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Metabolic health and body size phenotypes: Trends and prevalence: Data from NHANES 1999-2010

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Abstract

Data from National Health and Nutrition Examination Survey for 1999-2010 were used to study trends in and prevalence of metabolically healthy (MH) and unhealthy individuals and obesity over 1999-2010. Over 1999-2010, while increasing trends in prevalence of obesity were observed for the total population ($p<0.01$), males ($p<0.01$), females ($p=0.02$), among 20-64 years old ($p<0.01$), among ≥65 years old ($p=0.02$), no trends were observed for prevalence of metabolically healthy and metabolically healthy obese ($p \geq 0.19$). Irrespective of gender, race/ethnicity, and age, MH had statistically significantly lower levels of SBP, DBP, TG, FPG, HOMA-IR, and CRP and higher levels of HDL than metabolically unhealthy (MUH) individuals. Adjusted prevalence of MH was higher among 20-64 years old than ≥65 years old ($p=0.03$), among females than males ($p<0.01$), and among normal weight than overweight and obese individuals ($p<0.01$). Race/ethnicity, smoking status, levels of and physical activity intake did not affect adjusted prevalence of MH.

Introduction

A variety of cardiometabolic variables have been used to define metabolic health in studies conducted by several authors as described in the recent review articles [1-3]. Of the 27 studies reviewed by Rey-Lopez *et al.* [1], ≥70% used blood pressure, high density lipoprotein cholesterol (HDL), fasting plasma glucose (FPG), and triglyceride levels (TG) as one of the cardiometabolic variables to define who is metabolically healthy (MH) and who is metabolically unhealthy (MUH). Less frequently used cardiometabolic variables included a surrogate measure of insulin resistance (HOMA-IR), waist circumference (WC), total cholesterol, C-reactive protein (CRP) and others [1]. Aguilar-Salinas *et al.* [4] classified individuals as being MH if they had (i) systolic blood pressure (SBP)<140 mm Hg and diastolic blood pressure (DBP)<90 mm Hg, (ii) HDL ≥ 40 mg/dL, and (iii) FPG<126 mg/dL and no treatment to lower FPG. On the other hand, Karelis *et al.* [5] followed National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) for lipid profiles and classified individuals as MH if they had "normal" values for four of the five cardiometabolic variables, namely, TG ≤ 1.7 mmol/L, HDL ≥ 1.3 mmol/L and no treatment to lower cholesterol levels, low density lipoprotein cholesterol ≤2.6 mmol/L and no treatment to lower cholesterol levels, total cholesterol ≤ 5.2 mmol/L, and HOMA-IR ≤ 1.95. Meigs *et al.* [6] also used criterion set proposed by ATP III but in addition, MH individuals were also classified solely based on the values of HOMA-IR set at 75th percentile for non-diabetic individuals. Wildman *et al.* [7] classified individuals as being MH if they had "normal" values for five of the six cardiometabolic indices, namely, (i) SBP<130 mm Hg and DBP<85 mm Hg and no treatment to lower blood pressure, (ii) fasting TG levels<150 mg/dL, (iii) HDL>40 mg/dL for males and >50 mg/dL for females, and no lipid-lowering medications, (iv) FPG<100 mg/dL and no use of antidiabetic medications, (v) HOMA-IR<5.13 based on 90th percentile, and (vi) CRP ≤ 0.1 mg/L based on 90th percentile. Thus, number of cardiometabolic indices used to define has varied from one study to another. In addition, cut offs used to separate MH from MUH individuals have also varied from one study to another. For example, while Aguilar-Salinas *et al.* [4] used a cut off of 126 mg/dL for FPG, Wildman et al (2008) used a cut off of 100 mg/dL. Wildman *et al.* [7] used a cut off of 5.13 for HOMA-IR, Karelis *et al.* [5] used a cut off of 1.95.

It should be no surprise that prevalence of MH or MUH individuals varies depending on the set of criteria used to define MH. However, more often than not, the prevalence of MH individuals has been studied in concurrence with body type phenotypes, namely, normal weight defined as those with body mass index (BMI) between 18.5 and 24.9 kg/m^2, overweight defined as those having BMI between 24.9 and 29.9 kg/m^2, and obese defined as having BMI ≥ 30 kg/m^2. Based on the data from 57 prospective studies, Prospective Studies Collaboration *et al.* [8] reported mortality rates to be lowest among those with a BMI between 22.5 and 25 kg/m^2, and for each BMI increase by 5 kg/m^2, an increase of about 30% in mortality was reported. At BMI of 30-35 kg/m^2, median survival was reported to be reduced by 2-4 years and at 40-45 kg/m^2, it was reported to be reduced by 8-10 years [8]. Given the excess mortality associated with higher BMI, of special focus and interest have been the estimates of the prevalence of those who are obese but MH [1-3] because they may be at lower risk of suffering cardiovascular events or all-cause mortality when compared with those who are obese as well as MUH [2,9]. Durward *et al.* [10] used three definitions of metabolic health and found only 3.4% of obese individuals to be classified as MH by all three definitions and 48.9% of obese individuals to be classified as MUH by all three definitions and 47.7% of obese individuals were classified as both MH and MUH depending up on which of the three definitions was used. In their review of 27 population based studies,

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Rey-Lopez *et al.* [1], based on 30 different definition of MH, found prevalence of MH to be between 6% and 75%. In addition, prevalence of MH obese was found to be higher among females and younger ages [1]. However, it should be noted that some of the studies reviewed by Rey-Lopez *et al.* [1] among Asian populations used BMI of 25 kg/m^2 as the cut off to define obesity and in two of the 27 studies, obesity was defined by WC. For example, van der A *et al.* [11], in a prospective cohort study of 22654 individuals aged 20-59 years, defined obesity by waist circumference of ≥ 102 cm for males and ≥ 88 cm for females. Velho *et al.* [12] also used abdominal obesity as one of the criterion to defined obesity in their population based study of 2557 males and 2803 females. However, in order to identify individuals with high metabolic risk, use of WC as a measure of obesity has been suggested to be more useful among normal weight and moderately obese individuals rather than among severely obese individuals and measures that are less strongly related to BMI maybe more informative to characterize MH obesity [3].

