## Title

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# Associations Between At-Risk Alcohol Use, Substance Use, and Smoking with Lipohypertrophy and Lipoatrophy Among Patients Living with HIV

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**Abstract**

To examine associations between lipohypertrophy and lipoatrophy and illicit drug use, smoking, and at-risk alcohol use among a large diverse cohort of persons living with HIV (PLWH) in clinical care. 7,931 PLWH at six sites across the United States completed 21,279 clinical assessments, including lipohypertrophy and lipoatrophy, drug/alcohol use, physical activity level, and smoking. Lipohypertrophy and lipoatrophy were measured using the FRAM body morphology instrument and associations were assessed with generalized estimating equations. Lipohypertrophy (33% mild, 4% moderate-to-severe) and lipoatrophy (20% mild, 3% moderate-to-severe) were common. Older age, male sex, and higher current CD4 count were associated with more severe lipohypertrophy ($p$ values <.001–.03). Prior methamphetamine or marijuana use, and prior and current cocaine use, were associated with more severe lipohypertrophy ($p$ values <.001–.009). Older age, detectable viral load, and low current CD4 cell counts were associated with more severe lipoatrophy ($p$ values <.001–.003). In addition, current smoking and marijuana and opiate use were associated with more severe lipoatrophy ($p$ values <.001–.03). Patients with very low physical activity levels had more severe lipohypertrophy and also more severe lipoatrophy than those with all other activity levels ($p$ values <.001). For example, the lipohypertrophy score of those reporting high levels of physical activity was on average 1.6 points lower than those reporting very low levels of physical activity (−1.6, 95% CI: −1.8 to −1.4, $p < .001$). We found a high prevalence of lipohypertrophy and lipoatrophy among a nationally distributed cohort of PLWH. While low levels of physical activity were associated with both lipohypertrophy and lipoatrophy, associations with substance use and other clinical characteristics differed between lipohypertrophy and lipoatrophy. These results support the conclusion that lipohypertrophy and lipoatrophy are distinct, and highlight differential associations with specific illicit drug use.

**Keywords:** lipoatrophy, lipohypertrophy, substance use, alcohol use, physical activity

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## Introduction

Over the last two decades, there has been a significant decline in HIV-related morbidity and mortality due to antiretroviral therapy (ART).[1,2] This has been accompanied by an increase in the body morphology changes of lipohypertrophy and lipoatrophy.[3] While a decrease in body morphology abnormalities over the next few years due to earlier treatment and the use of less toxic antiretroviral medications has been expected,[4] only a small decrease in lipoatrophy as measured by leg fat percentage has been seen in recent years.[4] While lipohypertrophy and lipoatrophy are often conceptualized as a single disorder called ''lipodystrophy,'' they are distinct entities with different etiologies.[5–7] Lipohypertrophy is characterized by fat accumulation particularly an increase in visceral fat in the abdomen, enlargement of the dorsocervical fat pad, and/or fat deposition in breast tissue.[5,8,9] Lipoatrophy is characterized by loss of subcutaneous fat often most pronounced on the face and extremities, with the legs and gluteal region affected more than the upper body.[5,6,8,10]

Metabolic complications of HIV, including lipohypertrophy and lipoatrophy, have been associated with ART, HIV infection itself, and other demographic and lifestyle factors such as age, sex, race/ethnicity, and sedentary lifestyle/physical activity levels.[3,7,8,11–15] Few studies have examined the role of behavioral factors such as substance use, and in particular, prior studies have not evaluated the independent association between lipohypertrophy or lipoatrophy and alcohol, smoking, and illicit drug use, including the role of individual drugs.[5,6,16] Furthermore, behavioral factors such as substance abuse, physical activity, and smoking are often correlated with each other.[17–19] Discerning the unique contributions of at-risk alcohol use, smoking, and other substance use will require considering these factors simultaneously.

We conducted this study to examine the associations between illicit drug use, smoking, and at-risk alcohol use and lipohypertrophy and lipoatrophy among a large, diverse, nationally distributed well-characterized cohort of persons living with HIV (PLWH) in clinical care.

## Methods

### *Study setting*

This observational cohort study was conducted among the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort. CNICS is a longitudinal observational study of PLWH from eight clinical sites receiving primary care from 1/1/1995 to present.[20]

### *Study subjects*

All PLWH 18 years of age or older who completed one or more clinical assessments of patient-reported outcomes (PROs) as part of a routine clinical visit before 11/2013 were eligible for the study. The PRO clinical assessment was integrated into clinical care between 2006 and 2012 at six participating CNICS sites. The study was approved by Institutional Review Boards at each site.

### *Data sources*

The CNICS data repository captures longitudinal data on the CNICS cohort.[20] The data repository integrates comprehensive clinical data from all outpatient and inpatient encounters, including standardized HIV-related information collected at enrollment (initial clinic visit) regarding prior ART history. Demographic, clinical, laboratory, and medication data are obtained from each site's electronic health record and other institutional data sources.

PLWH used tablet PCs with touch screens to complete the clinical assessment every 4–6 months. The assessment includes a morphology assessment that measures lipohypertrophy and lipoatrophy based on the Study of Fat Redistribution and Metabolic Change instrument (FRAM), which has been validated against objective imaging approaches such as MRI[5,6,21,22] and has key associations with relevant metabolic outcomes such as hypertension, as well as other clinical outcomes such as depression and quality of life.[23,24]

The assessment also includes drug use using a modified Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST),[25,26] alcohol use using the Alcohol Use Disorders Identification Test consumption questions (AUDIT-C),[27,28] cigarette use, and physical activity using the Lipid Research Clinic questionnaire.[29] We used web-based survey software developed specifically for PROs.[30,31] Patients who are medically unstable at the time of a visit, appear intoxicated, or do not speak English or Spanish are not asked to complete the assessment. Given the slow rate of change of body morphology, in 2012, the clinical assessment was programmed with a skip pattern such that it only gives the FRAM body morphology instrument annually even though they can take the assessment every 4–6 months.

### *Measurement of body morphology*

The FRAM body morphology instrument asks PLWH to rate changes in the amount of fat in specific body regions graded on a 7-point scale ranging from −3 to +3 for each region. No change was scored as 0; mild, moderate, and severe increases were scored as +1, +2, and +3; and mild, moderate, and severe decreases were scored as −1, −2, and −3. An overall lipohypertrophy score was calculated totaling all positive responses (indicating increases in size of body regions). An overall lipoatrophy score was calculated totaling all negative responses (indicating decreases in size).

