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Normal weight obesity: a risk factor for cardiometabolic dysregulation and cardiovascular mortality

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Aims We hypothesized that subjects with a normal body mass index (BMI), but high body fat (BF) content [normal weight obesity (NWO)], have a higher prevalence of cardiometabolic dysregulation and are at higher risk for cardiovascular (CV) mortality.

Methods and results We analysed 6171 subjects >20 years of age from the Third National Health and Nutrition Examination Survey (NHANES III) and the NHANES III mortality study, whose BMI was within the normal range (18.5–24.9 kg/m^2), and who underwent a complete evaluation that included body composition assessment, blood measurements, and assessment of CV risk factors. Survival information was available for >99% of the subjects after a median follow-up of 8.8 years. We divided our sample using sex-specific tertiles of BF%. The highest tertile of BF (>23.1% in men and >33.3% in women) was labelled as NWO. When compared with the low BF group, the prevalence of metabolic syndrome in subjects with NWO was four-fold higher (16.6 vs. 4.8%, $P < 0.0001$). Subjects with NWO also had higher prevalence of dyslipidaemia, hypertension (men), and CV disease (women). After adjustment, women with NWO showed a significant 2.2-fold increased risk for CV mortality (HR = 2.2; 95% CI, 1.03–4.67) in comparison to the low BF group.

Conclusion Normal weight obesity, defined as the combination of normal BMI and high BF content, is associated with a high prevalence of cardiometabolic dysregulation, metabolic syndrome, and CV risk factors. In women, NWO is independently associated with increased risk for CV mortality.

Keywords Normal weight obesity • Body fat • Metabolic syndrome • Cardiovascular risk factor • Mortality • Cardiovascular mortality

Introduction

The prevalence of obesity in the USA has risen remarkably over the past four decades, increasing from ~13% in the 60s, to over 30% in the most recent analyses of the National Health and Nutrition Examination Surveys (NHANES).[1–3] Although the gold standard definition of obesity is considered an excess in body fat (BF),[4] clinicians and epidemiologists usually rely on body mass index (BMI) as a means of defining the presence of adiposity or obesity. Body mass index has shown many advantages as a surrogate of BF, such as simplicity and reproducibility, and epidemiologic studies have shown an association between extreme values of BMI and increased mortality.[5–8] However, a significant limitation of using BMI is its failure to differentiate between an elevated BF content and preserved or increased lean mass, especially in patients with a BMI <30 kg/m^2.[9–15]

An excess in adiposity has been clearly associated with numerous comorbidities and pathophysiologic processes, including insulin resistance, altered lipid metabolism, and endothelial dysfunction.[16] Therefore, the determination of adiposity by methods more

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accurate than BMI could have public health implications.[3,17–20] We hypothesized that (i) BF, measured as a continuous variable, is associated with the prevalence of metabolic syndrome and its components in individuals with normal body weight, and that (ii) subjects who have normal body weight based on BMI and high BF content [normal weight obesity (NWO)] are at higher risk for cardiometabolic dysregulation and cardiovascular (CV) mortality when compared with normal weight subjects with low/preserved BF content.

Methods

Study design and subject selection

The NHANES III examined a representative sample of the US non-institutionalized civilian population from 1988 to 1994. It consists of a periodic survey using a stratified multistage probability sampling design to produce a generalizable health estimate of the US population. Details on design and conduct of the survey are available to the public at http://www.cdc.gov/nchs/nhanes.htm. Briefly, of a sample of 39 695 people selected for the NHANES III, 33 994 were interviewed and 30 818 submitted to an examination by a physician at a mobile examination centre which included extensive anthropometric, physiological, and laboratory testing. For this study, 14 025 adult subjects aged >20 years had bioelectrical impedance analysis to estimate body composition.[21] From those, we selected subjects with blood samples and with a normal BMI (18.5–24.9 kg/m^2), as defined by the US National Institutes of Health, resulting in a sample of 6171 subjects, 3042 men and 3129 women.

Anthropometric measurements and body composition analyses

All personnel performing NHANES III anthropometric and body composition measurements were previously trained and followed a strict protocol.[21–24] Body weight was measured with an electronic load cell scale to the nearest 0.01 kg. Participants wore only under-shorts and disposable paper shirts, pants and foam slippers. Stature was measured to the nearest 0.1 cm using a fixed stadiometer. Participants were positioned with heels, buttocks, back, and head against the upright surface of the stadiometer with the head positioned in the Frankfort horizontal plane. Waist and hip circumference were measured by a trained examiner and determined using a measuring tape positioned at the high point of the iliac crest for the waist and at the greatest circumference of the buttocks. The measurement was made with a minimal respiration to the nearest 0.1 cm, with the tape snug but not compressing the skin.[24] Body mass index was calculated as weight in kilograms divided by squared height in meters (kg/m^2) and waist-to-hip ratio was calculated as waist circumference divided by hip circumference. Children younger than 12 years of age, pregnant women and subjects with pacemakers were ineligible for bioelectrical impedance analysis. All subjects were requested to avoid eating or drinking anything except water during the fasting period. There were no restrictions on physical activity or alcohol consumption before the fasting period. The prediction equations for total body water and fat free mass use resistance measured with data from RJL bioelectrical impedance analyzers (Clinton Twp, MI, USA).[25] NHANES III resistance data were obtained using Valhalla impedance analyzers. Therefore, bioimpedance resistance was converted to RJL Res values (Ω) and was used to calculate BF as previously described by Chumlea *et al.*[26] The prediction equations used to estimate lean mass are the following:

Men: Lean mass $= -10.678 + 0.262$ kg $+ 0.652\ S^2/\text{Res} + 0.015$ Res

Women: Lean mass $= -9.529 + 0.168$ kg $+ 0.696\ S^2/\text{Res} + 0.016$ Res

where S^2/Res represent the stature squared divided by resistance (cm^2/Ω). We then calculated BF % as follows:

$$\text{BF}\% = \frac{\text{weight-lean mass}}{\text{weight}} \times 100$$

Detailed information on the bioelectrical impedance analysis procedure is presented elsewhere.[26]

Laboratory measurements

Lipids were measured enzymatically with the use of commercially available reagents (Cholesterol/HP, cat. no. 816302, and triglycerides/GPO, cat. no. 816370, both from Boehringer Mannheim). HDL cholesterol was measured in the clear supernatant after precipitating the other lipoproteins with heparin and $MnCl_2$ (1.3 g/L and 0·046 mol/L, respectively) and removing excess Mn^{2+} by precipitation with $NaHCO_3$. The biases (coefficients of variation) for cholesterol, triglycerides, and HDL-C averaged −0.3% (1.7%), −2.1% (3.9%), and 0.3% (3.4%), respectively. Glucose was measured using standard assay (Sigma chemical, St Louis, MO, USA), and plasma insulin was measured with the Pharmacia insulin radioimmunoassay kit (Pharmacia diagnostics, Sweden). We determined the insulin sensitivity index using the updated computer model homeostatic model assessment (HOMA2) index.[27] The apoB and apoAI were measured by radial immunodiffusion in the first 8.2% of the specimens during the first 5 months of the study and by rate immunonephelometry for the remaining specimens.[28] Serum leptin concentrations were measured by radioimmunoassay at Linco Research, Inc. (St Charles, MO, USA).[29] C-reactive protein was measured using a modification of the Behring latex-enhanced C-reactive protein assay (Behring Diagnostics, Westwood, MA, USA), as previously described.[30] Detailed methodology on laboratory procedures of NHANES III is published elsewhere.[31]

Normal weight obesity, metabolic syndrome, and cardiovascular risk factor definitions

Normal weight obesity was defined as subjects with a normal BMI (18.5–24.9 kg/m^2) and an excess in BF%, defined by the highest sex-specific tertiles of BF% (>23.1% in men and >33.3% in women). The updated ATP-III definition of metabolic syndrome[17] was met when three or more of the following criteria were present: (1) waist circumference ≥102 cm in men and ≥88 cm in women; (2) HDL <1.04 mmol/L (40 mg/dL) in men and <1.30 mmol/L (50 mg/dL) in women; (3) triglycerides ≥1.7 mmol/L (150 mg/dL) or specific treatment for this lipid abnormality; (4) systolic blood pressure≥130 mmHg or diastolic blood pressure ≥85 mmHg or treatment of previously diagnosed hypertension; and (5) fasting glucose ≥5.5 mmol/L (100 mg/dL) or previously diagnosed diabetes. Subjects were considered to have dyslipidaemia if they reported current usage of lipid medications, a self-reported diagnosis of hypercholesterolaemia, and/or HDL-cholesterol <1.04 mmol/L (40 mg/dL) in men and <1.30 mmol/L (50 mg/dL) in women, and/or triglycerides ≥1.7 mmol/L (150 mg/dL), and/or LDL-cholesterol ≥4.10 mmol/L (160 mg/dL).[32] Subjects were considered to be hypertensive if they were taking antihypertensive medications or had a self-reported diagnosis of hypertension or if their systolic pressure was ≥140 mmHg or diastolic pressure was ≥90 mmHg.[33] Subjects were considered to have diabetes if they reported current usage of anti-diabetic medications (insulin and oral medications), a self-reported diagnosis of diabetes and/or if their fasting morning plasma glucose was

≥7.0 mmol/L (126 mg/dL).[34] Cardiovascular disease was defined as the composite of self-reported history of myocardial infarction and stroke.[35] Subjects were considered as never or ever smokers (have you ever smoked more than 100 cigarettes in your life?).

Total and cardiovascular mortality assessment

NHANES III participants aged 17 years or older for whom data were available for matching were matched to the National Death Index to determine mortality status. The National Death Index was searched through 31 December 2000, for follow-up. NHANES III and the National Death Index are linked by probabilistic matching in the NHANES III mortality study. The National Center for Health Statistics conducted the linkage and created scores for potential matches. For a selected sample of NHANES III records, the Center reviewed the death certificate record to verify correct matches. Overall, 20 024 adult NHANES III participants were eligible for mortality follow-up by linkage with the National Death Index, of whom 3384 were identified as deceased. A complete description of the methodology used to link NHANES III records to the National Death Index can be found elsewhere.[36] Cardiovascular deaths were defined as those with ICD-9 codes 390–398, 402, and 404–429 and ICD-10 codes I00–I09, I11, I13, and I20–I51 (NHANES III codes 53–75). Person-months of follow-up were calculated for each participant based on the end of follow-up (date of death for those assumed deceased or 31 December 2000, for those assumed alive minus the date of the NHANES III examination). Mortality and CV mortality at follow-up were ascertained for 99% of our sample.

