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MODERATE INTENSITY STATIN THERAPY DOES NOT INCREASE ADVERSE MUSCLE EVENTS: A NETWORK META-ANALYSIS OF 153,000 PATIENTS

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MODERATE INTENSITY STATIN THERAPY DOES NOT INCREASE ADVERSE MUSCLE EVENTS: A NETWORK META-ANALYSIS OF 153,000 PATIENTS

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ABSTRACT

Objective: To estimate relative risk of statin-associated musculoskeletal symptoms (SAMS) by statin therapy intensity.

Setting: Network meta-analysis assessing multi-center RCTs across several countries.

Participants: Pubmed, Web of Science, Cochrane database, and clinicaltrials.gov were searched from January 1, 2010 - October 1, 2018 for doubled-blinded RCTs testing the effect of statin therapy on lipids with at least 1000 participants and two years of intended treatment. Two coders assessed articles for inclusion. Statin therapy was categorized by treatment intensity (placebo, moderate, high).

Outcomes: Pairwise and network meta-analysis (NMA) estimated relative risk (RR) and risk difference (RD) with random effects modeling. Heterogeneity was evaluated with the I^2 statistic. Outcomes included muscle symptoms (any, myalgia, and attrition due to muscle symptoms), rhabdomyolysis, and elevated creatine kinase (>10x upper limit of normal).

Results: Of 2801 RCTs, 24 (N=152,461) met inclusion criteria. NMA results indicated risk was significantly greater for high compared to moderate intensity statin therapy for any muscle problem (RR=1.04, 95% CI: 1.00,1.07; I^2=0%), myalgia (RR=1.04, 95% CI: 1.00,1.08; I^2=0%, NNH=173), attrition due to muscle problems (RR=1.37, 95% CI: 1.09,1.73, I^2=0%, NNH=218), and elevated CK (RR=4.69, CI: 2.50, 8.80; I^2=7%, NNH=527). Risk also was significantly higher for high intensity compared to placebo for any muscle problem (RR=1.05, 95% CI: 1.01,1.09, I^2=0%), myalgia (RR=1.13, 95% CI: 1.05,1.23; I^2=0%, NNH=182), attrition due to muscle problems (RR=1.55, 95% CI: 1.15,2.08, I^2=0%, NNH=187), and elevated CK (RR=5.37, CI: 2.48, 11.61; I^2=7%,

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NNH=589). Due to inconsistency of results across sensitivity analyses, estimates were inconclusive for rhabdomyolysis and CK. There were no significant differences in risk between moderate intensity therapy and placebo for all outcomes.

Conclusions: For each 200 patients on high intensity statins, one additional patient may experience SAMS or discontinue due to SAMS. Moderate intensity statins did not cause significant increases in SAMS.

Trial Registration: Prospero #CRD42019112758

Article Summary:

Strengths

- High-quality, large RCTs analyzed with low risk of heterogeneity bias
- Novel use of network meta-analysis to compare treatment intensities allows for large analysis of dose-dependent effect
- Rigorous coding of outcome terms allows for more granular investigation of outcome

Weaknesses

- Study-level data precludes meta-analysis with regression for relevant covariables affecting risk of outcome
- Heterogeneity of terms across trials prevented analysis of full trial set for each outcome.

Key Words: Statins, myalgia, nocebo, rhabdomyolysis, network meta-analysis

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Abbreviations:

Network Meta-Analysis (NMA) and pair-wise meta-analysis (MA), Risk Ratio (RR), Risk Difference (RD), Cholesterol Treatment Trialists' Collaboration (CTT), Statin Associated Muscle Symptoms (SAMS), Creatine Kinase (CK) & Upper Limit of Normal (ULN), End Stage Renal Disease (ESRD), Number Needed to Harm (NNH), Hazard Ratio (HR)

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INTRODUCTION

The Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis on patient-level data from large RCTs demonstrated that statin therapy is efficacious in reducing major vascular events.[1,2] Statin therapy is now prominent in cholesterol management guidelines. [3–8] Statin-associated muscle symptoms (SAMS), however, may lead to non-adherence or discontinuation with therapy and ultimately to poorer cardiovascular outcomes.[7] Most RCTs have shown small, insignificant increases in risk for SAMS, although patients taking statins may complain of muscle problems and may discontinue therapy due to muscle problems.[3] For example, a 2016 meta-analysis found a non-significant increase in myopathy. However, it did not report on the more mundane myalgias that often cause statin attrition.[3] These milder symptoms are the major public health concern, as statin non-adherence can lead to significant increases in risk of major adverse cardiovascular events.[3] Observational studies suggest that these mild SAMS may occur as often as 7-29% of patients.[7] One review[9] suggested that clinical observations of increased muscle problems with statin therapy may be due to patient expectations.

