Fake Anabolic Androgenic Steroids on the Black Market – a systematic review and meta-analysis

SUPPLEMENTAL MATERIAL

S 1.1. PROPORTION OF INERT AAS-SAMPLES

SUMMARY
INERT AAS-SAMPLES (No active ingredients):
24% (CI-95: 0.09 T0 0.49) OVERALL; WITH HIGH HETEROGENEITY (96%); SIGNIFICANTLY LOWER
(p < 0.05) IN EUROPE (15%) THAN IN BRAZIL (49%).
Meta-Regression by publication year showed a significant increase of inert AAS-samples over time
(p < 0.05).

Review: Inert

Proportions of inert AAS-sampels from 11 studies

Study	Events	Total	Proportion	95%-CI
Region = Europe Weber C., et. al., 2017, Switzerland Graham M., et. al., 2009, United Kingdom Tircova B., et. al., 2019, Czech Republic/ Slovakia Thevis M. et. al., 2008, Germany Coopman V., et. al., 2012, Belgium Pellegrini M., et. al., 2012, Italy Musshoff, F. et. al., 1997, Germany Forsdahl, G. et. al., 2011, Austria Random effects model Prediction interval Heterogeneity: $l^2 = 95\%$, $\tau^2 = 2.8760$, $p < 0.01$	50 10 57 0 1 2 1 1	17 73 16 22 10 15 	0.59 - 0.78 0.00 0.05 0.20 0.07 0.12	[0.07; 0.12] [0.33; 0.82] [0.67; 0.87] [0.00; 0.21] [0.00; 0.23] [0.03; 0.56] [0.00; 0.32] [0.00; 0.53] [0.03; 0.48] [0.00; 0.94]
Region = Brazil Neves D., et. al. 2013, Brazil Neves D., et. al. 2017, Brazil Lemos, V. F. et. al., 2021, Brazil Random effects model Prediction interval Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.70$	567 72 4	9 · · · · · · · · · · · · · · · · · · ·	0.52 0.44 0.49	[0.46; 0.51] [0.44; 0.61] [0.14; 0.79] [0.43; 0.55] [0.32; 0.66]
Random effects model Prediction interval Heterogeneity: $I^2 = 96\%$, $\tau^2 = 2.2264$, $p < 0.01$ Test for subgroup differences: $\chi_1^2 = 5.90$, df = 1 ($p = 1$	0.02)	2003 0 0.2 0.4 0.6 0.8		[0.09; 0.49] [0.01; 0.92]

Number of studies combined: k = 11 Number of observations: o = 2003 Number of events: e = 765

proportion 95%-Cl

 Random effects model
 0.2385 [0.0927; 0.4899]

 Prediction interval
 [0.0088; 0.9169]

 Quantifying heterogeneity:
 tau^2 = 2.2264; tau = 1.4921; I^2 = 95.9% [94.2%; 97.1%]; H = 4.95 [4.15; 5.90]

Test of heterogeneity:

Q d.f. p-value Test 244.79 10 < 0.0001 Wald-type 381.56 10 < 0.0001 Likelihood-Ratio

Results for subgroups (random effects model):

k proportion 95%-Cl tau² tau Q l² Region = Europe 8 0.1535 [0.0348; 0.4769] 2.8760 1.6959 139.34 95.0% Region = Brazil 3 0.4893 [0.4304; 0.5486] 0 0 0.71 0.0%

Test for subgroup differences (random effects model):

Q d.f. p-value Between groups 5.90 1 0.0151

Prediction intervals for subgroups:

95%-PI

Region = Europe [0.0021; 0.9408] Region = Brazil [0.3222; 0.6589]

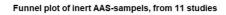
Details on meta-analytical method:

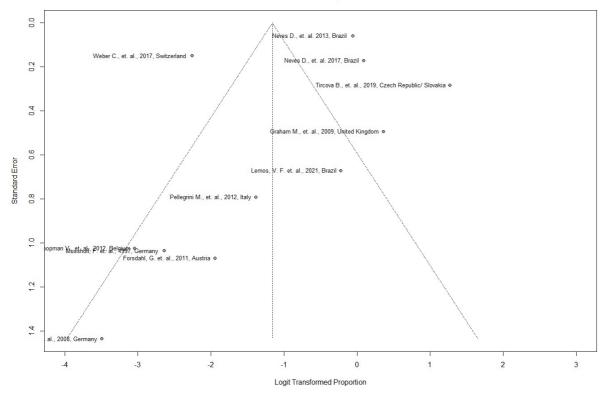
- Random intercept logistic regression model

- Maximum-likelihood estimator for tau^2

- Hartung-Knapp adjustment for random effects model
- Logit transformation
- Clopper-Pearson confidence interval for individual studies
- Continuity correction of 0.5 in studies with zero cell frequencies

(only used to calculate individual study results)





Linear regression test of funnel plot asymmetry Test result: t = -0.15, df = 9, p-value = 0.8858

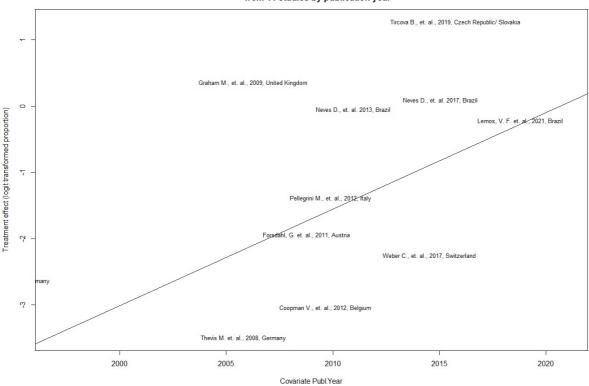
Sample estimates:

bias se.bias intercept se.intercept -2.9725 20.1245 -0.2619 0.2902

Details:

- multiplicative residual heterogeneity variance (tau^2 = 30.5153)
- predictor: inverse of total sample size
- weight: inverse variance of average event probability
- reference: Peters et al. (2006), JAMA

Meta-regression by publication year



Meta-regression of inert anabolic androgenic steroids from 11 studies by publication year

Mixed-Effects Model (k = 11; tau^2 estimator: ML)

tau^2 (estimated amount of residual heterogeneity): 1.5954
tau (square root of estimated tau^2 value): 1.2631
I^2 (residual heterogeneity / unaccounted variability): 95.1459%
H^2 (unaccounted variability / sampling variability): 20.6013

Tests for Residual Heterogeneity:

Wld(df = 9) = 230.6491, p-val < .0001 LRT(df = 9) = 364.3765, p-val < .0001

Test of Moderators (coefficient 2):

F(df1 = 1, df2 = 9) = 3.6433, p-val = 0.0886

Model Results:

estimate se tval df pval ci.lb ci.ub intrcpt -294.2141 153.5846 -1.9156 9 0.0877 -641.6467 53.2185 . Publ.Year 0.1456 0.0763 1.9088 9 0.0886 -0.0270 0.3182 .

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 '' 1

S 1.2. PROPORTIONS OF SUBSTITUTED AAS-SAMPLES

SUMMARY
SUBSTITUTED AAS-SAMPLES (Other ingredients then declared):
44% (CI-95: 0.27 T0 0.63) OVERALL; WITH HIGH HETEROGENEITY (92%); SIGNIFICANTLY HIGHER
(p = 0.05) IN EUROPE (51%) THAN IN BRAZIL (28%).
Meta-regression by publication year showed a decreasing trend of substituted AAS-samples over
time (p < 0.05)
(could be due to Musshoff, 1997 was an outlier)

Review: Substituted

Proportions of substituted AAS-Samples from 11 studies, grouped by geographical region

