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All-cause mortality among metabolically healthy and unhealthy individuals: role of body size phenotypes

Ram B Jain*

Private Consultant, Dacula, Ga, USA

Abstract

Objective: To evaluate all-cause mortality for metabolically healthy (MH) and unhealthy (MUH) individuals by body-size-phenotype.

Research design and methods: Data from National Health and Nutrition Examination Survey for 1999-2012 for ≥20 years old with ≥8 hours of fasting were obtained. Individuals were defined as metabolically healthy (MH) if they had "normal" values for at least five of the six cardiometabolic indices, namely, systolic-blood-pressure <130 mm Hg and diastolic-blood-pressure < 85 mm Hg and no treatment to lower blood pressure, fasting triglyceride levels <150 mg/dL, high density lipoprotein levels >40 mg/dL for males and >50 mg/dL for females and no use of lipid-lowering medications, fasting plasma glucose levels <100 mg/dL and no use of antidiabetic medications, insulin resistance computed as HOMA-IR <5.13, and C-reactive protein level ≤ 0.1 mg/L. Otherwise, they were defined as metabolically unhealthy (MUH). All-cause mortality rates by age, gender, and race/ethnicity were computed for each two-year survey period.

Results: With a mean follow up of 135.3 months, for 1999-2000 cohort, MH obese had lower all-cause mortality rates than MUH obese (5.2% *vs.* 12.1%, p=0.04). Among MUH individuals, all-cause mortality rates were highest for normal weight (24.5%) individuals and lowest among those who were obese (12.1%).

Conclusions: Lack of motivation among normal-weight MUH individuals to seek treatment for their metabolic abnormalities may be driving their mortality rates higher then MUH obese who may be actively seeking treatment for their metabolic abnormalities and engaging in healthy life-styles.

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]. Wildman *et al.* [4] classified individuals as being metabolically healthy (MH) if they had "normal" values for at least five of the six cardiometabolic indices, namely, (i) systolic blood pressure (SBP) <130 mm Hg and diastolic blood pressure (DBP) <85 mm Hg and no treatment to lower blood pressure, (ii) fasting triglyceride (TG) levels <150 mg/dL, (iii) high density lipoprotein (HDL) > 40 mg/dL for males and >50 mg/dL for females, and no lipid-lowering medications, (iv) fasting plasma glucose (FPG) <100 mg/dL and no use of antidiabetic medications, (v) insulin resistance (HOMA-IR) <5.13 based on 90th percentile, and (vi) C-reactive protein (CRP) ≤0.1 mg/L based on 90th percentile. Number of cardiometabolic indices used to define metabolic health has varied from one study to another. In addition, cut offs used to separate MH from metabolically unhealthy (MUH) individuals also varied from one study to another. For example, while Aguilar-Salinas *et al.* [5] used a cut off of 126 mg/dL for FPG, Wildman *et al.* [4] used a cut off of 100 mg/dL. Wildman *et al.* [4] used a cut off of 5.13 for HOMA-IR, Karelis *et al.* [6] used a cut off of 1.95.

More often than not, the prevalence of MH individuals has been studied in concurrence with body type phenotypes, namely, normal weight, overweight, and obese. Based on the data from 57 prospective studies, Prospective Studies Collaboration *et al.* [7] 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. Given the excess mortality associated with higher BMI, of 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 [2,8].

In a community based study of 1758 participants aged 50 years without diabetes and a median follow up of 30 years, an increased risk of cardiovascular deaths were reported among MUH normal weight, MH overweight, MUH overweight, MH obese, and MUH obese individuals when compared with MH normal weight individuals [9]. Based on a study of 5269 participants aged 39-62 years old, both MH as well as MUH obese individuals were reported to have increased risk of mortality when compared with MH normal weight individuals [10]. Hamer and Stamatakis [11] examined the risk of cardiovascular and all-cause mortality among MH obese individuals from among 22203 participants with mean age of 54.1 years without known history of cardiovascular disease at the baseline and after a mean follow up of 7 years, MH obese individuals were not found to be at a higher risk of cardiovascular disease when compared with MH non-obese individuals although both MUH obese and MUH non-obese were found to be at a higher risk of cardiovascular disease. However, MUH obese individuals were found to be at a higher risk of all-cause mortality when compared with MH obese individuals [11]. In a prospective cohort study among 2317 Korean participants aged over 60 years with a median follow up of 10.3 years, MUH normal weight individuals were found to have higher all-cause and cardiovascular mortality than MUH overweight and obese individuals and among the six-metabolic-health-body-size-phenotype combinations, MUH normal weight individuals had the highest and overweight and obese MH individuals had the lowest risk of cardiovascular and all-cause mortality [12]. MH abdominally obese individuals were shown to have 40% higher mortality rates than

Correspondence to: Ram B Jain, 2959 Estate View Ct, Dacula GA 30019, USA, Tel: 9107291049; E-mail: jain.ram.b@gmail.com

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MH abdominally non-obese individuals [13]. Based on mortality data from Italy, MUH obese individuals but not MH obese individuals were reported to have higher all-cause as well as cardiovascular mortality rates when compared with MH non-obese individuals [14].

With a mean follow up of 14.7 years for National Health and Nutrition Examination Survey [NHANES] III data conducted during 1988-1994, Durward *et al.* [15] estimated all-cause mortality rates among MH and MUH individuals across three body phenotypes. MUH obese individuals were found to have twice the risk of all-cause mortality ($p<0.01$) when compared with MH normal weight individuals but risk of all-cause mortality was not statistically significantly higher among MH obese, MH overweight, MUH overweight, or MUH normal weight individuals than MH normal weight individuals [15]. Kuk and Arden [16] also used NHANES III data with a follow up of 8.7 years to estimate risk of all-cause mortality among MH and MUH obese individuals and reported both MH and MUH obese individuals to have more than twice the risk of all-cause mortality than MH normal weight individuals.

While Kuk and Arden [16] and Durward *et al.* [15] have presented mortality data for NHANES III, none of these articles have presented any data that Choi *et al.* [12] termed as "obesity paradox" in which obese individual were reported to have lower mortality rates than normal weight individuals.