Stefan *et al.* [3] suggested physical fitness to be the one though not the sole marker to identify MH obese individuals. Metabolically healthy may be an intermediate rather a permanent low risk state [3] as was also shown by Appleton *et al.* [13] in their prospective cohort study of 4056 adults aged ≥ 18 years.

Wildman *et al.* [7] used data from National Health and Nutrition Examination Survey (NHANES) for the period 1999-2004 to estimate the prevalence of MH individuals among adults aged ≥ 20 years. Metabolically healthy were defined as mentioned previously. Among normal weight adults, 23.5% were found to be MUH and 51.3% overweight and 31.7% of obese adults were found to be MH. Mean age of MUH normal weight adult was 54.7 years as compared to 26.4 years for MH normal weight adults. Their mean WC was 86.8 cm compared to 81.2 cm for normal weight MH. Regarding recreational physical activity, 46.6% of normal weight MUH were engaged in zero daily metabolic equivalent tasks whereas 30.3% of normal weight MUH were engaged in zero daily metabolic equivalent tasks. The mean WC of MH over-weight and obese adults was 94.2 and 107.9 cm respectively as compared to 98.1 and 115.0 cm for MUH over-weight and obese adults. While MUH 43.8% and 38.9% of over-weight and obese adults respectively were engaged in ≥ 50 daily metabolic equivalent tasks (MET) respectively, 54.4% of MH over-weight adults and 47.3% of obese adults were engaged in daily MET respectively. Manu *et al.* [14] also used NHANES 1999-2004 dataset to compare the characteristics of MH obese and MH normal weight individuals. They [14] found these two groups to be similar in FPG and TG levels but MH obese were found to have higher levels of HOMA-IR (p<0.01), non-HDL cholesterol (p ≤ 0.04), and CRP (p<0.01) and lower levels of HDL (p<0.01) than normal weight MH individuals. These dysmetabolic characteristics among MH obese may signal increased risk of coronary artery disease [14].

Lynch *et al.* [15] suggested MH obese may have higher levels of circulating natural killer and cytotoxic T lymphocytes compared to MUH obese individuals or with fewer inhibitory molecules that may be providing protection against malignancy, infection, and metabolic disease in obesity. According to Aguilar-Salinas *et al.* [4], MH obese individuals may have adiponectin levels similar to normal weight individuals and higher than MUH obese individuals. MH obese, in spite of large body mass may be insulin sensitive because of lower visceral fat and early onset of obesity when compared with MUH normal weight and obese individuals [16].

In a recent article, Flegal *et al.* [17] have reported increasing linear trends over the period 2005-2014 in overall obesity among females (p<0.01) but not so among males (p=0.30). It may be of interest to know if increasing trends in obesity may be reflected in similar trends among MH and/or MUH obese individuals. Consequently, this study was undertaken to evaluate trends in prevalence of MH obesity and to compute prevalence rates of MH and MUH by body type phenotypes. Data for the period 1999-2010 from NHANES were selected for this purpose. Data were analyzed for each of the six NHANES cohorts, namely, 1999-2000, 2001-2002, 2003-2004, 2005-2006, 2007-2008, and 2009-2010 separately as well as for the entire period of 1999-2010. The analysis was restricted to adults aged ≥ 20 years.

Materials and methods

Data source and description

Data from NHANES (www.cdc.gov/nchs/nhanes.htm) for the years 1999-2010 for those ≥ 20 years old who have fasted for at least 8 hours prior to blood draw on demographics, body measures, alcohol use, blood pressure, diabetes status, physical activity, home interview smoking questionnaire, mobile examination center (MEC) smoking questionnaire, HDL levels, triglyceride levels, plasma glucose and insulin levels, C-reactive protein (CRP) levels were downloaded and match merged.

Sample sizes

Unweighted sample size for those ≥ 20 years old who have fasted for at least 8 hours prior to blood draw with non-missing values for blood pressure, HDL, triglyceride, CRP, and FPG and insulin was 12048. However, since there were 41 participants for whom sampling weights were recorded as zero in the public use data files, they were also excluded from the data analysis. Detailed sample sizes are given in Table 1. However, for some of the analyses conducted, the sample sizes were somewhat smaller because of missing values for alcohol intake, smoking status, and physical activity levels.

Derived variables

Those whose body mass index (BMI) was <18.5 kg/m^2 were excluded from the analysis. Those with BMI ≥ 18.5 kg/m^2 but less than 25 kg/m^2 were defined as normal weight, those with BMI ≥ 25 kg/m^2 but less than 30 kg/m^2 were defined as overweight, and those with BMI ≥ kg/m^2 were defined as obese. Smoking status was categorized as never smokers, former smokers, and current smokers. Those who self-reported as not smoking at least 100 cigarettes in life and also did not report smoking during the last five days in the MEC questionnaire were defined as never smokers. Those who self-reported as smoking at least 100 cigarettes in life but reported not smoking during the last five days in the MEC questionnaire were defined as former smokers. All those who reported smoking during the last five days were defined as current smokers. Self-reported levels of recreational physical activity were categorized as vigorous, moderate, none or minimal. For the years 1999-2006, participants were asked if they were engaged in (a) vigorous recreational activity for at least 10 minutes during the last 30 days that lead to heavy sweating or large increase in breathing or heart rate and (b) moderate activity for at least 10 minutes during the last 30 days that lead to only slight sweating or a slight to moderate increase in breathing or heart rate. For the years 2007-2010, instead of being asked about the activity during the last 30 days, activity status was enquired during a typical week. Those who self-reported being engaged in vigorous activity with or without being engaged in moderate activity were classified as being engaged in vigorous activity. Those who self-

Table 1. Unweighted sample sizes with weighted percents by body size phenotype, age, gender, and race/ethnicity for metabolically healthy and unhealthy participants in National Health and Nutrition Examination Survey 1999-2010.