Statistical analyses

Data for anthropometric and cardiometabolic variables were summarized by calculating means and standard errors for quantitative variables and numbers and percentages for categorical variables. We used BF as a continuous variable for the primary analysis in this study. For secondary analyses, we divided our sample of normal BMI subjects into sex-specific tertiles of BF: low BF content (<18.65% in men and <28.9% in women); medium BF content (second tertile); and high BF content, defined as NWO (>23.1% in men and >33.3% in women). We stratified all our analyses by sex based on the biologic effect of this variable on BF. All analyses were adjusted for age and race/ethnicity.

Only subjects with fasting and morning samples ($n = 2127$) were used for analyses of HOMA2, glucose, and metabolic syndrome. We performed log transformation to reduce the skewness of HOMA2, triglycerides, C-reactive protein, and leptin. We defined subjects as having an elevated apoB/apoAI ratio, C-reactive protein, and leptin if they were in the upper sex-specific quartile of these measurements. We calculated the prevalence and *P*-values for trend (adjusted for age and race) for metabolic syndrome, CV risk factors, and cardiometabolic measures between BF groups at baseline. To assess the effects of central obesity, we performed similar analyses using sex-specific tertiles of waist circumference and used the lowest tertile as the reference combining men and women. After testing the linearity of the association between BF% and metabolic syndrome, we used logistic regression models adjusted for age and race to determine if there was a dose response association between sex-specific quartiles of BF% with insulin sensitivity (lowest quartile as the reference). We applied Cox proportional hazard regression to estimate relations between BF% as a continuous variable and sex-specific tertiles of BF% with total and CV mortality for men and women (lowest tertile used as the reference). Hazard ratios were calculated after adjusting for age and race and smoking (model 1-reference), further adjustment for waist circumference (model 2), waist-to-hip ratio (model 3), and further adjustment for CV risk factors, namely dyslipidaemia, hypertension, diabetes, history of CV disease (model 4). The assumption of hazard proportionality was confirmed by examining interactions of survival time and timed-dependent variables in Cox models. Finally, to assess the generalizability of our results, we compared our selected population of subjects with normal BMI with body composition analyses and blood measurement to subjects in NHANES who did not have these measurements. A two-sided alpha of 0.05 was considered statistically significant. All analyses were weighted according to NHANES methodology and were performed using SAS version 9.1 and SUDAAN 9.0.3.

Results

Our study sample included 6171 subjects. Overall, weighted mean age ± standard error was 41.3 ± 0.31 years. From the total weighted sample, 77.7% were Non-Hispanic Whites, 9.4% were Non-Hispanic Blacks, 4.1% were Mexican Americans, and 8.6% were from a different ethnicity. The sample included in this study had similar distributions for age, sex, race, and BMI in comparison with the group excluded from the analysis that had a normal BMI but did not undergo body composition and laboratory evaluations (data not shown). All data are presented in our three pre-established tertiles of BF and stratified by sex.

Cardiometabolic parameters according to body fat

As age increased, the observed BF increased as well. After controlling for sex, age, and race, each BF percent was significantly associated with lower levels of HDL ($\beta = -0.0008$ mmol/L, *P*-value<0.0001) and higher levels of LDL ($\beta = 0.027$ mmol/L, *P*-value <0.0001), triglycerides (β=0.026 mmol/L, *P*-value <0.0001), apoB/A-I ratio ($\beta = 0.011$, *P*-value <0.0001), C-reactive protein (β=1.02 mg/dL, *P*-value <0.0001), and leptin ($\beta = 1.15$ ng/dL, *P*-value <0.0001). The results were similar when BF was categorized using sex-specific tertiles (*Tables 1* and *2*). In subjects with fasting morning blood samples ($n = 2127$), insulin sensitivity (HOMA-S) diminished progressively as BF increased ($\beta = -2.78$, *P*-value <0.0001, *Figure 1A* and *B*). Similar results were obtained for triglycerides ($\beta = 1.93$ mg/dL, *P*-value <0.0001) and insulin ($\beta = 0.97$ μg/L, *P*-value <0.0001), but not for fasting blood glucose ($\beta = 0.0003$ mg/dL per 1% increase of BF, *P*-value 0.21).

Metabolic syndrome and cardiovascular risk factors according to body fat

The prevalence of metabolic syndrome and of its individual components increased as the BF content increased in men and women (*Tables 3* and *4*). After adjusting for sex, age, and race/ethnicity, BF was associated with higher odds of having metabolic syndrome (OR = 1.11, 95% CI 1.09–1.14, for each percent of BF). With respect to CV risk factors, as BF increased, men had higher prevalence of dyslipidaemia and hypertension (*Table 3*), while in women, similar differences were observed in the prevalence of dyslipidaemia and CV disease (*Table 4*).

