Cardiovascular Toxicity of Illicit Anabolic-Androgenic Steroid Use

BACKGROUND: Millions of individuals have used illicit anabolic-androgenic steroids (AAS), but the long-term cardiovascular associations of these drugs remain incompletely understood.

METHODS: Using a cross-sectional cohort design, we recruited 140 experienced male weightlifters 34 to 54 years of age, comprising 86 men reporting ≥2 years of cumulative lifetime AAS use and 54 nonusing men. Using transthoracic echocardiography and coronary computed tomography angiography, we assessed 3 primary outcome measures: left ventricular (LV) systolic function (left ventricular ejection fraction), LV diastolic function (early relaxation velocity), and coronary atherosclerosis (coronary artery plaque volume).

RESULTS: Compared with nonusers, AAS users demonstrated relatively reduced LV systolic function (mean±SD left ventricular ejection fraction = 52±11% versus 63±8%; $P<0.001$) and diastolic function (early relaxation velocity = 9.3±2.4 cm/second versus 11.1±2.0 cm/second; $P<0.001$). Users currently taking AAS at the time of evaluation (N=58) showed significantly reduced LV systolic (left ventricular ejection fraction = 49±10% versus 58±10%; $P<0.001$) and diastolic function (early relaxation velocity = 8.9±2.4 cm/second versus 10.1±2.4 cm/second; $P=0.035$) compared with users currently off-drug (N=28). In addition, AAS users demonstrated higher coronary artery plaque volume than nonusers (median [interquartile range] 3 [0, 174] mL^3 versus 0 [0, 69] mL^3; $P=0.012$). Lifetime AAS dose was strongly associated with coronary atherosclerotic burden (increase [95% confidence interval] in rank of plaque volume for each 10-year increase in cumulative duration of AAS use: 0.60 SD units [0.16–1.03 SD units]; $P=0.008$).

CONCLUSIONS: Long-term AAS use appears to be associated with myocardial dysfunction and accelerated coronary atherosclerosis. These forms of AAS-associated adverse cardiovascular phenotypes may represent a previously underrecognized public-health problem.

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Clinical Perspective

What Is New?

- Millions of individuals have used anabolic-androgenic steroids (AAS) to gain muscle for athletic purposes or personal appearance.
- Preliminary findings have suggested that long-term AAS exposure may lead to both cardiomyopathy and atherosclerotic disease, but previous studies have been small or methodologically limited.
- Here, in the first large controlled study of its type, we demonstrate that long-term AAS use is associated with both systolic and diastolic myocardial dysfunction, as well as coronary atherosclerosis.
- Systolic functional deficits appear to recover after AAS discontinuation, whereas diastolic dysfunction appears less reversible.
- Atherosclerotic disease appears strongly associated with lifetime duration of AAS exposure.

What Are the Clinical Implications?

- Widespread illicit AAS use first appeared in the general population in the 1980s, and thus most AAS users are still young or middle-aged today.
- Thus, when clinicians encounter young or middle-age men who exhibit evidence of unexplained left ventricular dysfunction or premature coronary artery disease, the possibility of cardiotoxicity because of long-term AAS use should be considered in the differential diagnosis.
- It is notable that ≈80% of contemporary AAS users are simply recreational weightlifters rather than competitive athletes, and thus the possibility of AAS use should be considered even in individuals who do not identify themselves as athletes.

An estimated 2.9 to 4.0 million Americans have used supraphysiologic doses of illicit anabolic-androgenic steroids (AAS), including testosterone and its synthetic relatives, to gain muscle mass for athletics or personal appearance.[1] About 1 million of these individuals, almost all of whom are male, have developed AAS dependence, often leading to years of chronic AAS exposure.[2] Illicit AAS use did not become widespread in the general US population until the 1980s.[3] Thus, the oldest AAS users, who initiated AAS as youths in the 1980s, are only now reaching middle age, when the adverse effects of long-term use may become apparent. Therefore, these effects remain incompletely understood.

Previous studies have suggested an association between AAS use and cardiovascular disease, with a pathophysiologic link first proposed by early case reports of sudden cardiac death or ischemic stroke among young AAS-using men.[4–6] Subsequently, preclinical studies have shown that AAS exposure at supraphysiologic doses causes dyslipidemia,[7–9] stimulates cardiomyocyte hypertrophy,[10,11] impairs coronary arterial function,[12,13] reduces cardiac β-adrenoreceptor sensitivity,[14] potentiates oxidative cardiac stress,[15] lowers arrhythmic thresholds,[16] and induces myocyte apoptosis.[17] Most recently, investigations utilizing noninvasive cardiac imaging in human users have demonstrated preliminary evidence of AAS cardiotoxicity in the forms of myocardial dysfunction,[18–22] myocardial fibrosis,[23] and increased coronary artery calcification.[24]

In aggregate, data from these earlier studies suggest that illicit AAS use may cause a form of cardiomyopathy characterized by decreased left ventricular (LV) function[18,19,21–23,25,26] and may increase the risk of atherosclerotic disease.[1,7,8,24] To date, definitive associations between AAS exposure and either myocardial or coronary artery disease have yet to be demonstrated in a large human study. To address this issue, we conducted comprehensive cardiovascular evaluations of 86 long-term AAS users and 54 nonusers.

METHODS

Study Design

We conducted an observational study using a cross-sectional cohort design. We have previously presented the formal properties of this design,[27] which has been used both explicitly[28–31] and implicitly[32,33] in many earlier studies. This method identifies a dynamic cohort of individuals drawn from a given source population who in principle could have been enumerated in the past and followed to the present (termed the conceptual cohort). Instead of sampling from the conceptual cohort, one samples in the present from those currently available (the study cohort). With this design, estimates of effects derived from the study cohort are valid with respect to the conceptual cohort, subject to similar conditions for validity as other retrospective designs (eg, retrospective cohort and case-control studies).[27] We chose the cross-sectional cohort design because it can efficiently assess the association of outcomes with an uncommon exposure (eg, AAS use) in the same manner that a case-control design can efficiently assess the association of exposures with an uncommon outcome.

For the present study, we sampled from a source population of men who lift weights in gymnasiums and then compared exposed (ie, AAS-using) and nonexposed (ie, non-AAS-using) men from this group. We chose this source population because almost all long-term AAS users are male[2] and lift weights regularly.[1,34] We did not recruit from sporting venues because most AAS users are not competitive athletes but simply recreational weightlifters.[1,35,36]

Although this approach minimized the effects of confounding variables inherent to weightlifting, we considered that weightlifting or its associated lifestyle might be associated with specific cardiovascular characteristics. Therefore, in an ancillary study, we recruited a group of nonweightlifting and non-AAS-using men (frequency-matched in age to the weightlifters but never weightlifting >30 minutes per week at any time since 18 years of age), drawn from a roster of potential study volunteers maintained by Massachusetts General Hospital,

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and compared these nonweightlifters to the subgroup of non-AAS-using weightlifters from the primary study. These 2 groups (AAS nonusers and nonweightlifting and non-AAS-using men) exhibited no scientifically important or statistically significant differences on measures of cardiovascular physiology or pathology (Tables I–III in the online-only Data Supplement), indicating that weightlifting per se, of the duration and intensity selected by our recruitment techniques, was associated with little or no cardiovascular adaptation or pathology.

Participants

As described in our previous cross-sectional cohort studies involving AAS,[28,29] we advertised in gymnasiums for men 34 to 54 years of age who could bench-press 275 pounds for at least one repetition, currently or in the past to recruit AAS users and nonusers. On telephone screening, advertisement respondents were invited to participate without inquiring about AAS use to minimize selection bias that might arise if they knew in advance the exposure variable of interest. It is notable that AAS are typically ingested in courses or cycles, with deliberate intervening off-drug intervals.[1] Thus, our design anticipated that the AAS-using weightlifters would include 2 subgroups: those on-drug and those off-drug at the time of evaluation. We excluded AAS users reporting <2 years of cumulative lifetime AAS exposure. We imposed no specific exclusions for medical or psychiatric history.