SAMS also may be more likely with higher intensity therapy. Although this is assumed to be true, especially with the evidence against simvastatin 80 mg,[10,11] few RCTs have examined high intensity therapy[12,13]. This study used a network meta-analysis (NMA) to combine evidence across trials to estimate the risk of SAMS by treatment intensity. In contrast to pair-wise meta-analysis (MA) that directly estimates causal effects, a NMA can indirectly estimate risk between placebo and moderate, moderate and high, and

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between placebo and high intensity treatment – even though placebo, moderate, and high intensity treatment levels were not compared within a single trial. Results contribute to the debate about whether muscle adverse events are due solely to patient expectations or whether statins might have an independent effect on symptoms. Finally, this study contributes to the ongoing debate as to whether statins cause myalgias and attrition due to muscle problems without marked creatine kinase (CK) elevations.

METHODS

The Trials. PubMed, Cochrane Database, Web of Science, and clinicaltrials.gov were searched (Prospero #CRD42019112758 for search terms and strategy) from January 1, 2010 to October 1, 2018 to identify eligible trials. Double-blinded RCTs to improve lipid levels that comparing statin therapy to placebo or higher-lower dose statin therapy were selected. In order to detect most adverse events, RCTs were selected that had at least 1,000 participants with two years of intended follow-up, where statin treatment was not given with other prescription drug therapies, and results contained reports on muscle-related adverse events. All included trials were coded for quality with Oxford Center for Evidence-based Medicine ratings[14] and a five-point Jadad quality score.

Exposure Variable. Studies were classified by intensity of statin treatment ("high" or "moderate") according to American Heart Association definitions for potency in reduction of lipid levels.[15] High intensity signifies an expected 50% or greater reduction in LDL-C levels when taking that statin (i.e., 80 mg atorvastatin) and moderate signifies 30-50% reduction in LDL-C.[15]

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Outcome Variables. Adverse muscle-related events were coded into five main outcomes. The first outcome was for any patient-reported muscle complaint coded from reports of “muscle aches”, “pains”, “cramps”, “stiffness,” “musculoskeletal disorders,” etc. The second focused on only myalgia or muscle pain. The third focused on attrition due to musculoskeletal complaints. A fourth captured explicit reporting of rhabdomyolysis, with or without a trial definition. The fifth was elevated creatine kinase, greater than ten times the upper limit of normal (CK >10x ULN). This threshold was used to distinguish this outcome from less meaningful CK increases and also because CK>10xULN is commonly reported in RCTs. All outcomes were coded as reported by original investigators in published and online reports, and were independently coded by two people (JD, SW). Trial investigators were contacted for clarification, where needed.

Analysis. Published aggregate data from each trial were used. A crude estimate of incidence was calculated from the total number of cases observed divided by the total person-years (using the median or mean follow-up time for each study) and a chi square test was used to test for homogeneity in the proportion of incident cases across studies, within each arm, although these crude estimates ignored randomization. To facilitate interpretation and comparison of results to the original trials, risk of adverse effects was estimated with pooled relative risk (RR, random effects). A 0.50 continuity correction was added to aggregate frequencies for trials that observed zero cases of an outcome in either treatment arm. A pairwise meta analysis (MA) was used to estimate the RR (Mantel-Haenszel method) for causal effects of statins within treatment intensity

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subgroups from direct (head-head comparison) trials.[16,17] Because aggregations across studies are only meaningfully interpreted when results are consistent across studies, heterogeneity among RCTs was assessed with an index of consistency across trials (I^2, Q)[18,19] and funnel plots. When $I^2 \leq 25\%$, results are considered to be at low risk of bias due to heterogeneity; high values (>75%) indicate high risk of bias due to heterogeneity.[18,19] Residual I^2 represents the heterogeneity remaining after accounting for sub-groups of treatment intensity. Cochrane Q (a sub-component of I^2) indicates the probability that the observed heterogeneity is due to chance. Sensitivity analyses included omitting outliers identified in funnel plots and using a 0.10 as a "continuity correction".

A network meta-analysis (NMA)[20] used *all* available pairs of comparisons for each outcome to estimate increased risk between placebo and moderate intensity, between moderate and high intensity therapy, and between placebo and high intensity. The RR was used to estimate effect size (frequentist, inverse variance method), so that results would be comparable across original studies and the pairwise meta-analysis above. In contrast to a MA which provides a direct estimate of causal effects, a NMA provides indirect estimates or measures of association. A ratio test was used to test for consistency between NMA and MA estimates.[21] Heterogeneity was assessed with and I^2 and Q statistics.[18,19] Number needed to harm (NNH) was estimated when the pooled RR was significantly greater than 1.0 and the pooled absolute risk reduction (risk difference, RD) was significantly greater than 0.0.

Patient and Public Involvement

Patients were not involved in design or implementation of this study.