Table 1 Anthropometric and metabolic parameters in men with a normal body mass index by body fat tertiles

Variable (N = 3042)	BF<18.65% (N = 1011) Mean ± SE or number (%)	BF >18.65–23.15% (N = 1014) Mean ± SE or number (%)	BF >23.15 (N = 1017) Mean ± SE or number (%)	Age+race P_{adj}-value for trend
Age, years	37.0 ± 0.53	40.1 ± 0.54‡	43.4 ± 0.53*	<0.0001
Race				
Non-Hispanic White	155 (76.0)	162 (73.7)	84 (71.7)	<0.0001
Non-Hispanic Black	119 (11.4)	102 (10.1)	64 (10.4)*	
Mexican-Americans	82 (3.5)	120 (5.8)	82 (6.8)	
Other ethnicity	22 (8.9)	16 (10.1)	18 (10.9)	
Body mass index, kg/m^2	21.8 ± 0.05	22.7 ± 0.04*	23.5 ± 0.04*	<0.0001
Waist circumference, cm	80.2 ± 0.20	84.8 ± 0.19*	88.9 ± 0.20*	<0.0001
Hip circumference, cm	91.1 ± 0.15	93.2 ± 0.13*	94.6 ± 0.13*	<0.0001
Waist-to-hip ratio	0.88 ± 0.001	0.91 ± 0.001*	0.94 ± 0.001*	<0.0001
Body fat, %	14.8 ± 0.09	20.9 ± 0.04*	25.8 ± 0.06*	<0.0001
Body fat, kg	10.1 ± 0.08	14.6 ± 0.05*	18.5 ± 0.08*	<0.0001
Lean mass, kg	57.9 ± 0.22	55.4 ± 0.18*	53.0 ± 0.18*	<0.0001
Systolic blood pressure, mmHg	119 ± 0.5	122 ± 0.5	125 ± 0.5	0.18
Diastolic blood pressure, mmHg	72 ± 0.4	74 ± 0.4§	76 ± 0.3*	<0.0001
Low density lipoprotein, mmol/L	2.88 ± 0.04	3.15 ± 0.04†	3.43 ± 0.04*	<0.0001
High density lipoprotein, mmol/L	1.33 ± 0.01	1.27 ± 0.01‖	1.23 ± 0.01*	<0.0001
Triglycerides, mmol/L	1.11 ± 0.02	1.31 ± 0.03†	1.51 ± 0.03*	<0.0001
ApoB/apoAI ratio	0.62 ± 0.009	0.72 ± 0.009*	0.80 ± 0.008*	<0.0001
Glucose[a], mmol/L	5.21 ± 0.04	5.31 ± 0.03	5.38 ± 0.04	0.39
HOMA 2[a]				
Insulin resistance	0.73 ± 0.015	0.84 ± 0.016*	1.00 ± 0.022*	<0.0001
Insulin sensitivity	152.2 ± 2.48	133.3 ± 2.19*	111.5 ± 2.54*	<0.0001
β cell function	69.6 ± 1.02	73.3 ± 0.92§	79.3 ± 1.31*	<0.0001
C-reactive protein, mg/L	2.8 ± 0.1	3.3 ± 0.2	3.7 ± 0.2§	0.018
Leptin, μg/L	2.21 ± 0.05	3.66 ± 0.18*	4.38 ± 0.17*	<0.0001

[a]Fasting morning samples.
*P-value = <0.0001.
†P-value <0.001.
‡P-value <0.01.
§P-value <0.05.
‖P-value <0.07 when compared with BF<18.65%.

Total and cardiovascular mortality according to body fat

After a median follow-up of 8.83 years (interquartile range 7.25–10.33, 22 600 person-years), there were 787 deaths (34.64 deaths/1000 person-years), 470 in men (44.66 per 1000 man-years) and 317 in women (11.65 per 1000 woman-years). Of those, 337 were classified as CV deaths (14.91 CV deaths/1000 person-years), 195 in men (18.53 CV deaths/1000 man-years) and 142 in women (5.22 CV deaths/1000 woman-years).

In men and women, total and CV mortality increased as BF increased (*Table 5*). When BF was analysed as a continuous variable, BF was neither associated with the risk of death in men (HR 0.99, 95% CI 0.97–1.02) nor in women (HR 1.01, 95% CI 0.97–1.05). The lack of association was observed after adjusting for dyslipidaemia, hypertension, metabolic syndrome, smoking status, and waist circumference (HR in men 0.99, 95% CI 0.96–1.02; HR in women 1.01, 95% CI 0.97–1.05). Similarly, when we analysed mortality by tertiles, subjects with NWO were not at an increased risk for total mortality compared with the lowest sex-specific tertile of BF% (for men, HR = 0.90; 95% CI, 0.63–1.27 and for women HR 1.06, 95% CI 0.69–1.62, *Table 5*).

Interestingly, BF was associated with an increased risk for CV mortality in women (HR 1.06 per each percent of BF, 95% CI 1.01–1.12) and the association was stronger after adjusting for dyslipidaemia, hypertension, metabolic syndrome, smoking status, and waist circumference (HR 1.07, 95% CI 1.01–1.14). A similar association was found when we analysed CV mortality in women using BF tertiles; NWO women were at significantly

Table 2 Anthropometric and metabolic parameters in women with a normal body mass index by body fat tertiles

