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Peripheral fat distribution, the lipedema-associated phenotype, and lower prevalence of cardiometabolic disease in women: a cross-sectional study (NHANES 2011-2018)

Distribuição periférica da gordura, fenótipo associado ao lipedema e menor prevalência de doença cardiometabólica em mulheres: estudo transversal (NHANES 2011-2018)

Alexandre Campos Moraes Amato[1], Juliana Lelis Spirandeli Amato[1], Daniel Augusto Benitti[2]

Abstract

Background: Body fat distribution may be more relevant for cardiometabolic risk than total adiposity. The Buso criterion uses dual-energy X-ray absorptiometry (DXA) to identify a peripheral (gynoid) fat distribution pattern associated with lipedema, without establishing a clinical diagnosis of the condition.

Objectives: To evaluate the association between the peripheral fat distribution phenotype and the composite cardiometabolic outcome in women with different levels of body fat.

Methods: Cross-sectional study of 4,986 women aged 20-59 years from the National Health and Nutrition Examination Survey (NHANES) 2011-2018. The phenotype was defined as the ratio of leg fat to total fat ≥ 0.383, as measured by DXA. The composite outcome included diabetes, hypertension, high cholesterol, prediabetes, and cardiovascular disease. Survey-weighted logistic regression models were used, with analyses stratified by body fat and correction for multiple comparisons.

Results: The phenotype was associated with lower odds of the composite outcome (odds ratio = 0.49; 95% CI, 0.41-0.60; p < 0.001). There was no evidence of statistically significant interaction with the total fat category (p = 0.110). In the 25-38% body fat range, the outcome had a prevalence of 22.3% in women with the phenotype versus 49.4% in those without the phenotype.

Conclusions: The peripheral fat distribution phenotype was associated with lower odds of the composite cardiometabolic outcome across different levels of body fat. The cross-sectional design does not allow establishing temporality or causality.

Keywords: body fat distribution; body composition; absorptiometry, photon; cardiovascular diseases; obesity; lipedema.

Resumo

Contexto: A distribuição da gordura corporal pode ser mais relevante para o risco cardiometabólico do que a adiposidade total. O critério de Buso identifica, por absorciometria de raios X de dupla energia (*dual-energy X-ray absorptiometry*, DXA), um padrão de distribuição periférica (ginoide) da gordura associado ao lipedema, sem estabelecer seu diagnóstico clínico.

Objetivos: Avaliar a associação entre o fenótipo de distribuição periférica da gordura e o desfecho cardiometabólico composto em mulheres com diferentes níveis de gordura corporal.

Métodos: Estudo transversal com 4.986 mulheres de 20-59 anos do *National Health and Nutrition Examination Survey* (NHANES) 2011-2018. O fenótipo foi definido pela razão gordura das pernas/gordura total ≥ 0,383, medida por DXA. O desfecho composto incluiu diabetes, hipertensão, colesterol alto, pré-diabetes e doença cardiovascular. Foram utilizados modelos de regressão logística ponderados pelo desenho amostral, com análises estratificadas por gordura corporal e correção para múltiplas comparações.

Resultados: O fenótipo esteve associado a menores chances do desfecho composto (*odds ratio* = 0,49; intervalo de confiança de 95%: 0,41-0,60; p < 0,001). Não houve evidência de interação estatisticamente significativa com a categoria de gordura corporal (p = 0,110). Na faixa de 25-38% de gordura corporal, a prevalência do desfecho foi de 22,3% entre mulheres com o fenótipo e 49,4% entre aquelas sem o fenótipo.

Conclusões: O fenótipo de distribuição periférica da gordura esteve associado a menores chances do desfecho cardiometabólico composto em diferentes níveis de gordura corporal. O delineamento transversal não permite estabelecer temporalidade ou causalidade.

Palavras-chave: distribuição da gordura corporal; composição corporal; absorciometria de fóton; doenças cardiovasculares; obesidade; lipedema.

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Ethics committee approval: This study is a secondary analysis of anonymized, publicly available data from the National Health and Nutrition Examination Survey (NHANES), conducted by the National Center for Health Statistics (NCHS), which is part of the US Centers for Disease Control and Prevention. The original NHANES protocols were approved by the NCHS Research Ethics Review Board (Protocol No. 2011-17 for the 2011-2016 cycles and Protocol No. 2018-01 for the 2017-2018 cycle), and all participants provided written informed consent at the time of data collection. Because it exclusively involved secondary analysis of publicly available data with no possibility of individual participant identification, the present study does not require registration or review by the Brazilian CEP/CONEP system (Research Ethics Committee/National Research Ethics Commission) and therefore has neither a Certificate of Presentation for Ethical Review (CAAE) number nor a Consolidated Opinion number, as provided for in Article 1, sole paragraph, items II, III, and V, of National Health Council Resolution No. 510/2016, which excludes from its purview research using publicly accessible or public-domain information, databases containing aggregated information with no possibility of individual identification, and census research. US federal regulations, under 45 CFR 46.104(d)(4)(ii), also provide an exemption for research involving de-identified public-domain data.

