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# Anabolic steroids and cardiovascular risk: A national population-based cohort study

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ABSTRACT

*Background:* Non-therapeutic use of anabolic androgenic steroids (AAS) has been associated with various adverse effects; one of the most serious being direct cardiovascular effects with unknown long-term consequences. Therefore, large studies of the association between AAS and cardiovascular outcomes are warranted. We investigated cardiovascular morbidity and mortality in individuals who tested positive for AAS.

*Methods and results:* Between 2002 and 2009, a total of 2013 men were enrolled in a cohort on the date of their first AAS test. Mortality and morbidity after cohort entry was retrieved from national registries. Of the 2013 individuals, 409 (20%) tested positive for AAS. These men had twice the cardiovascular morbidity and mortality rate as those with negative tests (adjusted hazard ratio (aHR) 2.0; 95% confidence interval (CI) 1.2–3.3). Compared to the Swedish population, all tested men had an increased risk of premature death from all causes (standardized mortality ratio for AAS-positive: 19.3, 95% CI 12.4–30.0; for AAS-negative: 8.3, 95% CI 6.1–11.0).

*Conclusion:* Non-therapeutic exposure to AAS appears to be an independent risk factor for cardiovascular morbidity and premature death.



## 1. Introduction

Anabolic androgenic steroids (AAS) are synthetic derivatives of testosterone initially developed for clinical purposes (Woerdeman and de Ronde, 2011), but have received attention for their association with doping among athletes. Today, the non-therapeutic use of AAS has become a substantial problem among young recreational exercisers (Dunn and White, 2011). The reported population lifetime prevalence of AAS use in males varies between 1% and 5% in Western countries (Thiblin and Petersson, 2005) but may be much higher in selected settings, such as gyms (Mattila et al., 2010) or prison populations (Klotz et al., 2010). A strong association exists with weight training, even among people without competitive ambitions. AAS use has also become increasingly common among substance abusers (Petersson et al., 2010) and criminals (Klotz et al., 2007, 2010; Lundholm et al., 2010; Skarberg et al., 2010).

AAS use has been associated with a variety of psychiatric and somatic side effects. Some of these side effects are common, such as acne, testicular atrophy with reduced sperm count, and skin edema (Quaglio et al., 2009). Suggested mental side effects include aggressive behavior during use and depression after discontinuation (Thiblin and Petersson, 2005). Consequently, AAS abuse has been linked to violent crimes (Beaver et al., 2008; Lundholm et al., 2010; Pope and Katz, 1990; Skarberg et al., 2010) and suicide (Brower et al., 1989; Thiblin et al., 1999), although a direct causal relationship is uncertain.

Adverse cardiovascular effects are the most frequently reported among the suggested severe, potentially life-threatening, undesired consequences of AAS use. A number of case reports have described myocardial infarction in young AAS users (Thiblin and Petersson, 2005), and several echocardiography studies of AAS users have indicated that long-term AAS use may be linked to left ventricular hypertrophy and cardiac dysfunction, such as impaired ventricular inflow (Baggish et al., 2010). An association between use of AAS and cardiac hypertrophy has also been demonstrated in a study on deceased AAS users (Far et al., 2011). However, other studies have failed to demonstrate substantial effects of AAS on

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cardiac function (Zuliani et al., 1989; Palatini et al., 1996; Thompson et al., 1992; Hartgens et al., 2003; Hajimoradi and Kazerani, 2013). Indirect evidence of an increased risk of ischemic events has been provided by observational and experimental studies associating AAS use with atherogenesis, thrombogenesis, vasospasm, and endothelial dysfunction (Thiblin and Petersson, 2005; Maravelias et al., 2005). Direct cardiotoxic effects resulting in electrocardiographic disturbance have also been reported (Maior et al., 2013) and may result in contractile myocardial dysfunction (Baggish et al., 2010) and increased susceptibility to ischemic injury. However, the importance of non-symptomatic changes, such as left ventricular hypertrophy and endothelial dysfunction, remain controversial, and the mechanisms behind the possible effects of AAS on the heart are poorly understood (Angell et al., 2012).

