# Contribution of Ethnicity, Sex, and Age to the Relationship between Obesity and Mortality: Analyses from the U.S. National Health and Nutrition Examination Survey (NHANES)

**David Barbosa**

**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 KINESEOLOGY AND HEALTH SCIENCE

YORK UNIVERSITY
TORONTO, ONTARIO

APRIL 2022

# Abstract

**Background:**

Risk factors of obesity are well documented and there are various clinical tools used to assess the risk of obesity including Obesity scaling using BMI, metabolic syndrome, metabolic phenotyping and EOSS. What is still not known is how population demographics have changed over time and their association with obesity and obesity-related health risk.

**Methods:**

Data analysis was performed on a merged dataset of continuous cycles of the National Health and Nutrition Examination Survey (NHANES 1999–2014). Descriptive statistics, Kaplan-Meier curves and Cox proportional hazard regressions were performed on the participants and their assessments from the various clinical tools to visualize and determine patterns overtime.

**Results:**

Over time the proportion of individuals in high-risk groups increased across all clinical tools and these high risk groups demonstrated the greatest mortality over time. Over time we have seen the population of the US getting older and more ethnically diverse increasing the risk for obesity and other metabolic factors.

**Conclusion**:

In summary, of all the clinical tools assessed in this study, EOSS was the most robust method for the prediction of mortality risk over time. By contrasting the different preclinical tools, we were able to learn which factors are the most crucial in predicting risk of death, and in the future, may contribute to more targeted interventions.

# Table of Contents

# List of Tables

# List of Figures

# Acronyms and Abbreviations

| | |
|---|---|
| BMI - | Body Mass Index |
| CDC - | Centre for disease Control |
| CHF - | Congestive Heart Failure |
| CRF - | Cardiorespiratory Fitness |
| IDF - | International Diabetes Federation |
| EOSS - | Edmonton Obesity Staging System |
| MHO - | Metabolically Healthy Obese |
| MetS - | Metabolic Syndrome |
| MUO - | Metabolically Unhealthy Obese |
| NCEP ATP III - | National Cholesterol Education Program Adult Treatment Panel III |
| WC - | Waist Circumference |
| WHO - | World Health Organization |

# Introduction

Globally the prevalence of obesity and overweight individuals is on the rise[1–4]. As of 2016, the World Health Organization (WHO) estimated that 1.9 billion adults were overweight and 650 million had obesity, which represents a tripling of worldwide obesity levels since 1975 [5]. From 1980 through to 2008, average body mass index (BMI) increased approximately 0.4 $kg/m^2$ per decade in men, and 0.5 $kg/m^2$ per decade in women [1]. During this time frame, the cost for medical care related to obesity in the United States more than doubled to an estimated $147 (USD) billion [6]. The variation in prevalence of obesity rates between individuals and populations have been attributed to differences in a host of sociodemographic (e.g. age, sex, ethnic, socio-economic status and education, etc.)[7–9], behavioral (e.g. energy expenditure, excessive caloric intake, psychosocial stress, sleep habits, etc.)[7, 9, 10], and environmental factors (e.g. pollution, urbanization, food availability, etc.)[9, 11-14]; however, the "cause" for the *rise* in obesity over time is multifactorial and complex.

Due to its progressive, relapsing, and chronic nature, obesity is now classified by the American and Canadian Medical Associations as a chronic disease[15-16].Within the bariatric medicine community, "obesity" is typified by excess weight that impairs health; however, for surveillance and general screening purposes, it has been historically operationalized in (over)simplified ways through the use of anthropometric measurements [17]. Most notably, BMI ($kg/m^2$) has been used to classify individuals as underweight (<18.5 $kg/m^2$), "normal" weight (18.5 - <25 $kg/m^2$), overweight (25-<30 $kg/m^2$), and obese (≥30 $kg/m^2$)[16]. Obesity is further classified as Class I (BMI ≥30 - <35 $kg/m^2$), Class II (BMI ≥35 - <40 $kg/m^2$), and Class III (BMI ≥40 $kg/m^2$)[18]. Since the early 2000s, elevated abdominal obesity has also been used to track obesity-related

health risk [waist circumference (WC) of >102 cm in men and >88cm in women] by organizations such as the U.S. National Institutes of Health [19] and Health Canada[20]. While these anthropometrics offer an easy-to-use snapshot of obesity in a population or over time, a number of methodological limitations limit the interpretation and generalizability of their use.

## Obesity-Related Mortality Risk

According to the most recent *Global Burden of Disease Report* it was estimated in 2015, excess weight was responsible for approximately 4 million deaths worldwide [21]. Within low income countries, obesity is the fifth most prevalent risk factor for all-cause mortality (following high blood pressure, tobacco use, high glucose levels and physical inactivity), and the third highest in middle and high income countries[22]. It is now well-established that obesity is associated with an increased risk of developing a number of comorbidities, including many of the commonly referred to causes of death (e.g. type 2 diabetes, heart disease, and cancer) [9,21, 23–25]. These factors have led some experts to predict a reversal or a slowing of the life expectancy gains of high-income nations in the past decades[23].

The relationship between BMI and all-cause death was first described as a J-Shaped relation, with elevated risk amongst both underweight and obesity groups [26, 27]. More recently, variation in these relationships have been shown, particularly as it relates to age, sex, and ethnicity, with the underlying hypothesis being that body composition may be playing a role [26, 28]. More specifically, BMI cannot differentiate between lean muscle mass or fat [29], meaning that two individuals with the same BMI may have important differences in body fat percentage and location [30]. Health risks associated with a given BMI or excess weight may

also vary widely [31–34], since many studies use self-reported weights and heights, meaning that existing inconsistencies in how BMI relates to health risk may be further exaggerated [35].

## Age Variation and Obesity

As of 2018 the prevalence of obesity in adults aged 20 or older in the United States was roughly 42.4% [36]. Increasing steadily with age, BMI reaches a peak in late middle-age, followed by a gradual decline [21]. The age at which one gains weight has a large impact on their overall health and weight management [37]. Younger individuals who have an excess of weight generally will stay at a higher weight into adulthood and have an increased risk of developing chronic disease or disability at a younger age. Earlier onset of obesity may also contribute to a history of weight cycling and elevated health risk, due to a longer duration of obesity [38-40].

Although an elevated BMI is associated with higher all-cause mortality[26], at advanced ages, the J-shaped association between BMI and all-cause mortality weakens and shifts towards favouring individuals who are mildly overweight, causing the association to become more U-shaped [27]. This age-related effect is further displayed in a phenomenon known as the "obesity paradox": patients who have chronic diseases such as heart failure, kidney disease and hypertension have greater survival with excess weight when compared to leaner individuals [41–43]. Granted that having an excess of weight in this clinical population appears to be beneficial, any weight gain is still associated with a higher risk of disability or mortality. By contrast, voluntary weight *loss* in this population has not been shown to improve mortality [44]; instead, given the possibility of age-related loss of muscle (and the co-occurrence of sarcopenic obesity), weight loss in this population may in fact increase the risk of mortality [45, 46] and may be

contraindicated. To date, ongoing surveillance reporting for patterns of obesity does not uniformly exclude older adults (age 65+) from population prevalence estimates, which may artificially increase the prevalence, and confound the estimate of health risk.

## Sex Variation and Obesity

In adulthood, the prevalence of obesity is generally higher in women compared to men across all ages and ethnicities [21, 47]. Despite this, males typically have a higher prevalence of cardiometabolic disease and mortality risk than females, regardless of weight [48]. This is explained in part, by biological (sex) differences in metabolism and body fat composition that have been observed in men and women [48,49]. In general, women have more fat mass proportionally, while men proportionally have more muscle mass [48]. When women gain weight, the noticeable excess fat typically accumulates in the thighs and hips, whereas in men, noticeable excess weight accumulates in the abdomen [49]. This may translate to biological differences in obesity-related health risk. For example, in a study by Schorr et al. (2018), females had 42% fat mass while men had 33%; however, men had higher levels of ectopic fat compared to women, and fat located in the lower extremities was protective against cardiometabolic risk [48]. Moreover, for women, the highest prevalence in obesity is observed just after menopause (60 and 64 y) [21] where there is a rapid decrease in estrogen [50], which translates into a 3.3 fold higher risk of developing metabolic syndrome (MetS) during the period immediately following, as compared to before, the onset of menopause[51].

By contrast, the peak prevalence of obesity in men occurs between 50 and 54 years of age [21]. Unlike females, who very rapidly change their hormone composition, testosterone levels in men tend to decline slowly (at a rate of approximately 0.8% per year) in middle age [52].

Importantly, the level of free testosterone has an inverse relationship with obesity in that as free testosterone levels decrease, weight gain increases [53]. This relationship also works in reverse where excess weight will contribute to lower testosterone levels, which help to reinforce a closed system of decreasing testosterone and increased weight gain [53]. Lower levels of testosterone have also been linked to MetS, cardiac failure and heart disease [54].

## Ethnic Variation and Obesity

Beyond the age- and sex-variation described above, there are also considerable differences in the prevalence of obesity across different ethnic groups. According to the 2017-2018 U.S. NHANES, the prevalence of obesity in men was highest in Hispanic (45.7%), followed by Non-Hispanic White (44.7%), Non-Hispanic Black (41.1%) and with the lowest prevalence observed in Asian men (17.5%) [36]. In females, a similar, but slightly exaggerated pattern was found: Non-Hispanic Black women had the highest prevalence of obesity (56.9%) followed by Hispanic women (43.7%), White women (39.8%), and Asian women (17.2%) [36]. High-risk waist circumferences also varied greatly between ethnicities. While differences in the prevalence of obesity yields important information for targeted intervention, they may mask obesity-related health risks, due to differences in biological, social, and behavioral factors that are difficult to capture by BMI alone [47, 55]. In particular, South Asians have been shown to have a higher percentage of body fat than White individuals, and will have a higher likelihood of developing diabetes and cardiovascular disease for a given BMI [56-58]. Using standard BMI criteria, a segment of these high-risk ethnic groups (who would not be classified as obese but may be suffering from the complications of excess weight) would be missed – a finding commonly referred to as "hidden obesity" [59]. To address this limitation, the BMI cut-off

values for “overweight” and “obesity” are approximately 3 kg/m$^2$ lower, meaning that someone of South Asian descent would be considered overweight with a BMI of 22 kg/m$^2$ [56]. By contrast, African Americans have a much greater odds of developing hypertension compared to other ethnicities but have a much lower odds of developing MetS, and may have *lower* health risk for a given BMI in some populations [60, 61]. In keeping with these findings, the International Diabetes Federation (IDF) defines a high-risk waist circumference within Asians and Hispanics as ≥ 90 cm for men and ≥80 cm for women, ≥ 94 cm for men and ≥80 cm for women of African American decent, while maintaining higher WC action thresholds of ≥ 102 cm and ≥88 cm in men and women of all other ethnic groups [62].

## Pre-Clinical Risk Factor Tools

With the limitations of anthropometric assessment of obesity noted above, a number of “pre-clinical” risk factor tools (e.g. Metabolic Syndrome (MetS); Edmonton Obesity Staging System (EOSS); Metabolically Healthy Obesity (MHO), etc.) have been used either in place of, or in combination with, BMI and WC for the tracking of obesity-related health risk. While not designed specifically for this purpose, use of these tools may help to circumvent some of the demographic differences in ethnicity, sex, and age, that may help to better understand changing patterns of obesity prevalence and how excess weight relates to mortality risk at the population-level. A short review of these tools is included in the following sections.

## Obesity and the Metabolic Syndrome

There is a strong association between obesity and cardiovascular risk factors such as dysglycemia, dyslipidemia and hypertension [5]. Abdominal obesity, when paired with these other cardiometabolic risk factors creates a cluster effect which is known as Metabolic Syndrome

(MetS). While there are a number of definitions of MetS, the most common criteria are those of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) wherein an individual is classified with MetS if they have 3 or more of the following:

- High abdominal obesity - WC ≥102 cm in men and ≥88 cm in women
- High level of blood triglycerides - ≥150 mg/dl
- Low level of high-density lipoprotein (HDL) cholesterol - <40 mg/dl in men and <50 mg/dl in women
- High blood pressure (BP) - >130/85 mmHg (or pharmacotherapy)
- High fasting glucose - >110 mg/dl (or pharmacotherapy)

Individuals with MetS have a 5-fold increase in the risk of diabetes, a 2-fold increase in the risk of cardiovascular disease (CVD) and a 1.5-fold increase in the risk of all-cause mortality [63], [64]. Although abdominal obesity is a key component of the MetS, the incorporation of additional related metabolic risk factors may provide an added advantage to describe the risk of CVD or all-cause mortality.

## Metabolically Healthy Obesity and the "Fit-but-Fat" Paradox

A subgroup of individuals (6-35%) with elevated general weight or abdominal obesity, but no demonstrated risk factors or elevated mortality risk [65, 66], have been referred to as the "metabolically healthy obese" (MHO) phenotype. Although there is currently no universal definition of MHO (Stephan 2013), studies have differentially classified MHO as those with less than 3 cardiometabolic risk factors [31, 66], 1 or fewer metabolic risk factors [65], or an absence of hypertension, diabetes or hyperlipidemia [67, 68]. Due to the inconsistent nature of these definitions, many of the studies completed have reported that the MHO phenotype is associated

with CVD or greater mortality while including factors that are known to already be associated with these risks such as hypertension or glucose impairment [66]. In line with this, individuals who are classified as MHO will not have hypertension, glucose impairment, low HDL cholesterol levels, inflammation or liver function abnormalities even though they may be classified as "obese" by anthropometry [34]. More importantly, MHO without any metabolic risk factors except abdominal obesity do not have an increased mortality risk [65].

One of the key differentiators of metabolic health in the presence of excess weight is higher cardiorespiratory fitness (CRF) and physical activity (PA), something that is commonly referred to as the "fit but fat" paradox. Indeed, the protective effect of high CRF and regular PA on physical, function, and mental health is well known [69]. Physical activity, and moderate to high levels of CRF, are among the most important factors in reducing all-cause mortality among those living with obesity [70]. Multiple studies have found that regardless of weight, individuals who have higher CRF were less likely to die [70]. Compared to an age- and sex-matched individual with a high CRF, an unfit individual's relative risk of death is more than twice as high, regardless of their weight [71,72]. Currently, one half (54.1%) of U.S. adults are meeting recommended weekly levels of PA (i.e. 150+ minutes of moderate-intensity activities, or 75+ minutes of vigorous-intensity activities, or a combination of both) sufficient for health [73], and <10% would be considered fit-but-fat (i.e. an individual is physically fit but has excess weight) [74].

## Edmonton Obesity Staging System

While these previous clinical tools have largely focused on metabolic risk, the Edmonton Obesity Staging System (EOSS) [75], [76] takes a more holistic approach by incorporating

physical, functional, and mental health comorbidities. The EOSS staging tool uses both BMI-defined obesity classes (I-III) as well as its own criteria for obesity staging [75]. The EOSS criteria includes 5 stages from 0 to 4:

- In Stage 0 individuals have no symptomology, and in the presence of "obesity" would be prescribed counselling to prevent *further* increases in weight.
- In Stage 1, individuals have mild or subclinical symptoms. These patients will undergo surveillance and are prescribed weight loss interventions such as dieting and exercise.
- Stage 2 is characterized by the emergence of moderate symptoms and/or a chronic obesity-related disease. Patients in this stage will have close monitoring of their comorbidities and may be given advice on more aggressive management options such as bariatric surgery or pharmaceuticals.
- Stage 3 includes significant symptomology and/or established end stage organ damage. Patients at this stage require aggressive treatment of their obesity and comorbidities with surgery or pharmaceuticals.
- Finally, Stage 4 includes individuals with severe end stage disability or disease related to obesity. Because of the severity of disease and disability in this group, only palliative care would be advised

## Objectives

Previous research has examined the temporal contribution of lifestyle-related behaviors (e.g. energy expenditure and energy intake) on obesity, less research has been focused on how

population demographics have changed over time and their association with obesity and obesity-related health risk.

Given the heterogeneities described above, a closer examination of age-, sex-, and ethnic-related variation in the prevalence of obesity and its association with mortality risk is warranted. The overarching purpose of this work is therefore two-fold: i) to explore the extent to which obesity and obesity-related health risk (as defined by BMI and other tools) has varied across time, and the extent to which differences in age, sex, and ethnicity may be contributing to changes in the overall estimates.

### Specific Aims

Aim 1: To visualize the prevalence of overweight/obesity, MetS, metabolically healthy obesity and EOSS staging over time;

Aim 2: To examine sex, age and ethnic variations in these patterns, and;

Aim 3: To examine mortality trends over time in relation to each of the obesity assessment tools.

## Methods

### Participants

This study will make use of a merged dataset of continuous cycles of the National Health and Nutrition Examination Survey (NHANES 1999–2014), a series of representative surveys and mobile exam centre visits conducted nationwide in the United States by the Center for Disease Control (CDC). NHANES continuous cycles are released biannually, and the merged data set includes the 8studies which cover the time periods from 1999–2014. All participants provided written consent to take part in the study.

## Survey methods

Demographic information including age, sex, ethnicity, smoking status, alcohol consumption, poverty-to-income ratio, and time since immigration as well as PA level were assessed by self-reported questionnaire and are treated as covariates. Medical history and medication history were also recorded to determine the grading of the EOSS pre-clinical tool. Alcohol consumption was categorized into 3 levels; 1. non-drinkers, 2. moderate consumption (≤7 drinks per week for women and ≤14 per week for men and no binge drinking defined as ≥5 drinks in a day more than once a month) and 3. heavy consumption (>7 drinks per week for women, >14 per week for men or binge drinker) [77]. BMI and WC were measured by the trained technicians at a mobile exam centre visit. Responders who were under the age of 20 years, had a BMI <25 kg/m$^2$, were pregnant, had a history of cancer, did not fast for at least 8 hours prior to completing lab tests or are missing BMI, MetS, MHO status or EOSS staging information or missing mortality information were excluded from analysis (**Figure 1**). In addition, individuals missing any of the following covariables were excluded from the study: sex, education, level of physical activity, alcohol consumption, smoking history, income level, ethnicity or time in US. Individuals were not excluded if any of the medication use or medication history required for EOSS categorization was missing.

## Obesity Measurements

WHO recommended BMI cut-offs were used:

- Overweight ≥25 - <30 kg/m$^2$
- Obesity ≥30 kg/m$^2$
- Class I obesity ≥30 - <35 kg/m$^2$
- Class II obesity ≥35 - <40 kg/m$^2$

- Class III obesity ≥40 kg/$m^2$

## Metabolic Measurements

NCEP ATP III criteria for MetS and IDF criteria for WC will be used for metabolic factor cut-offs:

- High abdominal obesity (White or Other) – WC ≥102 cm in men and ≥88 cm in women
- High abdominal obesity (Black) – WC ≥94 cm in men and ≥80 cm in women
- High abdominal obesity (Hispanic) – WC ≥90 cm in men and ≥80 cm in women
- High level of blood triglycerides - ≥150 mg/dl
- Low level of high-density lipoprotein (HDL) cholesterol - <40 mg/dl in men and <50 mg/dl in women
- High blood pressure (BP) - >130/85 mmHg
- High fasting glucose - >110 mg/dl

## Metabolic Phenotype

A stringent definition of MHO was used in this study wherein an individual did not have any cardiometabolic risk factors (except abdominal obesity). In other words, MHO was classified as those with a BMI of ≥30 kg/$m^2$ and 0 cardiometabolic risk factors except for abdominal obesity. Conversely, MUO was classified as having a BMI of ≥30 kg/$m^2$ and 1 or more cardiometabolic risk factors, not including abdominal obesity. In addition, metabolically healthy not-obese (MHNO) was defined as having a BMI <30 kg/$m^2$ and 0 cardiometabolic risk factors (with the exception of abdominal obesity), and metabolically unhealthy not-obese (MUNO) was defined as those with a BMI <30 kg/$m^2$ and 1 or more cardiometabolic risk factors, not including abdominal obesity.

