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Adverse effects of anabolic androgenic steroids abuse on gonadal function, glucose homeostasis and cardiovascular function

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Disclosures

Received unrestricted research grants from:

- Antidoping Denmark
- Danish Heart Foundation

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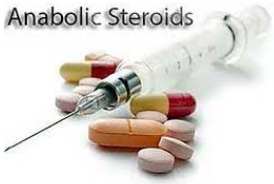
Agenda

- Background
- Study Protocol
- Results
  - Hormonal disturbances (Androgens and Fertility Markers)
  - Insulin Sensitivity
  - Blood Pressure and Arterial Stiffness
  - The Heart



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Hypotheses

Is AAS abuse associated with:

- Persistent symptoms of hypogonadism after AAS discontinuation?
- Decreased insulin sensitivity?
- Hypertension and arterial stiffness?
- Impaired cardiac function and myocardial fibrosis?

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Cross-sectional study ('Pseudo-longitudinal design')

No AAS → Current AAS abuse → After AAS abuse

Variables	Control Participants N=30	Current AAS Abusers N=37	Former AAS Abusers N=33	P-value
Age (years)	31.5 (1.2)	31.4 (1.4)	34.8 (1.2)	0.11
Accumulated duration on AAS (weeks)	-	142.3 (99.7 - 203.1)	111.8 (81.3 - 153.7)	0.32
Duration since AAS cessation (years)	-	-	2.6 (1.7 – 3.7)	

Exclusion Criteria: known DM/CVD, congenital hypogonadism, medically prescribed testosterone therapy

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Physical exam

- Orchidometer

Hormone analyses (morning)

- Total/free testosterone (+other androgens)
- Estrogens
- Gonadotropins
- Inhibin B og Anti-Müllerian Hormone

Questionaires

- Erectile dysfunction (IIEF-5)
- Depressive symptoms (BDI-II)
- SF-36

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Glucose tolerance (OGTT) and body composition

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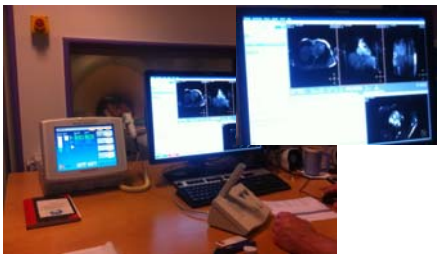

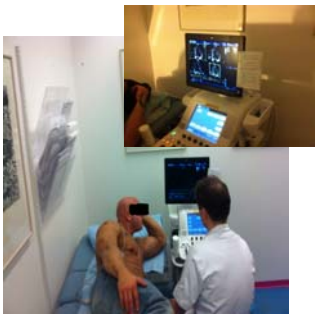

- 24-hour BP monitoring
- Pulse wave analysis (PWA)
- Advanced Echocardiography
- Cardiac MRI (with Late-Gadolineum Enhancement)
- Blood samples

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Results

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RESEARCH ARTICLE

Former Abusers of Anabolic Androgenic Steroids Exhibit Decreased Testosterone Levels and Hypogonadal Symptoms Years after Cessation: A Case-Control Study

Jon Jarløv Rasmussen[1]*, Christian Selmer[1], Peter Busch Østergren[2], Karen Boje Pedersen[3], Morten Schou[4], Finn Gustafsson[5], Jens Faber[1], Anders Juul[6], Caroline Kistorp[1]

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Rasmussen et al *PLOS ONE* (2016)

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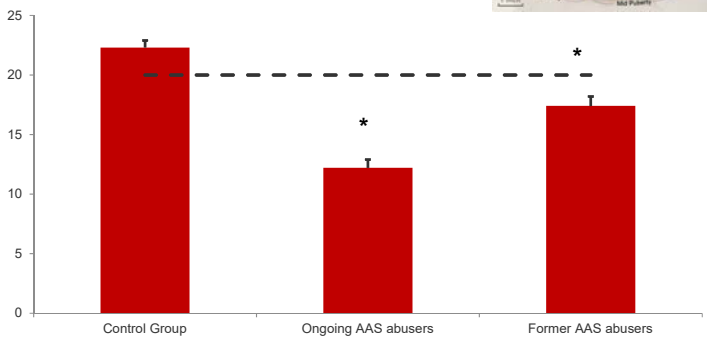
Testicular size



