)</td>
<td>37.7 (3.5)</td>
</tr>
<tr>
<td></td>
<td>34.4 (10.7)</td>
<td>34.9 (9.3)</td>
<td>34.2 (9.7)</td>
<td>30.7 (5.5)</td>
<td>30.7 (8.0)</td>
</tr>
<tr>
<td>Greatest Δ Wt (kg)</td>
<td>39.4 (2.6)</td>
<td>42.2 (5.8)</td>
<td>36.4 (1.4)</td>
<td>19.7 (3.3)</td>
<td>29.0 (1.9)</td>
</tr>
<tr>
<td></td>
<td>34.1 (21.8)</td>
<td>38.6 (25.0)</td>
<td>34.1 (19.1)</td>
<td>16.4 (13.6)</td>
<td>24.5 (22.7)</td>
</tr>
<tr>
<td>Greatest Δ BMI</td>
<td>14.0 (1.1)</td>
<td>12.5 (.68)</td>
<td>14.4 (.43)</td>
<td>7.0 (1.3)</td>
<td>10.6 (.50)</td>
</tr>
<tr>
<td></td>
<td>12.7 (8.4)</td>
<td>13.2 (8.9)</td>
<td>12.7 (8.3)</td>
<td>7.2 (6.7)</td>
<td>10.2 (7.3)</td>
</tr>
</tbody>
</table>

Abbreviations: CI(confidence interval); SE(standard error); IQR(interquartile range); kg(kilogram); cm(centimeter); BMI(body mass index = weight in kg/height in meter\(^2\)); ∆(change)

\(^a\) Age-adjusted to the 2000 census population using the recommended age distribution and age adjustment weights for NHANES 1999–2002 (20–39 yrs- wt: .396579 ; 40–59yrs- wt: .371795 ; 60+yrs- wt: .231626)

\(^b\) Current height is measured and used for all BMI metrics
We also identified the single outlier that pulled least weight to the right. This survey subject was a 28 year old diabetic male whose measured current weight in pounds was 267. The subject was diagnosed with diabetes at age 24 and his self reported lowest weight in pounds in adulthood was 255 (115.91 kgs), which occurred at age 27. All other diabetics in this race group reported a self report lowest weight under 80 kgs. The male subject self reported a greatest weight in pounds as 290, which occurred at age 25. Based on these findings, the observation was not dropped in any analysis.

4.3.2. Logistic regression analysis

Table 4.3 shows the results of 6 identical logistic regression models (Model 5, however, included EDUCATION and INCOME) that were analyzed with different approaches. Model 1 shows the logistic regression analysis that did not account for the complex survey design of NHANES 1999-2002. Model 2 was analyzed with probability weights and robust standard errors, Model 3 represents the correct design-based analysis, while Model 4 and 5 were the logistic regression results of bootstrapping using 1200 replications. The final model estimates were derived with multiple imputation, using m=20 imputations. Model 1 and Model 2 were used during the assessment and diagnostics phases of the regression analyses. Bootstrapped Model’s 4 and 5 provided information on the stability and reliability of the logistic regression results, and multiple imputation, which was used to address missing data, is shown in Model 6. The results of all six models plus the 7th model with the dropped Low BMI and ΔBMI exchanged for the variables least and greatest weight (kgs) in adulthood, show consistency with stability and reliability for both the point estimates and confidence intervals.
Table 4.3. Logistic regression models of diabetes among US adults, ages 20 and above, NHANES 1999–2002

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratios [95 % CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age$^2$ (yrs)</td>
<td>1.4 [1.3–1.5], 1.3 [1.2–1.5], 1.4 [1.3–1.4], 1.4 [1.3–1.4], 1.3 [1.2–1.3]</td>
</tr>
<tr>
<td>Age$^3$ (yrs)</td>
<td>.97 [.96–.98], .97 [.96–.98], .97 [.96–.98], .97 [.96–.98], .98 [.98–.99]</td>
</tr>
<tr>
<td>FHDM (Yes)</td>
<td>4.1 [3.2–5.4], 4.0 [2.7–5.7], 4.0 [2.9–5.5], 4.1 [3.7–4.7], 3.9 [3.4–4.4], 4.0 [3.1–5.1]</td>
</tr>
<tr>
<td>Black</td>
<td>2.4 [1.7–3.3], 2.3 [1.6–3.4], 2.3 [1.4–3.8], 2.4 [1.7–3.4], 1.9 [1.5–2.6], 2.0 [1.6–2.6]</td>
</tr>
<tr>
<td>Mexican</td>
<td>2.3 [1.7–3.1], 2.4 [1.7–3.5], 2.4 [1.6–3.6], 2.3 [1.8–3.0], 1.7 [1.3–2.4], 2.3 [1.9–2.8]</td>
</tr>
<tr>
<td>Asian</td>
<td>3.5 [1.6–7.6], 3.9 [1.4–11.0], 3.9 [1.4–10.8], 3.5 [1.8–5.8], 2.8 [1.2–5.0], 4.3 [2.4–7.5]</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2.7 [1.7–4.4], 2.6 [1.5–4.7], 2.6 [1.1–6.2], 2.7 [1.0–3.7], 1.8 [.85–2.8], 2.2 [1.3–3.6]</td>
</tr>
<tr>
<td>Lowbmi$^3$</td>
<td>1.08 [1.06–1.1], 1.08 [1.06–1.1], 1.08 [1.05–1.1], 1.08 [1.06–1.1], 1.07 [1.06–1.09], 1.06 [1.04–1.08]</td>
</tr>
<tr>
<td>Δ BMI$^d$</td>
<td>1.3 [1.2–1.4], 1.3 [1.2–1.4], 1.3 [1.2–1.4], 1.3 [1.2–1.4], 1.3 [1.1–1.3]</td>
</tr>
<tr>
<td>Δ BMI$^2d$</td>
<td>.995 [.993–.997], .995 [.992–.998], .994 [.991–.999], .994 [.992–.997], .995 [.992–.997], .998 [.994–1.001]</td>
</tr>
</tbody>
</table>