	Normal Weight (BMI 18.5- 25 kg/m²)			Overweight (BMI 25-30 kg/m²)			Obese (BMI ≥ 30 kg/m²)			Total (BMI ≥ 18.5 kg/m²)		
	Metabolically Healthy			Metabolically Healthy			Metabolically Healthy			Metabolically Healthy		
	Yes	No	Weighted percent healthy	Yes	No	Weighted percent healthy	Yes	No	Weighted percent healthy	Yes	No	Weighted percent healthy
Total	2346	1182	72.7	1834	2448	47.4	1066	3131	26.5	5246	6761	48.7
Males	1009	620	67	913	1457	43.7	385	1426	23.4	2307	3503	44.1
Females	1337	562	77	921	991	52.4	681	1705	29.1	2939	3258	53.2
Non-Hispanic White	1291	697	72.7	872	1226	46.6	403	1496	23.2	2566	3419	52
Non-Hispanic Black	398	140	79.4	309	344	52.9	303	668	34.7	1010	1152	51.4
Mexican American	389	191	75.5	428	622	47.4	251	679	32	1068	1492	48.8
Others	268	154	66.5	225	256	48.3	109	288	32.7	698	1300	50.6
Age: 20-64 Years	2049	605	79.2	1597	1543	53	959	2296	29.1	4605	4444	46.4
Age: ≥ 65 Years	297	577	35.2	237	905	21.7	107	835	11.6	641	2317	22.6

reported being engaged in moderate activity without being engaged in vigorous activity were classified as being engaged in moderate activity. Those who self-reported being not engaged in vigorous or moderate activity were classified as being engaged in none or minimal activity. Based on self-reported intake of the number of alcoholic drinks per day during the last 12 months, alcohol intake was categorized as having 0 drinks/d, 1-2 drinks/d, 3-4 drinks/d, >4 drinks/d, and unknown number of drinks/d.

Cardiometabolic abnormalities were defined the same way as by Wildman *et al.* [7]. Blood pressure was considered to be abnormal if average systolic blood pressure was ≥ 130 mm Hg and/or diastolic blood pressure was ≥ 85 mm Hg and/or participant self-reported using a prescription drug to reduce blood pressure. Triglyceride levels were considered to be abnormal if fasting triglyceride levels were ≥ 150 mg/dL. HDL levels were considered to be abnormal if they were <40 mg/dL for males or <50 mg/dL for females and/or participant self-reported using a prescription drug to lower lipid levels. Fasting glucose levels were considered to be abnormal if they were ≥100 mg/dL and/or participants self-reported using prescription drug or insulin to reduce glucose levels. CRP levels were considered to be abnormal if they were > 0.1 mg/L. HOMA-IR levels were considered to be abnormal if they were > 5.13. HOMA-IR was computed as (fasting serum insulin level in µu/mL)*(fasting plasma glucose levels in mmol/L)/22.5. MH participants were define as being abnormal on 0 or 1 of the six cardiometabolic parameters defined above and MUH, if they were abnormal on ≥ 2 of the six cardiometabolic parameters defined above.

Software

SAS University Edition software was used to analyze data for this study.

Statistical analyses

Unadjusted means and geometric means with 95% confidence intervals for MH and MUH for each body size phenotype for all six cardiometabolic parameters by age, gender, and race/ethnicity were computed by SAS Proc SURVEYREG and are given in Table 2. Adjusted prevalence rates with 95% confidence intervals for MH by age, gender, race/ethnicity, physical activity, poverty income ratio, daily alcohol intake, and six cardiometabolic parameters were computed by SAS Proc SURVEYREG and are given in Table 3. Time trends in the prevalence of MH and obesity were evaluated by using SAS Proc SURVEYREG and results are presented in Figure 1. Percent participants with abnormal levels of each of the six cardiometabolic variables by body phenotypes were computed by SAS Proc SURVEYMEANS and data are presented in Table 4.

Results

Cardiometabolic parameters for metabolically healthy *versus* unhealthy participants

Irrespective of body size phenotype, gender, race/ethnicity, and age, MH had lower levels of systolic blood pressure than MUH (p ≤ 0.01, Tables 2 and S1). The same was true for average levels of diastolic blood pressure (p ≤ 0.04, Table 2, S1) except that for NHB for normal weight participants and ≥ 65 years old, average diastolic blood pressure levels was not statistically significantly different for every body size phenotype (Tables 2 and S1). For MH participants, HDL levels were always higher than MUH participants and triglyceride levels were always lower for MH participants than for MUH participants (Tables 2 and S1; p<0.01). For example, for obese females, triglyceride levels were 94.1 mg/dL for MH participants and 147.2 mg/dL for MUH participants, a difference of more than 50% (Table 2, p<0.01). The ratio of the levels of HDL for MUH divided by MH participants was slightly higher than 80% irrespective of age, gender, and race/ethnicity. While the ratios of triglyceride levels among MUH and MH participants varied between 1.65 and 1.78 among 20-64 years old, this ratio varied between 1.34 and 1.52 among ≥65 years old. This means advantage of being MH over MUH among those ≥65 years old may be diluted when compared with those aged 20-64 years. Fasting glucose levels were always higher for MUH participants than for MH participants. The same was true for CRP levels (p<0.01, Table 2). HOMA-IR was observed to be higher among MUH participants than among MH participants (Tables S2 and S3).

Adjusted percent prevalence rates of metabolically healthy participants

Among senior citizens aged ≥65 years, adjusted prevalence of MH was lower than among 20-64 years old (19.4% *vs.* 21.5%, p=0.03, Table 3). Males had lower prevalence of MH than females (19.3% *vs.* 21.5%, p<0.01, Table 3). Race/ethnicity, physical activity level, and poverty income ratio did not affect prevalence of MH participants. Adjusted prevalence rates by body size phenotypes were 23.4%, 20.2%, and 17.8% for normal weight, overweight, and obese participants respectively (p<0.01, Table 3). Those who had 1-2 drinks/d of alcohol had lower prevalence of MH than those who had 3-4 drinks/d (20% *vs.* 22.3%, Table 3) and those who took 3-4 drinks/d had higher levels of MH

Table 2. Means (geometric means) with 95% confidence intervals for cardiometabolic parameters by body mass index (BMI), age, gender, and race/ethnicity for metabolically healthy and unhealthy participants in National Health and Nutrition Examination Survey 1999-2010.