Variable (N = 3129)	BF<28.9% (N = 1044) Mean ± SE or number (%)	BF >28.9–33.3% (N = 1040) Mean ± SE or number (%)	BF >33.3% (N = 1045) Mean ± SE or number (%)	Age + race P_{adj}-value for trend
Age, years	38.7 ± 0.53	43.7 ± 0.58*	46.7 ± 0.54*	<0.0001
Race				
Non-Hispanic White	260 (87.7)	200 (76.2)	108 (77.0)	<0.0001
Non-Hispanic Black	90 (6.1)	101 (8.5)*	54 (11.0)*	
Mexican-Americans	60 (2.0)	99 (3.4)	75 (4.5)	
Other ethnicity	18 (4.0)	27 (11.8)	9 (7.3)	
Body mass index, kg/m^2	20.7 ± 0.04	22.1 ± 0.04*	23.5 ± 0.03*	<0.0001
Waist circumference, cm	73.6 ± 0.18	78.3 ± 0.20*	83.3 ± 0.20*	<0.0001
Hip circumference, cm	91.3 ± 0.14	94.4 ± 0.14*	97.7 ± 0.15*	<0.0001
Waist-to-hip ratio	0.80 ± 0.001	0.83 ± 0.002*	0.85 ± 0.002*	<0.0001
Body fat, %	24.9 ± 0.10	31.0 ± 0.04*	35.6 ± 0.05*	<0.0001
Body fat, kg	13.7 ± 0.07	18.1 ± 0.06*	22.1 ± 0.07*	<0.0001
Lean mass, kg	41.3 ± 0.13	40.21 ± 0.13§	39.9 ± 0.11*	0.0002
Systolic blood pressure, mmHg	114 ± 0.5	117 ± 0.6	119.9 ± 0.62	0.22
Diastolic blood pressure, mmHg	69 ± 0.3	71 ± 0.3	72.1 ± 0.32*	<0.0001
Low density lipoprotein, mmol/L	2.79 ± 0.04	3.01 ± 0.04	3.21 ± 0.05*	<0.0001
High density lipoprotein, mmol/L	1.55 ± 0.01	1.5 ± 0.01§	1.49 ± 0. 01†	0.0039
Triglycerides, mmol/L	0.98 ± 0.53	1.14 ± 0.03†	1.54 ± 0.08*	<0.0001
ApoB/apoAI ratio	0.56 ± 0.008	0.64 ± 0.009†	0.68 ± 0.008*	<0.0001
Glucose[a], mmol/L	5.0 ± 0.04	5.11 ± 0.04	5.17 ± 0.04	0.27
HOMA 2[a]				
Insulin resistance	0.72 ± 0.011	0.87 ± 0.015*	0.98 ± 0.027*	<0.0001
Insulin sensitivity	151.7 ± 2.09	127.6 ± 1.92*	116.7 ± 2.59*	<0.0001
β cell function	78.1 ± 0.93	82.0 ± 1.10*	89.0 ± 1.55*	<0.0001
C-reactive protein, mg/L	3.1 ± 0.01	3.2 ± 0.01§	3.8 ± 0.01*	0.0001
Leptin, μg/L	6.40 ± 0.16	9.71 ± 0.22*	12.3 ± 0.28*	<0.0001

[a]Fasting morning samples.
*P-value ≤0.0001.
†P-value <0.001.
§P-value <0.05.
‖P-value <0.07 when compared with BF<28.9%.

higher risk for total CV mortality (HR 1.84, 95% CI 1.02–3.32). This association prevailed even after further adjustment (HR 2.2, 95% CI 1.03–4.67, *Table 5*). In men, BF was neither associated with CV mortality as a continuous variable (adjusted HR 0.99, 95% CI 0.95–1.04) nor as sex-adjusted tertiles (adjusted HR for NWO in men 1.07, 95% CI 0.67–1.72 when compared with the lowest tertile).

Impact of central obesity on cardiovascular risk and mortality

Figure 2A and *B* shows that sex-specific tertiles of waist circumferences were associated similarly to CV risk as sex-specific tertiles of BF%, suggesting that waist circumference can also stratify the risk for cardiometabolic dysregulation within subjects with a normal BMI. However, in contrast with NWO, the highest sex-specific tertile of waist circumference was not associated with an increased risk for CV mortality in women (HR = 1.42, 95% CI 0.69–2.94). Furthermore, the association between NWO and CV mortality in women was independent of waist circumference, as demonstrated in multivariate models including waist circumference as a covariate (*Table 5*). Additionally, waist circumference and waist-to-hip ratio were not significantly associated with a higher risk for total mortality in men or women.

Discussion

Metabolically obese normal weight subjects have been described since the late 1990s.[37] These subjects have been characterized as having blunted insulin sensitivity and low lean mass despite having a normal BMI, characteristics similar to subjects with NWO