Study	Events	Total		Proportion	95%-CI
Region = Europe Weber C., et. al., 2017, Switzerland Graham M., et. al., 2009, United Kingdom Tircova B., et. al., 2019, Czech Republic/ Slovakia Thevis M. et. al., 2019, Germany Coopman V., et. al., 2012, Belgium Pellegrini M., et. al., 2012, Italy Musshoff, F. et. al., 1997, Germany Forsdahl, G. et. al., 2011, Austria Random effects model Prediction interval Heterogeneity: $I^2 = 78\%$, $\tau^2 = 1.5601$, $p < 0.01$	274 7 16 10 12 8 14 0	17 73 16 22 10 15	*	0.41 0.22 0.62 0.55 - 0.80 - 0.93 0.00	[0.48; 0.56] [0.18; 0.67] [0.35; 0.85] [0.32; 0.76] [0.44; 0.97] [0.68; 1.00] [0.00; 0.37] [0.25; 0.77] [0.04; 0.96]
Region = Brazil Neves D., et. al. 2013, Brazil Neves D., et. al. 2017, Brazil Lemos, V. F. et. al., 2021, Brazil Random effects model Prediction interval Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.89$	330 41 3	1167 138 9 1314	***	0.30 0.33	[0.26; 0.31] [0.22; 0.38] [0.07; 0.70] [0.23; 0.34] [0.15; 0.46]
Random effects model Prediction interval Heterogeneity: $l^2 = 92\%$, $\tau^2 = 1.0461$, $p < 0.01$ Test for subgroup differences: $\chi_1^2 = 3.79$, df = 1 ($p = 0$	0.05)	2003	0.2 0.4 0.6 0.8	0.44	[0.27; 0.63] [0.06; 0.90]

Number of studies combined: k = 11 Number of observations: o = 2003

Number of events: e = 715

proportion	95%-CI
Random effects model	0.4419 [0.2692; 0.6300]
Prediction interval	[0.0645; 0.9009]

Quantifying heterogeneity:

tau² = 1.0461; tau = 1.0228; l² = 91.5% [86.8%; 94.5%]; H = 3.43 [2.75; 4.28]

Test of heterogeneity:

Q d.f. p-value Test

117.75 10 < 0.0001 Wald-type 141.26 10 < 0.0001 Likelihood-Ratio

Results for subgroups (random effects model):

k proportion 95%-Cl tau^2 tau Q l^2 Region = Europe 8 0.5083 [0.2465; 0.7656] 1.5601 1.2490 32.18 78.2% Region = Brazil 3 0.2846 [0.2342; 0.3411] 0 0 0.23 0.0%

Test for subgroup differences (random effects model):

Q d.f. p-value Between groups 3.79 1 0.0516

Prediction intervals for subgroups:

95%-PI

Region = Europe [0.0374; 0.9649] Region = Brazil [0.1547; 0.4639]

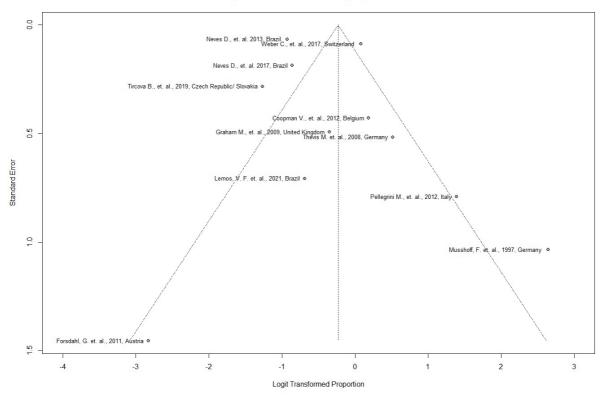
Details on meta-analytical method:

- Random intercept logistic regression model

- Maximum-likelihood estimator for tau^2
- Hartung-Knapp adjustment for random effects model
- Logit transformation
- Clopper-Pearson confidence interval for individual studies
- Continuity correction of 0.5 in studies with zero cell frequencies