Variable	Category*	Normal Weight (BMI 18.5- 25 kg/m²)			Overweight (BMI 25-30 kg/m²)			Obese (BMI>= 30 kg/m²)		
		Metabolically Healthy			Metabolically Healthy			Metabolically Healthy		
		Yes	No	p	Yes	No	p	Yes	No	p
Systolic Blood Pressure in mm Hg	Total	113.3 (112.5-114.1)	129.7 (128.2-131.1)	<0.01	115.5 (114.7-116.3)	127.7 (126.7-128.7)	<0.01	117.2 (116.3-118.2)	127.4 (126.7-128)	<0.01
	Males	116.4 (115.5-117.4)	127.5 (125.8-129.1)	<0.01	117.7 (116.8-118.7)	127.1 (126-128.2)	<0.01	119.6 (118.1-121)	127.6 (126.7-128.5)	<0.01
	Females	111.3 (110.3-112.2)	132 (129.6-134.5)	<0.01	113 (112-114.1)	128.6 (126.9-130.3)	<0.01	115.7 (114.5-116.8)	127.2 (126.2-128.2)	<0.01
	NHW	113.1 (112.2-114)	129.7 (128.2-131.3)	<0.01	115.4 (114.4-116.5)	127.7 (126.4-129)	<0.01	117.4 (116.1-118.8)	127.3 (126.4-128.1)	<0.01
	NHB	117 (115.8-118.1)	133.1 (129.3-136.9)	<0.01	120 (118-122)	133.2 (131.1-135.3)	<0.01	119.9 (117.9-121.9)	131 (129.3-132.7)	<0.01
	MA	110.9 (109.5-112.4)	125.3 (121.6-128.9)	<0.01	113.6 (112.5-114.6)	123.7 (121.9-125.4)	<0.01	114.5 (113-116.1)	125.1 (123.7-126.6)	<0.01
	OTH	112.8 (110.6-115)	129.4 (125.6-133.1)	<0.01	113.4 (111.6-115.2)	127 (124.5-129.5)	<0.01	114 (111.5-116.5)	125.1 (122.1-128)	<0.01
	A20-64	112.1 (111.3-112.8)	123.9 (122.1-125.7)	<0.01	114.5 (113.6-115.3)	123.7 (122.7-124.7)	<0.01	116.6 (115.7-117.5)	125.8 (125.2-126.5)	<0.01
	A65+	129.5 (126.6-132.4)	140.5 (138.1-142.8)	<0.01	127.4 (124.3-130.4)	139 (137.1-140.9)	<0.01	126.9 (122-131.8)	134.6 (132.8-136.4)	0.01
Diastolic Blood Pressure in mm Hg	Total	67.8 (67.3-68.4)	70.4 (69.4-71.3)	<0.01	69.1 (68.4-69.8)	72.4 (71.8-73)	<0.01	70.1 (69.2-71.1)	73.8 (73.2-74.4)	<0.01
	Males	68.7 (67.9-69.5)	71.8 (70.6-73)	<0.01	70.4 (69.5-71.2)	74 (73.3-74.8)	<0.01	71.8 (70.4-73.1)	75.8 (75-76.5)	<0.01
	Females	67.3 (66.6-68)	68.8 (67.4-70.1)	0.04	67.7 (66.8-68.6)	69.8 (68.8-70.8)	<0.01	69 (67.9-70.2)	72.1 (71.3-72.8)	<0.01
	NHW	67.8 (67.1-68.5)	70 (68.8-71.1)	<0.01	69.2 (68.5-70)	72.1 (71.3-72.9)	<0.01	70.8 (69.4-72.2)	73.6 (72.9-74.3)	<0.01
	NHB	69.3 (68.3-70.3)	71.1 (68.9-73.4)	0.17	70.8 (69.3-72.3)	75.7 (74-77.3)	<0.01	70 (68.6-71.4)	75.7 (74.5-76.9)	<0.01
	MA	65.2 (63.8-66.6)	69 (67.2-70.9)	<0.01	67.9 (66.9-68.9)	71.1 (69.9-72.2)	<0.01	68.4 (66.9-70)	72.9 (71.6-74.2)	<0.01
	OTH	68.6 (67-70.1)	72.7 (70.7-74.7)	<0.01	67.7 (65.7-69.6)	73.1 (71.3-74.9)	<0.01	68.2 (65.9-70.4)	74.1 (72.1-76.1)	<0.01
	A20-64	68 (67.4-68.6)	73.4 (72.2-74.6)	<0.01	69.4 (68.7-70.1)	74.5 (73.8-75.1)	<0.01	70.4 (69.5-71.4)	75.5 (74.9-76.2)	<0.01
	A65+	65.4 (63.4-67.4)	64.7 (63.5-65.9)	0.49	65.3 (63.4-67.3)	66.5 (65.3-67.7)	0.29	66.1 (64-68.1)	66.2 (65.2-67.1)	0.93
HDL in mg/dL	Total	60.1 (59.2-61)	50.3 (48.9-51.7)	<0.01	54.5 (53.7-55.4)	45.6 (45-46.2)	<0.01	53 (52.1-53.9)	44.2 (43.6-44.8)	<0.01
	Males	54.3 (53.3-55.3)	45.7 (44.2-47.4)	<0.01	50.1 (49.3-51)	42.4 (41.7-43.2)	<0.01	47.9 (46.8-49)	40.2 (39.5-40.9)	<0.01
	Females	64.2 (63.2-65.3)	55.7 (54-57.4)	<0.01	59.9 (58.6-61.2)	51.1 (50.1-52.2)	<0.01	56.8 (55.9-57.8)	48.2 (47.3-49)	<0.01
	NHW	60.7 (59.6-61.8)	50.8 (49.1-52.5)	<0.01	54.6 (53.6-55.7)	45.9 (45.2-46.7)	<0.01	52.5 (51.4-53.7)	43.7 (43-44.3)	<0.01
	NHB	60.5 (58.9-62.2)	51.3 (48.1-54.8)	<0.01	58.5 (56.9-60.1)	49.2 (47.5-50.9)	<0.01	56.2 (54.7-57.8)	48.5 (47.2-49.9)	<0.01
	MA	57.9 (56.3-59.5)	46.9 (44.3-49.7)	<0.01	52.8 (51.6-54)	42.3 (41.3-43.4)	<0.01	51.9 (50.2-53.7)	42.4 (41.3-43.5)	<0.01
	OTH	56.7 (54.4-59.2)	48.4 (45.5-51.5)	<0.01	51.9 (50-53.8)	43.8 (41.6-46.1)	<0.01	51.4 (49.2-53.7)	43.8 (42.2-45.5)	<0.01
	A20-64	59.6 (58.7-60.6)	48.1 (46.4-49.9)	<0.01	53.9 (53-54.8)	44 (43.2-44.7)	<0.01	52.7 (51.8-53.6)	43.1 (42.4-43.8)	<0.01
