Cardiovascular Toxicity of Illicit Anabolic-Androgenic Steroid Use

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Abstract

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

Methods—Employing a cross-sectional cohort design, we recruited 140 experienced male weightlifters aged 34–54 years, comprising 86 men reporting at least 2 years of cumulative lifetime AAS use and 54 non-using men. Using transthoracic echocardiography and coronary computed tomography angiography, we assessed 3 primary outcome measures: left ventricular (LV) systolic function (left ventricular ejection fraction [LVEF]), LV diastolic function (early relaxation velocity [E´]), and coronary atherosclerosis (coronary artery plaque volume).

Results—Compared to non-users, AAS users demonstrated relatively reduced LV systolic function (mean±SD LVEF = 52±11% vs. 63±8%; P<0.001) and diastolic function (E´ = 9.3±2.4 cm/s vs. 11.1±2.0 cm/s; P<0.001). Users currently taking AAS at the time of evaluation (N = 58) showed significantly reduced LV systolic (LVEF = 49±10% vs. 58±10%; P<0.001) and diastolic function (E´ = 8.9±2.4 cm/s vs. 10.1±2.4 cm/s; P=0.035) compared to users currently off-drug (N = 28). Additionally, AAS users demonstrated higher coronary artery plaque volume then nonusers (median [interquartile range] 3 [0, 174] mL^3 vs. 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 to 1.03 SD units]; P = 0.008).

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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 under-recognized public-health problem.

Keywords

Anabolic-androgenic steroids; cardiology; diastolic dysfunction; cardiomyopathy; atherosclerosis; men

INTRODUCTION

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 for 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 American 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.

Prior 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, pre-clinical 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 beta-adrenoreceptor sensitivity;[14] potentiates oxidative cardiac stress;[15] lowers arrhythmic thresholds;[16] and induces myocyte apoptosis.[17] Most recently, investigations utilizing non-invasive 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 prior studies suggest that illicit AAS use may cause a form of *cardiomyopathy* characterized by decreased 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 non-users.

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 prior 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 (e.g., 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 (e.g., 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 (i.e., AAS-using) and non-exposed (i.e., 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, since 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 non-weightlifting and non-AAS-using men (frequency-matched in age to the weightlifters, but never weightlifting more than 30 minutes per week at any time since age 18), drawn from a roster of potential study volunteers maintained by Massachusetts General Hospital, and compared these non-weightlifters to the subgroup of non-AAS-using weightlifters from the primary study. These 2 groups (AAS non-users and non-weightlifting and non-AAS-using men) exhibited no scientifically important or statistically significant differences on measures of cardiovascular physiology or pathology (Supplemental Tables 1–3), 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 prior cross-sectional cohort studies involving AAS,[28, 29] we advertised in gymnasiums for men age 34–54 who "could bench-press 275 pounds for at least one repetition, currently or in the past" to recruit AAS users and non-users. 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. Notably, 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 less than 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 (i.e. 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 (e.g., creatine) and illicit drugs (e.g., 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 greater than 26 kg/m^2 together with body fat below 10%, based on prior 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, Andover, MA) 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 bi-plane 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, Erlangen, Germany) 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 (Supplemental Methods).

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 to 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 (i.e., 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 African-American 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 non-users. Specifically, we used linear regression with the same set of potential confounding variables and the addition of a term for AAS user versus non-user 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 not only may influence functional outcomes, but also might itself 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 towards the null (that is, 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 the Supplemental Tables). Note that the augmented set of covariates would be expected to yield underestimates of the effect of AAS use, since 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 (i.e., 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 (i.e., on-drug vs. 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, College Station, TX). 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 prior to medical evaluation (9 AAS users, 1 non-user); 12 reported AAS use of less than 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 non-users. 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 prior to evaluation.

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

Cardiac structure and function

For the primary outcome variables of LVEF and É, AAS users showed significant deficits compared to non-users (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 non-users. 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 Supplemental Table 4). 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 É threshold of 8.5 cm/s,[44] with off-drug users showing only partially normalized É. Similar associations with currency of AAS use were found across other echocardiographic measures (Supplemental Table 4). 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% CI] in LVEF was −3.3% [−8.3% to 1.6%], P=0.19; and the estimated mean change in É was 0.1 cm/s [−1.0 to 1.2 cm/s], P=0.90).