The obesity paradox has been defined as a medical hypothesis (https://en.wikipedia.org/wiki/Obesity_paradox) which holds that obesity in the presence of MUH conditions like high cholesterol, may, counterintuitively, be protective and associated with greater survival in certain groups of people such as very elderly individuals or those with certain chronic diseases. It is further postulated that lower body mass index or normal values of cholesterol may be detrimental and associated with higher mortality in asymptomatic people (https://en.wikipedia.org/wiki/Obesity_paradox). The obesity paradox has been observed among patients with heart failure [17-19], patients undergoing hemodialysis [20], myocardial infarction [21], and acute coronary syndrome [22]. However, these inverse associations have also been suggested to be the result of biased analyses which ignores confounding (https://ldi.upenn.edu/voices/2014/08/07/explaining-the-obesity-paradox), for example, ignoring the difference between lean body mass and fatty mass.

A preliminary analysis of NHNAES for the period 1999-2010 did reveal such a pattern in which MUH normal weight individuals were observed to have higher mortality rates than MUH obese and/or overweight all-cause mortality rates. Consequently, this study was undertaken to compute all-cause mortality rates by metabolic-syndrome-body-size-phenotype. 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 at the time of participation in NHANES.

Materials and methods

Data on demographics, blood pressure, diabetes status, HDL levels, triglyceride levels, plasma glucose and insulin levels, C-reactive protein (CRP) for the years 1999-2010 available in NHANES for those aged ≥ 20 years were downloaded and match merged. Those who have fasted for less than 8 hours prior to blood draw were excluded from the database. In addition, mortality linked data files with follow up until December 31, 2011 for each two year NHANES wave were also downloaded.

Sample size with non-missing values for CRP, blood pressure, fasting plasma glucose and insulin, triglyceride, and sampling weights was 12048. Detailed sample sizes are given in Table 1.

The analyses were restricted to those with body mass index (BMI) ≥18.5 kg/m^2. Normal weights were defined as those who had BMI ≥18.5 kg/m^2 but less than 25 kg/m^2. Those with BMI ≥25 kg/m^2 but less than 30 kg/m^2 were defined as overweight. Those with BMI ≥ kg/m^2 were defined as obese.

In order to define cardiometabolic abnormalities, definitions used by Wildman *et al.* [4] were adopted. If the 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, the participant was considered to have the abnormal blood pressure. If fasting triglyceride levels were ≥150 mg/dL, the participants were considered to have abnormal triglyceride levels. Similarly, if HDL levels 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, the participants were considered to have abnormal levels of HDL. If participants had ≥100 mg/dL fasting glucose levels and/or participants self-reported using prescription drug or insulin to reduce glucose levels, participants were defined to have abnormal levels of fasting glucose. If participants' CRP levels were >0.1 mg/L, participants were considered to have abnormal levels of CRP. Finally, if participants' HOMA-IR levels were > 5.13, participants were considered to have abnormal levels of HOMA-IR. For the purpose of this study, HOMA-IR was computed as (fasting serum insulin level in μu/mL)×(fasting plasma glucose levels in mmol/L)/22.5. Participants

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/m^2)			Overweight (BMI 25-30 kg/m^2)			Obese (BMI≥ 30 kg/m^2)			Total (BMI≥ 18.5 kg/m^2)		
	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

were defined to be metabolically healthy (MH) if they had abnormal levels of 0 or 1 cardiometabolic parameters and metabolically unhealthy (MUH), if they were abnormal on ≥ 2 of cardiometabolic parameters as defined above.

Final status on mortality (outcome) was determined by the National Center for Health Statistics, Centers for Disease Control by using data from a variety of sources including National Death Index records, Death Master File from the Social Security Administration, mortality status from Centers for Medicare and Medicaid Services, and death certificates (https://www.cdc.gov/nchs/data/datalinkage/public_use_data_dictionary_11_17_2015.pdf). All those who could not be determined to have died were presumed alive at the time of follow up.

Data analyses were done by using SAS University Edition software (www.sas.com). SAS Proc SURVEYREG was used to compute all-cause mortality rates by body phenotypes for MH and MUH individuals by age, gender, and race/ethnicity for each survey period and for all six survey cycles together. These results are presented in Tables 2-4.

Results

For every NHANES cohort, irrespective of body size phenotype, gender, race/ethnicity, MH individuals almost always had lower all-cause mortality rates than MUH individuals (Table 2) though the differences were not always statistically significant (Table 3) probably because of relatively small number of deaths and not enough years of follow up. For example, for overweight 20-64 years old, mortality rates for 1999-2000 were 3.4% and 5.11% for MH and MUH individuals respectively (p=0.44, Tables 2 and 3). It should be noted that those aged ≥65 years were more often than not likely to have no statistically significantly differences between mortality rates among MH and MUH participants indicating the contribution of age to the mortality rates in addition to the contribution made by metabolic health. It should also be noted that among obese individuals, significant differences among MH and MUH participants were almost nonexistent indicating the negative contribution of obesity on the top of metabolic health (Tables 2 and 3). Even for the survey period 1999-2000 for which the longest follow up was available (Tables 2 and 3), statistically significant differences between mortality rates among MH and MUH individuals were observed for males (5.8% *vs.* 14.9%, p=0.03, Table 2) and MA (0.3% *vs.* 6.1%, p=0.01, Tables 2 and 3) only.

In order to single out the contribution of metabolic health and obesity, it is of interest to compare mortality rates between body phenotypes among MH and MUH participants separately. These data are provided in Tables 2 and 3. Among MH participants, there were almost no statistically significant differences between mortality rates for any cohort or by age, gender, and race/ethnicity (Tables 2 and 3). This may indicate that body phenotype does not affect mortality rates as long as you can be considered metabolically healthy.