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INTRODUCTION

Body fat distribution is increasingly recognized as a potentially more relevant determinant of cardiometabolic risk than total fat mass.[1,2] Visceral and truncal fat accumulation is associated with insulin resistance, whereas subcutaneous fat in the lower limbs appears to confer metabolic protection.[3-5] This sexual dimorphism in fat distribution, characterized by preferential storage of fat in gluteofemoral depots in women before menopause, has been proposed as a key mechanism for the lower cardiometabolic risk observed in premenopausal women.[6]

Several mechanisms have been proposed to explain the apparent protection conferred by gluteofemoral fat: greater adiponectin secretion, sequestration of fatty acids that would otherwise accumulate ectopically in the liver and muscles, lower lipolysis in these depots, and more favorable lipid partitioning.[5] These mechanisms characterize peripheral fat as a metabolically safe storage compartment, in contrast to the expansion of truncal and visceral fat.[3-5]

Lipedema is a chronic adipose tissue disorder affecting approximately 10% of women, characterized by bilateral and symmetrical accumulation of subcutaneous fat in the lower limbs, accompanied by pain and easy onset of ecchymosis.[7,8] Although it frequently coexists with an elevated body mass index (BMI), clinical cohorts report notably low prevalence rates of diabetes (2%), hypertension (13%), and dyslipidemia (11.7%).[9] Recent studies have shown that women with lipedema have more favorable glucose metabolism, higher adiponectin levels, and lower HbA1c levels than BMI-matched controls.[10,11] This pattern prompted the present study; however, it is important to emphasize that lipedema is a clinical diagnosis requiring the presence of pain and ecchymoses, in addition to physical examination, and cannot be established solely on the basis of isolated body composition measurements.

Dual-energy X-ray absorptiometry (DXA) enables precise quantification of regional body fat distribution. The Buso criterion (leg fat/total fat ≥ 0.383) showed 95% sensitivity and 73% specificity for identifying clinically diagnosed lipedema,[12] whereas ultrasound criteria represent a practical alternative.[13] The Buso criterion identifies a pattern of peripheral fat distribution, not a diagnosis of lipedema, and is therefore considered as such throughout the present study. However, it remains unclear whether the association between peripheral fat distribution and a lower prevalence of cardiometabolic alterations persists across different levels of total adiposity.

The objective of the present study was to estimate the association between the peripheral fat distribution phenotype (Buso criterion) and the prevalence of cardiometabolic disease in adult women, both in the general population and after stratification by total body fat percentage measured by DXA, in order to determine whether this association persists across the full spectrum of adiposity.

METHODS

Ethical considerations

This study consists of a secondary analysis of anonymized, publicly available data from the National Health and Nutrition Examination Survey (NHANES), conducted by the National Center for Health Statistics (NCHS), which is part of the US Centers for Disease Control and Prevention. The original NHANES protocols were approved by the NCHS Research Ethics Review Board (Protocol No. 2011-17 for the 2011-2016 cycles and Protocol No. 2018-01 for the 2017-2018 cycle), and all participants provided written informed consent at the time of data collection.

Because it exclusively involved secondary analysis of publicly available data with no possibility of individual participant identification, the present study does not require registration or review by the Brazilian CEP/CONEP system (Research Ethics Committee/National Research Ethics Commission) and therefore has neither a Certificate of Presentation for Ethical Review (CAAE) number nor a Consolidated Opinion number, as provided for in Article 1, sole paragraph, items II, III, and V, of National Health Council Resolution No. 510, April 7, 2016, which excludes from its purview research using publicly accessible or public-domain information, databases containing aggregated information with no possibility of individual identification, and census research. US federal regulations, under 45 CFR 46.104(d)(4)(ii), also provide an exemption for research involving de-identified public-domain data.

Study design and population

This cross-sectional study used NHANES data from 2011 to 2018, corresponding to four consecutive biennial cycles. The study report follows the recommendations of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) initiative for cross-sectional studies. The parent study identified 5,118 women aged 20 to 59 years with valid body composition measurements obtained by DXA. Of these, 132 (2.6%) had no available data on

total body fat percentage measured by DXA (variable DXDTOPF) and were excluded, resulting in a final sample of 4,986 women (Figure 1). In the parent study, the exclusion criteria included pregnancy, body weight greater than 204 kg, and invalid DXA scans.

Exposure

The phenotype under study, corresponding to peripheral fat distribution associated with lipedema and operationalized using the Buso criterion, was defined as a ratio of leg fat to total fat ≥ 0.383, with total fat defined as the sum of leg, trunk, and arm fat measured by DXA.[12] The Buso criterion was originally developed to identify, using DXA, a fat distribution pattern associated with lipedema. The threshold chosen was 0.383, derived from the original cutoff reported by Buso et al.[12] (optimal value by Youden's index = 0.384) and rounded as in the parent study. The practical difference between 0.383 and 0.384 is negligible, and the value of 0.383 is used consistently throughout the manuscript. Hereafter, this pattern is referred to as the "peripheral fat distribution phenotype" for short. It should be stressed that this criterion identifies a fat distribution pattern associated with lipedema but is not equivalent to a clinical diagnosis of the disease, which requires pain and ecchymoses, in addition to physical examination.

