OBESITY - RELATED HEALTH RISK: A TRAJECTORY BASED APPROACH

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A THESIS SUBMITTED TO
THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
MASTER OF SCIENCE

GRADUATE PROGRAM IN KINESIOLOGY
YORK UNIVERSITY
TORONTO, ONTARIO

November 2013

Abstract

The purpose of this study was to evaluate the Edmonton Obesity Staging System (EOSS) approach as a tool for the identification of obesity-related health risk. Using 20 years of follow-up data from the Coronary Artery Risk Development in Young Adults (CARDIA) study (N=5115; age 18-34), trajectory modelling analysis was used to identify distinct clusters of individuals following similar patterns of obesity using modified EOSS criteria. The final model acquired through the Proc Traj macro suggests that there are 4 distinct EOSS stage-increase trajectories. After adjusting for covariates, individuals in the medium risk trajectory were twice more likely to follow protein consumption guidelines (OR=2.08 95% CI=1.18-3.65), 47% less likely to be black (0.53, 0.37-0.76), 43% less likely to have a history of dieting (0.57, 0.37-0.86), and were also less likely to be either occasional (0.51, 0.29-0.9) or frequent (0.25, 0.14-0.45) weight cyclers when compared to the highest risk trajectory.

Acknowledgements

First I would like to acknowledge my graduate supervisor, Dr. Chris Ardern for his unwavering patience and support throughout this thesis. His guidance and timely suggestions have expedited the completion of this manuscript, and helped prevent some time-costly errors. He challenged my ideas and pushed me to think in multiple directions. I am incredibly grateful for your vigilant supervision and mentorship.

I would also like to acknowledge my second-reader and committee member, Dr. Hala Tamim, who provided very insightful feedback and gave me fresh ideas to better conceptualize the statistical portions of my thesis. She was always available when I had questions and did not hesitate to point out some inconsistencies in my work. Thank you for your support and commitment to my work.

I would also like to acknowledge Dr Jen Kuk, whose article-critiquing seminars challenged me to think and gave me countless ideas for the completion of this manuscript. She was very helpful in clearing up key concepts that were in one way or another incorporated into my work. In addition, I would like to thank my fellow students that have helped me and were there for me over my last two years at York. Thank you for your helpful suggestions, fair criticism and belief in my work.

Finally, I would like to acknowledge the National Institute of Health and the researchers at the Division of Preventive Medicine in University of Alabama at Birmingham for the colossal amount of work that went into the creation of the CARDIA dataset.

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List of Abbreviations

ADLs Activities of Daily Living

AMA American Medical Association

BIA Bioelectrical Impedance Analysis

BIC Bayesian Information Criterion

BMI Body Mass Index

BVI Body Volume Index

CCHS Canadian Community Health Survey

CDC Centre for Disease Control

CHD Coronary Heart Disease

CT Computed Tomography

DBP Diastolic Blood Pressure

DSM Diagnostic and Statistical Manual

DXA Dual-energy X-ray Absorptiometry

EOSS Edmonton Obesity Staging System

FRS Framingham Risk Scale

GAD Generalized Anxiety Disorder

HDL High-Density Lipoprotein

HTN Hypertension

IDF International Diabetes Foundation

LDL Low-Density Lipoprotein

MDS Major Depression Syndrome

METS Metabolic Syndrome

MRI Magnetic Resonance Imaging

NHANES National Health and Nutrition Examination Survey

NIH National Institute of Health

NHLBI National Heart, Lung, and Blood Institute

NIDDK National Institute of Diabetes and Digestive and Kidney Diseases

OHS Ontario Health Survey

OR Odds Ratio

PA Physical Activity

QMR Quantitative Magnetic Resonance

SAD Sagittal Abdominal Diameter

SBP Systolic Blood Pressure

SD Standard Deviation

SES Socio-Economic Status

WC Waist Circumference

WHR Waist-to-hip Ratio

WHO World Health Organization

1. Extended Introduction

1.1 General Obesity Issues

Obesity has been a constant, growing problem over the past several decades, affecting all segments of the population, regardless of sex, ethnicity, education and socio-economic status. It has become a global pandemic, with recent estimates suggesting that more than 500 million individuals are obese worldwide, and that this number is only going to get higher.[1] It is projected that by 2030, there may be as many as 1.12 – 1.35 billion obese individuals globally.[2] [3] Recent evidence from the United States shows that obesity is now, in fact, the country's leading cause of *preventable* death.[4] What's worse, this obesity-mortality relationship strengthens with age and with obesity severity.[5] [6] Not surprisingly, the American Medical Association (AMA) has recently (2013) voted to recognize obesity as a *disease* in the hopes of being able to better combat the obesity epidemic.[7] Some believe that this may lead to more resources being devoted toward researching and treating obesity, a problem that costs the American healthcare system almost $190 billion annually.[8] Others are more skeptical, suggesting that "medicalizing" obesity by declaring it a disease, would lead to more reliance on costly drugs and surgery without a similar investment in primary prevention through lifestyle modification.[9] Canada has also experienced a rise in obesity, with some research suggesting that the rates have exceeded 30% in half of the provinces, and that they are still expected to rise.[10] The prevalence of obesity in children has tripled over the past 30 years, with about 12-13% school-aged children being obese.[11]

The World Health Organization (WHO) defines obesity as an abnormal or excessive fat accumulation that presents a risk to health.[12] Multiple action plans and policy declarations have

been put into place to promote healthy diets and active lifestyles, to little benefit. Obesity is not just a simple weight gain; it can reduce life expectancy, lead to other illnesses, serious health complications, and eventual death.[13] Many of the leading causes of death also related to obesity, and it is known to increases the risk of hypertension, diabetes, coronary heart disease (CHD), dyslipidemia, stroke, liver & gall bladder disease, osteoarthritis, sleep apnea (respiratory problems) and some cancers (endometrial, breast, and colon).[14] [15] Beyond these physical conditions, obesity has also been associated with depression and social stigmatization, with some research also identifying a reciprocal relationship (i.e. depression may be predictive of obesity).[16] [17] [18]

Obesity is influenced by numerous factors, including sex, race, age, genes and socio-economic-status (SES), making it difficult to determine the true "cause".[19] The recently developed obesity systems map shows hundreds of pathways to obesity that form a complex web of overlapping and reinforcing causal factors.[20] An argument can be made that the obesity epidemic is a product of globalization. Improvements in transportation, agriculture and labour-saving technologies and various trade agreements have contributed to a marked increase in food availability by virtue of an increased production of high-calorie processed foods and the rapid expansion of fast-food chains and multinational food conglomerates.[21] [22] Combined with an overall decrease in total daily physical activity levels due to urbanization, mechanization, better transportation, and other changes in the physical and social environment have contributed to the observed rise in body weight.[20] These rapid changes in everyday life have magnified the overall burden of obesity and contributed to ensuing obesity-related health complications. Unfortunately, due to the complex, multi-factorial nature of this disease, there is no universal treatment for obesity. Despite evidence in support of low-calorie diets, healthy eating plans,

increased physical activity, psychological counselling, peer-support groups, and weight-loss surgery, among others, individualised weight loss is challenging.[23] In Canada, the lack of good cost-effectiveness studies of obesity prevention and management programs has hampered the public health decision making process.[24] Specifically, obese individuals generally have much higher costs associated with hospitalizations and day procedures and overall cause a greater strain on the economic system, with almost 40% greater hospitalization costs when compared to normal-weight adults.[25] The accurate identification of 'obesity' and those individuals who are likely to suffer the consequences of their excess weight is an important consideration within the universal healthcare system in Canada. Compounding the issue of obesity identification is the overall inaccuracy of the current anthropometric classification systems such as waist circumference (WC), and to a greater extent, Body Mass Index (BMI) especially considering the frequent use of self-reported data in major health studies.

1.2 BMI Application and Limitations

Most of the currently employed anthropometric approaches to the measurement of obesity are based on simple clinical measures. These often come in the form of weight, height, BMI and waist circumference (WC), and while they are quick and simple to use on the population level, they often lack the detail necessary for clinical decision making. Alternatively, there exist a number of very accurate quantitative measurements of body composition (e.g. bioelectrical impedance analysis, dual energy X-ray absorptiometry, CT scans, magnetic resonance spectroscopy, quantitative magnetic resonance (QMR), etc.), but their complexity, accessibility and cost remain a significant hindrance in their application in a day-to-day clinical setting.[26] They are nevertheless very useful in research settings especially for scientists

examining anti-obesity interventions due to their overall accuracy in measuring whole-body fat and lean mass in humans.[27] These will be discussed in greater detail in later sections.

When considering obesity on a global scale, it quickly becomes apparent that these techniques are not very useful for population-level interventions especially in low-income or developing countries. In most cases however, BMI is used as the predominant measure of obesity. This is not surprising, because BMI is very easy to use, can be quickly self-measured, and is very useful for clinical studies or any sort of population/sample comparative analysis. BMI has also been shown to be strongly correlated with body fat percentage in many different populations.[28 29 30] The BMI cut-offs have been accepted worldwide and are integrated into the Canadian clinical practice guidelines as follows; a BMI of 18.5 - 24.9 kg/m^2 is normal, 25.0 – 29.9 kg/m^2 is overweight and a BMI $\geq$ 30.0 kg/m^2 is considered obese.[31]

At the same time, there are multiple serious limitations to BMI, especially when looking at sex, age and racial/ethnic differences at the individual level. Women tend to have more body fat than men at any given BMI, with this relationship especially noticeable between young girls and boys.[32 33 34] A higher amount of muscle mass in men contributes to a heavy-set body size, which could create a false-positive classification of obesity, but with presumably a low level of fat mass and subsequent health risk.[35] Similarly, racial/ethnic differences in the body fat-BMI relationship have been observed, [36 37] leading to the development of race-specific BMI guidelines. [38 39] BMI might also underestimate obesity because of loss of muscle mass, lean tissue and bone density due to aging.[40 41 42] Finally, BMI is unable to discriminate between lean and fat tissue, and ignores medical conditions that affect height or body shape. The inability of BMI to distinguish between fat mass and fat free mass could contribute to either an under- or

over-estimation of the prevalence of obesity, depending on the population in which it is employed. As such, being unable to account for varied body frame (and the training-associated abdominal fat loss and muscle gain) size makes BMI a poor tool of choice for the study of some professional athletes and body-builders or even individuals in weight management programs.

To better illustrate this difference, in recent years, researchers have begun to use DXA scans (Dual-energy X-ray absorptiometry) scans to measure body composition and fat content with much higher overall accuracy.[43] While relatively expensive to use, it has nevertheless been very useful in clinical body composition analysis, particularly in identifying normal-weight but obese individuals.[44] These DXA scans can reveal that 2 individuals with the same BMI can have drastically different health and fitness profiles.[45] Because of these and other limitations, the accuracy and sensitivity of BMI has often been challenged, especially in the light of recent research into the 'fit-fat' paradox.[46] Specifically, research suggests that not all obese individuals are at increased health risk.[47] There is also evidence that obesity is independently associated with reduced cardiovascular fitness and that individual factors (health behaviours, adverse health conditions, race/ethnicity, income etc.) can play a role in its improvement.[48] Simply put, while useful in population level-analysis, the current anthropometric classification system is based on simple clinical measures, such as BMI have limited application for individual patients.

1.3 Alternative Obesity Measures - Waist Circumference

Waist circumference (WC) is another tool that has been used separately or in conjunction with the BMI for the measurement of obesity. It is the most straightforward, inexpensive way (simple measuring tape) of measuring abdominal obesity, irrespective of BMI. As of 2012, the National Institute of Health (NIH) WC cut-offs have been used as the standard method for WC

measurement in Canada.[49] According to these criteria, men with a WC greater than 102 cm (>40 in.) and women with a WC greater than 88 cm (>35 in.) are considered high risk. Despite the stronger relationship between abdominal obesity and health risk (than BMI and health risk), variation in the WC measurement site has contributed to imprecision in its use[44 50]

In addition, there are also some other key limitations. Besides the above-mentioned standardization issue, NIH suggests that at BMIs higher than 35, waist circumference has little additional predictive power of disease risk above the one predicted by BMI.[51 52] Some studies go a step further saying that WC is either impossible or useless altogether for measuring obesity risk in severely obese individuals.[53] In addition to this, it can altogether miss those that carry a large amount of fat in their hips. For instance, individuals with the same WC have been found to have significantly different levels of visceral fat, and this difference may contribute to the underestimation of obesity.[54] Complicating the relationship further is the fact that physical activity levels, ethnicity, genetics, medical history and diet preferences may also play a role in the variability of visceral fat.[55] However, it is fair to mention that carrying fat in other parts of the body is not as dangerous as having a large proportion of abdominal fat.[56] Similar to what was is seen with BMI, there are multiple age and ethnic/racial-related differences in fat distribution that can have an effect on WC and subsequent health-risk measures. [32 57 58] For example, the International Diabetes Federation (IDF) uses ethnic-specific criteria to define abdominal obesity for the metabolic syndrome.[59] Making things more difficult is the fact that there are no similar guidelines for children; an important limitation, considering the increasing world-wide child obesity rates and the recognized importance of early-age intervention in global obesity prevention.[60 61]

1.4 Alternative Obesity Measures – Waist-to-Hip Ratio

Another common measure used to evaluate abdominal obesity and to estimate the risk of developing obesity-related health problems is the waist to hip ratio (WHR). Much of the value of this ratio is that increased gluteofemoral fat mass reduces an individual's cardiovascular and metabolic risk.[62] Similar to WC, there are 2 accepted ways of measuring WHR. The World Health Organization states that the waist circumference should be measured at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest.[63] Hip circumference is to be measured around the widest portion of the buttocks, ensuring that the tape is parallel to the floor.[60] The NIH suggests that WC at the top of the iliac crest, while other independent researchers have taken the measurements at the point of the minimal waist.[46] [64] While most studies find no significant difference between the different types of measurement protocols, controversies remain and the issues are especially evident when comparing self-reported WHR numbers.[65] [66] The exact cut-offs for abdominal obesity are also in debate with WHO suggesting that they should be 0.9 for males and 0.85 for females, while the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) states that it is 1.0 and 0.8 for men and women respectively.[67] [68] Overall, WHR is considered the simplest measure of fat distribution. It requires no special training, knowledge or equipment and can be taken at home and is the least invasive way of measuring own body composition levels. It is directly tied to the concept of 'body-shape', and may better predict the development of cardiovascular-related health risk than BMI.[69] [70] [71] Some also find that WHR is a better predictor of overall mortality, especially of circulatory-related mortality.[72] Suffice to say, central obesity seems to be directly associated with mortality as demonstrated by a recent systematic review by a group of Mayo Clinic researchers.[73]

Here again, however, waist-to-hip ratio suffers from most of the key limitations seen in WC. Similar to WC, the main problem with WHR is that its accuracy decreases with increasing levels of obesity.[74] From a research standpoint the main concern then, is whether or not WHR actually adds anything new to the relationship between health risk and increased abdominal fat. In this regard, comparisons between WHR and WC are inconclusive. On the one hand, WHR takes into account the hip fat distribution that WC cannot measure; however, it is harder to measure, requiring 2 accurate measurements instead of 1, making WC the better choice in many settings.[75] It is also more difficult to interpret because changes in WHR can be the result of an increase in abdominal fat (WC), lower levels of lower body lean mass, or a the reverse combination.[76] [77] [78] As a result, an individual with a high waist circumference may benefit from weight loss exercise and diets, while an individual with small hips might benefit from resistance training to build up body mass. WHR sometimes fails to account for the different effects of adipose tissue in the abdominal and gluteofemoral regions.[79] Ethnic-specific differences have also been identified, with some studies showing that African-Americans have a lower visceral fat mass compared to that of individuals of European-descent.[80] Some studies find no difference whatsoever in metabolic risk factors or cardiovascular disease when comparing WC and WHR[81] [82] [83] while others show that it is superior for the assessment of mortality risk in the elderly, than either WC or BMI.[84] Other researchers question whether there is *any* additional value to measuring BMI and WHR, given the large inter-individual (e.g. sex, ethnic, etc.) and that that the associations between overall obesity, central adiposity, and adverse health outcomes may vary due to sex, as well ethnic and racial differences.[85] [86]

Finally, looking at WHR alone is often not enough to gauge the obesity-related risks because due to the nature of the ratio calculations, two individuals with the same WHR can have

drastically different BMIs. For example, a 250 pound, 6 foot male weightlifter can have a WHR of 1.0, with a BMI of 33.9. At the same time a 160 pound, 6 foot non-athletic male can also have a WHR of 1.0 but at the same time he will have a BMI of only 21.7. Just by looking at the WHR numbers, these two individuals seem identical, and both are at borderline obesity-related risk. The weightlifter, in fact is also obese, but that does not necessarily mean that they are unhealthy, unfit or at risk in any way. This is especially important to consider in light of the recent research into the 'metabolically healthy but obese' phenomenon.[87]

1.5 Alternative Obesity Measures – BVI, Skinfold Tests, SAD

This section will briefly cover a couple of additional, less frequently employed measures of adiposity including the body volume index (BVI), skinfold thickness tests and the sagittal abdominal diameter (SAD). First, the *body volume index* has recently been proposed as an alternative to BMI to assess body volume distribution to measure obesity and individual health risk.[88] Introduced early in 2000, BVI is an application that can be used in a 3D Full Body Scanner, to analyze abdominal area, and serve as an early warning system to help identify those individuals that are particularly at risk of heart disease, stroke, and diabetes.[89] The scanner itself is a seven-foot booth that has 16 sensors and 32 cameras and takes a virtual image of the person's shape using white light. The researchers behind BVI note that BMI was never intended to be an individual tool for obesity assessment, and that BVI will take each patient's own body shape and lifestyle factors into account when measuring obesity-related risks.[88] Pilot studies have shown much promise, including the ability to track changes occurring over time but further studies are necessary to determine possible uses for BVI scans in combating obesity.[90] Others suggest that while BVI is a more accurate obesity-measurement tool, it is also very expensive

and somewhat difficult to use.[91] While greater accuracy, consistency and speed of delivery (a full scan is estimated to take just 6 seconds to complete) are all major advantages of BVI, the combination of some software skills, the size of the scanner and the associated costs might make it unreasonable and unlikely to be used in family practices or small medical clinics.[92]

Second, *skinfold thickness* tests have been employed for decades and are used to estimate body fat percentage by measuring the fat under the skin also known as the subcutaneous adipose tissue. A special caliper is used to pinch the skin and measure the fat underneath it at specific sites of the body. There are 7 specific locations on the body and these measurements are combined to calculate percent body fat. Some advantages of skinfold thickness tests include their portability and convenience, their usefulness in assessing body composition, and the overall low costs and labour requirements.[93 94] They are also very reliable indices of regional fatness and are sometimes even used to predict whole body composition.[94] There are however some limitations to skinfold tests, mostly in caliper technique and in the way the measurements are taken. Skinfold tests require more skill and practical experience than other simple measures of obesity; to minimize measurement error and variability, standardized training is therefore required.[95 96] Similar to other discussed obesity measurement tools, skinfold measurements are difficult to obtain for many obese subjects because fat tissue can actually exceed the limits of the caliper or the clinicians are simply unable to grasp a double thickness of tissue.[97] Finally, because skinfold measurements only calculate subcutaneous fat they might not be very effective in measuring overall body fat percentage, especially in lean, athletic individuals. In light of the above, the usefulness and applicability of skinfold thickness tests in clinical, school, or community settings is somewhat limited.[97]

Another relatively recent measure of central obesity is the *sagittal abdominal diameter (SAD)*, a measure of the distance from the back to the upper abdomen. It is very simple to measure in either supine or standing position; has minimal associated costs, requires little to no prior training or expertise and is highly reproducible. It can also be measured at any point between the lower rib margin and the superior anterior iliac crest, giving it some flexibility and improving ease of use.[98] Studies show that SAD is a good predictor of CHD, increased metabolic risk, and insulin resistance in overweight and obese individuals.[99 99 100] An increase in SAD has been associated with an increased risk of sudden death, independent of BMI level and known CVD-related risk factors.[101] However, no standardized SAD cut-offs exist, making direct comparisons.[102 103] More importantly however, it is unclear whether SAD measures provide any clear advantage over waist circumference or BMI alone [104 105 106] or whether any of the results can be replicated in a larger population.[101 103 107] More research and larger prospective studies are needed to compare the clinical utility of SAD, and its potential effectiveness over other anthropometric measurements.[108]

1.6 Alternative Obesity Measures – Obesity Research Tools

Due to their expense and the high degree of technical skill required for their use, some of the most precise tools for obesity assessment are currently limited to the research environment. These include bioelectrical impedance, underwater weighting (Hydrodensitometry), Air-Displacement Plethysmography, Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI). Most of these measuring tools are very good predictors of obesity and in most cases are actually better than the previously-mentioned anthropometric tools, especially at the individual level. However, they are all either time consuming, difficult to use or very expensive,

and in the case of CT and MRI, are rarely used outside of the research settings.[20] Bioelectrical impedance analysis (BIA) estimates percent body fat by measuring resistance to the flow of a small electric current that gets passed through the body. Relatively small and inexpensive, it is nevertheless rarely used in population-level surveillance because of the quality of the different devices used, the types of measurements taken (location of fat is unknown), and the lack of information on its relevance to diverse ethnic groups.[109] [110] There are multiple different water-based measurement tools, and while very accurate in calculating body density, they all share significant limitations (time consuming, lots of specialized equipment, requiring individual water submersion) that make them difficult to use outside of the research setting.[111] Air-Displacement Plethysmography is conceptually analogous to underwater weighting, except that it estimates the air pressure difference between empty and occupied air chambers.[112] Unfortunately, while much more precise and easier to use than hydrodensitometry, the air chamber or "pod" is very expensive.[94] Despite being very good methods for measuring obesity, the above-mentioned tools are nevertheless unlikely to ever be used in small clinical practices, schools or for personal, individual use.

