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ORIGINAL RESEARCH

Lipoatrophy and lipohypertrophy are independently associated with hypertension*

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Objective

Lipoatrophy and lipohypertrophy are associated with metabolic abnormalities, but little is known about their impact on hypertension. We conducted this study to determine the associations of lipoatrophy and lipohypertrophy with hypertension.

Methods

A cross-sectional study of HIV-infected patients who completed a self-report body morphology assessment was performed. We defined hypertension as a clinical diagnosis, or a mean systolic blood pressure (BP) > 140 mmHg or diastolic BP > 90 mmHg in the previous 6 months. We used logistic regression to examine the association between hypertension and body morphology.

Results

Among 347 patients, there were 2278 BP readings in 6 months. In adjusted analyses, patients with moderate lipoatrophy [odds ratio (OR) 4.3; $P = 0.03$] or moderate lipohypertrophy (OR 4.3; $P = 0.006$) had four times the odds, and patients with mild lipohypertrophy (OR 2.3; $P = 0.03$) had twice the odds of having hypertension compared with patients without changes. We hypothesized that the impact of lipohypertrophy on hypertension was mediated, in part, through body mass index (BMI). When BMI was included in the analysis, increased BMI was significantly associated with hypertension (OR = 1.1; $P < 0.001$ per kg/m^2), and the association between lipohypertrophy and hypertension was no longer present. However, the association between moderate lipoatrophy and hypertension was strengthened (OR = 5.5; $P = 0.01$).

Conclusions

Lipoatrophy and lipohypertrophy are independently associated with hypertension and there is a dose–response effect with more severe lipoatrophy and lipohypertrophy. The association between lipohypertrophy (but not lipoatrophy) and hypertension appears to be mediated by BMI. Our results suggest that patient-based body morphology assessments are related to hypertension and may have potential implications for cardiovascular disease.

Keywords: blood pressure, HIV, hypertension, lipoatrophy, lipodystrophy, lipohypertrophy

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Introduction

The dramatic decline in HIV-related mortality as a result of highly active antiretroviral therapy (HAART) [1,2] has been accompanied by a rise in metabolic abnormalities, including the body morphology changes of lipoatrophy and lipohypertrophy [3,4], which are commonly grouped together as lipodystrophy. Lipoatrophy and lipohypertrophy are known to be associated with metabolic abnormalities such as dyslipidaemia [5–8], but little is known about their association with hypertension. Although lipoatrophy and lipohypertrophy are often conceptualized as a single disorder, they are distinct entities with different aetiologies [9,10]. Previous studies have not separately examined the association between lipoatrophy or lipohypertrophy and hypertension. We conducted this study to

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determine the associations of lipoatrophy and lipohypertrophy with hypertension among HIV-infected patients cared for at a university-based HIV clinic.

Methods

Study setting

This cross-sectional study was conducted on a convenience sample of patients in the University of Washington (UW) HIV Patients Cohort, a longitudinal observational study of HIV-infected patients who receive primary care in the UW Harborview Medical Center HIV Clinic. This study was approved by the UW Institutional Review Board.

Study participants

HIV-infected patients over 18 years of age who attended the clinic between 26 September 2005 and 3 January 2007 were eligible for the study.

Data sources

Patients used tablet PCs with touch screens to complete an assessment including lipoatrophy and lipohypertrophy [based on the Study of Fat Redistribution and Metabolic Change (FRAM) instrument] [9–11], drug use [Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)] [12,13], alcohol use [Alcohol Use Disorders Identification Test consumption questions (AUDIT-C)] [14,15], smoking status and physical activity [16]. As previously described [17], we used web-based survey software developed specifically for patient-based measures. Data were also obtained from the UW HIV Information System (UWHIS), which integrates comprehensive clinical data on the UW HIV Cohort from all outpatient and in-patient encounters including demographic, clinical, laboratory, medication and socioeconomic information. Clinical patient data such as blood pressure (BP), height and weight are routinely collected and integrated in the UWHIS.

Measurement of blood pressure

BP is measured at all clinic visits by nursing staff using a mercury sphygmomanometer. Although the clinic's protocol for measuring BP does not require a 5-min seated waiting period before the measurement, as is considered ideal [18], clinic flow patterns result in almost every patient being seated for at least 5 min before check-in.