Stratification variable

Total body fat percentage was obtained from the NHANES variable DXDTOPF, measured by DXA and encompassing all body regions. Participants were stratified into nine categories according to total body fat percentage: < 25%, 25-30%, 30-33%, 33-36%, 36-39%, 39-42%, 42-45%, 45-50%, and > 50%. In addition, the 25-38% total body fat range was examined descriptively, defined directly from the continuous values (≥ 25.0% and < 38.0%) rather than by combining the categories above; its limits therefore do not coincide with the stratum boundaries.

Outcome

The primary outcome was a composite cardiometabolic disease outcome, defined by the presence of diabetes (self-reported or HbA1c ≥ 6.5%), hypertension, high cholesterol, prediabetes, or cardiovascular disease (congestive heart failure, coronary artery disease, angina, acute myocardial infarction, or stroke).

Statistical analysis

All analyses accounted for the complex NHANES sampling design (R survey package, version 4.4.8), incorporating primary sampling units (SDMVPSU), pseudo-strata (SDMVSTRA), and exam sample weights (WTMEC2YR/4). Within each body fat

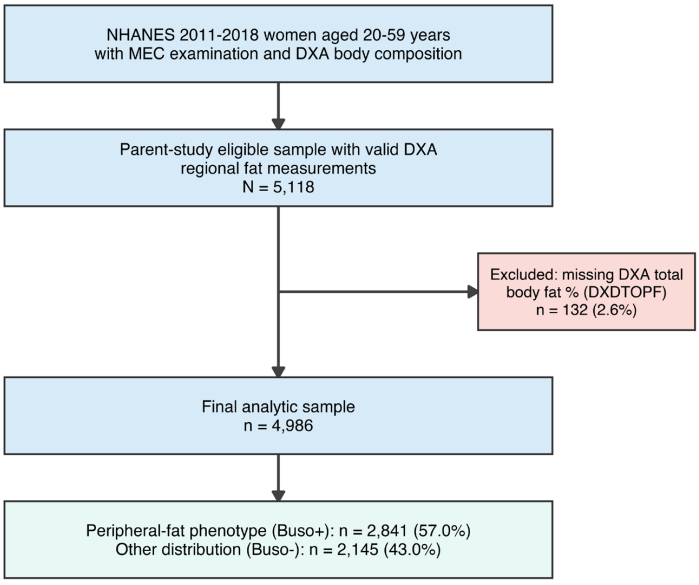


Figure 1. Sample selection flowchart. The eligible sample from the parent study included women aged 20 to 59 years with valid regional fat measurements obtained using DXA. DXDTOPF: NHANES variable corresponding to total body fat percentage; Buso+: presence of the peripheral fat distribution phenotype according to the Buso criterion; Buso−: absence of the peripheral fat distribution phenotype according to the Buso criterion. DXA: dual-energy X-ray absorptiometry; MEC: Mobile Examination Center; NHANES: National Health and Nutrition Examination Survey.

stratum, weighted logistic regression (quasibinomial family) was performed to estimate the odds ratio (OR) for cardiometabolic disease associated with the peripheral fat distribution phenotype, adjusted for age, race/ethnicity, and smoking: *cm_disease ~ phenotype + age + race/ethnicity + smoking*.

BMI was not included as a covariate in the main model because of its collinearity with the stratification variable. Correction for multiple comparisons was applied using the Benjamini-Hochberg method, controlling for the false discovery rate (FDR). A global model with an interaction term was used to assess whether the association differed across body fat categories, using the Rao-Scott adjusted F test. Sensitivity analyses included: (i) a model with additional adjustment for BMI; (ii) a model with additional adjustment for physical activity, education, household income, and menopausal/hysterectomy status; (iii) application of the alternative Dietzel criterion (leg fat/BMI ≥ 0.4637)[14]; and (iv) estimation of the main effect OR for each individual component of the composite outcome, adjusted for body fat category, age, race/ethnicity, and smoking.

Statistical significance was set at $p < 0.05$. For the stratified analyses and individual outcomes, p-values adjusted using the Benjamini-Hochberg method to control for the FDR < 0.05 were considered statistically significant. Baseline characteristics were described and compared between groups with and without the phenotype using weighted means and proportions according to the sample design, using the *t* test and Rao-Scott adjusted chi-square test (Table 1).

Table 1. Baseline characteristics of the sample according to fat distribution phenotype (weighted estimates for survey design; unweighted n).

