INTENSITY OF STATIN THERAPY AND MUSCLE SYMPTOMS:

A NETWORK META-ANALYSIS OF 153,000 PATIENTS

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29 RHABDOMYOLYSIS: Meta-Analysis Funnel Plot Continuity Correction = 0.1.

30 RHABDOMYOLYSIS: Meta-Analysis Forest Plot excluding simvastatin 80 mg trials.

31 RHABDOMYOLYSIS: Meta-Analysis Funnel Plot excluding simvastatin 80 mg trials

32 RHABDOMYOLYSIS: SUMMARY TABLE

33 CK >10x ULN: Meta-Analysis Forest Plot with Data

34 CK >10x ULN: Meta-Analysis Funnel Plot

35 CK >10x ULN: Meta-Analysis Forest Plot with outliers excluded.

36 CK >10x ULN: Meta-Analysis Funnel Plot with outliers excluded.

37 CK >10x ULN: Meta-Analysis Forest Plot with Continuity Correction = 0.1.

38 CK >10x ULN: Meta-Analysis Funnel Plot with Continuity Correction = 0.1.

39 CK >10x ULN: Meta-Analysis Forest Plot excluding simvastatin 80 mg trials.

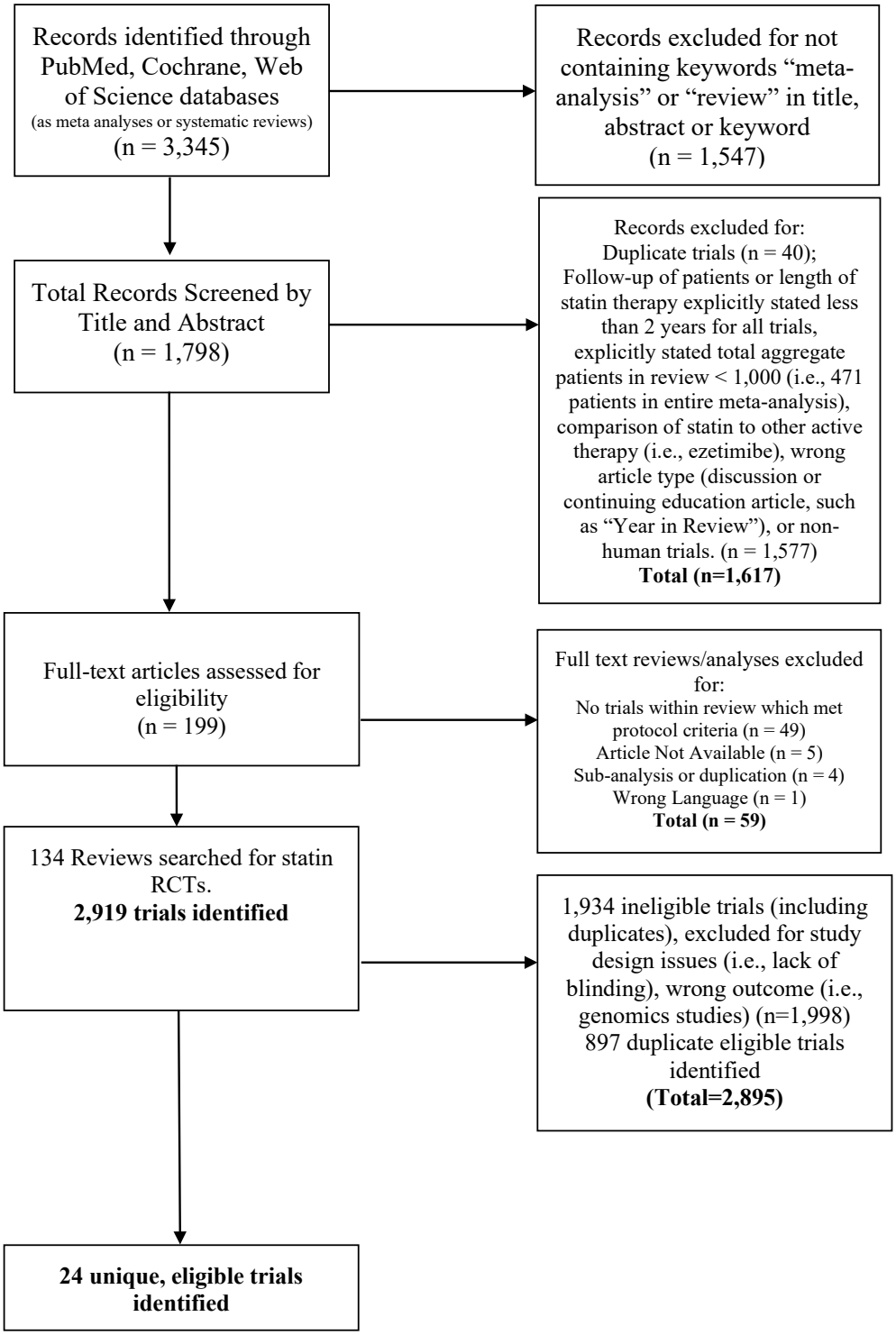
40 CK >10x ULN: Meta-Analysis Funnel Plot excluding simvastatin 80 mg trials

41 CK >10x ULN: SUMMARY TABLE

42 R Code for Meta-Analysis

43 R Code for Network Meta-Analysis

PRISMA FLOW SHEET



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Search Procedure

PRISMA FLOWCHART explanation

1. PubMed, Cochrane Database, Web of Science, and clinicaltrials.gov were searched in November 2018 by a professional research librarian (Prospero #CRD42019112758). The search was updated for November 2018 through February 1, 2021. Web of Science was not searched in this second phase, as institutional access to the database had expired. The following page (eTable 3: Search Strategy) details the MEDLINE search and keywords for the combined search. The strategy was to search for all systematic reviews and meta-analyses, in English or Spanish, to identify RCTs for inclusion. Articles containing the term "systematic review" or "meta-analysis" in the title, abstract, or keywords were retained (1,646 from original search and 351 from the updated search = 1,997).

2. Based on information in the abstract, articles were retained that might contain a trial that met inclusion criteria (191 from original search and 8 more from the updated search = 199). Review of the full article eliminated an additional 59 articles, yielding 140 articles for full review. One author (JD) reviewed abstracts and full texts of articles.

3. Review of the 140 unique articles identified 2919 trials (2,801 from the original search and 118 trials in the updated search). Then, double-blinded RCTs were selected from these reviews that compared statin therapy to placebo or higher-lower dose statin therapy (24 unique trials).

4. The 24 eligible trials were independently judged by both authors (JD, SW) for inclusion, then coded for quality and outcomes. There was complete agreement on quality ratings with the Oxford Center for Evidence-based Medicine ratings and the Jadad quality score. Ambiguities in coding of outcomes were resolved by contacting the study PI.

Sample Strategy: MEDLINE Search

3/1/2021 Ovid: Current Search History

Ovid® Wolters Kluwer

My Account | Ask a Librarian | Support & Training | Help | Feedback | Logged in as Julie Trumble at Moody Medical Library | Logoff

Search | Journals | Books | Multimedia | My Workspace | ACC CardioSource Plus | What's New

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to February 26, 2021>

#	Searches	Results	Type
1	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/	41740	Advanced
2	(statin or statins).tw.	40017	Advanced
3	atorvastatin.tw.	8871	Advanced
4	cerivastatin.tw.	664	Advanced
5	fluvastatin.tw.	1899	Advanced
6	lovastatin.tw.	3855	Advanced
7	pravastatin.tw.	4110	Advanced
8	simvastatin.tw.	9706	Advanced
9	lipitor.tw.	205	Advanced
10	baycol.tw.	14	Advanced
11	lescol.tw.	81	Advanced
12	mevacor.tw.	48	Advanced
13	altocor.tw.	0	Advanced
14	pravachol.tw.	25	Advanced
15	lipostat.tw.	26	Advanced
16	zocor.tw.	113	Advanced
17	mevinolin.tw.	401	Advanced
18	compactin.tw.	304	Advanced
19	fluindostatin.tw.	4	Advanced
20	rosuvastatin.tw.	3625	Advanced
21	Hydroxymethylglutaryl CoA Reductase Inhibitor".mp.	30952	Advanced
22	HMG-CoA Reductase Inhibitor".mp.	4260	Advanced
23	(cl 981 or cl981 or liptonorm).mp.	123	Advanced
24	(6 methylcompactin or mk 803 or mk803 or mevinolin or monacolin k).mp.	602	Advanced
25	(meglutol or 3 hydroxy 3 methylglutaric acid or 3 hydroxy 3 methylpentanedioic acid or beta hydroxy beta methylglutarate).mp.	183	Advanced
26	(bristacol or cs 514 or cs514 or elisor or eptastatin or lipemol or lipiat or ilostat or mevalotin or prareduct or pravacol or pravasin or rms 431 or rms431 or sq 31000 or sq31000 or selektine or vasten).mp.	56	Advanced
27	(crestor or zd 4522 or zd4522).mp.	73	Advanced
28	(mk733 or mk 733 or synvinolin).mp.	54	Advanced
29	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	63347	Advanced
30	Animals/ not Humans/	4760183	Advanced
31	29 not 30	56479	Advanced
32	limit 31 to (english or spanish)	52717	Advanced
33	limit 32 to (meta analysis or "systematic review")	1535	Advanced
34	limit 32 to (systematic reviews pre 2019 or systematic reviews)	3199	Advanced
35	33 or 34	3224	Advanced
36	remove duplicates from 35	3202	Advanced
37	limit 36 to yr="1990 - 2017"	2463	Advanced
38	(201601* or 201602* or 201603* or 201604* or 201605* or 201606* or 201607* or 201608* or 201609* or 201610* or 201611*).ez.	1083231	Advanced
39	37 or 38	1085687	Advanced
40	36 and 39	2668	Advanced
41	limit 36 to yr="2019 - 2020"	443	Advanced
42	201812*.ez.	93882	Advanced
43	202101*.ez.	136550	Advanced
44	42 or 43	230432	Advanced
45	36 and 44	42	Advanced
46	41 or 45	470	Advanced
47	limit 36 to yr="2019 - 2021"	501	Advanced
48	36 and 42	20	Advanced
49	47 or 48	512	Advanced
50	49 not 46	42	Advanced
51	from 50 keep 19, 26-27, 29, 33-37, 39, 42	11	Advanced

https://ovidsp.dc2.ovid.com/ovid-b/ovidweb.cgi 1/2

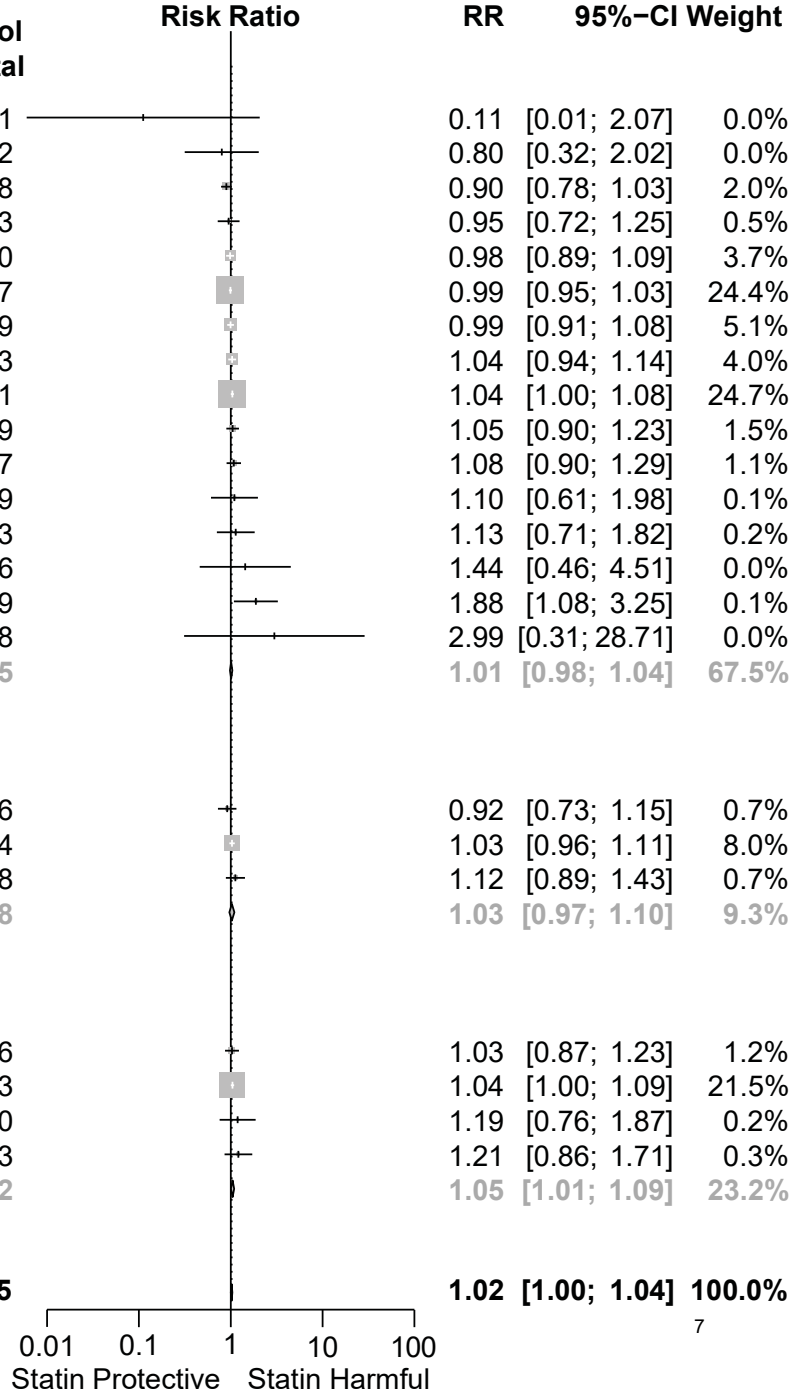
Crude Incidence Rates

	Placebo	Moderate Intensity	High intensity – with Simvastatin 80mg	High Intensity – without Simvastatin 80mg
Any Muscle Problems	38.8 cases per 1000 person years (9661/248993.8; 19 arms)*	41.1 cases per 1000 person years (10946/266265.8; 20 arms)*	44.0 cases per 1000 person years (4654/105761.54; 7 arms)*	32.7 cases per 1000 person years (1992/60873.1; 5 arms)*
Myalgia	6.2 cases per 1000 person years (1060/169746.5; 12 arms)*	14.9 cases per 1000 person years (3022/202684; 11 arms)*	38.9 cases per 1000 person years (3781/97082.8; 5 arms)*	20.5 cases per 1000 person years (1160/56675.1; 4 arms)*
Attrition due to Muscle	1.4 cases per 1000 person years (198/145,857.2; 8 arms)*	1.7 cases per 1000 person years (311/178940.2; 11 arms)*	3.5 cases per 1000 person years (173/ 49086.44; 3 arms)*	16.4 cases per 1000 person years (69/4198; 1 arm)*
Rhabdomyolysis	5.8 cases per 100,000 person years (13/225,713.6; 18 arms)**	6.9 cases per 100,000 person years (18/262803.8; 18 arms)**	1.4 cases per 100,000 person years (15/105822.3; 7 arms)**	8.2 cases per 100,000 person years (5/60933.9; 5 arms)**
Elevated CK	2.7 cases per 10,000 person years (41/153,768.1; 13 arms)*	2.9 cases per 10,000 person years (61/207814.1; 14 arms)*	9.4 cases per 10,000 person years (80/84712.4; 5 arms)*	0.8 cases per 10,000 person years (3/39824; 3 arms)*

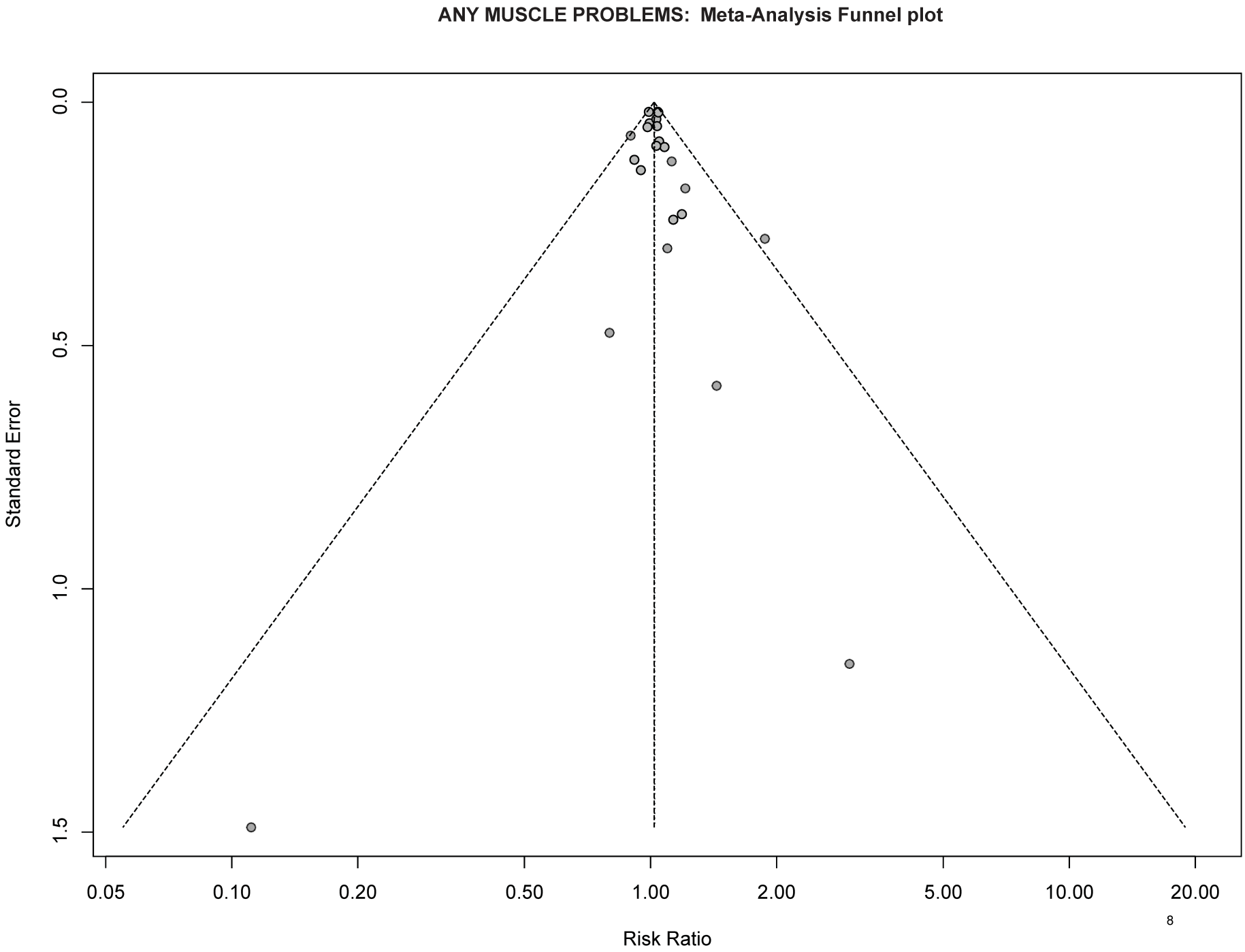
* Incidence rates significantly different across trials, $p<0.0001$