$^a$ Bootstrap estimation and bias corrected SE’s using 1200 replications
$^b$ Age is modeled using fractional polynomials powers(2 3)
$^c$ Lowbmi = kg/m$^2$, where kg = “self report least weight in kgs since age 18” and height is current measured height in centimeters converted to meters$^2$. Lowbmi is modeled as a fractional polynomial, power(3)
$^d$ Δ BMI = kg/m$^2$ difference between lowbmi and greatest BMI, where greatest BMI represents kg = self report greatest weight and height = current measured height in centimeters converted to meters$^2$. Δ BMI is modeled as a quadratic function
4.3.3. Graphical assessment of potential interaction of race with $\Delta$BMI

Figure 4.1 provides a graphical representation of the predicted probability of diabetes per one unit $\Delta$BMI by RACE up to $\Delta$BMI 10, and adjusting for all other variables in the model. A steep rise in the predicted probability of diabetes was revealed among Asians through this range of $\Delta$BMI relative Whites. At $\Delta$BMI 10, which represents $\approx 30$ kgs, the predicted probability of diabetes among Asians was double that of the next racial groups - Blacks, Other Hispanics, and Mexicans, whose predicted probabilities of diabetes were similar across levels of $\Delta$BMI. The apex of the predicted probability of diabetes for Asians occurred at $\Delta$BMI 12, while for other race groups the increase continued in the same fashion beyond $\Delta$BMI 20. Only whites exhibited a slow steady rise in the predicted probability of diabetes through the lower range of $\Delta$BMI. At higher levels of $\Delta$BMI, whites began to exhibit a larger increase in the predicted probability of diabetes per unit $\Delta$BMI (data not shown).

Figure 4.1. Predicted Probability of Diabetes per Unit $\Delta$BMI by Race, NHANES 1999-2002
4.3.4. Post hoc analysis

Post hoc analysis of glycosylated hemoglobin (HbA1c) among diabetics revealed that nonobese persons, Asians, and young adults had the highest mean A1c levels as shown in Table 4.5. The HbA1c, or otherwise known as the A1c test, is an indicator of glucose management over a two to three month period, and is considered the standard test to quantify glycosylated hemoglobin. The American Diabetics Association (ADA) criteria for the diagnosis of diabetes using the A1c test is $\geq 6.5\%$. Based on evidence for a risk reduction in microvascular and macrovascular complications, ADA guidelines recommend A1c values of $< 7\%$ for good glucose control among diabetics (ADA 2010).

Table 4.4. Correlation of A1c with average glucose

<table>
<thead>
<tr>
<th>A1c (%)</th>
<th>Mean Plasma Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/dL</td>
</tr>
<tr>
<td>6</td>
<td>126</td>
</tr>
<tr>
<td>7</td>
<td>154</td>
</tr>
<tr>
<td>8</td>
<td>183</td>
</tr>
<tr>
<td>9</td>
<td>212</td>
</tr>
<tr>
<td>10</td>
<td>240</td>
</tr>
<tr>
<td>11</td>
<td>269</td>
</tr>
<tr>
<td>12</td>
<td>298</td>
</tr>
</tbody>
</table>

These estimates are based on ADA glucose data of $\approx 2,700$ glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, and no diabetes. The correlation between A1c and average glucose was 0.92 (49). A calculator for converting A1c results into estimated average glucose (eAG), in either mg/dL or mmol/L, is available at http://professional.diabetes.org/eAG.