(only used to calculate individual study results)

Funnel plot of substituted AAS-sampels, from 11 studies



Review: Substituted

Linear regression test of funnel plot asymmetry

Test result: t = 0.86, df = 9, p-value = 0.4109

Sample estimates:

bias se.bias intercept se.intercept 11.1779 12.9628 -0.6281 0.1875

Meta-Regression by publication year

- Details: - multiplicative residual heterogeneity variance (tau^2 = 30.5153) - predictor: inverse of total sample size
- weight: inverse variance of average event
- probability
- reference: Peters et al. (2006), JAMA

Meta-regression of substituted anabolic androgenic steroids from 11 studies by publication year an۱ 2 Pellegrini M., et. al., 2012, Italy Freatment effect (logit transformed proportion) <u>_</u> Thevis M. et. al., 2008, Ge Coopman V., et. al., 2012, Belgium Weber C., et. al., 2017, Switzerland 0 Graham M., et. al., 2009, United Kingdom Lemos, V. F. et. al., 2021, Brazil Neves D., et. al. 2017, Brazil Neves D., et. al. 2013, Brazil 7 Tircova B., et. al., 2019, Czech Republic/ Slovakia N Forsdahl, G. et. al., 2011, Austria er P 2000 2005 2010 2015 2020 Covariate Publ.Year

Mixed-Effects Model (k = 11; tau^2 estimator: ML)

tau^2 (estimated amount of residual heterogeneity): 0.3928
tau (square root of estimated tau^2 value): 0.6268
I^2 (residual heterogeneity / unaccounted variability): 87.0071%
H^2 (unaccounted variability / sampling variability): 7.6965

Tests for Residual Heterogeneity:

Wld(df = 9) = 105.0720, p-val < .0001 LRT(df = 9) = 139.3046, p-val < .0001

Test of Moderators (coefficient 2):

F(df1 = 1, df2 = 9) = 8.1312, p-val = 0.0190

Model Results:

estimate se tval df pval ci.lb ci.ub intrcpt 251.5863 88.3322 2.8482 9 0.0191 51.7649 451.4076 * Publ.Year -0.1251 0.0439 -2.8515 9 0.0190 -0.2244 -0.0259 *

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 '' 1

S 1.3. PROPORTION OF ADULTERATED AAS-SAMPLES

SUMMARY ADULTERATED AAS-SAMPLES (= more ingredients then declared): 11% (CI-95: 0.02 TO 0.42) OVERALL; WITH HIGH HETEROGENEITY (92%); NO SIGNIFICANT DIFFERENCE (p = 0.47) BETWEEN EUROPE (13%) AND BRAZIL (5%). Meta-regression by publication year showed no significant effect.

Proportions of adulterated AAS-sampels from 10 studies

Study	Events Total	Proportion 95%-CI
Region = Europe Weber C., et. al., 2017, Switzerland Graham M., et. al., 2009, United Kingdom Thevis M. et. al., 2008, Germany Coopman V., et. al., 2012, Belgium Pellegrini M., et. al., 2012, Italy Musshoff, F. et. al., 1997, Germany Forsdahl, G. et. al., 2011, Austria Random effects model Prediction interval Heterogeneity: $I^2 = 0\%$, $\tau^2 = 6.8063$, $p = 0.55$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	0.39 [0.34; 0.43] 0.00 [0.00; 0.20] 0.38 [0.15; 0.65] 0.41 [0.21; 0.64] 0.00 [0.00; 0.31] 0.00 [0.00; 0.22] 0.88 [0.47; 1.00] 0.13 [0.01; 0.74] [0.00; 1.00]
Region = Brazil Neves D., et. al. 2013, Brazil Neves D., et. al. 2017, Brazil Lemos, V. F. et. al., 2021, Brazil Random effects model Prediction interval Heterogeneity: $J^2 = 75\%$, $\tau^2 = 0.6719$, $p = 0.4719$	82 1167 2 138 + 2 9 - 1314 - 02	0.07 [0.06; 0.09] 0.01 [0.00; 0.05] 0.22 [0.03; 0.60] 0.05 [0.00; 0.41] [0.00; 1.00]
Random effects model Prediction interval Heterogeneity: $I^2 = 96\%$, $\tau^2 = 4.4636$, $p < 0.1$ Test for subgroup differences: $\chi_1^2 = 0.53$, df	= 1 (<i>p</i> = 0.47) 0 0.2 0.4 0.6 0.8	0.11 [0.02; 0.42] [0.00; 0.96]