Rasmussen et al *PLOS ONE* (2016)

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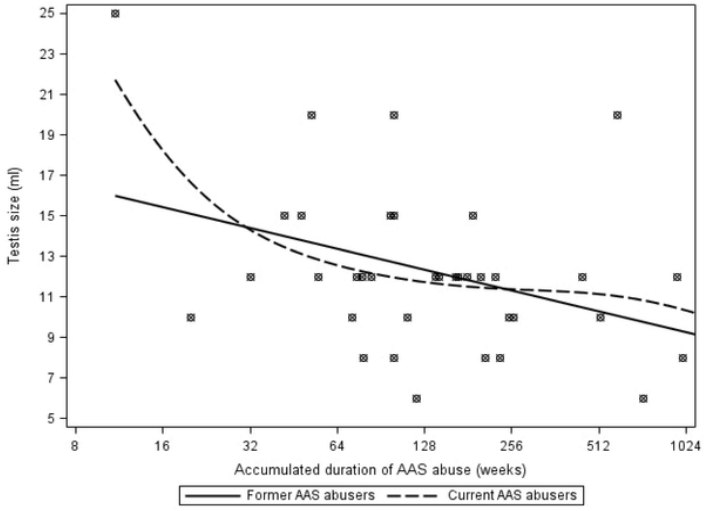
Fig 1. Association between accumulated duration of AAS abuse (log 2 scale) and testis size in current AAS abusers (spline function) and former AAS abusers.



Rasmussen JJ, Selmer C, Østergren PB, Pedersen KB, Schou M, et al. (2016) Former Abusers of Anabolic Androgenic Steroids Exhibit Decreased Testosterone Levels and Hypogonadal Symptoms Years after Cessation: A Case-Control Study. PLoS ONE 11(8): e0161208. doi:10.1371/journal.pone.0161208
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0161208

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Variable	Control group	Current AAS abusers	Former AAS abusers	p-value
	n = 30	n = 37	n = 33	
Testicular size (ml) ¶	22.3 (0.6) *b*	12.2 (0.7)	17.4 (0.8)	< 0.01
P-total testosterone (nmol/l)	18.8 (16.6–22.0) *b*	98.3 (47.4–122.7)	14.4 (11.9–17.7)	< 0.01
P-free testosterone (pmol/l)	480 (420–530) *b*	3780 (1870–5500)	410 (320–480)	< 0.01
P-androstendione (nmol/l) •	2.53 (2.27–2.82)	6.92 (5.41–8.84) *a*	2.33 (2.06–2.63)	< 0.01
P-DHEAS (nmol/l) ¶	4805 (391)	4929 (490)	4348 (302)	0.55
P-SHBG (nmol/l) •	33.3 (29.1–38.1)	8.4 (6.3–11.1) *a*	26.2 (20.7–33.1)	< 0.01
P-17 hydroxyprogesterone (nmol/l) •	2.88 (2.49–3.33)	0.14 (0.10–0.18) *a*	2.42 (1.86–3.15)	< 0.01
P-FSH (U/l)	4.2 (3.2–5.7)	0.3 (0.1–0.4) *a*	4.4 (3.3–6.2)	< 0.01
P-LH (U/l)	3.1 (2.5–3.9)	<0.1 (<0.1–0.1) *a*	3.6 (2.2–4.3)	< 0.01
S-inhibin B (pg/ml) ¶	175 (9)	81 (8) *a*	170 (11)	< 0.01
S-AMH (pmol/l) •	49.5 (41.6–59.0)	21.6 (16.3–28.7) *a*	44.7 (37.2–53.7)	< 0.01