Therefore, current understanding of the consequences of AAS use on cardiovascular risk is based primarily on indirect evidence and small observational studies (Angell et al., 2012). No large-scale epidemiological studies with long-term follow-up have investigated the potential association between AAS and cardiovascular events. The purpose of the present study was to estimate the association between non-therapeutic exposure to AAS and cardiovascular mortality and morbidity by means of long-term follow-up in a national cohort of men tested for AAS use.

## 2. Subjects and methods

### 2.1. Study population

All individuals tested for AAS at the Doping Laboratory at Karolinska University Hospital/Huddinge in Sweden who had a valid personal identification number and test date were enrolled in the cohort. Most individuals had their first test performed between 2002 and 2009. This laboratory was the only Swedish laboratory performing AAS analysis until January 1, 2008. Thereafter, analyses requested by the police were referred to the toxicological laboratory of the Swedish National Board of Forensic Medicine. Urine samples were provided by health care, police, prison and probation service, or customs. Doping tests of athletes performed by sports authorities do not contain personal identification numbers and, consequently, were not included in the study. The dates and results of the tests were combined with information from the national hospital discharge registry (Ludvigsson et al., 2011) and national cause of death registry using the unique personal identification numbers for person-based linkage (Ludvigsson et al., 2009). Individuals younger than 14 years ($n = 2$) or older than 55 years ($n = 13$) at the time of their first test were excluded from the cohort. The upper age limit was used to minimize the risk of including subjects who started to use AAS to counteract physical or sexual impairment, such as older men with short-term exposure. Women were excluded from the study because only 2.1% of the AAS-positive individuals were female. The study was approved by the regional ethical review board in Uppsala, Sweden.

### 2.2. Definition of AAS exposure

Testing positive for AAS at least once was defined as exposure. Testing negative for AAS at all times during the entire follow-up period was defined non-exposure. Exposure was also categorized according to the number of positive tests.

### 2.3. Definitions of outcomes

Cardiovascular events were defined as either a hospital episode with a diagnosis indicating a cardiovascular disorder (ICD-9 codes 39*–43*, 441–447, or 451–453 or ICD-10 codes I0*–I7* or I80-I82) that occurred after the first test for AAS, or an underlying cause of death from ICD-10 chapter IX. All-cause mortality was determined from the date of death in the cause of death registry.

### 2.4. Covariates

Age was used as the time scale in the time-dependent Cox regression analyses. An ecological variable indicating one of three different categories of socioeconomic status was defined based on the proportion of the population eligible for university education within each municipality. A proportion below the 30th percentile was categorized as low, a proportion above the 70th percentile as high, and all others as medium. These categories were assigned to each subject based on their residency. Country of birth was categorized as Sweden, European, or Non-European. AAS users have a propensity for concomitant abuse of other substances (McCabe et al., 2007). Alcohol-related disease (ICD-9: 291, 303, or 980; ICD-10: F10, T51, or X65) or substance abuse (ICD-9: 292, 304, 305, or 967–970; ICD-10: F11–F16, F18, F19, T40, X61, or X62) as indicated at hospital discharge or as cause of death were regarded as potential confounders in the multivariable analyses based on the assumption that these two variables are likely to be associated with AAS use and have a direct impact on the outcome (i.e., cardiac disease). Information on deaths related to alcohol or narcotics was retrieved from death certificate data. Individuals who use AAS also report irritability and depression/suicidal ideation as side effects (Thiblin and Petersson, 2005) and exhibit increased risk taking behavior (McCabe et al., 2007; Middleman et al., 1995). Hospital admissions for psychiatric disease or injury were also extracted from the data. A main cause of death from ICD-10 chapter XIX was considered to be caused by injury. Indicator variables were also defined for the principal hospital discharge diagnoses indicating injury (ICD-9 codes: 8**–9**; ICD-10 codes: S**–T**) or psychiatric disorders (ICD-9 codes: 29*–31*; ICD-10 codes: F**). Causes of injury and intentionality were derived from ICD-10 coding of external causes and classified according to the matrix developed by the National Center for Health Statistics, Centers for Disease Control, USA (MMWR, 1997). Psychiatric disease and injury were explored in univariate analyses but not considered appropriate to adjust for in the multivariable analyses. Psychiatric conditions and risk taking behavior, as reflected by these variables, could be risk factors for non-therapeutic AAS use, but they could also be caused by AAS exposure. Because an individual who tests positive for AAS many times may have been exposed long before the positive test, adjusting for such factors would be difficult. The univariate analysis also explored hospitalizations for cardiovascular disorders prior to testing positive for AAS, but they were not considered to influence exposure status and unlikely to confound the result.