## EOSS Staging Cut Offs

To establish EOSS classifications, staging criteria adapted from Padwal et al. 2011 and Canning et al. 2015 was used [78]:

Stage 0 – No reported EOSS factors

Stage 1 – No reported EOSS factors higher than stage 1 and one or more of the following;

- Glucose ≥ 5.6 - < 6.9 mmol/L
- Cholesterol ≥ 5.2 - <6.2 mmol/L
- Triglycerides ≥ 1.7 – <2.2 mmol/L
- HDL Cholesterol if male ≤ 1.6 - > 1 mmol/L or if female ≤ 1.6 - > 1.3 mmol/L
- LDL Cholesterol ≥ 3.3 - < 4.1 mmol/L
- Systolic Blood Pressure ≥ 130 - < 140 mmHg
- Diastolic Blood Pressure ≥ 85 - < 90 mmHg
- AST >30 U/L
- ALT if male >47 U/L or if female >30 U/L
- GFR ≥ 60- <90 mL/min/$m^2$
- Functional impairment

Stage 2 – No reported EOSS factors higher than stage 2 and one or more of the following;

- Glucose ≥ 6.9 mmol/L
- Diagnosed type 2 diabetes or type 2 diabetes medication
- Cholesterol ≥ 6.2 mmol/L
- Diagnosed hypercholesterolaemia
- Triglycerides ≥ 2.2 mmol/L
- HDL Cholesterol if male ≤ 1.0 mmol/L or if female ≤ 1.3 mmol/L
- LDL Cholesterol ≥ 4.1 mmol/L
- Diagnosed hyperlipidaemia or hyperlipidaemia medication
- Systolic Blood Pressure ≥ 140 mmHg

- Diastolic Blood Pressure ≥ 90 mmHg
- Diagnosed hypertension or hypertension medication
- Gout
- Oseteoarthritis
- Fatty liver disease
- GFR ≥ 30- <60 mL/min/$m^2$
- ADL limitations
- Other Depressive symptoms (not major depression)

Stage 3 – No reported EOSS factors higher than stage 3 and one or more of the following;

- Angina
- Heart attack
- Heart failure
- Coronary artery disease
- Stroke
- Major Depression
- GFR <30 mL/min/$m^2$

Stage 4 – Currently no data available for evaluation at this stage

## EOSS ANALYTIC NOTES

***Physical Health Criteria:*** Despite the availability of the most EOSS components, due to inconsistencies in data collection, measures of sleep apnea, dyspnea, chronic obstructive pulmonary disease (COPD), joint soreness, and anxiety were not able to be assessed. Osteoarthritis, congestive heart failure (CHF), CAD, angina, stroke, and gout were self reported. Gout information is only available from 2007 onwards. Due to the low number of EOSS 0 participants, EOSS 0 was grouped together with EOSS 1 in the analysis.

Glomerular Filtration rate was calculated using the CKD-EPI equation for glomerular filtration rate[79]:

$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black]

.

Fatty liver disease was diagnosed using the US FLI equation[80];

$$\text{US LFI} = (e^{-0.8073*\text{non-Hispanic Black} + 0.3458*\text{Mexican American} + 0.0093 * \text{age} + 0.6151 * \log(\text{GGT}) + 0.0249*\text{WC} + 1.1792*\log(\text{insulin}) + 0.8242*\log(\text{glucose}) - 14.7812})/(1+e^{-0.8073*\text{non-Hispanic Black} + 0.3458*\text{Mexican American} + 0.0093 * \text{age} + 0.6151 * \log(\text{GGT}) + 0.0249*\text{WC} + 1.1792*\log(\text{insulin}) + 0.8242*\log(\text{glucose}) - 14.7812})*100$$

If any participants had the hepatitis B surface antigen or hepatitis C antibody present or were considered a heavy alcohol consumers then they were coded as not having NAFLD.

***Mental Health Criteria:*** Depression was assessed using the PHQ - 9 questionnaire, which was only available from 2005 onwards. The questionnaire consists of the following 9 statements [81];

1. Little interest or pleasure in doing things
2. Feeling down, depressed, or hopeless
3. Trouble falling or staying asleep, or sleeping too much
4. Feeling tired or having little energy
5. Poor appetite or overeating
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down
7. Trouble concentrating on things, such as reading the newspaper or watching television
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual
9. Thoughts that you would be better off dead, or of hurting yourself

Responses included were;

- Not at all
- Several days
- More than half the days

- Nearly every day

Major Depression was classified when respondents selected “more than half the days” or “nearly every day” on 5 of the 9 statements including items 1 and/or 2. If 2-4 of the 9 statements had either “more than half the days” or “nearly every day selected” including items 1 and/or 2, then it was classified as other depressive syndrome.

As there is no available data on mental health from 1999-2004 EOSS was assessed only by functional and physical criteria during this time. All three components were used to assess EOSS grading from 2005 onwards.

***Functional Health Criteria:*** Functional limitations and activities of daily living (ADL) were assessed by reviewing health interview questions [82]. Functional limitation and ADL questions started with “By yourself and without using any special equipment, how much difficulty do you have” followed by a specific task.

The tasks for functional limitations were;

1. walking for a quarter of a mile [that is about 2 or 3 blocks]?
2. walking up 10 steps without resting?
3. stooping, crouching or kneeling?
4. lifting or carrying something as heavy as 10 pounds [like a sack of potatoes or rice]?
5. walking from one room to another on the same level?
6. standing up from an armless straight chair?

The tasks for ADL limitations were;

1. getting in or out of bed?
2. eating, like holding a fork, cutting food or drinking from a glass?
3. dressing {yourself/himself/herself}, including tying shoes, working zippers, and doing buttons?

Responses included;

- no difficulty
- some difficulty
- much difficulty

- unable to do

Starting in 2003-2004 the option “don’t do” was added, but due to a low number of responses, “don’t do” and “unable to do” response options were added together.

If a participant answered either “much difficulty” or “unable to do” to any of the functional limitation questions then they would be considered to have a mild-moderate impairment. If a participant answered either “much difficulty” or “unable to do” to any of the ADL limitation questions or that they required special equipment to move around then they would have a severe impairment.

Participants must have responded to at least 4 of 6 functional limitation questions and at least 2 of 3 ADL questions to be included in the study.

### Statistical analysis

To assess aim 1, a descriptive univariate analysis (chi-square) was used to assess the weighted demographics of the population and overweight/obesity, MetS status, MHO vs MUO and EOSS groups over time. For aim 2, a chi-squared analysis was used to assess differences in the prevalence (N, %) of male/female, age (20-44; 45-64, and 65+), and ethnicity (White, Black, Hispanic, and Other) across each of the proposed pre-clinical tools over time. For obesity-defined by BMI and WC, analyses were limited to groups within the age range where BMI tracking is generally recommended (i.e. age 20-64 y), and with the application of ethnic-specific anthropometric thresholds.

To assess aim 3, unadjusted Kaplan-Meier curves were used to assess group differences in all-cause mortality (i.e. survival probability) across each of the preclinical tools. Subsequent to this, a series of five weighted Cox proportional hazard regression models were used to estimate the risk of mortality across overweight/obesity, MetS (yes/no), MHO vs MUO and EOSS groups over time, as follows: Model 1 does not include any adjustments; Model 2 was adjusted for social factors (smoking status, alcohol consumption and physical activity level); Model 3 was adjusted for demographic factors (age, sex, ethnicity and immigration status); Model 4 was adjusted for socioeconomic factors (age, sex, income, education and immigration status), and; Model 5 includes all variables (age, sex, ethnicity, income, education, smoking status, alcohol

consumption, immigration status and physical activity level) with the addition of NHANES cycle.

Data analysis was conducted with SAS version 9.4 (SAS, Inc, Cary, NC), with statistical significance set at an alpha of 0.05. All analyses were weighted using SAS survey procedures with bootstrap replicates for robust estimates of variance.

## Results

A total of 10,852 participants aged 20 years or older were included in the final analysis from NHANES continuous (1999-2014), representing a total weighted sample of 61,817,017 (±1644616) individuals (Figure1, Table 1,2). In general, the sample was comprised of a higher proportion of males (53.5%, ± 0.9%), younger adults (20-44 years of age, 58.8%, ±1.0%), and non-Hispanic White (67.0%, ± 1.4%) participants. From 1999-2014, the prevalence of overweight declined (overweight: 55.5% [±2.1] in 1999-2000 to 45.8% in 2013-2014 [±1.5], Table 2), whereas the prevalence of class II (11.1%[±1.2] to 13.5%[±1.0]) and III obesity (5.2%[±0.8] to 12.1%[±1.2]) increased steadily. The prevalence of class I obesity remained relatively stable over time(28.2%[±2.1] in 1999-2000 to 28.6%[±1.8] in 2013-2014).

Table 3 reveals demographic variation in BMI, MetS, metabolic phenotype, and EOSS categories.

**Obesity**

Although there are more men than women in the study (33,089,942 or 53.5%[± 0.9%]), women have higher BMIs than males, and the overall proportion of women within the obesity range was higher (class II: 61.6% [±2.3%]; class III: 63.5%[± 2.5%]). Over time, both men and

women experienced large decreases in the proportion of overweight individuals from 1999-2000 to 2013-2014 (58.2%[± 2.7%]-52.7% [± 2.9%] and 52.4%[± 2.7%]-40.1%[± 2.1%], respectively), with increases in all three obesity categories over time for women, and increases in class II and III obesity in men (Figure 2a-b).

Although middle-aged adults (45-64) account for 32.6%(± .9%) of the study sample, they account for a greater proportion of individuals with obesity (class I: 34.8%[± 1.9%]; class II: 34.87%[± 2.1%], and; class III: 36.3%[± 2.4%]) cohorts (Table 3). Among younger individuals (20-44 y) there was a decreasing trend in the proportion of overweight, but increasing prevalence of obesity (Figure 3a). The same trends are observed for overweight and class III obesity for middle-aged and older adults (>65) over time, with slightly greater fluctuation within cycles (Figure 3c).

The ethnic group with the highest BMI with respect to their representation in the sample is the non-Hispanic Blacks. Whereas non-Hispanic Blacks account for 13.7%(± 0.8%) of the weighted sample, they represent 19.5% (± 1.8%) and 25.1%(± 2.1%) of individuals with class II or III obesity, respectively (Table 2). Of note, the non-Hispanic White and Hispanic ethnic groups demonstrate very similar trends in BMI over time, aside from a greater decrease in the proportion of overweight individuals in the Hispanic population (Figure 4a, 4b). In all groups except the Other ethnic group, the proportion of individuals in the overweight range decreased over time, while the prevalence of class III obesity increased (Figures 4a-d). The Other ethnic group also had a steep increase in the prevalence of overweight from1999-2000 (40.5%[± 12.5%]) and 2001-2002 (83.6%[± 5.2%]), followed by a rapid decline the following cycle (49.3%[± 10.5%]), with a marked increase in the proportion of individuals within the overweight range in 2011-14 (Figure 4d).

In a pooled sample of all study years, a Kaplan-Meier analysis was conducted to analyze survival probability by BMI category (Figure 14a). Although no difference in survival probability was observed ($\chi 2(3) = 5.816$, $p = 0.1587$), visual inspection suggested a trend towards slightly greater survival for individuals with class II obesity, and slightly lower survival for those with class III obesity. In models1, 2 and 4 there was no obesity categories which showed a significant change in risk of death over time compared to the overweight class (table 4). In model 3 the class III obesity subgroup demonstrated an increase in risk of death over time (HR=1.45, 1.01-2.07) compared to the overweight subcategory. When adjusting for all covariates (model 5), individuals in the class II obesity group showed a decrease in risk of death over time compared to the overweight group (HR=0.48, 0.23-0.99).

**MetS**

From 1999 to 2006 the prevalence of MetS was relatively stable (31.2%[± 2.6%] to 32.8%[± 3.0%]), followed by a sharp increase in 2007-2008 (40.1%[± 2.1%]), where it remained stable until 2013-2014. Throughout the duration of the analysis the prevalence of MetS never surpassed 50% (Table 2).

The proportion of men who had MetS increased linearly over time (figure 5a), whereas in women, the prevalence of Mets declined until a sharp increase in 2007-2008, after which a further decline occurred (Figure 5b). As expected, the prevalence of MetS increased markedly with age (Table 2). In adults under 45, the prevalence of MetS was stable between 1999 and 2006 (24.5%[± 3.0%]), followed by a marked increase to 35.8%(± 3.0%) in 2007-2008, and a gradual decline thereafter (Figure 6a). In middle aged adults, the proportion of individuals with MetS remained stable over the cycles with a minor trough from 2005-2008 (Figure 6b). By contrast, the prevalence of MetS increased and decreased inconsistently in older adults (Figure

6c). As seen in Table 2 the presence of MetS by ethnicity varied widely. For Hispanic individuals, the prevalence of MetS decreased between 1999-2004 (40.38% [± 3.0%] to 26.7%[± 2.3%]), then increased to a peak in 2009-2010 (46.28%[± 4.7%]), followed by a slow decline (Figure 7a). By contrast, in the non-Hispanic White group, the prevalence of MetS was relatively stable at ~31% until 2007-2008 where it increases and remains at ~40% for the duration of the cycles (Figure 7b). In the non-Hispanic Black population, the prevalence of MetS increased from 23.6%[± 4.5%] in 1999-2000 to 42.4% (± 3.9%) in 2009-2010, followed by a decrease to 32.1% (± 2.5%) in 2013-2014 (Figure 7c). No consistent pattern can be discerned within the Other ethnic group (Figure 7d).

Over time, there were significantly more deaths in individuals with MetS, compared to without MetS ($\chi 2(1) = 22.5198$, p = <0.0001) (Figure 14b). Compared to those without MetS (HR=1.00, referent), individuals with MetS had a 71% higher risk of all-cause death over time (HR 1.71, 1.29-2.26) (Table 4). When adjusting for social factors (Model 2), individuals with MetS remained at a 157%% higher risk of death (HR=1.65, 1.24-2.18), an effect that was abolished with Model 3 (HR=1.05, 0.78-1.40), Model 4 (HR=1.00, 0.76-1.31), and Model 5 (HR=1.08, 0.53-2.22).

**Metabolic Phenotype**

From 1999 to 2014 the two most prevalent BMI "phenotypes" were the MUNO and MUO (Table 2), representing 17.9% (± 0.9%) and 37.3% (± 1.0%) of the sample, respectively. Over time, the prevalence of MUO increased from 32.2% (± 2.3%) in 2001-2002, to 44.8% (± 1.1%) in 2013-2014, whereas the prevalence of MUNO fluctuated greatly. Compared to MUNO, the MHNO group followed an inverse gradient, and MHO fluctuated between 7.5% (± 1.6%) and 12.1% [± 2.2%]throughout the study period. In both males and females, the proportion of

individuals who were MUO increased over time, MUNO has decreased, and the proportion of MHO and MNHO individuals remained stable over time (Figure 8a,b). In general, there is a greater proportion of women who are MHO and MUNO compared to men (MHO: 54.9%[± 3.4%] vs 45.1%[± 3.4%], and; MUNO: 51.4% [± 1.3%] vs 48.6% [± 1.3%]), and a greater proportion of men who were MHNO and MUNO compared to women (55.0% [± 2.1%]vs 45.0%[± 2.1%], and 60.1[± 1.6%]% vs 40.0%[± 1.6%]).Young adults also make up the majority (58.8% [±1.0%]) of total sample and a greater proportion of the MUNO (72.9%[± 2.5%]) and MHO (75.3%[± 3.1%]) phenotypes (Figures 9a-c). While the prevalence of each phenotype varies across time, the prevalence of MHO and MHNO remain relatively stable with no net growth over time in all three age groups; the prevalence of MUO is increasing in all three age cohorts, and; the prevalence of MUNO is decreasing. When considering patterns of obesity phenotypes by ethnicity, all ethic groups aside from the other ethnic category had a decrease in MUO prevalence over time and an increase in MUNO (Figure 10a-d). Of note, Hispanic individuals experienced the largest increase in the proportion of MUO compared to the other ethnicities, with an increase from 24.7% [± 2.8%] in 2001-2002 to 48.5% [± 4.7%] in 2013-2014 (Figure 10a). By comparison, Non-Hispanic White and Non-Hispanic Black individuals increased from 33.1%(± 2.5%)-45.1%(± 1.3%) and 36.0%(± 3.9%)-48.4%(± 2.9%), respectively, in the same time (Figure 10b-c). Moreover, Non-Hispanic White and Other ethnic indiciduals were the only two groups which saw an increase in MHNO over time (Figure 10b,d).

When considering patterns of all-cause death, individuals with no metabolic risk factors (i.e. metabolically health), regardless of obesity, had lower risk of death ($\chi 2(3) = 38.6867$, $p = <0.0001$) (Figure 14c). No differences in survival probably were observed between individuals with and without obesity in the presence of metabolic risk factors (Figure 14c). In the Model 1,

metabolically unhealthy individuals regardless of obesity, demonstrated a higher mortality risk compared to those with MHNO (MUNO: HR=2.57, 1.58-4.19; MUO: HR=2.51, 1.56-4.04) (Table 3). When adjusting for social factors (Model 2), individuals with metabolic risk factors remained a higher risk of death (MUNO: HR=2.42, 1.47-3.98; MUO: HR=2.34, 1.44-3.81) compared to those who have MHNO. In Model 3, only the MUO group (HR=1.59,1.04-2.42) had a higher risk, and in Model 4, no differences were seen. Finally, within Model 5, only those in the MHO group were at a reduced risk of death compared to the MHNO group (HR=0.23, 0.07-0.77).

**EOSS**

Over all study years, approximately three-quarters of the study sample was EOSS Stage 2 (72.6%[± 0.7%]), with relatively similar proportions of EOSS Stage 0&1 (13.8%[± 0.7%] combined), and EOSS Stage 3 (13.5%[± 0.7%]) (Table 2). Over time, there has been a steady decline in the prevalence of EOSS 2 (74.8% [± 1.5%] in 1999-2000 to 66.0%[± 2.2%] in 2013-2014), whereas the prevalence of EOSS 0&1 increased marginally from 1999-2000 to 2001-2002, followed by a decline in 2003-2004 to 2007-2008, after which time it has remained stable. By contrast, the prevalence of EOSS 3 increased in each cycle from 2001-2002 (8.3%[± 1.5%]) to 2013-2014 (24.3%[± 1.8%]). Whereas there were few sex differences in these patterns, there was a higher proportion of women (58.6%[± 1.8%]) in the EOSS 3 category, and a higher proportion of men (62.3%[± 2.6%]) in EOSS 0&1 (Figure 11a-b). In both men and women, the proportion of individuals in EOSS 2 decreased over time. In women, the prevalence of EOSS 0&1 and EOSS 3 were virtually identical from 1999 to 2006, and an increase in EOSS 3 and decrease of EOSS 0&1 beyond 2007. In males, the proportion of EOSS 3 did not surpass EOSS 0&1 until 2009-2010.