From the above overview, it seems apparent that most of the anthropometric measures currently in use have very key limitations and are only useful and accurate enough when dealing with specific subsets of the population or when a combined measurement approach is employed. The measurement tools with most potential are rarely used outside of the research setting due to a combination of high costs, low availability and technical complexity. The lower cost methods tend to be unable to clearly outline the severity of health conditions, especially at an individual level. Furthermore, given that few individuals are able to successfully maintain their weight loss, the risk of 'weight cycling' on health must also be considered.[113] [114] [115] It is therefore apparent,

that alternative obesity screening tools are needed, if obesity treatment protocols are to be truly optimized. The following section will take an in-depth look into one such alternative screening tool, and examine its practicality and effectiveness as assessed to date.

1.7 Edmonton Obesity Staging System - Overview

First introduced in 2009 by Sharma and Kushner, the Edmonton obesity staging system (EOSS) is a novel clinical and functional staging system that allows clinicians to describe the psychological, quality of life, and morbidity and functional limitations associated with excess body fat.[116] It aims to refine existing screening strategies by incorporating both physical and mental dimensions of health, in order to more accurately identify the morbidity and health risks of a given individual.[117] This clinical staging system was created in the hopes of both improving obesity prognosis and guiding subsequent obesity treatments in individuals. Using BMI "obesity" cut-offs as its basis, EOSS is also able to provide information on disease comorbidities and functional limitations not seen in any other classification systems.

Simply put, EOSS is able to evaluate how "sick" an individual is, and then provide treatment steps or suggestions. Urgency of intervention and patient prioritization for interventions can be considered as additional outcomes of the system. This prioritizing can ensure not only a greater degree of accuracy in identifying individuals that would benefit from specific surgery or procedures, but also reducing weight times, procedural expenditures and increasing the overall effectiveness of any given health intervention. For example, recent studies on weight loss procedures illustrate the fact that EOSS might be a good tool to use to redefine indications for bariatric surgery in obese individuals and to assist in the triage of very high-risk

individuals.[118] [119]. The potential improvements in both patient selection and resource allocation are reasons enough to further investigate EOSS as a clinically-valid obesity-management tool.

The proposed staging system has a simple structure consisting of medical history, clinical and functional assessments and additional or routine diagnostic check-ups. A complete summary of EOSS and its related components can be found in Sharma and Kushner (2009) or at Dr. Arya Sharma's website[120]. In general, EOSS consists of 5 stages (0-4) that are organized in an increasing level of severity. Each stage lists the necessary stage-inclusion criteria, followed by possible solutions or suggestions as to what to do for that particular stage (**Appendix B, Table 1**). To be classified as "Stage 0", an individual would need to be obese (BMI > 30 kg/m^2), and show no medical, mental or functional problems. This individual would fit the 'metabolically healthy but obese' profile as mentioned previously. The EOSS level of each individual would be based on the *highest-stage risk factor present* (**Appendix B, Table 1**). Therefore, a medically and psychologically healthy obese individual that nonetheless demonstrates moderate functional limitations (i.e. difficulty moving up and down the stairs, arm pain after moderate exertion, trouble running, etc.) would be considered stage 2 since his functional limitation is the highest level limitation available. From the examples above, the risk management plan for a stage 0 individual would focus primarily on preventing further weight gain and identifying the reasons behind the current increased body weight. For the functionally limited stage 2 individual, the focus would be on trying to first improve his functional problem and then implement some sort of a weight-reducing program. It may very well be that the patient's functional disability is preventing him or her from moving, exercising or losing weight in general. The obvious exception here is stage 4 individuals who would most likely be palliative patients with terminal illnesses or other severe (most likely untreatable) conditions. For instance, not only would

weight reduction be the least of the problems for cancer patients, but it might actually be severely detrimental to their health (since cancer commonly results in weight loss).[121]

These management steps, in concordance with current anthropometric classification systems (i.e. BMI) would give clinicians a detailed snapshot of the patient's health and provide them with an outline of some possible treatment pathways. The lack of scientific studies looking at obesity risk-factor management make this an important topic of study, especially considering the multi-factorial nature of obesity development. The effective implementation of a risk-identification system as EOSS can not only identify these high-risk individuals but may also theoretically help to alleviate the financial and the social burdens associated with obesity. Thus, a longitudinal approach is essential to identify factors that could contribute to obesity in the early stages of adulthood, and that could play a role in future weight gain or weigh fluctuation. To this end, the study objectives were as follows:

1.8 Study Research Objectives

Objective 1: To identify trajectories of EOSS stages (1 to 3) over 20 years of follow-up in the CARDIA dataset.

Objective 2: To determine characteristics of groups at high-risk of obesity-related health risk in both overweight/obese trajectories and EOSS trajectories.

1.9 CARDIA study summary

To better evaluate EOSS as a potential risk identification-prediction tool, it is essential to look at a longitudinal study to see long-term changes and trends of specific conditions or any

other variables. Beginning in 1985-6, The Coronary Artery Risk Development in Young Adults (CARDIA) is a long-running (26 years +) longitudinal US study that looks at the development of heart disease in black and white individuals in 4 different centers across the US.[122] It is sponsored by the National Heart, Lung, and Blood Institute of the National Institutes of Health (NHLBI) and had follow-up examinations during 1987-1988 (Year 2), 1990-1991 (Year 5), 1992-1993 (Year 7), 1995-1996 (Year 10), 2000-2001 (Year 15), 2005-2006 (Year 20), and 2010-1011 (Year 25).[123] Due to due to NHLBI data access limitations, only data for 20 years will be used in this paper. The study had a relatively low drop-out rate with about 72% of the sample still available for examination at year 20 (**Appendix B, Figure 1**). The recruitment and distribution of respondents was reviewed and pooled by age, sex, education (high school or less and more than high school) and race, to get an approximately equal number of participants in each category and in each examination center. The 4 examination centres were located in Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. Each of the examination centres were chosen for the availability of a representative biracial population. There were 5115 individuals in the study at baseline. After merging all the data, 3690 participants remained. Most of the individuals that were excluded were individuals who dropped out of the study before it finished (N=1400). Others were dropped due to duplicate patient IDs (N=20) and missing height/weight variables (N=5) which were excluded due to the inability to measure BMI.

While the aims and objectives of each follow-up have varied, all the collected data is believed to factor in or be related to heart disease. Data has been collected on a wide range of measurements including metabolic factors (blood pressure, lipids, cholesterol, glucose, etc.), physical measurements (weight, height), substance use (alcohol and tobacco), diet and exercise patterns, medication history, behavioral and psychological variables and certain co-morbidites

(medical and family history of known conditions and diseases). Although some additional conditions (i.e. atherosclerosis), and advanced diagnostic scans were also employed at specific examinations (i.e. abdominal CT scan during Year 25), there were largely irrelevant to the study objectives.

In CARDIA, it is possible to track changes in health and lifestyle habits (i.e. disease, exercise, smoking patterns, etc.) across early-to-mid adulthood and this is key because the CARDIA cohort, born 1955-1968, has been influenced substantially by the obesity epidemic at ages younger than participants in other established NHLBI cohorts.[127] Multiple observations of the same individual can also provide the researchers with a better idea of the direction of the causal relationship and to some extent, explain the strength of the statistical association.[124] The CARDIA database contains the majority of the variables used in the EOSS definition, making it an excellent way to test both the effectiveness of EOSS, and the usefulness of the trajectory modelling approach in evaluating obesity and obesity-related comorbidities.

1.10 Trajectory Modelling Overview

First introduced in 1993 by Nagin and Land as a tool to analyze the concept of a "criminal career", trajectory modelling has come to be widely used by other disciplines and especially in clinical practices where it is used to study the etiology and developmental course of various diseases, patient response to clinical treatments, and other applications.[125] Trajectory modeling is a type of group-based Bayesian, semi-parametric model that is used with longitudinal data. It allows researchers to group data based on different parameters and distributions.[126] Trajectory models can also work with time-varying covariates and can account for different types of data including count, binary, psychometric scales and normal

distributions.[127] The calculated trajectory shows the probability of group membership over time. These groups are helpful in identifying high-risk individuals or other specific subpopulations and are also able to approximate data for missing individuals (with 2 or more years). Unlike other types of trajectory modelling, group-based trajectory modelling makes no innate assumptions about the population distribution, and rather serves as a statistical device for approximating the unknown distribution of trajectories across population members.[128] Another advantage is that it can be used to facilitate causal inference especially when random assignment to treatment condition is not possible.[129]

In the current thesis, a custom proc Traj macro was used to create the trajectories in SAS (9.3). One major advantage of Proc Traj is that it uses all the available inputted data for both the outcome and the risk factors. An intercept and a regression coefficient is then estimated for each of the outcome groups in the model. The Wald test is used to test the significance of the estimated intercept and regression coefficient, and the final model is chosen based on the Bayesian Information Criterion (BIC). Developed by Gideon E. Schwarz in 1978, the BIC is the standard approach for model fitting and selection.[130] BIC introduces a penalty to balance the increase in the likelihood with the number of parameters. The best model is the one with the smallest negative BIC in the most complex model. For more information on BIC, see Jones (2001).[131] For this study, data was tested with 2, 3, 4, 5 models to identify the best model 'fit' on the basis of Bayesian stats and posterior probability to determine the final number of trajectories. With a well-defined model each individual in the dataset had a high probability of belonging to one particular group and a low probability of belonging to each of the others. The final model illustrates the probability of each individual belonging to a particular EOSS stage trajectory (low-risk, stable, high-risk) change associated with that particular trajectory. The corresponding

EOSS stage definitions were created based on **Appendix B, Table 1** and with reference to available EOSS-related research papers. Please refer to **Appendix B**, **Figure 2** for a short example of a Proc Traj Syntax.

1.11 Manuscript Foreword

Given the multifactorial nature of obesity, no single factor is responsible for its global rise. Very few studies have looked at obesity trends and the associated prevalence of obesity-related conditions as complex patterns of health status over an extended period of time.[131] In particular, potential obesity co-morbidities and covariates such as the psychological, socio-functional and emotional factors and their effect on lifetime obesity trends have not been adequately studied. The following paper will demonstrate an example of how EOSS can be used to study obesity in a longitudinal setting. The Coronary Artery Risk Development in Young Adults (CARDIA) study will be used for this analysis. Patterns of overweight and obesity will be scrutinized using trajectory modelling analysis, and compared against the development of comorbidities as they relate to EOSS stage framework. A longitudinal dataset such as CARDIA therefore allows for examination of individual risk factors, and clusters of conditions, while also contributing to an improved understanding of the ways in which individuals move through different EOSS stages through the subsequent check-ups.

Obesity – Related health risk: A trajectory based approach

Manuscript

Roman Matveev

November, 2013

2. 1 Introduction

Worldwide it is estimated that 1.3 billion individuals are overweight, more than 500 million of whom are obese.[132] Increased food availability, combined with an increase in caloric intake as well as a reduction in physical activity have made obesity a global pandemic.[133] This trend is especially noticeable in Canada, where a recent *Obesity in Canada* report revealed that approximately one in four adults are obese.[134] There are many known causes of obesity and obesity-related diseases but there is no universal treatment. This problem is compounded by the by the inaccuracy of the current anthropometric classification systems such as waist circumference (WC), and to a greater extent, Body Mass Index (BMI).

Commonly employed anthropometric measures are based on simple clinical measures. Weight, height, and waist circumference (WC) are simply not precise or accurate enough to account for many health risks and comorbidities. The often-used BMI, for example, does not take into account a person's body fat content, and is very unreliable in athletes, pregnant women, the very young or very old and ignores medical conditions that affect height or body shape.[135] The accuracy of these measures has often been challenged, especially considering recent research into the 'fit-fat' paradox,[46] bone and fat mass studies,[35] and individual factors such as health behaviours, adverse health conditions, race/ethnicity, and income.[48] Other anthropometric tools are available but are either somewhat inaccurate and cumbersome to use or cost prohibitive.,[26] and it has become clear that other approaches are necessary to optimize the treatment and management of obesity-related risk factors.

Proposed by Sharma and Kushner in 2009, the Edmonton Obesity Staging System (EOSS) aims to refine existing screening strategies by incorporating both physical and mental

dimensions of health, in order to more accurately identify the health risks of a given individual.[117] At its core, EOSS is a clinical staging system that complements anthropometric measures and, serves as a tool for determining prognosis and guiding obesity treatment.[136] Very few studies have looked at obesity trends and the associated prevalence of obesity-related conditions over an extended period of time.[133 137 138] Furthermore, the psychological, socio-functional and emotional factors of obesity and obesity-related diseases have not been adequately assessed in a longitudinal setting. This aim of this study is to therefore to identify trajectories of EOSS stages (1 to 3) over 20 years of follow-up in the CARDIA dataset and to determine characteristics of groups at high-risk of obesity-related health risk.

2.2 Methods

2.2.1 Participants

The Coronary Artery Risk Development in Young Adults (CARDIA) is a U.S. longitudinal cohort study that examines the development of heart disease in black and white individuals and that is sponsored by the National Heart, Lung, and Blood Institute of the National Institutes of Health (NHLBI).[124] It began in 1985-86 and consisted of 5115 black and white, relatively healthy individuals of both sexes, aged 18-30 years (2 age groups: 18-24 and 25-30). Individuals were pooled to allow for an equal representation across all age-sex-race groups in each of the 4 examination centres across the United States. Due to NHLBI data access limitations, only data for 20 years was used in this study. After merging the follow-up data and removing individuals with multiple missing variables (N=1 425), the final sample consisted of 3690 participants with baseline and follow-up information. An additional 508 people were removed due to key missing response variables during the whole-model computations leaving a

total of 3182 individuals for the final, year 20 analysis. Because of EOSS exclusion criteria, only individuals with the Body Mass Index (BMI) of 30 kg/m^2 were used for the EOSS portion of the analysis, resulting in 365 obese individuals being available at baseline. Baseline Demographic variables included gender, age, ethnicity and level of education [those with no highschool education, only a highschool diploma, a college or university degree, and those that have a Master's degree and above (including professional degrees)].

2.2.2 Key medical variables

EOSS Components

Data has been collected at baseline and each follow-up on a wide range of measurements including metabolic factors (blood pressure, lipids, cholesterol, glucose, etc.), physical measurements (height, weight), substance use (alcohol and tobacco), diet and exercise patterns, behavioral and psychological variables and certain comorbidities (medical and family history of known conditions and diseases). Phlebotomy followed standard protocols, with blood being drawn in a completely upright position and frozen (-70^0C) immediately after drawing. BMI classification was based on the World Health Organization (WHO) cut-offs and was measured with the standard formula: weight in kilograms divided by the square of the height in metres (kg/m)[139]. Specific details on each EOSS variable if provided in section 3.3.

Other Measures

The updated NCEP ATP III (2004) cut-offs were used to identify participants with the metabolic syndrome (MetS)[140], and Canadian Cardiovascular Society worksheets were used to calculate the Framingham risk scores (FRS).[141] [142] See **Appendix B, Table 2** for a detailed

overview of the MetS and FRS definition used. Physical activity intensity was subsequently estimated based on the Centre for Disease Control and Prevention (CDC) physical activity guidelines.[143] Individuals were asked questions about the number of times they had taken part in specific activities over the past year, and these scores were later added to create a single "physical activity intensity score". Males were considered "inactive" if the total score was less than 336 units, "moderately active" if they scored between 336 and 610 units and "active" if they had above 610. For females, the cut-offs were: < 192, between 192 and 400 and > 400 for inactive, moderately active and active, respectively.

Anyone who ate at a fast food place more than twice per week was considered a frequent consumer of fast food.[144] Individuals were considered occasional weight cyclers if they reported losing and regaining more than 10 pounds at least 1-4 times throughout their lives.[145] Those that reported losing weight more than 5 times were considered frequent weight cyclers **(Appendix C, Table 3)**. Meeting dietary guidelines for protein, fat and carbohydrate consumption was calculated as a percentage based on the daily intake energy requirements as outlined in the Dietary Guidelines for Americans 2010 report. Individuals had to have consumed between 45-65% carbohydrate, 10-35% protein and 20-35% fat daily to meet the corresponding macronutrient guidelines.[146]

2.2.3 EOSS

Similar to other papers written on this topic, a modified EOSS definition was used to account for missing variables.[9] Most importantly, the lack of any physical/functional variables meant that the functional subset of EOSS was omitted entirely. Furthermore, in order to maintain a reasonable sample size and to avoid loss of power, some variables were grouped together by

type (i.e. all types of cancers were just grouped under "cancer") or by category (i.e. "mental disorders" was a broad definition and included personality disorders, depressions, psychotic problems, etc.). The criteria used for EOSS categorization was based on the highest-stage risk factor present as shown in **Table 1.** For example, an individual with no mental disorders, physical impairments and normal-level fasting glucose and blood pressure but who has hypercholesterolemia would be categorized as EOSS stage 2, based on the most highest risk factor present. A detailed description of the EOSS criteria is provided in Sharma and Kushner (2009).[116 147]

2.2.4 Statistical Analysis

Data are presented as means with standard deviations (SD) or as % proportions. ANOVA and Fisher's Exact Chi-squared analysis was performed to test for baseline differences between the 4 different trajectory groups. For ease of comparison with the obese population, underweight, normal and overweight individuals were all categorized as "non-obese". Trajectory modelling was used to identify distinct clusters of individuals following similar patterns of obesity calculated over time.[130] Proc Traj, a modified SAS macro was used for this analysis.[127] This macro is not part of the base SAS program, and was downloaded from the Jones' main webpage.[148] The Bayesian Information Criterion (BIC) was used for model selection. The model with the most complexity and the lowest BIC value was chosen as the optimal model.[149] Multinomial logistic regression was then used to develop a character profile of each EOSS trajectory. Additional factors (diet history, calories consumed, drinking habits, exercise patterns, education level, and metabolic syndrome) were compared between the different EOSS stages and these were adjusted for age, sex, smoking status and exam year using forward step-wise

selection. Additional covariates included fast-food consumption frequency and weight-cycling history; however, due to insufficient follow-up data, only baseline data was used for these 2 variables. SAS 9.3 was used for all statistical calculations with statistical significance set at $p < 0.05$.

2.3 Results

The baseline distribution of all continuous & categorical variables for all obese individuals is shown in **Table 2**. In total, there were 365 obese individuals at baseline, which accounted for about 10% of the overall sample. The EOSS stage categorization was as follows: 3.3% were stage 0 (N=12), 38.9% stage 1 (N=142), 54.5% stage 2 (199) and 3.3% (N=12) were stage 3. In the trajectory model at baseline, there were 6 individuals in the no-risk (group 1), 227 individuals in the medium risk (group 2), 93 in high risk (group 3) and 39 in chronic risk (group 4) groups. Compared with the chronic risk individuals, medium risk individuals were slightly older, heavier, were likely to be male and moderate drinkers, have higher SBP and DBP but lower HDL levels (all $p < 0.05$). They were also a lot less likely to have heart problems ($p < 0.01$). In order to prevent the loss of power, all EOSS-related trajectory calculations were not stratified due to the uneven sex (27.9% male) and ethnic (26.0% white) distribution as well as an overall low sample size in the obese sample.

To better understand and evaluate the diagnostic and differential capabilities of EOSS, prevalence of MetS and Framingham Risk Scores were used for comparative purposes (**Figure 1**). Overall, there were only 0.3% (N=1) of individuals with MetS amongst the obese sample at baseline. This number however increased at a somewhat consistent rate, with MetS being prevalent in almost 50% of all obese individuals by year 20. Unfortunately, due to missing data,

no MetS or Framingham scores could be calculated for the first follow-up at examination year 2. Nevertheless, EOSS demonstrated a similar pattern of risk growth and disease prevalence tendencies to both METS and FRS, especially on an individual stage basis. For example, EOSS stage 3 (which includes CHD incidence) risk growth was very similar in nature to the observed Framingham CHD risk pattern. Likewise, Stage 2 has a pattern similar to the observed METS trend for both the obese and the normal portions of the sample (**Figure 1**).

Trajectory analysis identified 4 distinct clusters of individuals progressing through EOSS stages over 20 years of follow-up (**Figure 2).** Individuals in group 3 had one or more EOSS-related risk factors at baseline that contributed to a steep increase in risk over the next 10 years. Groups 2 and 4 show similar growth patterns with baseline risk factors playing a deciding role in group membership and subsequent development of health risk. About 14% of the individuals (group 4) exhibited high risk factors at baseline that worsened with time, whereas 4% of the individuals (N=54) showed a surprising *decrease* in overall EOSS stage risk. All 4 of the observed trajectories tended to plateau at around age 40 (5^{th} follow-up, year 15 of the study, **Figure 1**).