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RESULTS

Searches yielded 134 relevant reviews, including 2801 RCTs that reduced to 24 unique RCTs that met eligibility requirements (eFigure 1). Of the 24 RCTs: 17 were placebo-moderate intensity comparisons,[22–42] 3 were placebo-high intensity comparisons,[43–45] and 4 were moderate-high intensity comparisons[10–13] (Table 1). The active blood pressure treatment arm of the HOPE trial[35] was excluded, but the statin only and placebo only arms were retained, allowing for a statin and placebo comparison. Two trials compared moderate and high intensity therapy using 80 mg/day of simvastatin.[10,11] All 24 RCTs scored the highest quality (1) on the Oxford rating and on the Jadad scale 18 scored 5/5 and 6 scored 4/5 (missing detail on random assignment). The RCTs included heterogenous patient populations, e.g., healthy middle-aged adults[24,35,41,44] to ESRD patients. Sample sizes ranged from 1,255[22] to 20,536[38] with follow-up periods from 1.9[44] to 6.7[10] years. Of the 24 RCTs, six were included in the 2006 meta-analysis,[46] 17 in the 2014 systematic review,[47] 23 in the 2016 meta-analysis,[3] and 18 in the 2013 NMA.[48] None of the previous analyses separated trials into sub-groups by treatment intensity. Crude estimates of incidence increased with intensity of treatment from placebo to moderate intensity to high intensity therapy, but with heterogeneity across trials (eTable 1).

Any Muscle Symptoms. Twenty-three trials reported some type of muscle symptom[10,13,23–27,29,33,37,38,44,45] myositis,[32] myalgia,[12,22,28,30,31,40,43] myopathy,[22,36] or discontinuation due to muscle-related symptoms.[11,13,34] The pairwise meta-analysis pooled across subsets of trials indicated consistent trial results with non-significant

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increases in risk for any muscle problem (Figure 1) between placebo and moderate intensity therapy and between placebo and high intensity therapy, but a significant increase between moderate and high intensity therapy (RR=1.05, CI: 1.01, 1.09; 4 RCTs, N=30,720; I^2=0%). Sensitivity analyses indicated that results were essentially unchanged without an outlier[28] identified on the funnel plot, with a 0.10 correction, or without the simvastatin 80 mg trials. (eFigures 2-9).

The NMA pooled direct and indirect evidence from all 23 trials and suggested increased risk with higher intensity therapy. Results indicated a non-significant 1% increase in risk between placebo and moderate intensity therapy (Table 2), a significant 4% increase between moderate and high intensity therapy, and a significant 5% increase between placebo and high intensity therapy. Results were homogeneous across studies (I^2=0%; Q, p=0.54) and closely paralled causal effect sizes estimated in the pairwise meta-analysis (p=0.48). Pooled RDs between pairs of treatment groups were not significantly different from zero. Inclusion of the two simvastatin 80mg trials did not meaningfully change risk, but comparisons with high intensity were statistically significant, likely due to the increased sample size (eTable 2).

Myalgia or pain. Thirteen RCTs reported cases of myalgia,[23,27–30,40,42–45] attrition due to myalgia,[24,26] or pain and/or weakness.[38] The pairwise meta-analysis indicated (Figure 2) non-significant increases in myalgia between placebo and moderate intensity and between placebo and high intensity, but a significant increase between moderate and high intensity (RR=1.04, 95% CI: 1.00;1.09, 2 RCT, n=22065; I^2=0%). The three trials comparing placebo and high intensity therapies suggested moderate heterogeneity in

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results (I^2=45%). Funnel plots did not suggest bias by any of the studies and there were no zero cells (Figures 10-11). Inclusion of the simvastatin 80 mg trial did not meaningfully change the magnitude of risk, although results were significant for high intensity compared to moderate intensity therapy possibly due to increased sample size (eFigures 12-13).

The NMA results combining direct and indirect evidence for all 13 trials suggested a significant increase in myalgia with increased therapy intensity (Table 2). There was a non-significant 9% increase in risk between placebo and moderate intensity therapy, a significant 4% increase between moderate and high intensity therapy, and a 13% significant increase in risk for high intensity therapy compared to placebo without heterogeneity. Results were homogeneous across studies (I^2=0%, Q, p=0.48) and were similar to those from the direct meta-analysis (p=0.63). The pooled RD was significant between high and moderate intensity (NNH=173) and between high intensity and placebo (NNH=154) with low heterogeneity (I^2=20%; Q, p=0.25). Inclusion of the simvastatin 80 mg trial did not change the magnitude of risk although results were significant for high intensity compared to moderate intensity therapy (eTable 2).