Since LVEF and É differed by group (i.e., AAS user vs. non-user) and by subgroup based on currency of use (i.e., current vs. 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 É, 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

non-users. Examining LVEF, among AAS users, there was a significant association between increased LV mass index and decreased LVEF (estimated mean change [95% CI] 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 non-users, there was no significant association 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, there was a significant association 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/s [−0.49 to −0.13 cm/s], P<0.001). Among non-users, the 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/s [0.04 to 0.68 cm/s], P<0.001).

Coronary artery atherosclerosis

AAS users showed significantly higher coronary plaque volume than non-users (Table 3 and Figure 2). Upon 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). Notably, 3 (3%) AAS users had experienced prior myocardial infarctions due to underlying atherosclerotic disease, documented by cardiac catheterization, occurring at ages 38 (ST-segment myocardial infarction with complete occlusion of left anterior descending artery), 43 (Non ST-segment myocardial infarction with 99% occlusion of both the right coronary and left circumflex coronary arteries), and 46 (ST-elevation myocardial infarction with complete occlusion of a 2nd obtuse marginal artery), and after 17, 11, and 5 years of cumulative lifetime AAS exposure, respectively. In addition, one AAS user had presented at age 42, after 20 years of cumulative lifetime AAS exposure, with congestive heart failure and underwent stenting of the left circumflex and 1st obtuse marginal arteries. None of the 54 non-users had a history of myocardial infarction or stenting.

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 less than 15% change in the estimates for the primary outcomes and preservation of statistical significance for all results identified as such in the primary analysis (Supplemental Tables 5–7). We also reanalyzed the echocardiographic findings while omitting the three men with prior myocardial infarctions. This analysis produced negligible changes in the findings, with the estimated mean differences between users and nonusers on the two primary outcome variables changing by less than 2% when these three 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 observational 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 non-users with the following four 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 non-users 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 both in 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 non-users, 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, that 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. Importantly, participants in the current 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-aged 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 (e.g., LV systolic dysfunction) while others may be more permanent, perhaps irreversible (e.g., LV diastolic dysfunction and coronary atherosclerosis), deserves rigorous assessment. Longitudinal studies of illicit AAS users with hard clinical endpoints, 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 underlying conceptual cohort (that is, becoming unavailable for study in the present) that is differential with respect to exposure status. For example, AAS users might be more likely than non-users 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 there remains substantial residual bias due *unmeasured* confounders. Third, because both AAS users and non-users 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 non-weightlifters 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 (e.g., misclassifying surreptitious AAS users as non-users 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 (due to the potential for inclusion of surreptitious AAS users in the non-user group, and the much less likely inclusion of individuals falsely reporting AAS use in the user group) and random for within-group comparisons among AAS users (due to the low likelihood of an association between cardiac outcomes and error in the predictor variables). Both of these sources would likely bias results towards 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 (e.g., 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.

Conclusions

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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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 for personal appearance.

- Preliminary findings have suggested that long-term AAS exposure may lead to both cardiomyopathy and atherosclerotic disease, but prior 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.

- Although systolic functional deficits appear to recover following AAS discontinuation, 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-aged men who exhibit evidence of unexplained left ventricular dysfunction or premature coronary artery disease, the possibility of cardiotoxicity due to long-term AAS use should be considered in the differential diagnosis.