** The incident proportion of cases was not significantly different across trials, although a chi square test may have been insensitive to differences among such small proportions ($p>0.05$)

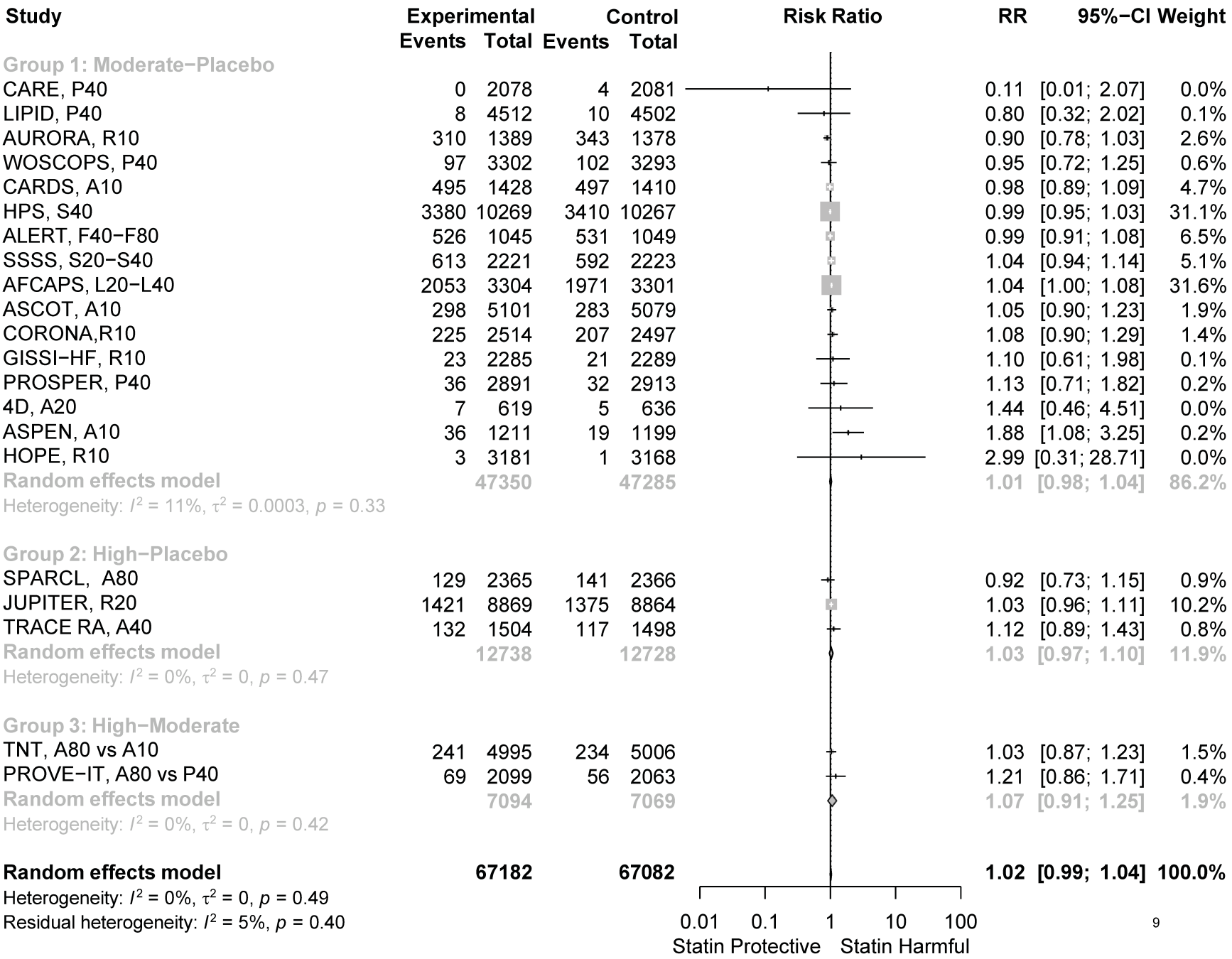
ANY MUSCLE PROBLEMS: Meta-Analysis Forest plot with data.



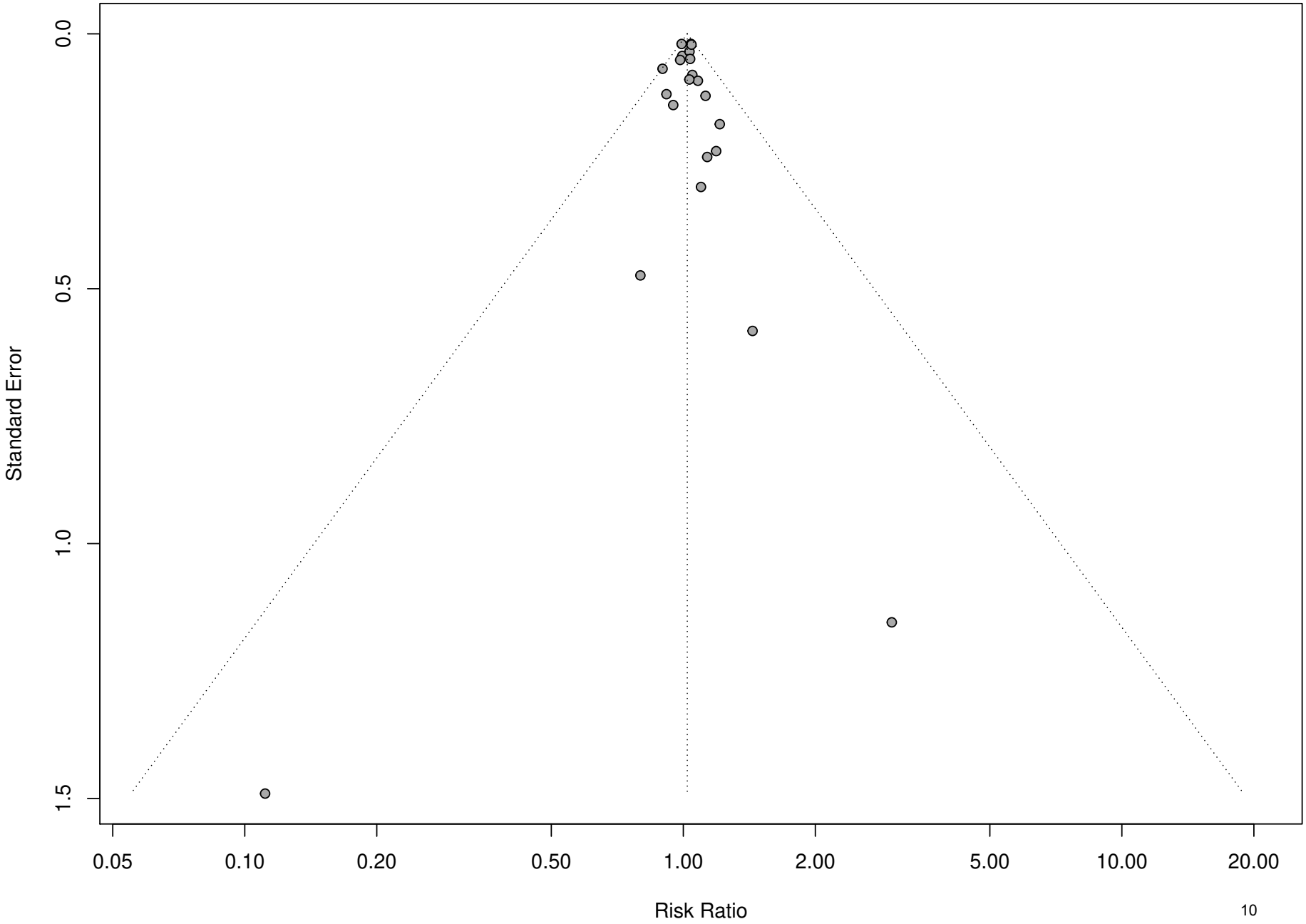
Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	Weight
Group 1: Moderate−Placebo							
CARE, P40	0	2078	4	2081	0.11	[0.01; 2.07]	0.0%
LIPID, P40	8	4512	10	4502	0.80	[0.32; 2.02]	0.0%
AURORA, R10	310	1389	343	1378	0.90	[0.78; 1.03]	2.0%
WOSCOPS, P40	97	3302	102	3293	0.95	[0.72; 1.25]	0.5%
CARDS, A10	495	1428	497	1410	0.98	[0.89; 1.09]	3.7%
HPS, S40	3380	10269	3410	10267	0.99	[0.95; 1.03]	24.4%
ALERT, F40−F80	526	1045	531	1049	0.99	[0.91; 1.08]	5.1%
SSSS, S20−S40	613	2221	592	2223	1.04	[0.94; 1.14]	4.0%
AFCAPS, L20−L40	2053	3304	1971	3301	1.04	[1.00; 1.08]	24.7%
ASCOT, A10	298	5101	283	5079	1.05	[0.90; 1.23]	1.5%
CORONA,R10	225	2514	207	2497	1.08	[0.90; 1.29]	1.1%
GISSI−HF, R10	23	2285	21	2289	1.10	[0.61; 1.98]	0.1%
PROSPER, P40	36	2891	32	2913	1.13	[0.71; 1.82]	0.2%
4D, A20	7	619	5	636	1.44	[0.46; 4.51]	0.0%
ASPEN, A10	36	1211	19	1199	1.88	[1.08; 3.25]	0.1%
HOPE, R10	3	3181	1	3168	2.99	[0.31; 28.71]	0.0%
Random effects model		**47350**		**47285**	**1.01**	**[0.98; 1.04]**	**67.5%**
Heterogeneity: I^2 = 11%, τ^2 = 0.0003, p = 0.33							
Group 2: High−Placebo							
SPARCL, A80	129	2365	141	2366	0.92	[0.73; 1.15]	0.7%
JUPITER, R20	1421	8869	1375	8864	1.03	[0.96; 1.11]	8.0%
TRACE RA, A40	132	1504	117	1498	1.12	[0.89; 1.43]	0.7%
Random effects model		**12738**		**12728**	**1.03**	**[0.97; 1.10]**	**9.3%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.47							
Group 3: High−Moderate							
TNT, A80 vs A10	241	4995	234	5006	1.03	[0.87; 1.23]	1.2%
SEARCH, S80 vs S20	2621	6031	2512	6033	1.04	[1.00; 1.09]	21.5%
A to Z, S40−S80 vs S20	41	2263	34	2230	1.19	[0.76; 1.87]	0.2%
PROVE−IT, A80 vs P40	69	2099	56	2063	1.21	[0.86; 1.71]	0.3%
Random effects model		**15388**		**15332**	**1.05**	**[1.01; 1.09]**	**23.2%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.79							
Random effects model		**75476**		**75345**	**1.02**	**[1.00; 1.04]**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.51							
Residual heterogeneity: I^2 = 0%, p = 0.50							


ANY MUSCLE PROBLEMS: Meta-Analysis Funnel plot
Standard Error
0.0
0.5
1.0
1.5
0.05
0.10
0.20
0.50
1.00
2.00
5.00
10.00
20.00
Risk Ratio

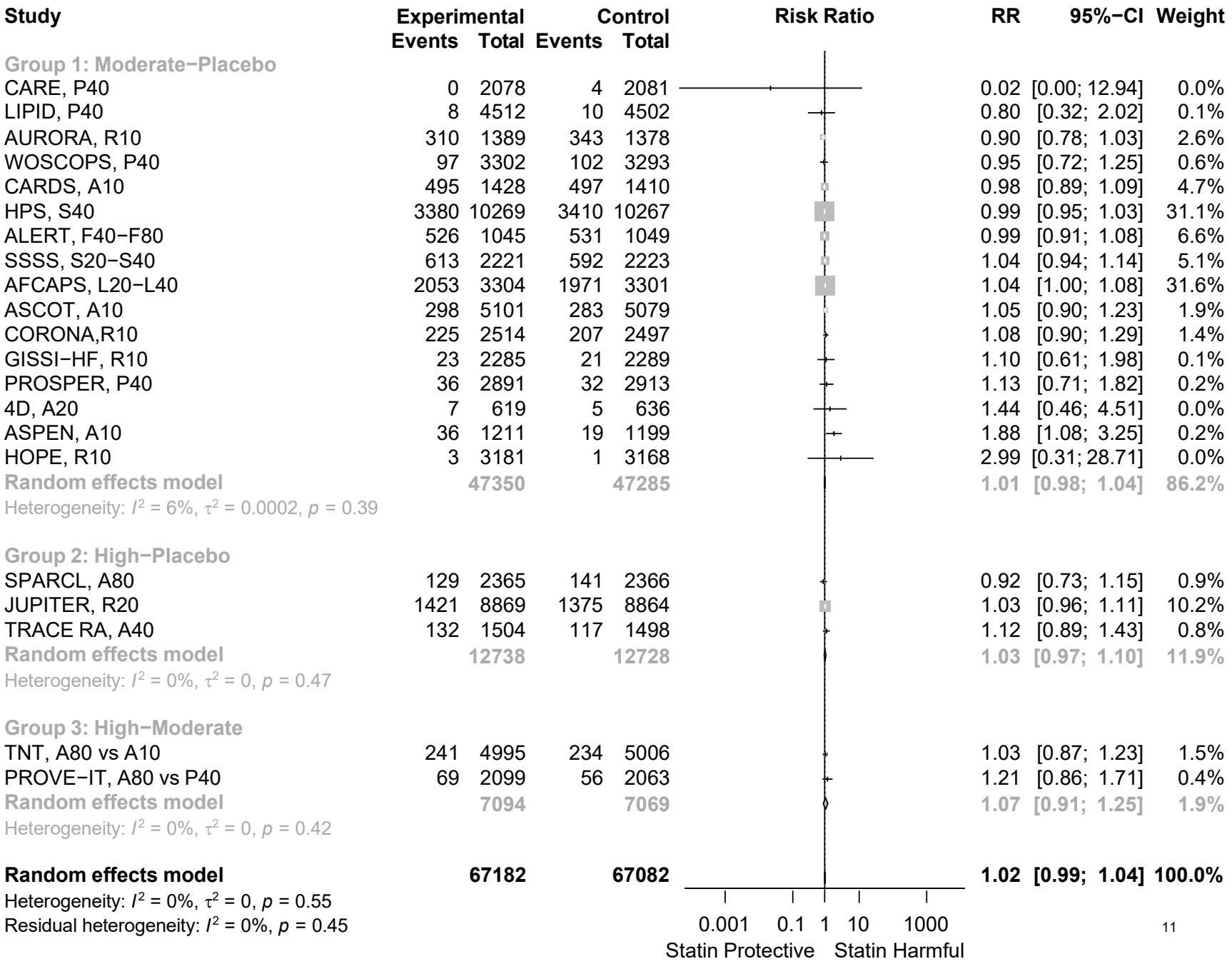
GENERAL MUSCLE PROBLEMS. Outliers excluded. Forest plot.