From: (ADA 2010)
<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean HbA1c (%)</th>
<th>[95 % CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI Categories</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>8.27</td>
<td>[6.87–9.67]</td>
</tr>
<tr>
<td>Overweight</td>
<td>8.35</td>
<td>[7.51–9.19]</td>
</tr>
<tr>
<td>Obese</td>
<td>7.68</td>
<td>[7.18–8.18]</td>
</tr>
<tr>
<td>Morbidly Obese</td>
<td>7.57</td>
<td>[6.91–8.23]</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>7.80</td>
<td>[7.02–8.58]</td>
</tr>
<tr>
<td>Black</td>
<td>8.01</td>
<td>[7.53–8.50]</td>
</tr>
<tr>
<td>Mexican</td>
<td>7.89</td>
<td>[7.47–8.31]</td>
</tr>
<tr>
<td>Asian</td>
<td>8.69</td>
<td>[8.03–9.34]</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8.49</td>
<td>[7.51–9.47]</td>
</tr>
<tr>
<td><strong>Age Group (yrs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Age (SE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–39</td>
<td>8.54</td>
<td>[7.34–9.74]</td>
</tr>
<tr>
<td>29.9 (.20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–59</td>
<td>7.76</td>
<td>[7.41–8.11]</td>
</tr>
<tr>
<td>48.5 (.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60+</td>
<td>7.32</td>
<td>[7.13–7.51]</td>
</tr>
<tr>
<td>71.1 (.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Family History of Diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>8.37</td>
<td>[7.34–9.40]</td>
</tr>
<tr>
<td>Yes</td>
<td>7.87</td>
<td>[7.42–8.31]</td>
</tr>
</tbody>
</table>

Our results are consistent with Sheehy and colleagues recent findings that ADA criteria failed to recommend diabetes screening for 3,000 patients who were non-obese and younger than age 45 years old (Sheehy et al. 2010). The focus on frank obesity and older age may be inadvertently contributing to long term glycemic exposure among those with both undiagnosed and diagnosed diabetes and who are traditionally considered lower risk.
4.4. Discussion

4.4.1. Primary analysis

In this multi-ethnic exploratory observational study on obesity and diabetes, we applied a biologic hypothesis to help develop the study design, operationally define the variables under investigation, establish novel surrogates for biologic categories, and formulate *a priori* predictions applied to a statistical model of diabetes in the US adult population. The results are consistent with previous large multi-ethnic studies that have investigated the relation of various obesity metrics, such as BMI, with risk of type 2 diabetes (Shai et al. 2006, McNeely and Boyko 2004).

Despite lower obesity levels on all selected anthropometric measures, operationally defined Asians exhibited the highest burden of diabetes compared to all other race groups. After controlling for major known risk factors of diabetes, the odds of diabetes was highest among Asians. Although subgroup sample sizes were too small to introduce interaction terms in the regression model and large variances resulted in the inability to detect statistically significant differences between minority race groups, type two error was not a major factor for the specific substantive questions under investigation. This is because, a result of no significant differences in diabetes burden between the leanest versus heaviest racial subgroups does not refute the Energy Storage Capacity Hypothesis.

Graphical evaluation of potential interaction revealed that Asians, although significantly leaner than all other racial groups, also had a higher predicted probability of diabetes at nearly every level of ΔBMI up to \( \approx 30 \) kg, even after controlling for all other risk factors in the model. Moreover, the predicted probability of diabetes among Asians was not additive and depended on the magnitude of weight gain. These results align with studies that have investigated BMI change or BMI and prevalence of diabetes by race categories (Shai et al. 2006, Pan et al. 2004).

Among adult diabetics, mean A1c levels were higher for Asians, the non-obese, people with no family history of diabetes, and those younger than age 45. These results are
consistent with Sheehy and colleagues findings of high-risk patients who were non-obese, young, and who were missed based on ADA diabetes screening guidelines (Sheehy et al. 2010). Long-term glycemic exposure among apparently lower-risk subgroups throughout the natural history of type 2 diabetes is concerning in light of the serious health consequences that can occur due to glycemic under-vigilence.

4.4.2. Study assumptions

The three major assumptions underlying this study are the following:

(1) The Asian subgroup is comprised of Asians, especially among the self report diabetics.

(2) Diabetes cases were predominately lifestyle related (eg, obesity pathways model).

(3) The biologic surrogate measures of Asian ethnicity for low adipocyte cellularity and weight gain for increasing fat cell size, accurately characterize the intended biologic phenomenon described by the Energy Storage Capacity Hypothesis.

If these assumptions are correct, then the predictions formulated based on the Energy Storage Capacity Hypothesis are accurate and the hypothesis is not refuted. The results of this study suggest that the Energy Storage Hypothesis might be a reasonable alternative obesity-disease paradigm from which to launch new approaches to the study of obesity and related diseases, allow for further exploration of the hypothesis under a more stringent study design and methodology, test the hypothesis against the standard paradigm, and stimulate new ideas for primary and secondary prevention of obesity and related diseases across the BMI continuum.

4.4.3. Study strengths

The strength of this study is that we identified gaps in previous research and attempted to address those in our design. For example, we chose NHANES 1999-2002 as the data source for this study. NHANES is a cross-sectional probability survey of the US non-institutionalized population. NHANES has high unit response rates and employs data collection methods that
include detailed face-to-face interviews along with physical examinations and anthropometric, clinical and biochemical tests (NHANES 2005). The results, therefore, can be considered representative of the general US adult population during the surveyed time period and potential biases that could be attributed to non-response or self report measures are reduced.