- Notably, about 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.
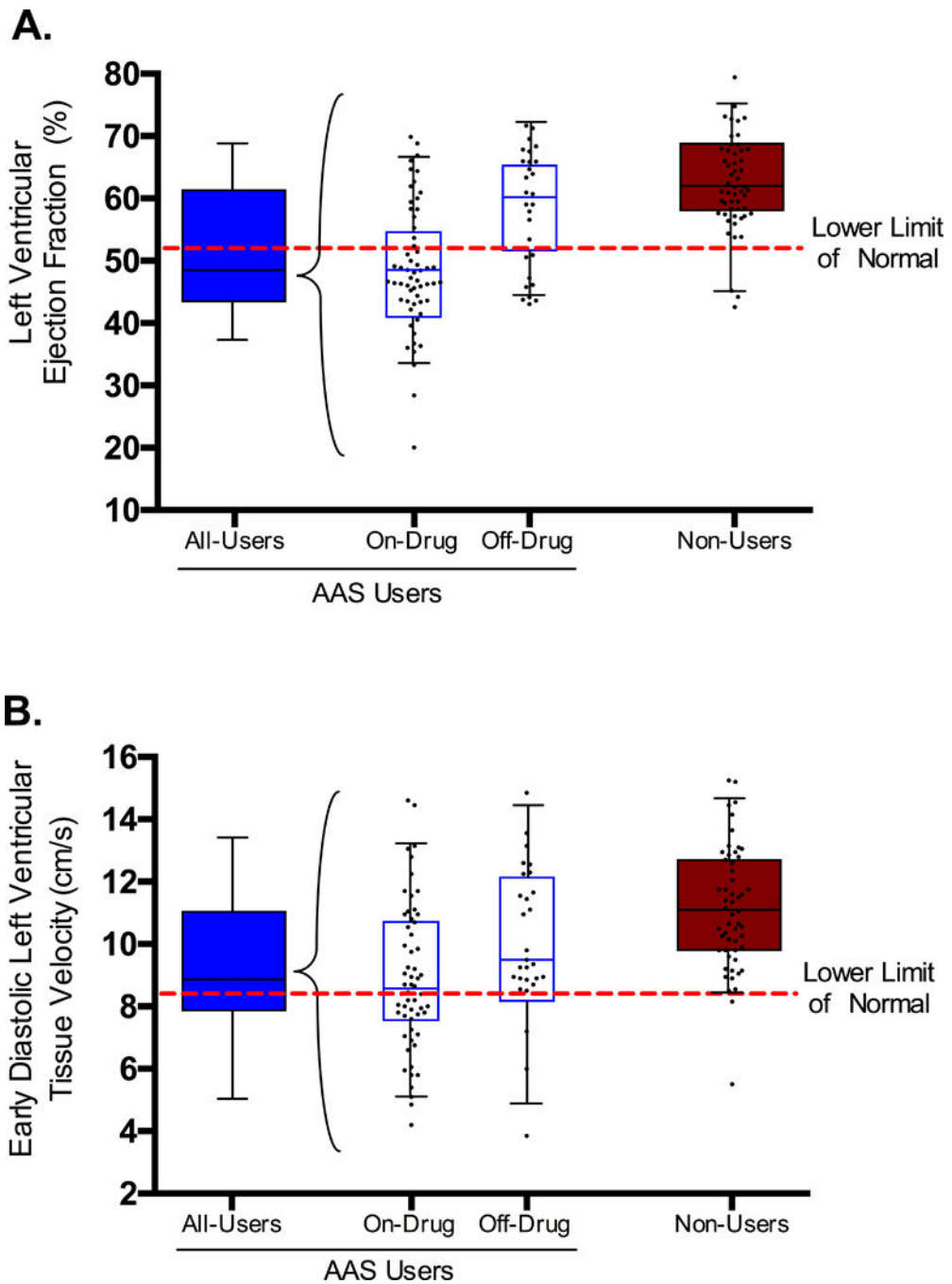
A.

B.

Figure 1. Left Ventricular Systolic and Diastolic Function in Anabolic-Androgenic Steroid Users and Comparison Non-Users

Panel A shows boxplots of left ventricular ejection fraction in anabolic-androgenic steroid (AAS) users (N=86), shown as an entire group (left side of figure) and as subgroups of individuals who were on-drug (N=58) and off-drug (N=28) at the time of evaluation (middle of figure). Non-users (N=54) appear on the right. On this variable, the estimated mean difference (95% confidence interval) between on-drug AAS users 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 non-users, the difference is −13.6% (−17.3% to −9.8%); P<0.001;