Characteristic	Total	Phenotype+	Phenotype−	p
	(n = 4,986)	(n = 2,841)	(n = 2,145)	
Age (years), mean (SD)	39.3 (11.6)	37.3 (11.7)	42.5 (10.9)	<0.001
BMI (kg/m²), mean (SD)	28.7 (7.2)	26.4 (6.3)	32.2 (7.2)	<0.001
Total body fat (%), mean (SD)	38.5 (6.3)	36.9 (6.6)	41.1 (4.8)	<0.001
Leg fat/trunk fat ratio, mean (SD)	0.88 (0.26)	1.04 (0.21)	0.65 (0.10)	<0.001
Race/ethnicity, %				<0.001
· Non-Hispanic White	61.4	64.6	56.4	
· Non-Hispanic Black	11.3	12.8	8.9	
· Mexican-American	9.8	6.2	15.6	
· Other Hispanic	7.5	7.0	8.2	
· Non-Hispanic Asian	6.4	6.1	7.0	
· Other/multiracial	3.6	3.3	4.0	
Smoking, %				0.004
· Never	65.3	67.6	61.7	
· Current	18.9	17.8	20.5	
· Former smoker	15.9	14.6	17.8	
Physical activity, %				<0.001
· Low	26.4	22.2	33.0	
· Moderate	39.9	40.1	39.5	
· High	33.7	37.7	27.5	
Higher education degree, %	34.6	40.7	25.1	<0.001
High household income (> US$ 75,000), %	37.6	41.1	32.1	<0.001
Postmenopausal, %	31.9	25.5	41.9	<0.001

BMI = body mass index; SD = standard deviation. Phenotype+: Buso criterion ≥ 0.383. P-values from ***t*** tests and Rao-Scott chi-square tests weighted for survey design.

Table 1. Continued...

Characteristic	Total (n = 4,986)	Phenotype+ (n = 2,841)	Phenotype– (n = 2,145)	p
Previous hysterectomy, %	11.1	7.1	17.2	<0.001
Cardiometabolic disease (composite), %	39.5	29.7	54.7	<0.001
Diabetes, %	6.5	1.8	13.6	<0.001
Hypertension, %	19.6	12.6	30.5	<0.001
High cholesterol, %	22.1	16.9	30.1	<0.001
Prediabetes, %	6.6	4.9	9.2	<0.001
Cardiovascular disease, %	2.7	1.7	4.3	<0.001

BMI = body mass index; SD = standard deviation. Phenotype+: Buso criterion ≥ 0.383. P-values from *t* tests and Rao-Scott chi-square tests weighted for survey design.

Because this was a secondary analysis of a fixed-size sample, no *a priori* sample size calculation was performed. The final sample comprised 4,986 women and provided adequate precision, as reflected by the narrow confidence intervals for the main effect. In a *post hoc* statistical sensitivity analysis, considering 2,841 women with the peripheral fat distribution phenotype, 2,145 without the phenotype, and a weighted outcome prevalence of 54.7% in the group without the phenotype, it was estimated that the sample would enable detection, with 80% statistical power and a two-sided significance level of 5%, of ORs of 0.85 or lower or, conservatively assuming a design effect of 2.0, ORs of 0.80 or lower. These values are closer to the null than the estimate observed in the study (OR = 0.49).

RESULTS

Population

The final sample included 4,986 women, with a weighted mean total body fat percentage of 38.5%. The peripheral fat distribution phenotype, defined by the Buso criterion, was present in 2,841 women (57.0%). Table 1 presents the baseline characteristics of the groups. Compared with women without the phenotype, those with the phenotype were, on average, younger (37.3 vs. 42.5 years), had a lower BMI (26.4 vs. 32.2 kg/m^2) and lower total body fat percentage (36.9% vs. 41.1%), as well as higher levels of physical activity and education and a lower proportion of postmenopausal women ($p < 0.05$ for all comparisons). The prevalence of the phenotype ranged from 96.4% in the < 25% total body fat stratum to 40.4% in the > 50% stratum.

Primary outcome

In the main effects model, the phenotype was associated with an OR of 0.49 (95% CI, 0.41-0.60; $p < 0.001$), corresponding to 51% lower odds of the composite cardiometabolic outcome. The interaction between phenotype and body fat category was not statistically significant ($p = 0.110$); therefore, there was no statistical evidence that the magnitude of the association varied across different levels of adiposity. However, the absence of a statistically significant interaction does not show homogeneity of the effect (Figure 2).

Stratified analysis

The < 25% total body fat stratum (n = 4 controls) was excluded from the analysis because of violation of the positivity assumption. In the remaining eight strata, all ORs were below 1.0, four of which were statistically significant after adjustment using the Benjamini-Hochberg method to control for the FDR (ORs ranging from 0.23 to 0.67; Table 2; Figure 3).

Lowest prevalence range

In the 25-38% total body fat range, the prevalence of the composite cardiometabolic outcome was 22.3% among women with the phenotype (n = 1,359), compared with 49.4% among those without the phenotype (n = 561), corresponding to an absolute difference of 27.1 percentage points.