We were able to closely reproduce previously published crude population counts and prevalence estimates of BMI, BMI categories, and diagnosed diabetes derived by NHANES researchers (Cowie et al. 2006, Flegal et al 2002, Hedley et al. 2004). Reproducing prevalence estimates from criterion studies reduces the possibility of administrative error or inadvertent mishandling of the NHANES data. When possible, we followed methods that NHANES specifically recommends and which are routinely applied in most official NHANES publications. For example, we age-adjusted by direct standardization, using the population age distribution and age adjustment weights represented by distribution #12 (Klein and Schoenborn 2001).

Previous US research in this area also did not adequately control for some potential confounders, such as family history of diabetes, education, income, or origin of birth. Family history of diabetes is one of the strongest predictors of diabetes, while measures of socioeconomic status, such as education and income have been shown to be associated with race/ethnicity and diabetes. Although education, income, and place of birth were each significantly and independently related to diabetes burden, these variables did not confound the substantive questions under investigation. Nor did these variables add to the overall substantive model, so these covariates were dropped in this study. However, we believe that these variables may be important contributors under a different set of research objectives.

Another potential gap that we addressed is how missing data were handled. Although the most common approach for handling missing values is to do nothing, this non-interventional approach can result in biased point estimates if the missing values are not missing completely at random. In addition, loss of information increases variance, which may lead to type 2 error (Wayman 2003). For this study, we used multiple imputation to control potential bias of point estimates and to reduce increased variance due to loss of information among already
sparse sample sizes with certain ethnic groups, specifically the Asian subgroup. The results of the bootstrap analysis and multiple imputation revealed that point estimates and 95% CI's were stable and reliable (reproducible). Although variance was reduced as a result of multiple imputation, the possibility of type two error with respect to ethnic differences in diabetes prevalence persisted. This was because of the low actual sample size of the Asian subgroup, which resulted in wide confidence intervals, even after multiple imputation.

4.4.4. Study limitations

4.4.4.1. Misclassification bias. There are two major potential sources of misclassification bias: potential bias due to the outcome variable, DIABETES, and potential bias with the exposure subvariable, ASIAN race. First with respect to DIABETES: the outcome variable was not measured, but rather self reported based on the interview question "Has a doctor or other health care professional \textbf{EVER} told you that you have sugar diabetes." This question does not differentiate between types of diabetes, such as type 1 diabetes, which has an etiology that is entirely different from that of type 2 diabetes, or gestational diabetes, which is transient hyperglycemia during pregnancy (though predictive of future type 2 diabetes). These forms of diabetes collectively are estimated to represent less than 10% of all diabetes cases (CDC 2008). It is possible, though unlikely, that participants with these forms of DIABETES were overrepresented in the sample, potentially affecting population estimates of BMI metrics, RACE, and burden of DIABETES. Although we excluded pregnant women, it does not prevent the possibility that a number of female participants did not currently have DIABETES, but who, at one time, had gestational diabetes, and thus reported ever being diagnosed with DIABETES. However, post hoc analysis of A1c% revealed that the study participants who reported ever having diabetes, did in fact have mean A1c levels that were higher than those who did not report diabetes and that those higher mean A1c values are consistent with the diagnosis of diabetes.

The diabetes question also cannot capture a portion of the population who has DIABETES, but does not know it. This form of misclassification would tend towards subjects
at lower BMI’s, thus underestimating DIABETES cases among nonobese people since obese persons are less likely to have an underdiagnosis of diabetes (Sheehy et al. 2010, Flegal et al. 2010). To further investigate this in our study, we analysed the prevalence of self report diabetes among measured morbidly obese subjects ages 17 to 67, and compared these estimates with morbidly obese patients diagnosed with diabetes in the 2002 NHDS study. The 1999-2002 NHANES national diabetes estimates among the morbidly obese general population was 17.5%; 95% confidence interval [13.7 - 21.6]. The estimated prevalence fell within the lower bound of the 95% confidence interval of the bariatric patients and the upper bound for the all other hospital procedure discharges in the 2002 NHDS study, as did their mean age (Scott et al. 2006).

These results suggest that underdiagnosis of diabetes among morbidly obese patients may not be a serious problem. Still, this does not preclude the possibility that undiagnosed diabetes exists among nonobese persons or by BMI status within racial categories, which could bias estimates in direction and magnitude. The question “Has a doctor or other health professional ever told you that you have sugar diabetes” also cannot exclude people who no longer have DIABETES, due to lifestyle changes or bariatric surgery. In 2002, over 84,000 morbidly obese patients had an obesity surgery (Scott et al. 2006) and roughly 16% were diagnosed with diabetes. If diabetes resolves in over 80% to 85% of cases (Buchwald et al. 2004), that represents nearly 12,000 people with resolved diabetes due to bariatric surgery alone in year 2002. In addition, the number of bariatric surgeries continue to increase, with the bariatric patient profile expanding to ever younger and less obese people. Although NHANES publishes data on diabetes in terms of national prevalence estimates for a given set of survey years, the true measure might be better characterized as ever-burdened with diabetes. If NHANES modifies the diabetes question to ask about current diagnosis rather than ever diagnosed, diabetes prevalence estimates may be reduced. This might also be another reason why prevalence estimates have continued to increase in the United States.
A second source of potential misclassification bias could occur in classifying the “Other” Race category as ASIAN. Because this study was focused on an underlying biologic phenomenon, the categorization of ASIAN mattered only to the degree that the accuracy of ASIAN race, as a subgroup, could be considered phenotypically leaner than other race groups, and that this leanness is a result of inherently lower number of fat cells. Researchers have hypothesized that South Asians have a reduced or smaller storage capacity to store fatty acids in the primary subcutaneous adipose tissue compartments compared to other racial-ethnic groups, leading to more rapid storage and subsequent enhancement of secondary (abdominal) adipose storage compartments (Sniderman et al. 2007). This indirectly points to possible underlying ethnic differences in adipocyte cell distribution or site selective adipocyte volume or proliferation. Both assumptions are deserving of further research.