Similar to the other measures of obesity-related health risk, as age increased there was a higher prevalence of EOSS 3 and a decrease in EOSS 0&1 (Figure 12a-c). As expected, the prevalence of EOSS 0&1 was the highest in young adults (Figure 12a), with increasing EOSS 3 prevalence and decreasing EOSS 0&1in middle-aged (Figure 12b) and older aged adults (Figure 12c). While the Hispanic, Non-Hispanic White, and Non-Hispanic Black groups displayed increases in prevalence of EOSS 3 over time, Non-Hispanic White individuals had the greatest increase of EOSS 3 across all groups (Figure 13a-d).

When time-to-event analyses were conducted, a consistent inverse gradient between EOSS stage and survival probability was observed. Specifically, EOSS 3 had the lowest survivability probability while EOSS 0 & 1 had the highest probability of survival ($\chi 2(2) = 136.3687$, $p = <0.0001$) (Figure 14d). In Model 1, individuals in EOSS stage 3 (HR=6.44, 2.37-17.51) had markedly higher mortality risks compared to those in EOSS 0-1 (HR=1.00, referent) (Table 4). Adjusting for Model 2, EOSS stage 3: HR=6.87, 2.55-18.54) did not materially change this association. Models 3 to 5 did not demonstrate any change in risk in all cause mortality over time for EOSS 2 and EOSS 3 compared to EOSS 0-1.

## Discussion

The primary finding from this study is that over time the prevalence of obesity and health conditions has increased in the US population. More specifically, this analysis found that all measures of obesity-related health risk (obesity, MetS, MUO, and EOSS Stage 3) increased across time in U.S. adults, but were only partially accounted for by changes in the sociodemographic characteristics of the U.S. population over time. This is consistent with the current literature that shows an overall trend towards a decrease in health over the same period in the U.S. [83-85].

The population of the United States is getting proportionately older with the vast improvements of medicine and the aging baby boomers (born between 1946 through 1964) who in 2014 were still the largest cohort at the time [86-87]. The baby boomer cohort is also important to note because they have been found to have higher rates of chronic disease and more disability than previous generations due to increased rates of metabolic factors and obesity [86]. Increases in obesity may also be playing a part with increased longevity at advanced ages as there is a protective effect of increased weight and its protection against certain chronic diseases through the "obesity paradox" [41–43]. However, as one ages the risk of mortality still increases due general physiological decline [88]. Tinetti et al. found that in older individuals aged 65 and over that the main five causes of death were heart failure, dementia, chronic lower respiratory diseases and pneumonia and cancer [89]. While obesity is a risk factor for both heart failure and respiratory diseases – and obesity accounted for 32.4% of deaths in that study - one cannot discern that an individual has these afflictions from looking at their obesity or metabolic health.

Although women were found to have a greater risk for obesity within this study, a larger proportion of men were found to have a metabolic disease, as has been observed outside of this study [21,47-48]. Of the women with MetS, a larger proportion was found to have obesity compared to males. Over time, females had higher increases in obesity and metabolically unhealthy obesity compared to men; however, similar to Beltrán-Sánchez et al. [85], there was a trend towards a modest decrease in the prevalence of MetS in women. Interestingly, even though there was a larger number of metabolically unhealthy males, there was a greater proportion of women who were found to be EOSS stage 3 and this may be due to men having a higher mortality rate [90].

Building upon Padwal et al's initial paper [76] examining EOSS class and mortality risk, the current study includes models adjusting for social (Model 2), demographic (Model 3), socioeconomic factors (Model 4), and a complete Model (Model 5) including adjustment for NHANES cycle. With this study we have shown a greater predictive capacity for EOSS compared to not only BMI, but other common risk indices (i.e. MetS, and obesity phenotype).

Of all the preclinical assessments categorizing obesity on its own was the least reliable preclinical tool for assessing risk of death over time. In the Kaplan Meyer curve (Figure 14a) there was no difference in risk of death among the groups and visually other than Obesity II there is no divergence in risk of death over time until after 12.5 years. This was supplemented by the data in Table 3 which showed that in the different models the only group which consistently was found to have a significant decrease in death was Obesity II which was apparent in Models 1, 2 and 3. According to the obesity paradox [41], older individuals who are living with obesity tend to exhibit a lower risk of death compared to those with lower weights, and that weight loss among older adults can increase the risk of death in these individuals [41-46].

Importantly, the Kaplan-Meier curves for both Metabolic Phenotype and MetS are virtually identical. In both cases, the presence of absence of obesity in isolation is not a strong driving force for mortality in isolation; when taken together, this suggests that underlying conditions may be playing a larger part (Figure 14b-c). This study demonstrated that respondents, regardless of weight, were at a higher risk of death over time if they had poor metabolic health which is consistent with the current literature [65]. Risk of death is greatly reduced when individuals exercise and have a healthy lifestyle [70-75]. This pattern is prevalent in Model 2 where behavioral factors such as physical activity, smoking status and alcohol consumption are adjusted for. Reinforcing the multifactorial nature of obesity, the only main

effect that was found to be significant in Model 5 in any analysis was for MHO, who had a *lower* risk of death compared to the referent (MUNO).

Given that the EOSS preclinical tool is the most robust of the obesity measures we assessed, distinct differences between each of the different EOSS stages was not unexpected. For example, in figure 14d there is a clear descending gradient in risk of death over time, with EOSS stage 0-1, as the group with the lowest risk of death over time, and EOSS stage 3 with the greatest risk. Through-out all the models in Table 4, the EOSS preclinical tool displayed the most robust decrease in risk of death over time, compared to the other groups. This should be expected, as EOSS includes measures of the severity of co-morbidities, which allows for a better understanding of a person's overall health. EOSS also incorporates measures of mental health that are not captured in other pre-clinical tools. The importance of mental health to overall (general) health is well established, and studies have shown that mental health and obesity are related in a bidirectional manner [91-93].

Contributing to the aforementioned patterns, the U.S. population has become more ethnically diverse, with a decreasing proportion of non-Hispanic White individuals, and an increase in other ethnic groups over time. With these ethnic differences come differences in culture, diet and lifestyle which are important when assessing obesity, but are difficult to assess using BMI alone [47,55]. Collectively, these demographic changes over time may contribute, in part, to the observed changes in both the prevalence and health risk associated with obesity. At the same time, the U.S. population is increasing proportionally in age, due to the large baby boomer cohort. The resultant increase in longevity (through advances in health and healthcare in this age group) is reflected in a weaker relationship between obesity and metabolic health above age 65 y. Additionally, increasing ethnic diversity is creating a larger disparity with obesity and

metabolic health, by changing the composition of the U.S. population among both lower and higher risk groups. For example, South Asians are more likely to get cardiovascular disease [56,58], and Non-Hispanic Black individuals are at a lower risk of developing MetS, but have a higher risk of developing hypertension compared to other ethnicities [60,61]. In using EOSS and underlying conditions caused by metabolic disease and weight gain as an assessment of health risk, the varying influence of age-, sex-, and ethnicity on obesity-related health risk is minimized.

## Strengths and Weaknesses

Among the many strengths of the U.S. NHANES is the wide capture of obesity-related risk factors and representative sample on which to explore demographic-related changes in obesity and obesity-related health risk. However, due to the cross-sectional nature of NHANES, we are unable to assess causality or the incidence of obesity. Additionally, many of the key exposures are based on self-report, which introduce recall and healthy responder bias. This includes a change in physical activity reporting in the 2007-2008 cycle that greatly reduced the number of individuals in the study, and created large fluctuations in data during this cycle change. Notably, during this period there was a marked increase in the proportion of individuals with MetS, specifically in women and younger adults. As there were very few individuals classified as EOSS stage 0, EOSS stage 0 and stage 1 were combined throughout. From 1999-2004 EOSS was only assessed by physical and functional EOSS components as mental health criteria was not available during this time. Due to inconsistency in their measurement over time, some factors such as anxiety, COPD and muscle soreness were not available for study, whereas depression and gout were only available from 2005 onward. As anxiety data was not available for this study, depression was the only marker for mental health EOSS criteria. Moreover, due to the lack of specificity in response options for ethnicity, it is not possible to apply ethnic-specific WC

thresholds for the Asian population in the current analysis. Regarding ethnic differences, due to few respondents self-reporting their ethnicity as Other, large fluctuations in prevalence estimates must be interpreted with caution. The NHANES surveys commenced oversampling of Asian data in 2011 [94] leading to some notable changes in the last two cycles of the study with a decrease in overall weight (larger proportion of overweight individuals compared to obese) and an increase of MetS. These spikes are expected, as we know that Asian individuals tend have a higher body fat % than other ethnic groups [95] and are at a greater risk of developing metabolic health problems at a lower BMI [90].

## Conclusions and Future Directions

In summary, of all the clinical tools assessed in this study, EOSS was the most robust method for the prediction of mortality risk over time. Results from this analysis will provide new insight into how changing population demographics may have contributed to changes in how obesity is conceptualized at a population level. By contrasting the different preclinical tools, we were able to learn which factors are the most crucial in predicting risk of death, and in the future, may contribute to more targeted interventions. More in-depth studies are needed to compare other similar health utilization tools such as the Framingham and Reynolds Risk Scores which are used in cardiovascular risk to help build a more advanced tool that is responsive to demographic changes with time.

## Tables and Figures

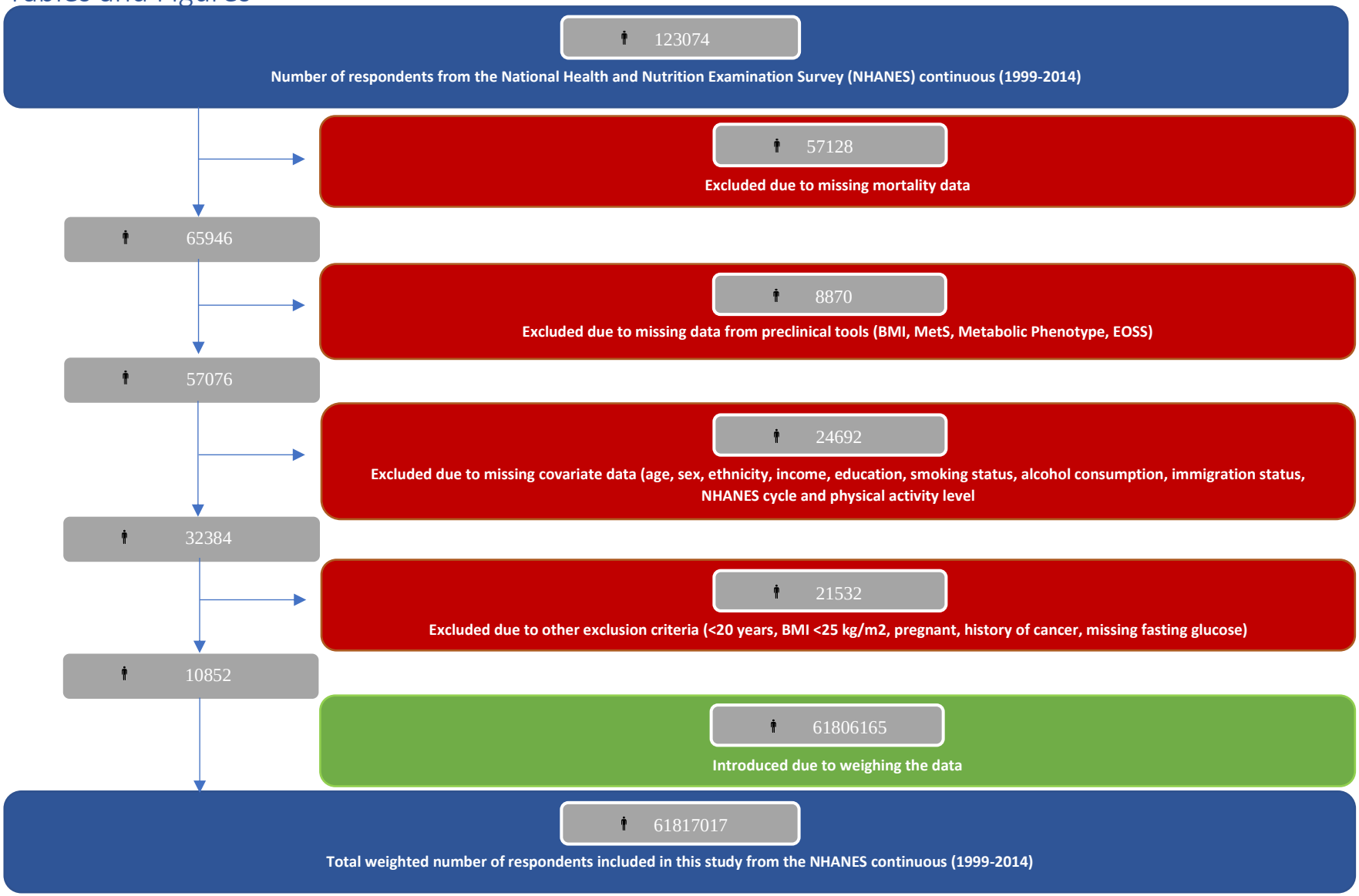


Figure 1 – Study design

Table 1 – Characteristics of unweighted sample in NHANES 1999-2014 by cycle.

| | YEAR | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1999-2000 (n=1430) | 2001-2002 (n=2074) | 2003-2004 (n=1865) | 2005-2006 (n=1519) | 2007-2008 (n=931) | 2009-2010 (n=1082) | 2011-2012 (n=930) | 2013-2014 (n=1021) | Total (n=10852) | P-value |
| **Age**, n (%) | | | | | | | | | | <0.0001[1] |
| 20-44 | 777 (54.3%) | 1202 (58.0%) | 1104 (59.2%) | 908 (59.8%) | 428 (46.0%) | 517 (47.8%) | 473 (50.9%) | 493 (48.3%) | 5902 (54.4%) | |
| 45-64 | 422 (29.5%) | 643 (31.0%) | 536 (28.7%) | 467 (30.7%) | 345 (37.1%) | 403 (37.2%) | 325 (34.9%) | 360 (35.3%) | 3501 (32.3%) | |
| 65+ | 231 (16.2%) | 229 (11.0%) | 225 (12.1%) | 144 (9.5%) | 158 (17.0%) | 162 (15.0%) | 132 (14.2%) | 168 (16.5%) | 1449 (13.4%) | |
| **Sex**, n (%) | | | | | | | | | | <0.0001[1] |
| Male | 685 (47.9%) | 1146 (55.3%) | 1019 (54.6%) | 815 (53.7%) | 422 (45.3%) | 507 (46.9%) | 451 (48.5%) | 456 (44.7%) | 5501 (50.7%) | |
| Female | 745 (52.1%) | 928 (44.7%) | 846 (45.4%) | 704 (46.3%) | 509 (54.7%) | 575 (53.1%) | 479 (51.5%) | 565 (55.3%) | 5351 (49.3%) | |
| **Ethnicity**, n (%) | | | | | | | | | | <0.0001[1] |
| Hispanic | 515 (36.0%) | 531 (25.6%) | 433 (23.2%) | 328 (21.6%) | 311 (33.4%) | 382 (35.3%) | 226 (24.3%) | 262 (25.7%) | 2988 (27.5%) | |
| Non-Hispanic White | 546 (38.2%) | 1018 (49.1%) | 905 (48.5%) | 646 (42.5%) | 362 (38.9%) | 430 (39.7%) | 331 (35.6%) | 400 (39.2%) | 4638 (42.7%) | |
| Non-Hispanic Black | 327 (22.9%) | 438 (21.1%) | 489 (26.2%) | 485 (31.9%) | 224 (24.1%) | 232 (21.4%) | 282 (30.3%) | 259 (25.4%) | 2736 (25.2%) | |
| Other including Multi-Racial | 42 (2.9%) | 87 (4.2%) | 38 (2.0%) | 60 (3.9%) | 34 (3.7%) | 38 (3.5%) | 91 (9.8%) | 100 (9.8%) | 490 (4.5%) | |
| **Income Level**, n (%) | | | | | | | | | | <0.0001[1] |
| Low income | 453 (31.7%) | 511 (24.6%) | 484 (26.0%) | 344 (22.6%) | 330 (35.4%) | 442 (40.9%) | 375 (40.3%) | 402 (39.4%) | 3341 (30.8%) | |
| Middle income | 529 (37.0%) | 716 (34.5%) | 681 (36.5%) | 558 (36.7%) | 331 (35.6%) | 385 (35.6%) | 318 (34.2%) | 339 (33.2%) | 3857 (35.5%) | |
| High income | 448 (31.3%) | 847 (40.8%) | 700 (37.5%) | 617 (40.6%) | 270 (29.0%) | 255 (23.6%) | 237 (25.5%) | 280 (27.4%) | 3654 (33.7%) | |
| **Level of Education**, n (%) | | | | | | | | | | <0.0001[1] |
| Less than high school diploma | 471 (32.9%) | 459 (22.1%) | 362 (19.4%) | 258 (17.0%) | 270 (29.0%) | 316 (29.2%) | 198 (21.3%) | 227 (22.2%) | 2561 (23.6%) | |
| High school diploma | 292 (20.4%) | 480 (23.1%) | 481 (25.8%) | 339 (22.3%) | 235 (25.2%) | 264 (24.4%) | 215 (23.1%) | 233 (22.8%) | 2539 (23.4%) | |
| Post-secondary education | 667 (46.6%) | 1135 (54.7%) | 1022 (54.8%) | 922 (60.7%) | 426 (45.8%) | 502 (46.4%) | 517 (55.6%) | 561 (54.9%) | 5752 (53.0%) | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Level of Alcohol Consumption**, n(%) | | | | | | | | | | <0.0001[1] |
| No alcohol consumption | 523 (36.6%) | 716 (34.5%) | 612 (32.8%) | 497 (32.7%) | 340 (36.5%) | 382 (35.3%) | 312 (33.5%) | 352 (34.5%) | 3734 (34.4%) | |
| Low to moderate alcohol consumption | 741 (51.8%) | 1027 (49.5%) | 1027 (55.1%) | 816 (53.7%) | 478 (51.3%) | 528 (48.8%) | 486 (52.3%) | 568 (55.6%) | 5671 (52.3%) | |
| High alcohol consumption | 166 (11.6%) | 331 (16.0%) | 226 (12.1%) | 206 (13.6%) | 113 (12.1%) | 172 (15.9%) | 132 (14.2%) | 101 (9.9%) | 1447 (13.3%) | |
| **Smoking History**, n (%) | | | | | | | | | | 0.1097[1] |
| Never smoked | 1062 (74.3%) | 1561 (75.3%) | 1371 (73.5%) | 1125 (74.1%) | 709 (76.2%) | 819 (75.7%) | 702 (75.5%) | 773 (75.7%) | 8122 (74.8%) | |
| Past smoker | 86 (6.0%) | 136 (6.6%) | 119 (6.4%) | 76 (5.0%) | 38 (4.1%) | 69 (6.4%) | 44 (4.7%) | 48 (4.7%) | 616 (5.7%) | |
| Current smoker | 282 (19.7%) | 377 (18.2%) | 375 (20.1%) | 318 (20.9%) | 184 (19.8%) | 194 (17.9%) | 184 (19.8%) | 200 (19.6%) | 2114 (19.5%) | |
| **Meeting Physical Activity Guidelines**, n (%) | | | | | | | | | | <0.0001[1] |
| Not meeting physical activity guidelines | 650 (45.5%) | 953 (45.9%) | 849 (45.5%) | 663 (43.6%) | 378 (40.6%) | 455 (42.1%) | 339 (36.5%) | 416 (40.7%) | 4703 (43.3%) | |
| Meets physical activity guidelines | 289 (20.2%) | 485 (23.4%) | 460 (24.7%) | 353 (23.2%) | 104 (11.2%) | 125 (11.6%) | 110 (11.8%) | 107 (10.5%) | 2033 (18.7%) | |
| Exceeds physical activity guidelines | 491 (34.3%) | 636 (30.7%) | 556 (29.8%) | 503 (33.1%) | 449 (48.2%) | 502 (46.4%) | 481 (51.7%) | 498 (48.8%) | 4116 (37.9%) | |
| **Time in US,** n (%) | | | | | | | | | | <0.0001[1] |
| Born in the US | 1052 (73.6%) | 1684 (81.2%) | 1530 (82.0%) | 1271 (83.7%) | 697 (74.9%) | 748 (69.1%) | 695 (74.7%) | 759 (74.3%) | 8436 (77.7%) | |
| Less than 10 years | 95 (6.6%) | 128 (6.2%) | 111 (6.0%) | 96 (6.3%) | 61 (6.6%) | 82 (7.6%) | 57 (6.1%) | 40 (3.9%) | 670 (6.2%) | |
| More than 10 years | 283 (19.8%) | 262 (12.6%) | 224 (12.0%) | 152 (10.0%) | 173 (18.6%) | 252 (23.3%) | 178 (19.1%) | 222 (21.7%) | 1746 (16.1%) | |
| **Obesity Categories,** n (%) | | | | | | | | | | <0.0001[1] |
| Overweight | 774 (54.1%) | 1222 (58.9%) | 963 (51.6%) | 754 (49.6%) | 462 (49.6%) | 510 (47.1%) | 431 (46.3%) | 464 (45.4%) | 5580 (51.4%) | |
| Obesity I | 412 (28.8%) | 520 (25.1%) | 571 (30.6%) | 437 (28.8%) | 273 (29.3%) | 312 (28.8%) | 305 (32.8%) | 290 (28.4%) | 3120 (28.8%) | |
| Obesity II | 163 (11.4%) | 217 (10.5%) | 185 (9.9%) | 176 (11.6%) | 110 (11.8%) | 137 (12.7%) | 113 (12.2%) | 146 (14.3%) | 1247 (11.5%) | |
| Obesity III | 81 (5.7%) | 115 (5.5%) | 146 (7.8%) | 152 (10.0%) | 86 (9.2%) | 123 (11.4%) | 81 (8.7%) | 121 (11.9%) | 905 (8.3%) | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **MetS,** n (%) | | | | | | | | | | <0.0001[1] |
| No MetS | 922 (64.5%) | 1373 (66.2%) | 1274 (68.3%) | 981 (64.6%) | 513 (55.1%) | 607 (56.1%) | 531 (57.1%) | 597 (58.5%) | 6798 (62.6%) | |
| Has MetS | 508 (35.5%) | 701 (33.8%) | 591 (31.7%) | 538 (35.4%) | 418 (44.9%) | 475 (43.9%) | 399 (42.9%) | 424 (41.5%) | 4054 (37.4%) | |
| **Metabolic Phenotype,** n (%) | | | | | | | | | | <0.0001[1] |
| MHNO | 201 (14.1%) | 385 (18.6%) | 382 (20.5%) | 241 (15.9%) | 99 (10.6%) | 144 (13.3%) | 127 (13.7%) | 149 (14.6%) | 1728 (15.9%) | |
| MUNO | 573 (40.1%) | 837 (40.4%) | 581 (31.2%) | 513 (33.8%) | 363 (39.0%) | 366 (33.8%) | 304 (32.7%) | 315 (30.9%) | 3852 (35.5%) | |
| MHO | 124 (8.7%) | 156 (7.5%) | 221 (11.8%) | 152 (10.0%) | 81 (8.7%) | 87 (8.0%) | 69 (7.4%) | 89 (8.7%) | 979 (9.0%) | |
| MUO | 532 (37.2%) | 696 (33.6%) | 681 (36.5%) | 613 (40.4%) | 388 (41.7%) | 485 (44.8%) | 430 (46.2%) | 468 (45.8%) | 4293 (39.6%) | |
| **EOSS Category,** n (%) | | | | | | | | | | <0.0001[1] |
| EOSS 0-1 | 198 (13.8%) | 354 (17.1%) | 319 (17.1%) | 206 (13.6%) | 94 (10.1%) | 105 (9.7%) | 90 (9.7%) | 95 (9.3%) | 1461 (13.5%) | |
| EOSS 2 | 1060 (74.1%) | 1513 (73.0%) | 1336 (71.6%) | 1106 (72.8%) | 646 (69.4%) | 740 (68.4%) | 628 (67.5%) | 683 (66.9%) | 7712 (71.1%) | |
| EOSS 3 | 172 (12.0%) | 207 (10.0%) | 210 (11.3%) | 207 (13.6%) | 191 (20.5%) | 237 (21.9%) | 212 (22.8%) | 243 (23.8%) | 1679 (15.5%) | |