Evaluation

Qualifying participants were evaluated at a screening interview, where they provided written informed consent for the study as approved by the McLean Hospital Institutional Review Board. We then obtained demographic data, lifetime exercise history (ie, exercise modalities, duration, intensity, and consistency), and fat-free mass index, a validated measure of muscularity.[29,37,38] Psychiatric and substance-use histories were obtained using the Structured Clinical Interview for *DSM–IV*.[39] We next assessed history of AAS use, including age at onset of use, maximum weekly dose of AAS (calculated as mg of testosterone equivalent),[40] cumulative lifetime years of use, lifetime dose ingested, time of most recent use, and types and doses of AAS taken during most recent (or current) use. We also assessed use of other performance-enhancing substances, including over-the-counter substances (eg, creatine) and illicit drugs (eg, human growth hormone, clenbuterol). Participants then provided urine samples to be tested for AAS[29,38] and head or axillary hair to be tested for opiates, cannabis, phencyclidine, amphetamines, and cocaine.[29,38] Men showing urine or hair findings inconsistent with their reported substance-use history were excluded from further evaluation. We also excluded men denying AAS use but exhibiting a fat-free mass index >26 kg/m^2 together with body fat <10% based on previous work showing that a combination of leanness and muscularity beyond these limits strongly suggests surreptitious AAS use.[37,41]

Men found to qualify after the screening interviews were then referred for a cardiovascular evaluation performed by investigators blinded to AAS status to characterize LV structure, LV function, and coronary atherosclerosis. Two-dimensional transthoracic echocardiography (iE33, Philips Medical Systems) was used to develop profiles of LV structure and function as previously detailed by our group.[42] The primary outcome variables for LV systolic and diastolic function were left ventricular ejection fraction (LVEF) as measured using the modified biplane method of disks[43] and early LV relaxation velocity (E´; average of basal septum and lateral wall values[44]), respectively. Second, coronary computerized tomography angiography (CTA) was performed using a dual-source 128-slice CT scanner (Definition Flash, Siemens Medical Systems), with a primary outcome variable of total coronary artery plaque volume.[45] Secondary CTA measures included number of atherosclerotic coronary segments, degree of stenosis of the worst segment, and Agatston calcium score.[46] Detailed echocardiographic and CTA methods are provided in the online-only Data Supplement.

Statistical Analysis

Based on our pilot data[18] and those of others,[1,24] our primary hypotheses were that AAS users would exhibit: (1) decreased LVEF, (2) decreased E´, and (3) increased coronary plaque volume compared with non-AAS-using weightlifters. We further hypothesized that within the AAS-user group, greater pathology on these variables would be associated with currency of AAS use (ie, on-drug versus off-drug status at the time of evaluation) and with cumulative lifetime duration of AAS exposure.

Using linear regression, we estimated the mean difference between groups on the outcome measures (technically, the estimated mean difference was the estimated beta coefficient corresponding to group status in a linear model that also included a set of covariates and was fitted using ordinary least-squares linear regression). To control for confounding, our primary analysis adjusted for a set of plausible confounding variables including: age; race/ethnicity (modeled as black versus all others); history of tobacco use, cocaine dependence, and alcohol dependence; weekly hours of aerobic activity in the last 10 years (modeled in tertiles of the distribution); and reported family history of coronary artery disease as defined by the presence of angina, myocardial infarction, angioplasty/stent, or coronary bypass surgery in a first-degree relative. For echocardiographic measures, we additionally adjusted for body surface area as calculated by the Mosteller formula. To explore the relationship between LV mass, a potentially important mechanistic mediator of LV functional impairment, and our primary functional outcome variables, we performed post hoc analyses examining the association of LV mass index with LVEF and E´ among AAS users and nonusers. Specifically, we used linear regression with the same set of potential confounding variables and the addition of a term for AAS-user versus nonuser group status to examine the relationships between LV mass index (LV mass in g/body surface area in m^2) and the primary cardiac function outcomes. Also, because resting heart rate could influence cardiac functional outcomes, we performed additional analyses of the primary cardiac functional outcomes by adding resting heart rate as a covariate. Note that heart rate may influence functional outcomes and also might be affected by current AAS use. In the latter eventuality, the estimated mean difference between groups adjusted for resting heart rate would likely be biased toward the null (ie, would potentially represent an overadjustment), thus producing an underestimate of the effect of AAS use.

In subsequent sensitivity analyses assessing the influence of adjustments using alternative sets of potential confounders,

we repeated all comparisons (1) with no adjustment for any covariates, (2) with the adjustment covariates reduced to only age and race (plus body surface area for echocardiographic measures), and (3) with the adjustment covariates augmented to include hypertension and dyslipidemia (as defined in Tables X–X in the online-only Data Supplement). It is important to note that the augmented set of covariates would be expected to yield underestimates of the effect of AAS use because hypertension and dyslipidemia are often effects of AAS use,[1,7,9,47] and adjustment for these variables would consequently adjust out effects of AAS mediated by these variables.

Because the distributions of coronary CTA measures contained many zero values (ie, no measurable coronary artery disease), we used ranked data for these analyses. Within the AAS-user group, we evaluated the association of all outcome measures with duration of use and currency of use (ie, on-drug versus off-drug) using linear regression with adjustment for the same set of covariates. To aid in interpretation of comparisons between groups and associations within groups involving rank-transformed data, we used standard deviation (SD) units to express the estimated difference in ranks for binary predictor variables and the estimated change in ranks for each 1-unit increase in continuous predictor variables. The SD units were calculated by dividing the estimated beta coefficient for the predictor variable from the linear regression model by the SD of the ranks for the entire sample used for a given model.

All models were fitted using Stata 14.1 software (StataCorp). We set α=0.05, 2-tailed. We did not perform corrections for multiple comparisons, so that the statistical significance of *P*-values for secondary outcomes, particularly those between 0.01 and 0.05, should be interpreted with caution.

RESULTS

Participants

Sample

We screened 165 men, of whom 25 were excluded from medical evaluation as follows: 10 qualified for participation but withdrew before medical evaluation (9 AAS users, 1 nonuser), 12 reported AAS use of <2 years duration, and 3 showed findings on drug testing or fat-free mass index inconsistent with their self-reports. The remaining sample comprised 86 AAS users and 54 nonusers. Among the AAS users, 58 (67%) were on-drug and 28 (33%) off-drug at evaluation. The off-drug users had last used AAS a median (interquartile range) of 15 (5, 70) months before evaluation.

Characteristics

AAS users and nonusers were similar on most characteristics (Table 1), but users showed higher body mass index and fat-free mass index, consistent with known effects of AAS.

Cardiometabolic Features

Compared with nonusers, AAS users displayed higher blood pressure (mean±SD systolic, 118±11 versus 115±10 mm Hg; diastolic, 76±9 versus 72±9 mm Hg) and a higher prevalence of dyslipidemia (N [%] with low-density lipoprotein cholesterol >160 mg/dL: 20 [23%] versus 7 [13%]).

Cardiac Structure and Function

For the primary outcome variables of LVEF and E´, AAS users showed significant deficits compared with nonusers (Table 2). In models further adjusted for resting heart rate, the estimated mean differences between groups were reduced by 15%, and this change had no impact on the statistical significance of these findings (*P*<0.001 for both). On other measures, AAS users exhibited higher LV mass index, thicker LV walls, and more concentric LV geometry than nonusers. On subsequent analyses examining the association of outcomes with duration and currency of AAS use, currency of use was strongly associated with greater pathology (Figure 1 and Table IV in the online-only Data Supplement). Specifically, 41 (71%) of the 58 on-drug users showed LVEFs falling below the normal threshold of 52%,[43] whereas off-drug users showed largely normal LVEFs. Twenty-nine (50%) on-drug users fell below the normal E´ threshold of 8.5 cm/second,[44] with off-drug users showing only partially normalized E´. Similar associations with currency of AAS use were found across other echocardiographic measures (Table IV in the online-only Data Supplement). In contrast, we found no significant associations between duration of AAS use and the primary outcome variables (for each additional 10 years of AAS exposure, the estimated mean change [95% confidence interval] in LVEF was −3.3% [−8.3 to 1.6], *P*=0.19; and the estimated mean change in E´ was 0.1 cm/second [−1.0 to 1.2 cm/second], *P*=0.90).

Because LVEF and E´ differed by group (ie, AAS user versus nonuser) and by subgroup based on currency of use (ie, current versus past AAS users), we further tested for interactions of group and subgroup status with LV mass index for each of these associations and found evidence for a significant interaction with AAS user group status (*P*=0.046 and *P*=0.016 for LVEF and E´, respectively) but not for currency of use among AAS users (*P*=0.21 and *P*=0.86, respectively). Therefore, we assessed the associations separately for AAS users and nonusers. Examining LVEF, among AAS users, a significant association occurred between increased LV mass index and decreased LVEF (estimated mean change [95% confidence interval] in LVEF for each 10 g increase in LV mass index −1.6% [−2.4 to −0.8], *P*<0.001). In contrast, among the nonusers, no significant association occurred between LV mass index and LVEF (estimated mean change in LVEF for each 10 g increase in LV mass index −0.2% [−1.5 to 1.2], *P*=0.80). Examining E´, among AAS users, a significant association occurred between increased LV mass index and reduced E´ (estimated mean change in E´ for each 10 g increase in LV mass index −0.31 cm/second [−0.49 to −0.13 cm/second], *P*<0.001). Among nonusers, the

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Table 1. Characteristics of Anabolic-Androgenic Steroid Users and Nonusers*

Characteristics	Users (N=86)	Nonusers (N=54)	*P* Value
Demographic features			
Age, y	42 (39–47)	43 (38–49)	0.79
Race†			
White	80 (93)	41 (76)	
Black	6 (7)	12 (22)	0.006
Asian	0	1 (2)	
Ethnic background†			
Not Hispanic	76 (89)	52 (96)	0.13
Hispanic	10 (11)	2 (4)	
Anthropomorphic measures			
Height, m	1.8 (1.7–1.8)	1.8 (1.7–1.8)	0.16
Body surface area, m^2‡	2.2 (2.1–2.3)	2.2 (2.0–2.3)	0.19
Body mass index§	31 (29–33)	29 (27–31)	<0.001
Fat-free mass index¶	26 (24–28)	23 (21–25)	<0.001
Exercise measures			
Age at onset of regular weightlifting, y	16 (14–20)	16 (15–20)	0.97
Lifetime duration of regular weightlifting, y	21 (15–26)	20 (12–28)	0.78
Time spent in aerobic exercise per week‖			
0–30 min	30 (35)	19 (35)	
31–120 min	24 (28)	22 (41)	0.18
>120 min	32 (37)	13 (24)	
Other potential cardiovascular risk factors			
Family history of coronary artery disease**	25 (29)	12 (22)	0.37
Lifetime history of substance use			
Regular cigarette smoking††	27 (31)	19 (35)	0.64
Alcohol dependence‡‡	12 (14)	7 (13)	0.87
Cocaine dependence‡‡	13 (15)	5 (9)	0.31
AAS use			
Age at onset of AAS use, y	23 (19–30)	—	
Cumulative lifetime total duration of AAS use, y	7.4 (4.0–11.6)	—	
Cumulative lifetime dose of AAS, g	366 (166–608)	—	

AAS indicates anabolic-androgenic steroids.

