Supplementary Material

For the manuscript: " Androgen-related symptoms are associated with functional vulnerability in midlife men".

This supplementary material provides additional correlation analyses and univariable regression models for androgen measures, cognitive function, and physical performance, supporting the main results.

Supplementary Table S1. Principal component loadings for the physical-performance composite score

Physical-performance test	Component loading
Six-minute walk test	0.808
Inverted Timed Up and Go	0.781
Normalized sit-to-stand power	0.778
Normalized grip strength	0.691
Brief-BESTest	0.544

The physical-performance composite score was derived using principal component analysis. One component was extracted and explained 53.9% of the total variance. Timed Up and Go was inverted so that higher values consistently indicated better physical performance. All tests loaded positively on the retained component.

Supplementary Table S2. Spearman correlations among androgen-related measures and qADAM scores

Variable	DHEA-S	SHBG	TT	cFT	cBT	qADAM
DHEA-S	—					
SHBG	-.269***	—				
TT	-.072	.723***	—			
cFT	.120*	.184***	.775***	—		
cBT	.136*	.179**	.759***	.961***	—	
qADAM	.043	.062	.172**	.190***	.209***	—

Analyses were performed in the total sample (n = 329). Higher qADAM scores indicate lower androgen-related symptom burden. DHEA-S: dehydroepiandrosterone sulfate; SHBG: sex hormone-binding globulin; TT: total testosterone; cFT: calculated free testosterone; cBT: calculated bioavailable testosterone; qADAM: quantitative Androgen Deficiency in the Aging Male questionnaire. *p < .05, **p < .01, ***p < .001.

Supplementary Table S3. Spearman correlations between qADAM scores and self-reported health-related indicators.

Self-reported indicator	All (n=329)	MA (n=223)	Older (n=106)
Sexual function status (1-5)	**.48*** **	**.47*** **	**.46*** **
QOL (WHO-5)	**.39*** **	**.47*** **	**.28** **
Self-rated health (0-100)	**.42*** **	**.50*** **	**.32*** **
Perceived health relative to previous year (1-3)	**.26*** **	**.29*** **	.17
Perceived health relative to age peers (1-3)	**.34*** **	**.46*** **	.13
Felt age (years)	**-.36*** **	**-.40*** **	-.17
Depression symptoms (BDI)	**-.42*** **	**-.47*** **	**-.30** **

Higher qADAM scores indicate lower androgen-related symptom burden. For all self-reported health-related indicators except felt age and depressive symptoms, higher scores indicate better perceived health status. Bold values indicate correlations that remained significant after false discovery rate (FDR) correction. qADAM: quantitative Androgen Deficiency in the Aging Male questionnaire; MA: middle-aged; QOL: quality of life; BDI: Beck Depression Inventory questionnaire. *p < .05, **p < .01, ***p < .001.

Supplementary Table S4. Cognitive performance across accumulated cognitive impairment categories.

Group	Sub-group	memory	attention	executive	global	Z-+
ALL (329)	Total	102.87 (12.24)	105.25 (8.56)	105.69 (11.90)	104.55 (8.03)	0
	0 (n=162, 49.2%)	108.24	109.09	112.56	109.91	~ +0.5
	1 (n=103, 31.3%)	100.68	105.98	104.24	103.63	~ -0.1
	2 (n=44, 13.4%)	96.36	95.48	92.11	94.50	~ -1
	3 (n=20, 6.1%)	85.0	91.80	87.30	88.0	~ -1.5
MA (223)	Total	102.7 (11.5)	105.7 (8.1)	106.9 (11.7)	105 (7.87)	0
	0 (n=112, 50.2%),	107.68	109.21	114.12	110.26	~ +0.5
	1 (n=69, 30.9%)	100.29	106.26	103.75	103.45	~ -0.02
	2 (n=30, 13.5%)	95.37	97.0	93.30	95.0	~ -1
	3 (n=12, 5.4%)	86.83	90.42	88.92	88.67	~ -1.5-2
OLD (106)	Total	103.4 (13.7)	104.4 (9.3)	103.4 (12)	103.7 (8.5)	0
	0 (n=53, 50%)	108.9	108.3	109.9	109	~ +0.5
	1 (n=35, 33%)	102	104.5	102.6	103	~ -0.1
	2 (n=10, 9.4%)	92.9	96.1	90.7	93.2	~ -1
	3 (n=8, 7.5%)	86.3	88.3	80	84.9	~ -1.5-2

Accumulated cognitive impairment was defined as the number of cognitive domains in the lowest age-specific quartile, ranging from 0 to 3. Values are presented across accumulated impairment categories for the total sample and stratified by age group. Higher scores indicate better cognitive performance. Data are presented as mean ± SD.