Among MUH participants, there were almost no statistically significant differences in mortality rates between overweight and obese for any NHANES cohort (Tables 2 and 3). However, there were some exceptions. For NHB, for 1999-2000, overweight had higher mortality rates than obese (24.5% *vs.* 10.5%, p=0.02, Tables 2 and 3). For ≥ 65 years old for 2001-2002, overweight had higher mortality rates than obese (36.9% *vs.* 18%, p=0.01, Tables 2 and 3). It is unknown why overweight may have higher mortality rates than obese. It may be a statistical artifact. However, it does seem that overweight have higher mortality rates than obese among MUH more often than not (Tables 2 and 3). In addition, quite often, normal weight MUH individuals were found to have statistically significantly higher mortality rates than both overweight and obese individuals. For example, for the period 1999-2010, normal weight males had statistically significantly higher mortality rates than both overweight (13.9% *vs.* 8%, p<0.01, Tables 2 and 3) and obese individuals (13.9% *vs.* 7.3%, p<0.01, Tables 2 and 3). The same was true for females (14.9% *vs.* 8.8% and 5.2%, p<0.01, Tables 2 and 3). However, except for the period 1999-2010, for those MUH participants who were aged ≥65 years, mortality rates for normal weight individuals did not vary from those who were overweight or obese. A closer look at the mortality rates for normal weight, overweight, and obese MUH participants reveals a decreasing trend in mortality rates though trends may not always be statistically significant. For example, for females for 1999-2000, the mortality rates for normal weight, overweight, and obese participants were 26.6%, 14.8%, and 9.8% respectively or the rates for the normal weights were 180% and 271% of what they were for overweight and obese individuals respectively. This was observed even though only 11.6% normal weight MUH participants had ≥4 metabolically abnormal variables while 21.9% overweight and 39.5% obese MUH participants had ≥4 metabolically abnormal variables (data not shown).

Average follow up rates in months from the time when the blood samples were drawn were similar among males and females, among NHW, NHB, MA, and OTH but follow up was larger for 20-64 years old than for ≥ 65 years old (Table 4). Mean follow up for the cohort of 1999-2000 was 135.3 months (Table 4) and only 22.4 months for the 2009-2010 cohort (Table 4).

Discussion

Mortality among metabolically unhealthy: obesity paradox

Among MUH individuals, obese as well as overweight individuals had higher mean (geometric mean) levels (lower for HDL) for almost all cardiometabolic parameters as compared to normal weight individuals (data not shown). For example, while mean DBP for normal weight individuals was 70.4 mm Hg, it was 72.4 mm Hg and 73.8 mm Hg for overweight and obese individuals respectively. While geometric mean HDL for normal weight individuals was 50.3 mg/dL, it was 45.6 mg/dL and 44.2 mg/dL for overweight and obese individuals respectively (data not shown). These patterns should put obese as well overweight MUH individuals at a higher risk of mortality than normal weight MUH individuals. However, observed mortality trends were found to be in opposite direction for almost every NHANES cohort except for 2009-2010. For example for 1999-2000 cohort with a mean follow up of 135.3 months, all-cause mortality rates for normal weight, overweight, and obese MUH individuals were 24.5%, 14.9%, and 12.1% respectively or, for obese MUH individuals mortality rates were less than half of what they were for normal weight MUH individuals. For all six cohorts together with a mean follow up of 78.1 months, all-cause mortality rates for normal weight, overweight, and obese MUH individuals were 14.3%, 8.3%, and 6.2% respectively. These inverse trends, depending up on the specific NHANES cohorts, were observed for males, females, NHW, those aged 20-64 years and ≥ 65 years but not necessarily for NHB, MA, and OTH.

Choi *et al.* [12] reported MUH normal weight individuals aged ≥ 60 years to have higher mortality rates than MH obese individuals of the same age. Similar results were observed in this study for some NHANES cohorts not only for those aged ≥ 60 years but also for all males, females, NHW, NHB, MA, and those aged 20-64 years old. For example, for the 1999-2000 cohort, mortality rate among MUH normal weight individuals was 24.5% and 5.2% among MH obese individuals.