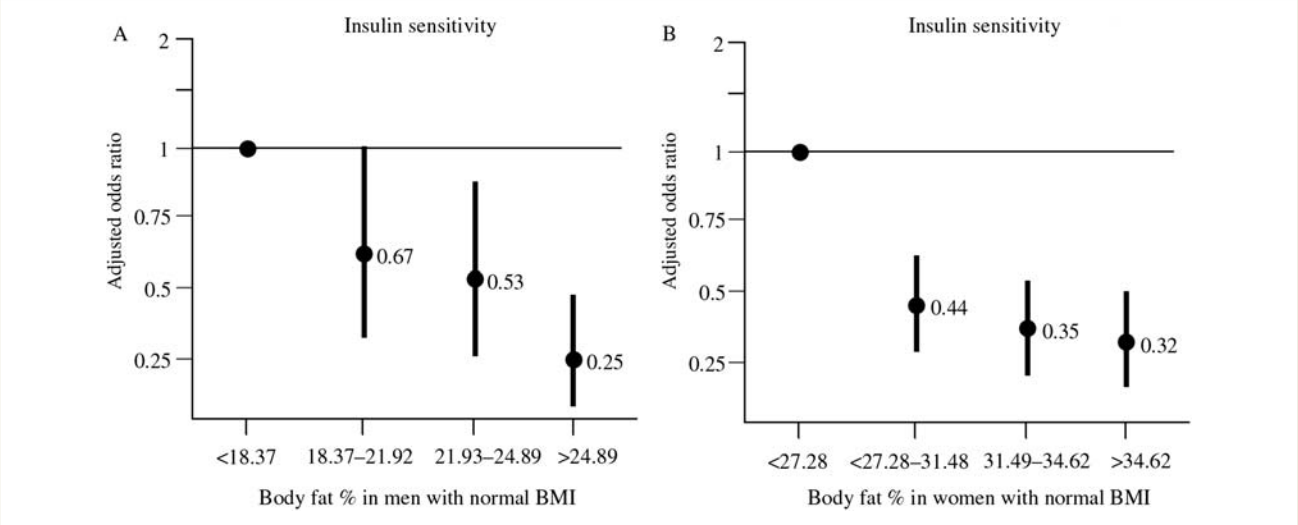

Figure 1 Risk for lower insulin sensitivity according to body fat percent quartiles (lowest quartile as the reference) in subjects with a normal body mass index. (*A*) Men, (*B*) women.

Table 3 Metabolic syndrome components, definition, and cardiovascular risk factors in men with a normal body mass index by body fat tertiles

Variable (*N* = 3042)	BF <18.65% (*N* = 1011)	BF >18.65–23.15% (*N* = 1014)	BF >23.15% (*N* = 1017)	Age+race P_{adj}-value for trend
Metabolic syndrome	N (%)	N (%)	N (%)	
Central obesity ATP (WC >102 cm)	2 (0.18)	4 (0.43)	23 (1.95)‡	0.0004
Central obesity by (W/H≥0.90) waist-to-hip ratio	270 (26.71)	347 (34.30)	396 (39.01)†	<0.0001
High triglycerides (>1.7 mmol/L) or lipid treatment	116 (11.95)	193 (21.02)†	283 (31.12)*	<0.0001
Low high-density lipoprotein (<1.04 mmol/L)	149 (18.10)	181 (21.25)	225 (27.20)*	<0.0001
High blood pressure (>130/>85 mmHg) or treatment for hypertension	319 (26.54)	353 (33.45)	484 (46.84)‡	0.0042
High fasting plasma glucose[a] (>5.55 mmol/L) or previously diagnosed diabetes	169 (16.58)	220 (21.51)	293 (28.62)‡	0.0044
Metabolic syndrome by ATP III criteria[a]	44 (5.28)	75 (8.34)	143 (15.83)*	<0.0001
Cardiovascular risk factors				
Dyslipidaemia	93 (10.62)	136 (16.05)§	189 (20.44)*	<0.0001
Hypertension	212 (14.86)	226 (19.68)§	342 (31.70)‖	0.039
Diabetes	40 (2.26)	40 (2.07)	50 (2.59)	0.30
Ever smokers	561 (57.00)	589 (59.67)	648 (63.27)	0.92
CVD (myocardial infarction+stroke)	46 (3.46)	63 (4.82)	69 (4.35)	0.67

P-values adjusted for age and race.
[a]Fasting morning samples.
**P*-value = <0.0001 when compared with BF <18.65%.
†*P*-value <0.001 when compared with BF <18.65%.
‡*P*-value <0.01 when compared with BF <18.65%.
§*P*-value <0.05 when compared with BF <18.65%.
‖*P*-value <0.07 when compared with BF <18.65%.

described in our study. The condition has been previously defined but its prevalence has never been studied in the general population. Results from our study suggest that NWO might be a key factor in the emerging worldwide epidemic of obesity, metabolic syndrome, diabetes, and coronary artery disease.

Our study shows that NWO is significantly associated with cardiometabolic dysregulation and a high prevalence of metabolic syndrome, which is in fact, similar to the prevalence of metabolic syndrome described in overweight subjects.[38] Additionally, this is the first study showing that in women, NWO is independently

Table 4 Metabolic syndrome components, definition, and cardiovascular risk factors in women with a normal body mass index by body fat tertiles

Variable ($N = 3129$)	BF <28.9% ($N = 1044$)	BF >28.9–33.3% ($N = 1040$)	BF >33.3% ($N = 1045$)	Age+race P_{adj}-value for trend
Metabolic syndrome	N (%)	N (%)	N (%)	
Central obesity ATP III (WC >88 cm)	21 (1.62)	96 (7.85)*	271 (24.22)*	<0.0001
Central obesity by (W/H≥0.85) waist-to-hip ratio	254 (24.31)	350 (33.70)‡	439 (42.02)*	<0.0001
High triglycerides (>1.7 mmol/L) or lipid treatment	99 (7.67)	159 (15.66)†	227 (22.16)*	<0.0001
Low high density lipoprotein (<1.3 mmol/L)	256 (23.84)	299 (28.67)‖	326 (31.69)‡	0.0024
High blood pressure (>130/>85 mmHg) or treatment for hypertension	260 (20.61)	336 (28.46)‖	387 (34.11)§	0.049
High fasting plasma glucose[a] (>5.55 mmol/L)or previously diagnosed diabetes	110 (8.67)	151 (14.10)§	193 (17.93)‡	0.0029
Metabolic syndrome by ATP III criteria[a]	52 (3.38)	103 (9.68)†	178 (17.24)*	<0.0001
Cardiovascular risk factors				
Dyslipidaemia	166 (16.16)	188 (18.06)	242 (23.98)‡	0.0012
Hypertension	210 (15.65)	262 (21.48)	300 (25.97)	0.25
Diabetes	27 (1.57)	34 (2.29)	49 (2.59)§	0.50
Ever smokers	417 (47.96)	386 (42.59)	412 (45.99)	0.35
CVD (myocardial infarction+stroke)	22 (1.28)	32 (2.11)	42 (3.60)‖	0.038