Supplementary Table S5. Spearman correlations between qADAM, androgen-related measures, and cognitive outcomes

Androgen-related measure	Cognitive outcome	All (n=329)	MA (n=223)	Older (n=106)
qADAM	Memory	.07	.05	.16
	Attention	**.18*** **	**.20** **	.11
	Executive function	**.13***	.08	**.23***
TT	Memory	.03	.06	-.04
	Attention	.04	.08	-.03
	Executive function	.04	.05	.001
cBT	Memory	.04	.04	.09
	Attention	.05	.04	.07
	Executive function	.03	-.01	.05
SHBG	Memory	-.003	.03	-.13
	Attention	-.02	.05	-.11
	Executive function	.01	.05	-.01
DHEA-S	Memory	.04	.07	.06
	Attention	.06	.02	.08
	Executive function	.11*	.05	.12

Higher qADAM scores indicate lower androgen-related symptom burden. NeuroTrax cognitive domain scores are age- and education-adjusted. False discovery rate correction was applied separately for qADAM-cognition correlations and androgen-cognition correlations across age groups. Bold values indicate correlations that remained significant after false discovery rate (FDR) correction. MA: middle-aged; qADAM: quantitative Androgen Deficiency in the Aging Male questionnaire; TT: total testosterone; cBT: calculated bioavailable testosterone; SHBG: sex hormone-binding globulin; DHEA-S: dehydroepiandrosterone sulfate. *p < .05, **p < .01, ***p < .001.

Supplementary Table S6. Univariable linear regression models between qADAM scores and cognitive outcomes

Cognitive outcome	Group	F	df	p	R^2 (%)	Adjusted R^2 (%)	β
Global cognition	All	17.80	1,327	<.001	5.2	4.9	.23
	MA	10.01	1,221	.002	4.3	3.9	.21
	Older	8.16	1,104	.005	7.3	6.4	.27
Memory	All	6.79	1,327	.010	2.0	1.7	.14
	MA	3.72	1,221	.055	1.7	1.2	.13
	Older	4.42	1,104	.038	4.1	3.2	.20
Attention	All	16.51	1,327	<.001	4.8	4.5	.22
	MA	15.25	1,221	<.001	6.5	6.0	.25
	Older	1.74	1,104	.190	1.6	0.7	.13
Executive function	All	8.22	1,327	.004	2.5	2.2	.16
	MA	2.98	1,221	.086	1.3	0.9	.12
	Older	6.05	1,104	.016	5.5	4.6	.23

Values are from univariable linear regression models with qADAM as the independent variable. Higher qADAM scores indicate lower androgen-related symptom burden. NeuroTrax cognitive scores are age- and education-adjusted. β values are standardized regression coefficients. qADAM: quantitative Androgen Deficiency in the Aging Male questionnaire; MA: middle-aged.

Supplementary Table S7. Physical performance across accumulated physical impairment categories.

Group	Sub-group	Grip (kg/kg), mean (SD)	STS power (W/kg), mean (SD)	Inverse TUG (seconds), mean (SD)	6MWT (meters), mean (SD)	Brief-BESTest (score), median (IQR)	Physical Composite score, mean (SD)
ALL	Total (n=291)	0.52 (0.10)	5.55 (1.36)	-5.8 (0.93)	705.13 (83.15)	22 [20-23]	0 (1)
	0 (n=117, 40.1%)	0.58	6.33	-5.32	756.42	23 [22-24]	0.78
	1 (n=73, 25.3%)	0.51	5.64	-5.69	712.36	22 [20-23]	0.06
	2 (n=48, 16.4%)	0.47	5.06	-5.99	669.08	21 [19.5-23]	-0.44
	3 (n=28, 9.6%)	0.45	4.55	-6.56	654.77	20 [19-21]	-0.90
	4 (n=16, 5.5%)	0.43	3.82	-7.08	575.94	18 [14.5-20]	-1.80
	5 (n=9, 3.1%)	0.38	3.46	-7.82	558.22	16 [14-20]	-2.34
MA	Total (n=194)	0.53 (0.11)	5.83 (1.34)	-5.66 (0.76)	722.05 (77.43)	23 [21-23]	0.25 (0.91)
	0 (n=87, 44.8%)	0.59	6.55	-5.24	766.26	23 [22-24]	0.86
	1 (n=47, 24.2%)	0.52	5.85	-5.61	723.64	22 [21-24]	0.14
	2 (n=29, 14.9%)	0.47	4.90	-5.96	675.66	22 [21-23]	-0.46
	3 (n=18, 9.3%)	0.46	5.06	-6.66	669.67	20.5 [20-21]	-0.90
	4 (n=10, 5.2%)	0.38	4.22	-6.31	599.06	17.5 [16-22]	-1.57
	5 (n=3, 1.5%)	0.36	3.44	-7.53	587.67	17 [16.5-18.5]	-2.08
OLD	Total (n=97)	0.49 (0.09)	5.0 (1.24)	-6.12 (1.14)	671.29 (84.26)	21 [19-22]	-0.50 (1.0)
	0 (n=32, 33.0%)	0.53	5.50	-5.58	720.59	22 [21-23]	0.43
	1 (n=41, 42.3%)	0.49	5.27	-5.85	684.51	20 [19-22]	-0.08
	2 (n=10, 10.3%)	0.48	4.38	-6.51	642.20	19 [18-21]	-0.41
	3 (n=6, 6.2%)	0.39	3.94	-6.86	590.17	20 [18-22]	-0.91
	4 (n=4, 4.1%)	0.53	2.97	-9.28	486.25	13.5 [9.5-17.5]	-2.0
	5 (n=4, 4.1%)	0.37	3.54	-7.97	520.75	14 [13.5-15]	-2.5