Table 2. Weighted percent mortality rates with 95% confidence intervals by survey year, body size phenotypes, 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)		
Survey Year	**Category***	**Metabolically Healthy**			**Metabolically Healthy**			**Metabolically Healthy**		
		Yes	No	p	Yes	No	p	Yes	No	p
1999-2000	Total	4.6 (2.1-7)	24.5 (18.7-30.3)	<0.01	6 (2.1-9.9)	14.9 (9.8-20)	0.01	5.2 (1-9.4)	12.1 (7.7-16.5)	0.04
	Males	8.5 (4.5-12.5)	22.8 (17.4-28.1)	<0.01	6.5 (2.4-10.6)	15 (9-21)	0.01	5.8 (-0.2-11.8)	14.9 (8.2-21.6)	0.03
	Females	1.9 (0.2-3.7)	26.6 (16.9-36.2)	<0.01	5.3 (-0.2-10.9)	14.8 (8.5-21.2)	0.06	4.7 (-0.3-9.7)	9.8 (4-15.6)	0.2
	NHW	3.8 (1.3-6.3)	27.1 (19.3-35)	<0.01	7.1 (1.4-12.8)	17.4 (10.5-24.3)	0.03	8.4 (0.7-16)	13.9 (8.1-19.6)	0.21
	NHB	4.7 (-1.5-10.8)	22.5 (-3.9-48.9)	0.14	8 (0.3-15.7)	24.9 (17.1-32.6)	0.01	4 (-0.8-8.9)	10.5 (2.8-18.2)	0.15
	MA	2.9 (-0.2-6)	10.2 (-2-22.5)	0.15	2.3 (-0.2-4.8)	10.8 (4.3-17.3)	0.03	0.3 (-0.2-0.8)	6.1 (1.8-10.3)	0.01
	OTH	11.6 (-1.1-24.4)	11.2 (-4.4-26.8)	0.95	0 (0-0)	5.1 (-0.7-11)	0.08	0 (0-0)	5.9 (-0.7-12.4)	0.07
	A20-64	2.7 (1.1-4.3)	13.4 (6.9-19.9)	<0.01	3.4 (0.8-5.9)	5 (1-9)	0.44	2.5 (-0.7-5.6)	7.2 (3.2-11.1)	0.08
	A65+	39.9 (17.7-62.2)	50.2 (41.1-59.2)	0.39	47.6 (15.8-79.3)	43 (35.1-50.9)	0.74	51.4 (15.8-87)	36.8 (25.8-47.8)	0.43
2001-2002	Total	5.1 (2.8-7.4)	19.2 (12.4-25.9)	<0.01	4.9 (2.7-7.1)	12 (8.1-15.8)	0.01	5.3 (2-8.5)	11.4 (6.9-16)	0.01
	Males	7.4 (3.8-11.1)	20.3 (15-25.5)	<0.01	5.5 (1.8-9.3)	11.9 (7.5-16.3)	<0.01	10 (-0.3-20.2)	12.3 (6-18.7)	0.67
	Females	3.5 (1.7-5.3)	18.1 (7.7-28.5)	0.01	4.1 (0.6-7.5)	12 (6.2-17.8)	0.06	3.5 (0.8-6.2)	10.6 (3.2-17.9)	0.08
	NHW	4.8 (1.9-7.8)	21.9 (13.9-29.9)	<0.01	4 (1-7.1)	13.7 (8.7-18.6)	<0.01	5.8 (0.5-11.2)	10.5 (5.9-15)	0.05
	NHB	10.8 (4.6-16.9)	30.7 (6.2-55.2)	0.06	9.9 (1.2-18.5)	8.2 (4.2-12.2)	0.74	7.3 (-2.5-17)	9.8 (4.3-15.3)	0.64
	MA	1.8 (-0.3-3.8)	8.4 (2.2-14.6)	0.03	5.6 (1.6-9.5)	3.5 (0.7-6.2)	0.43	3.2 (0.9-5.6)	7.7 (2.9-12.5)	0.17
	OTH	1.1 (-1.6-3.8)	6.2 (0.1-12.3)	0.12	4.8 (-6.4-16)	8.1 (2.8-13.3)	0.61	0 (0-0)	36.7 (-0.4-73.8)	0.05
	A20-64	1.6 (0.4-2.8)	7.7 (2.8-12.6)	0.01	3.2 (0.8-5.6)	5.2 (2.3-8.2)	0.31	4.3 (0.5-8)	10.4 (5.9-14.9)	0.01
	A65+	48.7 (33.5-64)	48.3 (31.4-65.1)	0.96	29.9 (7.1-52.7)	36.9 (26.4-47.5)	0.37	23.8 (-0.8-48.4)	18 (9.3-26.7)	0.66
2003-2004	Total	2.7 (1.2-4.2)	19.5 (14.5-24.5)	<0.01	4 (1.5-6.5)	9.6 (6-13.2)	0.02	2.3 (0.9-3.8)	7.5 (4.4-10.5)	0.01
	Males	4 (1.7-6.2)	19 (13.4-24.6)	<0.01	2.6 (-0.2-5.3)	10.3 (6.4-14.1)	<0.01	2.5 (-0.4-5.4)	9.1 (4.1-14.1)	0.02
	Females	1.8 (0.4-3.3)	19.9 (7.9-32)	0.01	5.5 (0.9-10.2)	8.6 (4.3-12.9)	0.29	2.2 (-0.4-4.7)	5.9 (2.8-9)	0.09
	NHW	2.2 (0.7-3.6)	18.8 (13.4-24.2)	<0.01	4.2 (0.9-7.4)	10.5 (5.8-15.2)	0.03	2.9 (0.8-4.9)	7.3 (2.9-11.6)	0.09
	NHB	1.6 (0.7-2.5)	27.2 (6.9-47.5)	0.02	7 (-1-15)	7.9 (1.2-14.6)	0.84	0.7 (-0.6-2)	11.9 (5.9-18)	<0.01
	MA	3.3 (-0.6-7.2)	10.6 (0.3-20.9)	0.15	3.1 (-2.3-8.6)	11.1 (3.3-19)	0.04	3.3 (-1.6-8.2)	6.4 (1.6-11.1)	0.37
	OTH	7.2 (-2.8-17.2)	19.6 (-1.9-41)	0.26	0 (0-0)	1 (-1.2-3.3)	0.35	0 (0-0)	1.6 (-1.4-4.6)	0.28
	A20-64	0.9 (-0.3-2.2)	10.3 (2.5-18.1)	0.02	2.7 (0.4-5)	3.7 (0.5-6.8)	0.67	0.4 (-0.2-1)	4.1 (1.7-6.5)	0.01
	A65+	30.9 (16.8-45)	36 (25.1-46.9)	0.52	20 (3.1-36.9)	27 (13.2-40.7)	0.39	29.3 (14.7-43.9)	21.6 (12.4-30.9)	0.44
2005-2006	Total	2.9 (2-3.9)	8.9 (4.1-13.7)	0.01	1.8 (0.1-3.6)	7.1 (3.7-10.5)	0.01	3 (0.1-5.9)	4.5 (2.8-6.2)	0.36
	Males	4.7 (2.9-6.4)	7.5 (1.8-13.2)	0.3	1 (-0.2-2.1)	7.4 (3-11.8)	0.01	6 (-1-13)	6.3 (3.2-9.3)	0.94
	Females	1.7 (0.3-3.1)	10.4 (4.5-16.4)	<0.01	2.9 (-0.2-6.1)	6.6 (0.6-12.6)	0.25	1.3 (-0.4-2.9)	2.8 (1.3-4.3)	0.23
	NHW	3.2 (2.1-4.3)	12.2 (5.8-18.6)	0.01	2.1 (-0.2-4.5)	8.4 (4.3-12.4)	0.01	1.9 (-0.8-4.6)	4.8 (3-6.6)	0.05
	NHB	1.7 (-0.7-4.2)	8.3 (-1.5-18)	0.19	1.9 (-2-5.7)	3.6 (-0.7-7.9)	0.55	3.3 (-1.4-8.1)	5.8 (0.8-10.9)	0.48
	MA	6.1 (-2.5-14.7)	0.9 (-1.2-2.9)	0.18	1.1 (-0.6-2.8)	2.2 (-1.6-6)	0.66	3.4 (-3.8-10.6)	2.5 (-1.6-6.6)	0.87
	OTH	0 (0-0)	0 (0-0)		0 (0-0)	6.3 (-7.3-20)	0.34	7.1 (-8.8-23)	0 (0-0)	0.36
	A20-64	1.5 (0.8-2.3)	1.1 (-1.3-3.4)	0.69	0.4 (-0.4-1.2)	3.3 (-0.4-6.9)	0.11	1.7 (-0.8-4.1)	1.6 (0.2-3)	0.97
	A65+	17.9 (6-29.8)	21.8 (13.7-29.8)	0.45	14.4 (-0.8-29.6)	15.6 (8.9-22.3)	0.86	19 (-8.3-46.4)	17.6 (10.7-24.5)	0.9
2007-2008	Total	0.7 (0-1.3)	9.9 (6.4-13.5)	<0.01	2.3 (0.7-3.9)	4.8 (3.3-6.3)	0.03	2.7 (-0.7-6.1)	3.7 (2.3-5.2)	0.52
	Males	0.5 (-0.3-1.4)	9.6 (5.7-13.5)	<0.01	3.1 (1.1-5.2)	2.9 (1.1-4.6)	0.79	3.5 (-3.4-10.4)	4.4 (1.4-7.3)	0.74
	Females	0.8 (-0.1-1.6)	10.3 (3.6-17)	0.01	1.5 (-0.9-3.8)	8.4 (5.4-11.3)	<0.01	2 (-0.7-4.7)	3.3 (1.2-5.3)	0.47
	NHW	0.6 (-0.2-1.4)	11.5 (6.9-16.1)	<0.01	2.6 (0.2-5)	5.1 (3.6-6.6)	0.1	4.1 (-1.5-9.8)	3.9 (2.2-5.6)	0.93
	NHB	1.7 (-1.1-4.5)	1.9 (-2.3-6.1)	0.93	3.2 (-0.8-7.1)	6.9 (1.7-12.1)	0.3	2 (-1.7-5.7)	6.6 (1-12.1)	0.19
	MA	0.9 (-0.9-2.7)	10.1 (-1-21.2)	0.09	1.7 (-0.8-4.1)	0.8 (-0.8-2.5)	0.32	0 (0-0)	1.1 (-0.8-3)	0.22
	OTH	0 (0-0)	5.9 (-2.2-14)	0.14	0 (0-0)	5.1 (-1.9-12)	0.14	0 (0-0)	1.1 (-0.1-2.4)	0.07
	A20-64	0.1 (-0.2-0.4)	1.9 (-0.5-4.3)	0.18	1 (-0.3-2.4)	0.6 (0.1-1.1)	0.54	2.1 (-1.3-5.5)	1.2 (0.2-2.2)	0.59
	A65+	7.1 (-2.4-16.5)	22.8 (14.8-30.9)	0	16.5 (4.3-28.6)	16.9 (12.9-20.9)	0.95	14.4 (-7.7-36.4)	14.8 (9.2-20.4)	0.97
2009-2010	Total	0.6 (0-1.2)	2.5 (0.9-4.2)	0.02	0.7 (-0.6-2)	1.7 (-0.2-3.6)	0.36	0.6 (-0.6-1.8)	1.3 (0.1-2.4)	0.45
	Males	1.6 (-0.1-3.3)	3.8 (1.2-6.4)	0.08	0 (0-0)	1.4 (-0.1-3)	0.07	1.4 (-1.3-4.1)	0.9 (0-1.9)	0.72
	Females	0 (0-0)	0.9 (-0.4-2.3)	0.16	1.3 (-1.3-3.9)	2.2 (-0.7-5.1)	0.64	0 (0-0)	1.6 (0.1-3.2)	0.04
	NHW	0.4 (-0.2-0.9)	2.6 (0.5-4.6)	0.03	0.9 (-1-2.7)	1.7 (-0.6-4)	0.55	1 (-0.9-3)	1 (-0.4-2.4)	0.96
	NHB	0.8 (-0.7-2.2)	7.1 (-7.6-21.7)	0.38	0 (0-0)	2.3 (-1.2-5.8)	0.18	0 (0-0)	2.2 (-0.5-5)	0.11
	MA	1.1 (-1.1-3.4)	1.9 (-1.4-5.2)	0.7	0.9 (-1.1-2.9)	2.5 (0.1-5)	0.3	0 (0-0)	1.2 (-0.2-2.7)	0.09
	OTH	1.4 (-1.6-4.3)	0.9 (-1.2-3)	0.78	0 (0-0)	0 (0-0)		0 (0-0)	2.1 (-0.5-4.7)	0.1
	A20-64	0.1 (-0.1-0.2)	1.3 (-0.6-3.1)	0.19	0.7 (-0.7-2.2)	0.5 (-0.1-1)	0.71	0.7 (-0.7-2)	0.7 (-0.1-1.6)	0.96
	A65+	5.8 (-0.7-12.4)	4.5 (0.7-8.2)	0.62	0 (0-0)	4.7 (-0.7-10.2)	0.08	0 (0-0)	3.4 (0.1-6.6)	0.04