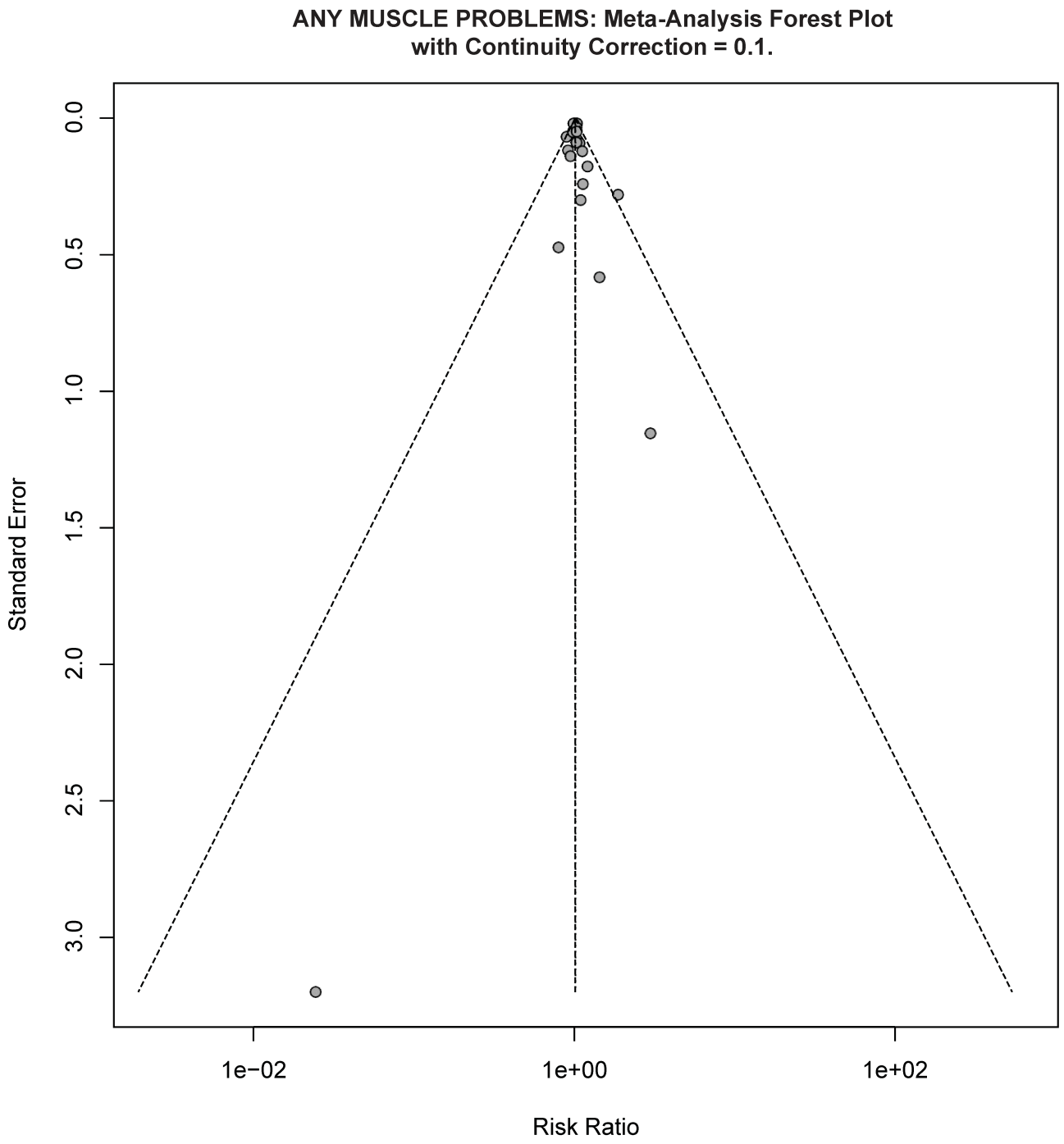


GENERAL MUSCLE PROBLEMS. Outliers excluded. Funnel plot.

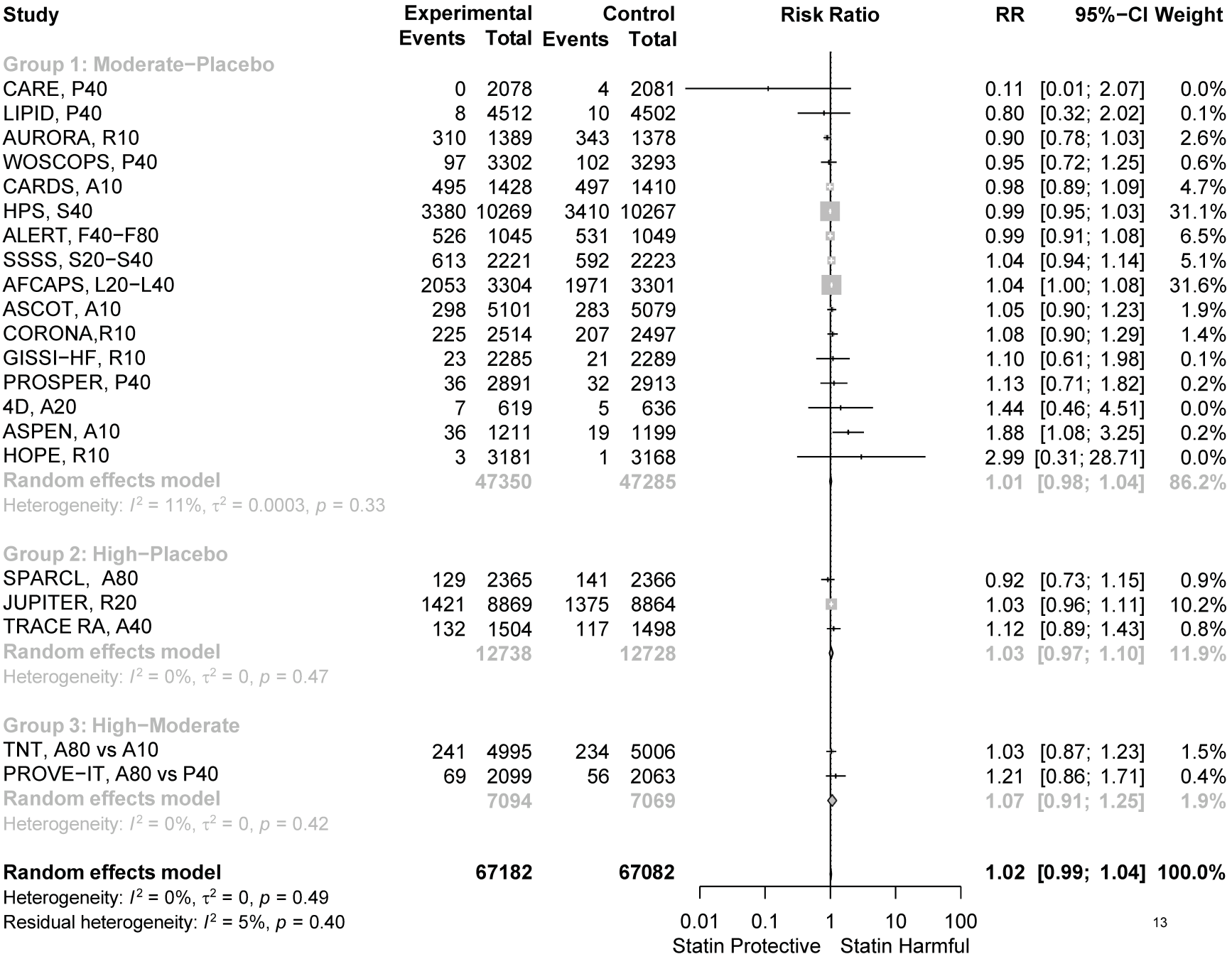


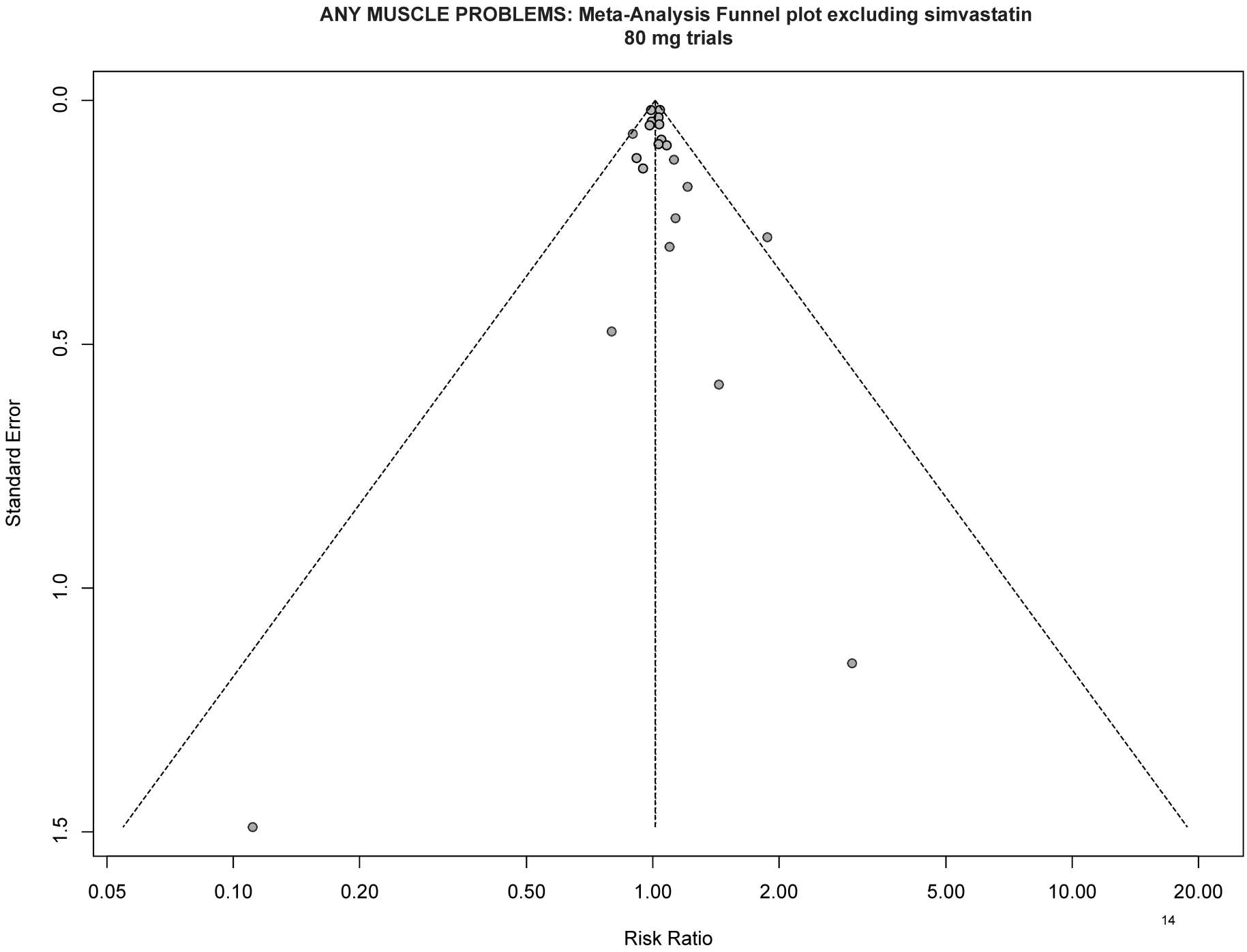
GENERAL MUSCLE PROBLEMS. Continuity Correction = 0.1. Forest plot.




ANY MUSCLE PROBLEMS: Meta-Analysis Forest Plot
with Continuity Correction = 0.1.
Standard Error
0.0
0.5
1.0
1.5
2.0
2.5
3.0
1e−02
1e+00
1e+02
Risk Ratio

ANY MUSCLE PROBLEMS: Meta-Analysis Forest plot excluding simvastatin 80 mg trials.

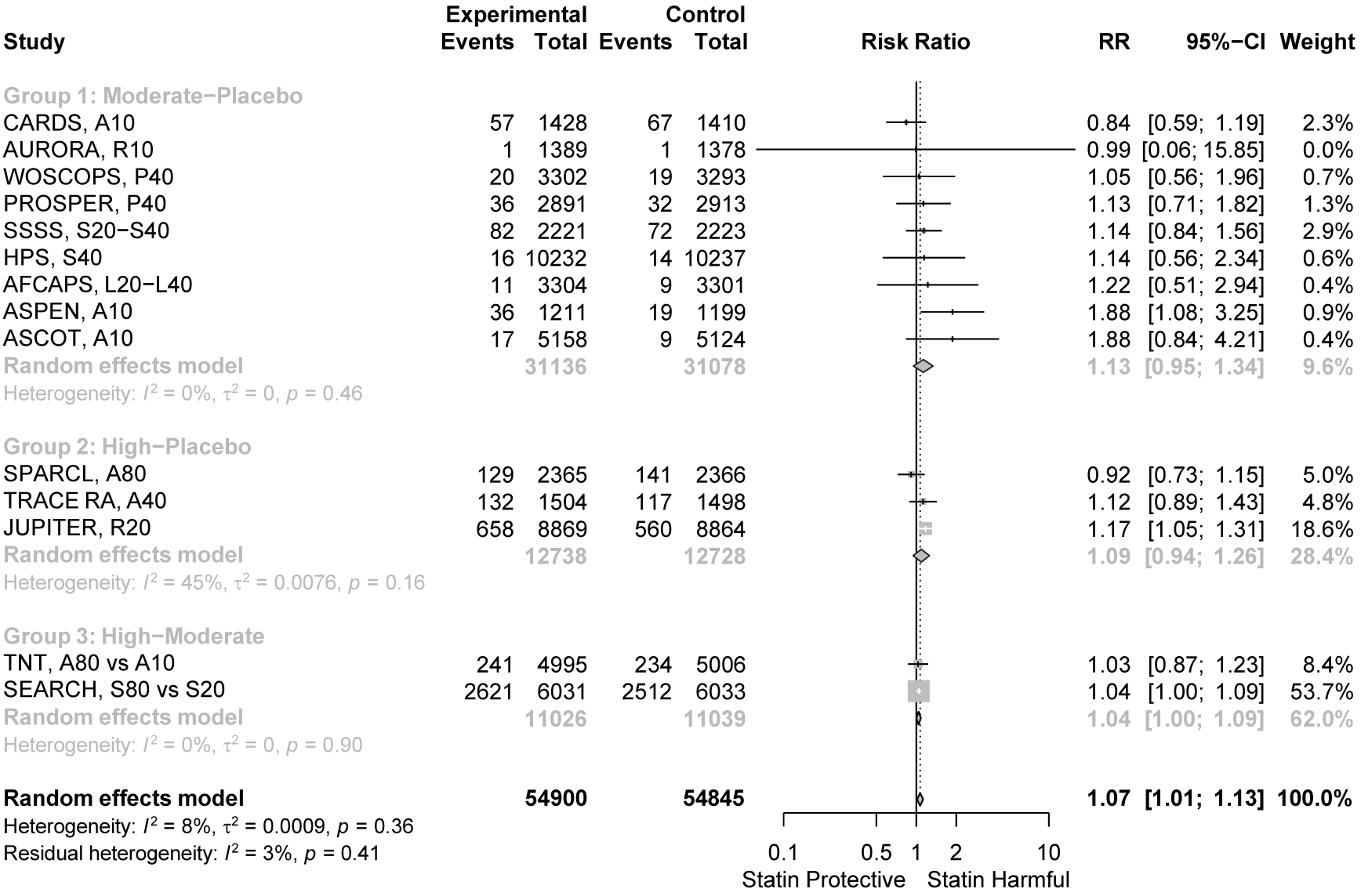


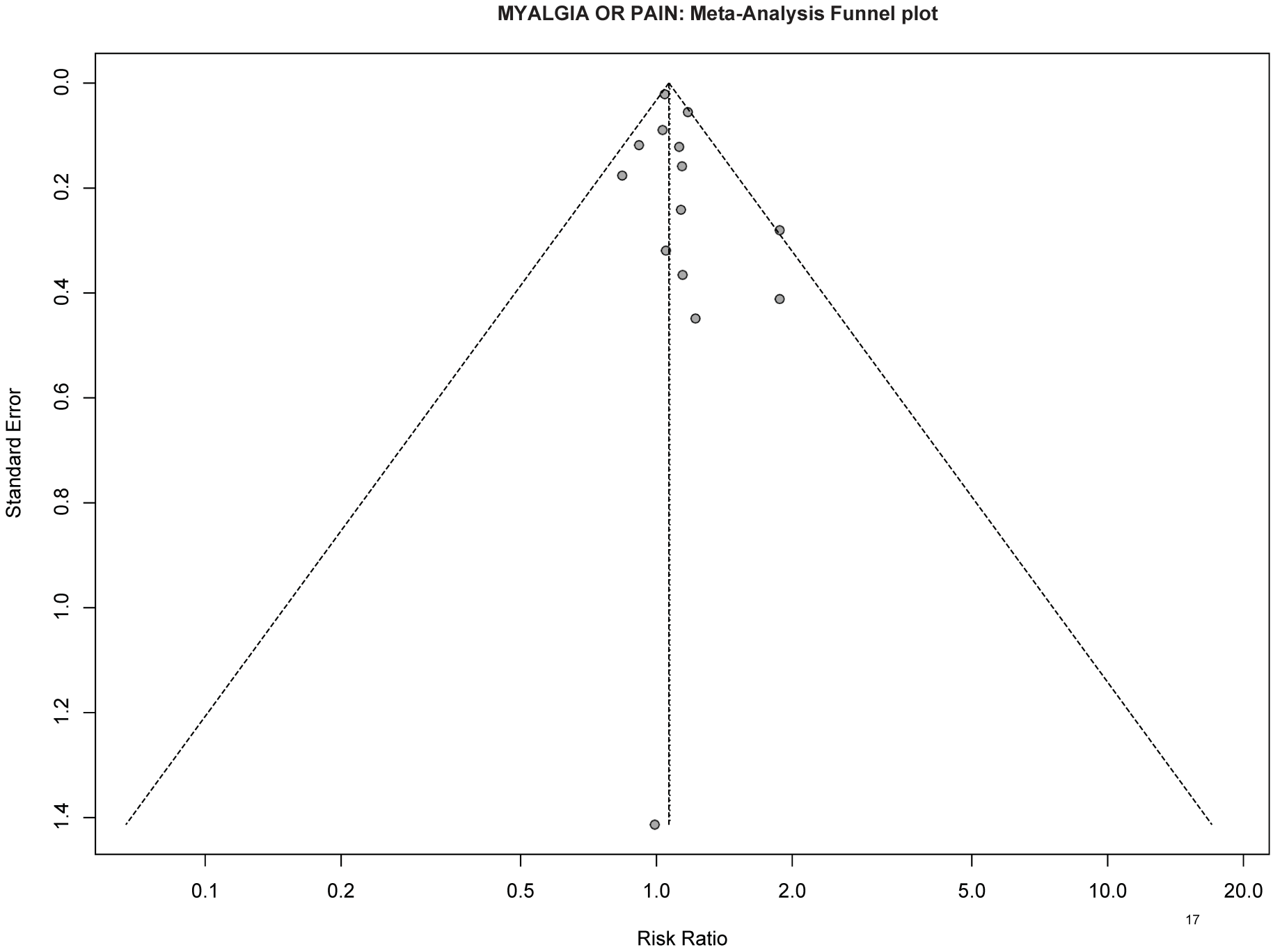

ANY MUSCLE PROBLEMS: Meta-Analysis Funnel plot excluding simvastatin 80 mg trials
Standard Error
0.0
0.5
1.0
1.5
0.05
0.10
0.20
0.50
1.00
2.00
5.00
10.00
20.00
Risk Ratio