Definition of hypertension

We defined hypertension as a mean systolic BP > 140 mmHg or diastolic BP > 90 mmHg within 6 months of the assessment, or a prior clinical diagnosis of hypertension [19]. We conducted further assessments requiring clinical diagnoses of hypertension to be confirmed by treatment with an antihypertensive medication [20]. Use of antihypertensive medications without a clinical diagnosis was not used in the primary definition of hypertension as these medications are often prescribed for other reasons. However, we also performed additional sensitivity analyses that included use of antihypertensive medications even without a clinical diagnosis in the definition of hypertension.

Body morphology

The FRAM body morphology instrument asks patients to rate changes in the amount of fat in specific body regions graded on a seven-point scale ranging from -3 to $+3$ for each of 11 body regions. No change was scored as 0; mild, moderate and severe increases were scored as $+1$, $+2$ and $+3$, respectively; and mild, moderate and severe decreases were scored as -1, -2 and -3, respectively. Overall lipohypertrophy (and lipoatrophy) scores were calculated by totalling all positive (negative) responses indicating increases (decreases) in the size of body regions. We scored FRAM using two categorizations [none, any lipoatrophy or any lipohypertrophy; or none, mild lipoatrophy (1–12 points), mild lipohypertrophy (1–12 points), moderate-to-severe lipoatrophy (> 12 points), or moderate-to-severe lipohypertrophy (> 12 points)]. Patients with both lipoatrophy and lipohypertrophy were categorized by the more severe abnormality.

Statistical analyses

We performed bivariate analyses comparing study subject characteristics with those of the overall UW HIV Cohort using χ^2 tests for categorical variables and *t*-tests for continuous variables. Among study subjects, we examined associations among hypertension, body morphology abnormalities, demographic characteristics (age, race, sex and risk factor for HIV transmission), and clinical characteristics [CD4 T-cell count nadir, current CD4 T-cell count, peak HIV-1 RNA level, current HAART use, current illicit drug use, smoking status, physical activity level and body mass index (BMI)]. We calculated BMI using the traditional Quetelet index: weight divided by height squared (kg/m^2) [21]. Baseline BMI was categorized as underweight (< 18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) and obese

($\geq 30\,kg/m^2$). CD4 T-cell counts were modelled per 100 cells/μL. We performed bivariate analyses of associations with mean BP values using *t*-tests. We used one-way analysis of variance (ANOVA) to examine the relationship between mean BP values and body morphology category. We performed pairwise comparisons for factors found to be statistically significant. We used multivariate logistic regression with hypertension as the dependent variable to examine associations between body morphology and hypertension while adjusting for other covariates. Models were repeated using log linear models as the high prevalence of the outcome decreased the likelihood of the odds ratio accurately representing the relative risk [22]. Two-tailed *P*-values of <0.05 were considered statistically significant.

Results

The assessment was completed by 347 individuals during the study period. These subjects had a total of 2278 BP readings taken within 6 months of the assessment. Mean age was 44 years, 86% were men, mean BMI was $26.2\,kg/m^2$, and average CD4 T-cell count nadir was 165 cells/μL (Table 1). At the time of assessment, 4% of subjects were underweight, 42% had a normal BMI, 33% were overweight, and 21% were obese. Characteristics of subjects in the study were similar to those of all patients receiving care at the HIV clinic during the study period (data not shown).

There were 70 subjects (20%) who reported no lipoatrophy or lipohypertrophy, 137 (39%) who reported mild lipohypertrophy, 101 (29%) who reported mild lipoatrophy, 25 (7%) who reported moderate-to-severe lipohypertrophy, and 14 (4%) who reported moderate-to-severe lipoatrophy. While it is theoretically possible for an individual to have both moderate-to-severe lipoatrophy and moderate-to-severe lipohypertrophy in different regions, this did not occur among any of the subjects in this study. There were seven individuals with moderate-to-severe lipoatrophy and mild lipohypertrophy, and six with moderate-to-severe lipohypertrophy and mild lipoatrophy. There were 105 subjects with both mild lipoatrophy and mild lipohypertrophy. Individuals with both lipoatrophy and lipohypertrophy were categorized according to whichever was more severe.