Sensitivity analyses

Additional adjustment for BMI mitigated the ORs but maintained the direction of the associations in all strata (for example, in the 36-39% stratum: primary model OR = 0.38; OR after additional adjustment for BMI = 0.52). Additional adjustments for physical activity, education, household income, and menopausal/hysterectomy status had virtually no effect on the overall association (fully adjusted model OR = 0.52; 95% CI, 0.42-0.64; primary

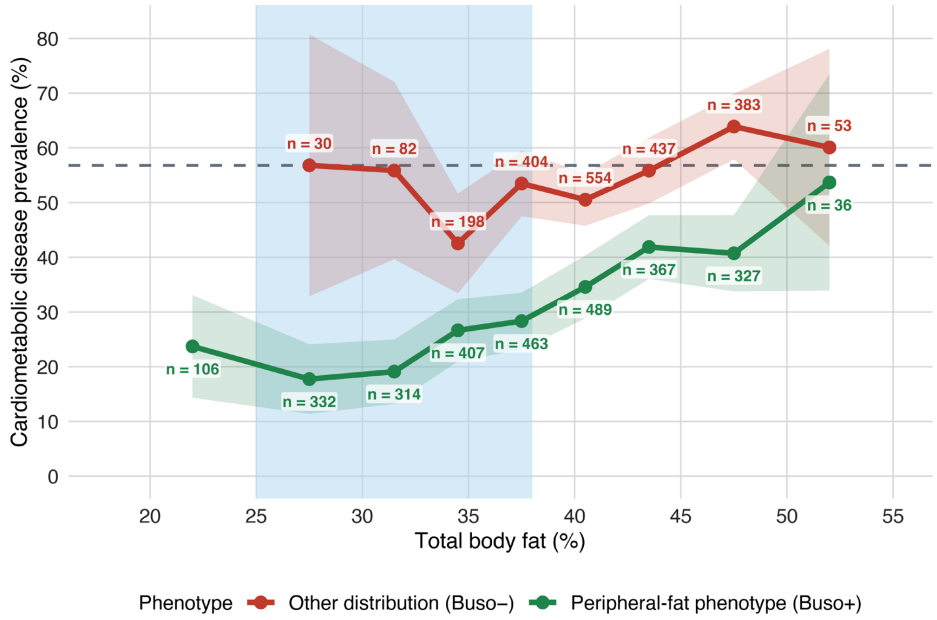


Figure 2. Prevalence of the composite cardiometabolic outcome according to body fat percentage and fat distribution phenotype. Prevalence rates were weighted according to the survey design. The composite outcome included diabetes, hypertension, high cholesterol, prediabetes, and cardiovascular disease. The lines represent women with (green) and without (red) the peripheral fat distribution phenotype, and sample sizes are indicated at each point. The blue shaded area represents the range of 25-38% total body fat, in which the lowest prevalence rates were observed. The dashed line represents the reference group (women without the phenotype in the 25-30% total body fat stratum), and the bands represent 95% CIs. Data from 4,986 women aged 20 to 59 years, National Health and Nutrition Examination Survey 2011-2018.

Table 2. Adjusted odds ratios for the composite cardiometabolic outcome according to total body fat percentage stratum.

Body fat	n	OR (95% CI)	Lower odds	Adjusted p
25-30%	362	0.29 (0.09-0.97)	71%	0.072
30-33%	396	0.23 (0.10-0.54)	77%	0.002
33-36%	605	0.65 (0.40-1.05)	35%	0.101
36-39%	867	0.38 (0.24-0.60)	62%	<0.001
39-42%	1,043	0.53 (0.39-0.72)	47%	<0.001
42-45%	804	0.67 (0.42-1.06)	33%	0.101
45-50%	710	0.41 (0.27-0.63)	59%	<0.001
> 50%	89	0.43 (0.09-2.01)	57%	0.243

95% CI = 95% confidence interval; OR = odds ratio. Model: cardiometabolic disease ~ phenotype + age + race/ethnicity + smoking. P-values adjusted using the Benjamini-Hochberg method to control for the false discovery rate. 95% CIs calculated using critical values from the *t* distribution, accounting for the survey design degrees of freedom.

model OR = 0.49). Analysis using the Dietzel criterion showed associations in the same direction in all six strata (with a virtually null OR in the 33-36% stratum: 0.99), two of which remained statistically significant after adjustment using the Benjamini-Hochberg method to control for the FDR (Figure 4).