The registries used in the present study do not contain data on smoking, thus making it impossible to control for that possible confounder.

### 2.5. Statistical analysis

For time to event analyses, person-time accumulated from the date of the first AAS test until an event or censoring on December 31, 2009. Events were defined sequentially as (a) deaths other than those caused by cardiovascular disorders or (b) cardiovascular events. For analysis of cardiovascular events, censoring was also done at the time of death from other causes.

By using gender and chronological 5-year age categories and annual calendar periods from 2002 through 2009, we created a contingency table of the observed number of deaths in the study population. Similarly, accumulated person-time for the corresponding gender, age groups, and calendar periods were calculated. The expected number of deaths was calculated by multiplying the age, gender, and time-specific person-times with the corresponding

incidences of deaths in the general Swedish population. Standardized mortality ratios (SMRs) were calculated by dividing the observed number by the expected number of deaths. The 95% confidence intervals (CIs) for the SMRs were estimated by assuming that the observed cases had a Poisson distribution using Byar's normal approximation (Breslow and Day, 1987).

To identify independent predictors of the time to event, a Cox proportional hazards model was applied with the AAS test result as a time updated exposure. The main model also included the following baseline covariates: age upon study entry (continuous), education level, country of birth, previous alcohol abuse, and substance abuse.

The statistical packages SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and R version 2.11.1 (R Foundation for Statistical Computing, Vienna, Austria) were used for data management and statistical analyses.

## 3. Results

### 3.1. Study population

A total of 3041 AAS tests were performed on 2013 individuals over 8 years. Twenty percent ($n = 409$) of these individuals tested positive for AAS at least once. The mean length of follow-up was 4.3 years. Individuals testing positive for AAS tended to be older when first tested, and more than 70% of all study subject were 30 years old or younger at the first test occasion (Table 1). Those testing positive were more likely to have Sweden as their country of birth, but there were no major differences in education level from those testing negative. Multiple tests were performed on 22% of the study population, and 26% of those testing positive did so on two or more occasions.

### 3.2. AAS exposure and cardiovascular events

When adjusting only for age, AAS exposure predicts an approximately doubled risk of a cardiovascular event. Adjusting for education level, country of birth, and previous alcohol or substance abuse attenuated, but maintained, the association with cardiovascular events (hazard ratio (HR) 2.0; 95% CI 1.2–3.3; Table 2).

There were 24 (5.9%) cardiovascular events among those who had tested positive for AAS at any occasion and 46 (2.8%) cardiovascular events among those who had never tested positive. When comparing different diagnostic categories, there were some imbalances between the groups, but the numbers were too small to allow any detailed analysis (Table 3).

### 3.3. AAS exposure and all-cause mortality

A total of 70 deaths occurred, 24 among the 409 subjects testing positive (mortality rate 13.5 per 1000 person-years) and 46 among 1604 individuals who tested negative (mortality rate 6.7 per 1000 person-years).