We conducted analyses using three scoring methods for body morphology. We examined lipohypertrophy and lipoatrophy categories (none, 0 points; mild, 1–12 points; and moderate-to-severe, >12 points), and also continuous lipohypertrophy and lipoatrophy scores. We also examined lipohypertrophy and lipoatrophy as binary outcomes (none vs. any).

### *Measurement of substance use*

There are several ways to score the ASSIST to measure substance use.[25,26] We used the ASSIST to operationally define use of four individual drug classes (marijuana, crack/cocaine, methamphetamines/crystal, and illicit opioids/heroin) and categorized use as current (past 3 months), prior, or never.

We calculated AUDIT-C scores for current alcohol use by summing the scores for each item (0–4 points each).[27] We used a score of ≥4 for men and ≥3 for women to define at-risk alcohol consumption.[32]

We used responses to the cigarette items to categorize PLWH as current smokers, past or ex-smokers, and nonsmokers.

### Measurement of physical activity

This 4-item instrument classifies PLWH into very low active, low active, moderately active, and highly active categories.[29]

### Statistical analyses

We performed bivariate analyses comparing participant characteristics to the overall cohort at the six participating sites using chi-squared tests and *t*-tests. We similarly compared demographic and clinical characteristics of those with completed assessments and those with assessments excluded due to missing body morphology or other information.

We examined associations between body morphology abnormalities, demographic characteristics, clinical characteristics, and behavioral factors. Demographic characteristics included age, race/ethnicity, sex, and HIV transmission risk factor. Clinical characteristics included CD4 count (current and nadir), peak HIV-1 RNA level, current ART use, duration of exposure to stavudine/didanosine, body mass index (BMI), and hepatitis C virus (HCV) status. BMI was measured as a continuous variable and as a categorical variable: underweight <18.5 kg/m$^2$, normal 18.5–24.9 kg/m$^2$, overweight 25.0–29.9 kg/m$^2$, and obese ≥30 kg/m$^2$. Duration of stavudine and/or didanosine was included as a key cause of body morphology abnormalities, particularly lipoatrophy.[33] Behavioral factors included current and past illicit drug use, at-risk alcohol use, current and past smoking status, and physical activity levels.

We used generalized estimating equations with an exchangeable correlation structure and robust standard errors to assess differences in body morphology associated with alcohol, cigarette smoking, and other substance use, while accounting for within-subject correlations between repeated measures.[34] Similarly, we used ordinal logistic regression adjusting for repeated measures for categorical lipohypertrophy and lipoatrophy; however, these models failed the assumption of proportional odds. We therefore repeated these analyses using logistic regression with 2 models: one for mild versus none, and the other for moderate-to-severe versus none for categorical lipohypertrophy and lipoatrophy. We conducted separate models for lipohypertrophy and lipoatrophy. We adjusted all analyses for age, race, sex, clinical site, currently receiving ART, duration of prior stavudine/didanosine, current and nadir CD4 cell count, viral load, HCV, at-risk alcohol use, smoking status, physical activity level, and current, past, or no substance use. We adjusted models evaluating lipohypertrophy for lipoatrophy, and adjusted models evaluating lipoatrophy for lipohypertrophy.

We conducted sensitivity analyses by repeating models limited to the subset of individuals known to be naive to ART when they initiated care at a CNICS site to ensure accurate capture of duration of didanosine/stavudine. We also conducted sensitivity analyses focused on belly fat (as an ordinal scale) instead of overall lipohypertrophy. Given the potentially evolving nature of lipohypertrophy and lipoatrophy,[4] we also considered sensitivity analyses with assessment of calendar year. We considered two-tailed *p*-values <.05 to be significant. We used Stata 13 for analyses.

## Results

Clinical assessments were completed 21,279 times by 7,931 PLWH. An additional 2,749 assessments were excluded due to missing information on body morphology, alcohol, or substance use. The majority of these were due to missing body morphology information as these items are automatically skipped if the body morphology instrument had been completed in the prior 364 days. There were no demographic (age, race, and sex) or clinical differences (CD4 count) for patients from excluded and included assessments. Table 1 describes demographic and clinical characteristics by baseline body morphology at each initial assessment. Mean age was 45 (SD 10), 87% were men, and mean current CD4 count was 523 cells/mm$^3$ (Table 1). Demographic and clinical characteristics of participants were similar to all individuals receiving care at the participating clinics during the study period (data not shown).

Among all 21,279 assessments, no lipohypertrophy or lipoatrophy was reported during 8,471 clinical assessments (40%), mild lipohypertrophy was reported during 7,123 assessments (33%), mild lipoatrophy was reported during 4,301 (20%) assessments, moderate-to-severe lipohypertrophy was reported in 803 (4%) assessments, and moderate-to-severe lipoatrophy was reported in 582 (3%) assessments. While it is theoretically possible for an individual to have both moderate-to-severe lipohypertrophy and moderate-to-severe lipoatrophy in different regions, this was only reported during two assessments. There were 157 assessments with moderate-to-severe lipohypertrophy and mild lipoatrophy (<1%), and 140 where individuals reported moderate-to-severe lipoatrophy and mild lipohypertrophy (<1%). There were 2,604 assessments where individuals reported both mild lipohypertrophy and mild lipoatrophy (12%). Individuals with both lipohypertrophy and lipoatrophy were categorized according to whichever was more severe; in the case of a tie (411 assessments, 1.9%), people were categorized as having lipoatrophy.

Bivariate analyses at baseline, female sex, older age, higher BMI, very low physical activity levels, and currently receiving ART (Table 1) were associated with lipohypertrophy. In contrast, older age, lower current and nadir CD4 cell counts, lower BMI, and very low physical activity levels were associated with lipoatrophy in bivariate analyses (Table 1).

When we examined substance use, rates of baseline body morphology category differed among PLWH who reported never, prior, or current use of opiates, cocaine/crack, methamphetamines, and marijuana ($p$ values<.001, $\chi^2$). A consistent pattern of body morphology was seen for only some drugs (Table 2). Smoking, but not current at-risk alcohol use, was associated with lipoatrophy and, in particular, current smoking was associated with moderate-to-severe lipoatrophy.