[1]Chi-Square p-value;

Table 2 – Characteristics of weighted sample in NHANES 1999-2014 by cycle.

| | YEAR | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1999-2000 (Weighted n 8347474) | 2001-2002 (weighted n 12694243) | 2003-2004 (weighted n 12035889) | 2005-2006 (weighted n 9399262) | 2007-2008 (weighted n 4345452) | 2009-2010 (weighted n 4656243) | 2011-2012 (weighted n 5163871) | 2013-2014 (weighted n 5174583) | Total (weighted n 61817017) | P-value |
| **Age**, weighted %, (±SE of %) | | | | | | | | | | <0.0001[1] |
| 20-44 | 62.7% (2.9) | 62.0% (1.7) | 63.4% (3.0) | 60.0% (2.5) | 50.5% (2.1) | 51.1% (2.7) | 52.7% (2.1) | 51.6% (1.7) | 58.8% (1.0) | |
| 45-64 | 27.9% (2.9) | 31.6% (1.3) | 29.3% (2.8) | 33.2% (1.9) | 39.0% (2.0) | 37.1% (3.0) | 36.5% (2.2) | 34.5% (1.3) | 32.6% (0.9) | |
| 65+ | 9.4% (0.8) | 6.4% (0.9) | 6.7% (0.7) | 6.8% (1.1) | 10.5% (1.1) | 11.8% (0.9) | 10.8% (1.7) | 13.9% (1.6) | 8.6% (0.4) | |
| **Sex**, weighted %, (±SE of %) | | | | | | | | | | <0.0001[1] |
| Male | 51.6% (3.0) | 58.0% (1.6) | 56.8% (2.8) | 54.8% (2.7) | 47.9% (0.9) | 50.4% (2.0) | 50.3% (1.4) | 46.5% (1.6) | 53.5% (0.9) | |
| Female | 48.4% (3.0) | 42.0% (1.6) | 43.2% (2.8) | 45.2% (2.7) | 52.1% (0.9) | 49.6% (2.0) | 49.7% (1.4) | 53.5% (1.6) | 46.4% (0.9) | |
| **Ethnicity**, weighted %, (±SE of %) | | | | | | | | | | <0.0001[1] |
| Hispanic | 19.4% (5.0) | 11.5% (2.1) | 13.3% (3.1) | 12.6% (1.7) | 16.5% (2.3) | 18.3% (3.6) | 16.7% (2.6) | 18.2% (3.7) | 15.0% (1.2) | |
| Non-Hispanic White | 63.2% (4.7) | 72.8% (2.4) | 70.3% (3.9) | 66.9% (3.2) | 62.9% (4.3) | 62.1% (3.5) | 65.9% (4.1) | 60.9% (4.4) | 67.0% (1.4) | |
| Non-Hispanic Black | 13.5% (2.7) | 11.2% (2.0) | 13.9% (2.0) | 15.8% (2.4) | 14.5% (2.9) | 15.1% (1.6) | 13.3% (2.5) | 15.1% (1.7) | 13.7% (0.8) | |
| Other including Multi-Racial | 3.9% (1.2) | 4.5% (1.2) | 2.6% (0.4) | 4.6% (1.3) | 6.1% (1.2) | 4.5% (1.0) | 4.1% (0.9) | 5.8% (0.5) | 4.3% (0.4) | |
| **Income Level**, weighted %, (±SE of %) | | | | | | | | | | <0.0001[1] |
| Low income | 24.9% (2.3) | 19.7% (1.5) | 19.7% (1.6) | 14.9% (1.3) | 24.4% (1.4) | 30.2% (2.1) | 29.3% (2.5) | 29.5% (3.4) | 22.4% (0.7) | |
| Middle income | 35.2% (2.6) | 32.2% (2.6) | 35.4% (3.7) | 36.4% (1.3) | 31.3% (2.3) | 34.9% (2.1) | 36.1% (2.8) | 33.6% (2.2) | 34.4% (1.2) | |
| High income | 39.9% (3.2) | 48.1% (2.7) | 44.9% (3.1) | 48.7% (3.3) | 44.2% (2.6) | 34.9% (3.0) | 34.5% (3.3) | 36.8% (3.6) | 43.1% (1.2) | |
| **Level of Education**, | | | | | | | | | | <0.0001[1] |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| weighted %, (±SE of %) | | | | | | | | | | |
| Less than high school diploma | 21.8% (2.1) | 12.9% (1.2) | 11.6% (1.5) | 12.1% (2.3) | 18.7% (2.4) | 19.1% (1.6) | 15.3% (1.8) | 16.4% (2.3) | 15.1% (0.7) | |
| High school diploma | 22.0% (3.5) | 25.1% (2.0) | 27.5% (1.9) | 21.2% (1.8) | 26.3% (1.7) | 25.2% (2.0) | 21.5% (2.1) | 21.9% (1.7) | 24.1% (0.8) | |
| Post-secondary education | 56.2% (3.0) | 62.0% (2.4) | 60.9% (1.9) | 66.7% (3.3) | 55.0% (2.9) | 55.6% (2.3) | 63.3% (2.5) | 61.7% (2.4) | 60.8% (1.0) | |
| **Level of Alcohol Consumption**, weighted %, (±SE of %) | | | | | | | | | | <0.0001[1] |
| No alcohol consumption | 31.6% (1.6) | 31.3% (6.1) | 28.4% (2.3) | 27.0% (2.5) | 30.7% (2.4) | 29.5% (1.6) | 25.9% (2.1) | 30.5% (3.8) | 29.4% (1.5) | |
| Low to moderate alcohol consumption | 55.2% (3.4) | 50.7% (5.1) | 59.4% (2.3) | 57.4% (3.6) | 56.7% (1.7) | 53.7% (2.2) | 58.0% (2.3) | 58.5% (3.8) | 55.9% (1.4) | |
| High alcohol consumption | 13.2% (3.0) | 18.0% (2.2) | 12.2% (2.2) | 15.6% (3.9) | 12.6% (1.7) | 16.8% (2.0) | 16.1% (2.7) | 10.9% (0.9) | 14.6% (1.0) | |
| **Smoking History**, weighted %, (±SE of %) | | | | | | | | | | <0.0001[1] |
| Never smoked | 71.5% (2.3) | 73.8% (3.4) | 72.9% (1.8) | 71.6% (3.4) | 75.7% (1.9) | 77.7% (1.3) | 76.3% (1.6) | 78.3% (1.7) | 74.0% (1.0) | |
| Past smoker | 6.2% (1.9) | 5.9% (0.9) | 6.0% (1.7) | 4.8% (1.0) | 3.4% (0.6) | 4.6% (0.7) | 4.8% (0.6) | 4.7% (0.7) | 5.3% (0.5) | |
| Current smoker | 22.2% (2.3) | 20.3% (2.9) | 21.1% (1.5) | 23.6% (3.1) | 20.9% (1.9) | 17.6% (1.3) | 18.9% (1.8) | 17.0% (1.6) | 20.7% (0.9) | |
| **Meeting Physical Activity Guidelines**, weighted %, (±SE of %) | | | | | | | | | | <0.0001[1] |
| Not meeting physical activity guidelines | 42.0% (2.2) | 42.6% (2.3) | 43.7% (2.6) | 40.5% (3.5) | 36.3% (2.2) | 37.6% (1.6) | 33.3% (2.2) | 40.5% (1.4) | 40.7% (1.0) | |
| Meets physical activity guidelines | 20.7% (1.7) | 25.4% (1.6) | 25.6% (1.3) | 25.9% (1.7) | 11.8% (1.7) | 11.9% (1.0) | 9.7% (1.4) | 11.7% (1.2) | 20.5% (0.6) | |
| Exceeds physical activity Guidelines | 37.3% (2.4) | 32.0% (2.4) | 30.7% (2.6) | 33.6% (3.2) | 51.9% (1.6) | 50.4% (2.1) | 56.9% (2.6) | 47.8% (1.4) | 38.9% (1.0) | |
| **Time in US,** weighted %, (±SE of %) | | | | | | | | | | <0.0001[1] |
| Born in the US | 81.4% | 89.0% | 87.2% | 87.7% | 84.4% | 80.6% | 84.9% | 82.4% | 85.6% | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | (4.4) | (2.0) | (2.7) | (2.4) | (2.1) | (2.5) | (1.9) | (2.2) | (1.0) | |
| Less than 10 years | 4.8% (1.6) | 3.9% (1.1) | 4.8% (1.2) | 4.3% (1.4) | 4.2% (0.9) | 5.5% (1.0) | 3.8% (0.8) | 2.7% (0.6) | 4.3% (0.5) | |
| More than 10 years | 13.8% (3.2) | 7.1% (1.3) | 8.0% (2.3) | 8.1% (1.5) | 11.3% (1.6) | 13.9% (1.8) | 11.4% (1.3) | 14.9% (1.8) | 10.1% (0.8) | |
| **Obesity Categories,** weighted %, (±SE of %) | | | | | | | | | | <0.0001[1] |
| Overweight | 55.5% (2.1) | 60.2% (3.1) | 53.8% (2.9) | 51.4% (3.5) | 53.4% (2.0) | 48.2% (1.9) | 48.8% (1.9) | 45.8% (1.5) | 53.5% (1.1) | |
| Obesity I | 28.2% (2.1) | 26.3% (2.6) | 30.0% (1.5) | 27.5% (2.7) | 27.3% (1.2) | 28.5% (1.4) | 31.4% (1.5) | 28.6% (1.8) | 28.3% (0.8) | |
| Obesity II | 11.1% (1.2) | 8.4% (0.9) | 9.1% (1.8) | 11.6% (1.7) | 11.4% (1.8) | 12.2% (1.4) | 11.3% (1.3) | 13.5% (1.0) | 10.5% (0.5) | |
| Obesity III | 5.2% (0.8) | 5.0% (0.9) | 7.1% (1.1) | 9.5% (1.3) | 7.9% (1.0) | 11.2% (1.1) | 8.4% (1.2) | 12.1% (1.2) | 7.7% (0.4) | |
| **MetS,** weighted %, (±SE of %) | | | | | | | | | | <0.0001[1] |
| No MetS | 68.8% (2.6) | 67.6% (2.6) | 68.5% (2.6) | 67.2% (3.0) | 59.9% (2.1) | 60.5% (2.6) | 60.0% (2.3) | 61.3% (2.2) | 65.6% (1.0) | |
| Has MetS | 31.2% (2.6) | 32.4% (2.6) | 31.5% (2.6) | 32.8% (3.0) | 40.1% (2.1) | 39.4% (2.6) | 40.0% (2.3) | 38.7% (2.2) | 34.3% (1.0) | |
| **Metabolic Phenotype,** weighted %, (±SE of %) | | | | | | | | | | <0.0001[1] |
| MHNO | 14.7% (1.2) | 19.9% (2.3) | 23.5% (2.4) | 16.7% (3.1) | 11.9% (2.0) | 15.6% (1.9) | 13.9% (1.9) | 17.8% (1.0) | 17.9% (0.9) | |
| MUNO | 40.8% (2.3) | 40.3% (2.6) | 30.2% (2.0) | 34.8% (2.3) | 41.4% (2.0) | 32.6% (1.3) | 34.9% (2.0) | 28.0% (1.2) | 35.6% (0.9) | |
| MHO | 8.5% (1.1) | 7.5% (1.6) | 12.1% (2.2) | 9.4% (0.9) | 8.5% (1.1) | 8.8% (1.3) | 8.2% (0.9) | 9.3% (1.1) | 9.2% (0.6) | |
| MUO | 35.6% (2.3) | 32.2% (2.3) | 34.1% (2.9) | 39.2% (3.1) | 38.1% (1.9) | 43.0% (2.2) | 43.0% (2.2) | 44.8% (1.1) | 37.3% (1.0) | |
| **EOSS Category,** weighted %, (±SE of %) | | | | | | | | | | <0.0001[1] |
| EOSS 0-1 | 14.2% (2.4) | 17.0% (1.5) | 17.1% (2.0) | 13.8% (1.9) | 10.0% (0.9) | 9.2% (1.1) | 9.5%) (1.9 | 9.7% (1.1) | 13.8% (0.7) | |
| EOSS 2 | 74.8% (1.5) | 74.7% (1.7) | 73.5% (2.0) | 73.1% (2.2) | 73.2% (1.4) | 69.7% (1.6) | 70.0% (2.5) | 66.0% (2.2) | 72.6% (0.7) | |
| EOSS 3 | 11.0% (2.1) | 8.3% (0.9) | 9.4% (0.9) | 13.1% (1.5) | 16.8% (1.3) | 21.1% (1.5) | 20.5% (2.6) | 24.3% (1.8) | 13.5% (0.6) | |

[1]Chi-Square p-value;