All comparative analysis were performed against the 4^{th} (most at-risk, most severe) trajectory group. Overall, group 4 was the highest risk group, primarily because it had a much higher proportion of EOSS stage 3 individuals (52.9% $p<0.0001$). In addition to this a greater proportion of black individuals were present in the higher-risk groups 3 and 4 (68.7% and 60.8% respectively, data not shown) Compared to 4^{th} trajectory, individuals in the 1st group were much less likely to be frequent weight cyclers (OR=0.34 95% CI=0.12-0.99). However, this relationship disappeared with subsequent adjustments. Individuals in group 2 were much more

likely to be male (OR=2.16 95% CI=1.47-3.17), be moderate drinkers (OR=1.92 95% CI=1.16-3.19), and follow established protein guidelines (OR=2.44 95% CI=1.41-4.22). They were also much less likely to be black (OR=0.63 95% CI=0.44-0.88), be on a diet at the time of the initial survey (OR=0.39 95% CI=0.25-0.63), have "ever" dieted (OR=0.4 95% CI=0.28-0.56), and to be occasional (OR=0.4 95% CI=0.23-0.69) or frequent (OR=0.2 95% CI=0.11-0.35) weight cyclers. Finally, group 3 individuals were more likely to be male (OR=2.33 95% CI=1.48-3.67), black (OR=1.58 95% CI=1.03-2.44), slightly older (OR=1.06 95% CI=1.003-1.13), and follow established protein guidelines (OR=3.28 95% CI=1.41-7.64) than the high-risk group 4 individuals. These crude ratio analyses are illustrated in **Appendix C, Table 6**. No sex or race interactions were observed.

Table 3 illustrates the final adjusted model of group membership. After adjusting each individual factors for each other, individuals in group 2 were 47% less likely to be black (OR=0.53 95% CI=0.37-0.76), 43% less likely to have a history of dieting (OR=0.57 95% CI=0.37-0.86), 49% less likely to be occasional weight cyclers (OR=0.51 95% CI=0.29-0.9) and 75% less likely to be frequent weight cyclers (OR=0.25 95% CI=0.14-0.45). They were also about two times more likely to follow protein consumption guidelines (OR=2.08 95% CI=1.18-3.65) as compared to the group 4, high-risk individuals. Individuals in group 3 were almost 2.7 times more likely to be male (OR=2.69 95% CI=1.64-4.41), 80% more likely to be black (OR=1.83 95% CI=1.16-2.88), be slightly older [In the 25-30 age group (OR=1.08 95% CI=1.02-1.15)] and about 2.8 times more likely to follow protein guidelines than group 4 individuals.

2.4 Discussion

Results from the current study provide preliminary insight into patterns of obesity-related health risk amongst obese individuals over 20 years of follow-up. In this sample of black and white men and women, weight history, dieting practice and macronutrient consumption have all shown to influence EOSS stage progression, and this knowledge can help clinicians better identify and manage high-risk individuals. Overall, EOSS helped identify critical risk-factors that place individuals in group 4 at a much greater obesity-related risk. More specifically, a higher proportion of these high-risk individuals reported cancer, coronary heart disease (CHD), and severe physical limitations during exercise.

Due to the initial sample collection criteria and study protocols, the vast majority of the participants were very healthy at baseline, and only 10% (of the initial sample) had obesity. Comparatively, data from NHANES shows a 13.6% prevalence of obesity among U.S. adults aged 20-29, in 1988-94 [150] and 36% in 2012.[151] In CARDIA the prevalence of obesity increased from 10% to about 29.6% over the 20 years of the study (**Figure 1**). Individuals who were healthy at the start of the study, have over time, worsened their overall health to a level similar to that of the modern US population.

In general, other studies show that weight increases with age and that SES also plays a role in this relationship, meaning that our observed increase in obesity can, at least, be partially explained through a natural aging mechanism.[152] The finding that a greater proportion of black individuals were present in the higher-risk groups 3 and 4 is also supported by literature on the variation in health risk and obesity patterns amongst different ethnic groups.[153] [154] Recent evidence suggests that compared with white men and women, black individuals have almost 50% higher obesity rates with black women having the highest prevalence of obesity.[155] [156] Education

did not play a role in group membership despite significant baseline differences between normal and obese individuals (X^2=12.64 $p < 0.01$), and could be potentially explained by the fact that only healthy individuals were selected for the study. Due to the longitudinal nature of the study, individuals were able to improve their education over time **(Appendix C, Table 3)**, thus limiting the initial differences; furthermore, evidence on the relationship between obesity and education is conflicting, with some studies showing strong inverse relationships, while others pointing to factors such as SES, income, social inequality, and built environment interactions (proximity to parks, gyms, healthcare facilities, etc.) as the more significant determinants of obesity.[157 158]

Other lifestyle factors also had a significant effect on group memberships. Specifically, group 2 (medium-risk) individuals were less likely to be weight cyclers and to have a history of diets while at the same time being much more likely to follow the established protein consumption guidelines. Similarly, group 3 (high-risk) individuals were also much more likely to follow the protein guidelines. After adjusting for exercise and all of the available dietary factors, most of the unadjusted and/or baseline associations disappeared. Both smoking and physical activity were not found to be significant predictors of group membership, despite evidence of a role in weight gain and BMI trajectories.[9 159] The physical activity definition used may not be optimal, which could be the reason why no effect was observed. Alternatively PA can actually exert influence through the EOSS variables themselves.

Weight cycling played a major role and was one of the variables that stayed constant even after multiple adjustments. In particular, individuals fitting the more stable, low change group 2 (medium-risk) trajectory were less likely to weight cycle than the other groups (**Figure 2**). Knowing the health risk associated with weight cycling, and the overall tendency of weight

cyclers to gain even more weight,[160 161] points to the reason as to why the stable individuals were the least likely to weight cycle. Coincidentally, group 2 (medium-risk) individuals are also the ones who were less likely to report ever having been on a diet, providing a further reason why their EOSS stage gain trajectory remained relatively unchanged over time. While fast food consumption, and adherence to fat and carbohydrate guideline differences were all non significant at baseline and after all subsequent adjustments, adherence to protein consumption guidelines was a very significant predictor of group membership, with both group 2 and 3 showing a much higher adherence rate than the high-risk group 4. This finding is in line with select research that suggests an increase in dietary protein (from 15% to 30% combined with a reduction of fat) can result in a significant weight loss.[162] Other studies show a variable effect, ranging from stable weight-maintenance to a loss of visceral fat with an increased protein-based diet.[163] When taken together, these findings may partially explain why lower-risk individuals were less likely to change EOSS stage and had higher adherence to protein consumption guidelines.

We used the Framingham risk score and MetS criteria to further evaluate the CARDIA sample and to see how it relates to other established risk assessment strategies in the general population. MetS prevalence increased from 0.03 % at baseline to ~19% after 20 years, yielding similar prevalences to other studies (22%).[164] For the obese, MetS prevalence increased from 0.3% - 42%, significantly lower than other national health studies (65%).[165] The Framingham risk score at year 20, when the individuals were roughly 45 years old, was overall lower than the reported risk scores for middle-aged adults in other US based studies. Specifically, one study that analyzed the NHANES III survey discovered that about 72.6% (age-adjusted) of all participants without CHD had a 10-year risk for CHD of <10% and 11.9% with a risk between 10% to

20%.[166] Comparatively, about 66.3% of our CARDIA sample had a CHD risk of <10% and about 18% were between 10% to 20%. Differences in sample inclusion and exclusion criteria, as well observed above average CHD prevalence rates could explain these observed disparities.

2.5 Study Limitations

The CARDIA study is a unique dataset that examines the development of heart disease in very healthy black and white US adults and is thus, not representative of the entire US population. On average, the sample was healthy at baseline, having no cancer and less than 1% diabetes and metabolic syndrome prevalence. Furthermore, because the dataset was not EOSS-tailored, many individuals did not have complete data for all the necessary variables and in some cases had to be excluded due to vital missing data (i.e. BMI). The EOSS definition used had to be modified in order to account for insufficient or unavailable variables, and may therefore represent and over or underestimate of EOSS stage. This was particularly noticeable in year 2 of the study where a much higher proportion of individuals were classified as stage 0 due to multiple missing metabolic variables (**Figure 2**). Furthermore, to reduce power loss and prevent over-stratification, different types of the same disorder/condition were combined under 1 broad heading. For example, all cancer sites were combined in one broad category. All psychological conditions as well as all other health problems (that were not included in any of the other categories) were also grouped under the corresponding broad definitions, and no assumptions were made about the effect that each had on specific EOSS stage placement or trajectory memberships.

2.6 Conclusion

Trajectory analysis has proven to be a very useful tool for testing the effectiveness of EOSS and for overall identification of obesity-related patterns and risk factors. Despite its theoretical nature, trajectory analysis was useful at predicting group differences in patterns of obesity-related health risk. Trajectory modelling, combined with an EOSS-based approach can help identify individuals at risk and serve as a visual guide to treatment formation and implementation. Future research is necessary to evaluate the clinical aspects of EOSS, in an effort to optimize obesity-related health risk and our understanding of risk profiles across trajectory groups.

2.7 Appendix (Paper)

Table 1: Edmonton Obesity Staging System breakdown		
Stage	Stage description (Sharma & Kushner 2009)	Modified definition*
0	No apparent obesity-related risk factors, medical, psychopathological & functional limitations (no impairment of well being).	No EOSS-relevant reported factors
1	- Presence of obesity-related subclinical risk factors (borderline hypertension, impaired fasting glucose, elevated liver enzymes, etc.) - Mild Physical Symptoms (dyspnea on moderate exertion, occasional aches and pains, fatigue, etc.) - Mild obesity-related psychological symptoms and/or mild impairment of well being.	- BP > 120/80 and < 139/89 mm HG - Fasting Glucose ≥ 100 and < 125 mg/100 ml - Cholesterol ≥ 200 and < 240 mg/100 ml - Triglycerides ≥ 150 and < 200 mg/100 ml - HDL < 60 mg/100 ml (Men), < 60 mg/100 ml (Women) - Have being diagnosed or currently suffering from ANY mental disorder. - Have medical problems that affect exercise ability to a minor extent (1/5 or 2/5)
2	- Presence of established obesity-related comorbidities requiring medical intervention (HTN, Type 2 Diabetes, sleep apnea, osteoarthritis, reflux diseases, polyscystic ovary syndrome, etc.) - Moderate obesity-related psychological symptoms (depression, eating disorder, etc.) - Moderate functional limitations in daily activities impacting quality of life	- Diagnosed hypertension or taking hypertensive medication - BP > 140/90 mm HG - Fasting Glucose ≥ 125 mg/100 ml - Diagnosed hypercholesterolemia or taking cholesterol lowering medication - Cholesterol ≥ 240 mg/100 ml - Diagnosed hypertriglyceridemia - Triglycerides ≥ 200 mg/100 ml - HDL < 40 mg/100 ml (Men), < 50 mg/100 ml (Women) - Being diagnosed AND currently suffering from mental disorders. - Additional medical problems (arthritis, gall bladder disease, ovary disease, etc.) - Have medical problems that affect exercise ability to a significant extent (3/5 or 4/5) - Diagnosed Diabetes
3	- Significant obesity-related end-organ damage (heart failure, myocardial infarction, diabetic complications) - Significant psychopathology (major depression, suicide ideation) - Significant functional impairment (unable to work, perform tasks), functional limitations or impairment of well being.	- Having being diagnosed with cancer - Having being diagnosed with coronary heart disease (CHD) - Have medical problems that affect exercise ability to a major extent (5/5)
4	- Severe (potential end-stage) disabilities from obesity-related comorbidities - Severe psychopathology (disabling) - Severe functional limitations or impairment of well being.	This stage was not examined as no relevant factors were available or reported
* Based on available CARDIA data		

Table 2: Distribution and significance of trajectory groups at baseline				
Continuous Variable Name	Group 1: No-risk (N=6)	Group 2: Medium Risk (N=227)	Group 3: High Risk (N=93)	Group 4: Chronic Risk (N=39)
Age (years) *	24.33 (4.46)	25.07 (3.62)	26.46 (3.39)	24.10 (3.86)
Height (cm)	167.33 (4.67)	167.49 (9.34)	168.34 (9.51)	165.08 (9.43)
Weight (lbs) *	225.23 (45.36)	213.63 (31.02)	213.46 (30.32)	198.96 (23.7)
WC (cm)	100.04 (14.19)	95.67 (9.86)	94.60 (8.85)	91.91 (8.39)
BMI (KG/m^2)	36.31 (5.50)	34.64 (4.22)	34.31 (4.44)	33.26 (2.72)
SBP (mm Hg) *	109.0 (4.69)	113.96 (10.74)	113.0 (9.54)	108.67 (10.19)
DBP (mm Hg) *	64.0 (3.85)	71.53 (8.59)	69.22 (8.58)	68.08 (7.70)
Calories (kcal)	1989.5 (781.9)	2657.5 (1362.7)	2856.2 (1556)	2297.3 (971.26)
Glucose (mg/dL)	87.83 (4.67)	83.6 (8.42)	84.44 (7.26)	83.87 (6.35)
TG1 (mg/dL)	69.67 (29.23)	80.74 (36.85)	73.22 (39.63)	82.26 (44.23)
HDL (mg/dL) +	51.83 (13.66)	44.82 (9.91)	52.3 (10.46)	47.74 (9.83)
Intensity (Exercise Units)	292.17 (240.9)	319.9 (253.0)	338.12 (262.7)	310.85 (204.3)
Categorical Variable Name				
Male *	0 (0%)	63 (27.8%)	33 (35.5%)	6 (15.4%)
Female	6 (100%)	164 (72.2%)	60 (64.5%)	33 (84.6%)
Black	4 (66.7%)	166 (73.1%)	74 (79.6%)	26 (66.7%)
White	2 (33.3%)	61 (26.9%)	19 (20.4%)	13 (33.3%)
No Highschool Education	0 (0%)	23 (10.3%)	6 (6.7%)	3 (7.7%)
Highschool	5 (83.3%)	150 (67.3%)	53 (59.6%)	26 (66.7%)
College or University	1 (16.7%)	50 (22.4%)	30 (33.7%)	10 (25.6%)
No Drinking *	4 (66.7%)	181 (79.7%)	68 (73.1%)	35 (89.7%)
Moderate	2 (33.3%)	38 (16.7%)	18 (19.4%)	1 (2.6%)
Heavy	0 (0%)	8 (3.6%)	7 (7.5%)	3 (7.7%)
Non Smoker	3 (50%)	128 (56.9%)	53 (57.6%)	20 (54.1%)
Former	0 (0%)	28 (12.4%)	6 (6.5%)	5 (13.5%)
On a Diet	5 (83.3)	175 (84.95%)	70 (80.5%)	32 (86.5%)
Not on a Diet	1 (16.7)	31 (15.05%)	17 (19.5)	5 (13.5%)
Ever Diet	1 (16.7)	84 (37%)	32 (34.4%)	13 (33.3%)
Never Diet	5 (83.3)	143 (63%)	61 (65.6%)	26 (66.7%)
Pre Hypertension	6 (100%)	207 (91.2%)	89 (95.7%)	39 (100%)
Hypertension	0 (0%)	17 (7.5%)	4 (4.3%)	0 (0%)
No Hypertension	0 (0%)	3 (1.3%)	0 (0%)	0 (0%)
Pre Hypercholesterolemia	4 (66.7%)	160 (70.5%)	66 (71%)	24 (61.5%)
Hypercholesterolemia	2 (33.3%)	52 (22.9%)	27 (29%)	11 (28.2%)
No Hypercholesterolemia	0 (0%)	15 (6.6%)	0 (0%)	4 (10.3%)

Pre Hyperglycemia	6 (100%)	220 (96.9%)	90 (96.8%)	39 (100%)
Hyperglycemia	0 (0%)	6 (2.6%)	3 (3.2%)	0 (0%)
No Hyperglycemia	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)
Pre-levels of Elevated TG	6 (100%)	221 (97.3%)	88 (94.6%)	38 (97.4%)
Elevated TG	0 (0%)	4 (1.8%)	3 (3.2%)	0 (0%)
Not Elevated TG	0 (0%)	2 (0.9%)	2 (2.2%)	1 (2.6%)
Pre-levels of Reduced HDL +	1(16.7%)	13 (5.7%)	24 (25.8%)	6 (15.4%)
Reduced HDL	3 (50%)	88 (38.8%)	48 (51.6%)	12 (30.8%)
Not Reduced HDL	2 (33.3%)	126 (55.5%)	21 (22.6%)	21 (53.8%)
Heart Problems (CHD) +	0 (0%)	5 (2.3%)	0 (0%)	7 (18.4%)
No Heart Problems	6 (100%)	217 (97.7%)	92 (100%)	31 (81.6%)
Diabetes	1 (16.7%)	5 (2.3%)	0 (0%)	1 (2.6%)
No Diabetes	5 (83.3%)	216 (97.7%)	92 (100%)	37 (97.4%)
Mental Disorders	1 (16.7%)	20 (8.9%)	5 (5.6%)	7 (17.95%)
No Mental Disorders	5 (83.3%)	204 (91.1%)	85 (94.4%)	32 (82.05%)
Other Health Problems	1 (16.7%)	22 (9.8%)	6 (6.6%)	0 (0%)
No Other Health Problems	5 (83.3%)	202 (90.2%)	85 (93.4%)	39 (100%)
Consumes Fastfood	2 (33.3%)	71 (31.3%)	28 (30.1%)	12 (30.8%)
Does Not Consume Fastfood	4 (66.7%)	156 (68.7%)	65 (69.9%)	27 (69.2%)
Frequent Weight Cyclers	3 (50%)	96 (43.6%)	34 (37.8%)	16 (41.0%)
Occasional Weight Cyclers	2 (33.3%)	118 (53.7%)	49 (54.4%)	23 (59%)
Not a Weight Cycler	1(16.7%)	6 (2.7%)	7 (7.8%)	0 (0%)
Meets Carb. Guidelines	3 (50%)	139 (61.2%)	44 (47.3%)	25 (64.1%)
Does Not Meet Carb. Guide.	3 (50%)	88 (38.8%)	49 (52.7%)	14 (35.9%)
Meets Protein Guidelines	5 (83.3%)	218 (96%)	87 (93.6%)	36 (92.3%)
Does Not Meet Protein Guide.	1 (16.7%)	9 (4%)	6 (6.4%)	3 (7.7%)
Meets Fat Guidelines	3 (50%)	83 (35.6%)	26(28%)	11 (28.2%)
Does Not Meet Fat Guide.	3 (50%)	144 (63.4%)	67 (72%)	28 (71.8%)
Low Exercise Intensity	2(33.3%)	101 (44.5%)	41 (44.1%)	12 (30.8%)
Moderate Exercise Intensity	2 (33.3%)	66 (29.1%)	30 (32.2%)	16 (41.0%)
High Exercise Intensity	2 (33.3%)	60 (26.4%)	22 (23.7%)	11 (28.2%)