ANY MUSCLE PROBLEMS SUMMARY: PAIRWISE AND NETWORK META-ANALYSIS RESULTS

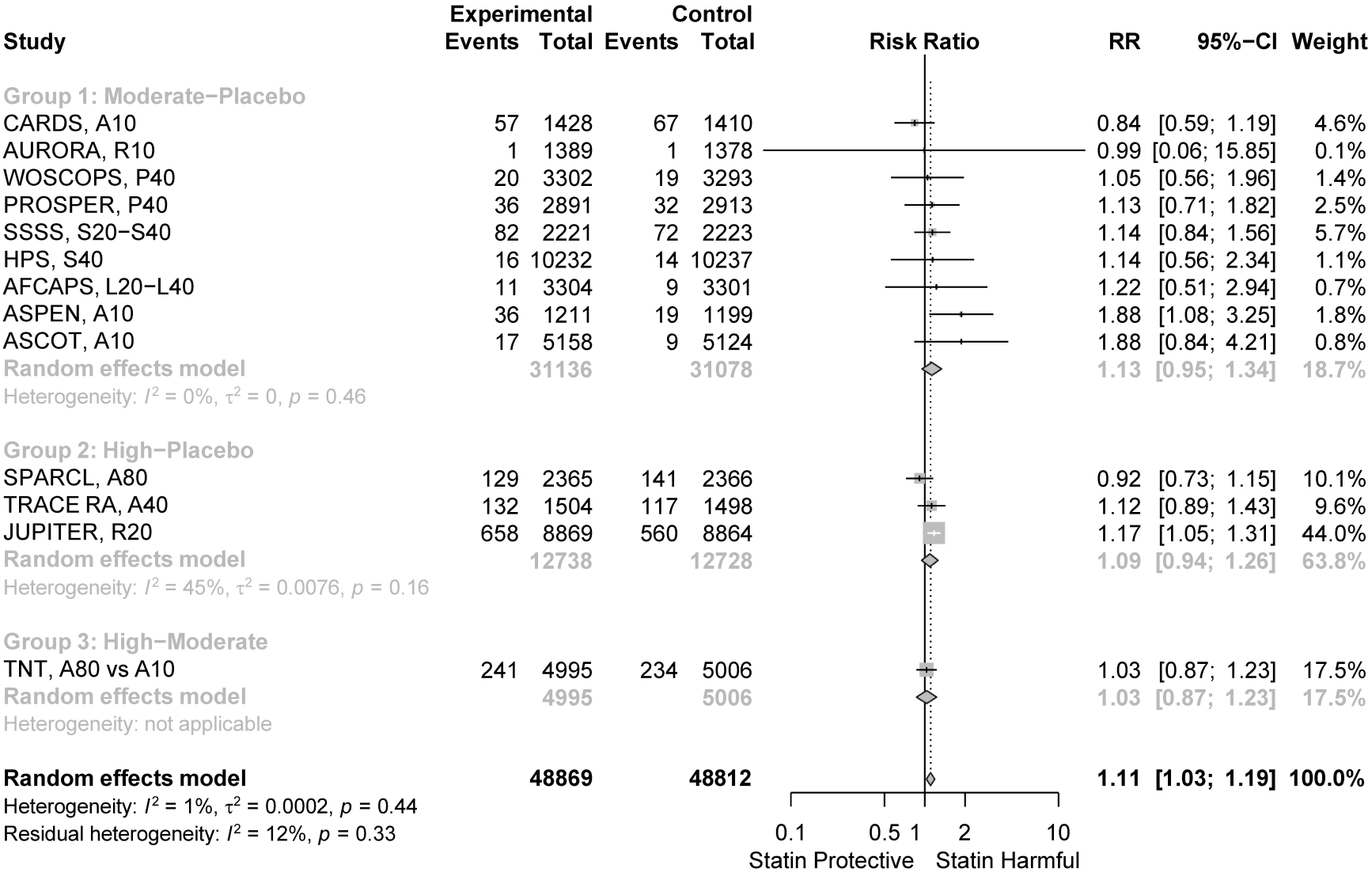
	Placebo – Moderate Intensity			**Moderate – High Intensity**			**Placebo – High Intensity**		
Outcome	RR (95% CI)	RD (95% CI)	NNH	RR (95% CI)	RD (95% CI)	NNH	RR (95% CI)	RD (95% CI)	NNH
Direct, M-H	1.011 (0.982, 1.042)	NA	--	1.046 (1.005, 1.089)	NA	--	1.030 (0.967, 1.097)	NA	--
Direct, IV	1.012 (0.989, 1.036)	0.000 (-0.001, 0.001)	--	1.046 (1.005, 1.089)	0.004 (-0.001, 0.009)	--	1.030 (0.967, 1.097)	0.002 (-0.005, 0.010)	--
NMA, IV	1.010 (0.988,1.033)	0.0001 (-0.001,0.001)	--	1.039 (1.004,1.075)	0.0037 (-0.0005,0.0078)	--	1.049 (1.010,1.089)	0.0037 (-0.0005,0.0079)	--
NMA Excluding S80	1.011 (0.988,1.036)	0.0001 (-0.001,0.001)	--	1.025 (0.963,1.091)	0.0028 (-0.0022,0.0079)	--	1.036 (0.977,1.099)	0.0029 (-0.0022,0.0079)	--
NMA CC=0.10	1.010 (0.988,1.033)	0.000* (-0.001,0.001)	--	1.039 (1.003, 1.075)	0.0037 (-0.0005,0.0078)	--	1.049 (1.010,1.089)	0.0037 (-0.0005,0.0079)	--
NMA CC = 0.0001	1.010 (0.988,1.033)	0.000* (-0.001,0.001)	--	1.039 (1.003,1.075)	0.0037 (-0.0005,0.0078)	--	1.049 (1.010,1.089)	0.0037 (-0.0005,0.0079)	--

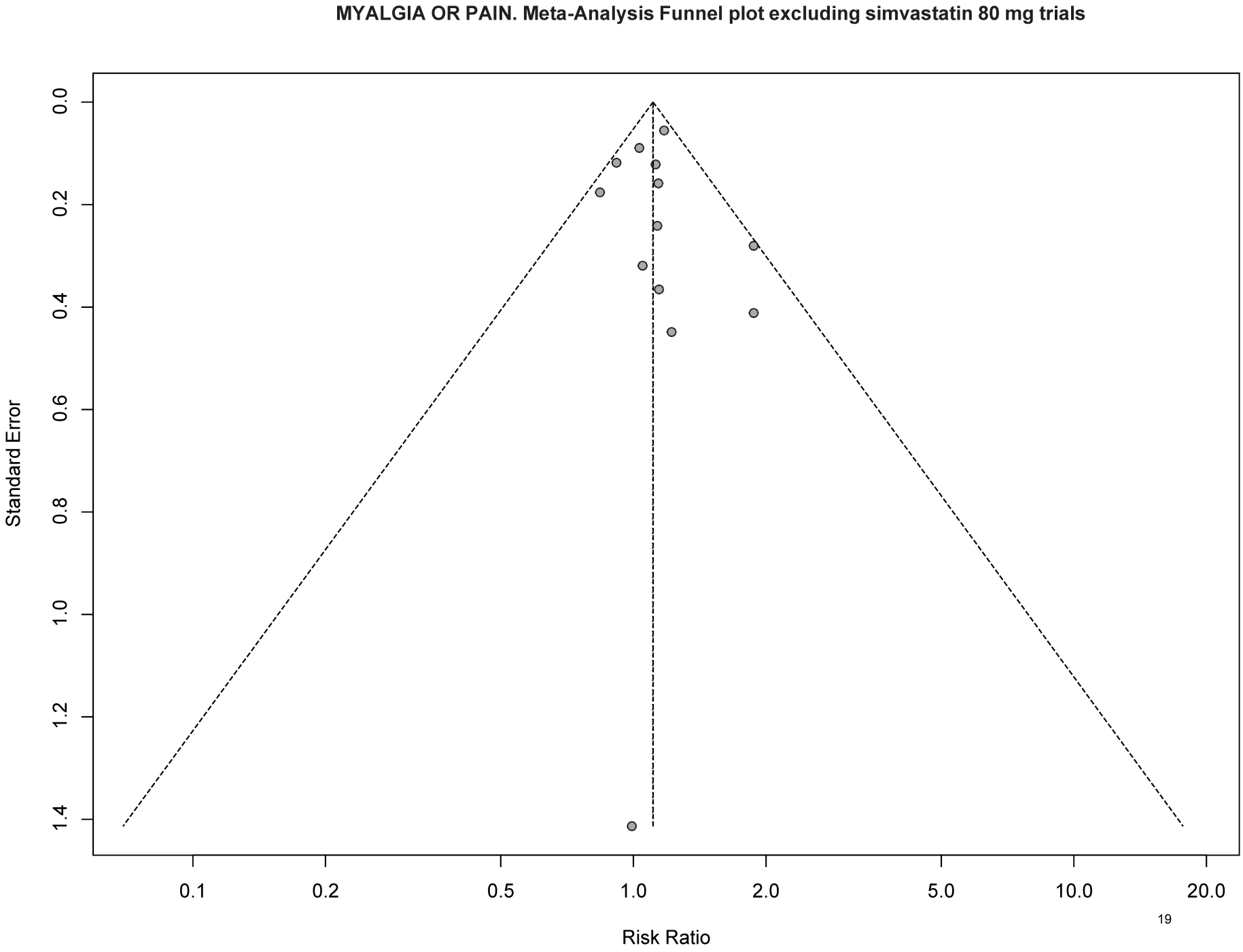
MYALGIA OR PAIN : Meta-Analysis Forest plot with data




MYALGIA OR PAIN: Meta-Analysis Funnel plot
Standard Error
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
0.1
0.2
0.5
1.0
2.0
5.0
10.0
20.0
17
Risk Ratio

MYALGIA OR PAIN: Meta-Analysis Forest plot excluding simvastatin 80 mg trials.

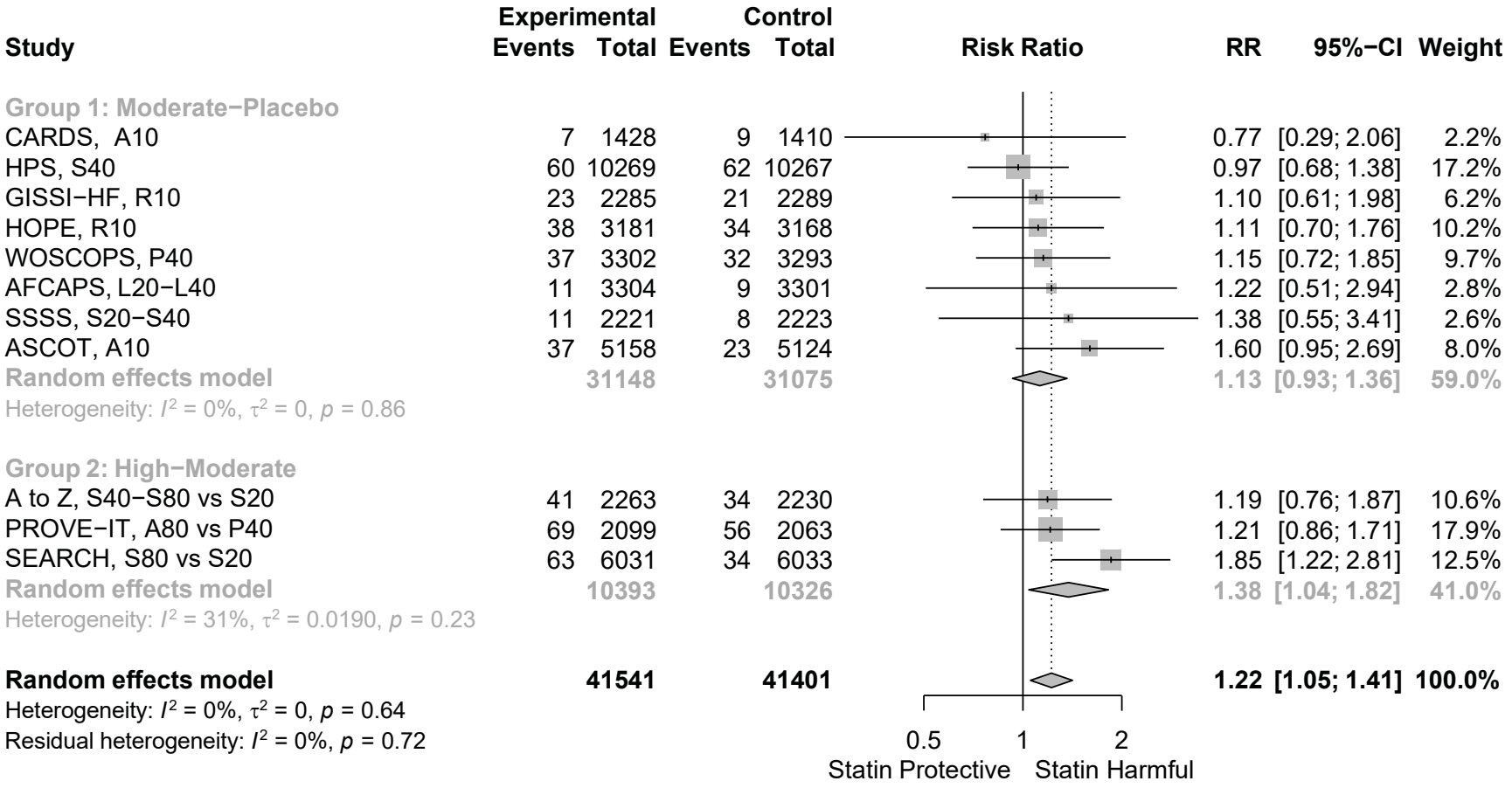


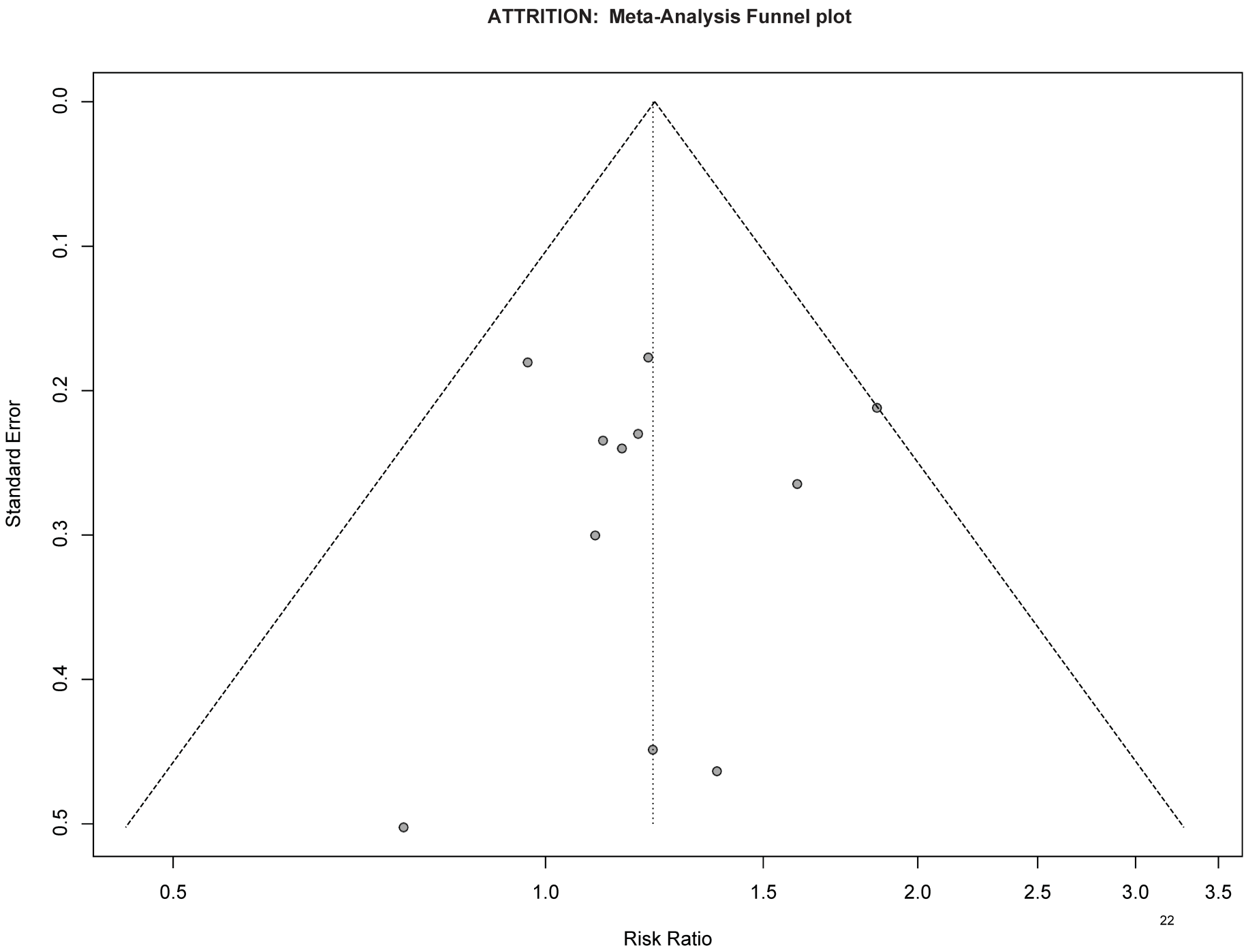

MYALGIA OR PAIN. Meta-Analysis Funnel plot excluding simvastatin 80 mg trials
Standard Error
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
0.1
0.2
0.5
1.0
2.0
5.0
10.0
20.0
19
Risk Ratio