### Multivariate analyses

Older age, female sex, and higher current CD4 count were all associated with more severe lipohypertrophy using continuous lipohypertrophy scores in adjusted analyses ($p$ values <.001–.03). In contrast, a higher CD4 cell count nadir and more than very low levels of physical activity were associated with less severe lipohypertrophy ($p$ values .001–.02) (Fig. 1). For example, the lipohypertrophy score of those reporting high levels of physical activity was on average 1.6 points lower than those reporting very low levels of physical activity (−1.6, 95% CI: −1.8 to −1.4, $p < .001$).

Table 1. Demographic and Clinical Characteristics of Patients at Initial Assessment Categorized by Body Morphology ($N = 7,931$)

| | | | *Lipohypertrophy* | | | | | *Lipoatrophy* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Neither lipoatrophy nor lipohypertrophy* | | *Mild* | | *Moderate-to-severe* | | | *Mild* | | *Moderate-to-severe* | | |
| | N = *3,156* | | N = *2,607* | | N = *260* | | | N = *1,664* | | N = *244* | | |
| *Characteristic* | N | % | N | % | N | % | p *value** | N | % | N | % | p *value*** |
| Sex | | | | | | | | | | | | |
| Male | 2760 | 87% | 2240 | 86% | 177 | 68% | | 153 | 92% | 207 | 85% | |
| Female | 396 | 13% | 367 | 14% | 83 | 32% | <.001 | 134 | 8% | 37 | 15% | <.001 |
| Race | | | | | | | | | | | | |
| White | 1538 | 49% | 1486 | 57% | 129 | 50% | | 942 | 57% | 135 | 55% | |
| Black | 927 | 29% | 602 | 23% | 70 | 27% | | 353 | 21% | 54 | 22% | |
| Hispanic | 531 | 17% | 397 | 15% | 52 | 20% | | 294 | 18% | 45 | 18% | |
| Other/Unknown | 160 | 5% | 122 | 5% | 9 | 4% | <.001 | 75 | 5% | 10 | 4% | <.001 |
| Age (years) | | | | | | | | | | | | |
| <30 | 447 | 14% | 224 | 9% | 19 | 7% | | 178 | 11% | 18 | 7% | |
| 30–39 | 800 | 25% | 543 | 21% | 44 | 17% | | 342 | 21% | 31 | 13% | |
| 40–49 | 1144 | 36% | 1092 | 42% | 120 | 46% | | 671 | 41% | 97 | 40% | |
| ≥50 | 765 | 24% | 748 | 30% | 77 | 30% | <.001 | 473 | 28% | 98 | 40% | <.001 |
| HIV transmission risk factor | | | | | | | | | | | | |
| MSM | 1994 | 63% | 1652 | 63% | 135 | 52% | | 1114 | 67% | 128 | 52% | |
| IDU | 308 | 10% | 351 | 13% | 37 | 14% | | 225 | 14% | 34 | 14% | |
| MSM & IDU | 69 | 2% | 61 | 2% | 5 | 2% | | 42 | 3% | 5 | 2% | |
| Heterosexual | 705 | 22% | 471 | 18% | 78 | 30% | | 236 | 14% | 61 | 25% | |
| Other/Unknown | 80 | 3% | 72 | 3% | 5 | 2% | <.001 | 47 | 3% | 16 | 7% | <.001 |
| $CD4^+$ cell count nadir (cells/$mm^3$) | | | | | | | | | | | | |
| 0–200 | 1456 | 46% | 1254 | 48% | 142 | 55% | | 790 | 47% | 153 | 63% | |
| 201–350 | 897 | 28% | 712 | 27% | 50 | 19% | | 421 | 25% | 49 | 20% | |
| >350 | 803 | 25% | 641 | 25% | 68 | 26% | .02 | 453 | 27% | 42 | 17% | <.001 |
| $CD4^+$ cell count current (cells/$mm^3$) | | | | | | | | | | | | |
| 0–200 | 427 | 14% | 325 | 12% | 34 | 13% | | 271 | 16% | 84 | 34% | |
| 201–350 | 584 | 19% | 440 | 17% | 46 | 18% | | 294 | 18% | 41 | 17% | |
| >350 | 2145 | 68% | 1842 | 71% | 180 | 69% | .3 | 1099 | 66% | 119 | 49% | <.001 |
| Hepatitis C virus | | | | | | | | | | | | |
| No | 2699 | 86% | 2078 | 80% | 211 | 81% | | 1328 | 80% | 180 | 74% | |
| Yes | 457 | 14% | 529 | 20% | 49 | 19% | <.001 | 336 | 20% | 64 | 26% | <.001 |
| Physical Activity Level | | | | | | | | | | | | |
| Very low | 575 | 18% | 778 | 30% | 111 | 43% | | 466 | 28% | 117 | 48% | |
| Low | 1483 | 47% | 1154 | 44% | 111 | 43% | | 654 | 39% | 79 | 32% | |
| Moderate | 613 | 19% | 435 | 17% | 29 | 11% | | 343 | 21% | 30 | 12% | |
| High | 485 | 15% | 240 | 9% | 9 | 3% | <.001 | 201 | 12% | 18 | 7% | <.001 |
| BMI ($N = 7,830$) | | | | | | | | | | | | |
| <18.5 | 80 | 3% | 13 | <1% | 8 | 3% | | 53 | 3% | 28 | 11% | |
| 18.5–24.9 | 1351 | 43% | 684 | 27% | 33 | 13% | | 810 | 49% | 151 | 62% | |
| 25–29.9 | 1285 | 41% | 1278 | 50% | 81 | 32% | | 624 | 38% | 55 | 23% | |
| ≥30 | 440 | 14% | 563 | 22% | 134 | 52% | <.001 | 149 | 9% | 10 | 4% | <.001 |
| Currently receiving ART | | | | | | | | | | | | |
| Yes | 2339 | 74% | 2144 | 82% | 223 | 86% | | 1341 | 81% | 184 | 75% | |
| No | 817 | 26% | 463 | 18% | 37 | 14% | <.001 | 323 | 19% | 60 | 25% | <.001 |

Individuals with both lipoatrophy and lipohypertrophy are categorized by the more severe body morphology.
*$Chi^2$ of no body morphology versus mild lipohypertrophy versus moderate-to-severe lipohypertrophy.
**$Chi^2$ of no body morphology versus mild lipoatrophy versus moderate-to-severe lipoatrophy.
MSM, men who have sex with men; IDU, injection drug user; BMI body mass index.

