BMJ Open Diabetes Research & Care

Differences in fat distribution between metabolically unhealthy people with normal weight versus obesity, NHANES 2011–2018

Seerat Anand,[1] Tejasvi Pasupneti,[2] Youngju Pak,[1] Sreevastav Teja Kalangi,[1] Rajesh Garg [1]

To cite: Anand S, Pasupneti T, Pak Y, *et al*. Differences in fat distribution between metabolically unhealthy people with normal weight versus obesity, NHANES 2011–2018. *BMJ Open Diab Res Care* 2025;**13**:e005118. doi:10.1136/bmjdrc-2025-005118

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjdrc-2025-005118).

Received 27 March 2025
Accepted 17 May 2025

[1]Endocrinology, Diabetes and Metabolism, Harbor-UCLA Medical Center, Torrance, CA, USA
[2]Department of Medicine, Harbor-UCLA Medical Center, Torrance, California, USA

Correspondence to
Dr Rajesh Garg;
rajesh.garg@lundquist.org

ABSTRACT

Introduction Metabolic abnormalities are present in 15–25% of adults with body mass index (BMI)<25 kg/m^2. While previous studies have shown that metabolically unhealthy individuals with lean body weight (MUL) and metabolically unhealthy individuals with obesity (MUO) exhibit increased visceral adiposity, direct comparisons between these groups have not been performed. Differences between the two groups may suggest different mechanisms of metabolic disease and may affect treatment strategies.

Research design and methods We used the National Health and Nutrition Examination Survey data (2011–2018) that included dual energy X-ray absorptiometry. Metabolic dysfunction was defined as the presence of ≥2 components of the metabolic syndrome, excluding obesity. The differences in body fat distribution between unhealthy and healthy individuals were studied with an interaction term to evaluate whether the effect of BMI differs by the metabolic health status.

Results We found that both MUL and MUO groups had increased android to gynoid fat ratio as compared with metabolically healthy groups with normal or lean weight (MHL) and metabolically healthy with obesity (MHO), respectively. Total fat and android fat were higher in MUL as compared with MHL individuals, in men as well as in women. Gynoid fat was higher in MUL men but not in women. However, MUO individuals had similar total fat but lower gynoid fat as compared with MHO individuals, in men as well as in women. Android fat was significantly higher in the male MUO group but not in the female MUO group.

Conclusions The study shows increased android fat as the main abnormality in MUL individuals and decreased gynoid fat as the main abnormality in MUO individuals. The differences in android and gynoid fat patterns between MUL and MUO groups suggest different mechanisms of metabolic dysfunction in people who are lean versus those with obesity.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Metabolically unhealthy lean and obese individuals are both known to have increased visceral adiposity compared with the corresponding healthy groups. Therefore, similar mechanisms are considered to play a role in causing metabolic dysfunction in the two body mass index (BMI) groups, and similar treatment strategies are used.

WHAT THIS STUDY ADDS

⇒ We compared fat distribution in metabolically unhealthy versus healthy individuals and its interaction with BMI. We found that while increased android fat was the main abnormality in unhealthy lean individuals, decreased gynoid fat was the main abnormality in unhealthy obese individuals.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Different patterns of fat distribution in lean and obese individuals suggest that pathophysiological mechanisms for metabolic dysfunction may be different in the two populations. The findings may have implications for future research on metabolic abnormalities in lean individuals.

INTRODUCTION

Metabolic syndrome (MetS) is a constellation of metabolic abnormalities that increase the risk of type 2 diabetes (T2D) and atherosclerotic cardiovascular disease (CVD).[1] According to the National Cholesterol Education Program's Adult Treatment Panel III (ATPIII), MetS is defined as the presence of three or more of the following abnormalities: waist circumference >102 cm (40 inches) in men and >88 cm (35 inches) in women, serum triglycerides ≥150 mg/dL (1.7 mmol/L), serum high-density lipoprotein (HDL) cholesterol <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women, fasting plasma glucose ≥100 mg/dL (5.5 mmol/L) or taking antidiabetes medications, and blood pressure ≥130/85 mm Hg or taking antihypertensive medications.[2] However, there are differences among experts about the definition of MetS and the relevance of MetS. While the ATPIII definition of MetS includes only waist circumference, the WHO and the

American Association of Clinical Endocrinologists definitions of MetS also include body mass index (BMI) as one of the criteria for obesity.[1 2] Visceral obesity and insulin resistance are considered the underlying mechanisms of MetS and are present in most people with BMI≥30 kg/m^2, and about 70% of them fit the criteria for MetS.[3 4] While the absence of features of MetS or the presence of less than three metabolic abnormalities in people with obesity may be considered as metabolically healthy, there is disagreement on the term metabolically healthy obesity (MHO).[5 6] Conversely, features of MetS are also present in a significant number of non-obese people with lower BMI.