A recent study by Stanhope and colleagues showed a selective increased deposition of visceral fat storage with dietary fructose as compared to glucose, even with comparable weight gain among overweight and obese humans (Stanhope et al. 2009). Subjects ingesting fructose exhibited higher levels of fasting plasma glucose, lower insulin sensitivity, and higher insulin levels. Indeed, fructose is metabolized differently than glucose in the body, but this is the first study to show selective deposition of excess energy based on the type of monosaccharide. Adipocyte number or volume were not assessed among these overweight and obese subjects, so their relative contribution to site-specific adiposity was unknown. Nonetheless, high fructose corn syrup is ubiquitous in the American/Western diet. Their study results support a possible pathway to diabetes via selective visceral fat storage, secondary to diet, which would disproportionately affect those with reduced cellularity and could explain why visceral fat is implicated in Asian risk for diabetes.

In this study, the operationally defined Asian race group exhibited significantly lower mean anthropometric measures compared to all other racial groups, including waist circumference, which is considered an acceptable surrogate for visceral fat (Hu 2008). Anthropometric indices are generally used in epidemiologic studies as surrogates for body fatness. The anthropometric results of this study are consistent with Mott and colleagues 1999 evaluation of
body fat and age in a healthy New York City volunteer sample (N=1,324) of 4 ethnic groups, ages 20 and older. Using a 4 compartment model of body composition which included measures of body volume, total body water, total body bone mineral mass, and body weight, Asian men and women both had mean lower fat mass at every decade of age compared to Whites, Blacks, and Puerto Ricans (Mott et al. 1999).

Asian diabetics in our study also exhibited a significantly lower mean current measured BMI compared to White, Black, and Mexican diabetics, as well as lower ∆BMI compared to all racial groups among those reporting diabetes, despite no significant difference in the self report mean age of onset of diabetes. Pan et al. compared the association of BMI and metabolic comorbidity between Taiwanese (in Taiwan), US Whites and US Blacks, and found the BMI-morbidity association was stronger in Taiwanese than US Blacks for all metabolic comorbidities studied and than that at nearly every level of BMI, the prevalences of hypertension, diabetes, and hyperuricemia were higher for Taiwanese than for US Whites (Pan et al. 2004).

The World Health Organization (WHO) has acknowledged the vast diversity in geography, culture, ethnicity, level of urbanization, nutrition transitions, as well as the social and economic conditions of people classified under the umbrella term of “Asian.” However, the WHO has also stated that what these populations have in common is a mean and median BMI that is lower than that observed in non-Asian populations, in large part, providing the rationale for developing lower Asian-specific BMI cutpoints (WHO 2004), but also providing the basis for potential underlying biologic differences by race, including the possibility of lower baseline adipose cellularity.

If the race group classified as OTHER by NHANES, but operationally defined as “Asian” in this study were actually a random mix of many different racial groups, then a reason other than the Energy Storage Capacity, would be needed to explain why this group weighed less, gained less weight, and exhibited a similar diabetes burden than that of the heaviest race groups. On the other hand, if the “Other” race category were not purely ASIAN, but did represent the underlying phenomenon of less fat cell numbers, then the Energy
Capacity Hypothesis would still be explanatory; any inadvertent mixing of fat cell number representation would reduce the magnitude of effect.

These issues point to the need for multidisciplinary approaches to the study of obesity and related diseases in populations that can account for the relative contribution of adipose cellularity and size on body fatness and subsequent risk to health. There are several quantitative methods available, albeit invasive, that assess adipocyte number and size (Bjornheden 2004). Although some researchers question their reliability (Sniderman et al. 2007), methods such as stereology (Cuellar and Solis 2005), direct counting and sizing approaches using microscopy (Harmelen et al. 2003), and computer image analysis (Bjornheden 2004, Chen and Farese 2002) are commonly used to estimate adipocyte size and number across a wide range of disciplines (Hausman et al. 2010, Ochs 2010, Kim et al. 2010, Cuellar and Solis 2005).