	A65+	66.3 (64.1-68.6)	54.5 (53-56.1)	<0.01	62.3 (60.4-64.3)	50.5 (49.5-51.6)	<0.01	57.4 (54.8-60.2)	49.5 (48.5-50.5)	<0.01
Triglyceride in mg/dL	Total	81.2 (79.5-82.9)	134.8 (128.5-141.5)	<0.01	93.7 (91.7-95.8)	160.8 (156.4-165.4)	<0.01	97.4 (94-100.9)	156.7 (152.4-161.2)	<0.01
	Males	85.8 (83.4-88.2)	132 (123.1-141.6)	<0.01	97.3 (94-100.6)	163.1 (156.6-169.9)	<0.01	102.5 (97-108.2)	167.8 (161.3-174.5)	<0.01
	Females	78.3 (76.2-80.5)	138 (130.4-146)	<0.01	89.9 (86.7-93.3)	157.3 (152.4-162.4)	<0.01	94.1 (90.3-98)	147.2 (142.8-151.7)	<0.01
	NHW	82.7 (80.7-84.8)	134.6 (126.3-143.4)	<0.01	95.4 (92.5-98.3)	162.8 (157.3-168.6)	<0.01	102.3 (98.2-106.6)	163.5 (158-169.2)	<0.01
	NHB	68.3 (65.5-71.3)	103.3 (94.7-112.6)	<0.01	76.7 (73.3-80.3)	121.4 (113.9-129.4)	<0.01	78.4 (73.7-83.5)	115.4 (109.6-121.4)	<0.01
	MA	82.5 (78.4-86.9)	154.5 (140.7-169.7)	<0.01	97.7 (93.3-102.2)	178.1 (166.8-190.3)	<0.01	105.4 (99.7-111.5)	169.1 (160.7-177.9)	<0.01
	OTH	82.1 (77.1-87.4)	145.8 (130.9-162.4)	<0.01	97.5 (90-105.5)	168.2 (156.2-181.1)	<0.01	101.5 (92-111.9)	165.4 (152.2-179.8)	<0.01
	A20-64	80.6 (78.9-82.4)	139.6 (130.6-149.3)	<0.01	93.5 (91.4-95.6)	166 (160.2-172)	<0.01	96.7 (93.2-100.4)	159.8 (154.8-165)	<0.01
	A65+	88.7 (84.6-93)	126.4 (120.6-132.4)	<0.01	96.4 (91.5-101.5)	147.3 (141.6-153.2)	<0.01	107 (100.2-114.2)	143.4 (137.9-149.3)	<0.01
Glucose in mg/dL	Total	91.9 (91.5-92.4)	105.7 (104.4-106.9)	<0.01	94.2 (93.6-94.8)	108.3 (107.2-109.4)	<0.01	94.7 (94-95.5)	111.7 (110.6-112.8)	<0.01
	Males	94.5 (93.9-95.2)	108 (106-110.1)	<0.01	96 (95.2-96.8)	109.2 (107.8-110.5)	<0.01	96.7 (95.6-97.8)	113.8 (112.2-115.6)	<0.01
	Females	90.3 (89.8-90.7)	103.1 (101.3-105)	<0.01	92.2 (91.3-93.1)	106.9 (105.2-108.7)	<0.01	93.4 (92.4-94.4)	109.8 (108.5-111.1)	<0.01
	NHW	91.9 (91.4-92.4)	104.3 (103-105.7)	<0.01	94.2 (93.4-95)	106.9 (105.7-108.1)	<0.01	95.6 (94.5-96.7)	111.1 (109.8-112.4)	<0.01
	NHB	90.8 (89.5-92.1)	108 (103-113.2)	<0.01	92 (91.1-92.9)	112 (107.8-116.4)	<0.01	92.5 (91.7-93.3)	113.6 (110.8-116.6)	<0.01
	MA	94.1 (92.8-95.3)	112.1 (107.4-117.1)	<0.01	95.3 (94.1-96.4)	110.7 (108.3-113.3)	<0.01	94.8 (93.7-96)	115.7 (112.4-119.1)	<0.01
	OTH	92.1 (91-93.1)	109.3 (104.8-114.1)	<0.01	95.2 (91.9-98.7)	113.2 (107.6-119.1)	<0.01	93.8 (91.5-96)	110.6 (106.3-115.1)	<0.01
	A20-64	91.7 (91.2-92.1)	104.2 (102.4-105.9)	<0.01	93.8 (93.1-94.5)	106.6 (105.4-107.9)	<0.01	94.5 (93.7-95.3)	110.3 (109.3-111.4)	<0.01
	A65+	95.8 (94.5-97.1)	108.5 (106.7-110.3)	<0.01	98.5 (96.5-100.6)	113 (111.2-114.8)	<0.01	98 (96.1-99.9)	118.2 (115.7-120.8)	<0.01
CRP in mg/dL	Total	0.08 (0.08-0.09)	0.17 (0.16-0.19)	<0.01	0.15 (0.14-0.16)	0.22 (0.21-0.24)	<0.01	0.27 (0.25-0.29)	0.41 (0.39-0.43)	<0.01
	Males	0.07 (0.07-0.08)	0.14 (0.12-0.17)	<0.01	0.12 (0.11-0.13)	0.18 (0.17-0.19)	<0.01	0.2 (0.17-0.22)	0.28 (0.27-0.3)	<0.01
	Females	0.09 (0.08-0.1)	0.22 (0.19-0.25)	<0.01	0.18 (0.17-0.2)	0.31 (0.28-0.34)	<0.01	0.33 (0.3-0.36)	0.57 (0.53-0.61)	<0.01
	NHW	0.09 (0.08-0.09)	0.19 (0.17-0.21)	<0.01	0.15 (0.14-0.16)	0.22 (0.2-0.23)	<0.01	0.25 (0.22-0.28)	0.39 (0.37-0.41)	<0.01
	NHB	0.07 (0.06-0.08)	0.23 (0.16-0.31)	<0.01	0.16 (0.14-0.18)	0.25 (0.21-0.29)	<0.01	0.26 (0.23-0.3)	0.52 (0.47-0.58)	<0.01
	MA	0.09 (0.08-0.11)	0.2 (0.15-0.27)	<0.01	0.14 (0.13-0.16)	0.24 (0.21-0.28)	<0.01	0.31 (0.26-0.36)	0.41 (0.37-0.45)	0.01
	OTH	0.07 (0.06-0.09)	0.11 (0.08-0.14)	0.04	0.13 (0.1-0.15)	0.22 (0.19-0.27)	<0.01	0.33 (0.27-0.41)	0.43 (0.36-0.51)	0.11
	A20-64	0.08 (0.08-0.09)	0.16 (0.14-0.18)	<0.01	0.14 (0.13-0.15)	0.21 (0.2-0.23)	<0.01	0.26 (0.24-0.29)	0.42 (0.4-0.45)	<0.01