**Table 1**
Characteristics of the study population.

| | No positive tests during follow-up ($n = 1605$) | Positive tests during follow-up ($n = 409$) | All study subjects ($n = 2114$) |
|---|---|---|---|
| Years of follow-up, mean (SD) | 4.3 (2.3) | 4.3 (2.4) | 4.3 (2.3) |
| Age at first test, *n* (%) | | | |
| 14–20 yr | 487 (30.3) | 83 (20.3) | 570 (28.3) |
| 21–25 yr | 338 (21.1) | 118 (28.9) | 456 (22.6) |
| 26–30 yr | 328 (20.4) | 104 (25.4) | 432 (21.4) |
| 31–40 yr | 315 (19.6) | 84 (20.5) | 399 (19.8) |
| 40–54 yr | 137 (8.5) | 20 (4.9) | 157 (7.8) |
| Number of performed tests, *n* (%) | | | |
| 1 | 1364 (85.0) | 203 (49.6) | 1567 (77.8) |
| 2 | 151 (9.4) | 98 (24.0) | 249 (12.4) |
| 3+ | 90 (5.6) | 108 (26.4) | 198 (9.8) |
| Number of positive tests, *n* (%) | | | |
| 0 | 1605 (100.0) | 0 (0.0) | 1605 (79.7) |
| 1 | 0 (0.0) | 289 (70.7) | 289 (14.3) |
| 2+ | 0 (0.0) | 120 (29.3) | 120 (6.0) |
| Period of test, *n* (%) | | | |
| Only tested with known dates | 1560 (97.2) | 352 (86.1) | 1912 (94.9) |
| Earlier tested without known dates | 45 (2.8) | 57 (13.9) | 102 (5.1) |
| Country of origin, *n* (%) | | | |
| Sweden | 1206 (75.1) | 342 (83.6) | 1548 (76.9) |
| European | 93 (5.8) | 18 (4.4) | 111 (5.5) |
| Non European | 306 (19.1) | 49 (12.0) | 355 (17.6) |
| Education, *n* (%) | | | |
| Low | 548 (34.1) | 139 (34.0) | 687 (34.1) |
| Middle | 776 (48.3) | 218 (53.3) | 994 (49.4) |
| High | 183 (11.4) | 41 (10.0) | 224 (11.1) |
| Missing data | 98 (6.1) | 11 (2.7) | 109 (5.4) |
| Pre-test events, *n* (%) | | | |
| Heart | 42 (2.6) | 15 (3.7) | 57 (2.8) |
| Psych | 533 (33.2) | 193 (47.2) | 726 (36.0) |
| Injury | 418 (26.0) | 157 (38.4) | 575 (28.6) |
| Pre-test alcohol, *n* (%) | | | |
| Yes | 188 (11.7) | 57 (13.9) | 245 (12.2) |
| No | 1416 (88.3) | 352 (86.1) | 1768 (87.8) |
| Pre-test drug, *n* (%) | | | |
| Yes | 371 (23.1) | 155 (37.9) | 526 (26.1) |
| No | 1233 (76.9) | 254 (62.1) | 1487 (73.9) |

**Table 2**
Multivariable analysis presenting hazard ratios of risk factors for cardiovascular events and all-cause death using Cox regression with age as time scale and time-dependent covariates.

| | Nr events | Incidence per 1000 pnyrs | Unadjusted | | Adjusted for education and country of birth | | Adjusted for education, country of birth, previous alcohol and drug abuse | |
|---|---|---|---|---|---|---|---|---|
| Death | | | | | | | | |
| Not exposed | 46 | 6.7 | 1.00 | Ref | 1.00 | Ref | 1.00 | Ref |
| Exposed | 24 | 14.0 | 2.05 | (1.24–3.38) | 1.99 | (1.20–3.31) | 1.69 | (1.02–2.82) |
| 0 positive tests | 46 | 6.7 | 1.00 | Ref | 1.00 | Ref | 1.00 | Ref |
| 1 positive test | 15 | 12.0 | 1.78 | (0.99–3.21) | 1.73 | (0.96–3.12) | 1.49 | (0.82–2.70) |
| 2+ positive tests | 9 | 19.1 | 2.74 | (1.33–5.65) | 2.71 | (1.31–5.64) | 2.21 | (1.06–4.60) |
| Trend | | | 1.17 | (1.05–1.31) | 1.17 | (1.05–1.31) | 1.17 | (1.02–1.34) |
| Cardiovascular event | | | | | | | | |
| Not exposed | 46 | 6.7 | 1.00 | Ref | 1.00 | Ref | 1.00 | Ref |
| Exposed | 24 | 14.0 | 2.18 | (1.32–3.62) | 2.03 | (1.22–3.38) | 1.99 | (1.19–3.33) |
| 0 positive tests | 46 | 6.7 | 1.00 | Ref | 1.00 | Ref | 1.00 | Ref |
| 1 positive test | 17 | 13.6 | 2.13 | (1.21–3.74) | 1.97 | (1.11–3.47) | 1.93 | (1.09–3.42) |
| 2+ positive tests | 7 | 15.0 | 2.34 | (1.05–5.25) | 2.20 | (0.98–4.97) | 2.16 | (0.95–4.90) |
| Trend | | | 1.11 | (0.96–1.29) | 1.11 | (0.96–1.28) | 1.11 | (0.95–1.29) |