In models adjusting for demographic and clinical factors, prior methamphetamine use, prior and current cocaine use, and prior marijuana use were all associated with more severe lipohypertrophy using the continuous scale ($p$ values <.001–.009), while current cigarette smoking was associated with less severe lipohypertrophy ($p$ value .05) (Fig. 1). There was no association with opiate or at-risk alcohol use.

Many of the same factors were associated with binary lipohypertrophy (any vs. none, Table 3, model 1) as an outcome. In addition, black race was significantly associated with being less likely to have lipohypertrophy compared with white race, and current ART use was associated with lipohypertrophy ($p < .001$–0.02). For example, a higher current CD4 cell count was associated with lipohypertrophy (CD4

Table 2. Substance Use at Initial Assessment Categorized by Body Morphology ($N = 7,931$)

| | | | *Lipohypertrophy* | | | | | *Lipoatrophy* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Neither lipoatrophy nor lipohypertrophy* | | *Mild* | | *Moderate-to-severe* | | | *Mild* | | *Moderate-to-severe* | | |
| | N = *3,156* | | N = *2,607* | | N = *260* | | | N = *1,664* | | N = *244* | | |
| *Characteristic* | N | % | N | % | N | % | p-*value** | N | % | N | % | p-*value*** |
| Methamphetamine use | | | | | | | | | | | | |
| None | 2153 | 68% | 1420 | 55% | 159 | 61% | | 869 | 52% | 147 | 60% | |
| Prior | 695 | 22% | 886 | 34% | 87 | 33% | | 523 | 31% | 68 | 28% | |
| Current | 309 | 10% | 301 | 12% | 14 | 5% | <.001 | 272 | 16% | 29 | 12% | <.001 |
| Cocaine use | | | | | | | | | | | | |
| None | 1799 | 57% | 1161 | 45% | 138 | 53% | | 728 | 44% | 118 | 48% | |
| Prior | 1143 | 36% | 1226 | 47% | 106 | 41% | | 780 | 47% | 102 | 42% | |
| Current | 214 | 7% | 220 | 8% | 16 | 6% | <.001 | 156 | 9% | 24 | 10% | <.001 |
| Opiate use | | | | | | | | | | | | |
| None | 2850 | 90% | 2186 | 84% | 218 | 84% | | 1377 | 83% | 203 | 83% | |
| Prior | 244 | 8% | 352 | 14% | 35 | 13% | | 227 | 14% | 30 | 12% | |
| Current | 62 | 2% | 69 | 3% | 7 | 3% | <.001 | 60 | 4% | 11 | 5% | <.001 |
| Marijuana use | | | | | | | | | | | | |
| None | 1296 | 41% | 754 | 29% | 103 | 40% | | 446 | 27% | 88 | 36% | |
| Prior | 1019 | 32% | 1049 | 40% | 96 | 37% | | 553 | 33% | 74 | 30% | |
| Current | 841 | 27% | 804 | 31% | 61 | 23% | <.001 | 665 | 39% | 82 | 34% | <.001 |
| Alcohol use | | | | | | | | | | | | |
| Not at risk | 2630 | 83% | 2152 | 83% | 231 | 89% | | 1370 | 82% | 211 | 86% | |
| At-risk | 526 | 17% | 455 | 17% | 29 | 11% | .03 | 294 | 18% | 33 | 14% | .2 |
| Cigarette smoking | | | | | | | | | | | | |
| None | 1301 | 41% | 895 | 34% | 94 | 36% | | 494 | 30% | 64 | 26% | |
| Prior | 710 | 23% | 753 | 29% | 74 | 28% | | 449 | 27% | 59 | 24% | |
| Current | 1145 | 36% | 959 | 37% | 92 | 36% | <.001 | 721 | 43% | 121 | 50% | <.001 |

*$Chi^2$ of no body morphology versus mild lipohypertrophy versus moderate-to-severe lipohypertrophy.
**$Chi^2$ of no body morphology versus mild lipoatrophy versus moderate-to-severe lipoatrophy.
Patients with both lipoatrophy and lipohypertrophy are categorized by the more severe body morphology.

cell count 201–350, OR 1.2: 95% CI 1.1–1.4, $p = .005$; CD4 cell count >350 OR 1.4: 95% CI 1.2–1.6, $p < .001$ compared to CD4 count ≤200) as was prior marijuana use compared with no use (OR 1.3, 95% CI: 1.2–1.4, $p < .001$). The association with current cocaine use was no longer significant ($p = .1$). Findings were similar in analyses that used a categorical lipohypertrophy outcome (none, mild, and moderate–severe lipohypertrophy Table 3, model 2). Findings were also similar in a model focused specifically on belly fat as the outcome (data not shown) with a similar pattern of findings as those seen with the categorical lipohypertrophy outcome shown in Table 3, model 2, except that the association with current cocaine use did not reach statistical significance.

With regard to lipoatrophy, older age, detectable viral load, and low current CD4 cell counts were associated with more severe lipoatrophy using continuous lipoatrophy scores in adjusted analyses, while African American or black race was associated with less severe lipoatrophy ($p$ values <.001–.008) (Fig. 1). For example, those with a current CD4 cell count of >350 cells/$mm^3$ had an average lipoatrophy score 1 point lower than those with a CD4 count <200 cells/$mm^3$ (−1.0, 95% CI: −1.2 to −0.7, $p < .001$). Compared with PLWH with very low physical activity levels, all other activity levels were associated with less severe lipoatrophy ($p$ values <.001).

In a model adjusting for demographic and clinical factors, current cigarette smoking, marijuana use, and opiate use were all associated with more severe lipoatrophy ($p$ values <.001–.03). In sharp contrast, there was a protective finding for at-risk alcohol use ($p = .001$) (Fig. 1).

The same factors were associated with lipoatrophy as a binary outcome (any vs. none), but in addition, male sex (OR 1.2: 95% CI 1.0–1.3, $p = .03$), current ART (OR 1.3: 95% CI 1.1–1.5, $p < .001$), and methamphetamine use (OR 1.3: 1.1–1.5, $p < .001$) were also significantly associated with lipoatrophy (Table 4, model 1). Findings were also similar in adjusted analyses that used a categorical outcome for lipoatrophy (none, mild, and moderate–severe lipoatrophy, Table 4, model 2).