The standard definitions of normal weight, overweight and obesity are based on the BMI cut-offs.[7] While MetS is considered a disease of obesity, the same metabolic abnormalities are present in 15–25% of the non-obese adults with BMI<25 kg/m^2, increasing their risk of T2D and CVD.[4 8 9] A study using the National Health and Nutrition Examination Survey (NHANES) (1999–2004) data showed that 23.5% of normal-weight adults (BMI<25 kg/m^2) had two or more metabolic abnormalities.[4] The prevalence may be even higher in certain ethnic groups like Southeast Asians.[10] In a 10-year follow-up study, lean individuals with two or more components of MetS had similar risk of death compared with those who were overweight/obese with MetS.[11] Another study using the NHANES data from 1999 to 2010 showed that normal-weight adults with MetS had the highest mortality risk, even higher than people with obesity and MetS.[12] These data highlight the importance of metabolic abnormalities in lean people.

It is well established that there is an increased amount of visceral fat in people with metabolically unhealthy obesity (MUO) as compared with those with obesity who are metabolically healthy (MHO).[13 14] The same is true for lean individuals who are metabolically unhealthy (MUL) as compared with those lean individuals who are metabolically healthy (MHL).[15–17] On the other hand, an increased amount of gluteofemoral fat or thigh fat has been shown to be associated with a lower risk of MetS in both populations, with normal weight as well as those with obesity.[18 19] In view of these data, current treatment strategies for MUL individuals are essentially the same as those for MUO individuals, derived mostly from the experience in the obese population. However, previous studies did not compare the difference (healthy vs unhealthy) in the lean group to the difference (healthy vs unhealthy) in the obese group. For example, we do not know whether the extent of increased visceral fat is similar or different in obese and lean unhealthy individuals. Differences in fat distribution may suggest differences in the underlying mechanisms of metabolic dysfunction, and this could have an impact on future research, treatment strategies or the effectiveness of current treatment strategies in lean individuals. Therefore, an investigation into similarities and/or differences between MUO and MUL groups may have implications for lean individuals with MetS. We hypothesized that the magnitude of the difference in abdominal fat between healthy and unhealthy is greater in lean individuals as compared with those with obesity. Therefore, in this study, we compared fat distribution between unhealthy individuals with normal or lean body weight and those with obesity relative to their healthy counterparts using the NHANES database.

METHODS

The database used in this study can be accessed from the NHANES website at https://wwwn.cdc.gov/nchs/nhanes/.[20] The NHANES protocol complies with the US Department of Health and Human Services Policy for the Protection of Human Research Subjects. Informed consent was obtained from all subjects involved in the original NHANES.

The NHANES database includes a cross-sectional sample of the nationally representative US population. This publicly available database provides deidentified information on demographic characteristics, physical examination (eg, weight, height, blood pressure), laboratory tests (eg, blood glucose, lipids), and acute or chronic health conditions along with medication use. We included participant data for four consecutive NHANES cycles (2011 through 2018) in our study because a subset of participants had undergone the whole-body composition assessment by dual energy X-ray absorptiometry (DXA) during these cycles. We excluded participants aged less than 18 years. We also excluded participants with missing BMI data and those with more than one missing variable used to define the metabolically healthy and unhealthy groups (detailed below). Participants without whole-body DXA measurements and those with 'Invalid' measurements, as defined by a validity variable from the NHANES database, were also excluded from this analysis.

Whole-body DXA scans were performed using Hologic Discovery A densitometers (Hologic, Bedford, Massachusetts) from 2011 onwards and analyzed with Hologic APEX software. DXA is the most widely accepted method of measuring body composition. Pregnant females were excluded from the DXA examination. The scans provided values for total mass, fat mass, lean mass and bone mineral content. In addition, the body composition in different areas of the body was included in the report. We used data related to total fat mass, lean body mass, android fat percent, gynoid fat percent and android/gynoid ratio as the most relevant variables for this study. The android area was defined as the lower trunk area bounded by two lines: the pelvic horizontal cut line on its lower side and a line automatically placed above the pelvic line. The gynoid area was also defined by two lines: the upper gynoid line was placed 1.5 times the height of the android region below the pelvic line, and the lower gynoid line was placed such that the distance between the two gynoid lines was twice the height of the android region. All these lines were automatically placed by Hologic APEX software. Lean mass percent was calculated from DXA