and for off-drug AAS users versus non-users, the difference is –4.1% (−8.6% to 0.3%); P=0.072. Panel B shows left ventricular early relaxation velocity in the same 4 groups. On this variable, the mean difference between on-drug AAS users and off-drug AAS users is −1.1 (−2.1 to −0.1) cm/s, P=0.035; for on-drug AAS users versus non-users, the difference is −2.2 (−3.1 to −1.4) cm/s, P<0.001; and for off-drug AAS users versus non-users, the difference is −1.1 (−2.2 to −0.1) cm/s; P=0.035.
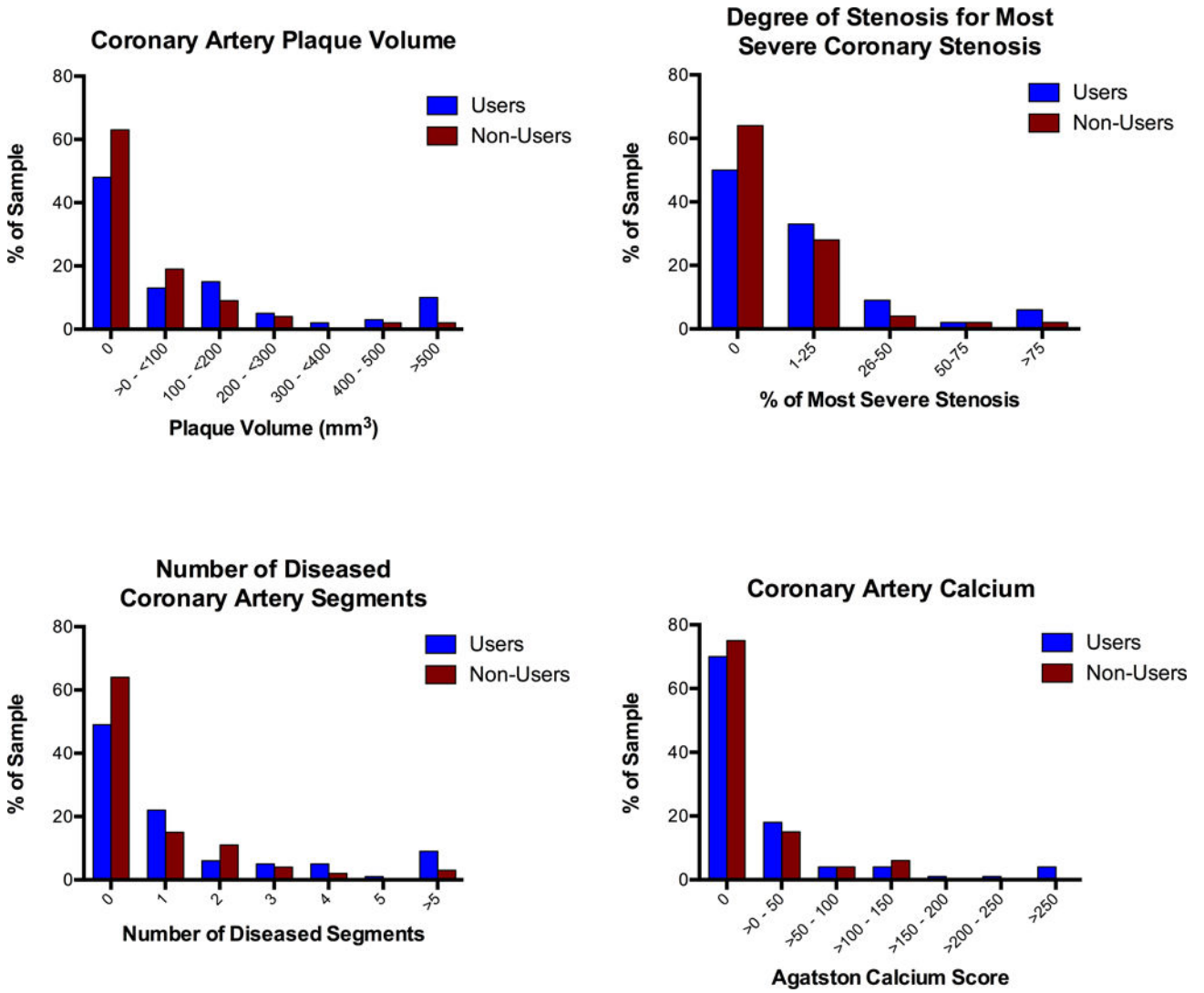
Figure 2. Distribution of Computed Tomography Coronary Angiography Measures in Anabolic-Androgenic Steroid Users and Non-Users

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 non-users (N=53). Note that the histograms for plaque volume and calcium score include for men with imputed values, as described in the footnote to Table 3.
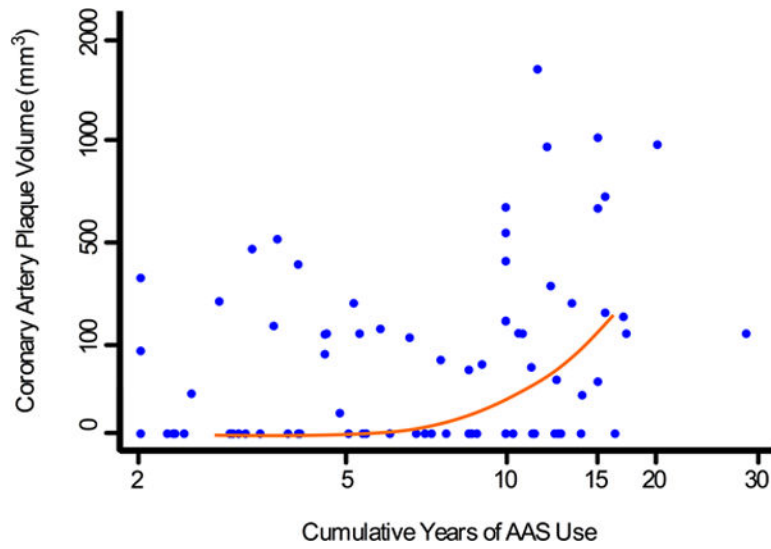
Figure 3. Relationship between Coronary Artery Plaque Volume and Cumulative Lifetime Duration of Anabolic-Androgenic Steroid Exposure