*Data are reported as median (interquartile range) or n (%) as appropriate. *P* values were obtained from a Wilcoxon rank-sum test or Fisher exact test.

†Race and ethnic background were self-reported.

‡By Mosteller formula.

§The body mass index is the weight in kilograms divided by the square of the height in meters.

¶The fat-free mass index is calculated as $(W(1–BF)/H^2) + 6.1(1.8–H)$, where W=weight in kg, H=height in m, and BF=percent body fat.[37]

‖Any self-reported aerobic exercise beyond ordinary daily activities.

**At least 1 first-degree relative reported to have had coronary artery disease, angina, heart attack, angioplasty/stent, or coronary artery bypass surgery.

††Any cigarette smoking beyond brief experimentation.

‡‡By the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*.[39]

Table 2. Echocardiographic Findings in Anabolic-Androgenic Steroid Users and Nonusers*

Variable	Users (N=86)	Nonusers (N=54)	Comparison: Estimated Difference (95% Confidence Interval)†	Comparison: *P* Value
Primary outcomes				
Left ventricular ejection fraction, %	52±11	63±8	−10 (−14 to −7)	<0.001
Average early left ventricular E´, cm/s	9.3±2.4	11.1±2.0	−1.9 (−2.7 to −1.0)	<0.001
Secondary outcomes				
Resting heart rate, beats/min	65±5	62±6	2.7 (0.7 to 4.7)	0.008
Left atrial diameter, cm‡	3.6±0.5	3.5±0.5	0.1 (−0.1 to 0.2)	0.42
Longitudinal 4-chamber strain§	−16±4	-20±3	4.6 (3.2–6.0)	<0.001
Early lateral ventricular E´, cm/s	10.6±3.1	12.5±2.3	−1.8 (−2.9 to −0.8)	<0.001
Early septal ventricular E´, cm/s	8.0±2.2	9.8±2.1	−1.9 (−2.7 to −1.1)	<0.001
Left ventricular end diastolic internal diameter, cm	5.0±0.6	4.8±0.5	0.1 (−0.1 to 0.3)	0.30
Left ventricular end systolic internal diameter, cm‡	3.6±0.7	3.2±0.5	0.3 (0.0 to 0.5)	0.018
Left ventricular end diastolic volume, mL	125±38	119±28	−0.5 (−13 to 12)	0.94
Left ventricular end systolic volume, mL	61±27	45±15	13 (5 to 21)	0.003
Interventricular septum thickness, cm	1.2±0.2	1.1±0.1	0.2 (0.1 to 0.2)	<0.001
Posterior wall thickness, cm	1.2±0.2	1.1±0.2	0.1 (0.0 to 0.2)	0.003
Left ventricular mass, g	245±62	192±40	44 (24 to 63)	<0.001
Left ventricular mass/body surface area, g/m^2	111±61	89±18	21 (11 to 30)	<0.001
Left ventricular mass/height, g/m	138±33	107±22	27 (16 to 38)	<0.001
Left ventricular mass/height$^{2.7}$, g/m$^{2.7}$	52±13	40±8	11 (7 to 16)	<0.001
Relative wall thickness	0.49±0.11	0.45±0.08	0.050 (0.014 to 0.087)	0.007

AAS indicates anabolic-androgenic steroids; and E´, relaxation velocity.
*Data are reported as means±SD.
†Estimated mean differences between groups adjusted for age, race, family history of coronary artery disease, cocaine dependence, regular tobacco use, alcohol dependence, aerobic exercise in the past 10 y, and body surface area by the Mosteller formula.
‡N=85 AAS users.
§N=84 AAS users.

relationship was of approximately equal magnitude but in the opposite direction, with a significant association between increased LV mass index and increased E´ (estimated mean change in E´ for each 10 g increase in LV mass index 0.36 cm/second [0.04–0.68 cm/second], *P*<0.001).

Coronary Artery Atherosclerosis

AAS users showed significantly higher coronary plaque volume than nonusers (Table 3 and Figure 2). On examining the association of CTA measures with currency and duration of AAS use, we found strong associations between lifetime duration of use on all angiographic measures of coronary pathology (Table 4 and Figure 3). However, we found no significant association between currency of use and plaque volume (estimated mean difference between on-drug and off-drug users in ranks: −0.07 SD units [−0.56 to 0.41], *P*=0.76). It is notable that 3 (3%) AAS users had experienced earlier myocardial infarctions because of underlying atherosclerotic disease, documented by cardiac catheterization, occurring at 38 years of age (ST-segment myocardial infarction with complete occlusion of left anterior descending artery), 43 years of age (non-ST-segment myocardial infarction with 99% occlusion of both the right coronary and left circumflex coronary arteries), and 46 years of age (ST-elevation myocardial infarction with complete occlusion of a second obtuse marginal artery) and after 17, 11, and 5 years of cumulative lifetime AAS exposure, respectively. In addition, 1 AAS user had presented at 42 years of age after 20 years of cumulative lifetime AAS exposure with congestive heart failure and underwent stenting of the left circumflex and first obtuse marginal arteries. None of the 54 nonusers had a history of myocardial infarction or stenting.

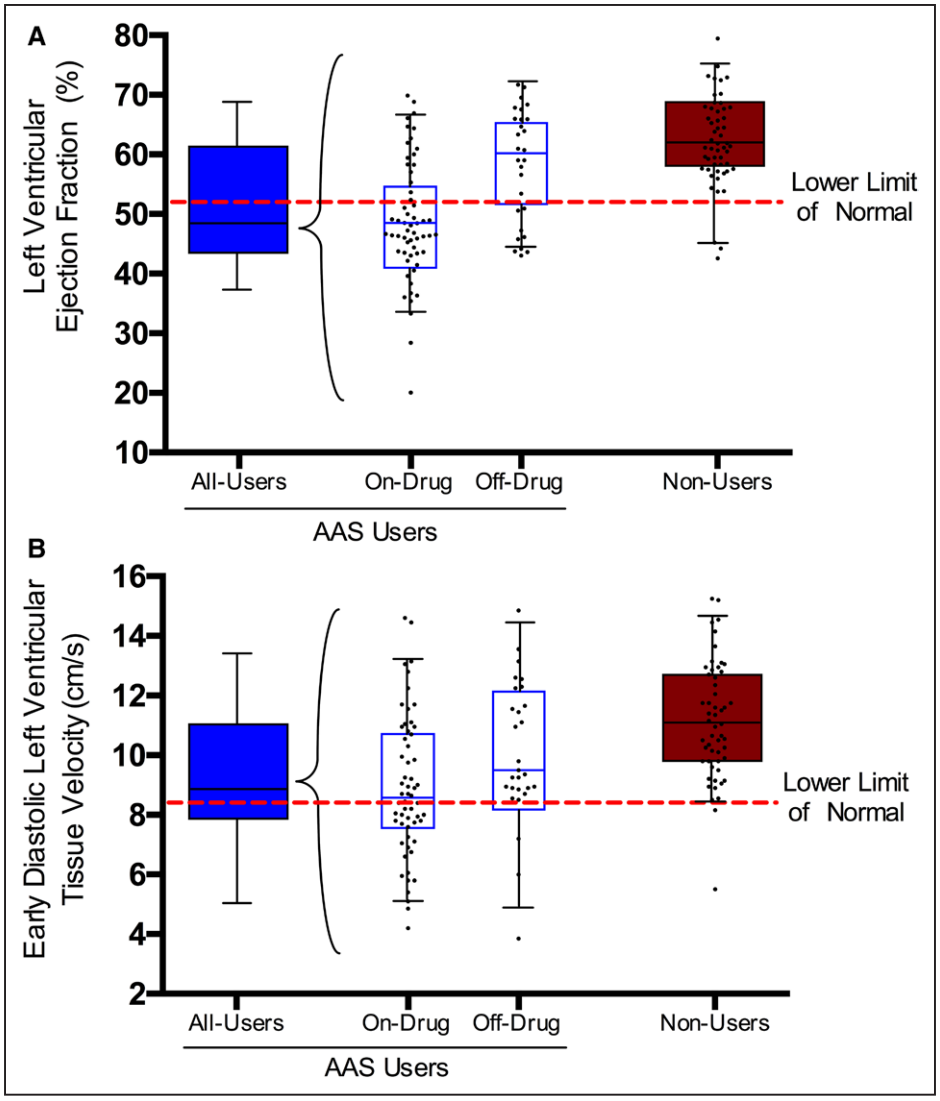

Figure 1. Left ventricular systolic and diastolic function in anabolic-androgenic steroid users and comparison nonusers.