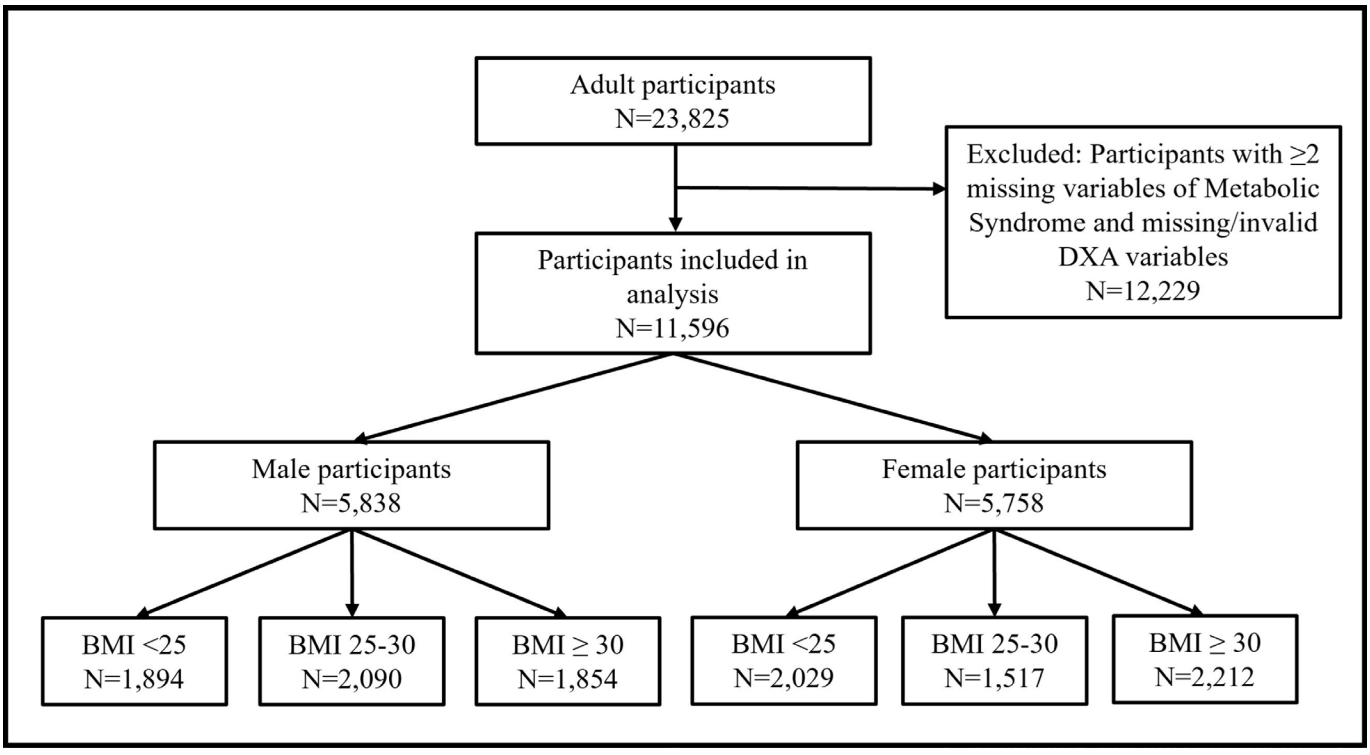

Figure 1 Study participants included in data analysis. BMI, body mass index; DXA, dual energy X-ray absorptiometry.

measured lean mass in grams (including bone weight), divided by the participant's body weight in grams and presented as a percentage. Other DXA indices were used as collected in the NHANES database. Full details of the DXA procedure can be found at website https://wwwn.cdc.gov/Nchs/Data/Nhanes/Public/2011/DataFiles/DXX_G.htm.

We extracted demographic data, physical examination data, laboratory data and DXA data for our study population. Detailed methods for all these measurements are available at the NHANES website. For this study, we defined abnormal blood pressure as systolic blood pressure ≥130 mm Hg, or diastolic blood pressure ≥85 mm Hg, or use of antihypertensive medication. An average of all available consecutive blood pressure measurements was used in this study. Abnormal blood glucose was defined as fasting blood glucose ≥100 mg/dL or glycosylated hemoglobin (HbA1c) ≥5.7% or 2-hour oral glucose tolerance test level ≥140 mg/dL or a previous diagnosis of diabetes or use of glucose-lowering medication. Abnormal HDL was defined as <40 mg/dL for males and <50 mg/dL for females. Triglyceride levels were considered abnormal if they were ≥150 mg/dL or if lipid-lowering medication was used. Being metabolically unhealthy was defined as the presence of ≥2 of these four metabolic abnormalities. Participants were considered metabolically healthy if they had ≤1 abnormality. We then split our study population into three groups based on BMI criteria: defined as lean for BMI<25 kg/m^2, overweight for BMI 25–30 kg/m^2 and obese for BMI≥30 kg/m^2. Data were further stratified by gender.

NHANES database 2011–2018 included 23 825 adult participants with age ≥18 years. However, only 12 476 had received a DXA scan for whole-body composition. After excluding those with missing data, we had 11 596 participants, which were included in our final analysis. Of these participants, 5838 were male and 5758 were female. Subjects with BMI<25 kg/m^2 were 1894 and 2029 males and females, respectively. Subjects with BMI 25–30 kg/m^2 were 2090 and 1517, and those with BMI≥30 kg/m^2 were 1854 and 2212 males and females, respectively (figure 1). In this study, 14.2% of participants with BMI<25 kg/m^2 were found to have ≥2 metabolic abnormalities and thus labeled as MUL.

Statistical analysis

Survey-weighted data were analyzed following NHANES analytic guidelines for combining data across years.[21] Descriptive statistics, such as weighted means and percentages, and 95% CIs were computed for outcome variables, including baseline measurements. Two-way analysis of variance was used to compare outcome variables across three BMI groups (lean, overweight, obese) and two metabolic health groups (metabolically healthy, unhealthy), with an interaction term included to evaluate whether the effect of BMI differs by metabolic health status. For multivariate analyses, two-way analysis of covariance was used with age, race (white vs others), and language (English vs others) as covariates. Since age was found to be most consistently associated with the outcomes, stratified analyses were also conducted by age groups ≤40 and >40 years. All analyses were performed

using SAS V.9.4 (SAS Institute), with the *Surveymeans*, *Surveyfreq* and *Surveyreg* procedures, considering p values <0.05 as statistically significant.