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).

Table 1

Characteristics of Anabolic-Androgenic Steroid Users and Non-Users. [*]

Characteristics	AAS Users (N = 86)	Non-Users (N = 54)	P Value
Demographic features			
Age, yr	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, yr	16 (14–20)	16 (15–20)	0.97
Lifetime duration of regular weightlifting, yr	21 (15–26)	20 (12–28)	0.78
Time spent in aerobic exercise per week#			
0–30 minutes	30 (35)	19 (35)	
31–120 minutes	24 (28)	22 (41)	0.18
Greater than 120 minutes	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, yr	23 (19–30)	—	
Cumulative lifetime total duration of AAS use, yr	7.4 (4.0–11.6)	—	
Cumulative lifetime dose of AAS, grams	366 (166–608)	—	

[*] Data are reported as median (IQR) or n (%) as appropriate. *P* values were obtained from a Wilcoxon rank sum test or Fisher's exact test. AAS indicates anabolic-androgenic steroids

[†] 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.

$\parallel$ 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.[37]

\# 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.[39]

Table 2

Echocardiographic Findings in Anabolic-Androgenic Steroid Users and Non-Users.[*]

Variable	AAS Users	Non-Users	Comparison Estimated difference (95% CI) [†]	P value
	(N = 86)	(N = 54)		
Primary outcomes				
Left ventricular ejection fraction, %	52±11	63±8	−10 (−14 to −7)	<0.001
Average early left ventricular relaxation velocity (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 to 6.0)	<0.001
Early lateral ventricular relaxation velocity (E′), cm/s	10.6±3.1	12.5±2.3	−1.8 (−2.9 to −0.8)	<0.001
Early septal ventricular relaxation velocity (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

[*] Data are reported as means±SD. AAS indicates anabolic-androgenic steroids; CI, confidence interval.

[†] 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 years, and body surface area by the Mosteller formula.

[‡] N = 85 AAS users

[§] N = 84 AAS users

Table 3

Computed Tomography Coronary Angiography Findings in Anabolic-Androgenic Steroid Users and Non-Users.[*]

Variable	AAS Users (N = 84)	Non-Users (N = 53)	Comparison Estimated difference in standardized ranks (95% CI) [†]	P Value
Primary outcome				
Plaque volume, mm³ [‡]	3 (0–174)	0 (0–69)	0.46 (0.10 to 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

[*] Data are shown as median (IQR). AAS indicates anabolic-androgenic steroids, CI, confidence interval.

[†] 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 years (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, the estimated mean difference (95% CI) between groups in standardized rank would be 0.43 (0.04 to 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 = 1–25%; 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

Association of Computed Tomography Coronary Angiography Variables with Lifetime Duration of Anabolic-Androgenic Steroid Use.[*]

Variable	Increase in standardized rank per 10-yr increase in duration of lifetime AAS use (95% CI) [†]	P Value
Primary outcome		
Plaque volume, mm³[‡]	0.60 (0.16 to 1.03)	0.008
Secondary outcomes		
Degree of stenosis for most severe stenosis[§]	0.68 (0.26 to 1.10)	0.002
Number of diseased coronary artery segments [‖]	0.75 (0.31 to 1.19)	< 0.001
Agatston calcium score[‡]	0.49 (0.06 to 0.92)	0.025

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

[†]
Represents the estimated increase in rank, measured in standard deviation units, for each 10-year 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 years (see text).

[‡]
Four AAS users had received prior 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, the increase (95% CI) in standardized rank per 10 years of AAS exposure would be 0.61 (0.11 to 1.12) for plaque volume and 0.48 (–0.04 to 0.99) for calcium score.

[§]
Represents the worst degree of stenosis of any coronary artery, on a scale of 0–4, where 0 = 0% stenosis; 1 = 1–25%; 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.