A, Boxplots of left ventricular ejection fraction in anabolic-androgenic steroid (AAS) users (N=86), shown as an entire group (**Left**) and as subgroups of individuals who were on-drug (N=58) and off-drug (N=28) at the time of evaluation (**Middle**); and nonusers (N=54) (**Right**). On this variable, the estimated mean difference (95% confidence interval) between on-drug and off-drug AAS users, adjusted for covariates as described in the text, is −9.5% (−13.8 to −5.2), $P<0.001$; for on-drug AAS users versus nonusers, the difference is −13.6% (−17.3 to −9.8), $P<0.001$; and for off-drug AAS users versus nonusers, the difference is −4.1% (−8.6 to 0.3), $P=0.072$. **B,** Left ventricular early relaxation velocity in the same 4 groups. On this variable, the mean difference between on-drug and off-drug AAS users is −1.1 (−2.1 to −0.1) cm/second, $P=0.035$; for on-drug AAS users versus nonusers, the difference is −2.2 (−3.1 to −1.4) cm/second, $P<0.001$; and for off-drug AAS users versus nonusers, the difference is −1.1 (−2.2 to −0.1) cm/second, $P=0.035$.

Sensitivity Analyses

Assessing the influence of alternative sets of potential confounders, using models with both reduced and augmented sets of covariates, we obtained results similar to those of the primary analysis, with <15% change in the estimates for the primary outcomes and preservation of statistical significance for all results identified as such in the primary analysis (Tables V–VII in the online-only Data Supplement). We also reanalyzed the echocardiographic findings while omitting the 3 men with previous myocardial infarctions. This analysis produced negligible changes in the findings, with the estimated mean differences between users and nonusers on the 2 primary outcome variables changing by <2% when these 3 men were excluded.

DISCUSSION

Illicit AAS use is widespread, but its long-term adverse effects remain poorly understood. A growing literature, largely comprised of case reports and small observa-

Table 3. Computed Tomography Coronary Angiography Findings in Anabolic-Androgenic Steroid Users and Nonusers*

Variable	Users (N=84)	Nonusers (N=53)	Comparison	
			Estimated Difference in Standardized Ranks (95% Confidence Interval)†	*P* Value
Primary outcome				
Plaque volume, mm^3‡	3 (0–174)	0 (0–69)	0.46 (0.10–0.82)	0.012
Secondary outcomes				
Degree of stenosis for most severe stenosis§	0.5 (0–1)	0.5 (0–1)	0.37 (−0.00 to 0.75)	0.052
Number of diseased coronary artery segments¶	0.5 (0–2)	1 (0–1)	0.36 (−0.01 to 0.74)	0.059
Agatston calcium score‡	0 (0–25)	0 (0–1)	0.18 (−0.17 to 0.52)	0.31

AAS indicates anabolic-androgenic steroids; and CI, confidence interval.

*Data are shown as median (interquartile range).

†Estimated mean difference between groups in rank, measured in standard deviation units, adjusted for age, race, family history of coronary artery disease, cocaine dependence, alcohol dependence, tobacco use, and aerobic exercise in the past 10 y (see text).

‡Four AAS users had received percutaneous coronary interventions, and thus their plaque volume and calcium score could not be quantified accurately. However, all 4 men showed extensive plaque as evidenced by their number of diseased segments and degree of stenosis for most severe stenosis. Therefore, for purposes of calculation, they were assigned the median values for plaque volume and calcium score, respectively, from among all study participants with nonzero plaque volume and calcium scores. If these cases were omitted entirely, then the estimated mean difference (95% confidence interval) between groups in standardized rank would be 0.43 (0.04–0.81) for plaque volume and 0.13 (−0.26 to 0.51) for calcium score.

§Represents the worst degree of stenosis of any coronary artery, on a scale of 0–4, where 0=0% stenosis, 1=1% to 25%, 2=26% to 49%, 3=50% to 69%, and 4=70% to 99%.

¶Represents the number of coronary artery segments showing any disease, with scores ranging from 0 to 10 diseased segments.

tional studies, suggests that AAS use may cause cardiovascular disease. We undertook the present study to examine cardiovascular health measures among long-term AAS users and otherwise similar nonusers with the following 4 key findings. First, AAS users demonstrated substantial impairment of LV systolic function as assessed by LVEF and longitudinal strain. This finding was driven almost entirely by those AAS users who were on-drug at the time of evaluation, suggesting that LV dysfunction may be a dynamically related to AAS-use patterns. Second, AAS users also showed impaired LV diastolic dysfunction, both relative to nonusers and also as defined by current diagnostic criteria.[44] In contrast to systolic function, which appeared largely normal among off-drug AAS users, LV diastolic function was impaired in both on-drug and off-drug users, suggesting a more permanent form of acquired pathology. Third, AAS users had significantly more LV hypertrophy, as reflected by LV mass index, than nonusers, suggesting an anabolic effect on cardiac muscle mass. In addition, the magnitude of LV hypertrophy among AAS users was directly related to the degrees of both systolic and diastolic function, suggesting a mechanistic link between LV hypertrophy and functional deterioration. Fourth, AAS use was associated with increased coronary atherosclerosis, and the severity of atherosclerotic disease was strongly associated with cumulative lifetime duration of AAS use. In aggregate, our findings suggest that long-term AAS use is associated with adverse cardiovascular phenotypes characterized by both myocardial pathology and coronary artery pathology, which may represent a clinically substantial and largely unrecognized public health problem.

Several scientific and clinical implications emerge from this study. First, improved identification of the adverse cardiovascular associations of AAS use may deter potential future users. Second, clinicians may be better informed about the potential adverse cardiovascular effects of AAS. It is important to note that participants in the present study were not elite or professional athletes, the small subset of the general population most commonly tied to AAS exposure, but rather a sample of middle-age men representing a reasonably broad socioeconomic and racial/ethnic distribution. Thus, when comparable men are found to have impaired LV function or premature coronary artery disease, it seems prudent for clinicians to now include AAS use on the differential diagnosis of possible causes. Third, data derived from the present cross-sectional study provide a foundation for critical future work. The hypothesis that some cardiovascular phenotypes associated with AAS use may wax and wane with drug exposure (eg, LV systolic dysfunction) while others may be more permanent, perhaps irreversible (eg, LV diastolic dysfunction and coronary atherosclerosis), deserves rigorous assessment. Longitudinal studies of illicit AAS users with hard clinical end points, and with interventions to impact drug exposure patterns and treat detected disease, are also of importance.

Limitations

Several threats regarding the internal validity of this study, as previously delineated in general for cross-sectional cohort studies,[27,29] deserve consideration. First, bias might arise through exiting from the under-