Attrition. Attrition due to muscle problems was reported by eight RCTs that compared moderate intensity statin therapy with placebo,[23,24,26,30,34–36,38,42] three that compared moderate with high intensity therapy,[10,11,13] and none that directly compared high intensity to placebo. In the pairwise meta-analysis (Figure 3), patients on moderate intensity statin therapy had a non-significant increase in attrition due to muscle

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problems compared to placebo. Patients on high intensity therapy had a 38% significantly higher attrition rate than those on moderate intensity (RR=1.38, 95% CI: 1.04, 1.82; 3 RCTs, N=20,719) with moderate heterogeneity across trials (I^2=31%). Funnel plots did not suggest bias and there were no zero cells. Exclusion of the two simvastatin 80 mg trials left only one moderate-high intensity comparison RCT (eFigures 14-17).

The NMA results for the 11 trials suggested that risk for attrition increased with intensity of therapy. There was a non-significant 13% increase in risk between placebo and moderate intensity therapy (Table 2), a 37% significant increase in risk between moderate and high intensity, and a 55% significant increase in risk between placebo and high intensity therapy. Results were homogenous across studies (I^2=0%; Q p=0.72) and closely paralled causal estimates provided by the meta-analysis, but the NMA provided an estimate for the placebo-high intensity comparison for which there were no head-to-head trials. The pooled RD between moderate and high intensity therapy was significant and the NNH was 218. The pooled RD between high intensity therapy and placebo also was significant and the NNH was 186. Exclusion of the two simvastatin 80 mg trials resulted in lower, non-significant risk increases between moderate and high intensity therapy and between placebo and high intensity (eTable 2).

Rhabdomyolysis. Rhabdomyolysis was reported on by 14 moderate intensity-placebo comparison RCTs,[22–26,28–30,33,34,37–40] four moderate-high intensity comparison RCTs,[10–

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[13] and three high intensity-placebo comparison RCTs.[43–45] Incidence of rhabdomyolysis was very low and statistical comparisons were not conclusive.

Pairwise meta-analysis indicated non-significant increases in rhabdomyolysis incidence between placebo and moderate intensity therapy, between moderate and high intensity, and between placebo and high intensity therapy (Figure 4). Results were were inconclusive as they were not robust across sensitivity analyses. Approximately half (22/42) of the cells were zeros and RR increased for moderate-high intensity comparison with a smaller correction (eFigures 15-18) and removal of the simvastatin 80 mg trials meaningfully changed estimates (eFigues 19-20).

NMA results indicated increased risk for rhabdomyolysis with increased intensity of therapy, although the results were not statistically significant (Table 2). There was a non-significant 22% increase in risk between placebo and moderate intensity therapy, a non-significant 33% increase between moderate and high intensity, and a non-significant 62% increase between placebo and high intensity therapy with consistency across trials (I^2=0%, Q p=0.99). Results remained non-significant after exclusion of simvastatin 80 mg trials (eTable 2), but suggested an increased RR for the placebo-moderate intensity therapy and decreased risk for moderate-high and placebo-high intensity comparisons. The NMA RR estimates based on all 21 trials were not significantly different from MA estimates based on estimates from the subsets of studies (p=0.31).

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Elevated CK. Of 16 RCTs, 11 compared rates of elevated creatine kinase (CK>10xULN) between placebo and moderate intensity therapy,[22–25,30,33,34,37–41] three compared moderate to high intensity therapy[10–12] and two compared high intensity therapy with placebo.[43,45] Incidence of elevated CK was low. Pairwise meta-analysis indicated (Figure 5) non-significant increases in CK elevation between placebo and moderate intensity therapy and between placebo and high intensity therapy. High intensity therapy caused a 388% significantly higher risk for elevated CK compared to moderate intensity therapy (RR=3.88, 95% CI: 1.05,14.31, 3 RCTs, n=26,558) with some heterogeneity among the three trials (I^2=50%). Estimates were not stable across sensitivity analyses. Removal of two possible outliers[10,24] (eFigures 21-24), adjustment for cells with zeros (9/32) (eFigures 25-26), and exclusion of simvastatin 80 mg trials meaningfully changed pooled RR estimates (eFigures 27,28).

Using evidence from all 16 trials, the NMA estimates indicated increased risk with increased intensity. NMA results indicated a non-significant 14% increase between placebo and moderate intensity therapy (Table 2), a significant 459% increase in CK elevation between moderate and high intensity, and 525% significant increase between placebo and high intensity with consistency across trials (I^2=7%, Q p=0.37). The NMA RR estimates based on all 16 trials were not significantly different from MA estimates (p=0.57). The pooled RD between moderate and high intensity therapy was significant and the NNH was 527. The pooled RD between high intensity therapy and placebo also was significant and the NNH was 589. Although results were homogeneous with the simvastatin 80 mg trials, exclusion of these trials meaningfully reduced risk associated

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with statin therapy between moderate and high intensity and between placebo and high intensity therapy (eTable 2).