We conducted sensitivity analyses limited to the 10,442 assessments completed by those known to be ART naive when they enrolled in CNICS. Findings from these sensitivity analyses were similar to those from the entire study cohort (data not shown). Findings from sensitivity analyses that also included calendar year were similar to those main models (data not shown).

## Discussion

In this study of 7,931 PLWH from six clinics from across the United States, we found a high prevalence of body morphology abnormalities: 60% had at least some degree of lipoatrophy or lipohypertrophy. Most abnormalities were mild, with only a small percentage reporting moderate-to-severe

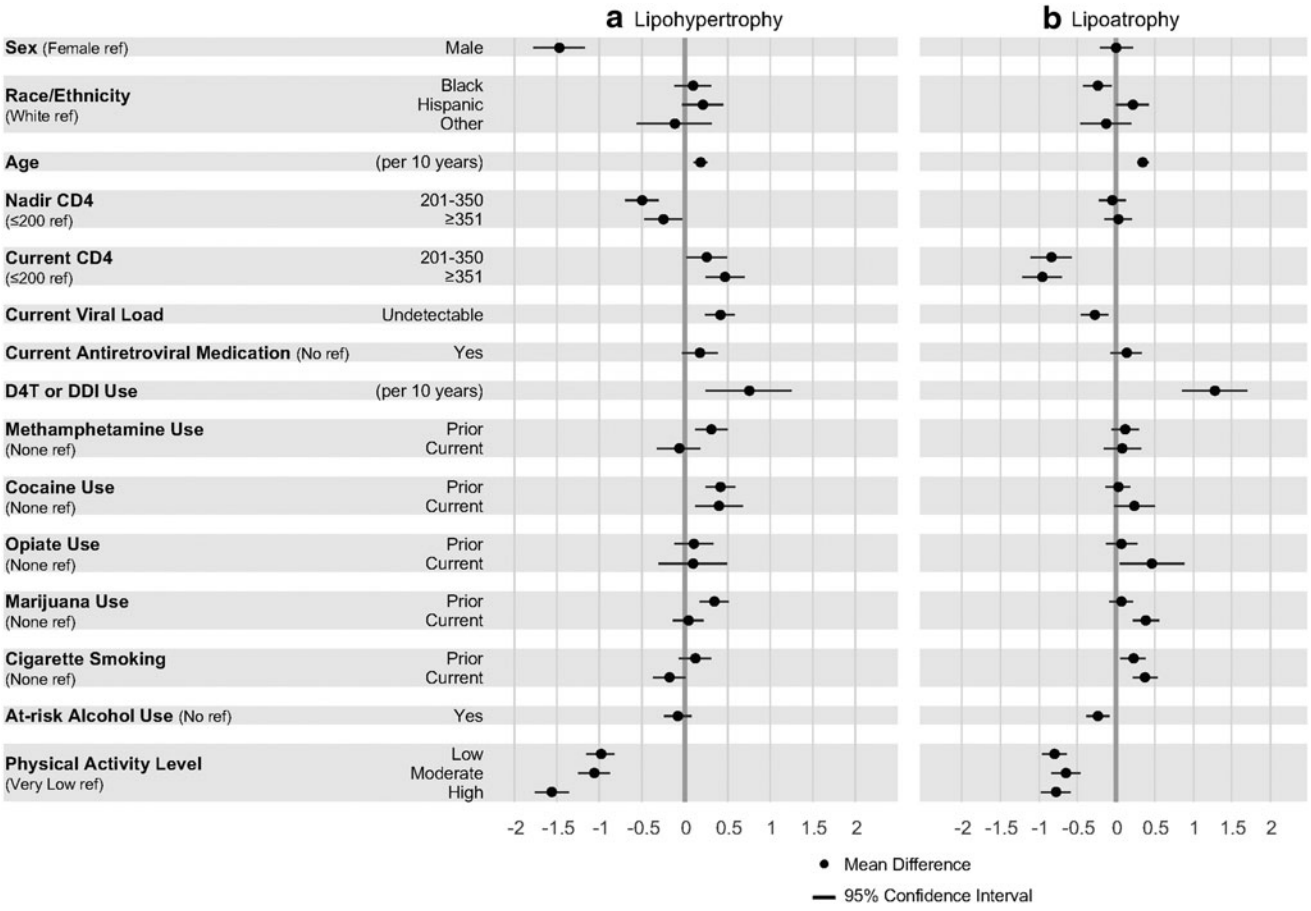


**FIG. 1.** Mean differences in continuous lipohypertrophy **(a)** and lipoatrophy **(b)** scores by demographic, clinical, and behavioral factors in adjusted analyses.

lipohypertrophy (4%) or moderate-to-severe lipoatrophy (3%). Behavioral factors differed in their associations with lipohypertrophy and lipoatrophy, highlighting the importance of considering these two distinct outcomes separately rather than combining them. Prior methamphetamine, cocaine, and marijuana use and current cocaine use were associated with more severe lipohypertrophy, although the impact of each of these individual factors was small. Current opiate and marijuana use, and current and past cigarette smoking were all associated with more severe lipoatrophy in adjusted analyses. Higher physical activity levels were associated with less severe lipohypertrophy and less severe lipoatrophy.

### *Alcohol use*

Alcohol use may increase the risk of lipodystrophy based on a link between alcoholism and the development of abnormal fat growth with mitochondrial replication deficits.[35] This prior study did not find an association between alcohol use and lipodystrophy, although there was a possible association between alcohol use and lipohypertrophy.[35] Other studies have also not found associations between alcohol use and lipodystrophy,[5,6,15,36] although few examined the distinct outcomes of lipohypertrophy and lipoatrophy.[5,6] The best information to date is from FRAM, which did not find associations between alcohol use and lipohypertrophy measured by visceral adipose tissue (VAT) or lipoatrophy measured by leg subcutaneous adipose tissue (SAT).[5,6] While FRAM had a smaller sample size than this study, a FRAM strength was the rigorous approach to body morphology measurement.[5,6]