P-values adjusted for age and race.
[a]Fasting morning samples.
**P*-value = <0.0001 when compared with BF <28.9%.
†*P*-value <0.001 when compared with BF <28.9%.
‡*P*-value <0.01 when compared with BF <28.9%.
§*P*-value <0.05 when compared with BF <28.9%.
‖*P*-value <0.07 when compared with BF <28.9%.

associated with an increased risk for CV mortality. These findings provide important insights into understanding obesity—subjects who would otherwise considered non-obese, based on a normal BMI, may actually have an excess in BF, and therefore be at high risk for cardiometabolic dysregulation and CV mortality. A normal BMI therefore does not necessarily imply protection from consequences of increased BF.

Supporting our current observations, recent studies have reported the presence of several metabolic abnormalities in women with normal BMI with a medium-to-high BF content. De Lorenzo *et al.*[39] reported that 28 women with high BF (>30%) had a significantly lower resting metabolic rate and oxygen consumption, when compared with 20 women with normal BMI and no excess in BF (<30%). Furthermore, in a similar group of women ($n = 20$), De Lorenzo *et al.*[40] noted that plasma levels of several inflammatory biomarkers, including interleukins, and C-reactive protein were significantly higher in women with a normal BMI but high BF content, supporting the concept that subjects with NWO may be predisposed to develop metabolic syndrome and CV disease.

Because bioimpedance does not give information about fat distribution, we explored the impact of central obesity in our results by performing analyses using sex-specific tertiles of waist circumference. Interestingly, an increased waist circumference (>87 cm in men and >82 cm in women) was similarly associated with CV risk as were sex-specific tertiles of BF% (*Figure 2A* and *B*). This has important clinical implications because devices for measuring BF are not widely available in clinical practice. In contrast, waist circumference can be easily and inexpensively measured. However, it is important to note that an increased waist circumference was not related to higher CV mortality as was BF content in subjects with NWO and only 2% of men had central obesity according to the ATP-III criterion. Thus, while central deposition of fat may play a crucial role in cardiometabolic abnormalities,[41–43] it does not fully account for the higher risk for CV mortality noted in subjects with NWO. Furthermore, we found that the higher CV mortality noted in subjects with NWO remained significant, even after adjustment for central obesity. Finally, the association between NWO and CV mortality persisted in women, even after adjusting for CV risk factors, several of which could be considered intermediate mechanisms linking NWO and mortality.

Our study has several potential limitations. First, we used an arbitrary cut-off for BF% based on tertiles to define NWO. The harmful effects of an excess in BF very likely follow a continuum rather than a specific threshold for acquiring clinically significant cardiometabolic disturbances. Unfortunately, neither the World Health Organization nor any major scientific society involved in the study of obesity has defined a normal value for BF%. We believe that the use of tertiles to classify those with a relatively high BF% is more valid than using an arbitrary cut-off not previously validated. Second, misclassification could have occurred in this study, as subjects could have had changes in their body composition during the follow-up period. However, this concern is true for most epidemiologic studies that only use baseline

Table 5 Total and cardiovascular mortality in men and women with a normal body mass index by body fat tertiles

Men (*N* = 3042)	**BF <18.65%**	**BF >18.65–23.15%**	**BF >23.15%**
Total mortality events, *n* = 470 (44.66 deaths/1000 man-years)	137 (16.23)	143 (16.17)	190 (75.62)
Hazard ratio			
Model 1	Reference	0.87 (0.59–1.27)	0.90 (0.63–1.27)
Model 2		0.92 (0.63–1.34)	0.99 (0.67–1.45)
Model 3		0.87 (0.57–1.31)	0.86 (0.57–1.30)
Cardiovascular mortality events, *n* = 195 (18.53 deaths/1000 man-years)	56 (6.63)	66 (7.46)	73 (29.05)
Hazard ratio			
Model 1	Reference	1.12 (0.65–1.91)	1.07 (0.67–1.72)
Model 2		1.15 (0.68–1.94)	1.14 (0.72–1.79)
Model 3		1.06 (0.58–1.94)	1.09 (0.61–1.96)
Model 4		1.09 (0.62–1.92)	1.17 (0.69–1.98)
Women (*N* = 3129)	**BF <28.9%**	**BF >28.9–33.3%**	**BF >33.3%**
Total mortality events, *n* = 317 (11.65 deaths/1000 woman-years)	97 (4.57)	102 (11.66)	118 (12.49)
Hazard ratio			
Model 1	Reference	0.92 (0.61–1.41)	1.06 (0.69–1.62)
Model 2		0.95 (0.62–1.45)	1.11 (0.71–1.75)
Model 3		0.91 (0.58–1.41)	1.04 (0.66–1.63)
Cardiovascular mortality events, *n* = 142 (5.22 deaths/1000 woman-years)	40 (4.44)	46 (5.25)	56 (5.92)
Hazard ratio			
Model 1	Reference	1.20 (0.65–2.22)	1.84 (1.02–3.32)
Model 2		1.21 (0.64–2.30)	1.88 (1.00–3.60)
Model 3		1.26 (0.66–2.40)	1.92 (1.06–3.47)
Model 4		1.39 (0.67–2.90)	2.20 (1.03–4.67)

Model 1: Adjusted for age, race, and smoking status.
Model 2: Adjusted age, race, smoking status, and waist circumference.
Model 3: Adjusted age, race, dyslipidaemia, hypertension, impaired fasting glucose, smoking, and waist-to-hip ratio.
Model 4: Adjusted for age, race, smoking status, waist circumference, dyslipidaemia, hypertension, diabetes, and CV disease.