The mean BP measured in the entire study cohort was 125/78 and varied by body morphology (see Table 1). Mean systolic BP was significantly lower among women compared with men (122.5 *vs.* 125.8 mmHg; $P = 0.04$). A trend towards higher systolic BP was seen among subjects with higher current CD4 T-cell counts ($P = 0.08$). No difference in systolic BP values were seen based on age, race, HIV transmission risk factor, CD4 T cell count nadir, current illicit drug use, physical activity, or current HAART use. No statistically significant differences were observed in diastolic BP values based on age, race, sex, HIV transmission risk factor, CD4 T-cell counts, current illicit drug use, physical activity, or current HAART use.

Among the 347 subjects included in the study, 123 (35%) were classified as having hypertension. Of these, 105 had a clinical diagnosis of hypertension (mean number of diagnoses per person 6; range 1–27), of whom 80 were receiving BP-lowering medications, 36 had a mean systolic BP >140 mmHg, and 27 had a mean diastolic BP >90 mmHg. Clinical diagnoses of hypertension were more common among subjects with body morphology abnormalities (35% of subjects with lipohypertrophy, 33% of subjects with lipoatrophy, and 16% of subjects with no abnormalities; one-way ANOVA, $P = 0.01$). Similarly, subjects with clinical diagnoses of hypertension receiving antihypertensive medications were more common in those with body morphology abnormalities (26% of subjects with lipohypertrophy, 25% of subjects with lipoatrophy, and 10% of those with no abnormalities; one-way ANOVA, $P = 0.02$). Clinical diagnoses of hypertension were also associated with older age ($P < 0.001$).

In multivariate analyses adjusting for age, race, sex, CD4 T-cell count nadir, and current CD4 T-cell count, subjects reporting any degree of lipoatrophy were more than twice as likely to meet the study definition of hypertension compared with those reporting no abnormalities [odds ratio (OR) 2.2; 95% confidence interval (CI) 1.0–4.5; $P = 0.04$], as were subjects with any degree of lipohypertrophy (OR 2.5; 95% CI 1.2–5.1; $P = 0.01$) (Table 2). Compared with subjects under 30 years of age, subjects aged 40–59 years or 50 years and older were significantly more likely to develop hypertension, as were those with higher current CD4 T-cell counts (Table 2). Similar findings were obtained using sensitivity analyses that more broadly defined hypertension as clinical hypertension diagnoses, use of antihypertensive medication, elevated systolic BP, or elevated diastolic BP, and using analyses with a more restricted hypertension definition of clinical hypertension diagnoses confirmed with antihypertensive medications, elevated systolic BP, or elevated diastolic BP (data not shown). Log linear models resulted in smaller relative risk point estimates than the ORs from logistic regression models, although the pattern of significant findings was the same (data not shown).

We then conducted additional analyses to examine body morphology severity. In multivariate analyses adjusting for age, race, sex, CD4 T-cell count nadir and current CD4 T-cell count, subjects with moderate-to-severe lipoatrophy were over four times as likely to have hypertension (OR 4.3;