4.4.4.2. Recall bias. Another potential source of bias is the recollection of least weight in adulthood and greatest weight in adulthood, both which were self report measures used to create the low BMI and ΔBMI variables. Although research has shown that people tend to under-report weight (women more so than men) and over-report height (men more so than women) (Gorber et al. 2007), there is little data available regarding the accuracy of self report historical recalled weight or self report weight changes over time. In a subsample of the Nurses Health Study, a high correlation (r=.87) was found between recalled weight at age 18 and measured weights from physical examination records (difference = -1.4 kg) (Troy et al. 1995).

We investigated the relation of age with lowest weight in adulthood, greatest weight in adulthood, and onset of diabetes among all racial groups. The results revealed that the unstandardized mean age of lowest reported weight in adulthood was between 20 and 22 years of age, for greatest weight in adulthood, mean age was between 38 and 40 years (except for Mexicans whose age distribution is shifted to the left; their mean age was 34 yrs old), and the mean age at onset of diabetes was between 45 and 49. Since type 2 diabetes
has been shown to go undetected between 4 and 7 years before a diagnosis is made (Harris et al. 1992), the age–weight gain–diabetes onset timeline seems to suggest that greatest weight in adulthood occurs around the time of actual onset of diabetes. If recall of age at maximum weight and age at onset of diabetes are accurate, then the temporal sequence of the obesity-disease etiologic timeline would hold, despite the cross-sectional design of NHANES.

4.4.5. Other findings

Whites seem to be protected against diabetes at the lower ends of the weight gain spectrum compared to other race groups. This could point to the possibility of either increased fat cell numbers of low to normal size range, or the possibility of increased ease in proliferative potential. That is, the enhanced capacity to make new fat cells as needed. It is also possible that perpetual dieting among White women, which does not have a strong socio-cultural basis among some ethnic groups (Mack et al. 2004, Gans et al. 2003, Kumanyika, Wilson & Guilford-Davenport 1993), could be protective for type 2 diabetes (Truesdale, Stevens, & Cai 2005).

For example, obese Black women are more likely to report being satisfied with their current weight and less likely to report trying to lose weight than either White or Hispanic women (Mack et al. 2004). A self-administered survey on weight-related attitudes and practices of Black women who attended health department clinics revealed that approximately 40% of moderately and severely overweight women considered their figures to be attractive or very attractive, which indicates a positive body image, and less preoccupation with dieting to become thin (Kumanyika, Wilson & Guilford-Davenport 1993). A multi-ethnic study by Truesdale and colleagues (2005) revealed that adults with a history of weight loss had more favorable metabolic markers than BMI matched adults who were weight maintainers over a 3 year period, but that glucose levels were not affected, except among those with diabetes at baseline (Truesdale, Stevens, & Cai 2005).
On the other hand, it may not be that Whites are protected, but rather that ethnic groups are at elevated risk due to other potential pathways related to the onset of type 2 diabetes (see diabetes pathways table). Even without weight gain, and after controlling for all major risk factors for diabetes, the predicted probability of diabetes among Blacks, Mexicans, and Other Hispanics, along with Asians, although low, was still higher than Whites. Studies on bariatric patients show that most, but not all cases of type 2 diabetes are resolved as a result of surgery (Buchwald et al. 2004). These findings point to a proportion of type 2 diabetes cases that may be independent of weight status and are also not explained by other known risk factors of diabetes.

Why do Asians exhibit a lower greatest weight than all other race groups? The Energy Storage Capacity Hypothesis only proposes that at a given level of excess energy, those with lower fat cell numbers are at greater risk for obesity related diseases compared to those with greater numbers of fat cells, which provide more storage capacity, all else being equal, and not that greatest weight per se would necessarily be lower. To investigate the possibility that there is a generational or cultural contribution, we stratified greatest weight in kgs by BORN: in the US versus elsewhere (not Mexico), and found that among all diabetics, greatest wt in kgs was lower among those born elsewhere compared to those born in the United States, but that Asians still reported the lowest greatest weight. There may be an Asian cultural bias against obesity that is not observed among other ethnic groups, or it might be that the Asian diet is less calorically dense than other ethnic diets resulting in less overall weight gain, or that Asians are more physically active. It may also be that in Asians, adipocyte proliferative potential is reduced, or once adipocytes reach critical size limits, adipocyte regulatory proteins are effective at halting or slowing down energy imbalance, so that continued energy intake is controlled and proliferation does not advance to the same degree as other race groups.
4.5. Conclusion

Obesity is a major predictor of type 2 diabetes, however, Asians appear to be at elevated risk for type 2 diabetes at much lower obesity levels, as defined by the BMI. Although numerous obesity-disease theories have emerged in recent years in the study of obesity and related diseases, contemporary thought in this exciting area is rarely invoked in epidemiologic studies. This cross-sectional study used the Energy Storage Capacity Hypothesis to aid in the study design of a multi-ethnic investigation of type 2 diabetes across the BMI continuum. Using Asian race and weight gain as novel surrogates for the underlying biologic phenomenon of the Energy Storage Capacity model, the results of this study, if major assumptions are correct, did not refute the hypothesis. We believe these findings provide the rationale for more rigorous study. We hope our treatment of this very important topic might stimulate interest, new ideas, and a fresh perspective in the epidemiologic study of obesity and related diseases, and in the primary and secondary prevention of obesity and type 2 diabetes.
CHAPTER 5

CONCLUSION

Scientific revolutions and change result from a breakdown of the prevailing paradigm - internal inconsistencies emerge, anomalous findings persist, and alternative viewpoints promise greater explanatory utility.