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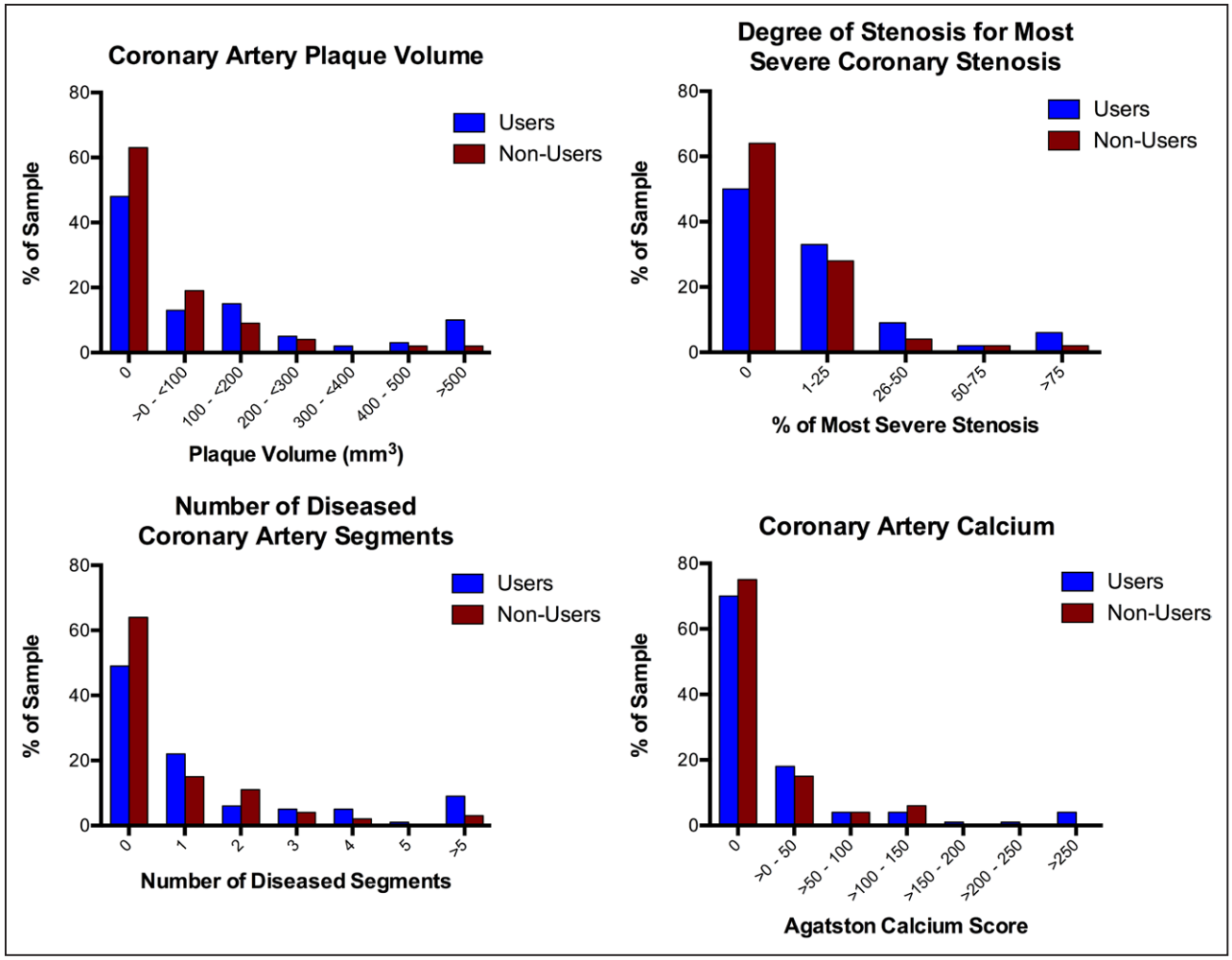

Figure 2. Distribution of computed tomography coronary angiography measures in anabolic-androgenic steroid users and nonusers.

Histograms displaying distribution of coronary artery plaque volume, degree of stenosis for most severe stenosis, number of diseased coronary artery segments, and coronary artery calcium for anabolic-androgenic steroid (AAS) users (N=84) and nonusers (N=53). The histograms for plaque volume and calcium score include for men with imputed values, as described in the footnote to Table 3.

lying conceptual cohort (ie, becoming unavailable for study in the present) that is differential with respect to exposure status. For example, AAS users might be more likely than nonusers to develop cardiovascular morbidity, stop weightlifting, and hence be unavailable for recruitment. Any resulting bias, however, would likely underestimate the effects of AAS use. Second, as in all observational studies, we cannot exclude residual confounding. However, given the lack of confounding seen with our measured potential confounders—as evidenced by similar estimates in sensitivity analyses using both reduced and augmented sets of potential confounders—it is unlikely that substantial residual bias remains because of unmeasured confounders. Third, because both AAS users and nonusers were weightlifters, the effects of AAS might be clouded if weightlifting contributed to cardiovascular pathology. However, our ancillary study comparing non-AAS-using weightlifters with nonweightlifters demonstrated that weightlifting alone (of the duration and intensity exhibited by our sample) had little effect on cardiac adaptation or pathology. Fourth, bias could arise from measurement error, particularly in the exposure variables (eg, misclassifying surreptitious AAS users as nonusers or inaccurately assessing the type, duration, dose, and currency of use). In particular, AAS users provided retrospective accounts, often spanning many years of time, of the use of illicit drugs of uncertain potency or authenticity. As such, estimates of participants' lifetime duration of AAS use and total lifetime AAS dose were only approximations. The effect of these various sources of measurement error would be expected to be differential for between-group comparisons (because of the potential for inclusion of surreptitious AAS users in the nonuser group and the much less likely inclusion of

Table 4. Association of Computed Tomography Coronary Angiography Variables With Lifetime Duration of Anabolic-Androgenic Steroid Use

Variable	Increase in Standardized Rank per 10-y Increase in Duration of Lifetime AAS Use (95% Confidence Interval)*	*P* Value
Primary outcome		
Plaque volume, mm^3†	0.60 (0.16–1.03)	0.008
Secondary outcomes		
Degree of stenosis for most severe stenosis‡	0.68 (0.26–1.10)	0.002
Number of diseased coronary artery segments§	0.75 (0.31–1.19)	<0.001
Agatston calcium score†	0.49 (0.06–0.92)	0.025

AAS indicates anabolic-androgenic steroids.

*Estimated increase in rank, measured in standard deviation units, for each 10-y increase in cumulative lifetime duration of AAS use, adjusted for age, race, family history of coronary artery disease, cocaine dependence, alcohol dependence, tobacco use, and aerobic exercise in the past 10 y (see text).

†Four AAS users had received previous percutaneous coronary interventions, and thus their plaque volume and calcium scores could not be measured accurately. However, all 4 of these men exhibited extensive plaque as evidenced by their number of diseased segments and degree of stenosis for most severe stenosis. Therefore, for purposes of calculation, they were assigned the median values for plaque volume and calcium score, respectively, from among all study participants with nonzero plaque volume and calcium scores. If these cases were omitted entirely, then the increase (95% confidence interval) in standardized rank per 10 y of AAS exposure would be 0.61 (0.11–1.12) for plaque volume and 0.48 (−0.04 to 0.99) for calcium score.

‡The worst degree of stenosis of any coronary artery, on a scale of 0–4, where 0=0% stenosis, 1=1% to 25%, 2=26% to 49%, 3=50% to 69%, and 4=70% to 99%.

§Represents the number of coronary artery segments showing any disease, with scores ranging from 0 to 10 diseased segments.

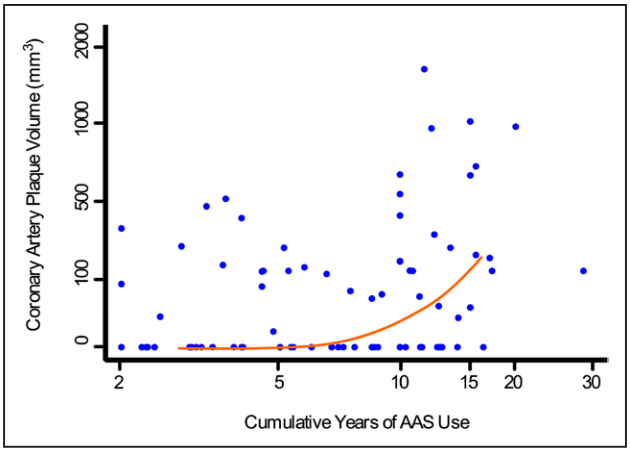

Figure 3. Relationship between coronary artery plaque volume and cumulative lifetime duration of anabolic-androgenic steroid exposure.
Scatter plot displaying coronary artery plaque volume and cumulative years of lifetime anabolic-androgenic steroid (AAS) exposure, with a median spline (red line) fitted to the data to aid in the visualization of the relationship between these variables. Because of the highly right-skewed distributions, the data are presented on a transformed scale (square root transformation for coronary artery plaque volume; logarithmic transformation for cumulative years of AAS use).

individuals falsely reporting AAS use in the user group) and random for within-group comparisons among AAS users (because of the low likelihood of an association between cardiac outcomes and error in the predictor variables). Both of these sources would likely bias results toward the null, thereby yielding an underestimate of the effects of AAS use.

Potential threats to external validity (generalizability) also require consideration. First, we recruited AAS users from gymnasiums. Thus, our results might not generalize to other AAS-using groups (eg, elite athletes). However, most AAS users are recreational weightlifters, and thus our results likely generalize to the population of AAS users of greatest public health importance. Second, despite the demographic diversity of our sample, white non-Hispanic men were overrepresented, and therefore our results might not generalize to the full racial/ethnic spectrum of AAS users. Overall, however, these potential threats to internal and external validity appear modest. Thus, our findings likely represent reasonably unbiased estimates of the associations of AAS exposure with adverse cardiovascular phenotypes.

CONCLUSION

Our findings suggest that AAS use is associated with LV dysfunction and premature coronary artery disease. These findings may inform public health initiatives to curb drug exposure and provide clinicians with information that will translate into improved patient care.

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DISCLOSURES

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FOOTNOTES

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Cardiovascular Toxicity of Illicit Anabolic-Androgenic Steroid Use

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SUPPLEMENTAL MATERIAL

Baggish AL, Weiner RB, Kanayama G, Hudson JI, Lu MT, Hoffmann U, Pope HG, Jr. Cardiovascular toxicity of illicit anabolic-androgenic steroid use

This supplementary material has been provided by the authors to provide readers with additional information about their work.