ANOVA used for categorical variables; FISHER's Exact Test used for continuous

* Significant at $p<0.05$

+ Significant at $p<0.001$

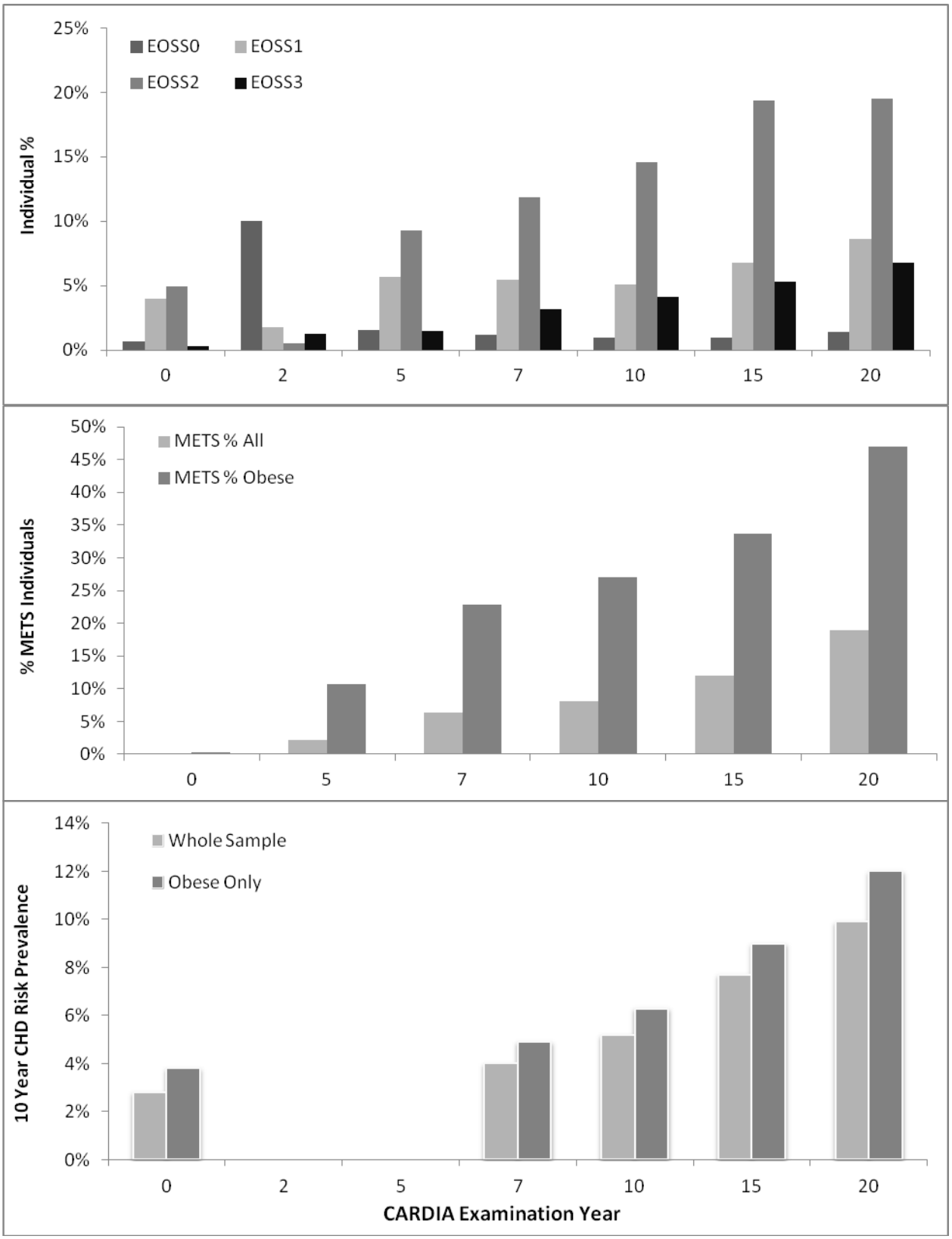


Figure 1: EOSS, METS & Framingham Risk Scales of Obese Individuals

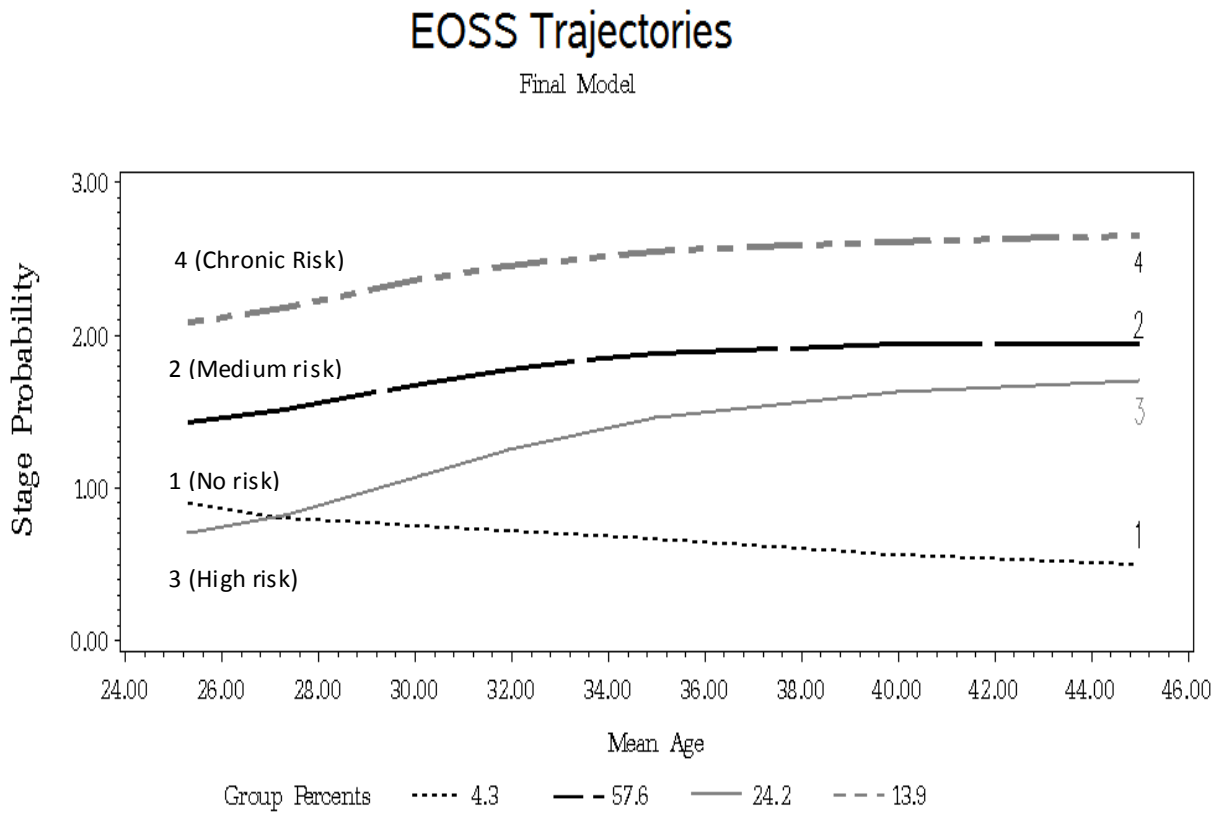


Figure 2: EOSS Trajectories CARDIA study

Table 3: Final Adjusted model of EOSS group membership

Variable	Group	Adjusted OR (95% CI)
Sex (Male vs. Female)	1	0.64 (0.29-1.53)
	2	1.48 (0.97-2.24)[+]
	3	2.69 (1.64 – 4.41)*
Race (Black vs. White)	1	1.84 (0.85-3.96)
	2	0.53 (0.37-0.76)*
	3	1.83 (1.16-2.88)*
Age	1	1.01 (0.92-1.11)
	2	1.01 (0.97-1.06)
	3	1.08 (1.02-1.15)*
Drinking (Moderate vs. Non Drinker)	2	1.33 (0.77-2.29)[+]
Currently On Diet	1	0.71 (0.24-2.12)
	2	0.64 (0.39-1.07)[+]
	3	1.3 (0.71-2.37)
Ever Diet	1	1.12 (0.51-2.45)
	2	0.57 (0.37-0.86)*
	3	1.57 (0.93-2.64)
Follows protein consumption guidelines	1	0.99 (0.36-2.74)
	2	2.08 (1.18-3.65)*
	3	2.79 (1.18-6.58)*
Weight Cycling (occasional vs. non)	1	0.65 (0.25-1.69)
	2	0.51 (0.29-0.9)*
	3	1.18 (0.58-2.4)
Weight Cycling (frequent vs. non)	1	0.35 (0.12-1.07)[+]
	2	0.25 (0.14-0.45)*
	3	0.76 (0.36-1.62)

* OR significant at $p < 0.05$.

[+] OR was significant at crude level before adjustments. Significance was lost after the variables were adjusted for each other.

3. Extended Discussion

3.1 EOSS Trajectory Discussion

This study has demonstrated how obesity-related health risk develops and identified individuals who might be particularly at risk. Trajectory modelling was useful in the analysis of obese individuals in CARDIA and has shown to be a useful way of estimating obesity-related risk. Combined with EOSS, trajectory modelling has helped identify specific factors that were prevalent in the different observed trajectory groups.

Proc Traj analysis identified 4 distinct groups of individuals progressing through EOSS stages over time. It is assumed that every subject in each group follows the same trajectory.[167] Multiple different groups were examined before selecting the final model. Using previous research and guidelines set out by Daniel S. Nagin (2010),[144] and after considering the BIC values, model complexity and clinical relevance, we selected a 4-group model as the most relevant to our EOSS and obesity examination. It showed the smallest available BIC number, was the most complex and had enough individuals in each group to perform meaningful subsequent analysis.

Generally, the stable "no-change" group is often the largest in the sample. However, due to the established global obesity trends and the knowledge that there is a constant age-related increase in body weight, we did not have a constant, "flat-line" trajectory group. That being said, our largest observed trajectory was the one that had the smallest probability of EOSS stage change.

Figure 2 in the **EOSS Manuscript** shows the final 4-group model with EOSS stage probability over the mean age of the participants. Each line indicates the predicted trajectory

derived from the estimated regression coefficients. At baseline, obese individuals had a much poorer health profile, were on average about 40% heavier and were statistically different from all others on all continuous variables ($p < 0.05$). In addition to this, they were primarily black, female, were less likely be currently on a diet or have a history of dieting, had reduced HDL counts, higher occurrence of diabetes and pre-hypercholesterolemia, were more likely to be non-drinkers and only have a high school education, as compared to the non-obese population. They also engaged less in physical activity and had a higher percentage of frequent weight cyclers (data not shown, $p < 0.001$). Multinomial logistic regression was used to predict specific group membership traits of the whole sample. Detailed univariate statistical results are presented in **Appendix C, Table 6**.

Subjects in group 2, which represented about 57.6% of the population, had the smallest probability of moving to another EOSS stage. On the other hand, individuals in group 3 (24.2% of the population) had the highest likelihood of stage change, while group 4 individuals (13.9% of the population) were the highest at-risk group. Finally individuals in group 1, which represented only 4.3% (N=54) of the population, showed a constant decrease in overall EOSS risk. However, our final adjusted model was unable to identify any key factors to differentiate this group. Although the unadjusted model did show that individuals in this group were about 66% less likely to be frequent weight cyclers, this effect was no longer significant after multivariable adjustment (**Manuscript Appendix, Table 3**).

3.2 EOSS Stage Analysis

Proc Traj analysis was completed for the whole CARDIA baseline obese population (N=365). A censored normal model was used for the maximum likelihood estimates. Each

individual's posterior group probability was significant at $p<0.0001$. Stage 0 individuals could be characterized as the 'healthy but obese' sample. They have a BMI greater than 30 kg/m^2 but at the same time have none of the risk factors associated with higher EOSS stages, metabolic syndrome or any other health problems, diseases, or co-morbidities. Individuals in Stage 0 remained a consistent minority (under < 5%) with only exam year 2 being the obvious exception (**Appendix C**, **Figure 4**). Because lipid information was not available, we cannot exclude bias to the null in these analyses, as the lack of lipid information in CARDIA may have underestimated EOSS stage in some groups.

To further understand the distribution (and accumulation) of risk factors over time, **Appendix C**, **Figures 5-7** provides a breakdown of each EOSS stage at baseline, exam 5 (year 10), and exam 7 (year 20). Please refer to **Appendix A.3** for a detailed overview of each EOSS variable used in the modified definition.

Reduced HDL seems to be a staple of EOSS stages 1 and 2 across all years of the study. Studies show that obesity is universally related to dyslipidemia which is mainly represented by a decrease in HDL-C levels.[168] This is also true in the general population, where the wide and constantly increasing prevalence of low HDL-C has led to the development of many specific therapies to combat this threat in an effort to reduce or prevent heart disease and to some extent reduce obesity.[197] As expected, high cholesterol is another condition that seems to be prevalent in EOSS stage 1 individuals across the study (App. B, figures 5-7). Obesity is a known risk factor for high cholesterol and both are subsequently associated with an increased risk of excess mortality.[169] Compared with baseline, more individuals in year 20 stage 1 had pre-hypertension, high blood glucose levels and high TG levels. They also had a lower proportion of pre-HDL individuals and lower mental disorders (**Appendix C, Table 3**).

Beyond the lipid limitations noted above, we did not have enough detailed information in CARDIA to classify stage 3 mental-psychological criteria (e.g. major depression syndrome, severe anxiety/panic attacks or psychiatric conditions such as schizophrenia). Recent research into the issue of mental health and disability has revealed that about 26% of the adult American population suffer from a diagnosable mental disorder, while 6% of the population suffers from a serious mental illness.[170] What is more interesting, especially from an EOSS perspective, is that mental disorders are the leading cause of disability in the U.S. and Canada.[171] The co-morbid nature of most of these disorders greatly affects health and the overall burden of disease, especially in obese individuals. More extensive research is needed on this topic.

3.3 Baseline sample generalizability

Overall, the initial sample was much healthier than the average American at baseline. To this end, we compared some of the observed rates with those found in NHANES III (1989-1994) dataset. This dataset was chosen because it was the closest (time-wise) large-scale survey that was easily accessible. The final CARDIA sample had 0 individuals with cancer (vs 4% reported in NHANES).[172] Additionally, CARDIA participants were much less likely to have hypertension (1.6% vs. 27%), high cholesterol (5% vs. 16%) and diabetes (0.06% vs. 43%), but be more likely to weight cycle (73% vs. 27%) and to be more active than average (68% vs. 30%). There was little to no difference in drinking (28% vs. 25%) and smoking habits (25% vs. 25% current, 13% vs. 25% former). Compared to other national samples of the time, smoking was less prevalent in the CARDIA sample.[134] The metabolic syndrome (MetS) prevalence in NHANES was about 6.7% amongst 20-29 year olds,[173] as compared to 0.05% in CARDIA, further highlighting that the trajectory results depict a transition (and development of health risk) from a "healthy" cohort. Please see Appendix A.2 for supplemental baseline vs. last follow-up year (Year 20) comparison.

3.4 Comparison to similar literature

This is the first study looking at EOSS-related trajectory modelling analysis. There have only been three EOSS studies to date that address weight loss, bariatric surgery and mortality risk. The exploratory nature of this study, combined with CARDIA's initial selection protocols and EOSS specifics, make it difficult to compare it to other literature or to generalize the findings. We can however, compare the general statistical methodology and the obesity related results. For instance, studies looking at BMI and weight trajectories have successfully used 4-group models to identify meaningful trajectories of childhood obesity.[174] Another study looking at leisure time physical activity in a 22-year longitudinal study has also used a 4-group model to link social factors with patterns of physical activity.[175] Similar in design to our study, others have been able to use Proc Traj in tandem with multivariable logistic regression to distinguish at-risk children, using pre- and early post-natal risk factors.[176] In general, most studies dealing with any type of obesity-related trajectory tend to select either 3-or 4-group models.[177] [178] [179] Although some studies have selected a greater number of trajectories, this tends to occur only when there is a clear outcome (i.e. mortality) or a select number of specific variables (i.e. insulin resistance).[180] Further, our study confirms that individuals develop (and experience) obesity in many different ways, as a major finding of this study was the large variation in obesity trajectories. Additionally, this study presented a complex model, incorporating many factors not previously used together to study obesity.

3.5 BMI Trajectory Example

It is not clear whether EOSS patterns are different from general weight-gain patterns in the CARDIA study. Therefore we conducted a similar 4-group trajectory modelling analysis of

categorical BMI trajectories (**Appendix C, Figure 8)**. Participants in the largest group (group 1), had the lowest risk of increasing their BMI over the course of the study. Individuals in groups 2 and 3 were more likely to gain weight (i.e. increase in BMI category), with trajectory 3 being the highest-risk group. Individuals who were obese at baseline (group 4) stayed obese, and their overall trajectory was very similar to that of group 1. More in-depth results can be found in Appendix A.4.

Overall, it seems that being white, having a history of smoking (whether current or former), having at least a college-level education and moderate-to-high exercise level was found to be protective of BMI increase. Low BMI individuals were more likely to maintain their weight if they did a lot of high intensity exercises, did not diet or weight cycle, did not consume fast food, and attained a higher level of education. The observed BMI trends were similar to the ones identified in the EOSS study. While the BMI categorical testing identified physical activity and education as important factors in the development of obesity, protein guideline adherence was not significantly associated with group membership (**Appendix C, Table 7**). Furthermore, the identified model had a lower BIC value and a poorer overall model fit, suggesting no distinct (or dominant) trajectories. A subsequent continuous BMI trajectory model was examined, but again, the model fit was inferior to both categorical BMI and EOSS trajectory analyses (**Appendix C, Figure 9**).

3.6 Study Limitations

As with any secondary analysis of this type, limitations with available variables, EOSS definitions and trajectory analysis must be discussed. Because this study makes use of existing data, certain information or specific questions on functional limitations and psychological

impairment were unavailable, resulting in the use of a modified EOSS definition. Further, the equal weighting of all co-morbid conditions in EOSS are weighted equally. Finally, perhaps the main limitation of EOSS is that individuals that fail to meet the current anthropometric cut-offs for obesity would not be considered for the system. These considerations are necessary due to the fact that the health risk associated with obesity starts earlier in Asian (and some other) ethnicities.[181] It is also important to note that mortality studies point out the fact that physical activity and other lifestyle factors can reduce the overall health risk and improve the health profile of an individual independent of BMI and that EOSS is able to successfully demonstrate this.[182] [183] Please refer to Appendix A.5 for an in-depth analysis of other EOSS, CARDIA and Trajectory-modelling limitations.

3.7 Future Research Directions

Trajectory modelling analysis is a useful tool for exploring weight-change patterns and other obesity-related health risks. It allowed us to look at time varying covariates and to study repeated measures over a prolonged period of time. Given the multifactorial nature of obesity, no single factor is responsible for its global rise. As a result, treatment is challenging, but commonly includes interventions targeting simple motivation, diets and exercise to more complex behaviour modification strategies, weight loss drugs, and in some cases, surgery.[184] The ability of Proc Traj to model multiple groups of the sample, was useful in identifying specific EOSS 'trends', and can be used in the future to do other health-related analysis. It is hoped that this research can help further establish EOSS as an effective, individualized obesity risk-identification tool and aid future research on this topic.

Future studies need to focus on creating a detailed EOSS-tailored dataset to better evaluate all obesity-related measures. Running a trajectory modelling analysis on a full-variable dataset would have most likely yielded a slightly different, but more representative result. It is unrealistic to get a dataset or conduct a clinical study simply for testing EOSS, but this could be done in a research setting by garnering existing chart data. In order to optimize the management of obesity-related health from a population perspective, further research is necessary to evaluate how each individual EOSS component (physical/functional, medical and mental) contributes to the overall health risk.

Appendix A: Additional Discussion Points

A.1 Summary of Observed Baseline Trends

Despite the initial balanced selection of individuals by sex, age, race and education, there were nevertheless significant sex and race-based baseline differences for the whole sample (**Appendix C, Table 1**). Most of the sex-based differences are understandable (i.e. men are in heavier and taller than women) and are in fact expected due to differential guidelines (i.e. WC, TG differences). However the race-based differences and the fact that they were significant for all the measured continuous variables are interesting and somewhat unexpected. Consistent with previous literature, black women had a much higher BMI than white women;[185] while it's true that group-based differences may exist in the body composition of blacks and whites, it does not explain the observed major differences in caloric consumption and exercise intensity.[186] White individuals also consumed fewer calories and had overall higher exercise intensity levels. This finding, however, is very similar to another study that concluded that in order to reduce their bodyweight below that of the average American, black Americans would need to be more restrictive in their caloric intake and be even more physically active.[187] It is important to note, however, that both caloric and exercise intensity differences were not significant in the obese-only portion of the baseline sample (**Appendix C, Table 2**). In fact, outside of expected divergences in weight and BMI, the only significant differences were for HDL and TG levels. These findings are essentially identical to what was found in a recent MetS study, suggesting that blacks are less likely than whites to have either elevated triglyceride or low high-density lipoprotein levels.[188] Once again, it seems like an ethnic-specific criteria may be necessary in order for better identification of high-risk black individuals.

Besides race and sex, significant differences were found for education (obese less likely to go to college), drinking habits (obese less likely to drink), diet patterns (obese were much less likely to be on a diet or to have ever dieted), hypercholesterolemia, reduced HDL, CHD, diabetes, weight cycling and exercise frequency (**Appendix C**, **Table 4**). Not surprisingly, obese individuals were much more likely to weight cycle, and to exercise less than the healthy weight / overweight sample. Unexpectedly however, obese individuals were less likely to have CHD. The reasons for this are not clear since obesity is known to substantially increase the risk of developing CHD.[189] [190]

Overall, the whole CARDIA population followed a standard pattern of growth over the 20 years of the study. As age increased, so did the BMI, WC, SBP, glucose, and triglyceride levels (**Appendix C, Table 5**). This is not unexpected, as many studies show that BMI, WC and systolic blood pressure increases with age.[191] Plasma glucose levels and triglyceride levels are also known to increase with age, with caloric-restriction being the most effective anti-aging therapy.[192] [193] [194] Exercise levels varied, but on average have decreased by about 20% from baseline. Studies show that the overall frequency of exercising at least once a week and the likelihood of continuing established exercise habits decline with age.[195]

A.2 Baseline vs. Year 20 Comparison

Overall, as expected, the number of obese individuals increased throughout the study years. The initial sample was much healthier than the average American population of the time with only about 10% of the sample being obese (**Appendix C, Table 3**). However, 20 years later, the obesity rates of the sample (29.6%) were much closer to the current American obesity statistics (35.7%)[196]. Prevalence of smoking, alcohol consumption and diet history remained relatively unchanged (data not shown). Fast food consumption rates varied throughout the years

but in general, they were lower than baseline and this reflects the observed age-related dieting tendencies in the general population.[197] [198] **Appendix C**, **Figure 1** shows the variables that had the largest change between baseline and year 20. Of particular interest is the fact that while exercise levels have gone down almost 50%, the number of individuals currently on a diet increased four-fold. This raises the much-contested issue of whether exercise or diet is more important in individual weight management and global obesity control. Individual factors, such as current conditions (i.e. heart problems, diabetes, physical injuries), all play a major role in any weight management solutions. Some studies suggest that increased energy intake combined with a reduction in physical activity are not the only reasons behind the obesity epidemic.[199] Others suggest that a weight loss diet is not enough, and that maintenance of that weight loss also requires regular exercise.[200] Exercise studies emphasize the fact that physical activity has beneficial health effects irrespective of weight loss.[201] Others, like the recently completed Look AHEAD trial, find that intensive efforts to lose weight by eating less and exercising more didn't provide any more protection against heart disease in a diabetic population.[202] Most studies, however, advocate that a combination of weight loss and exercise provides greater improvement in physical function than either intervention alone.[203] [204]

An overall increase in the number of EOSS Stage 2 and Stage 3 individuals can be in part attributed to an overall increase in all other medical conditions and disorders. Cancer, diabetes, CHD, hypertension, hypercholesterolemia, hyperglycemia, and triglyceride levels all increased significantly by year 20 of the study (**Appendix C, Figure 2**). HDL levels also decreased, with more than 40% of the remaining sample not meeting the accepted HDL cut-offs (**Appendix C, Table 3**). However, the CARDIA sample is still much healthier than the average population. **Appendix C**, **Figure 3** illustrates the comparison between the CARDIA sample and the general

US population on the above-mentioned health conditions and disorders. Data for the comparison was drawn from the Centres for Disease Control and Prevention (CDC)[205] [206], the American Diabetes Association[207], and the American Cancer Society[208]. Most of the available data is fairly recent, published within the past 5 years. Only the data for individuals ages 40-59 or 45-54 was used in the comparison to ensure that they are similar to the available year 20 CARDIA sample that was on average 45 years old. Surprisingly CARDIA had a slightly higher cancer and CHD prevalence rate and a much higher lowered-HDL rate (**Appendix C, Figure 3**). The differences in cancer rates can be due to the fact that the available population rates are not age-group specific and might underestimate the cancer prevalence in the 40-50 year olds. It is speculated that this number would be higher in this age group due to an increased prevalence of breast cancers in women.[209] The reasons behind the HDL and CHD differences are unclear. There are many reasons why individuals might have a lowered HDL including smoking, being overweight, lack of physical activity, poor dietary choices, genetics, medical conditions such as diabetes, and possibly some medications.[210] [211] The exact cause is difficult to pinpoint, what is known nonetheless is that low HDL cholesterol levels increase the risk of CHD.[212] [213] This can at least partially explain our observed finding but unfortunately, the reasons behind these particular trends in our dataset remain uncertain.