Table 1 Clinical and demographic characteristics of study patients

Characteristic	By body morphology: No body morphology abnormalities ($n = 70$) *n* (%)	By body morphology: Lipohypertrophy* ($n = 162$) *n* (%)	By body morphology: Lipoatrophy* ($n = 115$) *n* (%)	*P* value	Entire cohort *n* (%)
Sex					
Male	61 (87)	136 (84)	102 (89)		299 (86)
Female	9 (13)	26 (16)	13 (11)	0.5	48 (14)
Race					
White	48 (69)	111 (69)	89 (77)		248 (72)
Black	14 (20)	41 (25)	18 (16)		73 (21)
Other	8 (11)	10 (6)	8 (7)	0.2	26 (7)
Age (years)					
<30	10 (14)	4 (3)	8 (7)		22 (6)
30–39	21 (30)	52 (32)	18 (16)		91 (26)
40–49	28 (40)	72 (44)	54 (47)		154 (44)
≥ 50	11 (16)	34 (21)	35 (30)	**0.001**	80 (23)
Risk factor for HIV transmission					
Male sex-with-male	43 (61)	95 (59)	68 (59)		206 (59)
Injecting drug use	16 (23)	36 (22)	26 (23)		78 (22)
Heterosexual	11 (16)	30 (19)	17 (15)		58 (17)
Other/unknown	0	1 (1)	4 (4)	0.4	5 (1)
Current CD4 T-cell count (cells/μL)					
0–200	16 (23)	23 (14)	33 (29)		72 (21)
201–350	17 (24)	39 (24)	28 (24)		84 (21)
≥ 351	37 (53)	100 (62)	54 (47)	**0.045**	191 (55)
CD4 T-cell count nadir (cells/μL)					
0–200	39 (56)	110 (68)	83 (72)		232 (67)
201–350	20 (29)	37 (23)	25 (22)		82 (24)
≥ 351	11 (16)	15 (9)	7 (6)	0.1	33 (10)
Peak HIV-1 RNA level					
$\leq 10\,000$	7 (10)	16 (10)	12 (10)		35 (10)
10 001–100 000	18 (26)	42 (26)	26 (23)		86 (25)
$>100\,000$	45 (64)	104 (64)	77 (67)	0.9	226 (65)
Body mass index					
<18.5	3 (4)	1 (1)	10 (9)		14 (4)
18.5–25.0	36 (51)	52 (32)	59 (51)		147 (42)
25.1–30.0	23 (33)	61 (38)	29 (25)		113 (33)
>30.0	8 (11)	48 (30)	17 (15)	$<$**0.001**	73 (21)
Cigarette smoking					
Never	23 (33)	45 (28)	24 (21)		92 (27)
Current	28 (40)	69 (43)	57 (50)		154 (44)
Past	19 (27)	48 (30)	34 (30)	0.4	101 (29)
Currently receiving HAART					
Yes	48 (69)	135 (83)	90 (78)		273 (79)
No	22 (31)	27 (17)	25 (22)	**0.047**	74 (21)
Blood pressure					
Systolic	123.3 ± 10.2†	127.9 ± 12.9†	122.9 ± 12.2†	**0.001**	125.3 ± 12.4†
Diastolic	77.3 ± 7.7†	79.7 ± 8.9†	77.4 ± 9.0†	**0.04**	78.5 ± 8.7†
Hypertension‡	13 (19)	66 (41)	44 (38)	**0.004**	123 (35)

*Patients with both lipoatrophy and lipohypertrophy are placed in the more severe category.
†Mean ± standard deviation.
‡Hypertension definition based on mean systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or clinical diagnosis.
HAART, highly active antiretroviral therapy.
P values <0.05 are in boldface.

95% CI 1.2–15.6; $P = 0.03$) as subjects reporting no abnormalities, while those with mild lipoatrophy were approximately twice as likely to have hypertension; this latter difference was not statistically significant (OR 2.0; 95% CI 0.9–4.2; $P = 0.08$) (Table 2). Individuals with moderate-to-severe lipohypertrophy were over 4 times as likely to have hypertension as subjects reporting no abnormalities (OR 4.3; 95% CI 1.5–12.4; $P = 0.006$), and subjects with mild lipohypertrophy were over twice as likely to have hypertension (OR 2.3; 95% CI 1.1–4.7; $P = 0.03$) (Table 2). Compared with subjects <30 years of age, those aged 40–59 years or those 50 years or older were

Table 2 Odds ratios for factors associated with hypertension including any body morphology and body morphology severity

	Hypertension*		
Variable	Unadjusted models OR (95% CI, *P*)	Adjusted model 1† OR (95% CI, *P*)	Adjusted model 2‡ OR (95% CI, *P*)
Body morphology			
No abnormality	1 (ref)	1 (ref)	
Any lipoatrophy	**2.7 (1.3–5.5, 0.006)**	**2.2 (1.0–4.5, 0.04)**	
Any lipohypertrophy	**3.0 (1.5–5.9, 0.001)**	**2.5 (1.2–5.1, 0.01)**	
No abnormality	1 (ref)		1 (ref)
Mild lipoatrophy	**2.4 (1.2–5.0, 0.02)**		2.0 (0.9–4.2, 0.08)
Mild lipohypertrophy	**2.7 (1.3–5.4, 0.005)**		**2.3 (1.1–4.7, 0.03)**
Moderate lipoatrophy	**5.8 (1.7–19.8, 0.004)**		**4.3 (1.2–15.6, 0.03)**
Moderate lipohypertrophy	**5.6 (2.1–15.1, 0.001)**		**4.3 (1.5–12.4, 0.006)**
Age (years)			
<30	1 (ref)	1 (ref)	1 (ref)
30–39	5.9 (0.8–46.7, 0.09)	4.2 (0.5–34.1, 0.2)	4.4 (0.5–35.9, 0.2)
40–49	**13.4 (1.8–102.3, 0.01)**	**9.7 (1.2–77.2, 0.03)**	**9.4 (1.2–75.2, 0.04)**
>50	**23.2 (3.0–180.9, 0.003)**	**15.5 (1.9–126.3, 0.01)**	**14.9 (1.8–123.2, 0.01)**
Current CD4 T-cell count§	**1.1 (1.0–1.2, 0.01)**	**1.1 (1.0–1.3, 0.02)**	**1.1 (1.0–1.2, 0.02)**