DISCUSSION

A novel contribution of this study was the application of NMA to estimate the dose-response effect of statin therapy on muscle symptoms using clinically-meaningful categories of treatment intensity. The NMA estimates of RR closely paralleled the direct, causal estimates indicating reliability of estimates and increased risk with high intensity statin therapy. For patient-reported symptoms, there were nonsignificant increases in SAMS between placebo and moderate intensity therapy and significant increases between moderate and high intensity therapy. Because simvastatin 80mg therapy is now restricted because of muscle injury,[49] analyses also were run with and without those trials. This did not meaningfully affect results for patient-reported outcomes. Rhabdomyolysis and elevated CK also showed increased risk with higher intensity, but because of low incidence (with 25-50% zero cells), possible outliers, and inconsistency with and without the simvastatin 80 mg trials, results were inconclusive.

Double-blinded RCTs and traditional meta-analyses[3,46,47] suggest no significant increase in risk of muscle adverse events with statin therapy. Since most evidence comes from moderate intensity trials, possible adverse effects of high intensity therapy may be masked in aggregate estimates. Similarly, aggregation of heterogeneous outcomes and estimate for outcomes (e.g., myopathy) not explicitly reported by investigators could also mask an effect. In this study, high intensity therapy and focused

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definitions of patient-reported muscle problems detected higher risk. However, the absolute excess of SAMS was less than 1% for all outcomes. In previous meta-analyses, absolute excess of muscle problems also was small, but non-significant.[3,47] The 2016 meta-analysis estimated risk for extreme outcomes (myopathy and rhabdomyolysis), but did not analyze patient reports of milder SAMS that we present and that concern patients.

Dose-response analyses in individual RCTs, e.g., the TNT trial[12] comparing atorvastatin 10 mg to 80 mg and the SEARCH trial[10] comparing simvastatin 20 mg to 80 mg, and an NMA that compared dosage increments within brands[48] suggested no systematic increase in risk for myalgia or CK with higher dosages. These negative findings may have been due to smaller sample sizes, smaller dosage increments in restricted comparisons, or exclusion of the simvastatin 80 mg trials.[48] In this study, results were homogeneous including the simvastatin 80mg trials, and indicated high intensity therapy significantly increased myalgia compared to placebo even after their exclusion. The previous NMA identifed a dose-response relationship between statin dose and mildly elevated CK (2-3x ULN), but only for lovastatin and simvastatin.[48] CK>10xULN may be more interpretable than modest elevations, and in this study was significantly increased in high-intensity statin analyses. While removal of 80mg simvastatin trials had little effect on patient-reported symptoms, their exclusion resulted in smaller non-significant increases in risk for elevated CK. It is unclear if simvastatin 80mg was responsible for the significant increases in CK.

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A practical question concerns how large an excess of cases might be observed with statin therapy for myalgia/pain, attrition due to muscle problems, and elevated CK or rhabdomyolysis. Although estimates based on observational studies suggest that incidence of mild SAMS might be as high as 30% among statin users,[50] RCTs suggest a much lower rate. In this study, pooled risk estimates suggested that for each 173 patients on high intensity therapy one additional patient will experience statin-caused myalgia compared to moderate intensity therapy. Results also indicated that for each 200 patient on high-intensity statins, one additional patient will discontinue therapy due to muscle problems. This represents numerous patients who are at greatest risk for major vascular events, as these are often higher risk patients. Discontinuation of statins in the elderly (>75 yrs) may result in 33% increased risk of a cardiovascular event within 3 months [51] and adherence to statins in those 65 and older may reduce mortality by a third.[52]

Myalgias and attrition due to SAMS are important outcomes for the average patient, but have not received as much attention as rhabdomyolysis and myopathy. This study provides evidence that while blinded, moderate intensity statin-takers did not report significantly more general muscle problems or myalgias, but those on high intensity therapy did. Because many myalgia cases occurred without CK elevation increases, this also serves as evidence that SAMS occur in the absence of large elevations in CK. Clinicians with patients who are “statin intolerant” may consider decreasing intensity of statin therapy, rather than discontinuing it, in light of these findings.

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This analysis also contributes to the "nocebo" debate. A large, unblinded follow-up of RCT patients suggested SAMS are expectation-related.[27] They observed an incidence of 2.02% and 2.00% muscle-related adverse events in statin and placebo groups, respectively, when double-blinded (HR=1.03) and 1.26% and 1.00% in the statin and usual care groups when unblinded (HR=1.41).[27] Both comparisons indicate absolute differences less than 1%. Thus, both nocebo and causal effects are small, although they have moderate relative increases with statin therapy. SAMS with moderate intensity therapy may be the result of patient expectations, but with high intensity therapy SAMS may be due to expectations and statin therapy. SAMS are also linked to CP450 drug-drug interactions.[53,54]

A limitation of study-level meta-analyses is that definitions, assessment, and variable reporting of muscle-related outcomes differ across studies. Protocol differences likely resulted disparate incidence across studies. Estimates in this analysis may have under-estimated SAMS by excluding patients with statin hypersensitivity, as four studies[12,35,38,43] (n=48,950) employed statin "washout" phases and eight trials[22,23,28,30,32–35,45] (n=34,042) excluded patients with known statin hypersensitivity. Collins et al. noted that "statin hypersensitivity" exclusion was a rare occurrence across these trials, as almost all patients enrolled were statin-naïve at screening.[3] The risk of attrition due to SAMS and rhabdomyolysis was actually highest in SEARCH, where an eight week long, active run-in phase was conducted,[3,10] although no patients were excluded for elevated muscle enzymes.[10] Further, adverse events may have been increased due to the

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presence of co-morbidities; only three trials studied healthy adults (n=30,756).[24,35,44] Thus, these estimates may represent real-world risk of SAMS.