As a sensitivity analysis of the components of the composite outcome, main effect ORs were estimated for each individual component, adjusted for body fat category, age, race/ethnicity, and smoking. All ORs were below 1.0 and statistically significant (Table 3; Figure 5). In each body fat stratum, the phenotype mathematically corresponded to a threshold indicative of a lower proportion of truncal fat, a finding consistent with the literature on regional fat distribution and metabolic risk.[3-5]

DISCUSSION

We have shown that the peripheral fat distribution phenotype, identified by the Buso criterion, is associated

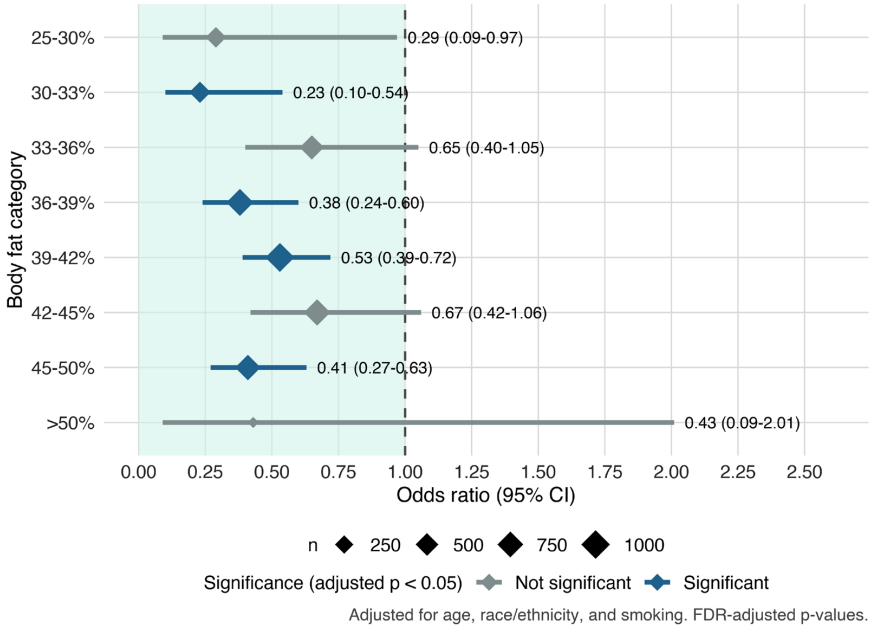


Figure 3. Adjusted odds ratio (OR) for cardiometabolic disease according to body fat stratum. Diamonds represent adjusted ORs and bars represent the corresponding 95% CIs. Models were adjusted for age, race/ethnicity, and smoking. P-values adjusted using the Benjamini-Hochberg method to control for the false discovery rate. Diamond size is proportional to the sample size in each stratum. Four of the eight analyzable strata showed statistically significant associations after adjustment of p-values using the Benjamini-Hochberg method, and all had ORs below 1.0. 95% CI = 95% confidence interval; OR = odds ratio.

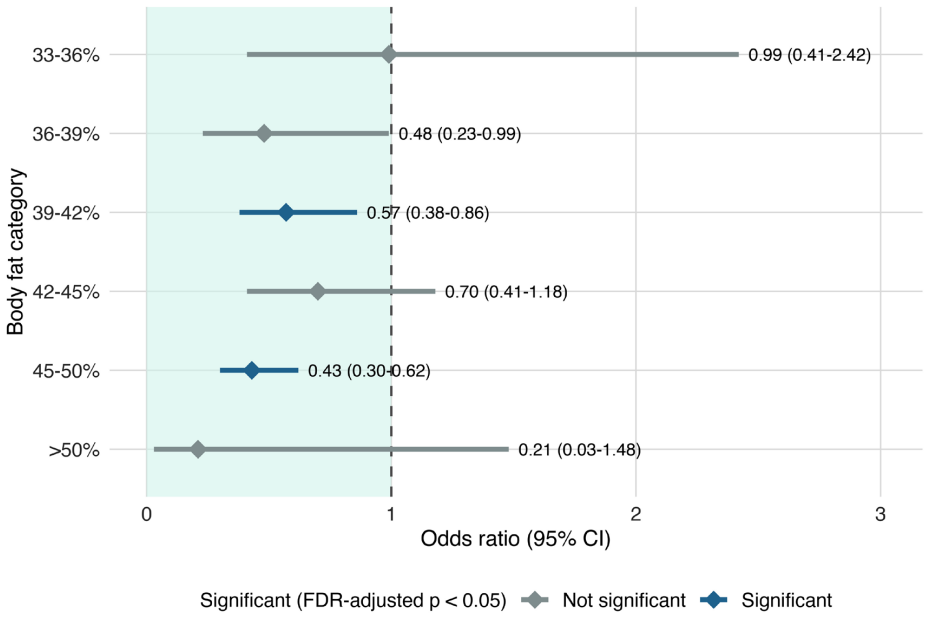


Figure 4. Sensitivity analysis using the Dietzel criterion (leg fat/BMI ≥ 0.4637). The same analysis as in Figure 3 was performed using the Dietzel criterion as an alternative definition of the phenotype. P-values adjusted using the Benjamini-Hochberg method to control for the false discovery rate. Two of the six analyzable strata (39-42% and 45-50% total body fat) showed statistically significant associations after adjustment of p-values using the Benjamini-Hochberg method; all six had ORs below 1.0, although the OR in the 33-36% stratum was virtually null (0.99). The smaller number of strata with statistically significant associations may be related to lower statistical power resulting from the application of a more restrictive criterion. 95% CI = 95% confidence interval; OR = odds ratio.