CONTENTS

Appendix A – Supplementary Methods

Transthoracic Echocardiography (TTE).

Image Acquisition. Cardiac ultrasound imaging was performed with a commercially available echocardiography system (iE-33, Phillips Medical Systems, Netherlands) with a 1.9- to 3.8-mHz phased-array transducer. Participants were imaged at rest ≥ 12 hours after their most recent exercise or weightlifting sessions. Two-dimensional imaging was performed from standard parasternal and apical transducer positions with frame rates confined to 60-100 Hz as determined on an individual subject basis for image optimization. All data were stored digitally and image analysis was performed using commercially available software on a dedicated work-station (Xcelera, Version 3.2.1.7-12-2011, Phillips Medical Systems, Netherlands). Images were analyzed with investigators blinded to subject AAS use status.

Image Analysis. Cardiac structural and functional measurements were made in accordance with current guidelines.[1, 2] Left ventricular (LV) volumes and ejection fraction were measured and calculated with the modified Simpson biplane technique. For the primary outcome variable LV ejection fraction, a value of ≥52% was used to define the lower limits of normal (Figure 1, main text).[1] LV mass was calculated using the area-length method, which was chosen because it accounts for LV morphology in both short- and long-axis dimension. Myocardial tissue velocities were measured using pulse wave Doppler tissue imaging with sampling at the acquired from apical 4-chamber view with frame rates ≥ 120 Hz. Reported tissue velocities represent the average of 3 consecutive cardiac cycles. The primary outcome variable, average early diastolic left ventricular relaxation velocity (E'), represents that average of values obtained from the basolateral and basal septal regions of the LV with an value of ≥8.5 cm/s used to define the lower limits of normal (Figure 1, main text).[2] Longitudinal strain measurements were made using commercially available speckle-tracking analysis software (Xcelera, Version

3.2.1.7-12-2011, Phillips Medical Systems, Netherlands).[3] Specifically, the highest-quality digital 2D apical 4-chamber view was selected for analysis. The endocardium was traced and a full thickness myocardial region of interest was selected. The software then automatically partitioned the LV into 6 segments including apical (n=2), septal (n=2), and lateral (n=2) territories and selected suitable speckles for tracking. The reliability of tracking was confirmed by the software's reliability parameter and by direct visual inspection to confirm appropriate systolic shortening. When either criterion suggested sub-optimal tracking efficiency, the endocardial trace and/or region of interest width were readjusted until an acceptable tracking score was obtained. By convention, longitudinal values are presented as negative numbers with lower (i.e. more negative) values representing greater systolic shortening. Measurements were obtained on 3 consecutive cardiac cycles and reported values represent a 3-cycle average. Resting heart rates represented the average values from the final 3 image loops of each participant's resting transthoracic echocardiographic assessment, a technique that ensured at least 15 minutes of quiet, uninterrupted physical inactivity.

Measurement Variability. The intraobserver and interobserver variability for LV mass and longitudinal strain were examined. Intraobserver variability was assessed by a single investigator using blinded assessment of 10 randomly selected subjects on 2 separate occasions. Interobserver variability was assessed in a group of 10 randomly selected subjects by 2 investigators blinded to each other's measurements and to study time point. Correlation coefficients for each measurement, derived from simple linear regression, were used to quantify variability with the following results: intraobserver LV mass (R^2= 0.946), intraobserver longitudinal strain (R^2= 0.968), interobserver LV mass (R^2= 0.921), and interobserver longitudinal strain (R^2= 0.972).

Coronary CT Angiography (CTA)

Image Acquisition. Participants had coronary CTA to assess for coronary artery plaque burden and calcification at the time of enrollment according to the guidelines of the Society of Cardiovascular Computed Tomography (SCCT).[4] Retrospectively ECG-gated CTA was performed on a dual-source 128-slice CT scanner (Definition Flash, Siemens Medical Systems, Erlangen, Germany). Prior to CTA, an 18 or 20 gauge antecubital intravenous (IV) catheter was placed. A brief interview prior to CT assessed for contraindications to metoprolol or nitroglycerin such as asthma or recent phosphodiesterase inhibitor use. Up to 20 mg of IV metoprolol was given in 5 mg aliquots at 5 minute intervals to achieve a hear rate of ≤65 beats per minute. A dose of 0.6 mg of sublingual nitroglycerin was given for coronary vasodilation. The CTA protocol included localizer images, a noncontrast ECG-gated high-pitch helical CT for assessment of coronary calcium, a test bolus of 20 cc IV contrast to time the proper delay for peak ascending aortic enhancement, and the CTA. All imaging was performed during an inspiratory breath hold; coverage included the heart from the diaphragm to the carina. For CTA 60-85 cc of iodinated IV contrast (iopamidol 370 g/cm3, Bracco Diagnostics, Princeton, NJ, USA) followed by a 40cc normal saline flush at a flow rate of 5 to 6 cc/second based on participant size was administered. The scan was performed with tube current modulation with a reference mAs of 370. Peak kilovoltage (kVp) was set to 120 for persons with a BMI ≥30 kg/m2 and 100 for <30 kg/m2. An adaptive pitch was used based on the heart rate, with a collimation of 128 x 0.6 mm and a rotation time of 280 ms. Noncontrast CT images were reconstructed with a slice thickness of 3 mm. CTA images were reconstructed with a slice thickness of 0.75 mm with a 0.4 mm overlap using a filtered back projection kernel at 5% intervals from 60-85% of the R-R interval for coronary evaluation, then again at a slice thickness of 1.5 mm without overlap at 5% intervals throughout the entire cardiac cycle. Image reconstruction was performed with a small

field of view of ≤20 cm to maximize spatial resolution. The cardiac phase or phases which minimized motion or other artifact were used for the analysis.

***Image Analysis*.** Image analysis was performed blinded to AAS use and all other clinical data on dedicated 3D workstations. The coronary artery calcium score (CACS) was calculated from the noncontrast images using the method of Agatston on a dedicated 3D workstation (MMWP, Siemens Medical Systems, Erlangen, Germany).[5] Coronary artery stenosis, the number of coronary artery segments with visible coronary plaque, and coronary artery plaque volume was assessed. Each participant's worst coronary artery stenosis was categorized as none, <25%, 25-49%, 50-69%, 70-99%, and 100% by visual inspection. Coronary plaque was defined as any discernable structure that could be assigned to the coronary artery wall on at least two orthogonal planes; the number of coronary artery segments with plaque was determined using a 17 segment model.[6] Semi-automated coronary plaque volume measurements were made using a second dedicated 3D workstation (AQi, Terarecon, Foster City, CA, USA). The workstation generated a centerline through the coronary artery lumen. The plaque length was established visually with markers at its proximal and distal extent. The inner luminal and outer wall coronary artery contours were automatically generated by the software and manually edited as necessary, and these voxels defined the coronary artery plaque volume in mm3. This volumetric technique for coronary plaque measurement has previously demonstrated excellent intra- and interobserver reproducibility.[7]

Appendix B – Supplementary Tables

Table 1: Demographic and Clinical Characteristics of Non-Anabolic-Androgenic-Steroid-Using Weightlifters and Non-Weightlifters.*

Characteristic	Non-AAS-Using Weightlifters (N = 54)	Non-Weightlifters (N = 50)
Demographic features		
Age, median (IQR), yr	43 (38–49)	43 (38-46)
Race, n (%) †		
White	41 (76)	45 (90)
Black	12 (22)	5 (10)
Asian	1 (2)	0
Ethnic background, n (%) †		
Not Hispanic	52 (96)	49 (98)
Hispanic	2 (4)	1 (2)
Anthropomorphic measures		
Height, median (IQR), m	1.8 (1.7-1.8)	1.8 (1.7-1.8)
Body surface area, median (IQR), m^2 ‡	2.2 (2.0–2.3)	2.0 (1.9–2.2)
Body mass index, median (IQR) §	29 (27-31)	26 (24-31)
Fat-free mass index, median (IQR) ‖	23 (21–25)	21 (19–22)
Exercise measures		
Time spent in aerobic exercise per week, n (%) #		
0-30 minutes	19 (35)	46 (92)
31-120 minutes	22 (41)	1 (2)
Greater than 120 minutes	13 (24)	3 (6)
Other potential cardiovascular risk factors		
Family history of coronary artery disease, n (%) **	12 (22)	12 (24)
Lifetime history of substance use, n (%)		
Regular cigarette smoking ††	19 (35)	18 (36)
Alcohol dependence ‡‡	7 (13)	4 (8)
Cocaine dependence ‡‡	5 (9)	5 (10)

* AAS indicates anabolic-androgenic steroids; IQR, interquartile range.

† Race and ethnic background were self-reported.

‡ By Mosteller formula.

§ The body mass index is the weight in kilograms divided by the square of the height in meters.

‖ The fat-free mass index is calculated as: $(W(1-BF)/H^2) + 6.1(1.8-H)$, where W = weight in kilograms, H = height in meters, and BF = percent body fat. (See reference 25 in the primary paper.)

Any self-reported aerobic exercise beyond ordinary daily activities.