Conclusion

Statins likely cause SAMS, but at much lower rates than observational data suggest. We found significant increases in risk for patient-reported muscle problems on high-intensity statins. Clinically-reported SAMS likely represent a combination of expectation bias and true adverse effects, with or without CK elevations.

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Contributorship Statement:

The first author (JD) was responsible for the design and implementation of the study analyses. He was one coder in selecting studies for inclusion, compiled the data for the outcomes of interest, analyzed the data in R, and is responsible for the final manuscript in its entirety. SW (Faculty PI) was responsible for the oversight and implementation of the project. She was the second coder for all trials and offered guidance and support in all decisions regarding design and implementation of the analysis.

Competing Interests:

None to disclose

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Data Sharing Statement:

All original data is available upon request from the corresponding author, and will be made publicly available on Dryad repository.

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TABLE 1: DESCRIPTION OF THE TRIALS

Trial Name	Total sample size	Special Population	Permit Prior statin†	Ave age	Run-in Period	Median Yrs F/U
Placebo-Moderate						
4D, A20[22]	1,255	DM II, ESRD	Y, -HS	66	Placebo	4.0
4S, S20-S40[23]	4,444	MI or angina	Y, -HS	59	Placebo	5.4
AFCAPS, L20-L40[24]	6,605	Healthy adults	N	58	Placebo+diet	5.2
ALERT, F40-F80[25]	2,094	Renal Trans	N	50	None	5.4
ASCOT, A10[26,27]	10,810	HTN+CVD risk	N	63	Not statin	3.3
ASPEN, A10[28]	2,410	DM II	Y, -HS	61	Placebo	4.0
AURORA, R10[29]	2,767	ESRD	N	64	Placebo	3.2
CARDS, A10[30,31]	2,838	DM II	Y, -HS	62	Placebo	4.0
CARE, P40[32]	4,159	MI	Y, -HS	59	Placebo	5.0
CORONA, R10[33]	5,011	ESRD	Y, -HS	73	Placebo	2.7
GISSI-HF, R10[34]	4,574	CHF	Y, -HS	68	None	3.9
HOPE-3, R10[35]	6,349	Healthy, CVD Risk	Y, -HS	66	Statin	5.6
LIPID, P40[36]	9,014	MI or angina	Y	62*	Placebo+diet	6.0 (*mean*)
LIPS, F80[37]	1,640	Coronary percut. intervention	Y	60	None	3.9
MRC/BHF (HPS), S40[38,39]	20,536	CHD/CHD Risk	N	64	Placebo, then statin	5 (*mean*)
PROSPER, P40[40]	5,804	Elderly, CHD risk	Y	75	Placebo	3.2 (*mean*)
WOSCOPS, P40[41,42]	6,604	Healthy males	Y	55	None	4.9 (*mean*)
Placebo-High						
JUPITER, R20[44]	17,802	Healthy adults	N	66	Placebo	1.9
SPARCL, A80[43]	4,731	CVA/TIA	Y	63	None	4.9
TRACE, A40[45]	3,002	RA	N, -HS	61	None	2.5
Moderate-High						
A to Z, S40-S80 vs 0-S20[11]	4,497	Acute Coronary Syndrome	N	61	None	1.98
PROVE-IT, A80 vs P40[13]	4,162	Acute Coronary Syndrome	Y, if <80mg	58	None	2.0 (mean)
SEARCH, S80 vs S20[10]	12,064	MI	Y	64	Statin+ Placebo	6.7
TNT, A80 vs A10[12]	10,001	CHD	Y	61	Statin	4.9

*Median

†Y=Yes, N=No, -HS=statin hypersensitivity exclusion

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TABLE 2: RELATIVE RISK AND RISK DIFFERENCE RESULTS FOR COMPARISONS OF TREATMENT INTENSITY PAIRS