MYALGIA OR PAIN SUMMARY: PAIRWISE AND NETWORK META-ANALYSIS RESULTS

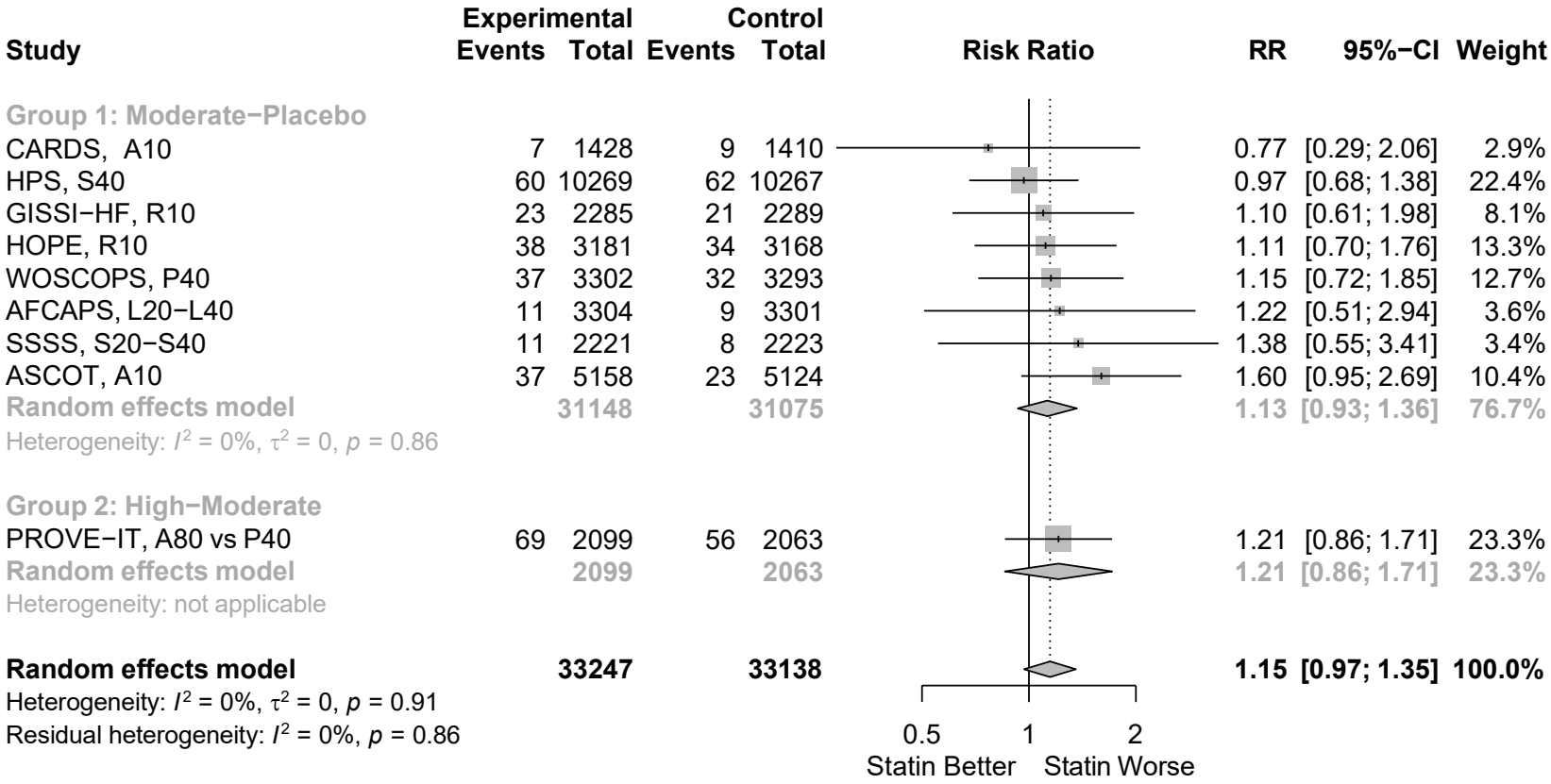
	Placebo – Moderate Intensity			**Moderate – High Intensity**			**Placebo – High Intensity**		
Outcome	RR (95% CI)	RD (95% CI)	NNH	RR (95% CI)	RD (95% CI)	NNH	RR (95% CI)	RD (95% CI)	NNH
Direct, M-H	1.130 (0.952, 1.341)	NA	--	1.043 (1.002, 1.086)	NA	--	1.092 (0.945, 1.261)	NA	--
Direct, IV	1.130 (0.952, 1.341)	0.0007 (-0.0005, 0.0019)	--	1.043 (1.002, 1.086)	0.0046 (-0.0030, 0.0123)	--	1.123 (1.025, 1.230)	0.0073 (0.0010, 0.0136)	143
NMA, IV	1.090 (0.9997,1.188)	0.0007 (-0.0005,0.0019)	--	1.041 (1.001,1.083)	0.0058 (0.0009,0.0107)	173	1.134 (1.046,1.230)	0.0065 (0.0016,0.0114)	154
Excluding S80	1.111 (0.971,1.270)	0.0007 (-0.0004,0.0018)	--	1.010 (0.881,1.158)	0.0048 (-0.0003,0.0099)	--	1.122 (1.021,1.233)	0.0055 (0.0005,0.0106)	182

ATTRITION: Meta-Analysis Forest plot with data

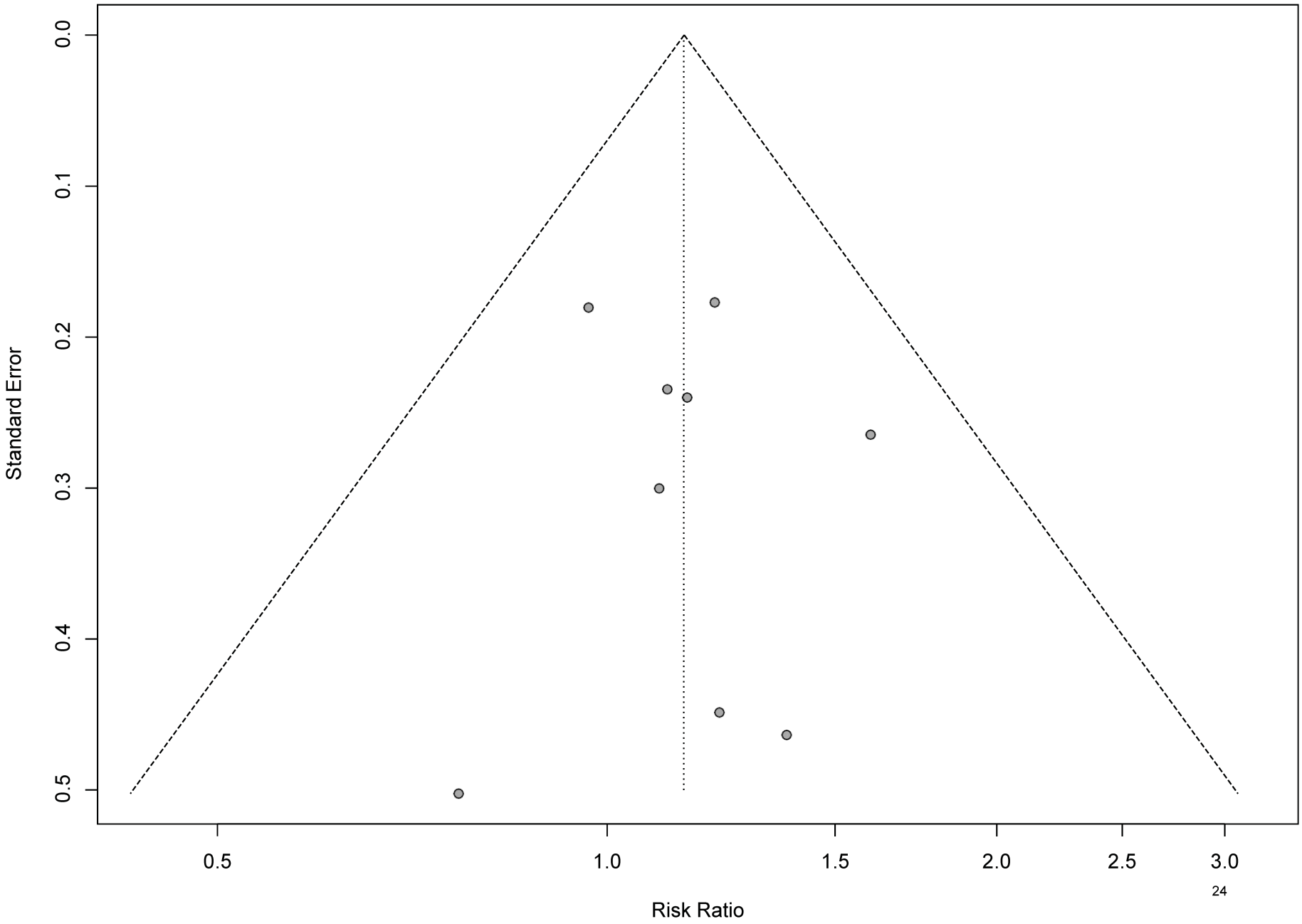



ATTRITION: Meta-Analysis Funnel plot
Standard Error
0.0
0.1
0.2
0.3
0.4
0.5
0.5
1.0
1.5
2.0
2.5
3.0
3.5
Risk Ratio

ATTRITION: Meta-Analysis Forest plot excluding simvastatin 80 mg trials.



ATTRITION: Meta-Analysis Funnel plot excluding simvastatin 80 mg trials

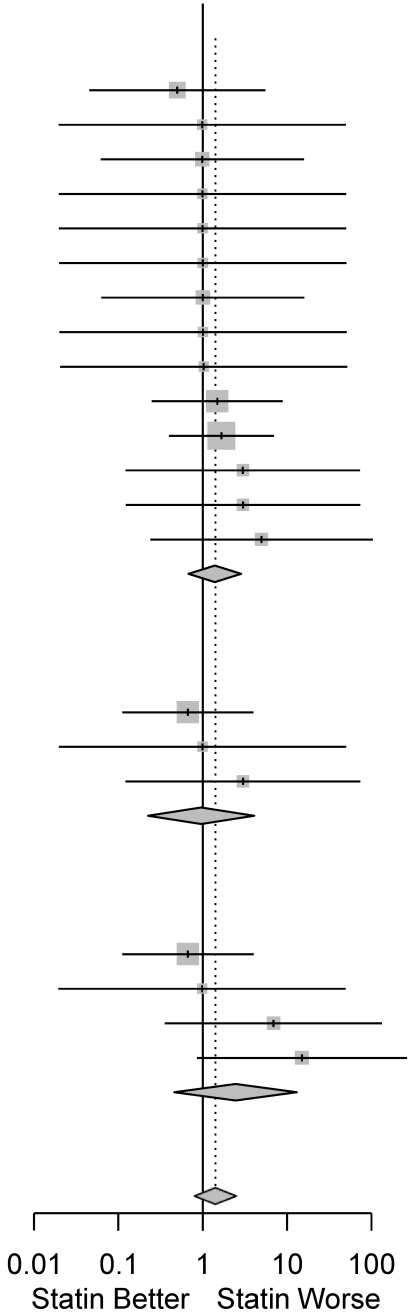


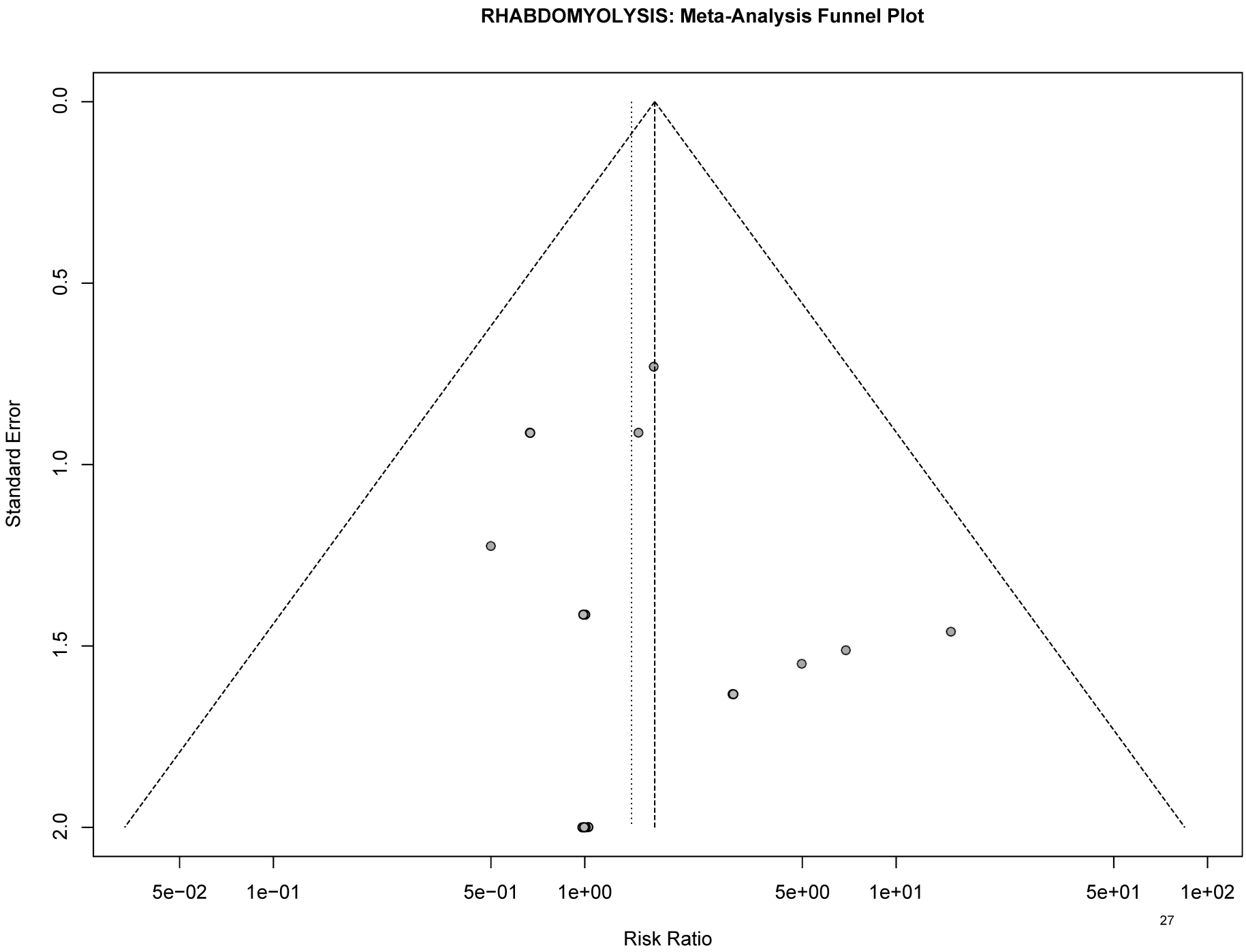
ATTRITION SUMMARY: PAIRWISE AND NETWORK META-ANALYSIS RESULTS

	Placebo – Moderate Intensity			**Moderate – High Intensity**			**Placebo – High Intensity**		
Outcome	RR (95% CI)	RD (95% CI)	NNH	RR (95% CI)	RD (95% CI)	NNH	RR (95% CI)	RD (95% CI)	NNH
Direct, M-H	1.127 (0.931, 1.364)	NA	--	1.378 (1.043, 1.822)	NA	--	NA	NA	--
Direct, IV	1.127 (0.931, 1.364)	0.0008 (-0.0004, 0.0020)	1000	1.372 (1.091, 1.726)	0.0046 (0.0018, 0.0074)	200	NA	NA	--
NMA, IV	1.127 (0.931,1.364)	0.0008 (-0.0004,0.0020)	--	1.372 (1.091,1.726)	0.0046 (0.0018,0.0074)	218	1.155 (1.147,2.084)	0.0054 (0.0023,0.0084)	187
Excluding S80	1.127 (0.931,1.364)	0.0008 (-0.0004,0.0020)	--	1.211 (0.856,1.714)	0.0057 (-0.0046,0.0161)	176*	1.365 (0.918,2.028)	0.0065 (-0.0039,0.0169)	154*