** At least one first-degree relative reported to have had "coronary artery disease, angina, heart attack, angioplasty/stent, or coronary artery bypass surgery."

†† Any cigarette smoking beyond brief experimentation.

‡‡ By the Structured Clinical Interview for DSM-IV. (See reference 27 in the primary paper.)

Table 2. Echocardiographic Measures in Non-Anabolic-Androgenic-Steroid-Using Weightlifters and Non-Weightlifters.*

	Weightlifters	Non-Weightlifters	Weightlifters vs. Non-Weightlifters	
	Mean (SD)		Estimated difference	P value
Variable	(N = 54)	(N = 50)	(95% CI) †	
Primary outcomes				
Left ventricular ejection fraction, %	63 (8)	61 (6)	1.4 (-2.5 to 5.4)	0.47
Average early left ventricular relaxation velocity (E´), cm/s	11.1 (2.0)	11.4 (2.7)	0.2 (-0.9 to 1.4)	0.70
Secondary outcomes				
Longitudinal 4-chamber strain	-20 (3)	-20 (3)	0.4 (-1.3 to 2.0)	0.65
Early lateral left ventricular relaxation velocity (E´), cm/s	12.5 (2.3)	12.9 (3.5)	-0.2 (-1.7 to 1.4)	0.82
Early septal left ventricular relaxation velocity (E´), cm/s	9.8 (2.1)	9.8 (2.3)	0.6 (-0.5 to 1.7)	0.26
Left ventricular end diastolic internal diameter, cm	4.8 (0.5)	4.7 (0.4)	0.1 (-0.2 to 0.3)	0.45
Left ventricular end systolic internal diameter, cm	3.2 (0.4)	3.2 (0.50)	0.0 (-0.2 to 0.3)	0.79
Left ventricular end diastolic volume, mL	119 (28)	111 (23)	11 (-2 to 24)	0.11
Left ventricular end systolic volume, mL	45 (15)	43 (12)	2.7 (-4.3 to 9.8)	0.44
Interventricular septum thickness, cm	1.1 (0.1)	1.1 (0.2)	-0.0 (-0.1 to 0.1)	0.69
Posterior wall thickness, mm	1.1 (0.2)	1.0 (0.2)	0.12 (0.03 to 0.21)	0.007
Left ventricular mass, g	192 (40)	178 (47)	17 (-3 to 38)	0.10
Left ventricular mass/body surface area, g/m^2	89 (18)	86 (19)	8.3 (-1.6 to 18.1)	0.10
Left ventricular mass/height, g/m	107 (22)	100 (26)	11 (-1 to 22)	0.074
Left ventricular mass/height$^{2.7}$, g/m$^{2.7}$	40 (8)	38 (9)	4.5 (0.0 to 9.0)	0.050
Relative wall thickness	0.45 (0.08)	0.44 (0.09)	0.014 (-0.031 to 0.059)	0.55

* AAS indicates anabolic-androgenic steroids; CI, confidence interval.

† Estimated mean differences between groups, adjusted for age; race; family history of coronary artery disease; lifetime history of cocaine dependence, alcohol dependence, or regular tobacco use; aerobic exercise in the past 10 years; and body surface area by the Mosteller formula.

Table 3. Computed Tomography Coronary Angiography Findings in Non-Anabolic-Androgenic-Steroid-Using Weightlifters and Non-Weightlifters.*

Variable	Weightlifters (N = 53) Median (IQR)	Non-weightlifters (N = 48) Median (IQR)	Weightlifters vs Non-Weightlifters Mean difference in standardized ranks (95% CI) †	P Value
Primary outcome				
Plaque Volume, mm^3	0 (0-69)	13 (0-104)	-0.40 (-0.92 to 0.11)	0.12
Secondary outcomes				
Degree of stenosis for most severe stenosis ‡	0 (0-1)	1 (0-1)	-0.32 (-0.82 to 0.18)	0.21
Number of diseased coronary artery segments §	0 (0-1)	0.5 (0-1)	-0.30 (-0.80 to 0.20)	0.23
Agatston calcium score	0 (0-0.58)	0 (0-3.7)	-0.25 (-0.74 to 0.23)	0.30

* CI indicates confidence interval; IQR, interquartile range.

† Estimated mean difference between groups in rank, measured in standard deviation units, adjusted for age; race; family history of coronary artery disease; lifetime history of cocaine dependence, alcohol dependence, or tobacco use; and aerobic exercise in the past 10 years (see text).

‡ Represents the worst degree of stenosis of any coronary artery, on a scale of 0-4, where 0 = 0% stenosis; 1 = 1-25%; 2 = 26-49%; 3 = 50-69%; and 4 = 70-99%.

§ Represents the number of coronary artery segments showing any disease, with scores ranging from 0 to 10 diseased segments.

Table 4. Echocardiographic Findings in On-drug Anabolic-Androgenic Steroid Users, Off-drug Users, and Non-Users.*

	AAS Users			Non-Users	Comparisons †					
	Mean (SD)				On-drug AAS vs. non-users		Off-drug AAS vs. non-users		On-drug AAS vs. off-drug AAS	
Variable	All users (N = 86)	On-drug (N = 58)	Off-drug (N = 28)	(N = 54)	Estimated difference (95% CI)	P value	Estimated difference (95% CI)	P value	Estimated difference (95% CI)	P value
Primary outcomes										
Left ventricular ejection fraction, %	52 (11)	49 (10)	58 (10)	63 (8)	-13.6 (-17.3 to -9.8)	<0.001	-4.1 (-8.6 to 0.3)	0.072	-9.5 (-13.8 to -5.2)	<0.001
Early left ventricular relaxation velocity (E´), cm/s	9.3 (2.4)	8.9 (2.4)	10.1 (2.4)	11.1 (2.0)	-2.2 (-3.1 to -1.4)	<0.001	-1.1 (-2.2 to -0.1)	0.035	-1.1 (-2.1 to -0.1)	0.035
Secondary outcomes										
Global longitudinal strain, 4 chambers	-16 (4)	-14 (3)	-18 (4)	-20 (3)	5.8 (4.4 to 7.2)	<0.001	2.1 (0.4 to 3.9)	0.017	3.7 (2.0 to 5.3)	<0.001
Left ventricular relaxation velocity components, cm/s										
Lateral	10.6 (3.1)	10.2 (2.9)	11.4 (3.3)	12.5 (2.3)	-2.2 (-3.3 to -1.1)	<0.001	-1.1 (-2.4 to 0.3)	0.11	-1.1 (-2.4 to 0.2)	0.087
Septal	8.0 (2.2)	7.6 (2.2)	8.7 (1.9)	9.8 (2.1)	-2.2 (-3.1 to -1.4)	<0.001	-1.2 (-2.2 to -0.2)	0.021	-1.1 (-2.0 to -0.1)	0.031
Left ventricular internal diameter, cm										
End diastole	5.0 (0.6)	5.1 (0.7)	4.9 (0.5)	4.8 (0.5)	0.2 (-0.1 to 0.4)	0.18	0.00 (-0.3 to 0.3)	0.89	0.1 (-0.1 to 0.4)	0.30
End systole	3.6 (0.7)	3.6 (0.8)	3.6 (0.5)	3.2 (0.5)	0.3 (0.1 to 0.6)	0.015	0.2 (-0.1 to 0.5)	0.17	0.1 (-0.2 to 0.4)	0.49
Left ventricular volume, mL										
End diastole	125 (38)	129 (39)	118 (37)	119 (28)	3 (-10 to 16)	0.64	-8 (-23 to 8)	0.34	11 (-4 to 26)	0.16
End systole	61 (27)	67 (29)	49 (16)	45 (15)	19 (11 to 28)	<0.001	0.5 (-10 to 11)	0.93	19 (9 to 29)	<0.001
Interventricular septum thickness, cm	1.2 (0.2)	1.2 (0.2)	1.2 (0.2)	1.1 (0.1)	0.2 (0.1 to 0.3)	<0.001	0.2 (0.1 to 0.3)	<0.001	0.0 (-0.1 to 0.1)	0.92
Posterior wall thickness, cm	1.2 (0.2)	1.2 (0.2)	1.1 (0.2)	1.1 (0.2)	0.1 (0.1 to 0.2)	<0.001	0.00 (-0.0 to 0.1)	0.31	0.1 (0.0 to 0.2)	0.039
Left ventricular mass, g	245 (62)	253 (67)	228 (47)	192 (40)	52 (31 to 73)	<0.001	27 (2 to 52)	0.038	25 (1 to 49)	0.045
Left ventricular mass/body surface area, g/m^2	111 (61)	115 (30)	104 (20)	89 (18)	24 (15 to 34)	< 0.001	13 (1 to 25)	0.030	11 (0 to 23)	0.047
Left ventricular mass/height, g/m	138 (33)	143 (36)	129 (25)	107 (22)	31 (19 to 43)	<0.001	17 (3 to 31)	0.016	14 (0 to 27)	0.045
Left ventricular mass/height$^{2.7}$, g/m$^{2.7}$	52 (13)	54 (14)	49 (10)	40 (8)	13 (9 to 18)	<0.001	8.0 (3 to 13)	0.004	5 (-0 to 10)	0.052
Relative wall thickness	0.49 (0.11)	0.50 (0.12)	0.49 (0.11)	0.45 (0.08)	0.053 (0.013 to 0.093)	0.010	0.046 (-0.002 to 0.093)	0.061	0.007 (-0.039 to 0.053)	0.77

* AAS indicates anabolic-androgenic steroids; CI, confidence interval.