Table 3 - Prevalence of obesity and health according to demographic subgroups (prevalence by preclinical tool for each demographic subgroup)

| | BMI Category | | | | MetS Status | | Metabolic Phenotype | | | | EOSS Category | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Overweight | Obesity I | Obesity II | Obesity III | No MetS | Has Mets | MHNO | MUNO | MHO | MUO | EOSS 0-1 | EOSS 2 | EOSS 3 |
| **Age**, weighted %, (±SE of %) | | | | | | | | | | | | | |
| 20-44 | 60.3% (1.2) | 57.1% (2.0) | 57.5% (2.2) | 56.3% (2.4) | 66.0% (1.4) | 45.1% (1.3) | 72.9% (2.5) | 54.0% (1.5) | 75.3% (3.1) | 52.5% (1.3) | 80.2% (2.6) | 60.9% (1.0) | 25.5% (1.9) |
| 45-64 | 30.5% (1.2) | 34.8% (1.9) | 34.9% (2.1) | 36.3% (2.4) | 28.3% (1.3) | 40.9% (1.3) | 23.7% (2.3) | 33.9% (1.5) | 22.7% (3.0) | 38.1% (1.3) | 17.8% (2.5) | 32.4% (1.0) | 49.0% (2.1) |
| 65+ | 9.2% (0.5) | 8.2% (0.7) | 7.6% (0.9) | 7.3% (1.1) | 5.8% (0.4) | 14.0% (0.8) | 3.4% (0.5) | 12.1% (0.7) | 2.0% (0.4) | 9.4% (0.6) | 2.0% (0.6) | 6.7% (0.4) | 25.5% (1.6) |
| **Sex**, weighted %, (±SE of %) | | | | | | | | | | | | | |
| Male | 58.4% (1.2) | 54.5% (1.7) | 38.4% (2.3) | 36.5% (2.5) | 53.2% (1.2) | 54.1% (1.4) | 55.0% (2.1) | 60.1% (1.6) | 45.1% (3.4) | 48.6% (1.3) | 62.3% (2.6) | 54.1% (1.0) | 41.4% (1.8) |
| Female | 41.6% (1.2) | 45.5% (1.7) | 61.6% (2.3) | 63.5% (2.5) | 46.8% (1.2) | 45.9% (1.4) | 45.0% (2.1) | 39.9% (1.6) | 54.9% (3.4) | 51.4% (1.3) | 37.7% (2.6) | 45.9% (1.0) | 58.6% (1.8) |
| **Ethnicity**, weighted %, (±SE of %) | | | | | | | | | | | | | |
| Hispanic | 15.4% (1.4) | 15.2% (1.4) | 14.3% (1.8) | 12.1% (1.4) | 14.39% (1.2) | 16.0% (1.4) | 16.1% (1.9) | 15.0% (1.4) | 14.6% (2.3) | 14.5% (1.1) | 18.6% (2.1) | 15.5% (1.3) | 8.4% (1.0) |
| Non-Hispanic White | 69.7% (1.6) | 66.1% (1.9) | 62.0% (2.7) | 59.3% (2.6) | 67.2% (1.5) | 66.8% (1.8) | 68.7% (2.6) | 70.1% (1.7) | 58.7% (3.8) | 65.4% (1.5) | 62.1% (3.0) | 66.6% (1.5) | 74.6% (1.7) |
| Non-Hispanic Black | 10.2% (0.8) | 15.3% (1.1) | 19.4% (1.8) | 25.0% (2.1) | 14.9% (1.0) | 11.6% (0.9) | 12.0% (1.2) | 9.2% (0.8) | 23.8% (2.8) | 16.4% (1.1) | 15.7% (1.7) | 13.6% (0.8) | 12.5% (1.1) |
| Other including Multi-Racial | 4.8% (0.6) | 3.4% (0.6) | 4.3% (1.1) | 3.5% (1.0) | 3.6% (0.4) | 5.6% (0.7) | 3.2% (0.9) | 5.6% (0.8) | 2.9% (1.0) | 3.8% (0.5) | 3.6% (0.9) | 4.3% (0.5) | 4.6% (1.0) |
| **Income Level**, weighted %, (±SE of %) | | | | | | | | | | | | | |
| Low income | 20.7% (0.9) | 20.8% (1.0) | 28.2% (2.1) | 32.6% (2.2) | 21.4% (0.9) | 24.4% (1.1) | 18.2% (1.6) | 22.0% (1.2) | 22.5% (2.4) | 24.9% (1.0) | 25.3% (2.2) | 20.9% (0.7) | 27.9% (1.7) |
| Middle income | 32.8% (1.4) | 37.5% (2.0) | 35.9% (2.5) | 32.9% (2.3) | 34.2% (1.3) | 34.9% (1.6) | 31.7% (2.4) | 33.3% (1.7) | 43.3% (3.8) | 34.7% (1.5) | 35.1% (2.8) | 34.5% (1.2) | 33.8% (1.9) |
| High income | 46.5% (1.4) | 41.7% (2.0) | 35.8% (2.4) | 34.4% (2.9) | 44.4% (1.3) | 40.7% (1.7) | 50.1% (2.5) | 44.7% (1.8) | 34.2% (2.9) | 40.4% (1.8) | 39.7% (2.8) | 44.7% (1.2) | 38.3% (2.5) |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Level of Education**, weighted %, (±SE of %) | | | | | | | | | | | | | |
| Less than high school diploma | 14.0% (0.8) | 17.1% (1.2) | 15.7% (1.5) | 13.9% (1.5) | 12.9% (0.7) | 19.3% (1.1) | 11.7% (1.3) | 15.2% (0.8) | 10.7% (1.6) | 17.7% (0.9) | 14.7% (1.5) | 14.1% (0.7) | 20.8% (1.6) |
| High school diploma | 23.4% (1.0) | 24.4% (1.5) | 25.1% (2.3) | 26.3% (2.3) | 22.4% (1.0) | 27.4% (1.3) | 22.9% (2.1) | 24.6% (1.3) | 18.5% (1.8) | 26.5% (1.5) | 20.8% (2.3) | 24.7% (1.0) | 24.0% (1.8) |
| Post-secondary education | 62.6% (1.1) | 58.4% (1.7) | 59.2% (2.7) | 59.7% (2.4) | 64.7% (1.1) | 53.3% (1.5) | 67.5% (2.5) | 60.1% (1.3) | 70.8% (2.5) | 55.8% (1.6) | 64.5% (2.8) | 61.2% (1.1) | 55.2% (2.2) |
| **Level of Alcohol Consumption** weighted %, (±SE of %) | | | | | | | | | | | | | |
| No alcohol consumption | 24.0% (1.3) | 32.2% (2.5) | 37.5% (2.8) | 46.3% (2.4) | 27.0% (1.5) | 34.1% (1.8) | 19.5% (1.7) | 26.2% (1.7) | 36.1% (3.8) | 35.6% (1.7) | 37.3% (4.0) | 26.5% (1.3) | 37.3% (2.0) |
| Low to moderate alcohol consumption | 58.8% (1.4) | 54.6% (2.4) | 51.8% (2.6) | 46.6% (2.6) | 57.5% (1.4) | 52.9% (2.0) | 63.3% (2.0) | 56.5% (2.0) | 53.9% (3.6) | 52.4% (1.9) | 37.3% (2.7) | 60.7% (1.4) | 49.6% (2.4) |
| High alcohol consumption | 17.2% (1.2) | 13.2% (1.5) | 10.7% (1.5) | 7.1% (1.2) | 15.5% (1.3) | 13.0% (1.1) | 17.3% (1.9) | 17.2% (1.5) | 10.0% (1.7) | 12.0% (1.2) | 25.4% (3.0) | 12.8% (0.9) | 13.1% (1.6) |
| **Smoking History**, weighted %, (±SE of %) | | | | | | | | | | | | | |
| Never smoked | 72.4% (1.3) | 76.7% (1.5) | 72.6% (2.5) | 76.9% (2.0) | 74.2% (1.2) | 73.5% (1.3) | 75.9% (2.1) | 70.7% (1.6) | 81.2% (2.3) | 74.4% (1.3) | 73.8% (2.8) | 74.5% (1.1) | 71.3% (2.0) |
| Past smoker | 6.0% (0.7) | 4.4% (0.8) | 5.9% (1.1) | 3.8% (1.0) | 5.9% (0.7) | 4.3% (0.5) | 6.4% (1.4) | 5.7% (0.9) | 4.7% (1.2) | 4.6% (0.6) | 6.0% (1.3) | 5.4% (0.6) | 4.1% (0.8) |
| Current smoker | 21.6% (1.2) | 18.9% (1.4) | 21.5% (2.1) | 19.3% (2.1) | 19.9% (1.1) | 22.2% (1.2) | 17.7% (1.8) | 23.6% (1.5) | 14.0% (1.9) | 21.0% (1.2) | 20.2% (2.5) | 20.0% (1.0) | 24.6% (1.7) |
| **Meeting Physical Activity Guidelines**, weighted %, (±SE of %) | | | | | | | | | | | | | |
| Not meeting physical activity guidelines | 38.1% (1.4) | 41.1% (1.4) | 43.4% (2.1) | 52.8% (2.3) | 38.0% (1.1) | 45.7% (1.4) | 35.2% (2.4) | 39.6% (1.6) | 37.8% (2.2) | 45.0% (1.3) | 38.5% (2.1) | 40.1% (1.2) | 45.9% (1.9) |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Meets physical activity guidelines | 21.1% (0.9) | 20.2% (1.2) | 20.7% (1.9) | 16.6% (1.7) | 21.0% (0.7) | 19.5% (1.1) | 21.0% (1.4) | 21.2% (1.0) | 20.9% (2.0) | 19.5% (1.0) | 19.9% (1.6) | 21.0% (0.7) | 18.1% (1.5) |
| Exceeds physical activity guidelines | 40.8% (1.4) | 38.6% (1.4) | 35.9% (2.1) | 30.6% (2.3) | 41.0% (1.1) | 34.8% (1.2) | 43.8% (2.3) | 39.3% (1.7) | 41.3% (2.8) | 35.5% (1.1) | 41.6% (2.5) | 38.9% (1.2) | 36.0% (1.9) |
| **Time in US,** weighted %, (±SE of %) | | | | | | | | | | | | | |
| Born in the US | 83.1% (1.3) | 86.3% (1.3) | 91.1% (1.0) | 92.5% (1.1) | 85.8% (1.1) | 85.1% (1.2) | 84.7% (1.9) | 82.3% (1.3) | 90.5% (1.7) | 87.9% (0.9) | 85.3% (1.9) | 84.5% (1.2) | 91.6% (1.0) |
| Less than 10 years | 5.6% (0.7) | 3.2% (0.6) | 2.4% (0.6) | 1.8% (0.6) | 4.5% (0.6) | 3.9% (0.6) | 6.0% (1.2) | 5.3% (0.7) | 2.6% (1.1) | 2.8% (0.4) | 5.8% (1.2) | 4.6% (0.5) | 1.3% (0.2) |
| More than 10 years | 11.3% (1.0) | 10.5% (1.0) | 6.5% (0.7) | 5.7% (0.9) | 9.7% (0.8) | 11.0% (1.0) | 9.2% (1.4) | 12.3% (1.0) | 6.6% (1.2) | 9.4% (0.7) | 8.8% (1.3) | 10.9% (0.9) | 7.1% (0.9) |

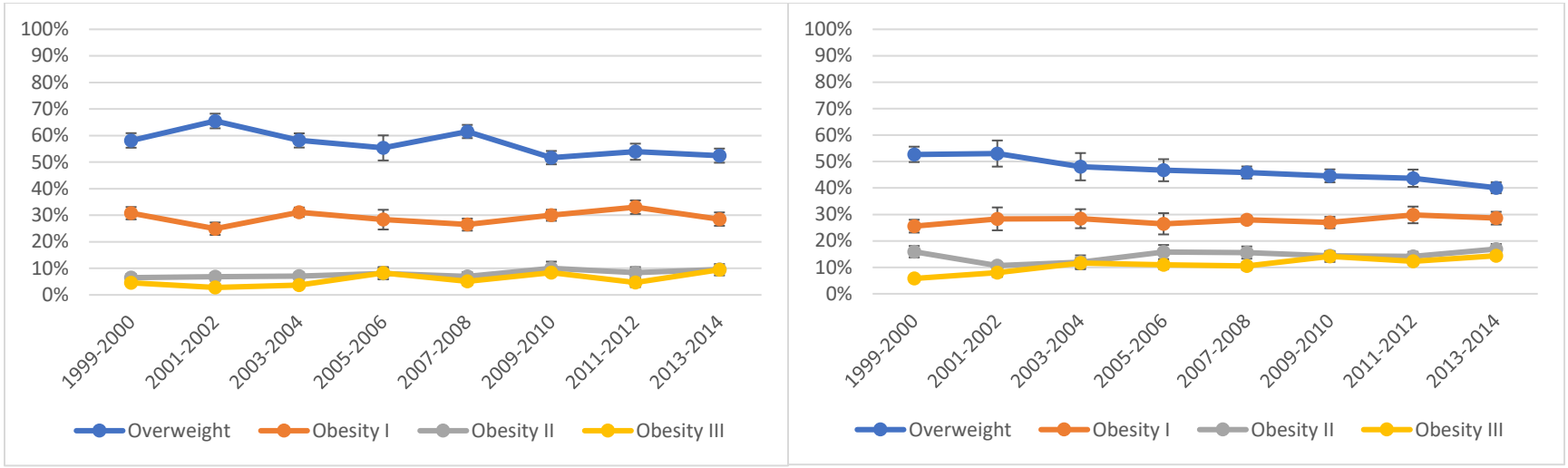


Figure 2 - Weighted percentage of sample obesity category allocation in sex over time. Panel A (left) – men; Panel B (right) – women.

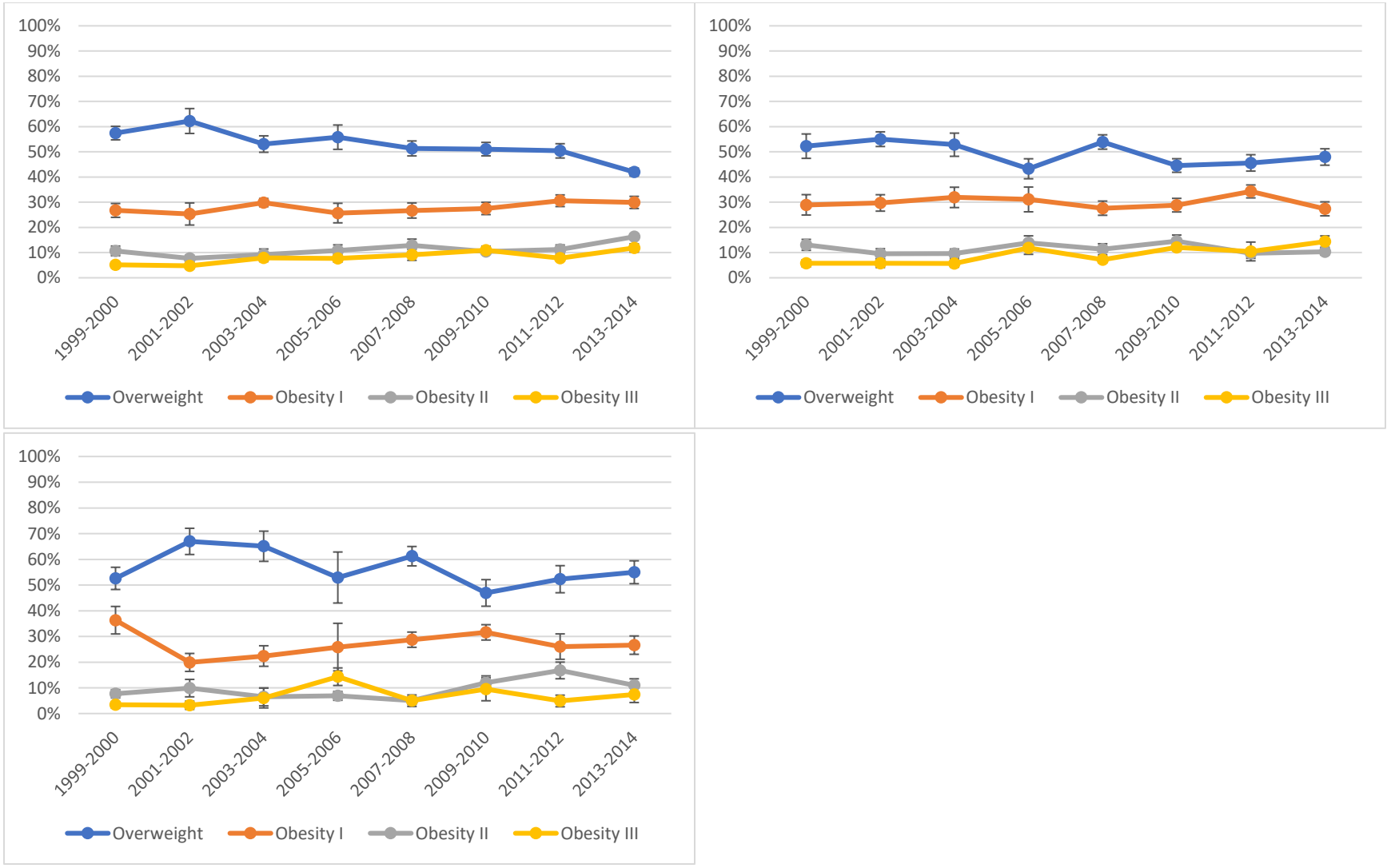


Figure 3 - Weighted percentage of sample obesity category allocation in age over time. Panel A (top left) - <45; Panel B (top right) - >=45 -<65; Panel C (bottom left) - >=65.

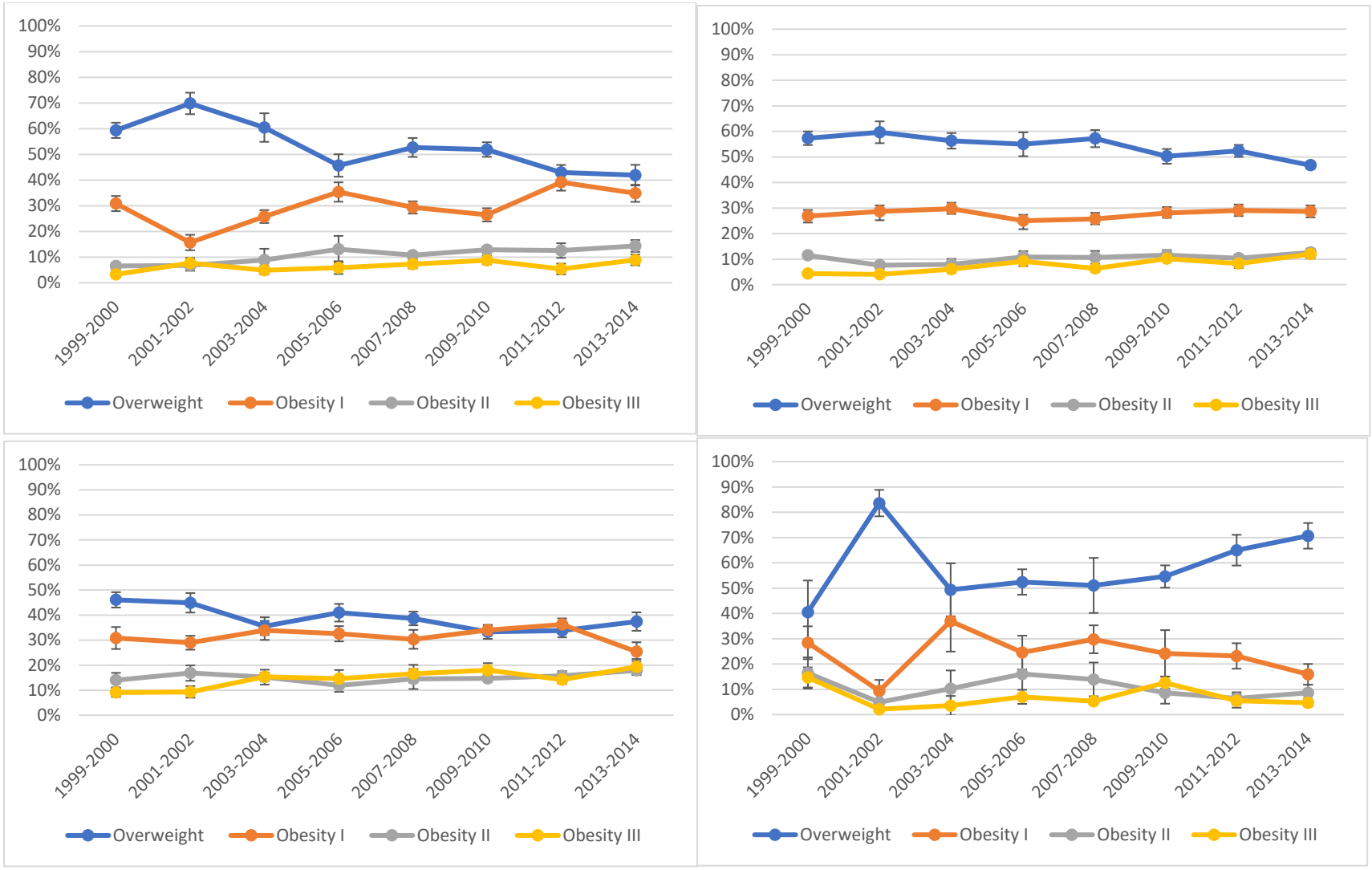


Figure 4 - Weighted percentage of sample obesity category allocation in ethnicity over time. Panel A (top left) – Hispanic; Panel B (top right) - Non-Hispanic White; Panel C (bottom left) - Non-Hispanic Black. Panel D (bottom right) - other ethnicity including multi-race.