Results are medians (25^{th}– 75^{th} percentiles) unless otherwise stated.
¶ Mean (standard error)
• Geometric mean (95% confidence interval)
Tukey's post-hoc test (mean and geometric mean) or Bonferroni's post-hoc test (medians)
a significant difference between the group of current AAS abusers and the two other groups
b significant difference among all three groups
AAS, anabolic androgenic steroids, **AMH,** anti-Müllerian hormone; **DHEAS,** dehydroepiandrosteronsulfate; **FSH,** follicle-stimulating hormone; **LH,** luteinizing hormone; **P-,** plasma; **S-,** serum **SHBG,** sexual hormone-binding globulin.

doi:10.1371/journal.pone.0161208.t002

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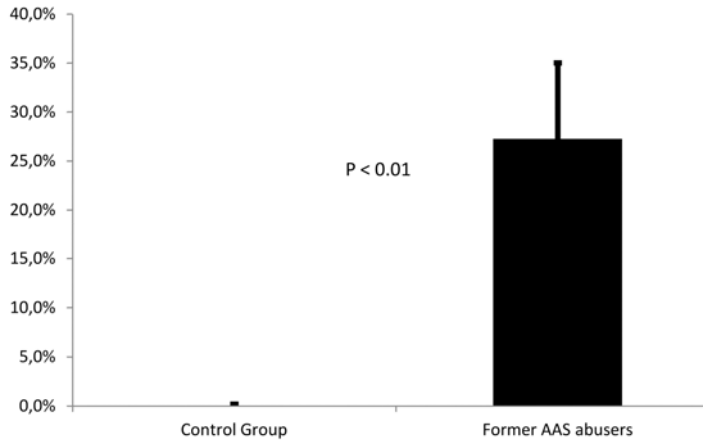
Total Testosterone < 12.1 nmol/l



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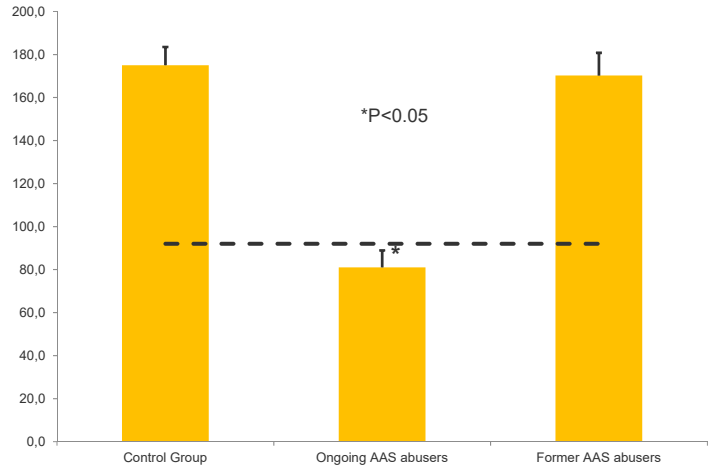
S-Inhibin B (pg/ml) (Sertoli cells, spermatogenesis)



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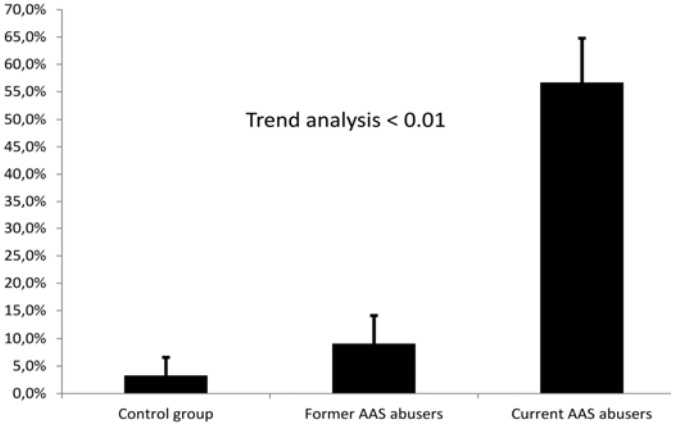
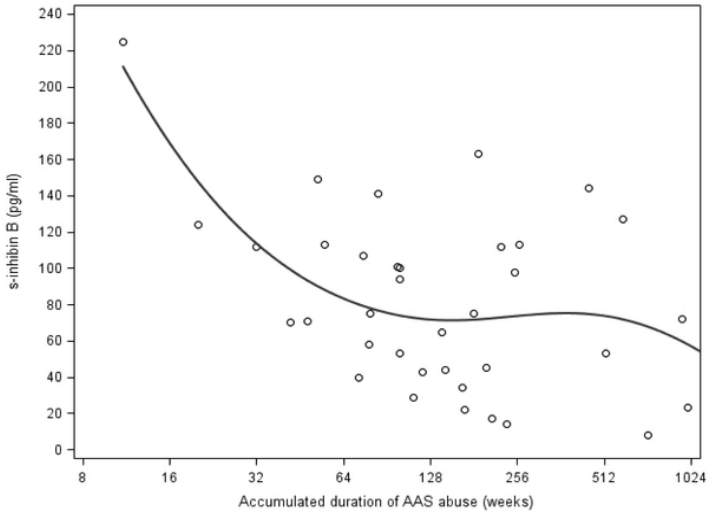
Impaired spermatogenesis (Inhibin B<92)