5.1. Discussion

The primary purpose of this dissertation is to present public health professionals with an alternative etiologic obesity-disease paradigm that better explains the obesity-disease risk relationship. Understanding the underlying pathogenesis creates an opportunity to view the twin epidemics of obesity and type 2 diabetes in a different light. Since the formulation of the Energy Storage Hypothesis in 2001, and specifically within the past several years, multidisciplinary evidence seems to be, although still within a medicalized framework and still without a public health perspective, quickly converging on a consensus interpretation of the concept of adipose cellularity as protective or at least adipocyte size as detrimental (Scherer and Unger 2010, Iozzo 2009). With new or updated information, the challenge for public health professionals now, is how best to respond. New or modified approaches in
the areas of epidemiologic obesity research, surveillance, and screening methods, as well as public health interventions should be considered and will be discussed in turn.

5.1.1. Research, surveillance, and screening

Data that is vital, but currently missing in the epidemiologic study of obesity and related diseases include family history of obesity and lifetime history of weight and height. This information would greatly aid in developing risk and prediction models of type 2 diabetes and improve explanatory power. These data would also add the necessary nuance that is needed for more sophisticated risk stratification, screening, and prevention programs.

For example, under the Energy Storage Capacity Hypothesis, an adult with a true genetic family history of obesity, without a family history of diabetes, and who is active, is highly protected from obesity related diseases, regardless of BMI. This individual may not be able to lose much, if any intentional weight, due to high adipose cellularity and a normal fat cell volume. This population subset should be eliminated from intensive interventional approaches to lose weight. Although heavyset and currently a target for public health intervention due to high BMI, they are not at high risk for the onset of obesity related diseases from a metabolic health perspective.

On the other hand, phenotypically lean adults who gain 5% - 10% weight, and who currently fall within the normal BMI category, may need to be targeted to lose excess weight. A very lean phenotype, which implies low adipose cellularity has a very narrow range of allowable weight gain. Based on this research and others, this subset of the nonobese BMI population often goes undetected, under-assessed, and/or undertreated. Thus, family history of obesity and weight history from birth and beyond could help to identify those at elevated risk of possible weight gain related pathogenesis, regardless of BMI status throughout the lifecourse.
Based on emerging evidence, the BMI is not able to adequately characterize obesity levels or classify health risk in diverse populations. How the BMI can best be used is to remain as a continuous variable for national and international weight status surveillance, completed disassociated from an obese label or a disease risk classification. Adding clarity to the obesity discussion is critical, as obesity diagnosis, and with it, disease risk classification is now occurring even in infants (McCormick et al. 2010). Using the current, but outdated public health obesity-disease paradigm could have severe consequences on infant growth, development, and future health.

For risk assessment, a relative index using an historic BMI temporal trend or previous BMI reading may provide better information at the individual and population level. To illustrate the idea of an index at the population level: A 2002 BMI relative index from 1998 to 2002 among Black females may be 1.0. This would imply very little weight change among this heavier sub group and it could be predicted and subsequently tested that the risk for type 2 diabetes, after accounting for age, has not increased among this group. A label of normal, overweight, or obesity is indeed, not required. Research should be conducted to investigate how family history of obesity and type 2 diabetes coupled with weight history and activity levels provide even more information regarding the ratio at which risk increases among subpopulations. Table 5.1 provides a crude model of how these data could be quantified.

<table>
<thead>
<tr>
<th>Type 2 Diabetes Genetics (+++)</th>
<th>No Type 2 Diabetes Genetics (−)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Gain (+)</td>
<td>No Weight Gain</td>
</tr>
<tr>
<td>No Family History of Obesity (+)</td>
<td>++++++++</td>
</tr>
<tr>
<td>Family History of Obesity (−)</td>
<td>+++++</td>
</tr>
</tbody>
</table>
5.1.2. Multidisciplinary collaboration and emerging risk factors

Greater multidisciplinary collaboration with basic science researchers, physiologists, neuroendocrinologists, agricultural food, nutrition, and animal scientists, along with other disciplines would greatly accelerate the ability to more thoroughly model the obesity-disease risk relationship from the molecular origins in man to diverse global populations. This is more important than ever, as our natural environment is increasingly modified by human activity. These modifications now include how food is grown, processed, genetically modified, or otherwise impacted by man in the name of efficiency and profit, and without the regulatory safety framework that is required of pharmacologic substances.