A.3 EOSS Variables Breakdown

Due to missing variables, a modified EOSS definition had to be used. This portion of the appendix will explain and give a detailed breakdown of each individual EOSS stage components. It is important to note, that due to multiple unavailable factors (terminal illnesses, cancer-specific outcomes, sever psychiatric-psychological conditions, etc.) we were unable to designate or examine EOSS stage 4. It is quite possible that there were, in fact, stage 4 individuals in this

dataset, but they were missed or excluded from the analysis. However the lack of severe disease information, combined with the terminal, end-stage criteria for Stage 4, could be an indication that there were no such cases in CARDIA or that they were possibly excluded from the survey by the chief investigators. The relatively low cancer frequency throughout the early stages of the study and the overall superior baseline health of the sample reduce the probability of possible palliative (stage 4) subjects.

Many variables used in the EOSS definition were combined in order to conserve power, and to avoid over-stratification. In particular this was done to CHD, cancer, mental disorders and the 'other health problems/diseases' variable. The initial CARDIA CHD examination question asked individuals whether they had any heart problem. The participants were not locked to choose specific options and rather reported all possible heart-related conditions. These included arrhythmias, congenital heart defects/disorders, heart failure, heart valve disease, heart attacks, various arterial diseases and CHD itself. All these conditions were combined under one CHD 'umbrella' term. The nature and number of different conditions reported prevented their meaningful categorization and this was avoided altogether to ensure a reasonable sample size.

Similarly cancer was a very diverse variable, with over 10 different reported cancer sub-types. To preserve power and to avoid over-stratification, all cancers were combined into one variable. Because of the low prevalence of cancer (0% at baseline, 4.7% at year 20), the combined variable was kept for the analysis, ignoring cancer-specific differences and their epidemiology. This is an obvious limitation of our study, especially knowing that there are a multitude of different cancers, each with their own, often unique treatment options.[214]

In addition, no distinction was made between the different mental, emotional, nervous and psychiatric disorders with all of the individual incidences combined into a 'mental disorders' variable. This was done because of the numerous response categories and the innate difficulty of ranking the severity of psychological disorders without knowing all the specifics (i.e. how it affects the individual, stage of condition, whether medications are helping, etc.). Deciding whether something like an anxiety disorder should be ranked higher (EOSS-stage wise) than a depressive disorder is difficult, ambiguous and error-prone. The *Diagnostic and Statistical Manual of Mental Disorders (DSM)* is the best available tool used to diagnose and classify mental and psychiatric disorders.[215] However, it does not attempt to rank the disorders in any way. Each disorder has varying levels of severity and attempting to rank them is very difficult. Standardizing such as classification system would be close to impossible.

We used the combined mental disorder variable, together with the 'other health problems/diseases' variable for the psychological components of EOSS. The reasons for this are two-fold. Many of the other health problems inadvertently included some psychological conditions (panic attacks). It is possible that the participants did not want to report these conditions as mental health issues, and as a result considered them to be part of the 'other problems' question. Second, the known co-morbid nature of some psychological disorders can help to possibly identify more individuals (improve sensitivity) who were missed by the mental disorders question.[216 217]

A.3.1 *Physical activity calculations*

Physical activity was calculated by the CARDIA researchers by adding a weighted sum of the number of months for each activity and the number of hours per week. The intensity level

of each activity was represented as the number of kilocalories believed to be spent in one minute of activity by an average male (70 kg). Running and vigorous racket sports, and other team sports (skiing, football, basketball, etc) were considered to be the most intense, followed by biking, swimming, vigorous exercise/dancing, shoveling/weight-lifting, carrying heavy objects/digging, vigorous team sports, non-strenuous sports (softball, volleyball, ping-pong), home exercise, gardening, home maintenance, and finally bowling/golf as the least intensive. Moderate intensity sports are combined with the high intensity sport to produce the Total intensity variable that was used for this analysis. Individuals were categorized into 3 groups, taking into account sex-based physical activity differences. Information on physical/functional limitations was only available starting from exam 4 (year 7). Individuals were asked whether or not they had medical problems that affect their exercise ability (discomfort, pain, breathing problems, etc.). Those that reported problems were subsequently asked to rate (on 5 point scale) how much these medical problems affected or interfered with their exercise ability. Using these 2 variables together, we have created the *problems exercising* variable that served as our classification for the functional limitations portion of EOSS.

A.3.2 *Smoking and Alcohol calculations*

Smoking and drinking preferences were self-reported at each exam follow-up. Participants were asked about their cigarette, cigar and pipe smoking practices, but these different preferences were not looked at separately and were instead combined into one smoking variable. Individuals were reported to be non-, former or current smokers. Similarly, individuals were designated as non-, moderate and heavy drinkers, based on their reported alcohol consumption practices. The CARDIA researchers created a formula to calculate alcohol consumption and it was as follows: total alcohol consumed = (#of beer drinks per week/7*14.2)

+ (#of wine drinks per week/7*21.3) + (#of liquor drinks per week/7*23.7). Drinks were then converted into millilitres of alcohol per day. Individuals that reported drinking less than 13.7 ml/day were considered non-drinkers, those that drank between 13.7 – 41.1 ml were moderate drinkers and everyone else above 41.1 were designated heavy drinkers. These cut-offs were similar to what was used in other alcohol-research studies.[218] [219] Similar to what was done by Kuk et al. (2011), most of the metabolic variables used in EOSS were divided into 3 levels. Blood pressure (SBP and DBP), cholesterol, glucose, HDL and triglyceride levels in individuals were defined as being in the normal range, close to established cut-offs (i.e. pre-hypertension), and above the cut-offs (i.e. hypertension). These were the so-called obesity-related subclinical risk factors which serve as good predictors for overall obesity risk.

A.4 Detailed BMI Trajectory Example Results

Appendix C, Figure 8 shows the results of a 4-group trajectory model of BMI *categories*. Unlike the EOSS results, the groups were more balanced, but at the same time showed fairly similar trajectories. Overall, there were 1387 individuals in group 1, 957 in group 2, 722 in group 3, and 624 in group 4. These trajectories can be described as "No-risk minimal weight gain", "Medium-risk moderate weight gain", "High-risk high weight gain" and "Chronic-risk stable weight" for groups 1, 2, 3 and 4 respectively. Unlike what was observed with EOSS trajectories, BMI category trajectories used the whole population and the group percentages were identical to the actual observed group membership rates.

Compared to group 4, group 1 ("no-risk") individuals were more likely to be slightly older (OR=1.06 95% CI =1.03-1.10), have at least a college education (OR=2.39 95% CI=1.43-4.00) be either current (OR=1.58 95% CI=1.21-2.08) or former (OR=1.94 95% CI=1.32-2.84) smokers and exercise at higher intensity (OR=1.64 95% CI=1.23-2.20). They were also much

less likely to be male (OR=0.48 95% CI=0.37-0.63), black (OR=0.16 95% CI=0.12-0.21), be on a diet (OR=0.34 95% CI=0.22-0.51) or have ever dieted before (OR=0.17 95% CI=0.13-0.23), eat fast food (OR=0.62 95% CI=0.48-0.80) or have a history of any type of weight cycling **(Appendix C, Table 7**). Group 2 individuals had normal level BMI at baseline and in general, became overweight by the last examination. Compared to the obese, group 4 trajectory, group 2 individuals were more likely to be older (OR=1.08 95% CI =1.04-1.12), have at least a college education (OR=2.08 95% CI=1.22-3.54), be former smokers (OR=1.6 95% CI=1.09-2.35), and exercise at higher intensity (OR=1.39 95% CI=1.04-1.86). Similarly to group 1, they were 70% less likely to black, 51% less likely to be on a diet, 73% less likely to have ever dieted before, and also 70% less likely to have ever weight cycled in their lives (**Table 7**).

All of these patterns were not unexpected and have been observed in other literature. For example, many studies show that smoking is inversely associated with weight gain.[220] Nicotine increases energy expenditure and could also reduce appetite, further contributing to the observed body weight differences.[221] But it has also been found that smokers who quit tend to gain weight.[240 222] One group of researchers has even suggested that the recently imposed smoking bans (i.e. in public places), have contributed to rising obesity rates in the U.S.[223] Others suggest that rising rates of sedentary behavior, combined with smoking habits contribute to the observed weight gain in smokers.[224] Many studies also show the negative effects of bad diets and systematic yo-yo-diets (aka weight cycling).[225 226 227] This would explain why the individuals that did not diet or weight cycle were much more likely to not gain weight, and thus remain in the lower risk groups. There are many known beneficial effects of various forms of exercise and these will not be discussed in detail in this paper. Suffice to say, many studies show that exercise is associated with weight loss, weight control and overall general health,[228 229] greater weight

loss following bariatric surgery,[230] reductions in risk for all-cause and cardiovascular mortality[231] [232] and can even help reduce the risk of various neurodegenerative diseases.[233]

A.5 Trajectory-based and other limitations

A.5.1 CARDIA limitations

Because this study makes use of existing data, no information was available on functional impairments or disabilities in the presence of specific health conditions or diseases. It is therefore unclear to what extent the disease affects his daily life. This prevented the creation of an EOSS stage 4 category, which in turn may have underestimated EOSS stage and subsequent obesity-related risks.

Also, while there was some information available on the various psychological and psychosocial problems, it was not inclusive enough to provide reliable evidence for the psychopathology portion of the EOSS definition. The only applicable information was drawn from the component of the medical history questionnaire that dealt with nervous, emotional, or mental disorders. This component was a simple yes/no question, followed by a few follow-up questions. The options for the condition were 'under control', 'still have' and 'cured or gone'. Similar to what was discussed in the heart disease example above, it is not clear how an individual with an emotional disorder (i.e. GAD – general anxiety disorder) who indicates that they "still have" the condition was actually affected by the condition. In addition to this it is very difficult to understand how specific psychological conditions relate to obesity. For example, an individual suffering from a major depression disorder (MDD) can have periods of agitation, low self-esteem and loss of interest or pleasure in activities that were once enjoyed[234] but this does not mean that he does not participate in physical activity or that he became obese because of these periodic depression bouts.

A.5.2 EOSS Limitations

Some of the EOSS criteria or treatment options are very flexible and can be subject to opinion bias or misinterpretation. Clinical definitions, management steps or treatment protocols for conditions such as hyperglycemia may change over time or might not be constant across different ethnicities and countries. Independent clinicians/researchers might consider one condition or disease more prevalent in their region and would thus attribute more importance to this condition. This could be an especially serious problem with certain mental disorders, where due to cultural standards or beliefs, a diagnostic bias could result in a misdiagnosis or underestimate the overall health risk. For example, a clinician utilizing EOSS in US will attribute a higher weight to diabetes, especially when diagnosing Hispanic/Latino and non-Hispanic black patients, two populations known to have a higher prevalence of this disease.[235] It is important to note, however, that while these obesity-related conditions are important, their exact effect on the various EOSS stages is questionable and that ultimately, the health risk will not be predicted equally by each different condition. However, our analysis was able to demonstrate that some conditions are much more likely to be present in a particular EOSS stage, with for example, CHD being the most frequently reported stage 3 condition, and reduced HDL being present in the vast majority of stage 2 individuals.

The risk assessment and subsequent disease prognosis can be subjective in the sense that an individual that has lived with a chronic disease for an extended period of their lives and had therefore, structured their lives accordingly, might in fact, suffer less from the debilitating effects and/or physical limitations of that particular condition (i.e. arrhythmia). On the other hand, a recently diagnosed individual with the same condition might indicate that this circumstance is preventing them from doing everyday tasks and that they are subsequently under severe

psychological stress. The impact of their condition might also change over time, as in the case where a patient learns to cope and live with his or her condition (managing their symptoms, establishing new patterns of daily life, etc.), thus reducing the overall negative impact on their everyday lives.[236] What this implies is that EOSS stage severity might not be very comparable between different individuals. Two individuals might have the same physical limitation but one reports suffering minor limitations and is categorized as stage 1, while the other feels that he is much worse off and is categorized stage 2. There is also a fine line between what could be considered a 'moderate' versus 'severe' quality of life limitation.

Psychological impact and functional performance are also subject to self-report bias (differences in perception, social desirability, embarrassment etc); however, other classification systems and studies, such as the NHANES or social anxiety questionnaires have incorporated similar measures into their structure and it has worked well in clinical practice.[237] [238] [239] While it is clear that a stage 0 individual would have no psychopathology of any kind, it becomes difficult to rank and judge the various psychological issues for subsequent EOSS stages. This level of impairment is very challenging to evaluate and its subsequent assignment to a particular EOSS stage could pose a difficulty to the researcher. For example, an obese individual (BMI = 33) with schizophrenia (a significant psychopathology) who is otherwise relatively healthy would have class I, EOSS stage 2 or 3 obesity. Would that individual actually require pharmacological or surgical weight loss interventions? Or would treating schizophrenia alone suffice? For this particular case, some evidence exists that patients with schizophrenia might be prone to obesity,[240] while other evidence shows that certain medications might actually contribute to weight loss in schizophrenics with type II diabetes.[241]

A.5.3 Trajectory Modelling Limitations

Given the relatively new nature of the trajectory modelling analysis and the experimental nature of its health-related application, it is important to consider some issues inherent with this type of statistical analysis. This paragraph will discuss some of the known issues associated with it, and identify additional issues that we discovered while working on this paper. It is often difficult to choose the number of groups for the final model. Some use a specific fit statistic such as the Bayesian Information Criterion to make their decision. Others use the clinical validity of the observed model. Alternatively, it is suggested that a combination of formal statistical criteria as well the usefulness and validity of the model as it relates to the research question should be used to justify the model choice.[144] These are all fairly vague suggestions that are difficult to standardize because of the fact that group-based trajectory models are fairly new in clinical research. Additionally, the groups created using Proc Traj are not valid, 'real' groups. Rather they are representations of approximate patterns of change over given time. Thus they can potentially change over time or with additional follow-ups. However, same-group individuals are assumed to follow an identical pattern of change, meaning that intra-group variability cannot be measured.[189] Furthermore, a large sample size is required to be able to successfully identify specific trends, especially in complex, multiple-group models.

Finally there are a couple general limitations in this thesis. First of all, this report did not evaluate the theory or the effectiveness of trajectory modelling as a concept. The detailed statistical models and theory were not reviewed. The main focus was on examining EOSS as an effective obesity risk evaluation & prediction tool in a longitudinal setting. In this regard, trajectory modelling analysis was used to establish patterns of EOSS stage shift and the subsequent identification of associated risk factors. As mentioned before, the oversimplification and combination of certain variables was a major limitation in this paper. The inability to look at

obesity-specific cancers or other obesity-related health problems reduced the overall effectiveness of our analysis. The lack of any high-quality physical-functional variables could have underestimated EOSS stage severity and forced us to use a modified EOSS definition, different from the one designed by the original creators. Unfortunately, this limitation prevented us from evaluating the contributions of each individual EOSS component to the overall obesity-related health risk. We were also unfortunately unable to include built environment interactions, socio-economic status, and other individual variables (i.e. familial history) which are known to influence obesity relationships and could have been the reasons for our observed gender and ethnicity differences.[242]

Appendix B: Stage Descriptions and other Guidelines

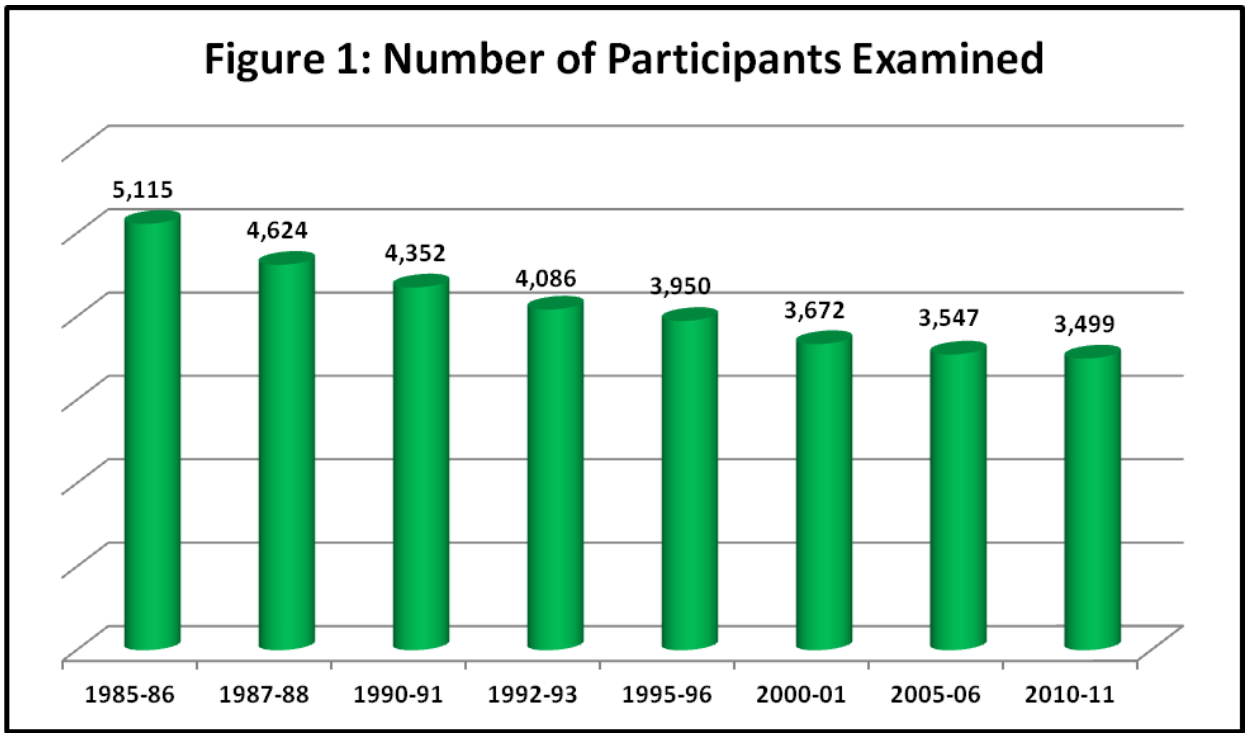


Table 1: EOSS stage descriptions[148]

EOSS Stage	Medical Limitations[1]	Mental (Psychological) Limitations[1]	Functional Limitations[1]	Management Steps
Stage 0*	None	None	None	Identify factors contributing to increased weight. Counsel to prevent further weight gain (healthy eating and increased physical activity).
Stage 1	Obesity-related SUBCLINICAL risk factors (borderline hypertension, impaired fasting glucose, etc)	Mild impairments to well-being, or mild psychological symptoms (Quality of life is not affected)	Mild physical symptoms. No medical treatment is required. (dyspnea, aches, fatigue on exertion)	Investigate other (non weight-related) risk factors. More intense lifestyle interventions combined with monitoring of risk factors and health status.
Stage 2	Established obesity-related comorbidities (Type 2 Diabetes, Sleep Apnea, Osteoarthritis, HTN, etc.). Medical Intervention is required.	Moderate psychological symptoms (depression, eating disorder, anxiety disorder)	Moderate functional limitations. Quality of life is beginning to be impacted.	Start obesity treatments (consider all behavioral, pharmacological and surgical options). Close monitoring and managing comorbidities.
Stage 3	Significant obesity-related end-organ damage (myocardial infarction, heart failure, diabetic complications, etc).	Significant obesity-related psychological symptoms (major depression, suicide ideation)	Significant functional limitations (unable to work, reduced activity). Quality of life is significantly affected.	Intensified obesity treatment. Aggressive management of comorbidities.
Stage 4	End-stage life-threatening obesity-related comorbidities	Severe psychological symptoms	Severe functional limitations. Most likely palliative care required.	Aggressive obesity management (as deemed feasible). Palliative measures including pain management, occupational therapy, psych. support.