	A65+	0.13 (0.11-0.15)	0.22 (0.19-0.25)	<0.01	0.18 (0.16-0.21)	0.25 (0.23-0.27)	<0.01	0.29 (0.25-0.35)	0.34 (0.31-0.38)	0.16
HOMA-IR	Total	1.36 (1.32-1.41)	2.08 (1.97-2.19)	<0.01	1.86 (1.8-1.92)	3.03 (2.95-3.12)	<0.01	2.62 (2.53-2.71)	4.74 (4.61-4.88)	<0.01
	Males	1.41 (1.36-1.46)	2.11 (1.96-2.26)	<0.01	1.91 (1.82-2.01)	3.08 (2.97-3.19)	<0.01	2.8 (2.65-2.96)	5.14 (4.9-5.39)	<0.01
	Females	1.33 (1.28-1.39)	2.05 (1.93-2.17)	<0.01	1.8 (1.74-1.86)	2.96 (2.81-3.11)	<0.01	2.5 (2.39-2.62)	4.41 (4.23-4.58)	<0.01
	NHW	1.32 (1.28-1.38)	2.01 (1.88-2.14)	<0.01	1.79 (1.71-1.87)	2.88 (2.78-2.99)	<0.01	2.55 (2.42-2.68)	4.59 (4.42-4.77)	<0.01
	NHB	1.44 (1.36-1.53)	2.14 (1.89-2.43)	<0.01	1.86 (1.75-1.98)	3.29 (3.08-3.52)	<0.01	2.61 (2.44-2.8)	5 (4.7-5.32)	<0.01
	MA	1.53 (1.43-1.65)	2.31 (2.07-2.58)	<0.01	2.14 (2.04-2.24)	3.59 (3.4-3.79)	<0.01	2.89 (2.76-3.03)	5.58 (5.25-5.92)	<0.01
	OTH	1.48 (1.37-1.59)	2.37 (2.14-2.62)	<0.01	2.09 (1.95-2.24)	3.49 (3.07-3.96)	<0.01	2.8 (2.51-3.12)	4.95 (4.49-5.45)	<0.01
	A20-64	1.37 (1.32-1.41)	2.1 (1.96-2.25)	<0.01	1.87 (1.81-1.93)	3.02 (2.91-3.13)	<0.01	2.63 (2.54-2.73)	4.82 (4.66-4.98)	<0.01
	A65+	1.31 (1.22-1.41)	2.04 (1.89-2.2)	<0.01	1.72 (1.58-1.87)	3.07 (2.92-3.24)	<0.01	2.45 (2.27-2.64)	4.42 (4.14-4.71)	<0.01