1999-2010	Total	2.8 (2.2-3.4)	14.4 (12.4-16.4)	<0.01	3.1 (2.2-4)	8.3 (7.1-9.5)	<0.01	3 (2-4)	6.2 (5.2-7.3)	<0.01
	Males	4.6 (3.5-5.7)	13.9 (11.7-16.1)	<0.01	3 (2-4)	8 (6.5-9.5)	<0.01	4.2 (2.1-6.4)	7.3 (5.7-8.9)	0.02
	Females	1.6 (1.1-2.1)	14.9 (11.5-18.3)	<0.01	3.3 (1.8-4.7)	8.8 (7-10.6)	<0.01	2.1 (1.2-3.1)	5.2 (3.8-6.6)	<0.01
	NHW	2.6 (1.8-3.3)	16.2 (13.5-18.9)	<0.01	3.3 (2.1-4.5)	9.3 (7.7-11)	<0.01	3.6 (2-5.1)	6.4 (5.1-7.8)	<0.01
	NHB	4 (2.3-5.6)	15.8 (9.3-22.4)	<0.01	5.2 (2.8-7.5)	7.7 (5.5-9.8)	0.14	2.5 (1-4.1)	7.2 (5.2-9.2)	<0.01
	MA	2.6 (1.1-4.2)	6 (3.3-8.7)	0.01	2.3 (1-3.6)	4.8 (2.7-6.9)	0.03	1.6 (0.2-2.9)	3.7 (2.2-5.2)	0.07
	OTH	3.4 (0.5-6.2)	7.3 (2.4-12.2)	0.11	0.7 (-0.7-2.1)	4.6 (2-7.2)	0.01	1.7 (-1.7-5.2)	5.2 (0.4-10)	0.24
	A20-64	1.2 (0.8-1.6)	6.4 (4.4-8.5)	<0.01	1.8 (1.1-2.5)	3.1 (2-4.1)	0.06	1.8 (0.8-2.8)	3.8 (2.9-4.8)	<0.01
	A65+	23.3 (17.3-29.2)	29.2 (25.4-33)	0.06	18 (11.2-24.8)	23 (19.8-26.2)	0.14	19.4 (10.2-28.6)	17 (14-20.1)	0.62