RESULTS

Comparisons of demographic, physical examination and laboratory variables are shown in table 1. Participants in the unhealthy groups were older and had higher BMI than those in the healthy groups.

Comparisons of body fat indices as measured by DXA and its interaction with BMI are shown in table 2 and online supplemental table 1. There was an increase in total body fat as well as android to gynoid fat ratio in unhealthy groups in lean as well as obese populations. However, the increase in android percent fat was more prominent in the lean population as compared with the obese population. The lean unhealthy groups had a slightly higher gynoid fat. However, obese unhealthy groups had lower gynoid fat relative to the healthy obese groups.

Among males, the MUL individuals had significantly more total percent fat than MHL individuals (difference in means 2.72, p<0.001) but this difference was not significant between the MUO and MHO individuals (0.34, p=0.306). A similar pattern was observed in females; difference in mean total percent fat of 1.95 (p<0.001) between MUL and MHL, 0.003 between MUO and MHO (p=0.991). Similarly, the android fat percent in males was much higher in MUL versus MHL (difference in means 4.18, p<0.001) but less so in MUO versus MHO participants (difference in means 0.91, p=0.008). Among females, the android fat percent was higher in MUL versus MHL groups (the difference in mean 3.19, p<0.001) but not different in the MUO versus MHO groups (difference in means 0.12, p=0.652). Different trends were seen when comparing the mean gynoid fat percent. Among males, the difference in mean gynoid fat percent was 1.99 (p<0.001) between MUL and MHL, while it was −0.87 (p=0.012) in MUO versus MHO individuals. Among females, the difference in mean gynoid fat percent between MUL and MHL individuals was 0.15 (p=0.752), while it was −1.62 (p<0.001) between MUO and MHO individuals. Thus, metabolically obese unhealthy participants had a significantly lower mean gynoid fat percent than obese healthy participants. Finally, the difference in means of android to gynoid fat ratio in MUL males versus MHL males was 0.092 (p<0.001), and in MUO males versus MUH males was 0.063 (p<0.001). The difference in means of android to gynoid fat ratio in MUL females versus MHL females was 0.083 (p<0.001), and in MUO females versus MUH females was 0.040 (p<0.001).

Similar findings were observed in the multivariate analyses, where age, race (white vs others), and language (English vs others) were used as covariates. A statistically significant interaction between BMI and metabolic groups (p<0.05) was found for all four DXA outcomes in both sexes (table 2). Among the covariates, age and race were the most consistently associated with the outcomes, while language showed a less consistent association. Data analysis stratified by age is shown in online supplemental table 2.

DISCUSSION

This study demonstrates that metabolically unhealthy lean and obese groups had similarity in overall fat distribution with increased android to gynoid fat ratio compared with respective healthy groups. However, the main abnormality in lean unhealthy groups was a higher android percent fat mass, while the main abnormality in the unhealthy obese groups was a lower gynoid percent fat mass. This suggests that despite several similarities, there are subtle differences in fat distribution between individuals who are lean versus those who are obese in the presence of metabolic abnormalities. In particular, android fat may play a larger role in lean individuals, and lower gynoid fat may play a larger role in those with obesity, suggesting a difference in the underlying mechanisms responsible for metabolic abnormalities in lean individuals as compared with those with obesity.

It is well established that increased android fat mass is associated with an increase in insulin resistance and MetS.[3 22] Decreased gynoid or gluteofemoral fat mass is also associated with MetS abnormalities. In one study, increased thigh fat was associated with lower glucose and lipid levels after accounting for abdominal fat that was associated with high glucose and lipid levels.[23] In the Women's Health Initiative study, in postmenopausal women with normal BMI, lower gluteofemoral fat mass, estimated by DXA, was associated with a higher incidence of CVD independent of increased trunk fat mass.[15] Evidence from precise phenotyping studies and from genetic studies shows that increased gluteofemoral and leg fat mass is protective of cardiometabolic diseases.[22 24] Increased gluteofemoral fat mass is also independently associated with a better lipid and glucose profile, as well as a decrease in cardiovascular and metabolic risks.[18] One recent study showed higher vaspin levels were associated with decreased gluteofemoral fat and increased risk of T2D.[25] Thus, decreased gluteofemoral fat mass may explain some of the metabolic abnormalities in MUO individuals.

This study confirms the findings from our previous study comparing MUL and MHL individuals,[16] but it expands the findings by including a comparison between the lean population and that with obesity. The study draws attention to the lean population with metabolic abnormalities while much of the published literature has focused on the population with obesity. In general, individuals with obesity, with or without MetS, are at a higher risk of T2D and CVD than lean individuals.[26] Among individuals with obesity without metabolic abnormalities, BMI is independently associated with increased risk of T2D and CVD,[8] but the risk is increased by almost twofold in the presence of metabolic abnormalities associated

Table 1 Baseline data compared across BMI groups in metabolically healthy versus unhealthy individuals in the male and female populations