* Also no sign of other obesity-related risk factors

[1] Patient has to display 1 of either of the 3 categories to be classified to the relevant EOSS stage.

Table 2: Metabolic Syndrome and Framingham Risk Score Guidelines			
US National Cholesterol Education Program Adult Treatment Panel III Updated (2004) Metabolic Syndrome Guidelines		Canadian Cardiovascular Society Framingham Heart Study 10-year Coronary Heart Disease Development Guidelines (2009)	
Risk Factor	**Guidelines**	**Risk Factor**	**Guidelines**
Elevated Waist Circumference	Men > 40 inches (102 cm) Women > 35 inches (88 cm)	Age	Older individuals at higher risk
Elevated Triglycerides	= or > 150 mg/dL (1.7 mmol/L)	Sex	Males at higher risk
Reduced HDL cholesterol	Men < 40 mg/dL (1.03 mmol/L) Women < 50 mg/dL (1.29 mmol/L)	Smoking	Higher risk for Smokers
High Blood Pressure (HBP)	= or > 130/85 mm Hg or use of HBP Medication	Total cholesterol	<200 mg/dL 'Desirable' 200-239 mg/dL 'Borderline-high' 240 mg/dL or > 'High'
Elevated Fasting Glucose (Hyperglycemia)	= or > 100 mg/dL (5.6 mmol/L) or use of hyperglycemic medication	HDL cholesterol	< 40 mg/dL 'Major risk' 40 to 59 mg/dL 'Normal' 60 mg/dL 'Protective'
		Systolic Blood Pressure	< 130 (mm Hg) 'No risk' 130-159 (mm Hg) 'risk' >160 (mm Hg) 'high risk'
		Diabetes	Higher risk for Diabetics

```
proc traj data=box.trialdata outplot=plot outstat=OS out=out;
VAR EOSS STAGE1-EOSS_STAGE7; INDEP age1-age7;
MODEL cnorm;
MAX 5;
NGROUPS 4;
ORDER 2 3 3 3;
ID PID;
run;
%trajplot (plot, os, 'Title', 'Subtitle', 'probability of EOSS Stage',
'age');
```

Where **VAR** is the variable of interest. **ID** is the subjects in the population.

INDEP defines the time variable over which the outcome is modeled.

MODEL identifies the type of model and **NGROUPS** is the number of groups.

ORDER assigns the order of each equation (i.e. linear, quadratic, etc.)

%TRAJPLOT is a macro statement that is responsible for a graphical output

Figure 2: Proc Traj EOSS Example

Appendix C: Detailed Analysis Figures

Table 1: T-tests of Baseline Differences between Sex & Race (N=3690)						
	Male vs. Female			Black vs. White		
Variable Name	Male Mean (SD)	Female Mean (SD)	Signif.	Black Mean (SD)	White Mean (SD)	Signif.
Height (cm)	177.6 (6.6)	164.3 (6.4)	P <.0001	169.4 (9.3)	171.2 (9.3)	P <.0001
Weight (lbs)	168.1 (27.2)	144.4 (32.5)	P <.0001	159 (35.5)	151.3 (28.8)	P <.0001
WC (cm)	81.21 (8.2)	73.74 (10.6)	P <.0001	77.9 (11.1)	76.26 (9.4)	P <.0001
BMI (Kg/M^2)	24.18 (3.4)	24.31 (5.3)	NS	25.17 (5.3)	23.37 (3.5)	P <.0001
SBP (mm Hg)	114.7 (10.4)	106.4 (9.6)	P <.0001	111.4 (10.9)	108.9 (10.6)	P <.0001
DBP (mm Hg)	70.66 (9.9)	66.72 (8.8)	P <.0001	68.83 (10.0)	68.15 (9.0)	P <.05
Calories (KCal)	3570 (1909.5)	2322.4 (1147.2)	P <.0001	3127.1 (1970.3)	2648.5 (1247.1)	P <.0001
Glucose (mg/dL)	83.98 (10.04)	80.24 (12.2)	P <.0001	81.33 (12.7)	82.46 (10.1)	P <.05
TG (mg/dL)	75.36 (43.6)	64.61 (32.9)	P <.0001	64.79 (31.8)	73.83 (43.3)	P <.0001
HDL (mg/dL)	50.62 (12.5)	55.98 (12.6)	P <.0001	54.73 (12.9)	54.48 (12.7)	P <.0001
Intensity (METs Units)	517.4 (322.5)	345.4 (254.5)	P <.0001	382.3 (310.5)	460.6 (283.3)	P <.0001

Table 2: OBESE Baseline Differences between Sex & Race (N=365)						
	Male (N=102) vs. Female (N=263)			Black (N=270) vs. White (N=95)		
Variable Name	Male Mean (SD)	Female Mean (SD)	Signif.	Black Mean (SD)	White Mean (SD)	Signif.
Height (cm)	178.5 (6.7)	163.2 (6.2)	P <.0001	166.9 (9.2)	169.0 (9.6)	NS
Weight (lbs)	228.7 (23.6)	205.8 (30.7)	P <.0001	214.6 (32.9)	205.4 (22.1)	P <.05
WC (cm)	99.34 (6.2)	94.4 (10.2)	P <.0001	95.49 (10.3)	93.84 (7.1)	NS
BMI (Kg/M^2)	32.6 (2.2)	35.2 (4.5)	P <.0001	35.01 (4.5)	32.8 (2.3)	P <.0001
SBP (mm Hg)	118.4 (9.8)	111 (9.9)	P <.0001	113.5 (10.6)	111.9 (9.9)	NS
DBP (mm Hg)	71.7 (8.6)	70 (8.5)	NS	70.31 (8.7)	70.84 (8.2)	NS
Calories (KCal)	3552.6 (1702.3)	2311.9 (1146.7)	P <.0001	2678.7 (1443.5)	2601.6 (1184.5)	NS
Glucose (mg/dL)	85.1 (6.9)	83.5 (8.2)	NS	83.68 (8.1)	84.58 (7.1)	NS
TG (mg/dL)	96.65 (45.9)	71.88 (32.5)	P <.0001	74.69 (38.1)	90.49 (36.8)	P <.001
HDL (mg/dL)	44.09 (9.9)	48.33 (10.6)	P <.001	48.13 (10.8)	44.37 (9.4)	P <.05
Intensity (Ex. Units)	465.5 (303.2)	267.9 (200.9)	P <.0001	314.3 (257.5)	348.1 (226.2)	NS

Table 3: Categorical Variable Distribution at each follow-up (N=3692)							
	Examination Year						
	Exam 1 (Base)	**Exam 2 (Year2)**	**Exam 3 (Year 5)**	**Exam 4 (Year7)**	**Exam 5 (Year10)**	**Exam 6 (Year15)**	**Exam 7 (Year 20)**
Variables	Total (%)	Total (%)	Total (%)	Total (%)	Total (%)	Total (%)	Total (%)
Race							
Black	1798 (48.7)	1782 (48.5)	1676 (47.7)	1676 (47.8)	1709 (48.5)	1550 (47.1)	1382 (45.7)
White	1894 (51.3)	1889 (51.5)	1835 (52.3)	1834 (52.2)	1816 (51.5)	1742 (52.9)	1642 (54.3)
Sex							
Male	1654 (44.8)	1642 (44.7)	1568 (44.66)	1572 (44.8)	1580 (44.8)	1469 (44.6)	1316 (43.5)
Female	2038 (55.2)	2029 (55.3)	1943 (55.34)	1938 (55.2)	1945 (55.2)	1823 (55.4)	1708 (56.5)
Education							
No Highschool	256 (7.1)	170 (4.9)	148 (4.3)	144 (4.2)	0	0	0
Highschool	2150 (59.2)	1858 (53.7)	1691 (48.7)	1581 (46.1)	1577 (47.1)	1270 (41.0)	1092 (38.2)
College or Univ.	1224 (33.7)	1434 (41.4)	1262 (36.4)	1273 (37.1)	1290 (28.5)	1278 (41.3)	1205 (42.1)
Prof. or Masters and higher	0	0	367 (10.6)	433 (12.6)	485 (14.4)	549 (17.7)	562 (19.7)
BMI category							
Underweight	143 (3.9)	108 (3.1)	66 (1.9)	309 (8.37)	272 (7.4)	439 (11.9)	684 (18.5)
Normal	2323 (62.9)	1999 (56.8)	1789 (51.2)	1587 (42.98)	1431 (38.8)	1091 (29.5)	894 (24.2)
Overweight	861 (23.3)	929 (26.4)	1009 (28.9)	1051 (28.5)	1128 (30.55)	1107 (30.0)	1022 (27.7)
Obese	365 (9.9)	480 (13.7)	629 (18.0)	745 (20.2)	861 (23.25)	1055 (28.6)	1092 (29.6)
Drinking							

No Drinking	2655 (72.2)	2555 (73.0)	2652 (75.9)	2608 (74.8)	2624 (74.8)	2477 (75.4)	2191 (73.9)
Moderate	788 (21.4)	728 (20.8)	635 (18.2)	651 (18.7)	659 (18.8)	607 (18.5)	602 (20.3)
Heavy	236 (6.4)	215 (6.2)	206 (5.9)	228 (6.5)	224 (6.4)	201 (6.1)	174 (5.8)
Smoking							
Non Smoker	2159 (58.9)	2059 (58.5)	2050 (58.5)	2030 (58.1)	2054 (58.5)	1978 (60.2)	1861 (62.1)
Former	482 (13.1)	493 (14.0)	509 (14.5)	559 (16.0)	586 (16.7)	598 (18.2)	585 (19.5)
Current	1028 (28.0)	967 (27.5)	944 (26.95)	905 (25.9)	869 (24.8)	709 (21.6)	550 (18.4)
On a Diet							
Yes	276 (8.4)	245 (18.2)	NA	235 (18.1)	280 (35.7)	292 (32.5)	313 (33.5)
No	3027 (91.6)	1099 (81.8)		1066 (81.9)	504 (64.3)	605 (67. 5)	623 (66.5)
Ever Diet							
Yes	1328 (36.0)	1359 (38.7)	NA	1315 (37.6)	785 (22.3)	898 (27.3)	940 (31.2)
No	2359 (64.0)	2152 (61.3)		2186 (62.4)	2730 (77.7)	2390 (72.7)	2073 (68.8)
Hypertension							
Prehypertension	147 (4.0)	110 (3.0)	108 (2.9)	153 (4.1)	201 (5.5)	247 (6.7)	284 (7.7)
Yes	60 (1.6)	52 (1.4)	111 (3.0)	111 (3.0)	167 (4.5)	324 (8.8)	266 (7.2)
No	3485 (94.4)	3530 (95.6)	3473 (94.1)	3428 (92.9)	3324 (90.0)	3121 (84.5)	3142 (85.1)
Hypercholesterolemia							
Precholestrol.	643 (17.4)	NA	628 (17.0)	641 (17.4)	612 (16.6)	786 (21.3)	774 (21.0)
Yes	154(4.2)		156 (4.2)	151 (4.1)	169 (4.6)	199 (5.4)	188 (5.1)
No	2895 (78.4)		2908 (78.8)	2900 (78.5)	2911 (78.8)	2707 (73.3)	2730 (73.9)
Hyperglycemia							

Prehyperglyce.	62 (1.7)	NA	NA	326 (8.8)	214 (5.8)	193 (5.2)	679 (18.4)
Yes	13 (0.3)			30 (0.8)	50 (1.35)	63 (1.7)	139 (3.8)
No	3617 (98.0)			3336 (90.4)	3428 (92.85)	3436 (93.1)	2874 (77.8)
Problems Exercising							
Mild	NA	NA	NA	159 (16.7)	143 (15.4)	84 (15.9)	81 (15.8)
Moderate				435 (45.7)	390 (42.1)	254 (47.9)	218 (42.4)
Severe				357 (37.5)	394 (42.5)	192 (36.2)	215 (41.8)
Elevated TG							
Pre-levels	91 (2.5)	NA	129 (3.5)	171 (4.6)	213 (5.8)	256 (6.9)	282 (7.6)
Yes	42 (1.1)		93 (2.5)	129 (3.5)	179 (4.9)	239 (6.5)	257 (7.0)
No	3559 (96.4)		3470 (94.0)	3392 (91.9)	3300 (89.3)	3197 (86.6)	3153 (85.4)
Reduced HDL							
Pre-levels	1814 (49.1)	NA	1534 (41.5)	1467 (39.7)	1392 (37.7)	1212 (32.8)	1153 (31.2)
Yes	860 (23.3)		1136 (30.8)	1300 (35.2)	1495 (40.5)	1659 (44.9)	1553 (42.1)
No	1018 (27.6)		1022 (27.7)	925 (25.1)	805 (21.8)	821 (22.3)	986 (26.7)
Cancer							
Yes	0	74 (2.1)	40 (1.1)	60 (1.7)	74 (3.8)	96 (2.9)	140 (4.65)
No	3673 (100)	3431 (97.9)	3463 (98.9)	3442 (98.3)	1861 (96.2)	3186 (97.1)	2870 (95.35)
Heart Problems (CHD)							
Yes	217 (6.0)	237 (6.8)	294 (8.4)	354 (10.1)	372 (10.6)	369 (11.3)	320 (10.8)
No	3432 (94.0)	3242 (93.2)	3193 (91.6)	3138 (89.9)	3124 (89.4)	2886 (88.7)	2649 (89.2)
Diabetes							

Yes	22 (0.06)	31 (0.09)	53 (1.5)	103 (2.9)	128 (3.7)	161 (4.9)	203 (6.8)
No	3637 (99.4)	3466 (99.1)	3443 (98.5)	3395 (97.1)	3383 (96.3)	3107 (95.1)	2797 (93.2)
Mental Disorders							
Yes	260 (7.1)	243 (7.0)	NA	159 (4.5)	202 (5.7)	241 (7.3)	183 (6.1)
No	3389 (92.9)	3247 (93.0)		3336 (95.5)	3311 (94.3)	3037 (92.7)	2802 (93.9)
Other Health Problems/ Diseases							
Yes	303 (8.3)	231 (6.6)	347 (9.9)	249 (7.1)	287 (8.2)	254 (7.8)	285 (9.5)
No	3358 (91.7)	3252 (93.4)	3148 (90.1)	3252 (92.9)	3229 (91.8)	3023 (92.2)	2717 (90.5)
Fastfood consumption							
Yes	1079 (29.2)	NA	647 (17.5)	935 (25.3)	914 (24.8)	741 (20.1)	852 (23.1)
No	2613 (70.8)		3045 (82.5)	2757 (74.7)	2778 (75.2)	2951 (79.9)	2840 (76.9)
Weight Cycling							
Frequent	732 (20.0)	NA	NA	NA	NA	NA	NA
Occasional	1915 (52.5)						
No	1005 (27.5)						
Meeting Carbohydrate Guidelines							
Yes	2020 (54.7)	NA	NA	NA	NA	NA	NA
No	1672 (45.3)						
Meeting Protein Guidelines							
Yes	3496 (94.7)	NA	NA	NA	NA	NA	NA
No	196 (5.3)						

Meeting fat consumption guidelines							
Yes	1153 (31.2)	NA	NA	NA	NA	NA	NA
No	2539 (68.8)						
Presence of Metabolic Syndrome							
Yes	2 (0.05)	NA	80 (2.2)	237 (6.4)	299 (8.1)	443 (12.0)	698 (18.9)
No	3690 (99.95)		3612 (97.8)	3455 (93.6)	3393 (91.9)	3249 (88.0)	2994 (81.1)
Exercise Frequency & Intensity							
Low	1187 (32.1)	1514 (41.0)	1596 (43.2)	1820 (49.3)	1846 (50.0)	1903 (51.5)	2056 (55.7)
Moderate	1251 (33.9)	1199 (32.5)	1131 (30.6)	1067 (28.9)	1053 (28.5)	993 (26.9)	904 (24.5)
High	1254 (34.0)	979 (26.5)	965 (26.2)	805 (21.8)	793 (21.5)	796 (21.6)	732 (19.8)

Table 4: Obese vs. Not Obese baseline categorical comparison (N=3690)				
Variables	Not Obese	Obese	X^2 Value	Significance
Race:			103.8	P < 0.0001
Black	1526 (45.9)	270 (74.0)		
White	1799 (54.1)	95 (26.0)		
Sex:			46.53	P < 0.0001
Male	1552 (46.7)	102 (27.9)		
Female	1773 (53.3)	263 (72.1)		
Education:			12.64	P < 0.01
No Highschool	224 (6.9)	32 (9.0)		
Highschool	1915 (58.5)	234 (65.5)		
College or Univ.	1132 (34.6)	91 (25.5)		
Drinking:			9.2	P < 0.05
No Drinking	2365 (71.4)	288 (78.9)		
Moderate	729 (22.0)	59 (16.2)		
Heavy	218 (6.6)	18 (4.9)		
Smoking:			4.8	NS
Non Smoker	1953 (59.1)	204 (56.7)		
Former	443 (13.4)	39 (10.8)		
Current	911 (27.5)	117 (32.5)		
On a Diet:			29.02	P < 0.0001
Yes	2743 (92.5)	282 (83.9)		
No	222 (7.5)	54 (16.1)		
Ever Diet:			141.85	P < 0.0001
Yes	2229 (67.1)	130 (35.6)		
No	1091 (32.9)	235 (64.4)		
Has Hypertension:			4.84	NS
Prehypertension	126 (3.8)	21 (5.8)		
Yes	57 (1.7)	3 (0.8)		
No	3142 (94.5)	341 (93.4)		
Hypercholesterolemia:			19.17	P < 0.0001
Pre	551 (16.6)	92 (25.2)		
Yes	135 (4.0)	19 (5.2)		
No	2639 (79.4)	254 (69.6)		
Hyperglycemia:			0.53	NS
Pre	53 (1.6)	9 (2.5)		
Yes	12 (0.4)	1 (0.3)		
No	3260 (98.0)	355 (97.2)		
Elevated TG:			0.004	NS
Pre	84 (2.5)	7 (1.9)		
Yes	37 (1.1)	5 (1.4)		
No	3204 (96.4)	353 (96.7)		
Reduced HDL:			134.4	P < 0.0001
Pre	1662 (50.0)	151 (41.4)		
Yes	690 (20.8)	170 (46.6)		
No	973 (29.2)	44 (12.0)		
CHD:			4.7	P < 0.05
Yes	204 (6.2)	12 (3.4)		
No	3085 (93.8)	346 (96.6)		

Diabetes:			12.22	P < 0.0005
Yes	15 (0.5)	7 (2.0)		
No	3285 (99.5)	350 (98.0		
Mental Disorder:			2.6	NS
Yes	227 (6.9)	33 (9.2)		
No	3062 (93.1)	326 (90.8)		
Other Health Problems:			0.021	NS
Yes	273 (8.3)	29 (8.0)		
No	3026 (91.7)	331 (92.0)		
Fast Food Consumption:			0.6	NS
Yes	966 (29.0)	113 (31.0)		
No	2359 (71.0)	252 (69.0)		
Weight Cycling			174.24	P < 0.0001
Frequent	582 (17.7)	149 (42.0)		
Occasional	1722 (52.3)	192 (54.0)		
No	991 (30.0)	14 (4.0)		
Meeting Carbohydrate Guidelines			1.56	NS
Yes	1808 (54.4)	211 (57.8)		
No	1517 (45.6)	154 (42.2)		
Meeting Protein Guidelines			0.009	NS
Yes	3148 (94.8)	346 (94.8)		
No	177 (5.2)	19 (5.2)		
Meeting fat consumption guidelines			1.16	NS
Yes	1029 (31.0)	123 (33.7)		
No	2296 (69.0)	242 (66.3)		
Presence of Metabolic Syndrome			0.51	NS
Yes	1 (0.03)	1 (0.3)		
No	3326 (99.97)	364 (99.7)		
Exercise Frequency & Intensity			22.4	P < 0.0001
Low	1031 (31.0)	156 (42.7)		
Moderate	1136 (34.2)	114 (31.2)		
High	1158 (34.8)	95 (26.1)		