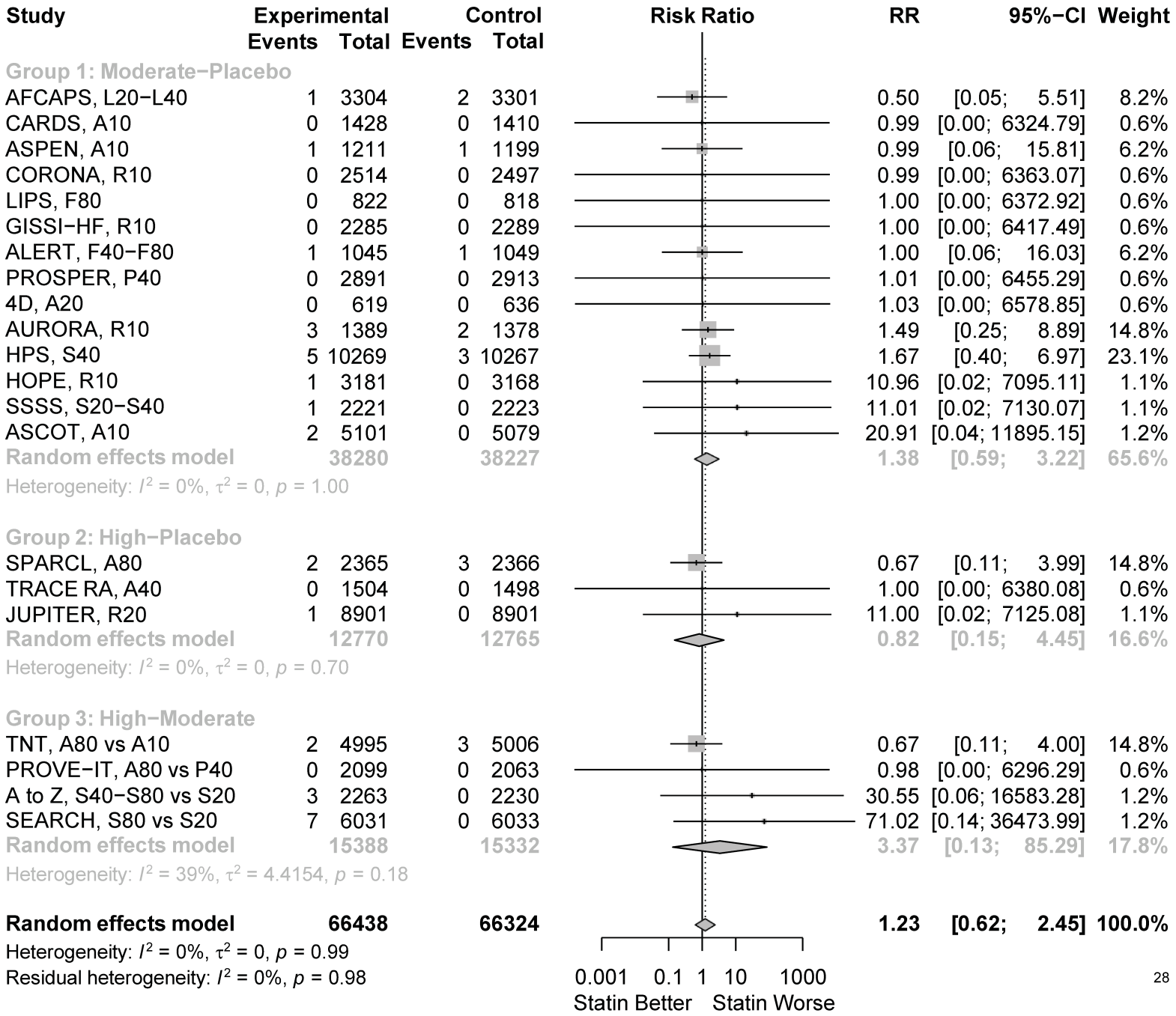
RHABDOMYOLYSIS: Meta-Analysis Forest Plot with Data

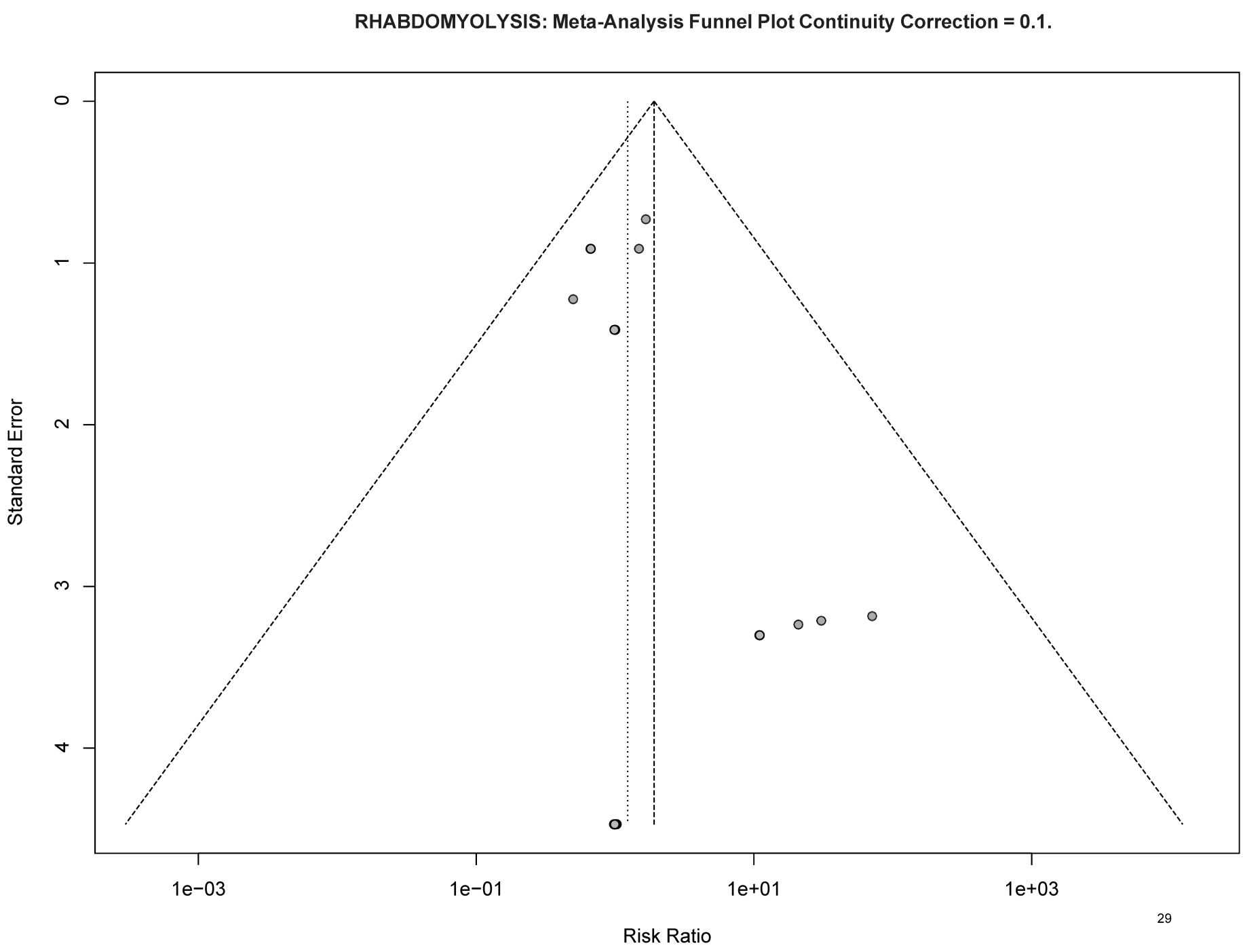
Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	Weight
Group 1: Moderate−Placebo							
AFCAPS, L20−L40	1	3304	2	3301	0.50	[0.05; 5.51]	5.8%
CARDS, A10	0	1428	0	1410	0.99	[0.02; 49.73]	2.2%
ASPEN, A10	1	1211	1	1199	0.99	[0.06; 15.81]	4.3%
CORONA, R10	0	2514	0	2497	0.99	[0.02; 50.04]	2.2%
LIPS, F80	0	822	0	818	1.00	[0.02; 50.09]	2.2%
GISSI−HF, R10	0	2285	0	2289	1.00	[0.02; 50.46]	2.2%
ALERT, F40−F80	1	1045	1	1049	1.00	[0.06; 16.03]	4.3%
PROSPER, P40	0	2891	0	2913	1.01	[0.02; 50.76]	2.2%
4D, A20	0	619	0	636	1.03	[0.02; 51.70]	2.2%
AURORA, R10	3	1389	2	1378	1.49	[0.25; 8.89]	10.4%
HPS, S40	5	10269	3	10267	1.67	[0.40; 6.97]	16.2%
HOPE, R10	1	3181	0	3168	2.99	[0.12; 73.31]	3.2%
SSSS, S20−S40	1	2221	0	2223	3.00	[0.12; 73.67]	3.2%
ASCOT, A10	2	5101	0	5079	4.98	[0.24; 103.67]	3.6%
Random effects model		38280		38227	1.39	[0.68; 2.86]	63.9%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 1.00							
Group 2: High−Placebo							
SPARCL, A80	2	2365	3	2366	0.67	[0.11; 3.99]	10.4%
TRACE RA, A40	0	1504	0	1498	1.00	[0.02; 50.16]	2.2%
JUPITER, R20	1	8901	0	8901	3.00	[0.12; 73.63]	3.2%
Random effects model		12770		12765	0.96	[0.22; 4.09]	15.7%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.72							
Group 3: High−Moderate							
TNT, A80 vs A10	2	4995	3	5006	0.67	[0.11; 4.00]	10.4%
PROVE−IT, A80 vs P40	0	2099	0	2063	0.98	[0.02; 49.51]	2.2%
A to Z, S40−S80 vs S20	3	2263	0	2230	6.90	[0.36; 133.46]	3.8%
SEARCH, S80 vs S20	7	6031	0	6033	15.00	[0.86; 262.66]	4.0%
Random effects model		15388		15332	2.45	[0.46; 13.05]	20.3%
Heterogeneity: I^2 = 34%, τ^2 = 0.9919, p = 0.21							
Random effects model		**66438**		**66324**	**1.41**	**[0.80; 2.51]**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.99							
Residual heterogeneity: I^2 = 0%, p = 0.99							



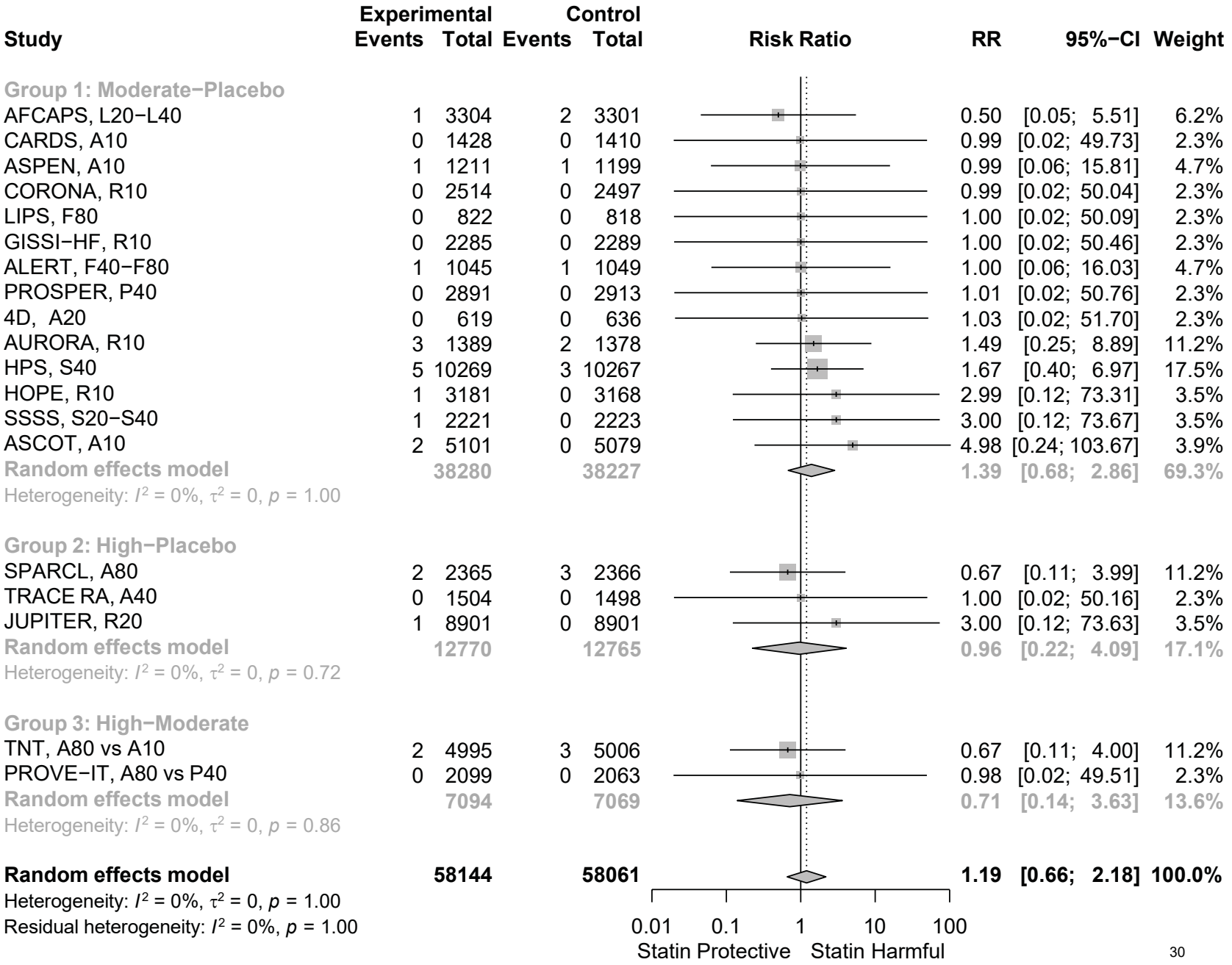

RHABDOMYOLYSIS: Meta-Analysis Funnel Plot
Standard Error
0.0
0.5
1.0
1.5
2.0
5e−02
1e−01
5e−01
1e+00
5e+00
1e+01
5e+01
1e+02
Risk Ratio

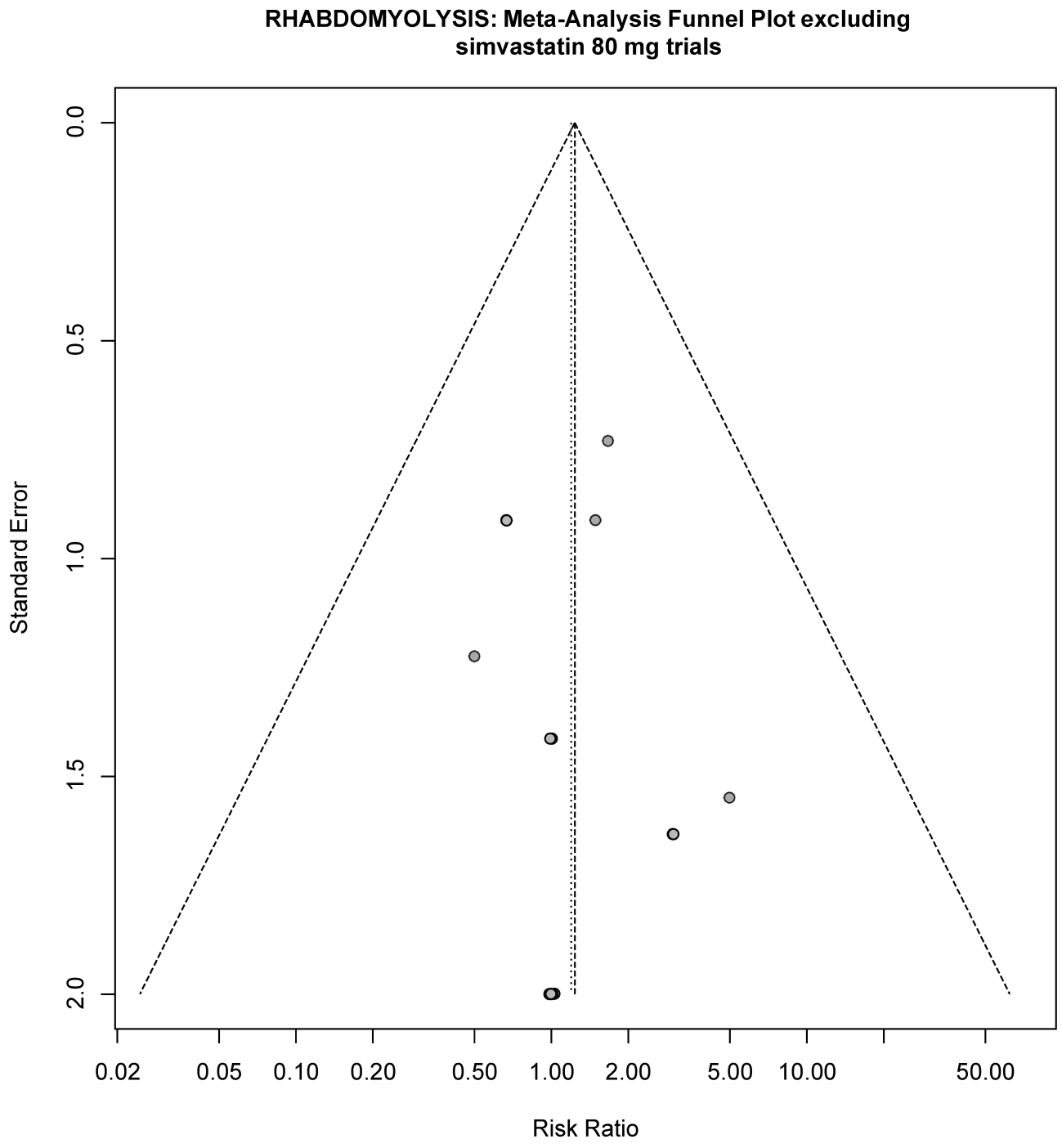
RHABDOMYOLYSIS: Meta-Analysis Forest Plot with Continuity Correction = 0.1.




RHABDOMYOLYSIS: Meta-Analysis Funnel Plot Continuity Correction = 0.1.
Standard Error
0
1
2
3
4
1e−03
1e−01
1e+01
1e+03
Risk Ratio
29

RHABDOMYOLYSIS: Meta-Analysis Forest plot excluding simvastatin 80 mg trials.