	BMI<25 kg/m^2		BMI 25–30 kg/m^2		BMI≥30 kg/m^2		Interaction
Males	**Healthy n=1575**	**Unhealthy n=319**	**Healthy n=1349**	**Unhealthy n=741**	**Healthy n=874**	**Unhealthy n=980**	**P value**
Age (years)	32 (31 to 33)	44 (42 to 46)	37 (36 to 38)	46 (45 to 46)	36 (35 to 37)	43 (43 to 44)	<0.001
Age >40 years (%)	24.17	62.25	40.02	71.01	37.23	63.14	0.010
Race: white (%)	60.91	60.22*	61.34	58.71*	58.26	61.33*	0.319
Language: English (%)	95.50	95.80*	91.72	88.98*	91.62	90.35*	0.544
BMI (kg/m^2)	22.1 (22.0 to 22.3)	22.9 (22.7 to 23.1)	27.2 (27.1 to 27.3)	27.7 (27.5 to 27.9)	34.0 (33.6 to 34.3)	35.4 (34.9 to 35.8)	<0.001
Waist (cm)	81.9 (81.4 to 82.5)	88.0 (86.7 to 89.3)	95.7 (95.2 to 96.2)	99.0 (98.3 to 99.8)	111.6 (110.5 to 112.7)	116.7 (115.7 to 117.8)	<0.001
FBG (mg/dL)	95.9 (94.8 to 97.0)	117.5 (105.9 to 129.0)	97.7 (96.4 to 98.9)	113.2 (109.8 to 116.5)	100.4 (98.5 to 102.4)	119.8 (115.5 to 124.0)	0.299
HbA1c (%)	5.2 (5.2 to 5.3)	5.8 (5.6 to 6.1)	5.3 (5.2 to 5.3)	5.9 (5.8 to 6.1)	5.4 (5.3 to 5.4)	6.1 (6.0 to 6.2)	0.733
2-hour GTT (mg/dL)	89.6 (86.8 to 92.3)	114.1 (102.3 to 125.9)	93.2 (89.3 to 97.1)	124.5 (116.7 to 132.2)	107.6 (102.0 to 113.3)	134.4 (125.8 to 134.1)	0.618
TC (mg/dL)	175.2 (172.7 to 177.7)	190.2 (183.3 to 197.1)	189.5 (186.5 to 192.6)	203.4 (197.6 to 209.2)	196.0 (192.3 to 199.6)	193.9* (190.2 to 197.7)	<0.001
HDL (mg/dL)	55.0 (54.0 to 56.0)	49.2 (46.0 to 52.4)	49.6 (48.8 to 50.5)	43.0 (41.9 to 44.1)	46.5 (45.3 to 47.6)	39.7 (38.9 to 40.6)	0.860
TG (mg/dL)	79.6 (74.5 to 84.7)	150.5 (131.4 to 169.7)	91.2 (86.5 to 95.9)	189.4 (167.0 to 211.8)	96.1 (90.3 to 101.9)	197.5 (179.0 to 216.0)	0.009
SBP (mm Hg)	115.4 (114.8 to 116.1)	128.6 (125.3 to 131.9)	117.8 (116.9 to 118.6)	126.2 (124.4 to 128.0)	120.2 (119.2 to 121.3)	130.1 (128.8 to 131.5)	0.056
DBP (mm Hg)	67.6 (66.7 to 68.4)	76.0 (73.8 to 78.2)	71.1 (70.3 to 72.0)	77.1 (75.9 to 78.3)	73.1 (72.1 to 74.1)	78.7 (77.5 to 79.9)	0.104
HTN (%)	14.40	73.34	23.20	69.20	29.47	79.31	0.024
Diabetes (%)	5.43	34.22	6.57	50.52	10.61	51.92	0.023
Females	**n=1789**	**n=240**	**n=1103**	**n=414**	**n=1128**	**n=1084**	
Age (years)	35 (34 to 36)	48 (46 to 49)	38 (37 to 39)	46 (45 to 48)	37 (36 to 38)	44 (43 to 45)	<0.001
Age >40 years (%)	34.75	78.00	44.21	73.41	40.52	66.50	0.001
Race: white (%)	67.43	59.76*	63.06	57.20*	58.18	55.39*	0.596
Language: English (%)	96.65	93.81	92.17	86.96	93.02	90.89	0.242
BMI (kg/m^2)	21.8 (21.7 to 21.9)	22.3 (22.0 to 22.6)	27.3 (27.1 to 27.4)	27.6 (27.4 to 27.9)	35.6 (35.2 to 36.0)	37.6 (37.0 to 38.0)	<0.001