† Estimated mean differences between groups, adjusted for age; race; family history of coronary artery disease; lifetime history of cocaine dependence, alcohol dependence, or regular tobacco use; aerobic exercise in the past 10 years; and body surface area by the Mosteller formula.

Table 5. Comparison of Echocardiographic Findings in Anabolic-Androgenic Steroid Users and Non-Users Using Reduced and Augmented Sets of Covariate Adjustments.*

	AAS Users vs. Non-Users Comparisons with Reduced Set of Covariate Adjustments †		AAS Users vs. Non-Users Comparisons with Augmented Set of Covariate Adjustments ‡	
Variable	Estimated difference (95% CI)	P Value	Estimated difference (95% CI)	P Value
Primary outcomes				
Left ventricular ejection fraction, %	-10 (-14 to -7)	<0.001	-10 (-14 to -6)	<0.001
Average early left ventricular relaxation velocity (E´), cm/s	-1.9 (-2.7 to -1.1)	<0.001	-1.8 (-2.6 to -10.9)	<0.001
Secondary outcomes				
Longitudinal 4-chamber strain	4.7 (3.3 to 6.0)	<0.001	4.5 (3.1 to 5.9)	<0.001
Early lateral ventricular relaxation velocity (E´), cm/s	-1.9 (-2.9 to -0.9)	<0.001	-1.7 (-2.8 to -0.7)	0.001
Early septal ventricular relaxation velocity (E´), cm/s	-1.9 (-2.6 to -1.1)	<0.001	-1.8 (-25 to -1.0)	<0.001
Left ventricular end diastolic internal diameter, cm	0.1 (-0.1 to 0.3)	0.23	0.1 (-0.1 to 0.3)	0.32
Left ventricular end systolic internal diameter, cm	0.3 (0.1 to 0.5)	0.010	0.3 (0.1 to 0.5)	0.017
Left ventricular end diastolic volume, mL	0.7 (-11 to 13)	0.91	-0.2 (-12 to 12)	0.97
Left ventricular end systolic volume, mL	13 (5 to 21)	0.001	13 (4 to 21)	0.004
Interventricular septum thickness, cm	0.2 (0.1 to 0.2)	<0.001	0.2 (0.1 to 0.2)	<0.001
Posterior wall thickness, cm	0.1 (0.0 to 0.2)	<0.001	0.1 (0.0 to 0.2)	0.004
Left ventricular mass, g	46 (27 to 65)	<0.001	43 (22 to 63)	<0.001
Left ventricular mass/body surface area, g/m^2	22 (13 to 30)	< 0.001	20 (11 to 29)	< 0.001
Left ventricular mass/height, g/m	28 (18 to 39)	<0.001	26 (15 to 37)	<0.001
Left ventricular mass/$height^{2.7}$, $g/m^{2.7}$	12 (8 to 16)	<0.001	11 (7 to 15)	<0.001
Relative wall thickness	0.050 (0.015 to 0.087)	0.006	0.048 (0.011 to 0.086)	0.011

* AAS indicates anabolic-androgenic steroids; CI, confidence interval.

† Estimated mean difference between groups, adjusted only for age and race.

‡ Estimated mean difference between groups, adjusted for age; race; family history of coronary artery disease; lifetime history of cocaine dependence, alcohol dependence, or regular tobacco use; aerobic exercise in the past 10 years; hypertension (reported by history, OR showing current systolic pressure greater than 140 mm Hg OR diastolic pressure greater than 90 mm Hg at evaluation); and dyslipidemia (reported by history, OR showing low-density lipoprotein cholesterol greater than 160 mg/dL at evaluation).

Table 6. Comparison of Computed Tomography Coronary Angiography Findings in Anabolic-Androgenic Steroid Users and Non-Users Using Reduced and Augmented Sets of Covariate Adjustments.*

	AAS Users vs. Non-users Comparisons with Reduced Set of Covariate Adjustments †		AAS Users vs. Non-users Comparisons with Augmented Set of Covariate Adjustments ‡	
Variable	Mean difference in standardized ranks (95% CI)	P Value	Mean difference in standardized ranks (95% CI)	P Value
Primary outcome				
Plaque Volume, mm^3 §	0.44 (0.10 to 0.79)	0.012	0.41 (0.05 to 0.77)	0.028
Secondary outcomes				
Degree of stenosis for most severe stenosis ‖	0.37 (0.01 to 0.73)	0.046	0.30 (-0.08 to 0.68)	0.12
Number of diseased coronary artery segments #	0.35 (-0.01 to 0.71)	0.055	0.29 (-0.09 to 0.67)	0.13
Agatston calcium score §	0.16 (-0.17 to 0.50)	0.33	0.12 (-0.23 to 0.47)	0.49

* AAS indicates anabolic-androgenic steroids; CI, confidence interval.

† Estimated mean difference between groups in rank, measured in standard deviation units, adjusted only for age and race.

‡ Estimated mean difference between groups in rank, measured in standard deviation units, adjusted for age; race; family history of coronary artery disease; lifetime history of cocaine dependence, alcohol dependence, or regular tobacco use; aerobic exercise in the past 10 years; hypertension (reported by history, OR showing current systolic pressure greater than 140 mm Hg OR diastolic pressure greater than 90 mm Hg at evaluation); and dyslipidemia (reported by history OR showing low-density lipoprotein cholesterol greater than160 mg/dL at evaluation).

§ Four AAS users had received percutaneous coronary interventions, and thus their plaque volume and calcium score could not be quantified accurately. However, all 4 men showed extensive plaque as evidenced by their number of diseased segments and degree of stenosis for most severe stenosis. Therefore, for purposes of calculation, they were assigned the median values for plaque volume and calcium score, respectively, from among all study participants exhibiting nonzero plaque volume and calcium scores.

‖ Represents the worst degree of stenosis of any coronary artery, on a scale of 0-4, where 0 = 0% stenosis; 1 = 1-25%; 2 = 26-49%;3 = 50-69%; and 4 = 70-99%.

Represents the number of coronary artery segments showing any disease, with scores ranging from 0 to 10 diseased segments.

Table 7. Association of Computed Tomography Coronary Angiography Variables with Lifetime Duration of Anabolic-Androgenic Steroid Use Assessed With Reduced and Augmented Sets of Covariate Adjustments.*

	Reduced Set of Covariate Adjustments †		Augmented Set of Covariate Adjustments ‡	
Variable	Mean increase in standardized ranks (95% CI)	P Value	Mean increase in standardized ranks (95% CI)	P Value
Primary outcome				
Plaque volume, mm^3 §	0.60 (0.18 to 1.02)	0.005	0.58 (0.13 to 1.02)	0.011
Secondary outcomes				
Degree of stenosis for most severe stenosis ‖	0.69 (0.29 to 1.08)	< 0.001	0.64 (0.21 to 1.06)	0.004
Number of diseased coronary artery segments #	0.76 (0.35 to 1.18)	< 0.001	0.70 (0.26 to 1.14)	0.002
Agatston calcium score §	0.56 (0.16 to 0.96)	0.007	0.47 (0.03 to 0.90)	0.035

* AAS indicates anabolic-androgenic steroids; CI, confidence interval.

† Estimated increase in rank, measured in standard deviation units, for each 10-year increase in lifetime duration of AAS use, adjusted only for age and race.

‡ Estimated increase in rank, measured in standard deviation units, for each 10-year increase in lifetime duration of AAS use, adjusted for age; race; family history of coronary artery disease; lifetime history of cocaine dependence, alcohol dependence, or tobacco use; aerobic exercise in the past 10 years; hypertension (reported by history, OR showing current systolic pressure greater than 140 mm Hg OR diastolic pressure greater than 90 mm Hg at evaluation); and dyslipidemia (reported by history OR showing low-density lipoprotein cholesterol greater than 160 mg/dL at evaluation).

§ Four AAS users had received prior percutaneous coronary interventions, and thus plaque volume and calcium score could not be measured accurately in these men. However, all 4 of these men exhibited extensive plaque as evidenced by their number of diseased segments and degree of stenosis for most severe stenosis. Therefore, for purposes of calculation, they were assigned the median values for plaque volume and calcium score, respectively, from among all study participants exhibiting nonzero plaque volume and calcium scores.

‖ Represents the worst degree of stenosis of any coronary artery, on a scale of 0-4, where 0 = 0% stenosis; 1 = 1-25%; 2 = 26-49%; 3 = 50-69%;and 4 = 70-99%.

Represents the number of coronary artery segments showing any disease, with scores ranging from 0 to 10 diseased segments.

Appendix C – References

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