Number of studies combined: k = 10 Number of observations: o = 1930 Number of events: e = 312

proportion	95%-CI
Random effects model	0.1125 [0.0221; 0.4162]
Prediction interval	[0.0007; 0.9575]

Quantifying heterogeneity:

tau² = 4.4636; tau = 2.1127; l² = 96.3% [94.7%; 97.4%]; H = 5.22 [4.36; 6.25]

Test of heterogeneity:

 Q d.f.
 p-value
 Test

 245.49
 9 < 0.0001</td>
 Wald-type

 322.24
 9 < 0.0001</td>
 Likelihood-Ratio

Results for subgroups (random effects model):

k proportion 95%-CI tau^2 tau Q I^2

Region = Europe70.1315 [0.0079; 0.7419] 6.8063 2.6089 5.090.0%Region = Brazil30.0540 [0.0047; 0.4090] 0.6719 0.8197 8.02 75.0%

Test for subgroup differences (random effects model):

Q d.f. p-value Between groups 0.53 1 0.4653

Prediction intervals for subgroups:

95%-Pl Region = Europe [0.0001; 0.9959] Region = Brazil [0.0000; 0.9999]

Details on meta-analytical method:

- Random intercept logistic regression model

- Maximum-likelihood estimator for tau^2

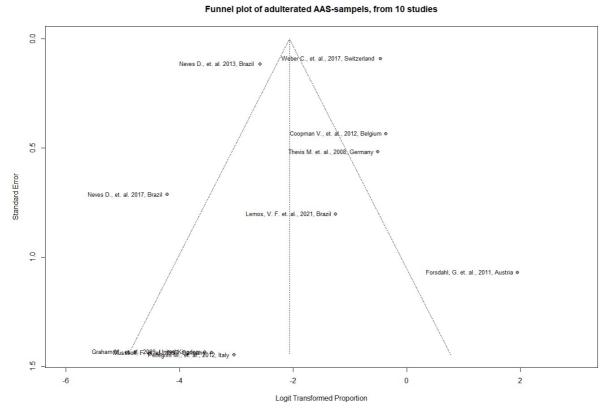
- Hartung-Knapp adjustment for random effects model

- Logit transformation

- Clopper-Pearson confidence interval for individual studies

- Continuity correction of 0.5 in studies with zero cell frequencies

(only used to calculate individual study results)



Review: Adulterated

Linear regression test of funnel plot asymmetry

Test result: t = 0.50, df = 8, p-value = 0.6335

Sample estimates:

bias se.bias intercept se.intercept 14.6240 29.5095 -1.3168 0.4895

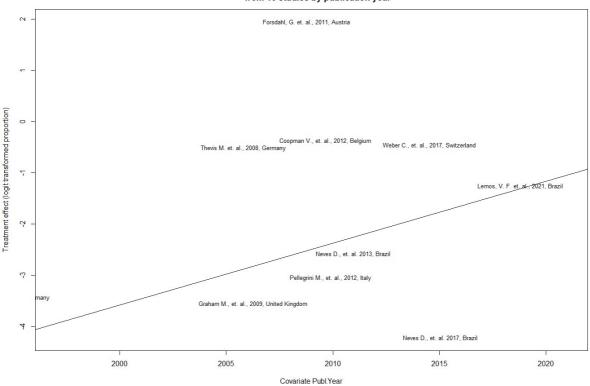
Details:

- multiplicative residual heterogeneity variance (tau^2 = 46.8001)
- predictor: inverse of total sample size weight: inverse variance of average event

probability

- reference: Peters et al. (2006), JAMA

Meta-regression by publication year



Meta-regression of adulterated anabolic androgenic steroids from 10 studies by publication year

Mixed-Effects Model (k = 10; tau^2 estimator: ML)

tau^2 (estimated amount of residual heterogeneity): 4.5401
tau (square root of estimated tau^2 value): 2.1307
I^2 (residual heterogeneity / unaccounted variability): 96.9090%
H^2 (unaccounted variability / sampling variability): 32.3515

Tests for Residual Heterogeneity:

Wld(df = 8) = 137.7571, p-val < .0001 LRT(df = 8) = 199.2876, p-val < .0001

Test of Moderators (coefficient 2):

F(df1 = 1, df2 = 8) = 0.6845, p-val = 0.4320

Model Results:

estimate se tval df pval ci.lb ci.ub intrcpt -244.8259 293.4994 -0.8342 8 0.4284 -921.6368 431.9850 Publ.Year 0.1206 0.1458 0.8273 8 0.4320 -0.2156 0.4568

SUMMARY

Over-concentrated AAS-SAMPLES (= higher concentration than anticipated): 33% (CI-95: 0.06 TO 0.81) OVERALL; WITH HIGH HETEROGENEITY (96%); SIGNIFICANTLY LOWER (p < 0.01) IN EUROPE (12%) THAN IN BRAZIL (64%). Meta-regression by publication year showed no significant effect.

Proportions of over-concentrated AAS-sampels from 4 studies

Study	Events	Total		Proportion 95%-CI
Region = Europe Weber C., et. al., 2017, Switzerland Tircova B., et. al., 2019, Czech Republic/ Slovakia Random effects model Prediction interval Heterogeneity: I^2 = 80%, τ^2 = 0.0837, p = 0.02	34 13	383 73 456	*	0.09 [0.06; 0.12] 0.18 [0.10; 0.29] 0.12 [0.00; 0.83]
Region = Brazil Neves D., et. al. 2017, Brazil Campos E., et. al., 2020, Brazil Random effects model Prediction interval Heterogeneity: I^2 = 14%, τ^2 = 0, p = 0.28	21 20	36 28 64		0.58 [0.41; 0.74] 0.71 [0.51; 0.87] - 0.64 [0.06; 0.98]
Random effects model Prediction interval Heterogeneity: $I^2 = 96\%$, $\tau^2 = 1.7103$, $p < 0.01$ Test for subgroup differences: $\chi_1^2 = 45.43$, df = 1 ($p < 100$	0.01)	520	0.2 0.4 0.6 0.8	0.33 [0.06; 0.81] - [0.00; 1.00]

Number of studies combined: k = 4 Number of observations: o = 520 Number of events: e = 88

proportion	95%-CI
Random effects model	0.3348 [0.0557; 0.8111]
Prediction interval	[0.0009; 0.9965]

Quantifying heterogeneity:

tau² = 1.7103; tau = 1.3078; l² = 96.4% [93.4%; 98.1%]; H = 5.29 [3.90; 7.17]

Test of heterogeneity:

Q d.1	f. p-value	Test
83.89	3 < 0.0001	Wald-type
92.49	3 < 0.0001 l	ikelihood-Ratio

Results for subgroups (random effects model):