Continued

Table 1 Continued

Males	BMI<25 kg/m^2		BMI 25–30 kg/m^2		BMI≥30 kg/m^2		Interaction
	Healthy n=1575	Unhealthy n=319	Healthy n=1349	Unhealthy n=741	Healthy n=874	Unhealthy n=980	P value
Waist (cm)	79.2 (78.7 to 79.7)	83.7 (82.4 to 85.0)	91.9 (91.3 to 92.4)	95.4 (94.4 to 96.3)	108.8 (107.8 to 109.7)	115.3 (114.2 to 116.3)	0.001
FBG (mg/dL)	92.2 (91.3 to 93.0)	102.1 (98.8 to 105.4)	94.6 (93.4 to 95.7)	110.7 (106.3 to 115.2)	96.9 (95.7 to 98.1)	119.2 (115.3 to 123.0)	<0.001
HbA1c (%)	5.2 (5.2 to 5.2)	5.6 (5.5 to 5.7)	5.2 (5.2 to 5.3)	5.9 (5.7 to 6.0)	5.3 (5.3 to 5.4)	6.1 (6.0 to 6.2)	<0.001
2-hour GTT (mg/dL)	95.0 (92.6 to 97.5)	117.7 (105.9 to 129.5)	100.7 (95.9 to 105.6)	129.5 (118.9 to 140.0)	107.0 (102.6 to 111.4)	137.7 (131.2 to 144.3)	0.405
TC (mg/dL)	182.2 (179.7 to 184.8)	195.9 (186.9 to 204.8)	193.2 (189.3 to 197.1)	205.7 (200.0 to 211.3)	191.0 (188.4 to 193.7)	197.3 (193.4 to 201.1)	0.214
HDL (mg/dL)	66.0 (64.8 to 67.2)	55.7 (52.5 to 58.9)	61.5 (59.9 to 63.1)	48.7 (46.9 to 50.4)	54.8 (53.9 to 55.7)	46.5 (45.6 to 47.4)	0.002
TG (mg/dL)	70.2 (66.4 to 74.0)	118.7 (105.3 to 132.2)	82.7 (77.7 to 87.7)	157.7 (143.6 to 171.8)	87.3 (83.0 to 91.6)	151.8 (136.8 to 166.7)	0.021
SBP (mm Hg)	109.8 (109.0 to 110.6)	123.6 (120.8 to 126.4)	112.0 (111.2 to 112.8)	122.4 (120.6 to 124.1)	115.6 (114.8 to 116.3)	125.6 (124.3 to 126.9)	0.063
DBP (mm Hg)	67.4 (66.8 to 68.1)	72.8 (70.6 to 75.1)	68.7 (67.7 to 69.7)	73.8 (72.7 to 75.0)	70.4 (69.8 to 71.0)	74.3 (73.3 to 75.4)	0.280
HTN (%)	11.05	74.09	14.71	67.35	21.59	68.01	0.024
Diabetes (%)	4.44	43.14	6.76	51.67	9.22	64.29	0.023

All values are expressed as mean (adjusted CIs). Number of subjects varied for individual variables.
The healthy versus unhealthy groups were significantly different except for race and language in males and race in females.
*Statistically non-significant.
BMI, body mass index; DBP, mean diastolic blood pressure; FBG, fasting blood glucose; GTT, post oral glucose tolerance test for blood glucose; HDL, high-density lipoprotein; HTN, hypertension; SBP, mean systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Table 2 Densitometry fat indices compared across BMI groups in metabolically healthy versus unhealthy individuals in the male and female populations

	BMI<25 kg/m^2		BMI 25–30 kg/m^2		BMI≥30 kg/m^2		Interaction
Males	**Healthy n=1575**	**Unhealthy n=319**	**Healthy n=1349**	**Unhealthy n=741**	**Healthy n=874**	**Unhealthy n=980**	**P value**
Total fat percent (%)	21.1 (20.7–21.4)	23.8 (22.9–24.7)	26.4 (26.1–26.8)	27.6 (27.2–28.0)	31.8 (31.3–32.2)	32.1* (31.7–32.6)	<0.001
Android fat percent (%)	22.3 (21.8–22.7)	26.4 (25.3–27.6)	30.7 (30.3–31.2)	33.2 (32.6–33.7)	37.6 (37.1–38.1)	38.5 (38.1–39.0)	<0.001
Gynoid fat percent (%)	24.1 (23.8–24.5)	26.1 (25.3–26.9)	28.6 (28.3–29.0)	28.5* (28.0–28.9)	32.6 (32.2–33.1)	31.7 (31.3–32.2)	<0.001
Android/gynoid fat ratio	0.92 (0.91–0.93)	1.01 (0.98–1.04)	1.08 (1.06–1.09)	1.17 (1.16–1.19)	1.16 (1.15–1.17)	1.22 (1.21–1.24)	0.021
Lean mass percent (%)	79.4 (79.1–79.8)	76.7 (75.8–77.6)	74.1 (73.7–74.4)	72.8 (72.4–73.2)	68.5 (68.0–69.0)	68.1* (67.6–68.6)	0.001
Females	**n=1789**	**n=240**	**n=1103**	**n=414**	**n=1128**	**n=1084**	
Total fat percent (%)	32.4 (32.0–32.8)	34.4 (33.5–35.2)	39.0 (38.7–39.4)	39.6 (39.1–40.1)	43.8 (43.4–44.1)	43.8* (43.5–44.1)	0.001
Android fat percent (%)	29.9 (29.4–30.3)	33.1 (31.8–34.3)	39.1 (38.7–39.5)	40.4 (39.8–41)	45.4 (45.0–45.8)	45.5* (45.1–45.9)	<0.001
Gynoid fat percent (%)	38.8 (38.4–39.1)	38.9* (38.0–39.8)	43.1 (42.8–43.4)	42.3 (41.6–42.9)	45.9 (45.6–46.3)	44.3 (44.0–44.6)	0.003
Android/gynoid fat ratio	0.77 (0.76–0.78)	0.85 (0.82–0.88)	0.91 (0.90–0.92)	0.96 (0.95–0.98)	0.99 (0.98–1.00)	1.03 (1.02–1.04)	0.006
Lean mass percent (%)	68.0 (67.6–68.4)	66.0 (65.1–66.9)	61.3 (61.0–61.6)	60.7 (60.2–61.2)	56.4 (56.0–56.7)	56.3* (56.0–56.6)	0.001