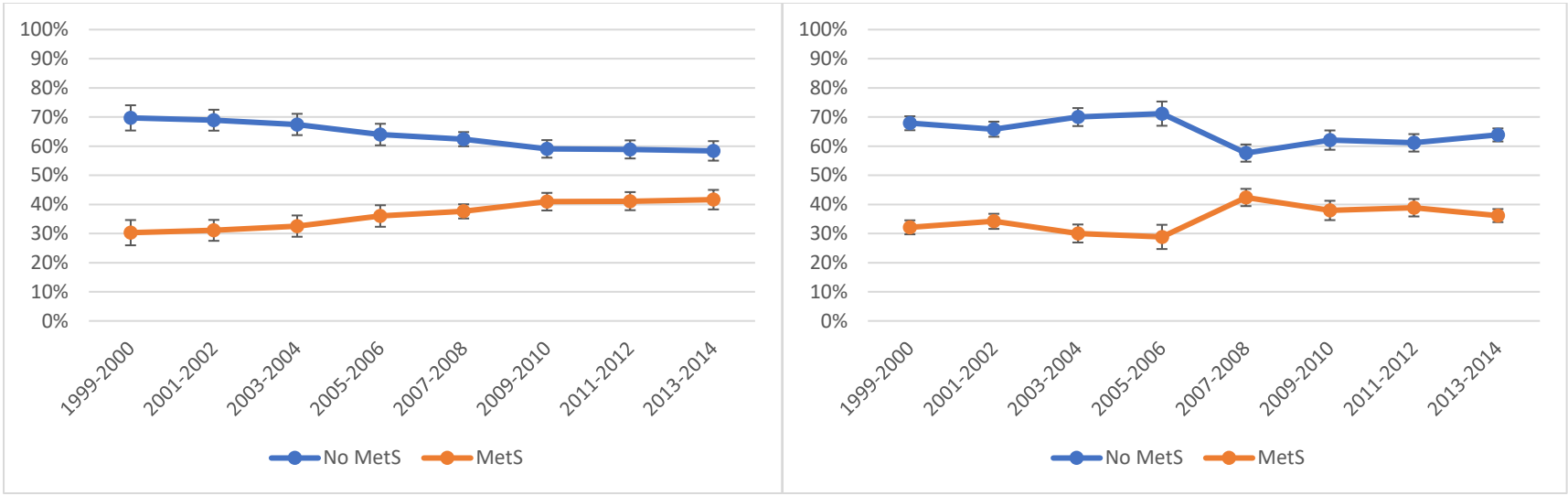


Figure 5 - Weighted percentage of sample MetS category allocation in sex over time. Panel A (left) – men; Panel B (right) – women.

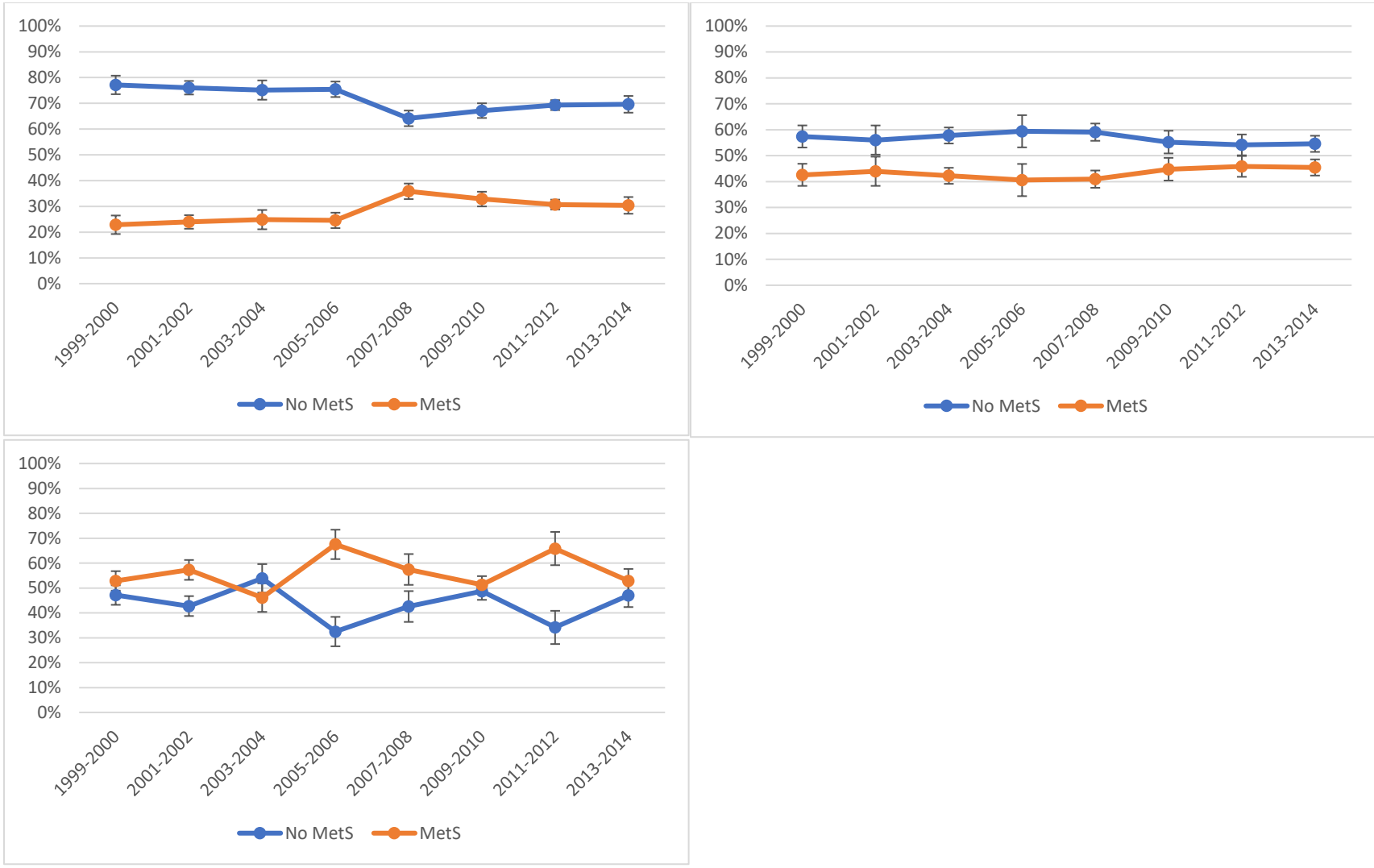


Figure 6 - Weighted percentage of sample MetS category allocation in age over time. Panel A (top left) - <45; Panel B (top right) - >=45 -<65; Panel C (bottom left) - >=65.


Figure 7 - Weighted percentage of sample MetS category allocation in ethnicity over time. Panel A (top left) – Hispanic; Panel B (top right) - Non-Hispanic White; Panel C (bottom left) - Non-Hispanic Black. Panel D (bottom right) - other ethnicity including multi-race.

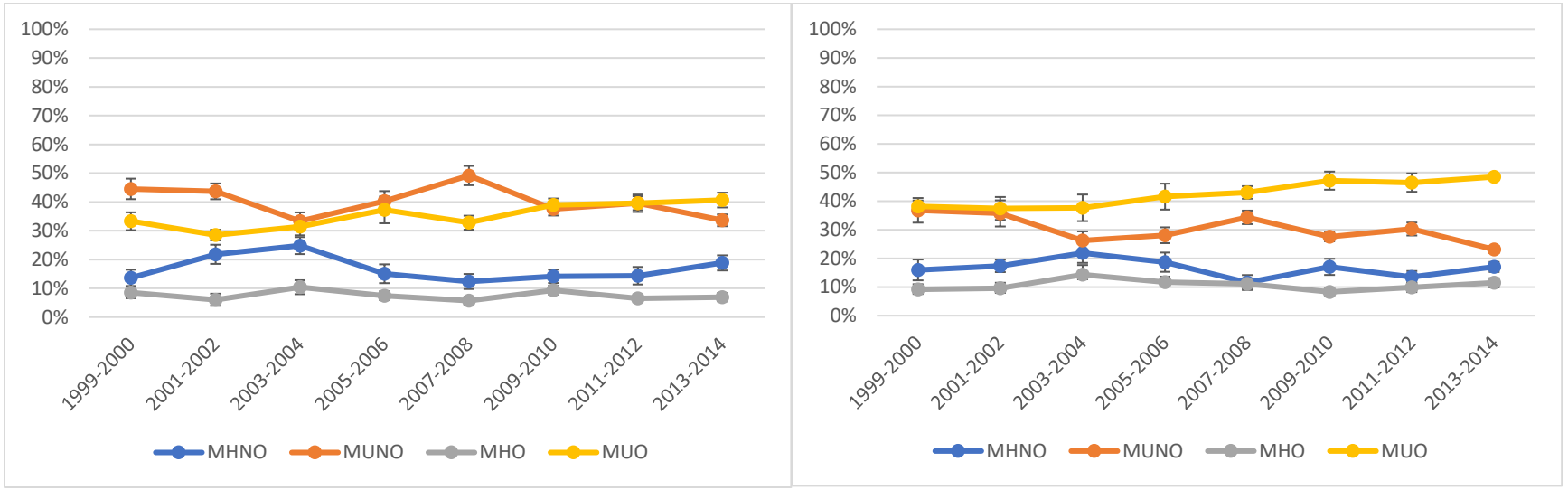


Figure 8 - Weighted percentage of sample metabolic health category allocation in sex over time. Panel A (left) – men; Panel B (right) – women.

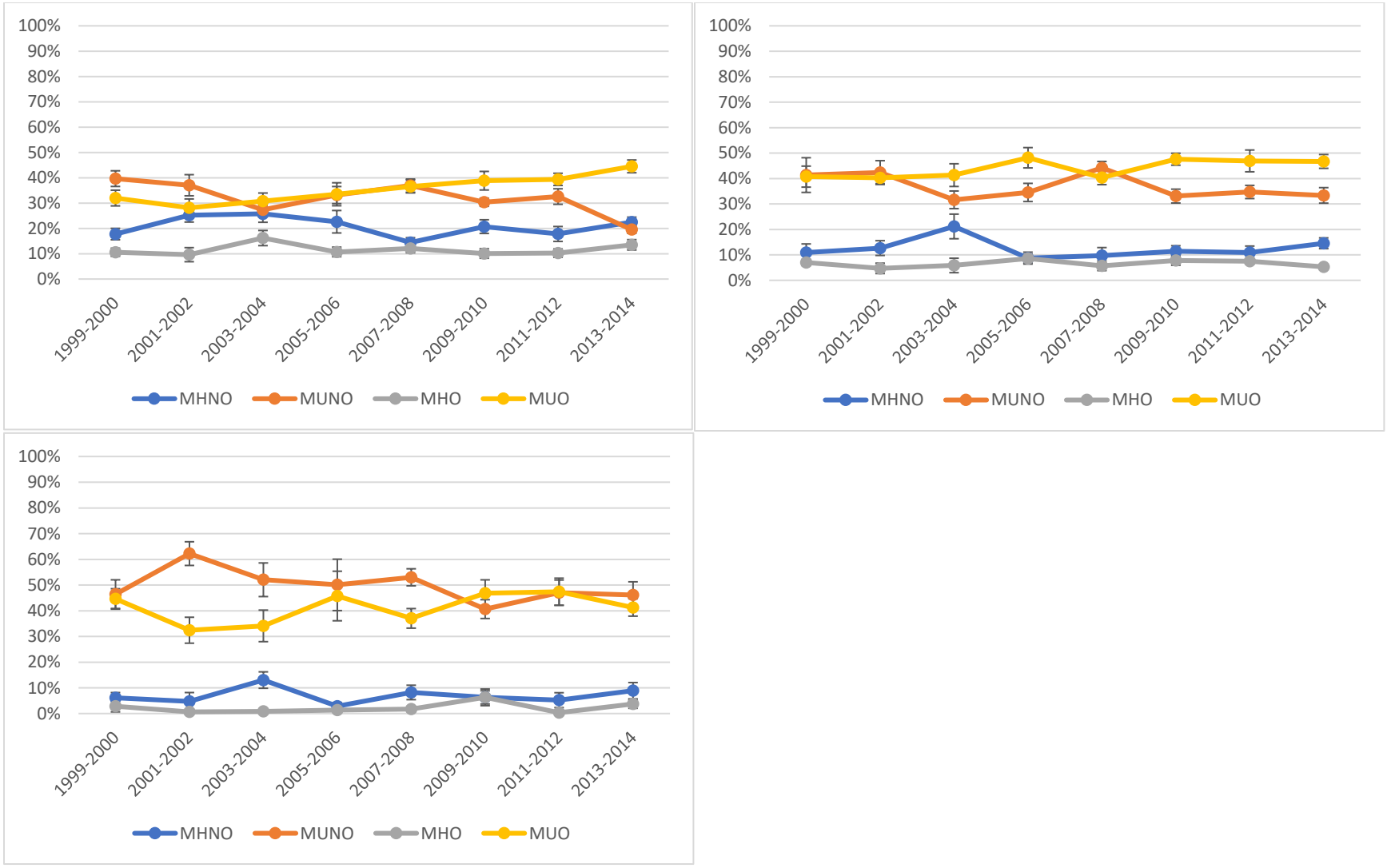


Figure 9 - Weighted percentage of sample metabolic health category allocation in age over time. Panel A (top left) - <45; Panel B (top right) - >=45 -<65; Panel C (bottom left) - >=65.

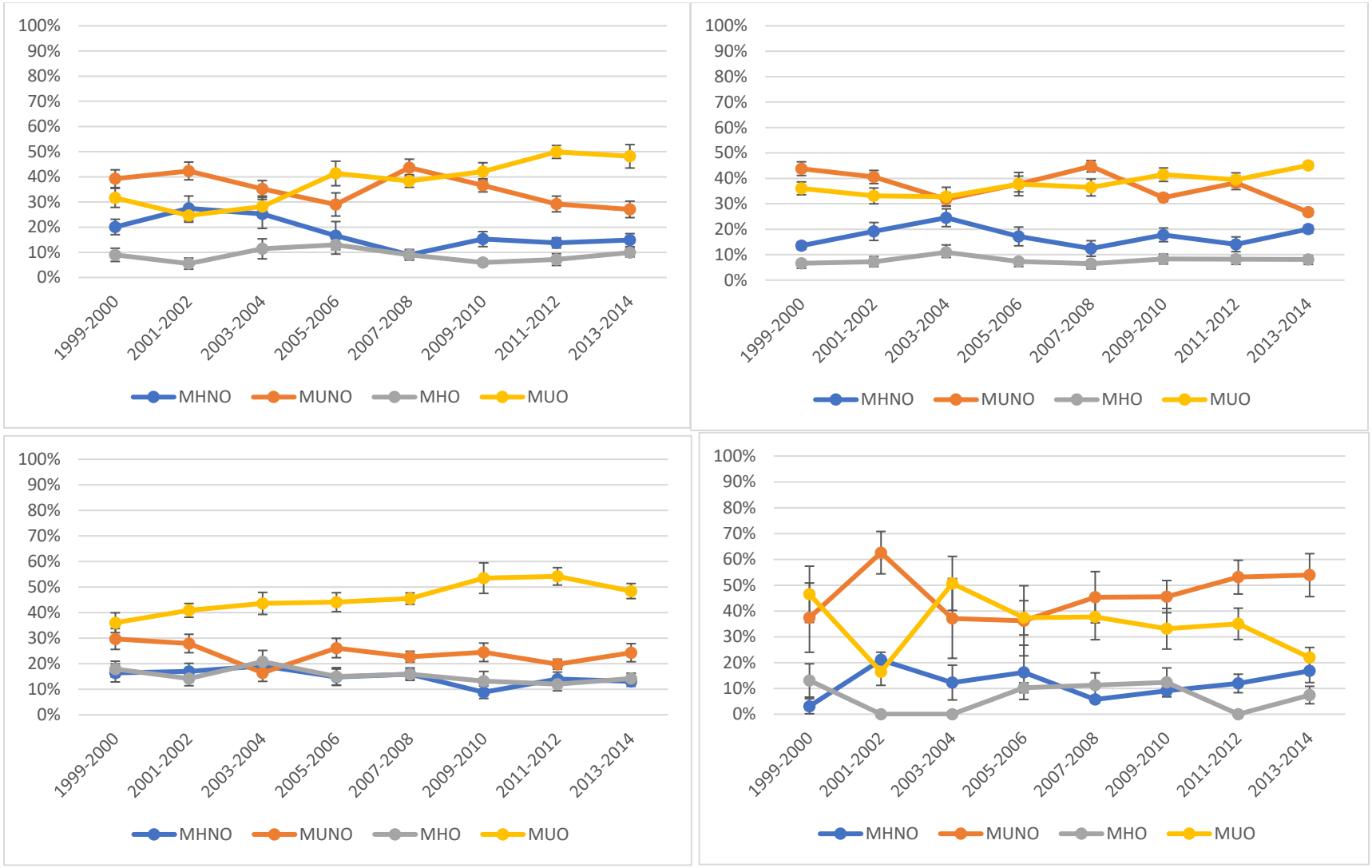


Figure 10 - Weighted percentage of sample metabolic health category allocation in ethnicity over time. Panel A (top left) – Hispanic; Panel B (top right) - Non-Hispanic White; Panel C (bottom left) - Non-Hispanic Black. Panel D (bottom right) - other ethnicity including multi-race.

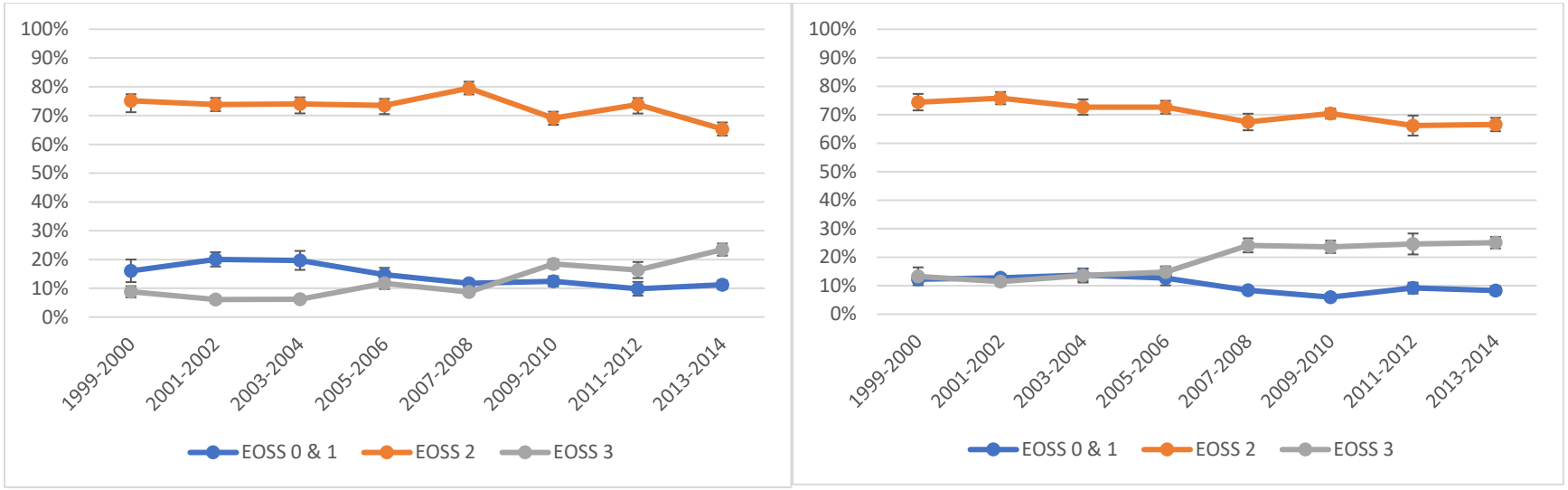


Figure 11 - Weighted percentage of sample EOSS category allocation in sex over time. Panel A (left) – men; Panel B (right) – women.