We found an association between current at-risk alcohol use and a slight decrease in risk of lipoatrophy, and did not find an association between at-risk alcohol use and lipohypertrophy. While the association between alcohol use and lower risk for lipoatrophy is intriguing, this study does not allow conclusions to be drawn regarding the direction of the association. It may be that more severe lipoatrophy and associated factors, including longer duration of HIV infection, may be leading to less alcohol use rather than the reverse. Understanding the potential impacts of alcohol use on body morphology and other outcomes is important given the high prevalence of at-risk alcohol use among PLWH.[30,37,38]

### *Substance use*

General population studies have provided conflicting findings on the associations between body morphology, BMI, or body weight status and specific substances with different findings for past versus current use as well as men versus women.[39–41] Despite this, some substances, such as alcohol, nicotine, and marijuana potentially impact appetite.[42–44]

Table 3. Association Between Demographic, Clinical, and Behavioral Factors and Lipohypertrophy in Adjusted Analyses

| | *Model 1* | *Model 2a* | *Model 2b* |
|---|---|---|---|
| | *Lipohypertrophy binary (none vs. any) OR, 95% CI,* p-*value* | *Lipohypertrophy categorical (none vs. mild) OR, 95% CI,* p-*value* | *Lipohypertrophy categorical (none vs. moderate–severe) OR, 95% CI,* p-*value* |
| Sex | | | |
| Female | Ref | Ref | Ref |
| Male | 0.7; 0.6–0.8, **<.001** | 0.7: 0.7–0.8, **<.001** | 0.3; 0.3–0.4, **<.001** |
| Race | | | |
| White | Ref | Ref | Ref |
| Black | 0.9; 0.8–1.0, **.02** | 0.9; 0.8–1.0, **.004** | 1.2; 0.9–1.5, .3 |
| Hispanic | 1.0; 0.9–1.1, .5 | 0.9; 0.8–1.0, .3 | 1.3; 1.0–1.7, .07 |
| Other | 0.8; 0.6–0.9, **.01** | 0.8; 0.6–1.0, **.02** | 0.9; 0.4–1.7, .7 |
| Age (per year) | 1.01; 1.00–1.01, **<.001** | 1.01; 1.00–1.01, **<.001** | 1.01; 1.00–1.02, .1 |
| $CD4^+$ cell count nadir (cells/$mm^3$) | | | |
| 0–200 | Ref | Ref | Ref |
| 201–350 | 0.8; 0.8–0.9, **.006** | 0.9; 0.8–1.0, **.004** | 0.5; 0.4–0.7, **<.001** |
| 351 or greater | 0.9; 0.8–1.0, **.005** | 0.9; 0.8–1.0, **.01** | 0.8; 0.6–1.0, .07 |
| Current $CD4^+$ cell count (cells/$mm^3$) | | | |
| 0–200 | Ref | Ref | Ref |
| 201–350 | 1.2; 1.1–1.4, **.005** | 1.2; 1.0–1.3, **.03** | 1.3; 0.9–1.8, .1 |
| 351 or greater | 1.4; 1.2–1.6, **<.001** | 1.3; 1.2–1.5, **<.001** | 1.5; 1.1–2.1, **.01** |
| Current viral load | | | |
| Detectable | Ref | Ref | Ref |
| Undetectable | 1.2; 1.1–1.3, **<.001** | 1.2; 1.0–1.3, **.005** | 1.2; 1.0–1.6, .1 |
| Current antiretroviral medications | | | |
| No | Ref | Ref | Ref |
| Yes | 1.2; 1.1–1.4, **.001** | 1.2; 1.0–1.3, **.005** | 1.5; 1.1–2.0, **.01** |
| D4T or DDI use (per year) | 1.03; 1.01–1.05, **.003** | 1.03; 1.01–1.05, **<.001** | 1.06; 1.01–1.11, **.02** |
| Methamphetamine use | | | |
| None | Ref | Ref | Ref |
| Prior | 1.2; 1.1–1.4, **<.001** | 1.2; 1.1–1.4, **<.001** | 1.0; 0.8–1.4, .8 |
| Current | 1.1; 0.9–1.2, .3 | 1.1; 0.9–1.2, .3 | 0.6; 0.4–1.0, **.04** |
| Cocaine use | | | |
| None | Ref | Ref | Ref |
| Prior | 1.2; 1.1–1.3, **<.001** | 1.2; 1.1–1.3, **.002** | 1.7; 1.3–2.3, **<.001** |
| Current | 1.1; 1.0–1.3, .1 | 1.1; 1.0–1.3, .1 | 1.6; 1.0–2.6, **.03** |
| Opiate use | | | |
| None | Ref | Ref | Ref |
| Prior | 1.1; 0.9–1.2, .4 | 1.1; 0.9–1.2, .4 | 1.1; 0.8–1.5, .5 |
| Current | 1.0; 0.8–1.3, .8 | 1.0; 0.8–1.3, .8 | 1.2; 0.6–2.4, .7 |
| Marijuana use | | | |
| None | Ref | Ref | Ref |
| Prior | 1.3; 1.2–1.4, **<.001** | 1.3; 1.2–1.4, **<.001** | 1.2; 0.9–1.5, .2 |
| Current | 1.1; 1.0–1.2, .09 | 1.1; 1.0–1.2, **.03** | 0.8; 0.6–1.1, .2 |
| Cigarette smoking | | | |
| Never | Ref | Ref | Ref |
| Prior | 1.1; 1.0–1.3, .09 | 1.2; 1.0–1.3, **.005** | 1.0; 0.8–1.3, .8 |
| Current | 0.9; 0.8–1.0, **.05** | 0.9; 0.8–1.0, .08 | 0.8; 0.6–1.1, .2 |
| Alcohol use | | | |
| Not at-risk | Ref | Ref | Ref |
| At-risk | 1.1; 1.0–1.2, .2 | 1.1; 1.0–1.2, .3 | 0.7; 0.5–0.9, **.02** |
| Physical activity level | | | |
| Very low | Ref | Ref | Ref |
| Low | 0.6; 0.6–0.7, **<.001** | 0.7; 0.6–0.7, **<.001** | 0.4; 0.3–0.4, **<.001** |
| Moderate | 0.6; 0.6–0.7, **<.001** | 0.6; 0.6–0.7, **<.001** | 0.3; 0.2–0.4, **<.001** |
| High | 0.4; 0.4–0.5, **<.001** | 0.4; 0.4–0.5, **<.001** | 0.1; 0.1–0.2, **<.001** |

Also adjusted for site, HCV status, and lipoatrophy.
All associations presented are adjusted Odds Ratios.
*p* values $< 0.05$ are *bolded*.