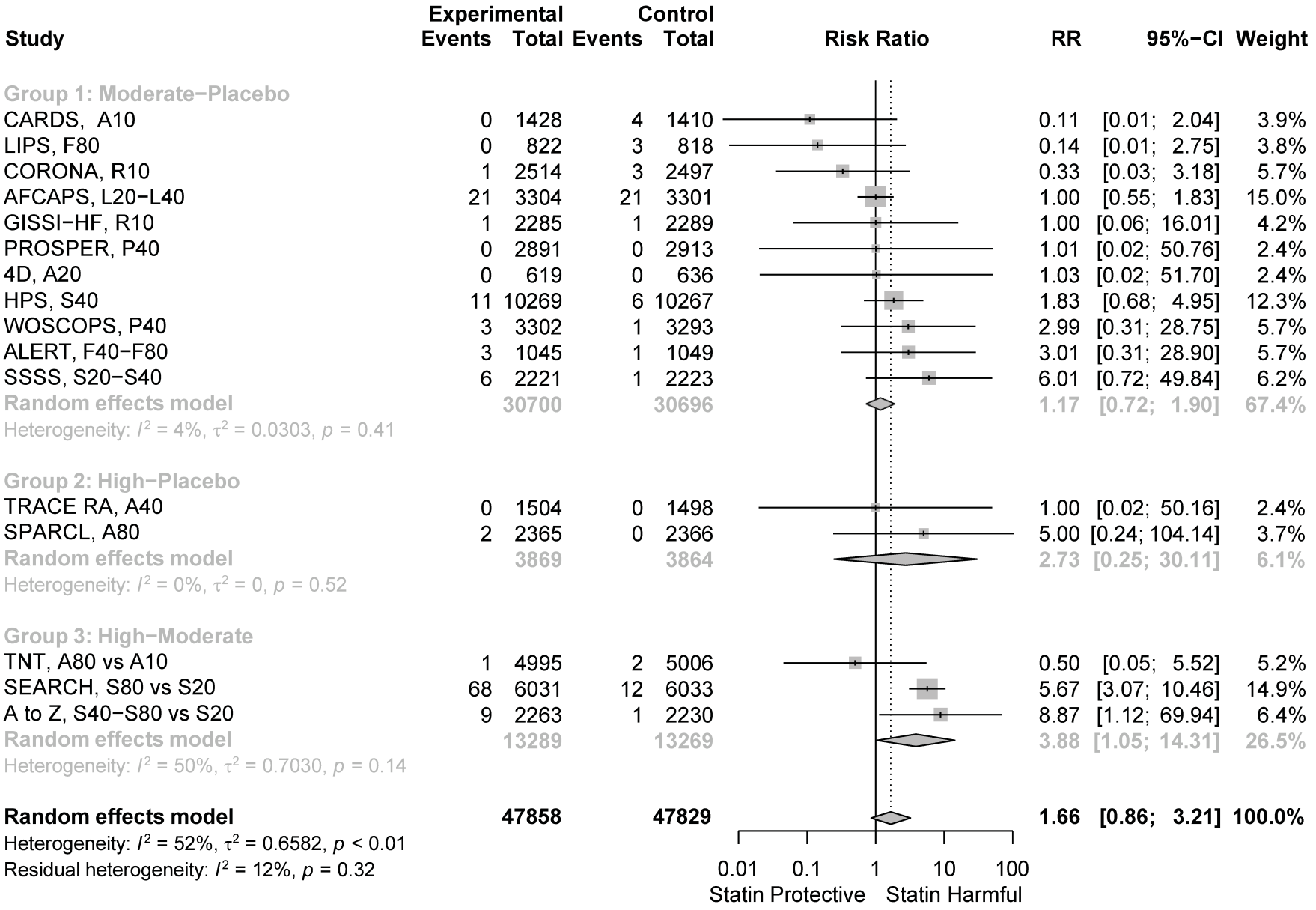


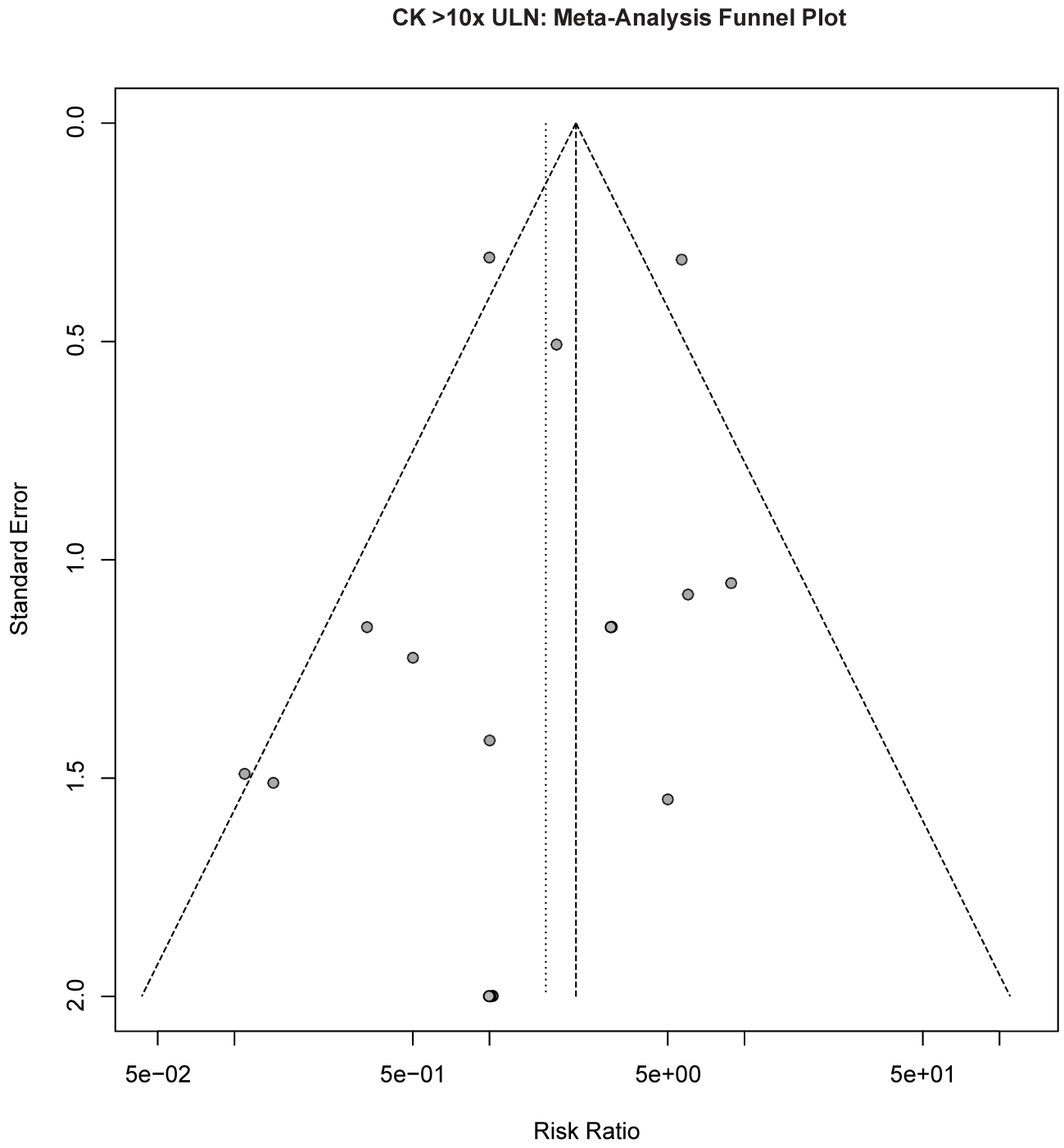

RHABDOMYOLYSIS: Meta-Analysis Funnel Plot excluding simvastatin 80 mg trials
Standard Error
0.0
0.5
1.0
1.5
2.0
0.02
0.05
0.10
0.20
0.50
1.00
2.00
5.00
10.00
50.00
Risk Ratio

RHADOMYOLYSIS SUMMARY: PAIRWISE AND NETWORK META-ANALYSIS RESULTS

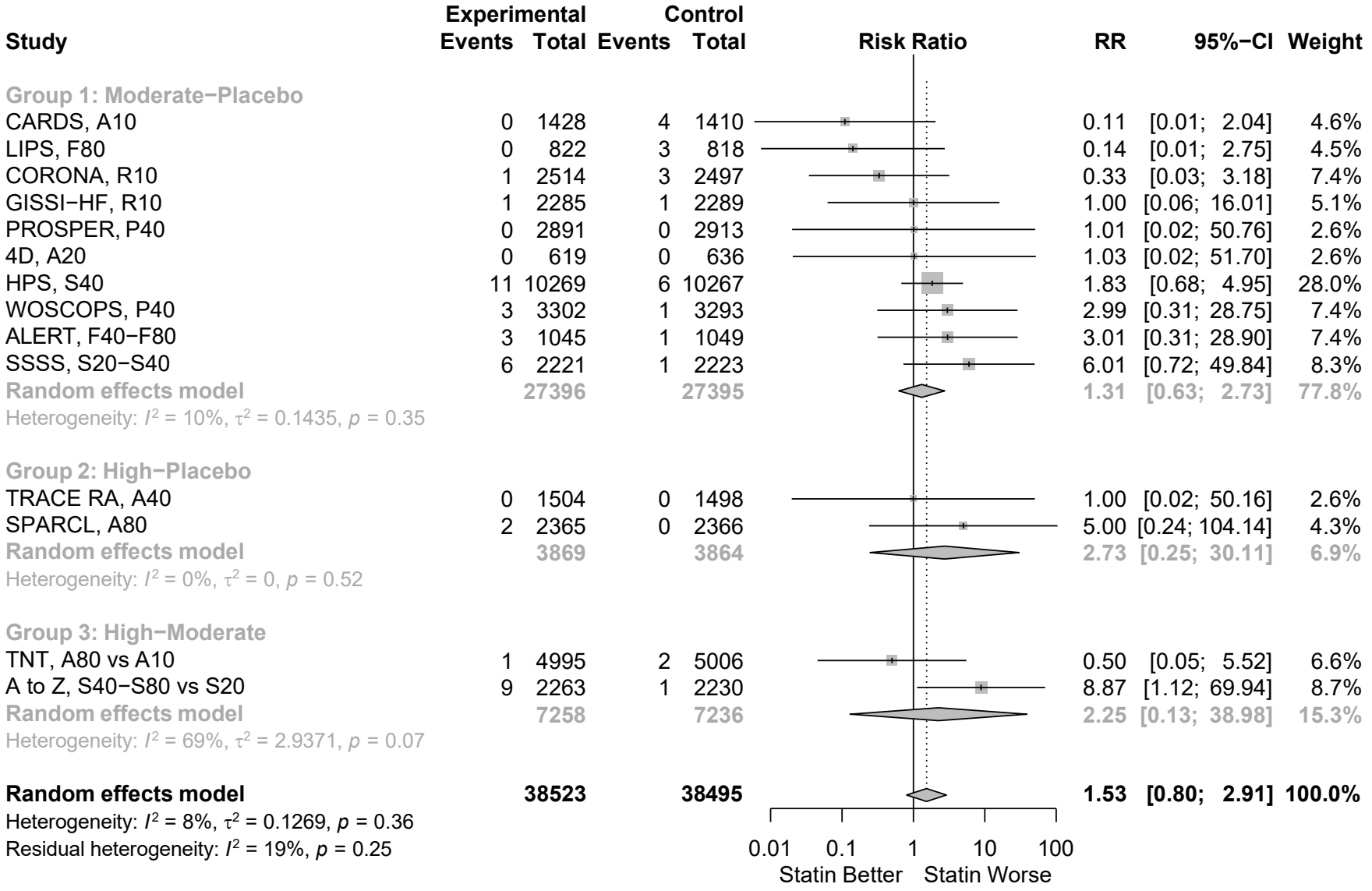
	Placebo – Moderate Intensity			**Moderate – High Intensity**			**Placebo – High Intensity**		
Outcome	RR (95% CI)	RD (95% CI)	NNH	RR (95% CI)	RD (95% CI)	NNH	RR (95% CI)	RD (95% CI)	NNH
Direct, M-H	1.394 (0.679, 2.864)	NA	--	2.451 (0.460, 13.053)	NA	--	0.960 (0.225, 4.092)	NA	--
Direct, IV	1.394 (0.679, 2.864)	0.0001 (-0.0001, 0.0004)	--	1.994 (0.556, 7.147)	0.0004 (-0.0001, 0.0009)	--	0.959 (0.225, 4.092)	0.0001 (-0.0002, 0.0004)	--
NMA, IV	1.225 (0.624,2.405)	0.0001 (-0.0002,0.0003)	--	1.326 (0.487,3.614)	0.0001 (-0.0002,0.0004)	--	1.624 (0.579,4.553)	0.0002 (-0.0001,0.0005)	-
NMA Excluding S80	1.389 (0.701,2.752)	0.0001 (-0.0002,0.0003)	--	0.701 (0.222, 2.209)	0.0001 (-0.0002,0.0004)	--	0.974 (0.316,2.997)	0.0002 (-0.0001,0.0005)	--
NMA CC=0.10	1.269 (0.571,2.820)	0.0000* (-0.0001,0.0002)	--	0.892 (0.259,3.066)	0.0001 (-0.0001,0.0003)	--	1.131 (0.326,3.927)	0.0001 (-0.0001,0.0003)	--
NMA CC = 0.0001	1.199 (0.514,2.799)	0.0000* (-0.0000,0.0000)	--	0.610 (0.161,2.317)	0.0000* (-0.0000,0.0000)	--	0.732 (0.193,2.778)	0.0000* (-0.0000,0.0000)	--

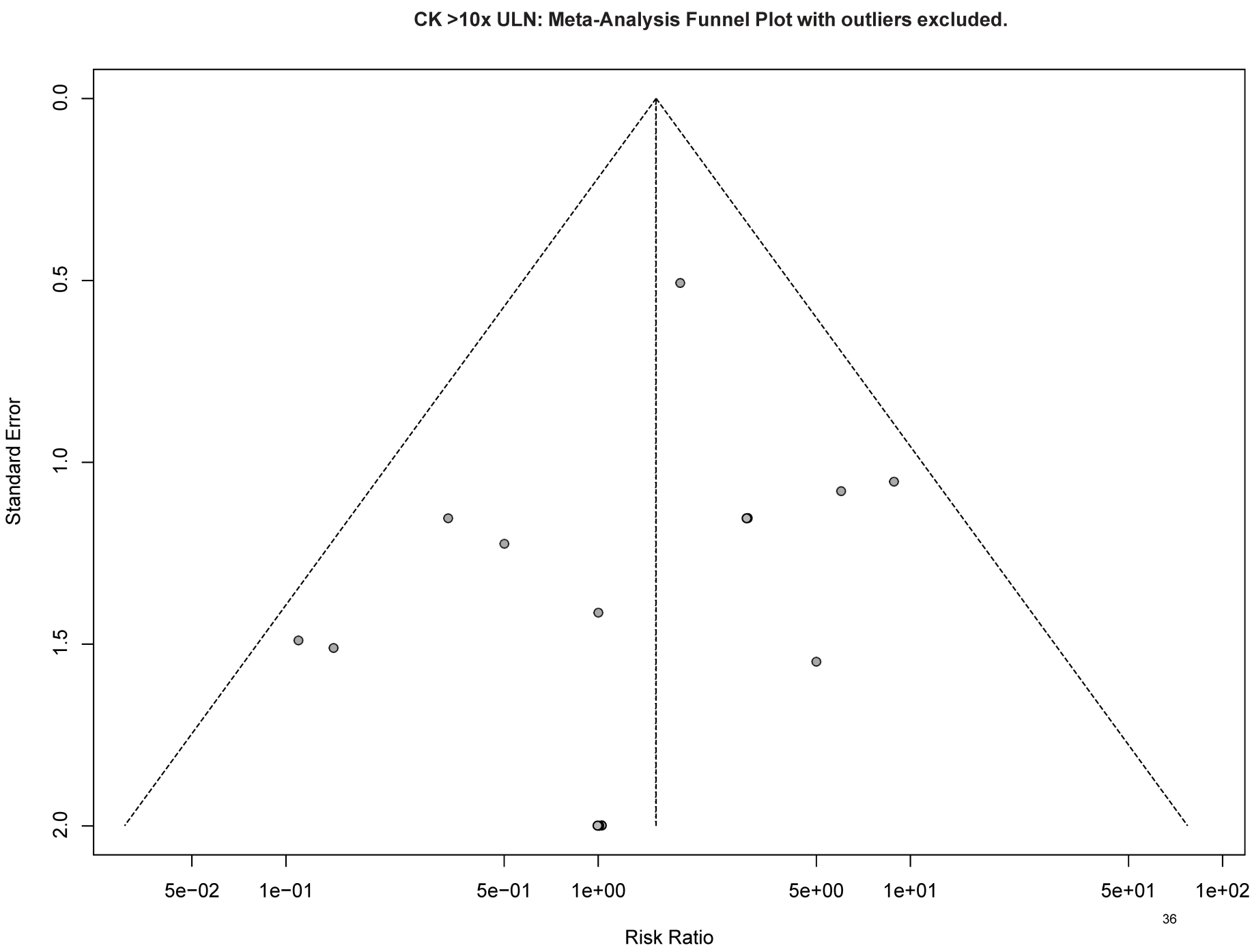
CK >10x ULN: Meta-Analysis Forest Plot with Data