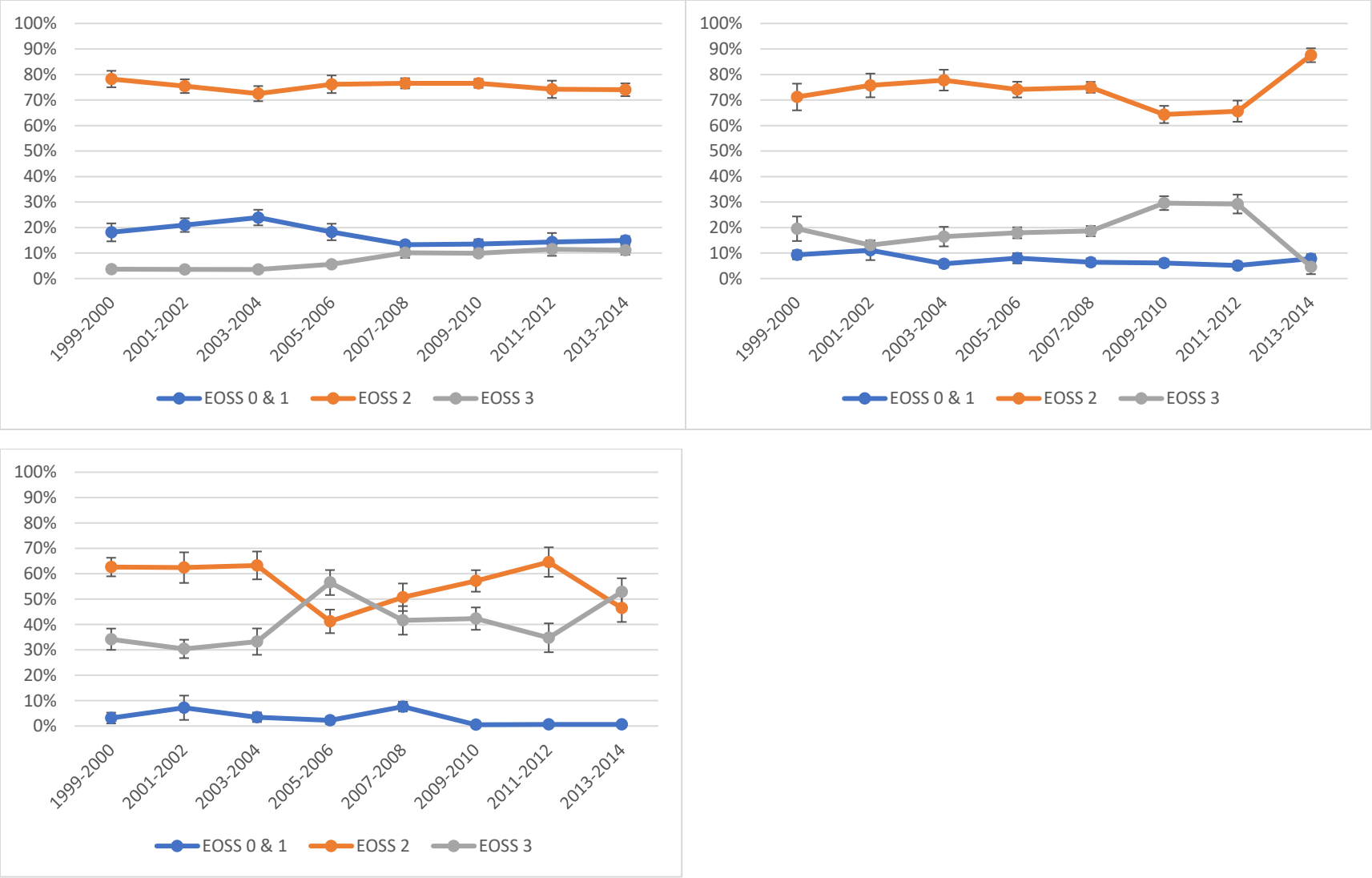


Figure 12 - Weighted percentage of sample EOSS category allocation in age over time. Panel A (top left) - <45; Panel B (top right) - >=45 -<65; Panel C (bottom left) - >=65.

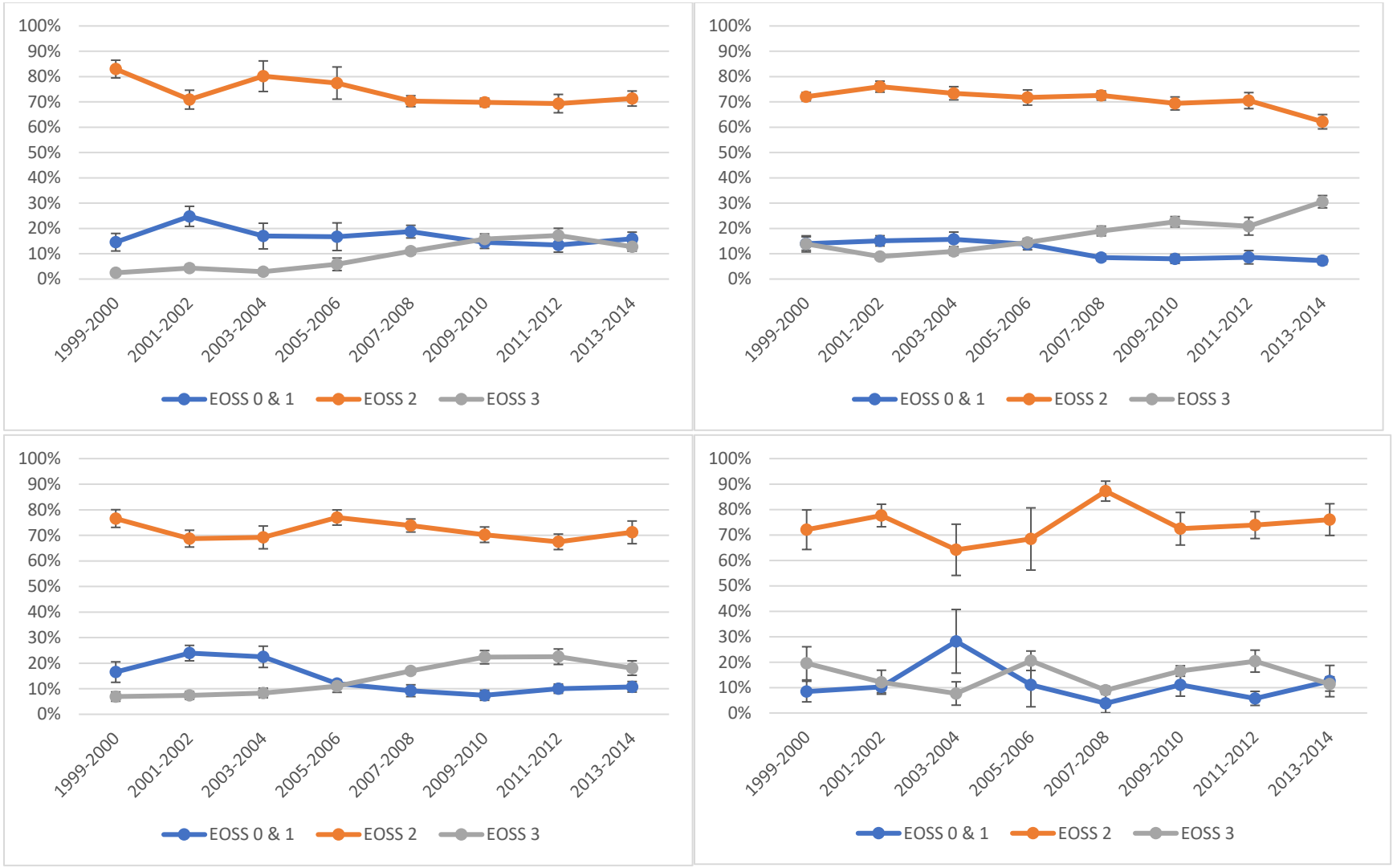


Figure 13 - Weighted percentage of sample EOSS category allocation in ethnicity over time. Panel A (top left) – Hispanic; Panel B (top right) - Non-Hispanic White; Panel C (bottom left) - Non-Hispanic Black. Panel D (bottom right) - other ethnicity including multi-race.

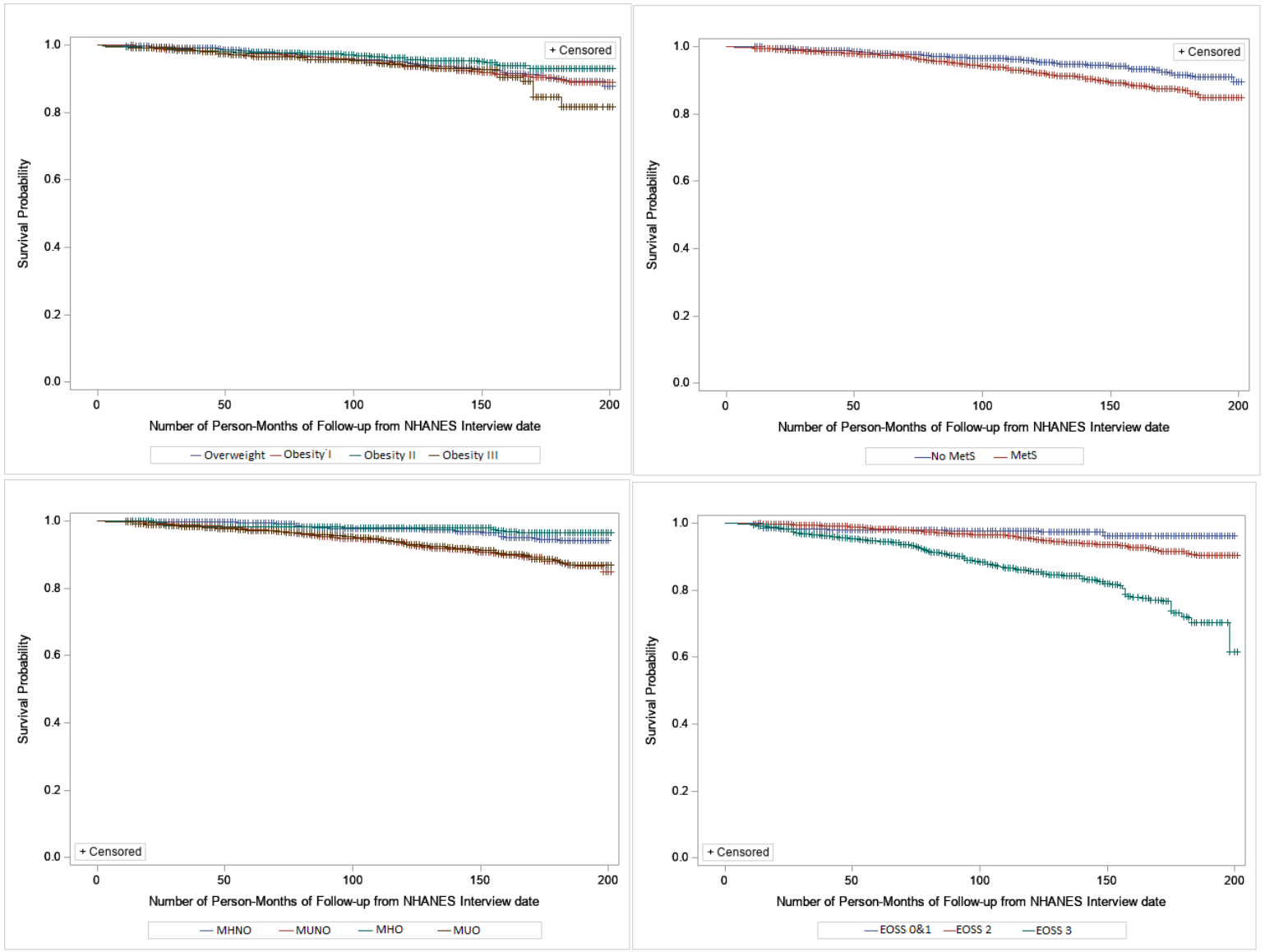


Figure 14 – Kaplan-Meier survival curves. Panel A (top left) - Obesity Categories; Panel B (top right) - MetS categories; Panel C (bottom left) - Metabolic Phenotype categories; Panel D (bottom right) -EOSS categories.

Table 4 – Cox regressions of the preclinical assessment tools under the following models; Model 1 -unadjusted, Model 2 – adjusted for social factors, Model 3 – adjusted for demographic factors, Model 4 -adjusted for socioeconomic factors, model 5 – adjusted with all covariates.

| | **Model 1[1]** | | **Model 2[2]** | | **Model 3[3]** | | **Model 4[4]** | | **Model 5[5]** | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Hazard Ratio (95% CI) | P Value | Hazard Ratio (95% CI) | P Value | Hazard Ratio (95% CI) | P Value | Hazard Ratio (95% CI) | P Value | Hazard Ratio (95% CI) | P Value |
| **Obesity Categories** | | | | | | | | | | |
| Overweight | 1.00 (ref) | - | 1.00 (ref) | - | 1.00 (ref) | - | 1.00 (ref) | - | 1.00 (ref) | - |
| Obesity I | 1.095 (0.83-1.44) | 0.5110 | 1.10 (0.83-1.45) | 0.5088 | 1.10 (0.85-1.42) | 0.4795 | 1.06 (0.82-1.38) | 0.6398 | 1.40 (0.93-2.11) | 0.1079 |
| Obesity II | 0.73 (0.48-1.11) | 0.1399 | 0.70 (0.46-1.05) | 0.0865 | 0.77 (0.50-1.18) | 0.2259 | 0.76 (0.49-1.16) | 0.1981 | 0.48 (0.23-0.99) | 0.0488 |
| Obesity III | 1.32 (0.91-1.92) | 0.1395 | 1.22 (0.83-1.80) | 0.3107 | 1.45 (1.01-2.07) | 0.0428 | 1.30 (0.89-1.90) | 0.1688 | 1.56 (0.60-4.03) | 0.3575 |
| **MetS** | | | | | | | | | | |
| No MetS | 1.00 (ref) | - | 1.00 (ref) | - | 1.00 (ref) | - | 1.00 (ref) | - | 1.00 (ref) | - |
| Has MetS | 1.71 (1.29-2.26) | 0.0003 | 1.65 (1.24-2.18) | 0.0006 | 1.05 (0.78-1.40) | 0.7525 | 1.00 (0.76-1.31) | 0.9864 | 1.08 (0.53-2.22) | 0.8245 |
| **Metabolic Health Category** | | | | | | | | | | |
| MHNO | 1.00 (ref) | - | 1.00 (ref) | - | 1.00 (ref) | - | 1.00 (ref) | - | 1.00 (ref) | - |
| MUNO | 2.57 (1.58-4.19) | 0.0002 | 2.42 (1.47-3.98) | 0.0006 | 1.53 (0.97-2.42) | 0.0659 | 1.47 (0.93-2.34) | 0.0985 | 0.99 (0.47-2.08) | 0.9800 |
| MHO | 0.75 (0.31-1.84) | 0.5344 | 0.74 (0.31-1.80) | 0.5077 | 0.90 (0.37-2.17) | 0.8146 | 0.88 (0.37 – 2.09) | 0.7726 | 0.23 (0.07-0.77) | 0.0175 |
| MUO | 2.51 (1.56-4.04) | 0.0002 | 2.34 (1.44-3.81) | 0.0008 | 1.59 (1.04-2.42) | 0.0307 | 1.48 (0.96-2.28) | 0.0755 | 1.26 (0.66-2.41) | 0.4803 |
| **EOSS Category** | | | | | | | | | | |
| EOSS 0-1 | 1.00 (ref) | - | 1.00 (ref) | - | 1.00 (ref) | - | 1.00 (ref) | - | 1.00 (ref) | - |
| EOSS 2 | 1.96 (0.73-5.25) | 0.1779 | 2.24 (0.82-6.11) | 0.1134 | 1.32 (0.47-3.72) | 0.5905 | 1.41 (0.50-4.01) | 0.5153 | 1.65 (0.30-8.94) | 0.5573 |
| EOSS 3 | 6.44 (2.37-17.51) | 0.0003 | 6.87 (2.55-18.54) | 0.0002 | 2.07 (0.70-6.11) | 0.1830 | 2.15 (0.72-6.37) | 0.1672 | 2.46 (0.45-13.57) | 0.2986 |

[1]No adjustments; [2]adjusted for social factors (smoking status, alcohol consumption and physical activity level); [3]adjusted for demographic factors (age, sex, ethnicity and immigration status); [4]adjusted for socioeconomic factors (age, sex, income, education and immigration status). [5]adjusted for all covariates (age, sex, ethnicity, income, education, smoking status, alcohol consumption, immigration status, NHANES cycle and physical activity level).

# References


[1] M. M. Finucane *et al.*, “National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants.,” *Lancet (London, England)*, vol. 377, no. 9765, pp. 557–67, Feb. 2011.

[2] C. Arroyo-Johnson and K. D. Mincey, “Obesity Epidemiology Worldwide.,” *Gastroenterol. Clin. North Am.*, vol. 45, no. 4, pp. 571–579, 2016.

[3] C. M. Hales, C. D. Fryar, M. D. Carroll, D. S. Freedman, and C. L. Ogden, “Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007-2008 to 2015-2016,” *JAMA*, vol. 319, no. 16, p. 1723, Apr. 2018.

[4] L. Abarca-Gómez *et al.*, “Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults,” *Lancet*, vol. 390, no. 10113, pp. 2627–2642, Dec. 2017.

[5] World Health Organization, “Fact Sheet - Obesity and overweight,” 2018. [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. [Accessed: 29-May-2019].

[6] E. A. Finkelstein, J. G. Trogdon, J. W. Cohen, and W. Dietz, “Annual Medical Spending Attributable To Obesity: Payer-And Service-Specific Estimates,” *Health Aff.*, vol. 28, no. 5, pp. w822–w831, Sep. 2009.

[7] K. A. Thurber *et al.*, “Obesity and its association with sociodemographic factors, health behaviours and health status among Aboriginal and non-Aboriginal adults in New South Wales, Australia,” *J. Epidemiol. Community Health*, vol. 72, no. 6, pp. 491–498, Jun. 2018.

[8] G. Pavela, D. W. Lewis, J. Locher, and D. B. Allison, “Socioeconomic Status, Risk of Obesity, and the Importance of Albert J. Stunkard.,” *Curr. Obes. Rep.*, vol. 5, no. 1, pp. 132–9, Mar. 2016.

[9] A. Goyal, K. R. Nimmakayala, and J. Zonszein, “Is There a Paradox in Obesity?,” *Cardiol. Rev.*, vol. 22, no. 4, pp. 163–170, 2014.

[10] G. Beccuti and S. Pannain, “Sleep and obesity.,” *Curr. Opin. Clin. Nutr. Metab. Care*, vol. 14, no. 4, pp. 402–12, Jul. 2011.

[11] R. McConnell, F. D. Gilliland, M. Goran, H. Allayee, A. Hricko, and S. Mittelman, “Does near-roadway air pollution contribute to childhood obesity?,” *Pediatr. Obes.*, vol. 11, no. 1, pp. 1–3, Feb. 2016.

[12] J. de Bont *et al.*, “Ambient air pollution and overweight and obesity in school-aged children in Barcelona, Spain,” *Environ. Int.*, vol. 125, pp. 58–64, Apr. 2019.

[13] R.P. Lopez, "Neighborhood risk factors for obesity." *Obesity*. vol., pp. 15:2111–2119, 2007.