*NHW: Non-Hispanic white; NHB: Non-Hispanic black; MA: Mexican American; OTH: Other unclassified race/ethnicities; A20-64: Age 20-64 years; A65+: Age≥ 65 years

Table 3. Significance probabilities as determined by t-tests for the differences between weighted mortality rates by survey year, body mass index (BMI), age, gender, and race/ethnicity for metabolically healthy and unhealthy participants in National Health and Nutrition Examination Survey 1999-2010.

Survey Year	Category	Significance probabilities among metabolically healthy participants			Significance probabilities among metabolically unhealthy participants		
		Between Normal weight and overweight	Between Normal weight and obese	Between overweight and obese	Between Normal weight and overweight	Between Normal weight and obese	Between overweight and obese
1999-2000	Total	0.48	0.8	0.82	0.01	<0.01	0.32
	Males	0.38	0.44	0.86	0.02	0.06	0.99
	Females	0.25	0.27	0.88	0.03	<0.01	0.23
	NHW	0.24	0.24	0.83	0.09	0.01	0.35
	NHB	0.57	0.87	0.25	0.85	0.27	0.02
	MA	0.72	0.11	0.13	0.9	0.43	0.06
	OTH	0.07	0.07	-	0.48	0.58	0.78
	A20-64	0.59	0.85	0.63	0.02	0.09	0.21
	A65+	0.7	0.57	0.88	0.16	0.04	0.43
2001-2002	Total	0.88	0.91	0.85	0.04	0.09	0.86
	Males	0.31	0.61	0.4	<0.01	0.02	0.92
	Females	0.78	0.99	0.81	0.33	0.33	0.72
	NHW	0.66	0.7	0.54	0.04	0.03	0.34
	NHB	0.82	0.57	0.67	0.08	0.1	0.63
	MA	0.01	0.37	0.28	0.17	0.86	0.08
	OTH	0.5	0.39	0.37	0.54	0.08	0.11
	A20-64	0.16	0.14	0.62	0.32	0.41	0.07
	A65+	0.19	0.12	0.76	0.25	<0.01	0.01
2003-2004	Total	0.23	0.72	0.19	<0.01	<0.01	0.36
	Males	0.36	0.43	0.96	0.01	0.03	0.7
	Females	0.11	0.81	0.19	0.06	0.03	0.34
	NHW	0.15	0.6	0.46	0.01	<0.01	0.28
	NHB	0.15	0.25	0.12	0.09	0.14	0.36
	MA	0.96	1	0.97	0.94	0.35	0.25
	OTH	0.14	0.14	-	0.09	0.1	0.78
	A20-64	0.15	0.41	0.05	0.04	0.09	0.77
	A65+	0.24	0.88	0.46	0.32	0.03	0.5
2005-2006	Total	0.23	0.97	0.46	0.41	0.06	0.11
	Males	0	0.69	0.15	0.99	0.7	0.6
	Females	0.46	0.69	0.27	0.22	0.01	0.16
	NHW	0.32	0.4	0.9	0.21	0.03	0.1
	NHB	0.97	0.59	0.64	0.23	0.52	0.3
	MA	0.23	0.61	0.52	0.63	0.47	0.89
	OTH	-	0.36	0.36	0.34	-	0.34
	A20-64	0.06	0.92	0.3	0.25	0.75	0.36
	A65+	0.65	0.94	0.75	0.25	0.29	0.6
2007-2008	Total	0.05	0.24	0.86	0.01	<0.01	0.27
	Males	0.02	0.38	0.92	<0.01	0.02	0.4
	Females	0.55	0.39	0.73	0.61	0.04	0.01
	NHW	0.11	0.22	0.68	0.01	0.01	0.31
	NHB	0.53	0.92	0.67	0.23	0.08	0.93
	MA	0.37	0.31	0.17	0.08	0.1	0.82
	OTH	-	-	-	0.85	0.22	0.26
	A20-64	0.18	0.25	0.63	0.32	0.59	0.3

	A65+	0.2	0.54	0.86	0.09	0.16	0.56
2009-2010	Total	0.9	0.95	0.95	0.46	0.26	0.67
	Males	0.07	0.92	0.28	0.09	0.05	0.5
	Females	0.3	-	0.3	0.39	0.55	0.75
	NHW	0.6	0.49	0.88	0.55	0.29	0.55
	NHB	0.27	0.27	-	0.56	0.5	0.97
	MA	0.89	0.3	0.34	0.69	0.56	0.3
	OTH	0.35	0.35	-	0.38	0.4	0.1
	A20-64	0.34	0.35	0.95	0.38	0.56	0.62
	A65+	0.08	0.08	-	0.94	0.66	0.64
1999-2010	Total	0.48	0.74	0.86	<0.01	<0.01	0.01
	Males	0.01	0.79	0.32	<0.01	<0.01	0.51
	Females	0.04	0.37	0.21	<0.01	<0.01	<0.01
	NHW	0.25	0.22	0.79	<0.01	<0.01	<0.01
	NHB	0.42	0.29	0.07	0.03	0.01	0.77
	MA	0.73	0.31	0.41	0.47	0.12	0.3
	OTH	0.09	0.44	0.59	0.33	0.55	0.79
	A20-64	0.11	0.23	1	<0.01	0.02	0.23
	A65+	0.23	0.51	0.82	0.01	<0.01	0.01