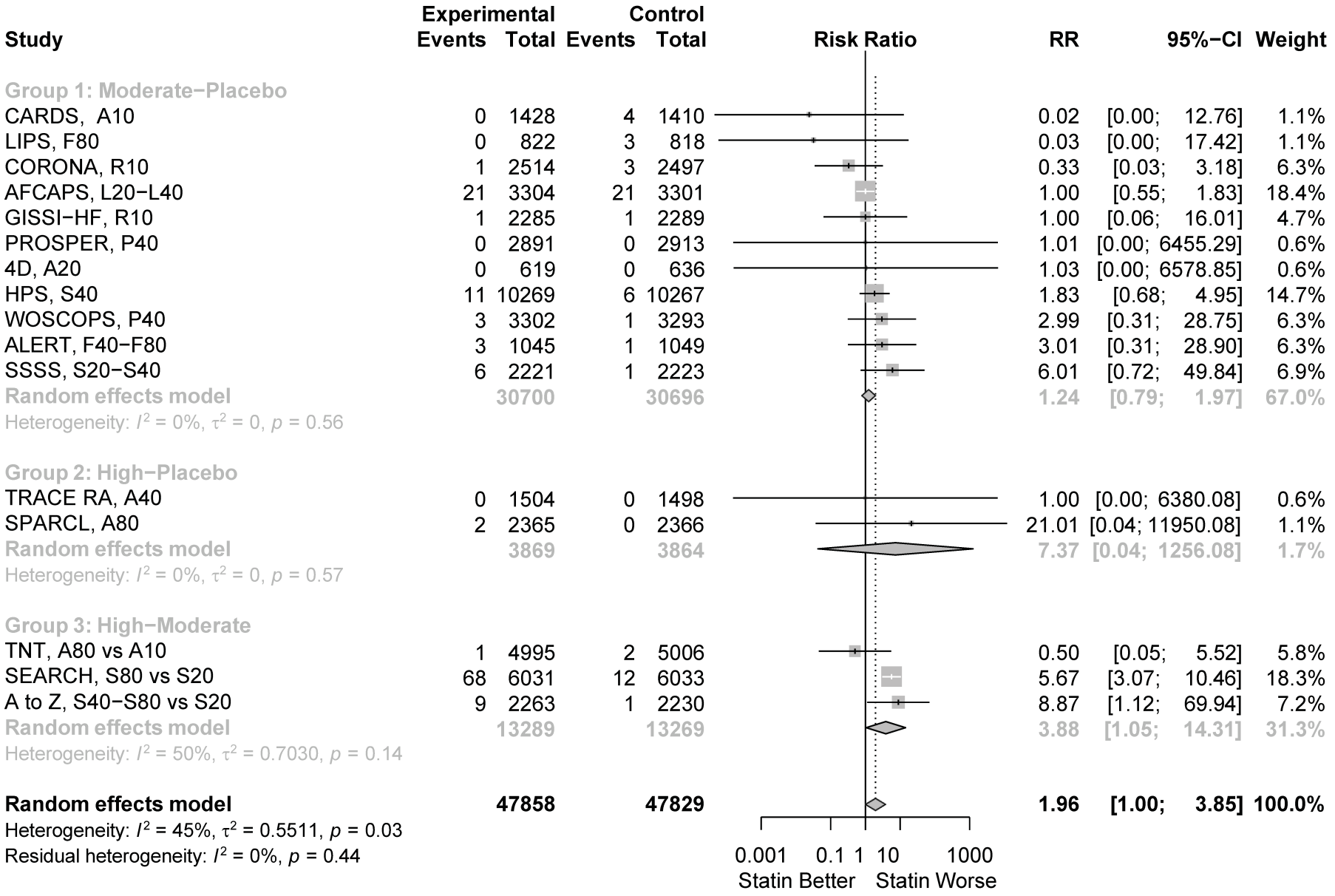

CK >10x ULN: Meta-Analysis Funnel Plot
Standard Error
0.0
0.5
1.0
1.5
2.0
5e−02
5e−01
5e+00
5e+01
Risk Ratio

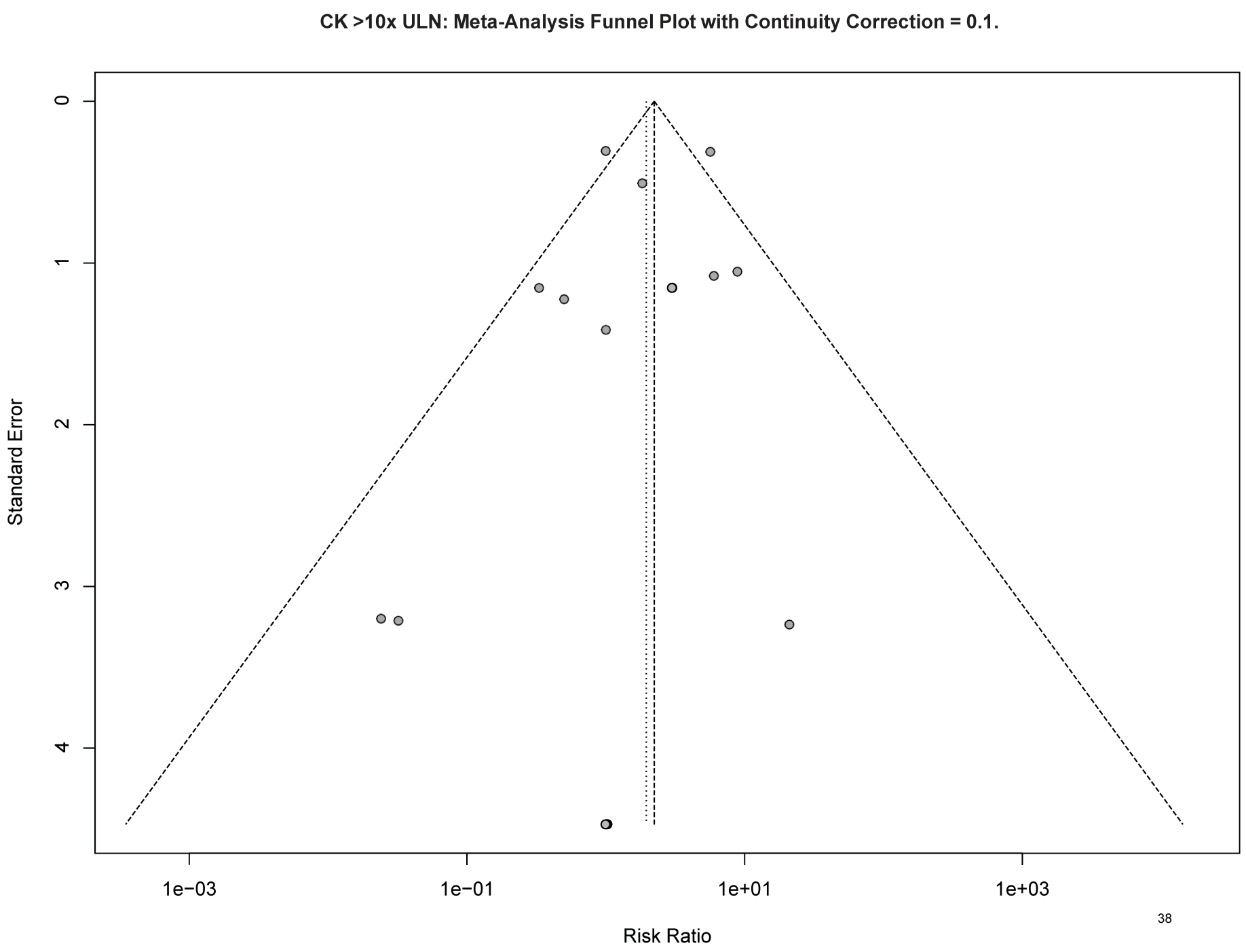
CK >10x ULN: Meta-Analysis Forest Plot with outliers excluded.



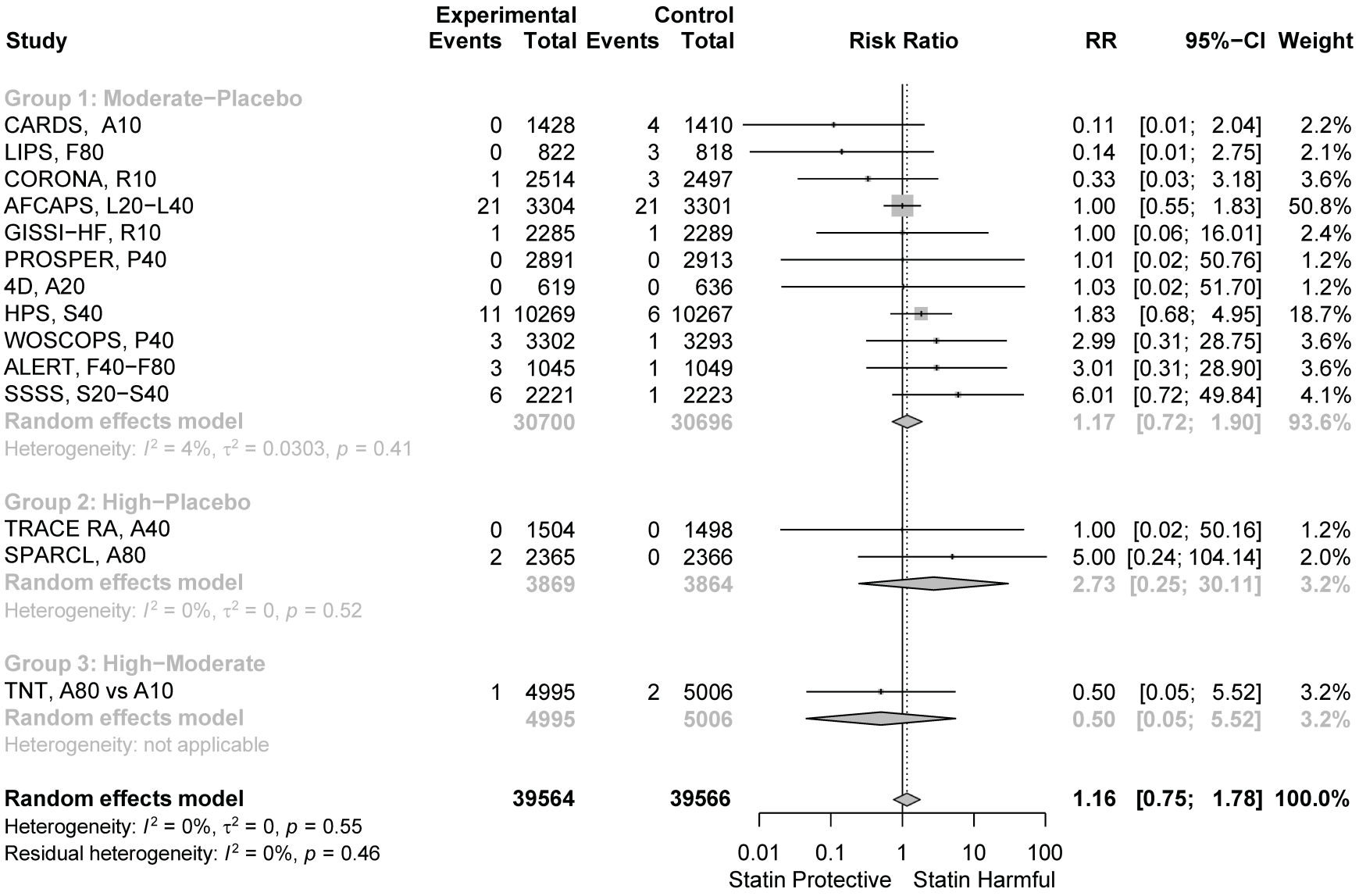

CK >10x ULN: Meta-Analysis Funnel Plot with outliers excluded.
Standard Error
0.0
0.5
1.0
1.5
2.0
5e−02
1e−01
5e−01
1e+00
5e+00
1e+01
5e+01
1e+02
Risk Ratio

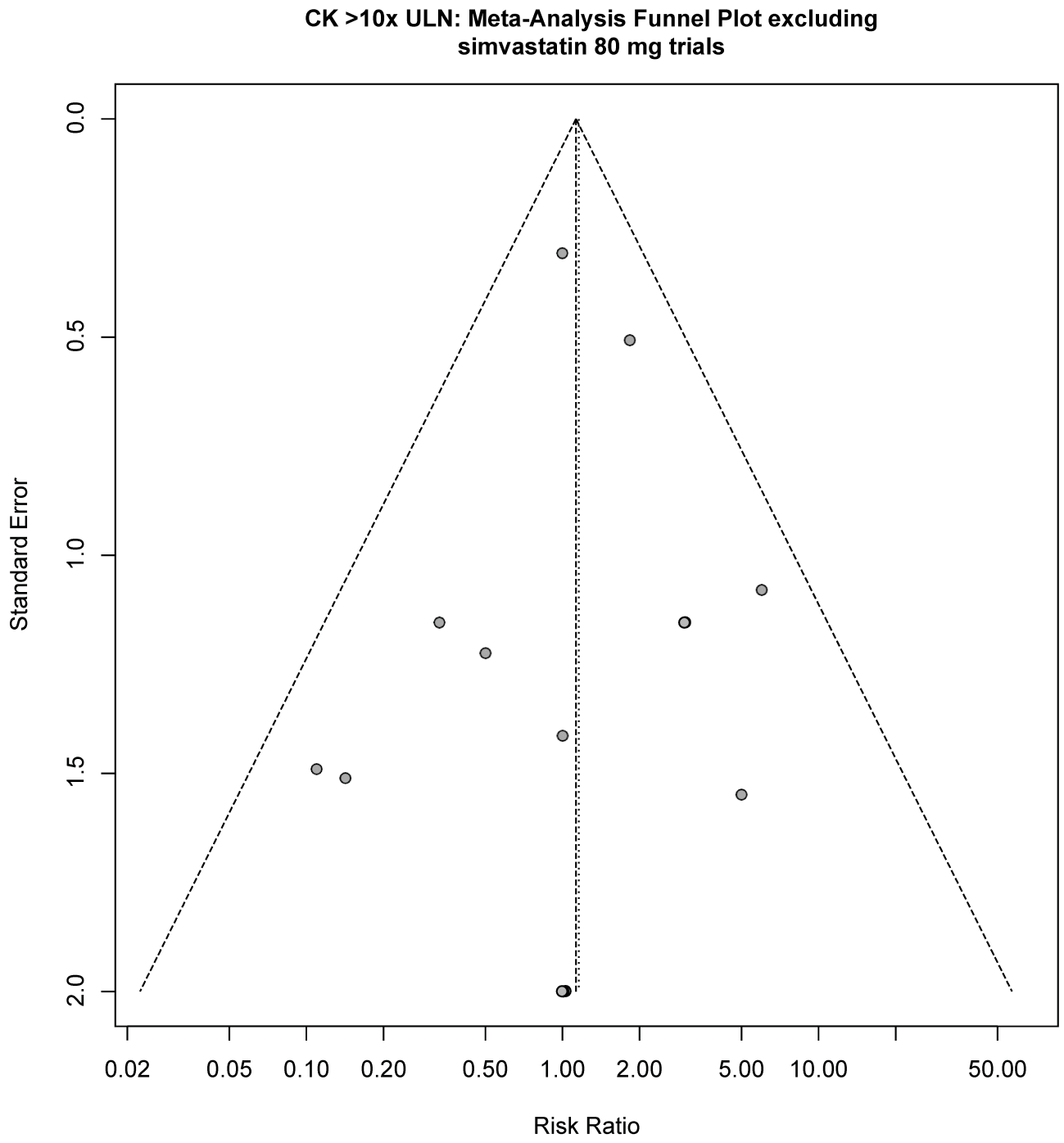
CK >10x ULN: Meta-Analysis Forest Plot with Continuity Correction = 0.1.




CK >10x ULN: Meta-Analysis Funnel Plot with Continuity Correction = 0.1.
Standard Error
0
1
2
3
4
1e−03
1e−01
1e+01
1e+03
Risk Ratio
38

CK >10x ULN: Meta-Analysis Forest Plot excluding simvastatin 80 mg trials.




CK >10x ULN: Meta-Analysis Funnel Plot excluding simvastatin 80 mg trials
Standard Error
0.0
0.5
1.0
1.5
2.0
0.02
0.05
0.10
0.20
0.50
1.00
2.00
5.00
10.00
50.00
Risk Ratio

CK>10XULN SUMMARY: PAIRWISE AND NETWORK META-ANALYSIS RESULTS

	Placebo – Moderate Intensity			**Moderate – High Intensity**			**Placebo – High Intensity**		
Outcome	RR (95% CI)	RD (95% CI)	NNH	RR (95% CI)	RD (95% CI)	NNH	RR (95% CI)	RD (95% CI)	NNH
Direct, M-H	1.171 (0.722, 1.900)	NA	--	3.880 (1.052, 14.314)	NA	--	2.731 (0.428, 30.106)	NA	--
Direct, IV	1.178 (0.700, 1.985)	0.0000* (-0.0010, 0.0010)	--	4.861 (2.388, 9.894)	0.0030 (0.0011, 0.0049)	333	2.720 (0.240, 30.828)	0.0004 (-0.0016, 0.0025)	--
NMA, IV	1.143 (0.686,1.905)	-0.0003 (-0.0012,0.0007)	--	4.594 (2.320,9.098)	0.0019 (0.0005,0.0034)	527	5.252 (2.293,12.028)	0.0017 (0.0002,0.0031)	589
NMA Excluding S80	1.189 (0.765,1.848)	0.0002 (-0.0003,0.0006	--	1.073 (0.194,5.939)	-0.0000* (-0.0007,0.0007)	--	1.276 (0.230,7.063)	0.0002 (-0.0006,0.0009)	--
NMA CC=0.10	1.246 (0.790,1.964)	-0.0002 (-0.0010,0.0005)	--	5.123 (2.906,9.033)	0.0016 (0.0004,0.0028)	625	6.381 (3.094,13.161)	0.0013 (0.0002,0.0025)	770
NMA CC = 0.0001	1.297 (0.818,2.058)	-0.0000* (-0.0002,0.0001)	--	5.115 (2.891,9.049)	0.0001 (-0.0002,0.0003)	--	6.636 (3.186,13.819)	0.0001 (-0.0001,0.0003)	--

R Code for Meta-Analysis

```
## Attrition MA:

AE_Drop_meta <- read.csv("C:/Users/14795/Desktop/Statin_Meta/Final
Sheets - Copy/Attrition.csv", header=T)

mb1_Attrition <- metabin(X1, Statin.Total, X2, Placebo.Total,

                data = AE_Drop_meta, studlab = Study, label.right =
                "Statin Harmful", label.left = "Statin Protective",


                allstudies=TRUE, incr=0.5, sm = "RR", digits=3,

                byvar = AE_Drop_meta$Study.Intensity, bylab = "Study
Design", comb.fixed = FALSE,

                print.byvar = FALSE)

summary(mb1_Attrition)
```

R Code for Network Meta-Analysis

```
## Attrition NMA:


##
p3 <- pairwise(list(treat1, treat2),



               list(X, X1),
               list(Total, Total.1),
               data=net_attrition, studlab = Study)
net3_attrition <- netmetabin(p3,   method = "Inverse", title =
"Attrition NMA",
                    reference.group = "Placebo", sm = "RR",  comb.fixed
= FALSE,
                    studlab = p3$Study )


net3_attrition
```