Rasmussen et al. *PLOS ONE* (2016)

Fig 4. Association between accumulated duration of AAS abuse (log 2 scale spline function) and serum inhibin B levels in current AAS abusers.



Rasmussen JJ, Selmer C, Østergren PB, Pedersen KB, Schou M, et al. (2016) Former Abusers of Anabolic Androgenic Steroids Exhibit Decreased Testosterone Levels and Hypogonadal Symptoms Years after Cessation: A Case-Control Study. PLoS ONE 11(8): e0161208. doi:10.1371/journal.pone.0161208
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0161208

Fig 5. Association between accumulated duration of AAS abuse (log2 scale) and serum anti-Müllerian hormone levels (AMH, log2 scale) in current AAS abusers.

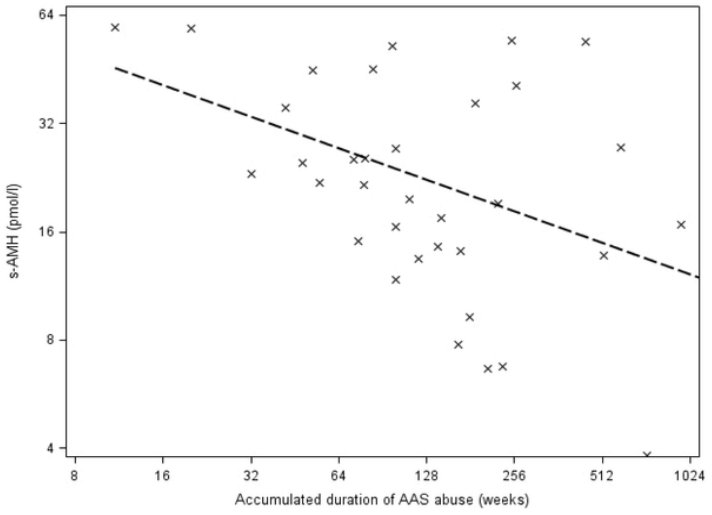


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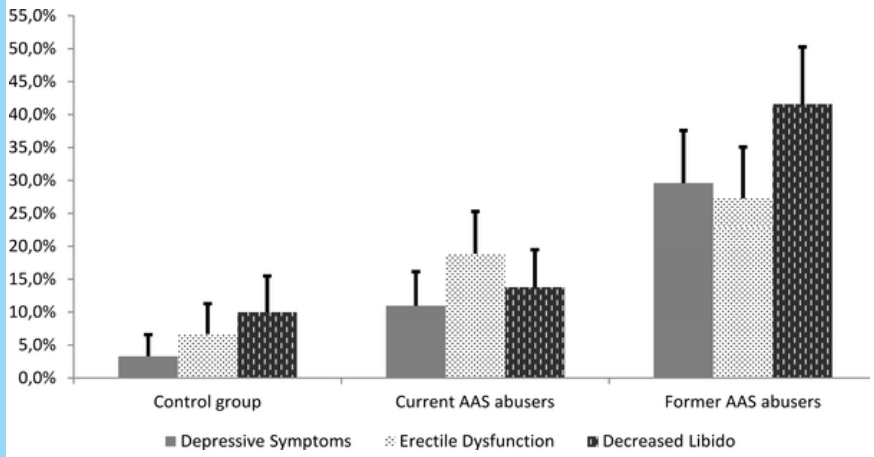
Fig 6. Symptoms of depression, erectile dysfunction and decreased libido in the three groups.