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

For this cohort, MUH normal weight individuals aged 20-64 years had mortality rate of 13.4% while MH obese individuals had mortality rate of 2.5%. However, for 1999-2000 cohort for 65+ years old, this observation could not be confirmed because while MUH normal weight individuals had a mortality rate of 50.2%, MH obese individuals had a mortality rate of 51.4%. On the other hand, for 2001-2002 cohort with a mean follow up of 99.1 months, among those aged >= 65 years, MUH normal weights had a mortality rate of 48.3% and MH obese had a mortality rate of 23.8%. Similarly, for all six cohorts together with a mean follow up of 65.1 months, MUH normal weights had a mortality rate of 29.2% and MH obese had a mortality rate of 19.4%. Similar to the observations made by Choi *et al.* [12], MUH normal weights aged ≥ 65 years did have higher SBP (140.5 *vs.* 126.9 mm Hg, data not shown), higher TG (126.4 *vs.* 107.0 mg/dL), and higher FPG (108.5 *vs.* 98.0 mg/dL, data not shown) than MH obese individuals. Relatively lower levels of SBP, TG, and FPG among MH obese individuals may have provided protection in spite of their being obese. Possible explanations as provided by Choi *et al.* (12) include the possibility that normal weight individuals may be more fragile when confronted with cardiometabolic abnormalities than metabolically normal obese individuals. In addition, obese individuals may seek earlier, more aggressive treatment for obesity and metabolic abnormalities than MUH normal weight individuals.

While Choi *et al.* [12] did not present and discuss comparative mortality data for MUH normal weight, overweight, and obese individuals, some of the arguments put forth by them seem to be applicable to the inverse mortality trends observed among MUH normal weight, overweight, and obese individuals in this study. MUH normal weight individuals may have false sense of "security" because of their normal weight in spite of the existence of the metabolic abnormalities and as such, may delay or postpone seeking early and aggressive medical treatment to cure metabolic abnormalities. On the other hand, MUH overweight and obese may be conscious enough to seek not only early medical treatment for both obesity and metabolic disorders but also may engage in other "healthy" recreational activities on a consistent basis more often than MUH normal weight individuals.

Mortality among metabolically healthy: role of body size phenotypes

Irrespective of gender, race/ethnicity, and age there were almost no statistically significant differences in mortality rates among normal weight, overweight, and obese MH individuals for any of the six NHANES cohorts or for all six cohorts combined. This was noted in spite of some observed differences in mean (geometric mean) levels of some cardiometabolic parameters. For example, geometric mean levels of HDL among MH normal weight, overweight, and obese individuals were 60.1, 54.5, and 53.0 mg/dL (data not shown) respectively. Similarly, geometric mean levels of TG among MH normal weight, overweight, and obese individuals were 81.2, 93.7, and 97.4 mg/dL (data not shown) respectively. Differences were even more pronounced for HOMA-IR and CRP. Geometric mean levels of CRP among MH normal weight, overweight, and obese individuals were 0.08, 0.15, and 0.27 mg/dL (data not shown) respectively; and geometric mean levels of HOMA-IR among MH normal weight, overweight, and obese individuals were 1.36, 1.86, and 2.62 (data not shown) respectively. Relatively higher abnormal levels of these cardiometabolic parameters among overweight and obese should expose them to higher risk of mortality. But, mortality rates were similar among MH individuals for all three body phenotypes or in other words, being overweight or obese did not increase the risk of mortality. This, as previously pointed out may be due to overweight and obese being conscious of adverse health consequences, seek timely and adequate medical treatment and engage in healthy life styles in terms of diet and/or physical fitness.

Mortality: metabolically healthy *vs.* metabolically unhealthy

Irrespective of NHANES cohort and body size phenotype, statistically significantly higher mortality rates were observed for the total population, males, females, NHW, and those aged 20-64 years between MUH and MH individuals. However, the ratios of mortality rates for MUH divided by the mortality rates for MH was substantially higher among normal weight individuals than among obese and overweight individuals. For example, for 1999-2000 cohort ratios of mortality rates for MUH divided by MH for the total population were 5.3, 2.5, and 2.3 among normal weight, overweight, and obese individuals. For 1999-2010 cohort, ratios of mortality rates for MUH divided by MH for males were 2.7, 2.3, and 2.6 among normal weight, overweight, and obese individuals. For the same cohort, ratios of mortality rates for MUH divided by MH for males were 14.0, 2.8, and 2.1 among normal weight, overweight, and obese individuals. This means mortality risk differential between MH and MUH individuals was substantially higher among normal weight individuals than among

Table 4. Mean follow up with 95% confidence intervals in months by survey year, age, gender, and race/ethnicity for metabolically healthy and unhealthy participants in National Health and Nutrition Examination Survey 1999-2010.