Two-way analysis of covariance (ANCOVA) was used with age, race (white vs others), and language (English vs others) as covariates to derive p value for interaction.
*Statistically non-significant with p>0.05. The healthy versus unhealthy groups were significantly different for all other variables.
BMI, body mass index.

with increased visceral fat and decreased gynoid fat.[27] Thus, there is a variable contribution of increased subcutaneous fat, increased visceral fat and decreased gynoid fat to the causation of metabolic abnormalities in people with obesity.[14] However, in lean or normal-weight individuals, an increased proportion of visceral fat seems to be the main cause of metabolic abnormalities. Although we saw increased gynoid fat in MUL individuals that may be related to increased total fat, we think the overall balance was more toward dominant android fat in this group. Thus, the negative effect of much higher android fat might have neutralized the positive effect of increased gynoid fat on metabolic parameters in lean individuals.

Our observations are important because a significant percentage of lean or normal-weight adults have metabolic abnormalities, highlighting a need for different treatment strategies among MUL and MUO individuals. Despite the concept of metabolically obese lean or metabolically unhealthy normal-weight individuals being recognized for a long time,[28 29] treatment strategies have not been studied in this population. Current treatment of metabolic abnormalities is derived mostly from studies in the obese populations. We suggest further studies be conducted focused specifically on the unhealthy lean population.

The strength of this study lies in its large, nationally representative sample from the NHANES dataset, with body fat distribution measured using DXA, the gold standard technique. Although a priori power calculations were not feasible due to the fixed survey design, subgroup sizes were substantial, including 120 to over 1000 participants even within the MUL group, making the study unlikely to be underpowered. In fact, some comparisons may be overpowered, and results should be interpreted with attention to both statistical and clinical significance. The main limitation is missing variables in a substantial number because DXA was done in only a subset of participants. The observed differences in fat distribution between unhealthy and healthy groups were modest and may partly reflect measurement variability, though our findings align with prior studies. Additionally, the cross-sectional nature of NHANES limits causal inference, and despite adjustment for key covariates and stratified analyses, residual confounding cannot be entirely ruled out. While the overall sample was large, some subgroup comparisons, particularly those involving smaller strata such as younger females, may have limited power for detecting interaction effects. Therefore, such findings should be considered hypothesis generating and require validation in prospective or mechanistic studies to clarify their clinical implications. In addition, there was a significant age difference between healthy and unhealthy groups across all BMI categories, with unhealthy people being older than healthy people. The age difference was wider in lower BMI categories than higher BMI categories and may have contributed to unhealth in the lean group. Despite these limitations, the patterns observed were consistent across analyses and suggest biologically plausible differences that warrant further investigation in prospective and mechanistic studies. Our goal was to investigate the differences between unhealthy and healthy phenotypes irrespective of the events leading to metabolic unhealth.

We conclude that there are subtle differences in fat distribution between MUL and MUO individuals, suggesting different mechanisms leading to metabolic abnormalities. The differences are small and may not be directly clinically relevant but will lead to further studies to investigate the biological or genetic basis of our findings. One previous study linked metabolic abnormalities in lean individuals to lipodystrophy genes.[30] There may also be hormonal differences (eg, 11-beta-hydroxysteroid dehydrogenase activity) between the MUL and MUO individuals. However, further research is needed to understand these mechanisms and to develop treatment strategies for lean individuals with MetS.

Acknowledgements We acknowledge the statistical support received from the CTRC at the Lundquist Institute.

Contributors SA: conceptualization, data curation, formal analysis, investigation, methodology, validation, visualization, writing. TP: conceptualization, data curation, formal analysis, investigation, methodology, writing. YP: formal analysis, investigation, methodology, resources, software, supervision, validation, visualization, writing. STK: data curation, formal analysis, investigation, methodology, writing. RG: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing. RG is the guarantor of this work and takes full responsibility for the entire project, including the study design, access to data, and the decision to submit and publish the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Ethical review and approval were waived for this study as it solely used publicly available data for research and publication. This study was deemed exempt from review by the Ethics Committee of the Lundquist Institute and Harbor-UCLA Medical Center because no human subjects were enrolled for this study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. National Health and Nutrition Examination Survey. Available from: https://wwwn.cdc.gov/nchs/nhanes/.