**Table 3**
Cardiovascular events captured from diagnoses either at hospital discharge or in connection with autopsy and categorised. Note that some subjects had multiple diagnostic categories. The percentages are in relation to the number of subjects in each exposure category. The results are summarized according to result of anabolic androgen steroid (AAS) testing. This summary is purely descriptive and should be interpreted with caution due to the small numbers in each category.

| | AAS negative (count) | AAS negative (%) | AAS positive (count) | AAS positive (%) |
|---|---|---|---|---|
| Hypertensive diseases (I10–I15) | 4 | 0.25 | 6 | 1.47 |
| Ischemic heart diseases (I20–I25) | 6 | 0.37 | 4 | 0.98 |
| Arrythmias (I44–I45. I47–I49) | 13 | 0.81 | 3 | 0.73 |
| Cerebrovascular diseases (I60–I69) | 6 | 0.37 | 3 | 0.73 |
| Heart failure (I50) | 3 | 0.19 | 3 | 0.73 |
| Pericarditis, endocarditis, myocarditis (I30–I33, I38–I41) | 7 | 0.44 | 2 | 0.49 |
| Pulmonary heart disease and diseases of pulmonary circulation (I26–I28) | 2 | 0.12 | 2 | 0.49 |
| Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified (I80–I89) | 5 | 0.31 | 1 | 0.24 |
| Cardiomyopathy (I42–I43) | 1 | 0.06 | 0 | 0 |
| Diseases of arteries, arterioles and capillaries (I70–I79) | 1 | 0.06 | 0 | 0 |
| Valvular diseases (I34–I37) | 2 | 0.12 | 0 | 0 |
| Other (I51–I52) | 4 | 0.25 | 0 | 0 |

Irrespective of the AAS test result, the study population had a substantially higher mortality risk than would be expected compared with the general population. The AAS-positive group had an SMR of 18.3 (95% CI 11.7–27.3), and the AAS-negative group had an SMR of 8.2 (95% CI 6.0–11.0). An even higher risk was found among those with more than one positive test. Among those testing positive, individuals with only one positive test had an SMR of 16.9 (95% CI 9.8–27.3), compared to an SMR of 23.2 (95% CI 9.3–47.8) for those testing positive on multiple occasions. A previous diagnosis of alcohol-related or substance abuse-related disease had a similar impact on the SMR as AAS exposure (Table 4).

Information on cause and manner of death was available for those who had died before 2009 ($n = 55$). Approximately 40% (7/18) of deaths among those who had tested positive for AAS were intentional (homicide or suicide), compared with 14% (5/37) among those who tested negative. The reverse pattern was seen for unintentional injury that caused 6% (1/18) of deaths in AAS-positive subjects compared to 22% (8/37) of deaths in AAS-negative. There were no other obvious differences with respect to cause and manner of death (Table 5).