Table 5: Continuous Variable Distribution at each follow-up (N=3690)							
	Examination Year						
	Exam 1 (Base)	**Exam 2 (Year2)**	**Exam 3 (Year 5)**	**Exam 4 (Year7)**	**Exam 5 (Year10)**	**Exam 6 (Year15)**	**Exam 7 (Year 20)**
Variables	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	24.87 (3.6)	26.95 (3.6)	29.97 (3.6)	31.98 (3.6)	34.94 (3.6)	40.1 (3.63)	45.1 (3.56)
Height (cm)	170. 3 (9.3)	170.1 (9.3)	170.4 (9.3)	170.9 (9.2)	170.8 (9.2)	170.96 (9.2)	170.7 (9.25)
Weight (lbs)	155.0 (32.5)	159.4 (34.6)	165.7 (37.5)	170.7 (39.1)	175.1 (41.2)	183.1 (43.3)	186.7 (44.0)
WC (cm)	77.1 (10.3)	79.3 (11.1)	81.3 (11.8)	83.4 (13.5)	85.2 (13.4)	88.7 (13.9)	91.1 (14.5)
BMI (kg/m^2)	24.2 (4.5)	25.0 (4.9)	25.9 (5.4)	26.5 (5.7)	27.2 (6.0)	28.4 (6.3)	29.1 (6.4)
SBP (mmHg)	110.1 (10.8)	107.6 (10.7)	107.6 (11.8)	108.4 (12.1)	109.8 (12.6)	112.8 (14.6)	116.4 (15.0)
DBP (mmHg)	68.5 (9.5)	67.4 (9.5)	69.2 (10.3)	69.1 (10.2)	72.3 (10.1)	74.4 (11.5)	72.9 (11.4)
Calories (KCAL)	2881.5 (1656.7)	2468.8 (1765.9)	NA	3003.4 (1893.5)	NA	NA	NA
Glucose (mg/dl)	81.9 (11.4)	NA	NA	89.1 (14.5)	87.3 (15.4)	85.9 (17.9)	97.0 (23.4)
Triglycerides (mg/dl)	69.4 (38.4)	NA	76.5 (57.8)	82.7 (62.5)	88.5 (62.2)	101.7 (78.9)	107.3 (77.1)
Total HDL Cholesterol (mg/dl)	53.6 (12.8)	NA	53.7 (14.0)	52.3 (14.1)	50.5 (13.9)	50.9 (14.5)	54.5 (16.6)
Total PA Intensity score (exercise units)	422.5 (299.4)	382.2 (284.5)	380.0 (293.9)	340.4 (274.8)	330.9 (275.6)	347.4 (283.7)	338.5 (277.5)
Heavy Intensity Only (exercise units)	297.6 (232.1)	252.0 (223.5)	250.4 (230.0)	218.4 (216.0)	209.2 (214.8)	213.1 (220.2)	203.8 (211.2)

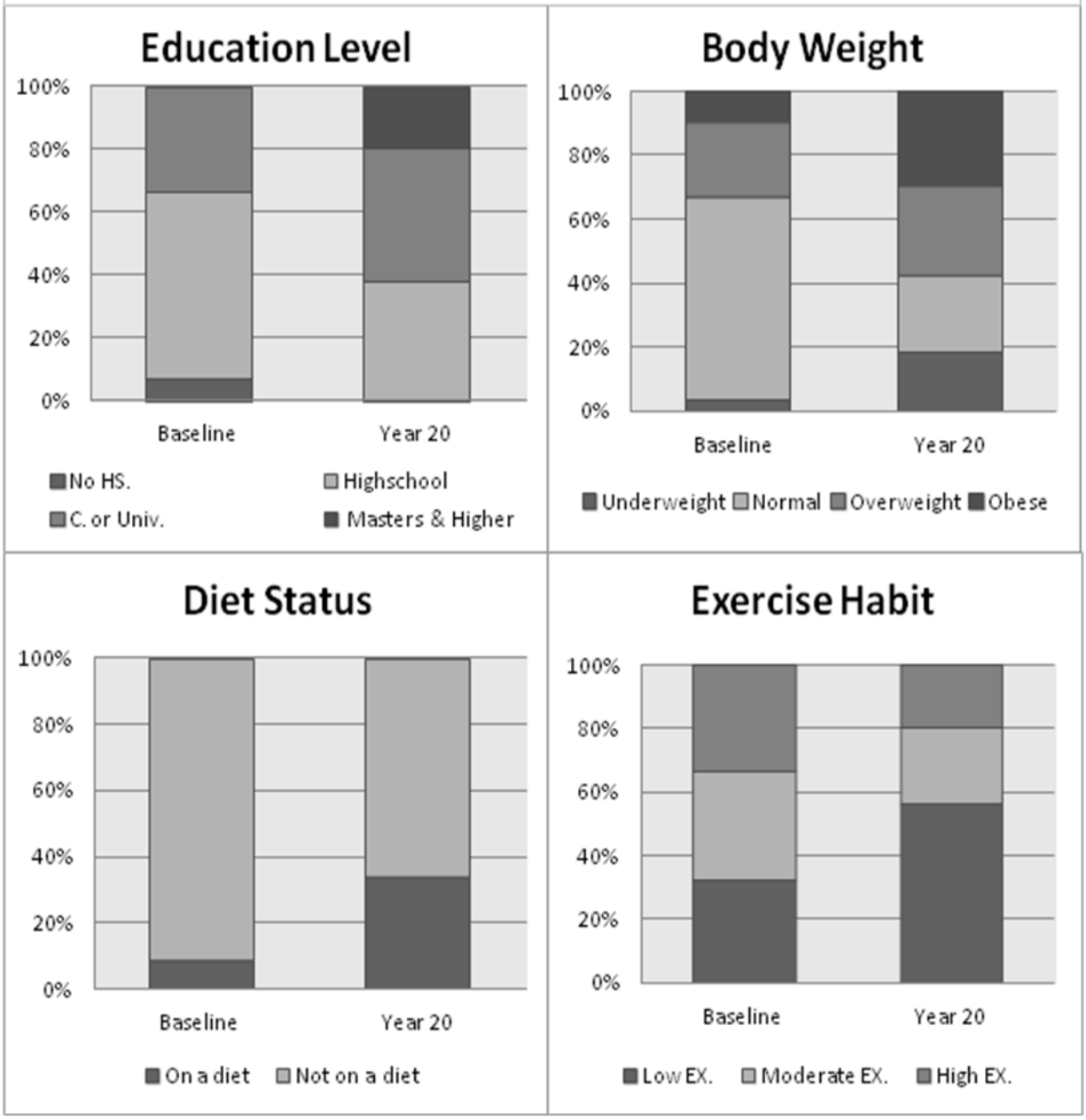
Table 6: Logistic Regression Univariate Results		
Variable	Group**	Unadjusted OR (95% CI)
Sex (Male vs. Female)	1	0.67 (0.3-1.52)
	2	2.16 (1.47-3.2)*
	3	2.33 (1.48 – 3.67)*
Race (Black vs. White)	1	2.09 (0.998-4.38)
	2	0.63 (0.44-0.88)*
	3	1.58 (1.03-2.44)*
Age	1	0.98 (0.89-1.07)
	2	1.00 (0.96-1.05)
	3	1.06 (1.00-1.13)*
Education (HighSchool (HS) vs. No HS)	1	2.03 (0.42-9.76)
	2	1.07 (0.54-2.09)
	3	1.29 (0.56-3.01)
Education (College + vs. No HS)	1	1.20 (0.23-6.21)
	2	1.02 (0.51-2.05)
	3	0.91 (0.38-2.19)
Drinking (Moderate vs. Non-Drinker)	1	1.85 (0.78-4.38)
	2	1.93 (1.16-3.19)*
	3	1.68 (0.93-3.03)
Drinking (Heavy vs. Non-Drinker)	1	0.83 (0.17-4.10)
	2	1.21 (0.58-2.52)
	3	1.04 (0.42-2.60)
Smoking (Former vs. Non-Smoker)	1	0.15 (0.02-1.16)
	2	1.18 (0.70-1.94)
	3	0.66 (0.34-1.29)
Smoking (Current vs. Non-smoker)	1	1.24 (0.59-2.63)
	2	1.35 (0.89-2.04)
	3	1.07 (0.65-1.77)
Currently On Diet	1	0.62 (0.22-1.72)
	2	0.39 (0.25-0.63)*
	3	1.19 (0.68-2.07)
Ever Diet	1	0.80 (0.41-1.57)
	2	0.39 (0.28-0.56)*
	3	1.04 (0.68-1.59)
Follows carbohydrate consumption guidelines	1	0.90 (0.46-1.76)
	2	0.99 (0.71-1.40)
	3	0.87 (0.57-1.33)

Follows protein consumption guidelines	1	0.87 (0.32-2.37)
	2	2.43 (1.41-4.21)*
	3	3.28 (1.41-7.64) *
Follows fat consumption guidelines	1	1.55 (0.75-3.22)
	2	1.48 (0.995-2.21)
	3	1.35 (0.84-2.19)
Eats Fastfood	1	0.68 (0.32-1.46)
	2	0.83 (0.57-1.20)
	3	1.09 (0.69-1.70)
Exercise Intensity (Moderate vs. Low)	1	0.69 (0.30-1.57)
	2	0.99 (0.65-1.50)
	3	1.13 (0.68-1.89)
Exercise Intensity (High vs. Low)	1	0.80 (0.36-1.77)
	2	1.04 (0.68-1.58)
	3	1.05 (0.63-1.77)
Weight Cycling (occasional vs. non)	1	0.68 (0.27-1.71)
	2	0.40 (0.23-0.69)*
	3	1.24 (0.62-2.48)
Weight Cycling (frequent vs. non)	1	0.34 (0.12-0.99)*
	2	0.19 (0.11-0.34)*
	3	0.90 (0.44-1.85)
* OR significant at $p < 0.05$.		
** All group comparisons are performed against the high-risk, Group 4.		

Table 7: Factors associated with BMI Category stages		
Variable	Group	Odds Ratio Estimates 95% Wald Confidence Limits
Sex (Male vs. Female)	1	0.48 (0.37-0.63)*
	2	1.15 (0.89-1.50)
	3	1.23 (0.95-1.61)
Race (Black vs. White)	1	0.16 (0.12-0.21)*
	2	0.30 (0.23-0.39)*
	3	0.48 (0.36-0.62)*
Age	1	1.06 (1.03-1.10)*
	2	1.08 (1.04-1.12)*
	3	1.00 (0.96-1.04)
Education (HighSchool (HS) vs. No HS)	1	1.16 (0.74-1.81)
	2	1.37 (0.86-2.17)
	3	1.43 (0.89-2.27)
Education (College + vs. No HS)	1	2.39 (1.43-4.00)*
	2	2.08 (1.22-3.54)*
	3	1.66 (0.96-2.85)
Smoking (Former vs. Non-Smoker)	1	1.94 (1.32-2.84)*
	2	1.60 (1.09-2.35)*
	3	1.45 (0.98-2.16)
Smoking (Current vs. Non-smoker)	1	1.58 (1.21-2.08)*
	2	1.02 (0.78-1.35)
	3	0.92 (0.69-1.22)
Currently On Diet	1	0.34 (0.22-0.51)*
	2	0.49 (0.33-0.74)*
	3	0.77 (0.53-1.11)
Ever Diet	1	0.17 (0.13-0.23)*

	2	0.27 (0.20-0.36)*
	3	0.43 (0.32-0.58)*
Eats Fastfood	1	0.62 (0.48-0.80)*
	2	0.78 (0.60-1.01)
	3	0.99 (0.76-1.28)
Exercise Intensity (Moderate vs. Low)	1	1.12 (0.85-1.49)
	2	1.20 (0.91-1.60)
	3	1.22 (0.92-1.64)
Exercise Intensity (High vs. Low)	1	1.64 (1.23-2.20)*
	2	1.39 (1.04-1.86)*
	3	1.43 (1.06-1.92)*
Weight Cycling (occasional vs. non)	1	0.21 (0.15-0.31)*
	2	0.31 (0.21-0.46)*
	3	0.49 (0.33-0.73)*
Weight Cycling (frequent vs. non)	1	0.07 (0.05-0.11)*
	2	0.13 (0.09-0.21)*
	3	0.28 (0.20-0.43)*
* OR significant at $p < 0.05$.		
** All group comparisons are performed against the high-risk, Group 4.		

Figure 1: Baseline vs. Year 20 variable comparison



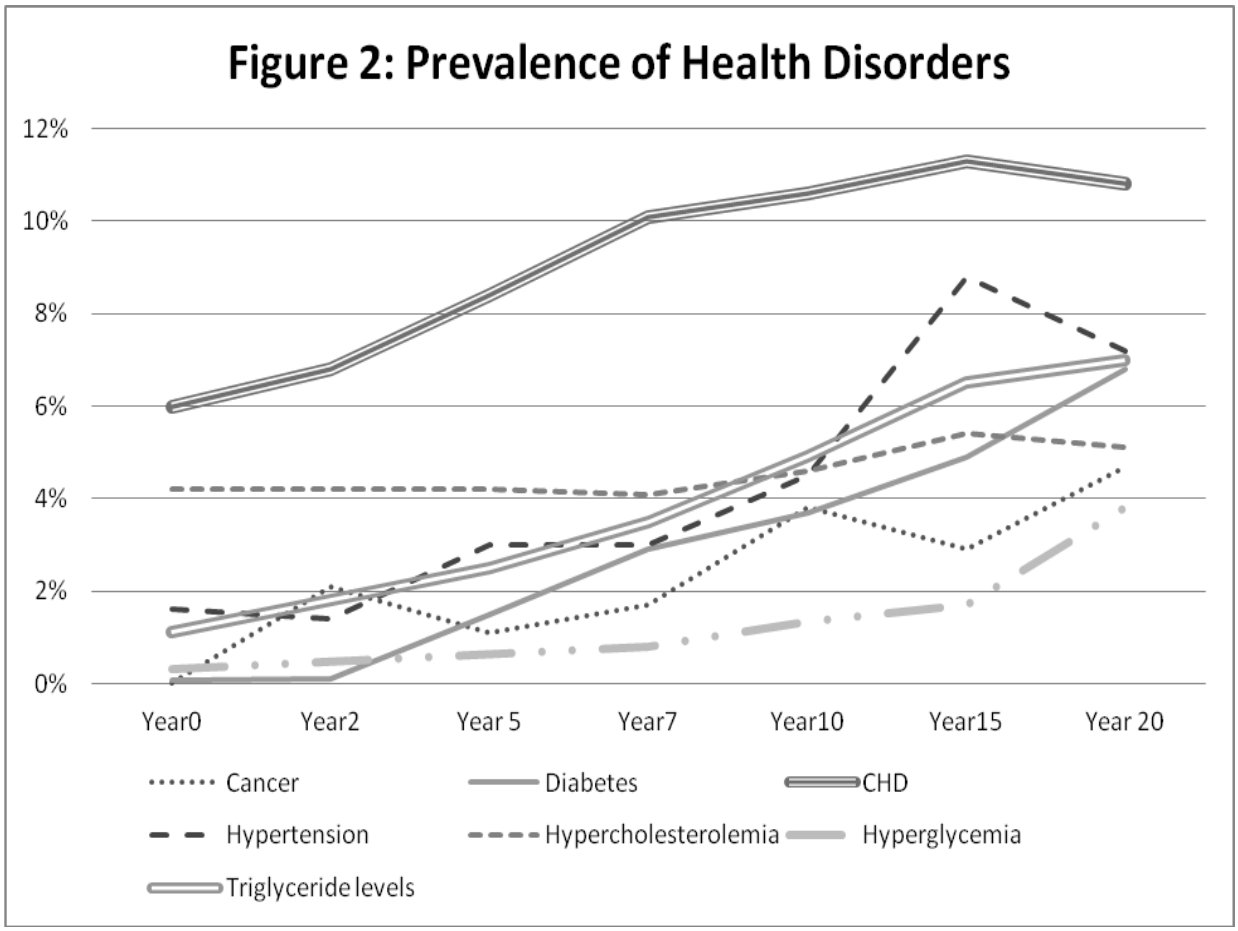


Figure 2: Prevalence of Health Disorders
12%
10%
8%
6%
4%
2%
0%
Year0
Year2
Year 5
Year7
Year10
Year15
Year 20
Cancer
Diabetes
CHD
Hypertension
Hypercholesterolemia
Hyperglycemia
Triglyceride levels

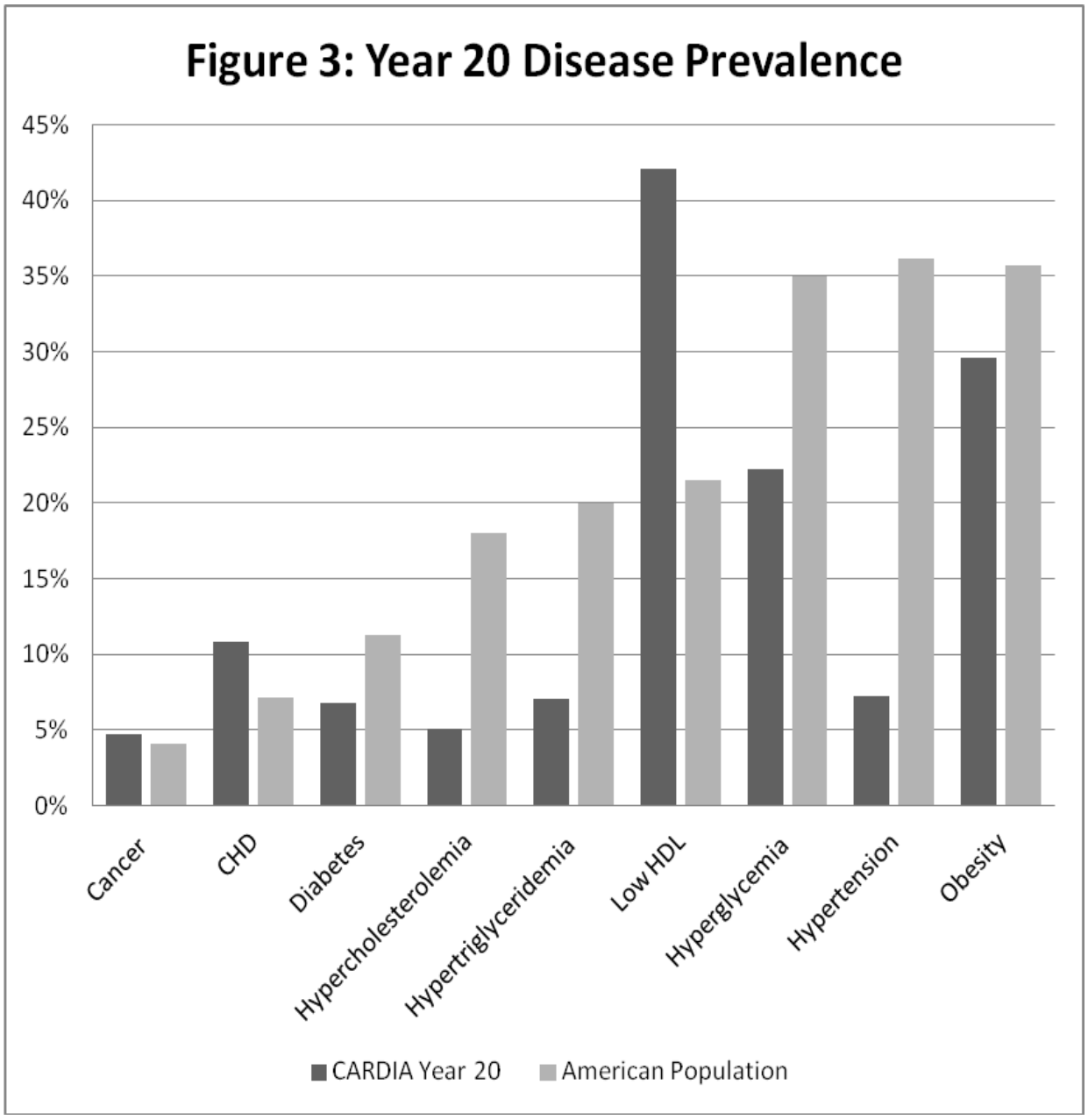


Figure 3: Year 20 Disease Prevalence
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
Cancer
CHD
Diabetes
Hypercholesterolemia
Hypertriglyceridemia
Low HDL
Hyperglycemia
Hypertension
Obesity
CARDIA Year 20
American Population