ORCID iD

Rajesh Garg http://orcid.org/0000-0002-7779-1619

REFERENCES

1 Grundy SM. Metabolic syndrome update. *Trends Cardiovasc Med* 2016;26:364–73.
2 Grundy SM, Cleeman JI, Daniels SR, *et al*. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005;112:2735–52.
3 Björntorp P. Metabolic implications of body fat distribution. *Diabetes Care* 1991;14:1132–43.
4 Wildman RP, Muntner P, Reynolds K, *et al*. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). *Arch Intern Med* 2008;168:1617–24.
5 Muñoz-Garach A, Cornejo-Pareja I, Tinahones FJ. Does Metabolically Healthy Obesity Exist? *Nutrients* 2016;8:320.
6 Smith GI, Mittendorfer B, Klein S. Metabolically healthy obesity: facts and fantasies. *J Clin Invest* 2019;129:3978–89.
7 ElSayed NA, Aleppo G, Bannuru RR, *et al*. 8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Care in Diabetes–2024 . *Diabetes Care* 2024;47:S145–57.
8 Aung K, Lorenzo C, Hinojosa MA, *et al*. Risk of developing diabetes and cardiovascular disease in metabolically unhealthy normal-weight and metabolically healthy obese individuals. *J Clin Endocrinol Metab* 2014;99:462–8.
9 Kwon B-J, Kim D-W, Her S-H, *et al*. Metabolically obese status with normal weight is associated with both the prevalence and severity of angiographic coronary artery disease. *Metab Clin Exp* 2013;62:952–60.
10 Pemminati S, Prabha Adhikari MR, Pathak R, *et al*. Prevalence of metabolic syndrome (METS) using IDF 2005 guidelines in a semi urban south Indian (Boloor Diabetes Study) population of Mangalore. *J Assoc Physicians India* 2010;58:674–7.
11 Osadnik T, Banach M, Gierlotka M, *et al*. Lean metabolic syndrome is associated with similar long-term prognosis as metabolic syndrome in overweight/obese patients. Analysis 47,399 Patients from nationwide LIPIDOGRAM 2004–2015 cohort studies. *Eur Heart J* 2022;43.
12 Shi TH, Wang B, Natarajan S. The Influence of Metabolic Syndrome in Predicting Mortality Risk Among US Adults: Importance of Metabolic Syndrome Even in Adults With Normal Weight. *Prev Chronic Dis* 2020;17:E36.
13 Goodpaster BH, Krishnaswami S, Harris TB, *et al*. Obesity, regional body fat distribution, and the metabolic syndrome in older men and women. *Arch Intern Med* 2005;165:777–83.
14 Grundy SM, Adams-Huet B, Vega GL. Variable contributions of fat content and distribution to metabolic syndrome risk factors. *Metab Syndr Relat Disord* 2008;6:281–8.
15 Chen G-C, Arthur R, Iyengar NM, *et al*. Association between regional body fat and cardiovascular disease risk among postmenopausal women with normal body mass index. *Eur Heart J* 2019;40:2849–55.
16 Valderrábano RJ, Badour S, Ferri-Guerra J, *et al*. Body Fat Distribution in Lean Individuals with Metabolic Abnormalities. *Metab Syndr Relat Disord* 2023;21:79–84.
17 Stefan N, Schick F, Häring H-U. Causes, Characteristics, and Consequences of Metabolically Unhealthy Normal Weight in Humans. *Cell Metab* 2017;26:292–300.
18 Manolopoulos KN, Karpe F, Frayn KN. Gluteofemoral body fat as a determinant of metabolic health. *Int J Obes* 2010;34:949–59.
19 Okosun IS, Seale JP, Lyn R. Commingling effect of gynoid and android fat patterns on cardiometabolic dysregulation in normal weight American adults. *Nutr Diabetes* 2015;5:e155.
20 National health and nutrition examination survey. n.d. Available: https://wwwn.cdc.gov/nchs/nhanes
21 National health and nutrition examination survey, 2017–March 2020 prepandemic file: sample design, estimation, and analytic guidelines. Hyattsville, MD, 2022. Available: https://dx.doi.org/10.15620/cdc:115434
22 Stefan N. Causes, consequences, and treatment of metabolically unhealthy fat distribution. *Lancet Diabetes Endocrinol* 2020;8:616–27.
23 Snijder MB, Visser M, Dekker JM, *et al*. Low subcutaneous thigh fat is a risk factor for unfavourable glucose and lipid levels, independently of high abdominal fat. The Health ABC Study. *Diabetologia* 2005;48:301–8.
24 Stefan N. Metabolically Healthy and Unhealthy Normal Weight and Obesity. *Endocrinol Metab (Seoul)* 2020;35:487–93.
25 Wang HH, Chong M, Perrot N, *et al*. Vaspin: A Novel Biomarker Linking Gluteofemoral Body Fat and Type 2 Diabetes Risk. *Diabetes Care* 2024;47:259–66.
26 Meigs JB, Wilson PWF, Fox CS, *et al*. Body Mass Index, Metabolic Syndrome, and Risk of Type 2 Diabetes or Cardiovascular Disease. *J Clin Endocrinol Metab* 2006;91:2906–12.
27 Wilson PWF, D'Agostino RB, Parise H, *et al*. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation* 2005;112:3066–72.
28 Ruderman N, Chisholm D, Pi-Sunyer X, *et al*. The metabolically obese, normal-weight individual revisited. *Diabetes* 1998;47:699–713.
29 Ruderman NB, Schneider SH, Berchtold P. The "metabolically-obese," normal-weight individual. *Am J Clin Nutr* 1981;34:1617–21.
30 Yaghootkar H, Scott RA, White CC, *et al*. Genetic evidence for a normal-weight "metabolically obese" phenotype linking insulin resistance, hypertension, coronary artery disease, and type 2 diabetes. *Diabetes* 2014;63:4369–77.