*Hypertension defined as a clinical diagnosis, or mean systolic blood pressure >140 mmHg, or diastolic blood pressure >90 mmHg.
†Model 1 adjusted for body morphology category (no abnormality, any lipoatrophy or any lipohypertrophy) as well as age, sex, race, CD4 T-cell count nadir and current CD4 T-cell count.
‡Model 2 adjusted for severity of body morphology category (none, mild lipoatrophy, mild lipohypertrophy, moderate lipoatrophy or moderate lipohypertrophy) as well as age, sex, race, CD4 T-cell count nadir and current CD4 T-cell count.
§Modelled per 100 cells/μL, and thus, compared with patients with a CD4 T-cell count of 200 cells/μL, a person with a CD4 T-cell count of 300 cells/μL would have a 10% increase in risk of hypertension.
OR, odds ratio using logistic regression; CI, confidence interval.
Results are in boldface for *P* values <0.05.

more likely to have hypertension, as were those with higher current CD4 T-cell counts (Table 2).

Effect of BMI

Mean systolic BP values were highest among subjects whose BMI was obese (129.7 mmHg) *vs.* those who were overweight (127.3 mmHg), normal (122.8 mmHg), or underweight (112.2 mmHg) (one-way ANOVA, $P<0.001$; all pairwise comparisons, $P<0.05$ except for obese *vs.* overweight). Mean diastolic BP values were highest among subjects whose BMI was obese (80.9 mmHg) *vs.* those whose BMI was overweight (80.6 mmHg), normal (76.2 mmHg), or underweight (71.3 mmHg) (one-way ANOVA, $P<0.001$; pairwise comparisons, $P<0.05$ except for obese *vs.* overweight, and underweight *vs.* normal).

We tested the hypothesis that the impact of lipohypertrophy on hypertension was mediated, in part, through a higher BMI. When BMI was added to the multivariate model, it was significantly associated with hypertension (OR = 1.1; 95% CI 1.04–1.16; $P<0.001$ per kg/m^2), and the associations between moderate lipohypertrophy or mild lipohypertrophy and hypertension were no longer present. However, the association between moderate lipoatrophy and hypertension remained after adjusting for BMI (OR = 5.5; 95% CI 1.5–20.2; $P=0.01$). The results for age and current CD4 T-cell count were similar when BMI was included in the model (data not shown).

Discussion

We found that lipoatrophy and lipohypertrophy were associated with hypertension among HIV-infected individuals and found a stepwise increase in the likelihood of hypertension associated with more severe lipoatrophy or lipohypertrophy. Patients with moderate lipoatrophy or moderate lipohypertrophy had a fourfold increase in hypertension compared with patients with no body morphology abnormalities. In addition, our results suggest that the increased risk of hypertension associated with lipohypertrophy was mediated, at least in part, through an increased BMI. In contrast, patients with lipoatrophy had an increased risk of hypertension compared with those without anthropometric abnormalities even after adjusting for BMI. Older age and higher current CD4 T-cell count were also associated with hypertension.