[14] J. Hebebrand, A. Hinney, "Environmental and genetic risk factors in obesity.," *Child Adolesc Psychiatr Clin N Am*. vol.18 no.1, pp. 83-94, Jan. 2009.

[15] A. M. Association, “Recognition of Obesity as a Disease,” *Am. Med. Assoc.*, pp. 1–7, 2013.

[16] Canadian Medical Association, “Obesity as a chronic medical disease - Canadian Medical Association,” 2015. [Online]. Available: https://policybase.cma.ca/en/permalink/policy11700. [Accessed: 29-May-2019].

[17] R. E. Brolin, “Bariatric Surgery and Long-term Control of Morbid Obesity,” *JAMA*, vol. 288, no. 22, p. 2793, Dec. 2002.

[18] World Health Organization, “Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation. World Health Organ Tech Rep Ser,” *Who*, pp. 1–253, 2004.

[19] O. E. Initiative, “The Evidence Report,” *Evid. Rep.*

[20] Canada. Health Canada., *Canadian guidelines for body weight classification in adults.* Health Canada, 2003.

[21] T. G. 2015 O. Collaborators, “Health Effects of Overweight and Obesity in 195 Countries over 25 Years,” *N. Engl. J. Med.*, vol. 377, no. 1, pp. 13–27, Jul. 2017.

[22] WHO, “Global Health Risks,” *WHO Libr. Cat. Data Glob.*, pp. 1–70, 2009.

[23] S. J. Olshansky *et al.*, “A Potential Decline in Life Expectancy in the United States in the 21st Century,” *N. Engl. J. Med.*, vol. 352, no. 11, pp. 1138–1145, Mar. 2005.

[24] M. Agha and R. Agha, “The rising prevalence of obesity: part A: impact on public health,” *Int. J. Surgery. Oncol.*, vol. 2, no. 7, p. e17, Aug. 2017.

[25] A. H. Mokdad *et al.*, “Prevalence of Obesity, Diabetes, and Obesity-Related Health Risk Factors, 2001,” *JAMA*, vol. 289, no. 1, p. 76, Jan. 2003.

[26] J. Stevens, J. Cai, E. R. Pamuk, D. F. Williamson, M. J. Thun, and J. L. Wood, “The Effect of Age on the Association between Body-Mass Index and Mortality,” *N. Engl. J. Med.*, vol. 338, no. 1, pp. 1–7, Jan. 1998.

[27] E. Di Angelantonio *et al.*, “Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents,” *Lancet*, vol. 388, no. 10046, pp. 776–786, Aug. 2016.

[28] J. Bigaard *et al.*, “Body Fat and Fat-Free Mass and All-Cause Mortality,” *Obes. Res.*, vol. 12, no. 7, pp. 1042–1049, Jul. 2004.

[29] M. Wellens, RI., Roche, AF, Khamis, HJ., Jackson, AS., Pollock, “Relationships between Body Mass Index and body composition,” *Obes. Res.*, vol. 4, no. 1, pp. 35–44, 1996.

[30] C. S. Yajnik and J. S. Yudkin, “The Y-Y paradox,” *Lancet*, vol. 363, no. 9403, p. 163, Jan. 2004.

[31] R. P. Wildman, “The Obese Without Cardiometabolic Risk Factor Clustering and the Normal Weight With Cardiometabolic Risk Factor Clustering,” *Arch. Intern. Med.*, vol. 168, no. 15, p. 1617, 2008.

[32] S. X., L. M.J., L. J.N., H. J.W., C. N., and H. S.P., “Cardiorespiratory fitness and adiposity as mortality predictors in older adults,” *J. Am. Med. Assoc.*, vol. 298, no. 21, pp. 2507–2516, 2007.

[33] K. M. Flegal, B. I. Graubard, D. F. Williamson, and M. H. Gail, “Cause-Specific Excess Deaths

Associated With Underweight, Overweight, and Obesity," *JAMA*, vol. 298, no. 17, p. 2028, Nov. 2007.

[34] C. Iacobini, G. Pugliese, C. Blasetti Fantauzzi, M. Federici, and S. Menini, "Metabolically healthy versus metabolically unhealthy obesity," *Metabolism*, vol. 92, pp. 51–60, Mar. 2019.

[35] M. A. Gosse, "How accurate is self-reported BMI?," *Nutr. Bull.*, vol. 39, no. 1, pp. 105–114, 2014.

[36] National Institute of Diabetes and Digestive and Kidney Diseases, "Overweight & Obesity Statistics," 2021. [Online]. Available: https://www.niddk.nih.gov/health-information/health-statistics/overweight-obesity [Accessed: 30-Mar-2022].

[37] L. Abarca-Gómez *et al.*, "Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults," *Lancet*, vol. 390, no. 10113, pp. 2627–2642, Dec. 2017.

[38] A. S. Singh, C. Mulder, J. W. R. Twisk, W. Van Mechelen, and M. J. M. Chinapaw, "Tracking of childhood overweight into adulthood: a systematic review of the literature," *Obes. Rev.*, vol. 9, no. 5, pp. 474–488, Mar. 2008.

[39] P. S. MacLean, J. A. Higgins, E. D. Giles, V. D. Sherk, and M. R. Jackman, "The role for adipose tissue in weight regain after weight loss," *Obes. Rev.*, vol. 16, pp. 45–54, Feb. 2015.

[40] K. Strohacker, K. C. Carpenter, and B. K. McFarlin, "Consequences of Weight Cycling: An Increase in Disease Risk?," *Int. J. Exerc. Sci.*, vol. 2, no. 3, pp. 191–201, 2009.

[41] A. Oreopoulos, K. Kalantar-Zadeh, A. M. Sharma, and G. C. Fonarow, "The Obesity Paradox in the Elderly: Potential Mechanisms and Clinical Implications," *Clin. Geriatr. Med.*, vol. 25, no. 4, pp. 643–659, Nov. 2009.

[42] K. Vemmos *et al.*, "Association Between Obesity and Mortality After Acute First-Ever Stroke," *Stroke*, vol. 42, no. 1, pp. 30–36, Jan. 2011.

[43] A. L. Clark, J. Chyu, and T. B. Horwich, "The obesity paradox in men versus women with systolic heart failure.," *Am. J. Cardiol.*, vol. 110, no. 1, pp. 77–82, Jul. 2012.

[44] M. K. Shea *et al.*, "The effect of intentional weight loss on all-cause mortality in older adults: results of a randomized controlled weight-loss trial.," *Am. J. Clin. Nutr.*, vol. 94, no. 3, pp. 839–46, Sep. 2011.

[45] R. H. Coker and R. R. Wolfe, "Weight Loss Strategies in the Elderly: A Clinical Conundrum," *Obesity*, vol. 26, no. 1, pp. 22–28, Jan. 2018.

[46] M. Hamer and G. O'Donovan, "Sarcopenic obesity, weight loss, and mortality: the English Longitudinal Study of Ageing," *Am. J. Clin. Nutr.*, vol. 106, no. 1, pp. 125–129, Jul. 2017.

[47] R. Kanter and B. Caballero, "Global gender disparities in obesity: a review.," *Adv. Nutr.*, vol. 3, no. 4, pp. 491–8, Jul. 2012.

[48] M. Schorr *et al.*, "Sex differences in body composition and association with cardiometabolic risk," *Biol. Sex Differ.*, vol. 9, no. 1, p. 28, Dec. 2018.

[49] M. A. Bredella, "Sex Differences in Body Composition," in *Advances in experimental medicine and*

*biology*, vol. 1043, 2017, pp. 9–27.

[50] J. Kozakowski, M. Gietka-Czernel, D. Leszczyńska, and A. Majos, “Obesity in menopause - our negligence or an unfortunate inevitability?,” *Prz. menopauzalny = Menopause Rev.*, vol. 16, no. 2, pp. 61–65, Jun. 2017.

[51] M. Kwaśniewska *et al.*, “Smoking status, the menopausal transition, and metabolic syndrome in women,” *Menopause J. North Am. Menopause Soc.*, vol. 19, no. 2, pp. 194–201, Feb. 2012.

[52] H. A. Feldman *et al.*, “Age Trends in the Level of Serum Testosterone and Other Hormones in Middle-Aged Men: Longitudinal Results from the Massachusetts Male Aging Study,” *J. Clin. Endocrinol. Metab.*, vol. 87, no. 2, pp. 589–598, Feb. 2002.

[53] M. N. T. Fui, P. Dupuis, and M. Grossmann, “Lowered testosterone in male obesity: mechanisms, morbidity and management.,” *Asian J. Androl.*, vol. 16, no. 2, pp. 223–31, 2014.

[54] R. D. Stanworth and T. H. Jones, “Testosterone for the aging male; current evidence and recommended practice.,” *Clin. Interv. Aging*, vol. 3, no. 1, pp. 25–44, 2008.

[55] K. Ball, G. D. Mishra, and D. Crawford, “Social factors and obesity: an investigation of the role of health behaviours,” *Int. J. Obes.*, vol. 27, no. 3, pp. 394–403, Mar. 2003.

[56] WHO Expert Consultation, “Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies.,” *Lancet (London, England)*, vol. 363, no. 9403, pp. 157–63, Jan. 2004.

[57] P. M. McKeigue, G. J. Miller, and M. G. Marmot, “Coronary heart disease in South Asians overseas: A review,” *J. Clin. Epidemiol.*, vol. 42, no. 7, pp. 597–609, 1989.

[58] K. R. Bainey and B. I. Jugdutt, “Increased burden of coronary artery disease in South-Asians living in North America. Need for an aggressive management algorithm,” *Atherosclerosis*, vol. 204, no. 1, pp. 1–10, May 2009.

[59] B. Teucher, S. Rohrmann, and R. Kaaks, “Obesity: Focus on all-cause mortality and cancer,” *Maturitas*, vol. 65, no. 2, pp. 112–116, Feb. 2010.

[60] M. D. Deboer, “Ethnicity, obesity and the metabolic syndrome: implications on assessing risk and targeting intervention.,” *Expert Rev. Endocrinol. Metab.*, vol. 6, no. 2, pp. 279–289, Mar. 2011.

[61] S. E. Walker, M. J. Gurka, M. N. Oliver, D. W. Johns, and M. D. DeBoer, “Racial/ethnic discrepancies in the metabolic syndrome begin in childhood and persist after adjustment for environmental factors.,” *Nutr. Metab. Cardiovasc. Dis.*, vol. 22, no. 2, pp. 141–8, Feb. 2012.

[62] International Diabetes Federation (IDF), “Worldwide Definition of the Metabolic Syndrome,” *Epidemiolgy Prev.*, vol. 50, no. 3, p. 514211, 2006.

[63] A. Engin, “The Definition and Prevalence of Obesity and Metabolic Syndrome,” in *Advances in experimental medicine and biology*, vol. 960, 2017, pp. 1–17.

[64] K. G. M. M. Alberti *et al.*, “Harmonizing the Metabolic Syndrome,” *Circulation*, vol. 120, no. 16, pp. 1640–1645, Oct. 2009.

[65] J. L. Kuk, M. Rotondi, X. Sui, S. N. Blair, and C. I. Ardern, “Individuals with obesity but no other metabolic risk factors are not at significantly elevated all-cause mortality risk in men and

women," *Clin. Obes.*, vol. 8, no. 5, pp. 305–312, 2018.

[66] H. Lin, L. Zhang, R. Zheng, and Y. Zheng, "The prevalence, metabolic risk and effects of lifestyle intervention for metabolically healthy obesity: a systematic review and meta-analysis: A PRISMA-compliant article.," *Medicine (Baltimore).*, vol. 96, no. 47, p. e8838, Nov. 2017.

[67] R. Caleyachetty *et al.*, "Metabolically Healthy Obese and Incident Cardiovascular Disease Events Among 3.5 Million Men and Women," *J. Am. Coll. Cardiol.*, vol. 70, no. 12, pp. 1429–1437, Sep. 2017.

[68] N. Eckel, Y. Li, O. Kuxhaus, N. Stefan, F. B. Hu, and M. B. Schulze, "Transition from metabolic healthy to unhealthy phenotypes and association with cardiovascular disease risk across BMI categories in 90 257 women (the Nurses' Health Study): 30 year follow-up from a prospective cohort study," *Lancet Diabetes Endocrinol.*, vol. 6, no. 9, pp. 714–724, Sep. 2018.

[69] D. E. R. Warburton, C. W. Nicol, and S. S. D. Bredin, "Health benefits of physical activity: the evidence.," *CMAJ*, vol. 174, no. 6, pp. 801–9, Mar. 2006.

[70] D. Lee, E. G. Artero, X. Sui, and S. N. Blair, "Mortality trends in the general population: the importance of cardiorespiratory fitness," *J. Psychopharmacol.*, vol. 24, no. 4_supplement, p. 27, Nov. 2010.

[71] P. A. McAuley *et al.*, "Fitness, Fatness, and Mortality: The FIT (Henry Ford Exercise Testing) Project," *Am. J. Med.*, vol. 129, no. 9, pp. 960-965.e1, Sep. 2016.

[72] V. W. Barry, M. Baruth, M. W. Beets, J. L. Durstine, J. Liu, and S. N. Blair, "Fitness vs. Fatness on All-Cause Mortality: A Meta-Analysis," *Prog. Cardiovasc. Dis.*, vol. 56, no. 4, pp. 382–390, Jan. 2014.

[73] C. L. Ogden, M. D. Carroll, B. K. Kit, and K. M. Flegal, "Prevalence of Childhood and Adult Obesity in the United States, 2011-2012," *JAMA*, vol. 311, no. 8, p. 806, Feb. 2014.

[74] G. E. Duncan, "The fit but fat concept revisited: population-based estimates using NHANES," *Int. J. Behav. Nutr. Phys. Act.*, vol. 7, no. 1, p. 47, May 2010.

[75] A. M. Sharma and R. F. Kushner, "A proposed clinical staging system for obesity," *Int. J. Obes.*, vol. 33, no. 3, pp. 289–295, Mar. 2009.

[76] R. S. Padwal, N. M. Pajewski, D. B. Allison, and A. M. Sharma, "Using the Edmonton obesity staging system to predict mortality in a population-representative cohort of people with overweight and obesity.," *CMAJ*, vol. 183, no. 14, pp. E1059-66, Oct. 2011.

[77] "Drinking levels defined.," *NIAAA Alcohol & Your Health website*. https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking. Accessed Feb 20, 2022.

[78] K. L. Canning, R. E. Brown, S. Wharton, A. M. Sharma, and J. L. Kuk, "Edmonton Obesity Staging System Prevalence and Association with Weight Loss in a Publicly Funded Referral-Based Obesity Clinic.," *J. Obes.*, vol. 2015, p. 619734, 2015.

[79] A.S. Levey, L.A. Stevens, C.H. Schmid, Y.L. Zhang, A.F. Castro, H.I. Feldman *et al*., "A new equation to estimate glomerular filtration rate," *Ann Intern Med*, vol. 150, no. 9, pp. 604–12, 2009.

[80] G. Bedogni, S. Bellentani, L. Miglioli, F. Masutti , M. Passalacqua, A. Castiglione, C. Tiribelli, "The

Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population," *BMC Gastroenterol*, vol. 6, p. 33, 2015.

[81] K. Kroenke, R.L. Spitzer, J.B. Williams, "The PHQ-9: validity of a brief depression severity measure," *J. Gen. Intern. Med.,* vol. 16, no. 9, pp. 606-13, Sep. 2001.

[82] D.E.Alley, V.W. Chang, "The changing relationship of obesity and disability, 1988-2004," *JAMA.*, vol. 298, pp. 2020-7, 2007.

[83] A. Hill, P Sevak, "Trends in medical conditions and functioning in the U.S. population, 1997–2017," *Disability and Health Journal*, vol. 14, no. 2, p. 101024, Apr. 2021. doi: 10.1016/j.dhjo.2020.101024. Epub 2020 Nov 14. PMID: 33257286.

[84] G. Kabat, W.Y. Wu, J. Bea, *et al*., "Metabolic phenotypes of obesity: frequency, correlates and change over time in a cohort of postmenopausal women," *Int. J. Obes.,* vol. 41, pp. 170–177, 2017. https://doi.org/10.1038/ijo.2016.179

[85] H. Beltrán-Sánchez, M.O. Harhay, M.M. Harhay, S. McElligott, "Metabolic phenotypes of obesity: frequency, correlates and change over time in a cohort of postmenopausal women," *Int. J. Obes.,* vol. 41, pp. 170–177, 2017. https://doi.org/10.1038/ijo.2016.179

[86] D. E. King, E. Matheson, S. Chirina, *et al.*, "The Status of Baby Boomers' Health in the United StatesThe Healthiest Generation?" *JAMA Intern. Med.,* vol. 173, no. 5, pp. 385-386, 2013. doi:10.1001/jamainternmed.2013.2006

[87] United States Census Bureau, "Annual Estimates of the Resident Population by Single Year of Age and Sex for the United States: April 1, 2010 to July 1, 2019 (NC-EST2019-AGESEX-RES)," National Population by Characteristics: 17 Jun. 2020 [Online]. Available: https://www.census.gov/data/datasets/time-series/demo/popest/2010s-national-detail.html [Accessed: 16-Aug-2021].

[88] A. Navaratnarajah, S. H. D. Jackson, "The physiology of ageing," *Medicine,* vol. 45, no. 1, pp. 6-10, 18 Nov. 2016. https://doi.org/10.1016/j.mpmed.2016.10.008.

[89] M.E. Tinetti, G.J. McAvay, T.E. Murphy, C.P. Gross, H. Lin, H.G. Allore, "Contribution of Individual Diseases to Death in Older Adults with Multiple Diseases," *Journal of the American Geriatrics Society,* vol. 60, no. 8, pp. 1448-56, Aug. 2012 doi: https://doi.org/10.1503/cmaj.200484

[90] T. Wu, A.S. Niubo, C. Daskalopoulou, *et al*., "Sex differences in mortality: results from a population-based study of 12 longitudinal cohorts," *CMAJ.,* vol. 193, no. 11, pp. 361-70, 15 Mar. 2021. doi: https://doi.org/10.1503/cmaj.200484

[91] F. Weiss, M. Barbuti, G. Carignani, A. Calderone, F. Santini, I Maremmani, G. Perugi, "Psychiatric Aspects of Obesity: A Narrative Review of Pathophysiology and Psychopathology," *J. Clin. Med.,* vol. 9, no. 8, pp. 2344, Jul. 2020. https://doi.org/10.3390/jcm9082344

[92] G. Shefer, Y. Marcus, N. Stern, "Is obesity a brain disease?," *Neuroscience and Biobehavioural Reviews,* vol. 37, no. 10, p. 2, pp. 2489-503, Dec. 2013. https://doi.org/10.1016/j.neubiorev.2013.07.015

[93] A. L. Lopresti, P. D. Drummond, "Obesity and psychiatric disorders: Commonalities in dysregulated biological pathways and their implications for treatment," *Progress in Neuro-Psychopharmacology and Biological Psychiatry,* vol. 45, pp. 92-9, 1 Aug. 2013.

https://doi.org/10.1016/j.neubiorev.2013.07.015

[94] R. Paulose-Ram, V. Burt, L. Broitman, N. Ahluwalia, "Overview of asian American data collection, release, and analysis: National health and nutrition examination Survey 2011–2018," *American Journal of Public Health*, vol. 107, pp.916–21, 2017. doi: 10.2105/AJPH.2017.303815

[95] N. Kapoor, J Furler, T. Paul, N. Thomas, B. Oldenburg, "The BMI–adiposity conundrum in South Asian populations: Need for further research," *Journal of Biosocial Science*, vol. 51, no. 4, pp. 619-21, Apr. 2019. doi:10.1017/S0021932019000166