**Table 4**
Standardized mortality ratios.

| | Observed/expected number of deaths | SMR | 95% CI |
|---|---|---|---|
| All study subjects | 70/6.9 | 10.1 | (7.91–12.8) |
| Exposure to AAS | | | |
| No | 46/5.6 | 8.23 | (6.03–11.0) |
| Yes | 24/1.3 | 18.3 | (11.7–27.3) |
| Diagnosis indicating alcohol abuse before first test for AAS | | | |
| No | 51/6.0 | 8.45 | (6.29–11.1) |
| Yes | 19/0.9 | 21.9 | (13.2–34.3) |
| Diagnosis indicating other substance abuse before first test for AAS | | | |
| No | 27/5.2 | 5.23 | (3.45–7.61) |
| Yes | 43/1.7 | 24.7 | (17.9–33.3) |

## 4. Discussion

In this nationwide, population-based cohort study of subjects tested for AAS during a seven-year period, a positive test result was associated with increased cardiovascular morbidity and all-cause mortality. Irrespective of test result, the population subjected to AAS testing has a substantially increased risk of mortality standardized for age and gender compared with the general population. Using time-updated covariates, repeat positive tests also indicated a dose-response pattern for both premature death and cardiovascular events.

Considering the young age of the study subjects and the similar SMR patterns related to AAS exposure and previous alcohol or substance abuse problems, most deaths can reasonably be assumed to be related to substance abuse, and the AAS-positive group was likely burdened by a more pronounced substance abuse problem. Thus, the finding of a stronger association with premature death in those who have tested positive for AAS two or more times compared to those who had only one positive test indicates that more

**Table 5**
Cause and manner of death in 55 males who have tested positively or negatively for use of AAS.

| Cause and manner of death | AAS-positive | AAS-negative |
|---|---|---|
| Natural death (disease) | | |
| Atherosclerotic cardiovascular disease | 0 | 1 |
| Cardiac hypertrophy | 1 | 1 |
| Myocarditis | 0 | 1 |
| Pneumonia | 0 | 1 |
| Ruptured esophageal varices | 0 | 1 |
| Acute myeloid leukemia | 0 | 1 |
| Cause of death unclear | 0 | 2 |
| Unnatural death | | |
| Homicide | 3 | 1 |
| Suicide | 4 | 4 |
| Traumatic accident | 1 | 8 |
| Poisoning illicit drugs or pharmaceuticals | 5 | 13 |
| Acute alcohol intoxication* | 2 | 1 |
| Drowning | 1 | 0 |
| Dependence syndrome | 1 | 2 |
| Total | 18 | 37 |

* Including one case of positional asphyxia and one case of aspiration during intoxication.

advanced use of AAS was connected to more advanced substance abuse in the study population. This assumption is in line with earlier studies that demonstrated a strong connection between AAS and substance abuse in Swedish AAS users (Petersson et al., 2006a, 2006b, 2010; Skarberg et al., 2009; Garevik and Rane, 2010) and that a considerable proportion of those who died did so due to drug overdose (Petersson et al., 2006b). In other words, the major explanation for the high mortality among AAS users could be a general substance abuse problem. However, the relatively high proportion of intentional death (homicide or suicide) in the AAS-positive group may be related more specifically to the use of AAS. There is evidence for an association between use of AAS and criminality (Garevik and Rane, 2010; Klotz et al., 2007, 2010; Lundholm et al., 2010; Skarberg et al., 2010), as well as for an increased risk for suicide (Brower et al., 1989; Thiblin et al., 1999). The same pattern with a relatively high proportion of intentional death among ASS users compared with users of other illicit drugs was noted in an earlier Swedish study based on medico-legally examined deceased substance abusers (Petersson et al., 2006b).

It has been suggested that AAS may serve as a gateway to opioid dependence (Arvary and Pope, 2000). The same investigators have later questioned this possibility providing some evidence for AAS abuse being part of a general tendency for drug abuse (Kanayama et al., 2010), a position that seems to be supported by a study demonstrating that many AAS users fulfill DSM IV criteria for substance abuse and dependence (Copeland et al., 2000). However, a fairly recent review article on the use of AAS and polypharmacy came to the conclusion that there is little data to answer the question whether AAS serve as a risk factor for use of other drugs or if it is the other way round (Dodge and Hoagland, 2011). Since many of the AAS positive subjects in the present study appear to have had a drug abuse diagnosis prior to the first AAS positive test, this may be regarded as a finding consistent with the hypothesis that AAS abuse usually is related to a general tendency for drug abuse. However, this suggested support for the common diatheses hypothesis must be regarded with great caution since there is no information on AAS use patterns before the AAS testing in our data.