For example, recent research has identified a possible role of xenobiotic chemicals to disrupt homeostatic energy balance. These substances, also called obesogens, are chemical molecules that exhibit adipogenic properties and are considered possible promoters of obesity (Grün and Blumberg 2006). Organotins are a chemical class of organic pollutant with endocrine disrupting potential that have been identified as agonist ligands for nuclear receptors. PPAR-γ is the nuclear receptor which plays the primary role in adipocyte differentiation (Grün and Blumberg 2006). Genetically modified seed (which is now ubiquitous in the United States) for crops such as corn, soy, beet, and rapeseed (canola), along with specifically developed pesticide, is currently approved by the United States Federal Drug Administration (FDA) and United States Department of Agriculture (USDA), without minimum labeling laws or safety studies. If these food and feed crops prove to introduce obesogens or other deleterious properties into the food supply, the implication for long-term human health in the United States could be profound.

5.1.3. Childhood metrics for obesity and disease risk classification

Although this dissertation has focused on adult obesity and type 2 diabetes, the prevention of the early onset of chronic diseases begins in childhood (Berenson et al. 1993). Currently, BMI-for-Age percentiles (to account for growth and development) is the metric used for obesity labeling and risk for future chronic disease classification (Kuczmarski et al. 2000).
This metric may be adequate for normal birthweight babies. However, for birthweight at the end ranges (high or low), BMI-for-Age percentiles may need to be modified. One suggestion might be to shift the BMI-for-Age percentile curves left or right, depending on the obesity and type 2 diabetes maternal history, both before and during pregnancy. The most recent ADA guidelines and position statement includes the need to identify glycemic status before and during pregnancy, acknowledging both the impact of glycemic and insulin exposure on the birthweight of the neonate and the increased risk of obesity and obesity related health problems in later life (ADA 2010, Dabelea et al. 2000).

The more conservative approach is to research and test under what set of circumstances and to what degree would it be appropriate to use a modified percentile chart and to what level of modification. In all cases, however, a detailed obesity, diabetes, and pregnancy history should determine if the birth weight is related to underlying genetics (eg, the whole family is genetically large) or due to the maternal-fetal environment (eg, undernutrition, overnutrition, as well as glycemic, insulin, or inflammatory exposure due to stress). These factors would add important information to the obesity-diabetes pathways model.

5.2. Public Health Obesity Campaigns: A Call for Change

Although the underlying objective of the recent White House national obesity campaign, *Let’s Move*, is stated to be less about weight and more about improved behaviors such as improved nutrition and increased levels of physical activity, the overall objective is to "fight childhood obesity [ and the specific goal is to ] solve the problem of childhood obesity within a generation so that children born today will reach adulthood at a healthy weight" (Obama 2010). This most current national obesity campaign is, therefore and unfortunately, no different than the previous childhood and adult obesity campaigns in 1998 and 2001 (USDHHS 2000). These public health campaigns apply the outdated paradigm of excessive fatness *per se* as the cause for an increased risk in obesity-related diseases, and use it, as the framework for action. Consequently, the same problems of heterogeneity of health risk
across the BMI continuum, within BMI categories, as well as continuing obesity stigma among heavier children based on obesity labeling will persist.

Success in public health and medicine is ultimately not measured by science’s promise of greater explanatory power or even of efficacy, but rather, how much more effective is the proposed alternative to the standard of care? Success is measured by shifting the population curve in a favorable direction, reducing disparity, and increasing efficiency. However, the path chosen of all possible paths, the legislation enacted, campaigns started, and messages delivered, all represent a confluence of scientific interpretation, choice, policy, politics, populace will, and finite resources. Public health education and promotion, along with population interventions therefore more strongly reflect the path that is ultimately chosen, which may not reflect the current body of evidence. Obesity has been considered a serious public health problem for nearly 60 years (Mayer 1953) and has been consistently on the public health agenda since the early 1980’s. Must another several decades pass before public health approaches to solving the enduring problem of obesity and related diseases more closely reflect contemporary scientific thought?
REFERENCES


Barker DJ, Erikkson JG, Forsen T, Osmond C. Fetal origins of adult disease: strength of effects and biologic basis. IJE 2002;06: 1235–1239.


Bray GA. Obesity is a chronic, relapsing neurochemical disease. IJO 2004;28: 34–38.


90


Misra A. Revisions of cutoffs of body mass index to define overweight and obesity are needed for the Asian-ethnic groups. IJO 2003;27: 1294–96.


Quan H, Parsons GA, Ghali WA. Validity of information on comorbidity derived from ICD-9-CCM administrative data. Med Care 2002;40: 675-85.


Ravussin E, Smith SR. Increased fat intake, impaired fat oxidation, and failure of fat cell proliferation result in ectopic fat storage, insulin resistance, and type 2 diabetes mellitus. Ann NY Acad Sci 2002;967: 363–78.

Reaven GM. Hypothesis: muscle insulin resistance is the (‘not-so’) thrifty genotype. Diabetologia 1998;41: 482–84.


Sims EA. Are there persons who are obese, but metabolically healthy? Metabolism 2001;50: 1499–04.


Stevens J. Ethnic-specific revisions of body mass index cutoffs to define overweight and obesity in Asians are not warranted. IJO 2003;27: 1297–99.