	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
Any Probs	1.01 (0.99,1.03)	0.000 (-0.001,0.001)	--	1.04 (1.00,1.07)	0.004 (-0.000,0.008)	--	1.05 (1.01, 1.09)	0.004 (-0.001, 0.008)	--
Myalgia	1.09 (0.99,1.19)	0.001 (-0.000,0.001)	--	1.04 (1.00-1.08)	0.006 (0.001, 0.010)	173	1.13 (1.05-1.23)	0.007 (0.002, 0.011)	182
Attrition	1.13 (0.93,1.36)	0.001 (-000,0.001)	--	1.37 (1.09,1.73)	0.005 (0.002, 0.007)	218	1.55 (1.15,2.08)	0.005 (0.002, 0.008)	187
Rhabdo.	1.22 (0.62,2.40)	-0.000 (-0.001,0.001)	--	1.33 (0.49,3.61)	0.002 (0.001,0.003)	--	1.62 (0.58,4.55)	0.002 (0.000, 0.003)	--
CK>10ULN	1.14 (0.71,1.85)	-0.000 (-0.001,0.001)	--	4.69 (2.50, 8.80)	0.002 (0.001, 0.003)	527	5.37 (2.48,11.61)	0.002 (0.000, 0.003]	589

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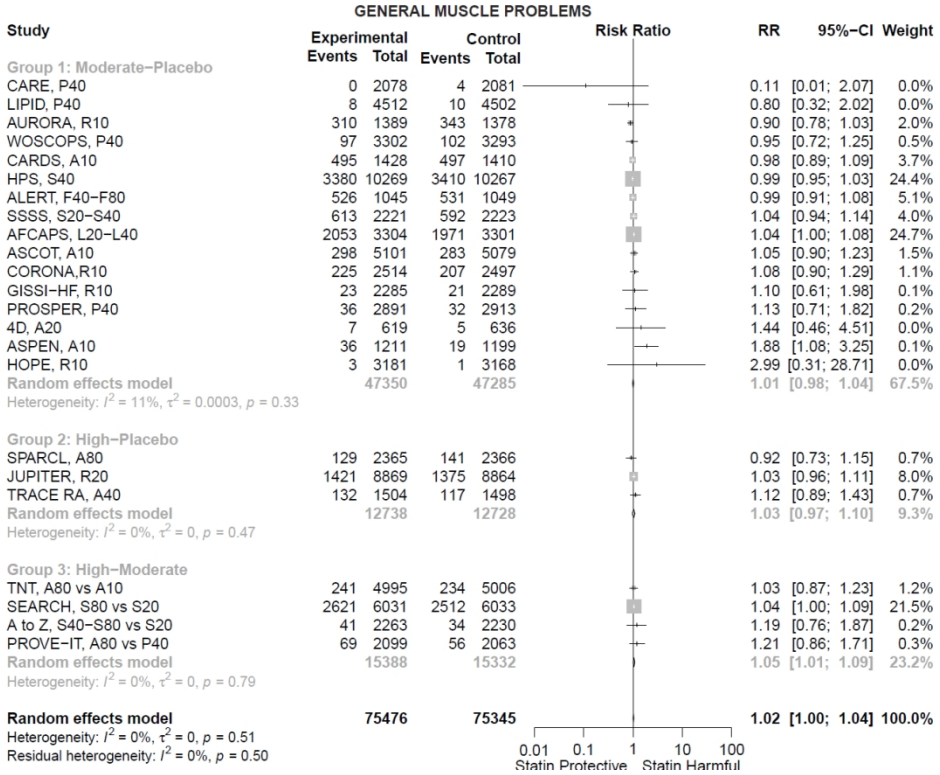

Figure 1

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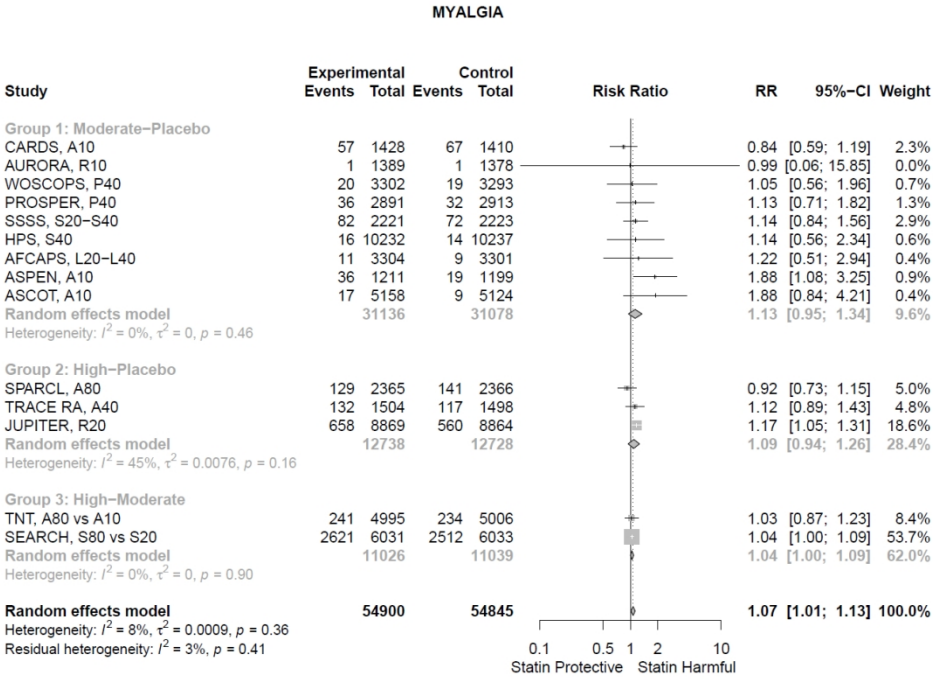