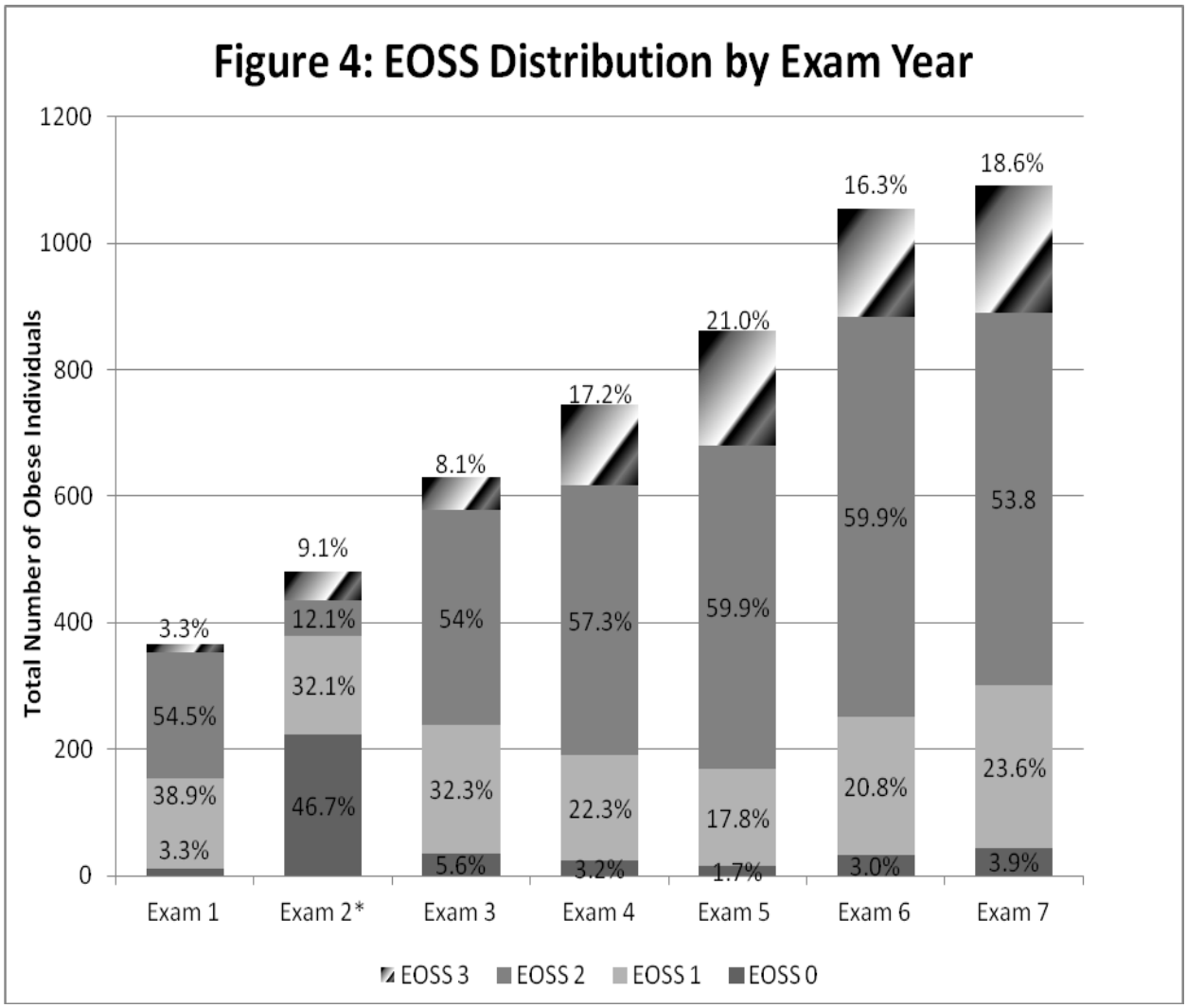


Figure 4: EOSS Distribution by Exam Year
Total Number of Obese Individuals
1200
1000
800
600
400
200
0
3.3%
54.5%
38.9%
3.3%
9.1%
12.1%
32.1%
46.7%
8.1%
54%
32.3%
5.6%
17.2%
57.3%
22.3%
3.2%
21.0%
59.9%
17.8%
1.7%
16.3%
59.9%
20.8%
3.0%
18.6%
53.8
23.6%
3.9%
Exam 1
Exam 2*
Exam 3
Exam 4
Exam 5
Exam 6
Exam 7
EOSS 3
EOSS 2
EOSS 1
EOSS 0

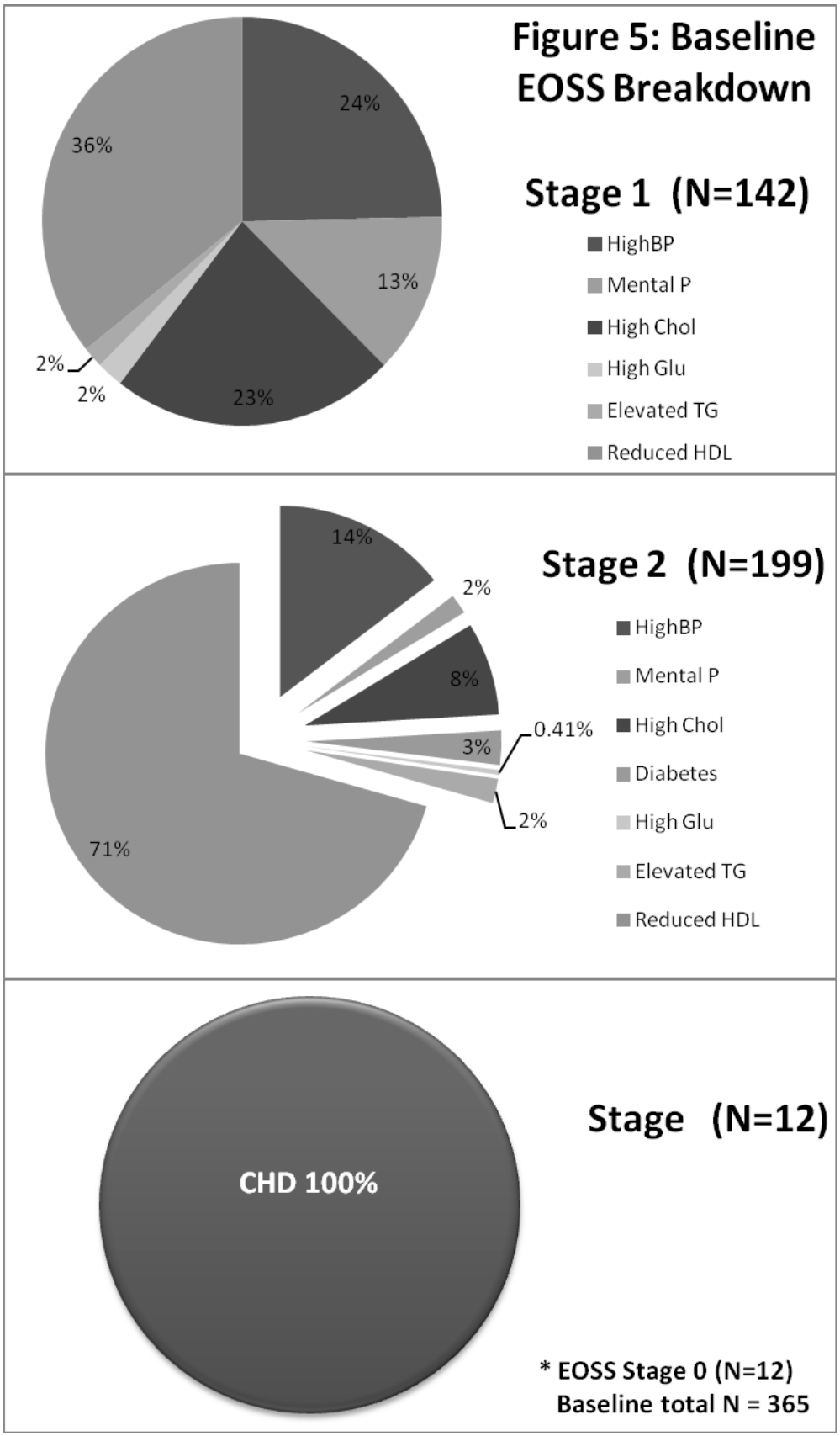


Figure 5: Baseline EOSS Breakdown
Stage 1 (N=142)
24%
13%
23%
2%
2%
36%
HighBP
Mental P
High Chol
High Glu
Elevated TG
Reduced HDL
Stage 2 (N=199)
14%
2%
8%
0.41%
3%
2%
71%
HighBP
Mental P
High Chol
Diabetes
High Glu
Elevated TG
Reduced HDL
Stage (N=12)
CHD 100%
* EOSS Stage 0 (N=12)
Baseline total N = 365

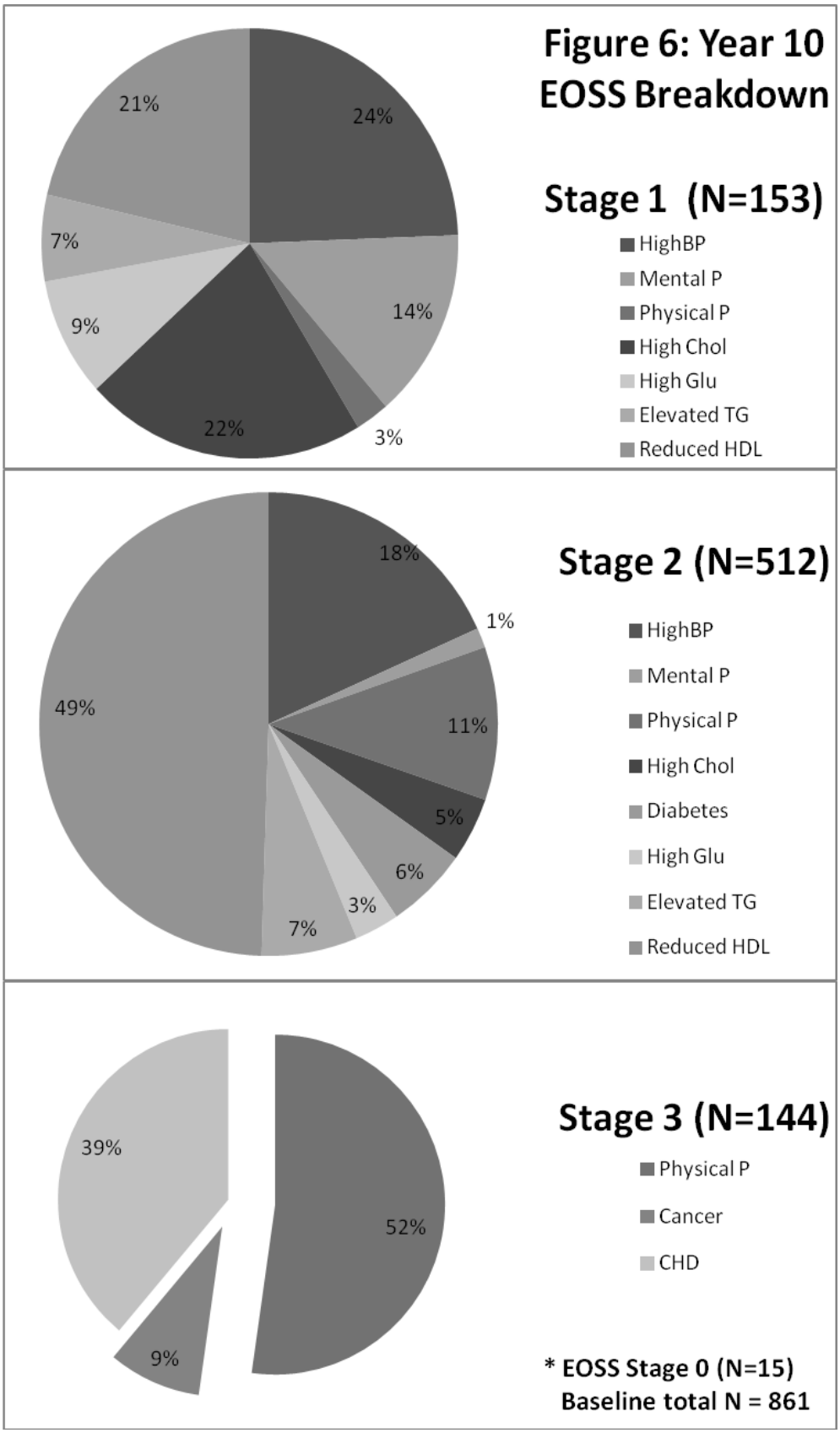


Figure 6: Year 10 EOSS Breakdown
Stage 1 (N=153)
24%
14%
3%
22%
9%
7%
21%
HighBP
Mental P
Physical P
High Chol
High Glu
Elevated TG
Reduced HDL
Stage 2 (N=512)
18%
1%
11%
5%
6%
3%
7%
49%
HighBP
Mental P
Physical P
High Chol
Diabetes
High Glu
Elevated TG
Reduced HDL
Stage 3 (N=144)
52%
9%
39%
Physical P
Cancer
CHD
* EOSS Stage 0 (N=15)
Baseline total N = 861

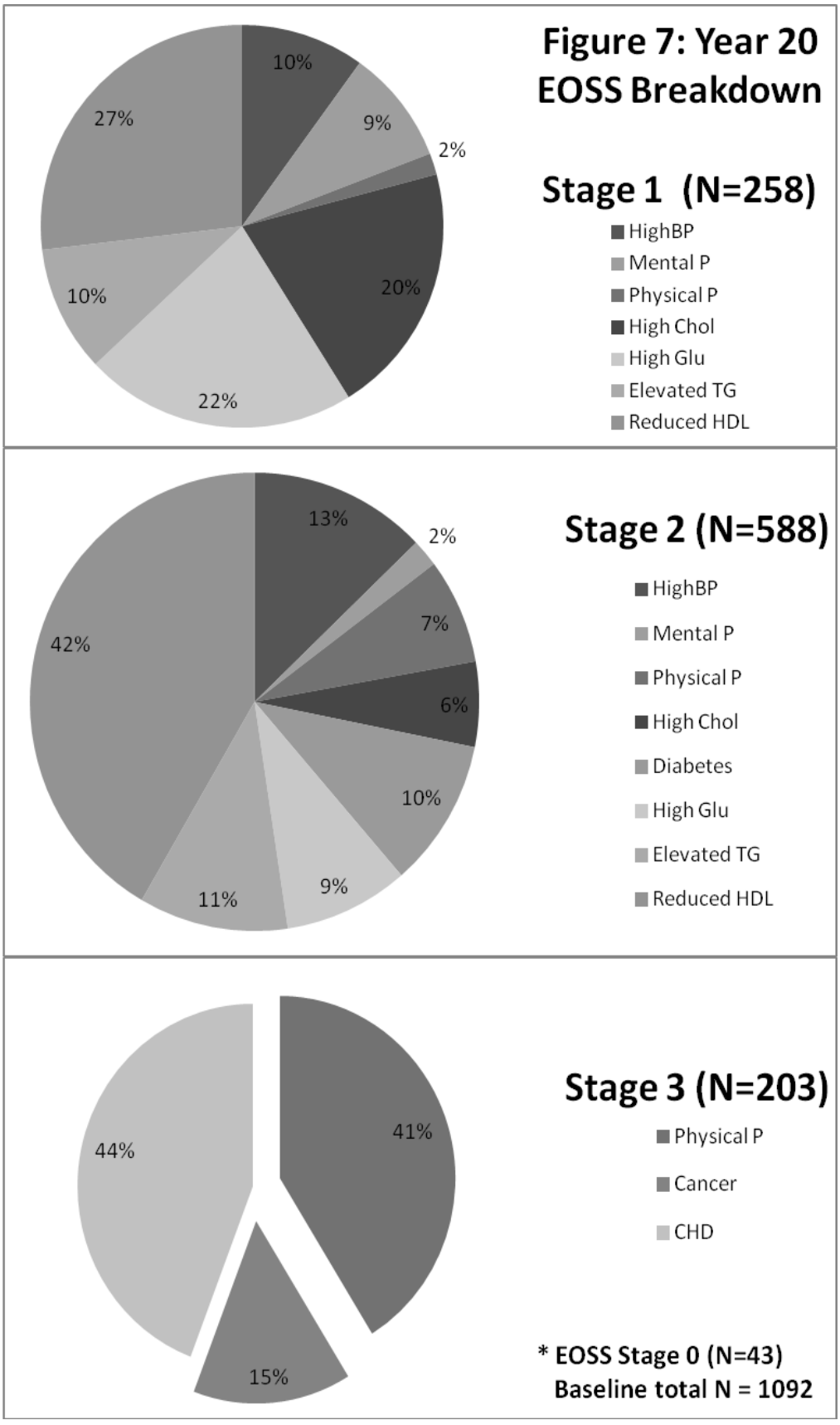


Figure 7: Year 20 EOSS Breakdown
Stage 1 (N=258)
10%
9%
2%
20%
22%
10%
27%
HighBP
Mental P
Physical P
High Chol
High Glu
Elevated TG
Reduced HDL
Stage 2 (N=588)
13%
2%
7%
6%
10%
9%
11%
42%
HighBP
Mental P
Physical P
High Chol
Diabetes
High Glu
Elevated TG
Reduced HDL
Stage 3 (N=203)
41%
15%
44%
Physical P
Cancer
CHD
* EOSS Stage 0 (N=43)
Baseline total N = 1092

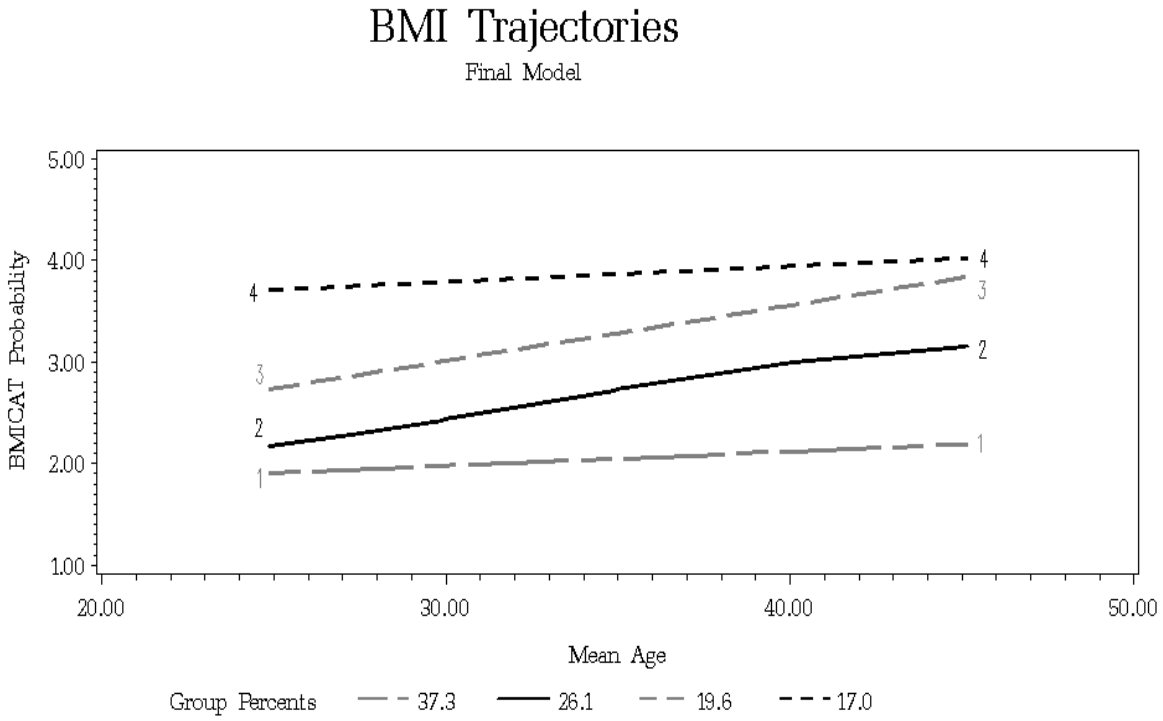


Figure 8: Trajectory Modelling of BMI Categories

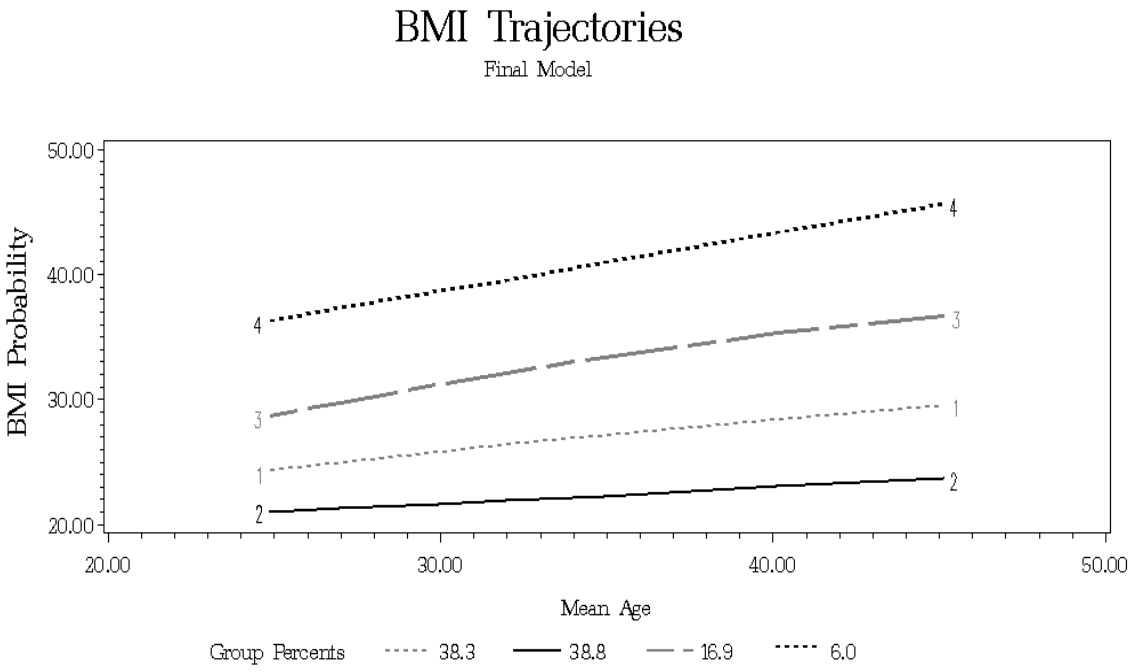


Figure 9: Trajectory Modelling of Continuous BMI

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