Table 4. Association Between Demographic, Clinical, and Behavioral Factors and Lipoatrophy in Adjusted Analyses

| | *Model 1* | *Model 2a* | *Model 2b* |
|---|---|---|---|
| | *Lipoatrophy binary (none vs. any) OR, 95% CI,* p-*value* | *Lipoatrophy categorical (none vs. mild) OR, 95% CI,* p-*value* | *Lipoatrophy categorical (none vs. moderate–severe) OR, 95% CI,* p-*value* |
| Sex | | | |
| Female | Ref | Ref | Ref |
| Male | 1.2; 1.0–1.3, **.03** | 1.2; 1.0–1.3, **.04** | 0.8 0.6–1.2, .3 |
| Race | | | |
| White | Ref | Ref | Ref |
| Black | 0.8; 0.7–0.9, **<.001** | 0.8; 0.7–0.9, **<.001** | 0.7; 0.6–1.0, **.04** |
| Hispanic | 1.0; 0.9–1.2, .4 | 1.0; 0.9–1.2, .5 | 1.2; 0.9–1.5, .3 |
| Other | 0.7 0.6–0.9, **.008** | 0.7; 0.6–0.9, **.008** | 0.9; 0.5–1.6, .8 |
| Age (per year) | 1.02; 1.02–1.03**, <.001** | 1.02; 1.02–1.02**, <.001** | 1.04; 1.03–1.05**, <.001** |
| $CD4^+$ cell count nadir (cells/$mm^3$) | | | |
| 0–200 | Ref | Ref | Ref |
| 201–350 | 1.0; 0.9–1.1, .7 | 1.0; 0.9–1.1, .6 | 0.9; 0.7–1.2, .5 |
| 351 or greater | 1.1; 1.0–1.2, .1 | 1.1; 1.0–1.3, .06 | 0.9; 1.6–1.2, .4 |
| Current $CD4^+$ cell count (cells/$mm^3$) | | | |
| 0–200 | Ref | Ref | Ref |
| 201–350 | 0.8; 0.7–0.9, **.001** | 0.9; 0.8–1.0, **.03** | 0.5; 0.4–0.7, **<.001** |
| 351 or greater | 0.8; 0.7–0.9, **<.001** | 0.9; 0.8–1.0, **.03** | 0.4; 0.3–0.6, **<.001** |
| Current viral load | | | |
| Detectable | Ref | Ref | Ref |
| Undetectable | 0.8; 0.7–0.9, **<.001** | 0.8; 0.7–0.9, **.001** | 0.7; 0.5–0.9, **.005** |
| Current antiretroviral medications | | | |
| No | Ref | Ref | Ref |
| Yes | 1.3; 1.1–1.5, **<.001** | 1.3; 1.2–1.5, **<.001** | 1.1; 0.8–1.5, .5 |
| D4T or DDI use (per year) | 1.1; 1.0–1.1, **<.001** | 1.1; 1.0–1.1, **<.001** | 1.1; 1.0–1.1, **<.001** |
| Methamphetamine use | | | |
| None | Ref | Ref | Ref |
| Prior | 1.1; 0.9–1.2, .4 | 1.1; 0.9–1.2, .4 | 1.0; 0.7–1.3, 1.0 |
| Current | 1.3; 1.1–1.5, **<.001** | 1.4; 1.2–1.6, **<.001** | 0.8; 0.5–1.1, .2 |
| Cocaine use | | | |
| None | Ref | Ref | Ref |
| Prior | 1.0; 0.9–1.1, .9 | 1.0; 0.9–1.1, .8 | 1.0; 0.7–1.3, 1.0 |
| Current | 1.1; 0.9–1.2, .6 | 1.0; 0.9–1.2, .6 | 1.4; 1.0–2.2, .08 |
| Opiate use | | | |
| None | Ref | Ref | Ref |
| Prior | 1.1; 1.0–1.2, .2 | 1.1; 0.9–1.2, .2 | 1.3; 1.0–1.8, .09 |
| Current | 1.3; 1.0–1.7, **.02** | 1.2; 1.0–1.7, **.04** | 2.0; 1.2–3.3, **.009** |
| Marijuana use | | | |
| None | Ref | Ref | Ref |
| Prior | 1.1; 1.0–1.3, **.03** | 1.1; 1.0–1.3, **.01** | 1.0; 0.7–1.3, .8 |
| Current | 1.6; 1.4–1.8, **<.001** | 1.6; 1.4–1.8, **<.001** | 1.6; 1.2–2.1, **.001** |
| Cigarette smoking | | | |
| Never | Ref | Ref | Ref |
| Prior | 1.2; 1.0–1.3, **.01** | 1.1; 1.0–1.3, **.04** | 1.5; 1.1–2.0, **.008** |
| Current | 1.2; 1.1–1.4, **<.001** | 1.2; 1.1–1.3, **<.001** | 1.6; 1.2–2.0, **.001** |
| Alcohol use | | | |
| Not at risk | Ref | Ref | Ref |
| At-risk | 0.9; 0.8–0.9, **.002** | 0.8; 0.7–0.9, **<.001** | 0.7; 0.5–1.0, **.05** |
| Physical activity level | | | |
| Very low | Ref | Ref | Ref |
| Low | 0.7; 0.7–0.8, **<.001** | 0.8; 0.7–0.8, **<.001** | 0.3; 0.3–0.4, **<.001** |
| Moderate | 0.9; 0.8–1.0, **.02** | 0.9; 0.8–1.0, .2 | 0.4; 0.3–0.5, **<.001** |
| High | 0.8; 0.7–1.0, **.01** | 0.9; 0.8–1.1, .2 | 0.3; 0.2–0.4, **<.001** |

Also adjusted for site, HCV status, and lipohypertrophy.
All associations presented are adjusted Odds Ratios.
*p* values $< 0.05$ are *bolded.*

In HIV-infected populations, one prior study suggested substance use was not a predictor of regional fat distribution;[36] however, this study was limited to Hispanic individuals and only examined current substance use, not past use. The authors did not distinguish between current and past use and did not evaluate individual drugs. Similarly, the FRAM study did not find associations between substance use and SAT or VAT.[5,6]

We found that prior methamphetamine and cocaine use were associated with lipohypertrophy, while current use of drugs such as marijuana and illicit opiates/heroin was associated with lipoatrophy. While associations between body morphology and individual drugs were small, it is notable that these associations are in the setting of adjusting for other illicit drugs as well as alcohol, smoking, and physical activity levels. We found key differences between associations of individual drugs with either lipohypertrophy or lipoatrophy. Our results reinforce the importance of examining the impact of drug use separately for each outcome.