*NHW=Non-Hispanic white, NHB=Non-Hispanic black, MA=Mexican American, OTH=Other unclassified race/ethnicities, A20-64=Age 20-464 years, A65+=Age>= 65 years

Table 3. Weighted adjusted percent prevalence of metabolically healthy individuals by age, gender, race/ethnicity, physical activity level, body size phenotype, smoking status, levels of fasting sugar, triglyceride, HDL, blood pressure, C-reactive protein, insulin resistance, average number of alcoholic drinks per day, and poverty income ratio.

Variable	Category**	% Prevalence (95% CI)	Statistically significant differences
Age in years	20-64 (A20)	21.5 (20-23)	A20 > A65+ (p=0.03)
	≥65 (A65+)	19.4 (17.1-21.6)	
Gender	Males (M)	19.3 (17.5-21.2)	M < F (p < 0.01)
	Females (F)	21.5 (19.8-23.2)	
Race/Ethnicity	NHW	21.2 (19.6-22.7)	
	NHB	19.9 (17.8-22.1)	
	MA	20 (18.2-21.8)	
	OTH	20.6 (18-23.2)	
Physical Activity	Vigorous	20.8 (18.9-22.7)	
	Moderate	20.2 (18.3-22)	
	None or minimal	20.3 (18.5-22.1)	
Body Mass Index in kg/m²	18.5-24.9 (N)	23.4 (21.3-25.4)	N > OV > OB (p < 0.01)
	25-29.9 (OV)	20.2 (18.3-22.1)	
	≥30 (OB)	17.8 (16-19.5)	
Smoking Status	Never	20.6 (18.9-22.4)	
	Former	20.5 (18.6-22.4)	
	Current	20.2 (18.3-22.1)	
Fasting Sugar in mg/dL	<100 (PSN)	36.9 (35.1-38.8)	PSN > PSAbN (p < 0.01)
	≥100 (PSAbN)	3.9 (2.2-5.6)	
Triglyceride in mg/dL	Normal (TgN)	35.3 (33.7-36.8)	TgN > TgH (p < 0.01)
	High (TgH)	5.6 (3.5-7.6)	
HDL in mg/dL	Normal (HDLN)	35.8 (34.1-37.5)	HDLN > HDL (p < 0.01)
	Low (HDLL)	5.1 (3.3-6.8)	
Blood Pressure*	Normal (BPN)	36.3 (34.3-38.3)	BPN > BPH (p < 0.01)
	High (BPH)	4.6 (2.9-6.2)	
C-reactive protein in mg/L	Normal (CRPN)	33.2 (31.8-34.7)	CRPN > CRPH (p < 0.01)
	High (CRPH)	7.6 (5-10.2)	
HOMA-IR	Normal	23.9 (22.3-25.5)	
	High	17 (14.7-19.2)	
Alcohol consumption in number of drinks per day	None (AL0)	21.3 (19.4-23.3)	
	1-2 (AL12)	20 (18.2-21.7)	AL12 < AL34 (p < 0.01)
	3-4 (AL34)	22.3 (20.1-24.6)	AL34 < ALUNK (p < 0.01), AL34 < ALUNK (p=0.04)
	≥4 (ALGT4)	18.7 (16.2-21.3)	
	Unknown (ALUNK)	19.8 (17.4-22.1)	
Poverty income ratio	Low	20.7 (19-22.4)	
	Medium	20.7 (19-22.5)	
	High	19.9 (17.9-21.9)	

*Blood pressure was considered normal if average systolic blood pressure was <130 mm Hg and average diastolic blood pressure was <85 mm Hg

**NHW=Non-Hispanic white, NHB=Non-Hispanic black, MA=Mexican American, OTH=Other unclassified race/ethnicities, A20-64=Age 20-464 years, A65+=Age>= 65 years

Table 4. Weighted percent individuals with abnormal levels of glucose, triglyceride, HDL, blood pressure, C-reactive protein, and insulin resistance by body size phenotype. Data from National Health and Nutrition Examination Survey 1999-2010.

	Normal Weight		Overweight		Obese		Total	
	Metabolically Healthy	**Metabolically Unhealthy**	**Metabolically Healthy**	**Metabolically Unhealthy**	**Metabolically Healthy**	**Metabolically Unhealthy**	**Metabolically Healthy**	**Metabolically Unhealthy**
Levels of Glucose	12.7	65.4	18.6	71.9	16.1	72.4	15.3	71.0
Triglyceride	5.4	45.4	9.8	57.1	9.6	53.3	7.6	53.2
HDL	11.3	57.8	15.1	63.4	15.1	68.5	13.2	64.9
C-Reactive Protein	1.4	13.9	2.2	10.8	5.5	22.3	2.4	16.8
HOMA-IR	0.2	7.5	0.5	17.6	3.4	43.9	0.9	28.3
Blood Pressure	11.7	63.1	12.8	60.7	15.3	65.7	12.7	63.5

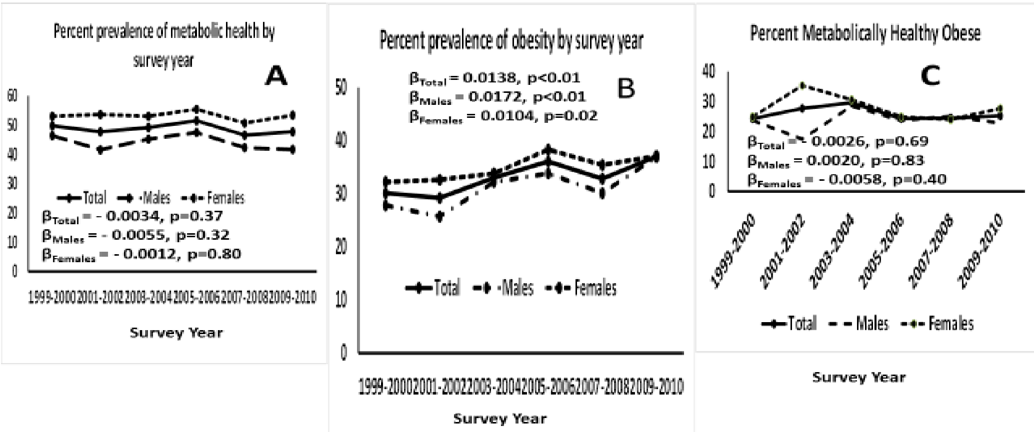

Figure 1. Percent prevalence of (A) metabolically healthy individuals by survey year, (B) obesity by survey year, (C) metabolically healthy obese by survey year.

prevalence than those who had >4 drinks/d (22.3% *vs.* 18.7%, p<0.01) and those who had unknown number of drinks/d (22.3% *vs.* 19.8%, p=0.04, Table 3). It was no surprise that those who had abnormal levels of HDL, triglyceride, glucose, blood pressure, CRP, and HOMA-IR had lower prevalence of MH participants than those with normal levels of these cardiometabolic parameters (p<0.01, Table 3).

Unadjusted trends in prevalence of metabolically healthy participants over 1999-2010

In general, no time trends in the prevalence of MH over 1999-2010 were observed (Figure 1) except that the prevalence rates for MH for NHB over time decreased (Figure S1, Panel A, β=-0.0291, p<0.01) from 62.3% in 1999-2000 to 44.3% in 2009-2010.