Table 3. Main effect odds ratios for each individual component of the composite cardiometabolic outcome (model adjusted for body fat category, age, race/ethnicity, and smoking).

Outcome	Cases (n)	OR (95% CI)	Adjusted p
Diabetes	465	0.17 (0.12-0.25)	<0.001
Hypertension	1,110	0.44 (0.35-0.57)	<0.001
High cholesterol	1,118	0.66 (0.52-0.84)	0.002
Prediabetes	341	0.66 (0.47-0.93)	0.019
Cardiovascular disease	169	0.52 (0.36-0.77)	0.002

95% CI = 95% confidence interval; OR = odds ratio. P-values adjusted using the Benjamini-Hochberg method to control for the false discovery rate.

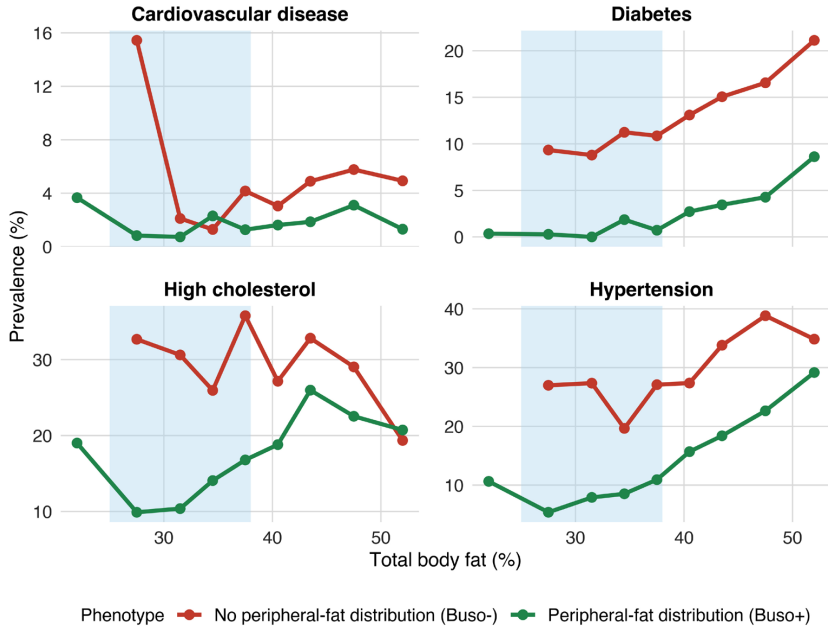


Figure 5. Prevalence of individual components of the composite cardiometabolic outcome according to body fat percentage and peripheral fat distribution phenotype. The panels show the prevalence of cardiovascular disease, diabetes, high cholesterol, and hypertension, weighted for survey design and stratified by the presence or absence of the fat distribution phenotype. Points corresponding to strata with fewer than 20 participants were suppressed. The blue shaded area highlights the 25-38% total body fat range, in which the lowest prevalence rates were observed.

with lower odds of the composite cardiometabolic outcome across different levels of adiposity. The overall adjusted OR of 0.49 (95% CI, 0.41-0.60) corresponds to 51% lower odds of this outcome. In addition, the not statistically significant interaction (p = 0.110) indicates that there is no statistical evidence that the association varies across different levels of adiposity. However, the magnitude of the ORs varied across strata (0.23-0.67), and the absence of a statistically significant interaction test result does not, in itself, constitute evidence of homogeneity of the effect. In addition, extreme strata, such as that with > 50% total body fat, had wide CIs (95% CI, 0.09-2.01), limiting the precision of inferences in these subgroups.

The consistency in the direction of the associations across different levels of body fat distinguishes this finding from the well-described phenomenon of metabolically healthy obesity, which tends to be unstable over time.[15] In each body fat stratum, the Buso criterion corresponds to a pattern characterized by a lower proportion of truncal fat; our findings may therefore represent a new parameterization of the established relationship between lower truncal fat accumulation and lower cardiometabolic risk.[3-5] The practical contribution of the criterion consists in providing a single standardized threshold, derived from measurements obtained using DXA, that summarizes regional fat distribution in a dichotomous measure

and allows the identification of women with a more peripheral fat distribution pattern across different levels of total adiposity, supplying potentially complementary information to classic anthropometric measures of central adiposity.

Peripheral fat distribution and the lipedema spectrum hypothesis

As a hypothesis to be investigated in future studies, our findings are consistent with the possibility that peripheral fat distribution represents an ancestral adaptive biological mechanism within a continuum of adipose tissue storage patterns.[16] One aspect that warrants explicit discussion is that 57% of the women in the sample met the Buso criterion, a proportion substantially higher than the estimated clinical prevalence of lipedema, approximately 10-12%, and the estimated prevalence of 12.3% among Brazilian women.[7,17] This discrepancy suggests that, when applied to the general population, the criterion predominantly identifies women without clinical lipedema and seems to capture a broader pattern of gynoid fat distribution, of which the clinical and symptomatic lipedema phenotype may represent a subset. Therefore, the results should be interpreted primarily as referring to body fat distribution and only secondarily, and exploratorily, in terms of their possible implications for lipedema.