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http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0161208

PLOS ONE

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AAS-induced hypogonadism

- Frequent condition among AAS abusers
- Decreased testosterone levels seem to persist among many former AAS abusers years after AAS discontinuation
- Spermatogenesis seem to recover within 6-12 months
- Withdrawal/hypogonadal symptoms persist years after AAS discontinuation

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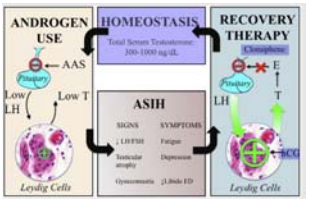
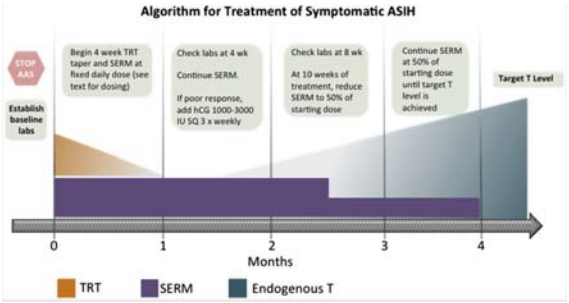
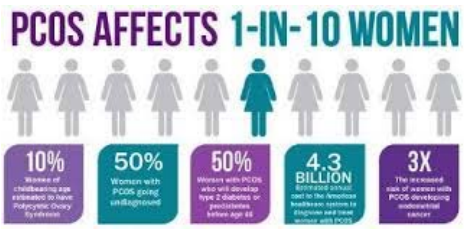
Perspectives: treatment with clomiphene?





Rahnema et al. *Fertility and Sterility* (2014)

Supraphysiologic levels of androgens→ Insulin resistance?



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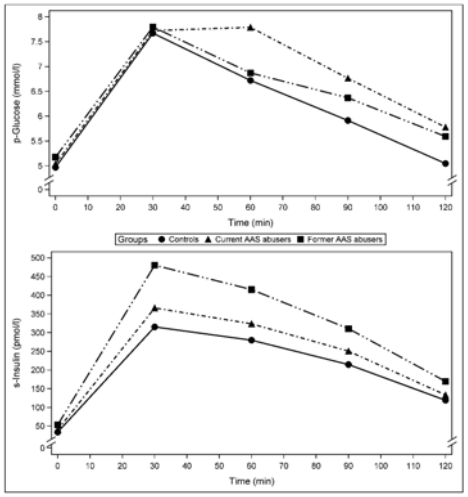
Oral glucose tolerance test (120 min)



Rasmussen et al. Clinical Endocrcrinology (in press)

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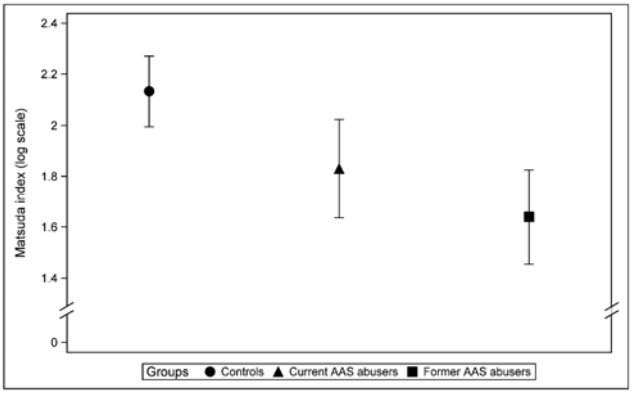
Insulin sensitivity (Matsuda index)