Unadjusted trends in prevalence of metabolically healthy obese participants and obesity over 1999-2010

Prevalence of obesity increased over time for the total population from 30.1% in 1999-2000 to 37% in 2009-2010 (p<0.01, Figure 1, Panel B), for males from 27.8% in 1999-2000 to 36.9% in 2009-2010 (p<0.01, Figure 1, Panel B), for females from 32.2% in 1999-2000 to 37.1% in 2009-2010 (p<0.01, Figure 1, Panel B), for NHW from 28.1% in 1999-2000 to 35.7% in 2009-2010 (p=0.01, Figure S1, Panel B), for NHB from 40.8% in 1999-2000 to 51.9% in 2009-2010 (p<0.01, Figure S1, Panel B), for 20-64 years old from 32.0% in 1999-2000 to 37.1% in 2009-2010 (p<0.01, Figure S2, Panel B), and for ≥65 years old from 29.7% in 1999-2000 to 36.5% in 2009-2010 (p=0.02, Figure S2, Panel B). However, these increasing trends in obesity were not reflected in percent obese who were found to be MH obese for either gender, race/ethnicity, or age group (Figures 1 and S1, S2, Panels C).

Percent participants with the levels of cardiometabolic abnormalities by body phenotypes among MH and MUH individuals

It was no surprise that percent participants with abnormal levels of cardiometabolic variables were substantially higher among MUH individuals than among MH individuals (Table 4). For example, percent participants with abnormal levels of FPG were 16.1% among MH obese, this percentage among obese MUH was 72.4% (Table 4). In addition, percent participants with abnormal levels of FPG, TG, and HDL were similar among overweight and obese MH but somewhat higher than among normal MH participants. For example, percent participants with abnormal levels of TG among overweight and obese MH were 9.8% and 9.6% respectively but among normal weight MH, this percentage was 5.4% (Table 4). Similar patterns were observed among MUH individuals for FPG, TG, and HDL. However, for CRP, HOMA-IR, and to some degree for blood pressure, there seems to be increasing pattern of abnormal levels among both MH and MUH individuals. For example, abnormal HOMA-IR level were observed at 0.2%, 0.5%, and 3.4% normal weight, overweight, and obese MH participants respectively, and at 7.5%, 17.6%, and 43.9% normal weight, overweight, and obese MUH participants respectively (Table 4).

Percent participants with abnormal WC (>102 cm for males, >88 cm for females) were 5.8%, 44.5%, and 93.7% among normal weight, overweight, and obese MH individuals respectively and all pairwise differences were statistically significant (p<0.01). Mean WC was 81.4 cm, 94.3 cm, and 108 cm among normal weight, overweight, and obese MH individuals respectively and all pairwise differences were statistically significant (p<0.01). Percent participants with abnormal WC were 15.7%, 57.2%, and 97.6% among normal weight, overweight, and obese MUH individuals respectively and all pairwise differences were statistically significant (p<0.01). Mean WC was 86.5 cm, 98.4 cm, and 115.4 cm among normal weight, overweight, and obese MUH individuals respectively and all pairwise differences were statistically significant (p<0.01).

Percent MH participants with no cardiometabolic abnormality by body size phenotypes were 57.2%, 41%, and 35.1% among normal weight, overweight, and obese individuals respectively and MH individuals with only one cardiometabolic abnormality were 42.8%, 59%, and 64.9% among normal weight, overweight, and obese individuals respectively. Abnormal levels of FPG and HDL were the most prevalent abnormalities. Among those MUH participants who had two cardiometabolic abnormalities, abnormalities rates were 60.4%, 46.7%, and 31.5% among normal weight, overweight, and obese individuals respectively and presence of diabetes with hypertension was the most prevalent pair of abnormalities. Among those MUH participants who had three cardiometabolic abnormalities, abnormalities rates were 28%, 31.4%, and 29% among normal weight, overweight, and obese individuals respectively and presence of diabetes and hypertension with abnormal HDL was the most prevalent triad of abnormalities. Among those MUH participants who had four cardiometabolic abnormalities, abnormalities rates were 9.7%, 16.1%, and 23.7% among normal weight, overweight, and obese individuals respectively and presence of diabetes, hypertension and abnormal HDL with abnormal CRP was the most prevalent quartet of abnormalities. Among those MUH participants who had five cardiometabolic abnormalities, abnormalities rates were 1.7%, 5.4%, and 13.7% among normal weight, overweight, and obese individuals respectively and presence of diabetes, hypertension, abnormal HDL, and abnormal CRP with HOMA-IR was the most prevalent set of abnormalities. Thus, prevalence rates of abnormalities among MUH individuals increase with increasing number of abnormalities among obese as compared to overweight and normal weight MUH individuals.

Discussion

Wildman *et al.* [7] did the adjusted analysis of prevalence for 1999-2004 NHANES data separately for MH and MUH individuals as compared to this study in which the adjusted analysis was done for the total sample, and as such, some of the results observed in this study are not necessarily similar to what was reported by them. In this study, males were found to have lower prevalence of metabolic health than females and for both MH and MUH, Wildman *et al.* [7] also observed the same results. It is unknown but possible that females may be more conscious of their health, seek early treatment, and strive to maintain a metabolically healthy profile. Also, there was a similarity of results between this study and Wildman *et al.* [7] regarding younger age groups (20-64 years old) having higher levels of adjusted prevalence of metabolic health than older age groups (≥65 years old). Prevalence of metabolic health was not found to be variable among race/ethnic groups among metabolically unhealthy normal weight individuals and among MA and NHW among metabolically healthy overweight and obese individuals by Wildman *et al.* [7]. For this study, race/ethnicity did not affect the prevalence of metabolic health. Smoking was not found to affect prevalence of metabolic health in this as well the study by Wildman *et al.* [7]. Level of physical activity ≥50 METs/d was found to be associated with higher prevalence of metabolic health among obese and overweight individuals [7] but physical activity was not found to affect prevalence of metabolic health in this study possibly because of the differences in how physical activity was defined in the two studies [18-23].

Conclusion

When adjustments were made for factors that affect metabolic health, females were found to be metabolically healthier than males (p<0.01). Race/ethnicity, smoking, poverty income ratio, and physical activity did not affect metabolic health.

Conflict of interest

Author declares that he has no financial or other conflicts that could have affected conclusions arrived at in this communication. No human subjects were used in this research and all data used in this research are available at no cost from www.cdc.gov/nchs/nhanes/htm.

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