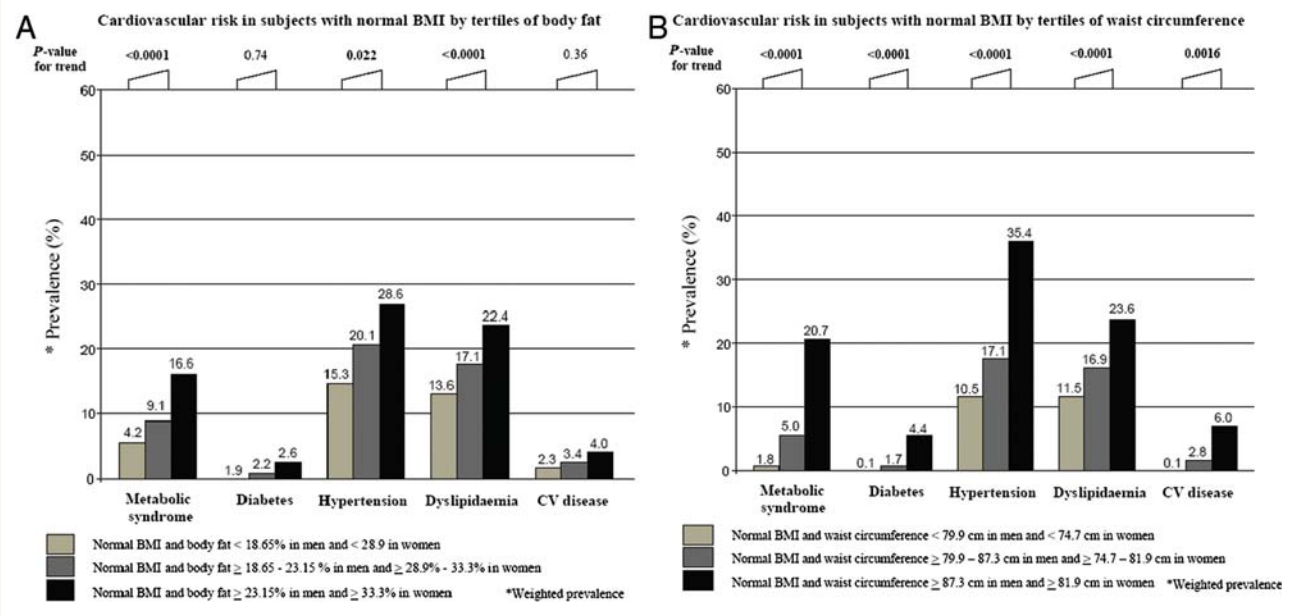

Figure 2 Comparison of metabolic syndrome components and definition (ATP-III) in subjects with a normal body mass index by sex-specific tertiles of body fat (A) and by sex-specific tertiles of waist circumferences (B).

information on the exposure variable, including those evaluating BMI. Third, bioelectrical impedance underestimates upper-body obesity, especially in athletes and elderly patients.[44] Other more accurate methods to estimate BF%, such as hydrostatic weighing or dual energy X-ray absorptiometry, may be preferable to estimate body composition.[45] Nevertheless, bioelectrical impedance's acceptable accuracy, simplicity, lack of radiation, and relatively low cost make it a practical and feasible alternative for measuring body fatness, especially in large populations.[46,47] Fourth, there were relatively few CV events at follow-up in our sample, limiting the statistical power to assess the relationship between NWO and mortality. The low rate of events may have occurred because our sample of normal weight subjects comprised a relatively healthy, young group, with a mean age of just over 40 years. Finally, due to the cross-sectional nature of our analyses linking BF content to cardiometabolic dysregulation, we cannot establish causality or directionality between these two factors. However, numerous studies in different settings have shown that increases in adiposity worsen most cardiometabolic measures, while adiposity reduction has been related to improvements in most cardiometabolic markers.[14,16] Furthermore, there is strong evidence showing an association between metabolic syndrome and CV mortality, supporting the notion that NWO may increase CV mortality by increasing cardiometabolic dysregulation.

Implications

Based on the latest US census and obesity prevalence data, we estimate that NWO is present in ~30 million Americans, many of whom may be unaware of their heightened cardiometabolic risk despite their normal BMI. Because self awareness of a condition is the initial step in behavioural modification and incorporation of therapeutic lifestyle changes, it might be relevant to incorporate BF measurement in the regular physical exam, using simple methods to diagnose NWO in clinical practice. The cardiometabolic dysregulation found in subjects with NWO, such as insulin resistance, altered lipid profile, and metabolic syndrome are potentially remediable if appropriately treated with diet, exercise, and possibly pharmacological therapies.

Conclusions

Normal weight obesity is associated with significant cardiometabolic dysregulation, including metabolic syndrome and CV risk factors. Furthermore, NWO appears to be associated independently with increased CV mortality in women. Screening for adiposity in subjects with a normal BMI could better identify those at higher risk for cardiometabolic disturbances and CV mortality.

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