In contrast to all-cause death, which is explained to a large extent by factors other than AAS use, the significant overrepresentation of cardiac events is likely to have a causal connection to AAS use. This notion is motivated by our findings that the difference remained after adjusting for the possible identified confounders (keeping in mind that smoking was not controlled for) and is also in line with a large body of scientific literature describing various adverse cardiac effects of illicit AAS use (Vanberg and Atar, 2010). Also the fact that the cardiovascular events appeared to be represented by cardiac diseases previously associated with use of AAS (e.g., sudden cardiac death and heart failure (Montisci et al., 2012; Sullivan et al., 1998; Thiblin et al., 2000) to a higher degree among the AAS-positive subjects than was the case for the AAS-negative subjects seems to support a causal connection. Two recent large-scale epidemiological studies reported an increased risk of myocardial infarction related to therapeutic testosterone treatment (Finkle et al., 2014; Vigen et al., 2013). A clinical trial on testosterone treatment in older men with limited mobility and a high prevalence of cardiovascular diseases was stopped prematurely due to increased cardiovascular events in the treatment group (Basaria et al., 2010).

We acknowledge that using repeated positive test results as a proxy for cumulative exposure is not entirely robust. For instance, there is no information on the reason for some subjects performing only one test and other subjects performing several tests. Thus, there is a risk for reversed causality; multiple tests were performed on the basis of disease thought to be related to use of AAS. However, the dose–response relationship indicated by using this updated strategy is in line with previous observations indicating such a relationship with cardiac disease (Thiblin and Petersson, 2005).

AAS is an elusive exposure to study, as it is illegal and associated with other illicit substance abuse and criminal behavior. Therefore, quantifying an individual's exposure to AAS remains exceedingly difficult. Defining exposure based on a positive test result and counting exposed person-time from the test date means that exposure was underestimated, possibly leading to conservative estimates. The actual duration of exposure will remain uncertain, and the actual dose unknown. Thus, the true extent of AAS use will be difficult to estimate. The population tested for AAS likely represents a small and vulnerable part of the population actually using AAS.

Although we had the opportunity to adjust for several possible confounders, one has to consider that there might have been other unmeasured confounders that increase the risk for cardiac disease and all-cause mortality. One obvious unmeasured confounder is smoking tobacco, since long-term heavy smoking doubles the rate of cardiovascular mortality (Jacobs et al., 1999). There is, however, no clear relation between use of AAS and use of tobacco (Dodge and Hoagland, 2011). One Norwegian study displayed that smokeless tobacco predicts lifetime use of AAS, whereas smoking did not (Wikstrom and Pedersen, 2001) which may also be of relevance for Swedish AAS users (Kindlund et al., 1998).

The present study has some unique strengths. The study was made possible by the centralized analysis of all AAS test samples and exact record linkage to national health care registries using unique personal identification numbers (Ludvigsson et al., 2009, 2011). Given the relative youth of the population studied and the low baseline incidence of cardiovascular outcomes, the large linked dataset still provides unique opportunities to study this difficult research question. In contrast to most previous studies reporting the effects of AAS in relation to self-reported AAS use, the use of AAS was determined objectively in the present study.

In conclusion, the results of the present study indicate that AAS use is an independent risk factor for cardiac events resulting in hospital admission or death.

## Author disclosures

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## Contributors

Hans Garmo made all statistical calculations.

Lars Holmberg contributed to the study design and took part in the further writing of the first manuscript as well as the revision of the manuscript.

Liisa Byberg contributed to the study design and took part in the further writing of the first manuscript as well as the revision of the manuscript.

Karl Michaëlsson contributed to the study design and took part in the further writing of the first manuscript as well as the revision of the manuscript.

Mats Garle provided raw data from the Doping Laboratory, contributed to the study design and took part in the further writing of the first manuscript as well as the revision of the manuscript.

Rolf Gedeborg handled all data management, contributed to the study design and took part in the further writing of the first manuscript as well as the revision of the manuscript.

All authors have approved the final article.

## Conflicts of interest

None.

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