Accumulated physical impairment was defined as the number of physical tests in the lowest age-specific quartile, ranging from 0 to 5. Values are presented for the total sample and stratified by age group. Grip strength was normalized to body weight. STS: sit-to-stand test; Inverse TUG: inverse Timed Up and Go time, where higher values indicate better performance; 6MWT: six-minute walk test; Brief-BESTest: Brief Balance Evaluation Systems Test; Composite score: physical performance composite score derived from principal component analysis. Values are presented as mean (SD), except for Brief-BESTest, which is presented as median [IQR].

Supplementary Table S8. Spearman correlations between androgen-related measures and individual physical performance tests

Androgen-related measure	Physical outcome	All	MA	Older
qADAM	Grip / weight	**.17****	**.18****	.09
	STS power	**.30*****	**.31*****	.17
	TUG	**-.22*****	**-.23*****	-.14
	6mwt	**.30*****	**.32*****	.19
	Brief-BEST	**.22*****	**.19****	.19
TT	Grip / weight	**.23*****	**.26*****	.18
	STS power	**.15****	**.22*****	.05
	TUG	**-.16****	**-.20****	-.10
	6mwt	**.24*****	**.27*****	.16
	Brief-BEST	**.13***	**.16***	.07
cBT	Grip / weight	**.21*****	**.17***	**.23***
	STS power	**.24*****	**.20****	.19
	TUG	**-.15****	-.14*	-.08
	6mwt	**.31*****	**.24*****	**.26****
	Brief-BEST	**.24*****	**.18****	.19
SHBG	Grip / weight	**.16****	**.28*****	.03
	STS power	.01	**.15***	-.07
	TUG	-.10	**-.18****	-.05
	6mwt	.07	**.21****	-.04
	Brief-BEST	-.08	.03	-.08
DHEA-S	Grip / weight	.08	-.01	.11
	STS power	**.19*****	**.16***	.08
	TUG	-.12*	-.06	-.09
	6mwt	**.17****	.11	-.07
	Brief-BEST	**.23*****	**.17***	.09

Sample sizes varied across physical performance tests because of missing data. Available sample sizes for the total sample, MA, and older groups, respectively, were: normalized grip strength, n = 322, 217, 105; normalized STS power, n = 329, 223, 106; TUG, n = 317, 214, 103; 6MWT, n = 303, 203, 100; and Brief-BESTest, n = 321, 217, 104. Higher qADAM scores indicate lower androgen-related symptom burden. Grip strength and STS power were normalized to body weight. For TUG, lower values indicate better performance. False discovery rate (FDR) correction was applied separately for qADAM-physical performance correlations and androgen-physical performance correlations across age groups. Bold values indicate correlations that remained significant after FDR correction. TT: total testosterone; cBT: calculated bioavailable testosterone; SHBG: sex hormone-binding globulin; DHEA-S: dehydroepiandrosterone sulfate; qADAM: quantitative Androgen Deficiency in the Aging Male questionnaire; MA: middle-aged; STS: sit-to-stand; TUG: Timed Up and Go; 6MWT: 6-minute walk test; Brief-BESTest: Brief Balance Evaluation Systems Test. *p < .05, **p < .01, ***p < .001.

Supplementary Table S9. Spearman correlations between androgen-related measures and the physical performance composite

Androgen-related measure	All (n=291)	MA (n=194)	Older (n=97)
qADAM	**.36*** **	**.36*** **	**.23***
TT	**.28*** **	**.34*** **	.12
cBT	**.34*** **	**.29*** **	**.25***
SHBG	.08	**.26*** **	-.06
DHEA-S	**.21*** **	.11	.13

The physical performance composite was derived using principal component analysis based on normalized grip strength, normalized STS power, TUG, 6MWT, and Brief-BESTest. Higher composite scores indicate better physical performance. Higher qADAM scores indicate lower androgen-related symptom burden. TT: total testosterone; cBT: calculated bioavailable testosterone; SHBG: sex hormone-binding globulin; DHEA-S: dehydroepiandrosterone sulfate; qADAM: quantitative Androgen Deficiency in the Aging Male questionnaire; MA: middle-aged; TUG: Timed Up and Go; 6MWT: 6-minute walk test; Brief-BESTest: Brief Balance Evaluation Systems Test. *p < .05, **p < .01, ***p < .001.