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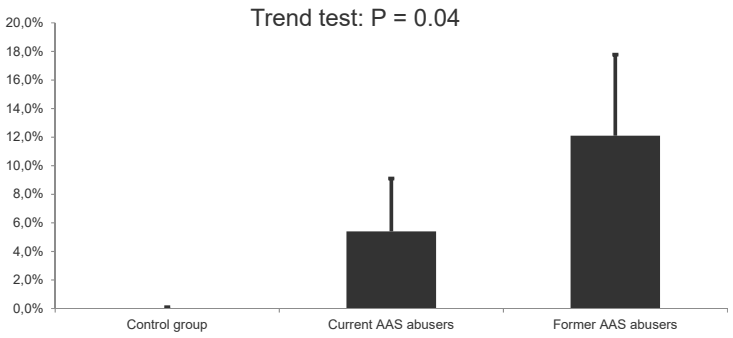
Impaired Glucose Tolerance



Rasmussen et al umpublished

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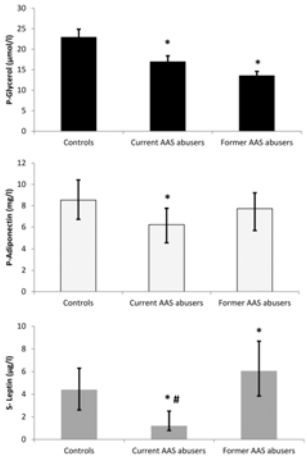
AAS → adverse effect on adipose tissue?



*P<0.05

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Body Composition

Body composition and fat mass distribution	Controls	Current AAS abusers	Former AAS abusers	
BMI (kg/m^2)	27.2 (0.6)	30.8 (0.4)	28.5 (0.6)	<0.01
Total lean mass (kg)	70.7 (1.5)	81.3 (1.4)	71.2 (1.6)	<0.01
Total fat mass (kg)	15.3 (0.9)	13.4 (0.5)	17.5 (0.8)	<0.01
Body fat (%)	17.5 (0.7)	14.1 (0.4)	19.4 (0.6)	<0.01
Abdominal VAT volume (cm^3)	293.3 (11.7)	388.4 (17.1)	347.4 (17.3)	<0.01
Android fat mass (g)	1300 (95)	1198 (54)	1603 (91) b	<0.01

Total testosterone inversely associated with fat mass:
Age-adjusted: -1.1 (-2.0 ; -0.1), P = 0.02)

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Cardiovascular risks

- Hypertension?
- Stroke?
- Dyslipidemia?
- Atherosclerosis?
- Sudden cardiac death?
- Heart Failure (myocardial fibrosis)?

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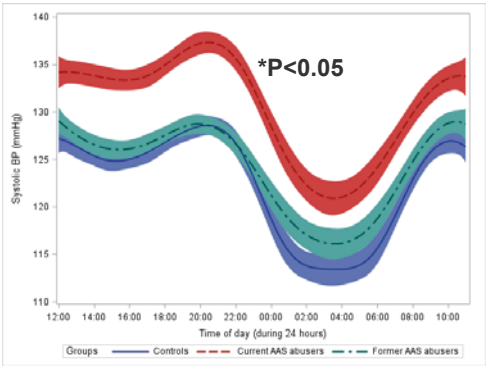
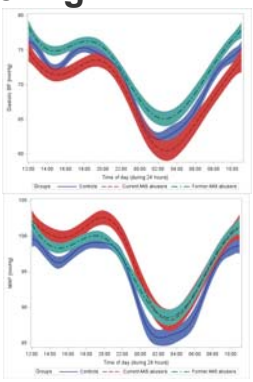
24-hour Blood Pressure Monitoring





- **Current AAS abusers exhibited higher 24-hour systolic BP compared with control participants (8.8 (2.9 ; 14.8) mmHg)**
- Diastolic BP and MAP did not differ among the 3 groups