Nevertheless, the possible relationship with lipedema represents the primary clinical motivation for the present study. Cohorts of patients with lipedema report low prevalence rates of diabetes, hypertension, and dyslipidemia, as well as a favorable metabolic profile, despite frequently elevated BMI.[9-11] Our findings extend this observation, previously described in clinical samples, by demonstrating in an unselected population-based sample that the fat distribution pattern associated with lipedema and identified by the Buso criterion was associated with lower odds of the composite cardiometabolic outcome across different levels of adiposity. These findings provide indirect support for the hypothesis that the fat distribution pattern associated with lipedema may be related to a more favorable metabolic profile, a hypothesis that should be investigated in studies involving participants with a clinical diagnosis of lipedema.

The direction of the association was consistent across different levels of body fat, a finding compatible with the hypothesis that this association is related to the fat distribution pattern and not simply to lower total adiposity. This interpretation is consistent with the hypothesis, derived from experimental models, that subcutaneous adipose tissue in the lower limbs acts as a "metabolic sink," sequestering lipids that might otherwise accumulate ectopically.[18,19] Inflammatory markers may be elevated in women with lipedema despite preserved glucose metabolism,[10] which is compatible with the hypothesis that the development of symptoms may be related to chronic inflammation or to the loss or overcoming of the protective metabolic effects attributed to peripheral fat. The possible transition from an asymptomatic to a symptomatic phenotype has been hypothesized to be related to hormonal[20] and dietary factors[21] capable of modulating chronic low-grade inflammation. These hypotheses, however, require investigation in longitudinal studies.

Clinical implications

The ratio of leg fat to total fat, measured by DXA, has the potential to provide information complementing the BMI in the assessment of cardiometabolic risk in women. For health care professionals treating patients with lipedema, the association with a more favorable metabolic profile does not diminish the clinical relevance of pain and functional impairment, which remain central factors in treatment decisions. Although the findings are consistent with the hypothesis of a metabolic buffering function of peripheral fat[18,19] and with approaches that prioritize inflammation management,[16] the cross-sectional study design does not allow therapeutic implications to be established or specific treatment recommendations to be supported.

Limitations

This study has some limitations. First, because of its cross-sectional design, the findings establish associations but not causal relationships or the temporal direction of these associations. In addition, the study is subject to survivorship and prevalence bias, since individuals with more severe or fatal disease may be underrepresented in the sample examined. Second, the Buso criterion identifies a fat distribution pattern associated with lipedema but cannot establish the clinical diagnosis of the disease. Third, at low levels of adiposity, the criterion has limited discriminative capacity: in the < 25% body fat stratum, 96% of women met the criterion, and the small number of women without the phenotype (n = 4) led to the exclusion of this stratum because of violation of the positivity assumption. This limitation reinforces the need for caution when interpreting results at the tail-ends of adiposity. Fourth, although the models were adjusted for age, race/ethnicity, and smoking, and the association remained virtually unchanged after additional adjustments for physical activity, education, household income, and menopausal/hysterectomy status, there remains the possibility of residual confounding by unmeasured or incompletely

measured factors, such as diet and access to health care. This limitation may be further influenced by the predominant use of self-reported outcomes. Fifth, the magnitude of the association varied across strata, and the absence of a statistically significant interaction does not constitute evidence of homogeneity of the effect. Sixth, the mathematical relationship between the Buso criterion and the proportion of truncal fat within each stratum limits the ability to attribute the associations observed specifically to the phenotype defined by the criterion, independently of the proportion of truncal fat. Finally, the body fat percentage used for stratification was obtained from the DXDTOPF variable, which includes fat in the head region, whereas the total fat used to calculate the Buso criterion excludes this region, resulting in a difference of approximately 3.6% between the two measures.

CONCLUSION

In this population-based sample of US women aged 20 to 59 years, the peripheral (gynoid) fat distribution phenotype was associated with lower odds of the composite cardiometabolic outcome (adjusted OR = 0.49; 95% CI, 0.41-0.60). The direction of the association was consistent across the eight analyzable body fat strata, although the magnitude of the ORs varied across strata and only four showed statistically significant associations after correction for multiple comparisons. These findings refer to a fat distribution pattern defined by DXA, not to a clinical diagnosis of lipedema. In addition, because of the cross-sectional study design, the results show an association but do not establish temporality or causality.

DATA AVAILABILITY

Available in a public repository with a DOI: "The data supporting the findings of this study are publicly available in the National Health and Nutrition Examination Survey (NHANES) public repository, maintained by the National Center for Health Statistics of the Centers for Disease Control and Prevention, and can be accessed at https://www.cdc.gov/nchs/nhanes/. The scripts used for the analyses in R and Python are available from the corresponding author (ACMA) upon request."

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