### *Smoking*

There are limited studies examining associations between smoking and lipohypertrophy and lipoatrophy. One small study did not find an association between smoking and lipodystrophy.[15] The FRAM study found an association between being a current smoker and less lipohypertrophy as measured by VAT, but did not find an association between being a current smoker and lipoatrophy as measured by SAT.[5,6] Another small study among Hispanic patients[36] found current smokers had less truncal fat consistent with our findings that current smoking was associated with less severe lipohypertrophy. The prior study of Hispanic patients also found that among males, current smokers had more appendicular fat.[36] In contrast, we found that in analyses that also took into account substance and alcohol use, the current and past smoking were both associated with more severe lipoatrophy.

### *Physical activity*

Prior studies often focused on lipodystrophy rather than lipohypertrophy and lipoatrophy. They found associations between physical activity level and lipodystrophy,[15,45] but were small studies unable to look at the simultaneous impact of physical activity and other behavioral factors.[45] An early trial of patients on indinavir, lamivudine, and either stavudine or zidovudine found that the absence of physical activity was associated with developing lipoatrophy, but not lipohypertrophy.[46] Other studies found a relationship between physical activity and lack of central fat accumulation[47] and moderate physical activity and waist circumference.[48] The FRAM study found an association between physical activity quartile and less SAT and VAT among men, and a suggestion of an association between physical activity and SAT, but not VAT among women.[5,6]

Our findings demonstrated associations between higher physical activity levels and both decreased lipohypertrophy and lipoatrophy across the spectrum of physical activity levels even when adjusting for other key behavioral factors that are often associated with physical activity levels. These findings suggest a possible protective association for higher levels of physical activity.

### *Measurement or scoring of lipohypertrophy and lipoatrophy*

Self-reported body morphology abnormalities have been scored in several ways, including as binary, categorical, and continuous outcomes.[49–53] Few comparisons have been made between approaches. Categorizing or dichotomizing outcomes can be advantageous for improving interpretability and ease of describing results. However, loss of information and loss of power have been described for dichotomizing or categorizing continuous data.[54]

We found differences using three scoring approaches, for example, current cocaine use was associated with lipohypertrophy when using the continuous and categorical approaches, but not binary, and the association between current ART use and lipohypertrophy was significant only with categorical and binary scoring, although the size of the association was also similar and suggestive to using continuous scoring. While differences existed, the pattern of findings was consistent for most associations across the three approaches. Furthermore, given the small differences in associations between scoring approaches, but the large differences in the associations between lipohypertrophy versus lipoatrophy, these findings suggest that differences in scoring approaches for lipohypertrophy and lipoatrophy have an impact, but that it is much smaller than the misclassification, loss of information, and potential erroneous conclusions that can be made by combining lipohypertrophy and lipoatrophy into one outcome.

### *Strengths*

A study strength was the assessment of individual illicit drug use, including current and past use in adjusted models that simultaneously consider other drugs, alcohol use, cigarette use, and physical activity levels. Drug use is often associated with other harmful behaviors such as smoking and alcohol use. The large sample size and comprehensive clinical data available, including information from the CNICS clinical assessment, facilitated examining the associations of these behaviors simultaneously. Use of the FRAM body morphology measure was an additional strength allowing us to examine both independent effects of lipohypertrophy and lipoatrophy as well as differences by the severity of body morphology abnormality. An advantage of FRAM assessments over DEXA scans or single-cut CT scans is that FRAM allows facial lipoatrophy changes to be included.

### *Limitations*

A limitation of this study is the relevance of body morphology abnormalities, particularly lipoatrophy in the current ART era. However, while key risk factors such as stavudine are rarely, if ever, used in care currently, many PLWH have now been alive and in care for many years. The percentage reporting lipoatrophy (mild or moderate-to-severe) in care in CNICS in 2015 (22%) was similar to the percentage in the study overall as shown in the results section (23%), suggesting that understanding these associations and mechanisms is still relevant in the current treatment era. Our study design precluded us from drawing conclusions regarding causality. We suspect that lower physical activity levels lead to increased risk of body morphology abnormalities; however, longitudinal studies are needed to elucidate these

relationships. Associations with lipohypertrophy can be complicated by misclassification and overlap with obesity. We do not address whether associations are due to direct effects of illicit drugs versus indirect effects, such as by changes in appetite. We focused on current alcohol use; all nondrinkers were a single group, including people who were never at-risk alcohol drinkers and people with prior at-risk alcohol use who became nondrinkers.[55,56] Additional studies are needed that parse these nuances before the potential impact of alcohol use on body morphology among PLWH can be well understood. An additional limitation is the potential for Type 1 errors when evaluating multiple covariates with two outcomes each of which has three parameterizations. Patterns of association that are similar across the three parameterizations provide some reassurance that those associations are less likely due to Type 1 errors. Finally, while the self-reported morphology assessment included in this study allowed inclusion of facial changes, MRI-based depot measures provide slightly different results.[5,6] Self-reported morphology results are closer to the perceived clinical syndrome. However, the differences between these results may shed light on how drug use affects perception as well as adipose tissue.

## Conclusions

We found a high prevalence of lipohypertrophy and lipoatrophy among this nationally distributed clinical cohort of PLWH, although most of these abnormalities were mild. Behavioral factors differed in their associations with lipohypertrophy and lipoatrophy. Prior methamphetamine, cocaine, and marijuana use and current cocaine use were associated with more severe lipohypertrophy. Current opiate and marijuana use, and current and past smoking were all associated with more severe lipoatrophy. While low levels of physical activity are associated with both lipohypertrophy and lipoatrophy, associations with substance use and other clinical characteristics differed between lipohypertrophy and lipoatrophy. These results support the conclusion that lipohypertrophy and lipoatrophy are distinct and should be examined separately rather than combined. These results also highlight the importance of examining the impact of drug use by an individual class of drug. These results may prove useful in counseling patients who wish to avoid body morphology changes and further our understanding of associations with these conditions and their possible mechanisms.

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## Author Disclosure Statement

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