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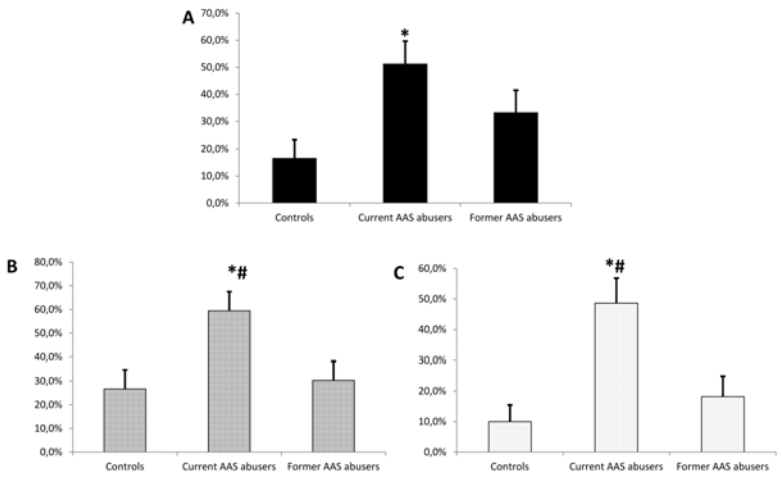
24-hour systolic hypertension



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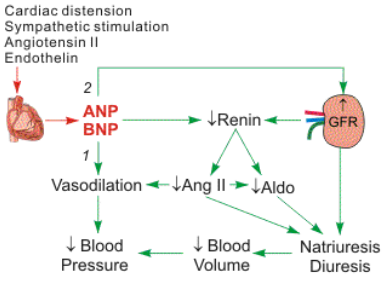
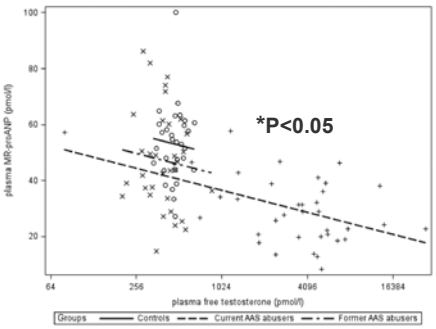
Cardiac natriuretic peptides and testosterone





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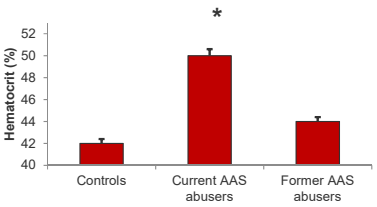
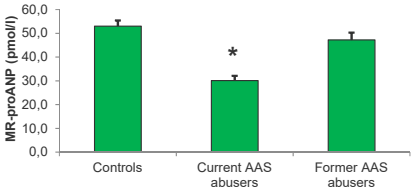
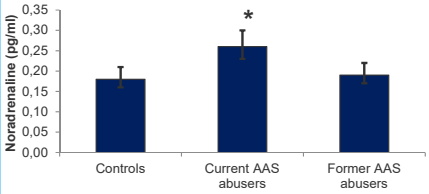
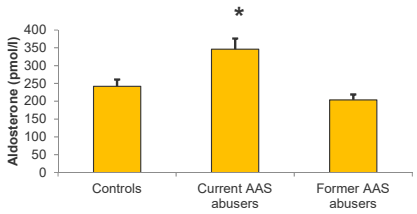
Lab Analyses









Rasmussen et al, unpublished

Adjustment for differences in lab analyses balanced differences in systolic BP (P = 0.94)

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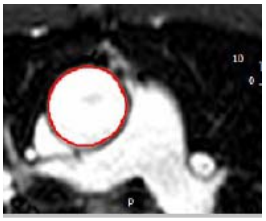
Method

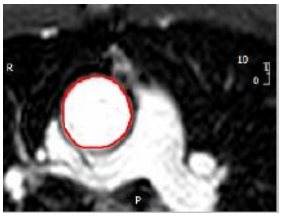
- **Central arterial stiffness?**
- Aorta Distensibility Index:

$$\frac{\text{max area} - \text{min area}}{\text{min area x pulse pressure}}$$

Maximal areal



Minimal areal



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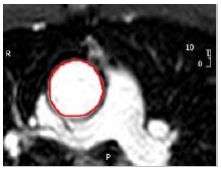
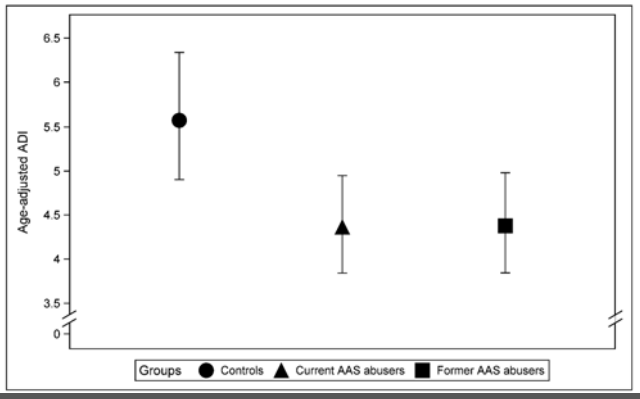
Aortic Stiffness