Previous studies have suggested a possible association between elevated BP or hypertension and lipodystrophy in HIV infection [7,23–27]. However, these studies did not examine the separate effects of lipoatrophy and lipohypertrophy on BP [7,23–27]. The largest of these, the multicohort Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, demonstrated a weaker association

between lipodystrophy and hypertension (OR 1.34; $P<0.05$) [24,27]. The accumulation of dorsocervical fat (known as a 'buffalo hump') in lipohypertrophy has been associated with elevated BP [28]. A case–control study of HIV-infected individuals on HAART found a high prevalence of hypertension compared with HIV-uninfected patients, and this was associated with the presence of lipodystrophy [23]. Another case–control study found that patients with lipodystrophy had higher diastolic BP values than HIV-uninfected controls but did not find a difference for systolic BP [7]. A small cohort study of 40 HIV-infected patients with lipoatrophy found that a large percentage had hypertension (50%) after 44 months [29]. Higher rates of elevated BP have been found among patients referred to a specialty clinic for body morphology or lipid abnormalities compared with controls [25]. However, to our knowledge, no previous studies have assessed the association between body morphology abnormality severity and hypertension adjusting for other key factors such as age.

A previous study suggested that the typical age-associated rise in systolic BP may not be present among HIV-infected individuals [30]. We did not see age-associated higher BP values as has been seen in HIV-uninfected individuals [31]. However, when we defined hypertension more broadly as either elevations in BP values or hypertension diagnoses, we did find an association with age. In fact, among patients aged 50 years and older, 41% were receiving BP-lowering medications compared with 23% of those between 40 and 49 years of age, 12% of those between 30 and 39 years of age, and 0% of patients younger than 30 years of age, suggesting the lack of higher BP values among older patients was a result of increased use of antihypertensive therapy.

We used a combined hypertension diagnosis that included both elevated BP values and clinical diagnoses of hypertension. This addresses a limitation of several previous studies in HIV-infected individuals that focused on BP values only [7,28] without including clinical hypertension diagnoses and antihypertensive medications and therefore may have missed associations with patients with treated elevated BP. The importance of the use of this combined outcome is highlighted by the lack of an age-associated increase in BP values but greater rates of hypertension diagnoses and treatment among older patients, as well as the lack of an increase in BP values but greater rates of hypertension diagnoses and treatment among patients with lipoatrophy compared with those with no abnormalities.

The strengths of our study include the comprehensive clinical data captured in our information system (UWHIS) which includes serial BP measurements, hypertension diagnoses, and use of antihypertensive medications. Furthermore, we used the FRAM clinical body morphology instrument, which has been shown to correlate with radiological measures of body composition, to distinguish lipoatrophy from lipohypertrophy, and allow assessment of lipoatrophy and lipohypertrophy severity [9,10,32].

A limitation of the study is that we did not perform radiological body composition assessments. However, the demonstration that the effect of lipohypertrophy is linked to BMI makes it likely that increased adiposity plays a role. In contrast, the lack of effect of BMI on the association with lipoatrophy and hypertension suggests that the diagnosis of lipoatrophy did not represent AIDS wasting; furthermore, those with very low BMI had lower BP. Measurement of BP in the clinical care setting may not be conducted in a uniform manner. We limited the impact of random measurement error by using average BP readings over a 6-month period. Another limitation is that, while the cross-sectional assessment of lipoatrophy and lipohypertrophy demonstrates a significant association of lipoatrophy and lipohypertrophy with hypertension, it does not allow conclusions to be drawn regarding the direction of the association. Although this study demonstrates an association between morphological abnormalities and hypertension, it does not evaluate the mechanism of this association. Finally, information regarding other potential risk factors for hypertension such as genetic factors and diet was not available. Further studies are needed to examine associations between body morphology abnormalities and hypertension over time.

In conclusion, we found that lipoatrophy and lipohypertrophy are significantly associated with hypertension among HIV-infected patients and that there is a dose–response effect, with more severe morphological abnormalities associated with a greater risk of hypertension. We found that the association between lipohypertrophy and hypertension may be an effect of obesity, as it reflects BMI, but that the association of lipoatrophy with hypertension is independent of BMI. Finally, our finding that patient-based assessments of morphological abnormalities are associated with clinical outcomes such as hypertension suggests that results from such patient-based assessments may have potential predictive implications for cardiovascular disease.

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Author contributions

H.C. designed the study and oversaw the analyses. H.C., R.H., and M.K. oversaw data collection. C.G. oversaw development of the body morphology assessment. All authors contributed to and have approved the final manuscript.

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