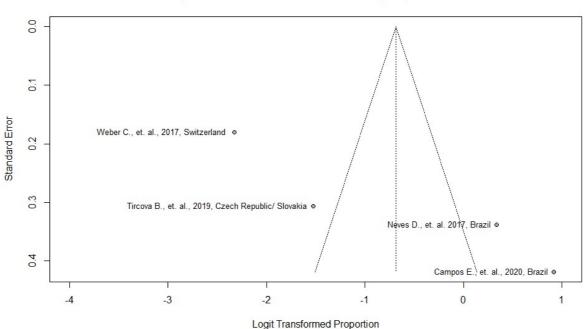
k proportion 95%-Cl tau² tau Q l² Region = Europe 2 0.1155 [0.0034; 0.8339] 0.0837 0.2893 5.08 80.3% Region = Brazil 2 0.6406 [0.0611; 0.9799] 0 0 1.16 14.0%

Test for subgroup differences (random effects model):

Q d.f. p-value Between groups 45.43 1 < 0.0001

Details on meta-analytical method:

- Random intercept logistic regression model
- Maximum-likelihood estimator for tau^2
- Hartung-Knapp adjustment for random effects model
- Logit transformation
- Clopper-Pearson confidence interval for individual studies

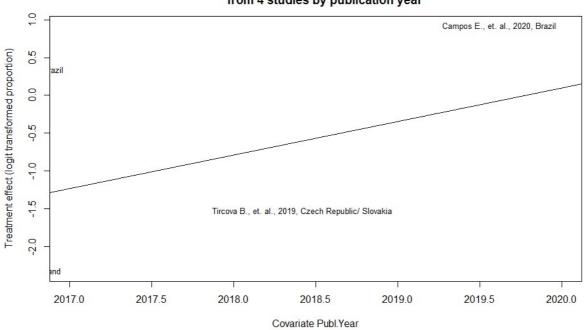


Funnel plot of over-concentrated AAS-sampels, from 4 studies

Linear regression test of funnel plot asymmetry

Number of studies (k=4) too small to test for small study effects

Meta-Regression by publication year



Meta-regression of over-concentrated anabolic androgenic steroids from 4 studies by publication year

Mixed-Effects Model (k = 4; tau^2 estimator: ML)

tau^2 (estimated amount of residual heterogeneity): 1.3825
tau (square root of estimated tau^2 value): 1.1758
I^2 (residual heterogeneity / unaccounted variability): 93.9229%
H^2 (unaccounted variability / sampling variability): 16.4552

Tests for Residual Heterogeneity:

Wld(df = 2) = 62.4323, p-val < .0001 LRT(df = 2) = 62.3534, p-val < .0001

Test of Moderators (coefficient 2):

F(df1 = 1, df2 = 2) = 0.8862, p-val = 0.4459

Model Results:

estimate se tval df pval ci.lb ci.ub intrcpt -897.0918 952.2405 -0.9421 2 0.4456 -4994.2520 3200.0684 Publ.Year 0.4442 0.4718 0.9414 2 0.4459 -1.5859 2.4742

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 '' 1

S2.2 PROPORTION OF UNDER-CONCENTRATED AAS-SAMPLES

SUMMARY (S2.2 is the inverse of S2.1)

Proportions of under-concentrated AAS-sampels from 4 studies

Study	Events	Total		Proportion	95%-CI
Region = Europe Weber C., et. al., 2017, Switzerland Tircova B., et. al., 2019, Czech Republic/ Slovakia Random effects model Prediction interval Heterogeneity: $l^2 = 80\%$, $\tau^2 = 0.0837$, $p = 0.02$	349 60	383 73 456		0.82	[0.88; 0.94] [0.71; 0.90] [0.17; 1.00]
Region = Brazil Neves D., et. al. 2017, Brazil Campos E., et. al., 2020, Brazil Random effects model Prediction interval Heterogeneity: $l^2 = 14\%$, $\tau^2 = 0$, $p = 0.28$	15 8	36 28 64		0.29	[0.26; 0.59] [0.13; 0.49] [0.02; 0.94]
Random effects model Prediction interval Heterogeneity: $l^2 = 96\%$, $\tau^2 = 1.7103$, $p < 0.01$ Test for subgroup differences: $\chi_1^2 = 45.43$, df = 1 ($p < 100$	0.01)	520	0.2 0.4 0.6 0.8	0.67	[0.19; 0.94] [0.00; 1.00]