- Aorta Distensibility Index:



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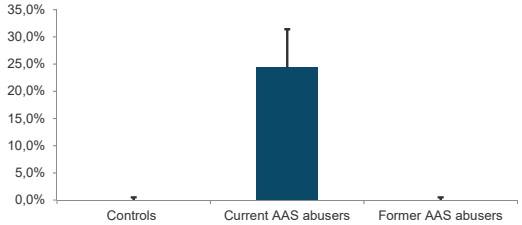
Albuminuria (Spot urine Albumin-creatinine-ratio)



Spearman's rank coeff among current AAS abusers:
24-hour systolic BP and urine ACR:
r = 0.39, P < 0.01

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Hazard ratios for cardiovascular events, positive doping tests

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)

Thiblin et al. *Drug and Alcohol Dependence* (2015)

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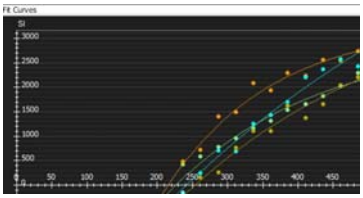
Cardiac MRI: Myocardial Fibrosis?

- No focal signs of myocardial scars (LGE)
- No indications of diffuse fibrosis (similar post T1 mapping time (P = 0.68))



REGION

Rasmussen et al, unpublished

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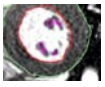
Cardiac MRI: Function and Dimensions

Variables	Controls	Current AAS abusers	Former AAS abusers	P-value
LV EF (%)	67.1 (1.0)	60.1 (1.2)*	66.7 (1.2)	P < 0.01
LV mass (g)	163 (6)	213 (7)*	152 (3)	P < 0.01
LV mass/total lean mass (g/kg)	2.3 (0.1)	2.6 (0.1)*	2.2 (0.1)	P < 0.01
RV EF (%)	54.2 (1.4)	48.1 (1.1)*	50.8 (1.8)	P < 0.01

No differences in ventricular volumes (adjusted for lean mass)

Measures of diastolic function and strain?



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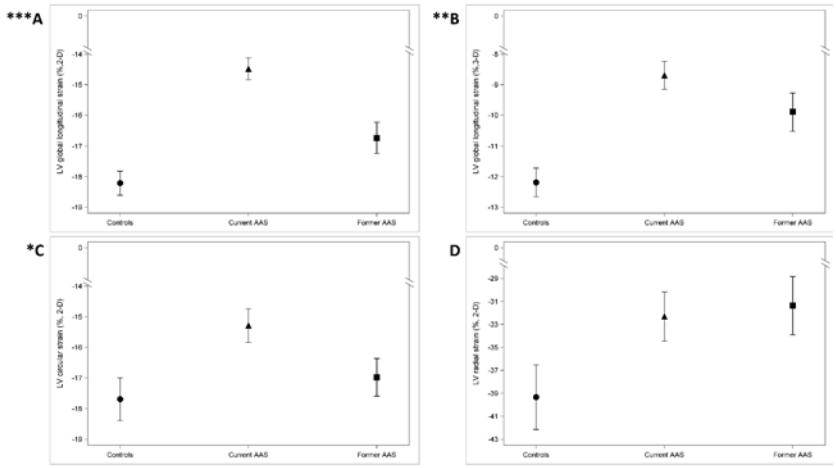
Strain



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Summary

- **AAS abuse leads to:**
  - Long-term subclinical hypogonadism
  - Decreased insulin sensitivity
  - Hypertension
  - Increased central arterial stiffness
  - Impaired cardiac function

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