Survey Year	Category*	Mean (95% CI)
1999-2000	Total	135.3 (132.8-137.8)
	Males	126 (122.8-129.2)
	Females	129.8 (126.3-133.2)
	NHW	127.2 (123.2-131.1)
	NHB	126.7 (122.7-130.8)
	MA	129.7 (127.2-132.2)
	OTH	128 (122.6-133.3)
	A20-64	138.8 (136.7-141)
	A65+	116.9 (112-121.8)
2001-2002	Total	115 (112.4-117.6)
	Males	106.5 (103.2-109.8)
	Females	109.7 (106.9-112.4)
	NHW	108.7 (104.8-112.5)
	NHB	104.8 (99-110.6)
	MA	109 (106-112.1)
	OTH	109.8 (107.2-112.4)
	A20-64	117.1 (115-119.2)
	A65+	99.1 (94.5-103.7)
2003-2004	Total	91.7 (87.9-95.6)
	Males	87.9 (85.1-90.7)
	Females	89.2 (85.7-92.6)
	NHW	87.4 (84.1-90.6)
	NHB	88.2 (82.8-93.5)
	MA	90.6 (88.9-92.3)
	OTH	87.9 (83.5-92.4)
	A20-64	94.3 (90.6-97.9)
	A65+	82.8 (79.4-86.1)
2005-2006	Total	69.7 (65.6-73.8)
	Males	67 (63.4-70.6)
	Females	68.4 (64.7-72.1)
	NHW	67.1 (63.3-71)
	NHB	68.8 (63.6-74)
	MA	68.9 (64.3-73.6)
	OTH	66 (62.2-69.8)
	A20-64	71.3 (67.4-75.2)
	A65+	64.2 (60.5-67.9)
2007-2008	Total	45.4 (42.2-48.5)
	Males	45.3 (41.9-48.7)
	Females	45.4 (41.8-48.9)
	NHW	43.5 (40.3-46.7)
	NHB	45.9 (41.4-50.3)
	MA	46.2 (40.3-52.1)
	OTH	45.7 (42-49.5)
	A20-64	47 (43.3-50.8)
	A65+	43.6 (40.3-46.9)
2009-2010	Total	22.4 (18.9-26)
	Males	22.8 (19.5-26)
	Females	22.6 (19.4-25.8)
	NHW	22.3 (18.8-25.8)
	NHB	21.7 (16-27.5)
	MA	25.7 (22.2-29.1)
	OTH	21 (17.7-24.4)
	A20-64	22.7 (19.2-26.3)
	A65+	22.6 (19.5-25.8)
1999-2010	Total	78.1 (75.6-80.5)
	Males	71.4 (69.2-73.7)
	Females	73.1 (70.8-75.5)
	NHW	73.7 (70.6-76.8)
	NHB	71.9 (66.9-77)
	MA	71.4 (65.8-77)
	OTH	72.1 (64.2-80)
	A20-64	79.5 (77-81.9)
	A65+	65.1 (62.6-67.6)

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

overweight and obese individuals. In addition, among normal weight individuals, risk differential was several times higher among females than males. The risk differential among male and female normal weight individuals was in the same direction for every cohort though the differences were diluted because of small number of deaths. For 1999-2010 data, the ratio of mortality rates for MUH divided by MH among normal weight individuals for males was 3.0 and it was 9.3 for females. Thus, there are two issues that need to be addressed.

First, why all-cause mortality differential between MH and MUH individuals is higher among normal weight individuals than among overweight and obese individuals? In the absence of any data on changes, if any, in metabolic health during the follow up period, a conclusive argument to explain these data cannot be put forth. However, as previously mentioned MUH normal weights may be ignorant, careless, or unwilling to admit their adverse metabolic health and as such, may not be too interested in seeking appropriate and timely treatment to modify adverse metabolic parameters and/or not willing to bring about relevant life style changes and as such, may keep falling farther and farther behind MH normal weights. On the other hand, MUH overweight and obese, maybe, because of the availability of information related to adverse health consequences of obesity, may be cognizant and willing to admit their adverse metabolic health and as such, may be eagerly interested in seeking appropriate and timely treatment to modify adverse metabolic parameters and/or willing to bring about relevant life style changes and as such, may be successful in reducing risk of all-cause mortality risk as close to their MH counterparts as possible.

Secondly, why, among normal weight individuals, all-cause mortality differential between MH and MUH individuals is higher among females than males? The reason behind this relatively large differential among females when compared to males need to be looked at. For 1999-2000 cohort, mortality rates among MH males and females were 8.5% and 1.9% respectively, or the ratio of male to female mortality rates was 4.5. On the other hand, among MUH, ratio of male to female mortality was 0.9. In other words, males had substantial higher mortality rates among than females among MH individuals but somewhat lower mortality rates among MUH individuals. Similar patterns were observed for almost every cohort as well as for all six cohorts together. For 1999-2010 cohorts, mortality rates among MH males and females were 4.6% and 1.6% respectively, or the ratio of male to female mortality rates was 2.9. On the other hand, among MUH, ratio of male to female mortality was 0.9. Thus, substantially lower mortality rates among MH females than MH males was driving the larger mortality differential among females between MH and MUH mortality rates when compared with males.

Do MH obese individuals have lower risk of mortality when compared with MUH obese? The data from this study seems to suggest they do, at least for the overall population and males and among those aged 20-64 years but not so among those aged ≥ 65 years. For 1999-2000, 2001-2002, and 2003-2004 cohorts as well as for all six cohorts together, MH obese did have lower mortality rates than MUH obese but for 2005-2006, 2007-2008, and 2009-2010 cohorts, these results were not observed. And, for none of the cohorts, 65+ years old MH obese had lower risk of mortality than 65+ years old MUH obese. Consequently, the advantage of lower mortality risk that MH obese have may be limited to those who are aged 20-64 years old. Somewhat similar results were observed for overweight MH and MUH individuals. It may be that the advantage that MH obese have than MUH obese may have may be limited to those who are younger. Using NHANES III data, Durward *et al.* [15] found MH obese to have lower risk of mortality than MUH obese but higher risk when compared with MH normal weight individuals. While MH obese were found to have lower risk of mortality than MUH obese, mortality risk between MH obese and normal weight individuals was not found to differ. However, Durward *et al.* (15) excluded those who were aged ≥ 60 years from their study. The follow up in Durward *et al.*'s (15) study was 14.7 years while the follow up for 1999-2000 cohort in this study was 11.3 years and lower than for all other cohorts. These and other differences between the two studies including how MH was defined may have resulted in different conclusions.

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Author contributions

Ram B. Jain was responsible for designing this study as well as conducting statistical analysis, writing and finalizing this manuscript.

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