Number of studies combined: k = 4 Number of observations: o = 520 Number of events: e = 432

proportion	95%-CI
Random effects model	0.6652 [0.1889; 0.9443]
Prediction interval	[0.0035; 0.9991]

Quantifying heterogeneity:

tau² = 1.7103; tau = 1.3078; l² = 96.4% [93.4%; 98.1%]; H = 5.29 [3.90; 7.17]

Test of heterogeneity:

Q d.f. p-value Test 83.89 3 < 0.0001 Wald-type 92.49 3 < 0.0001 Likelihood-Ratio

Results for subgroups (random effects model):

k proportion 95%-Cl tau^2 tau Q l^2 Region = Europe 2 0.8845 [0.1661; 0.9966] 0.0837 0.2893 5.08 80.3% Region = Brazil 2 0.3594 [0.0201; 0.9389] 0 0 1.16 14.0%

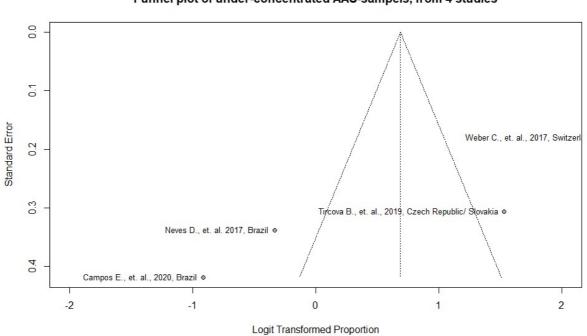
Test for subgroup differences (random effects model):

Q d.f. p-value Between groups 45.43 1 < 0.0001

Details on meta-analytical method:

- Random intercept logistic regression model

- Maximum-likelihood estimator for tau^2
- Hartung-Knapp adjustment for random effects model
- Logit transformation
- Clopper-Pearson confidence interval for individual studies

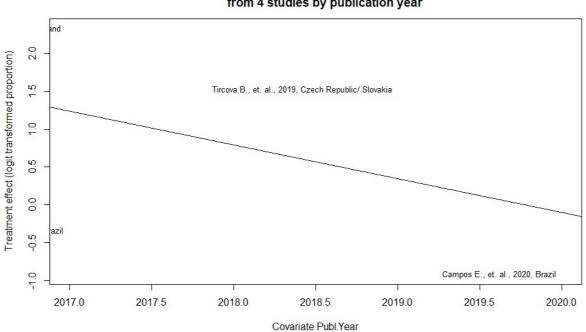


Funnel plot of under-concentrated AAS-sampels, from 4 studies

Linear regression test of funnel plot asymmetry

Number of studies (k=4) too small to test for small study effects

Meta-regression by publication year



Meta-regression of under-concentrated anabolic androgenic steroids from 4 studies by publication year

Mixed-Effects Model (k = 4; tau^2 estimator: ML)

tau^2 (estimated amount of residual heterogeneity): 1.3825
tau (square root of estimated tau^2 value): 1.1758
I^2 (residual heterogeneity / unaccounted variability): 93.9229%
H^2 (unaccounted variability / sampling variability): 16.4552

Tests for Residual Heterogeneity:

Wld(df = 2) = 62.4323, p-val < .0001 LRT(df = 2) = 62.3534, p-val < .0001

Test of Moderators (coefficient 2):

F(df1 = 1, df2 = 2) = 0.8862, p-val = 0.4459

Model Results:

estimate se tval df pval ci.lb ci.ub intrcpt 897.1058 952.2406 0.9421 2 0.4456 -3200.0548 4994.2663 Publ.Year -0.4442 0.4718 -0.9414 2 0.4459 -2.4742 1.5859

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1