Figure 2

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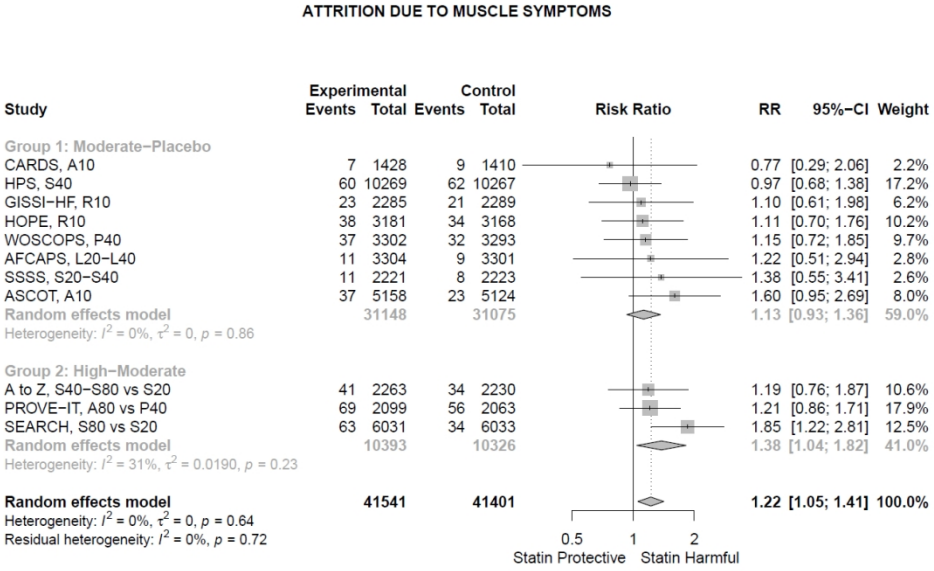

Figure 3

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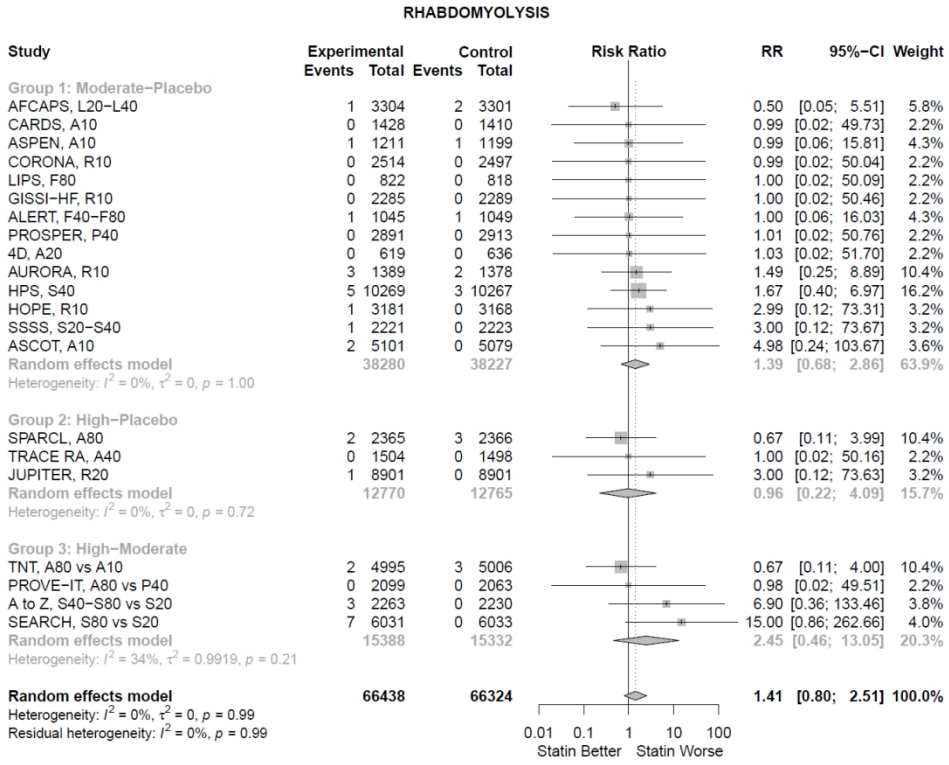

Figure 4

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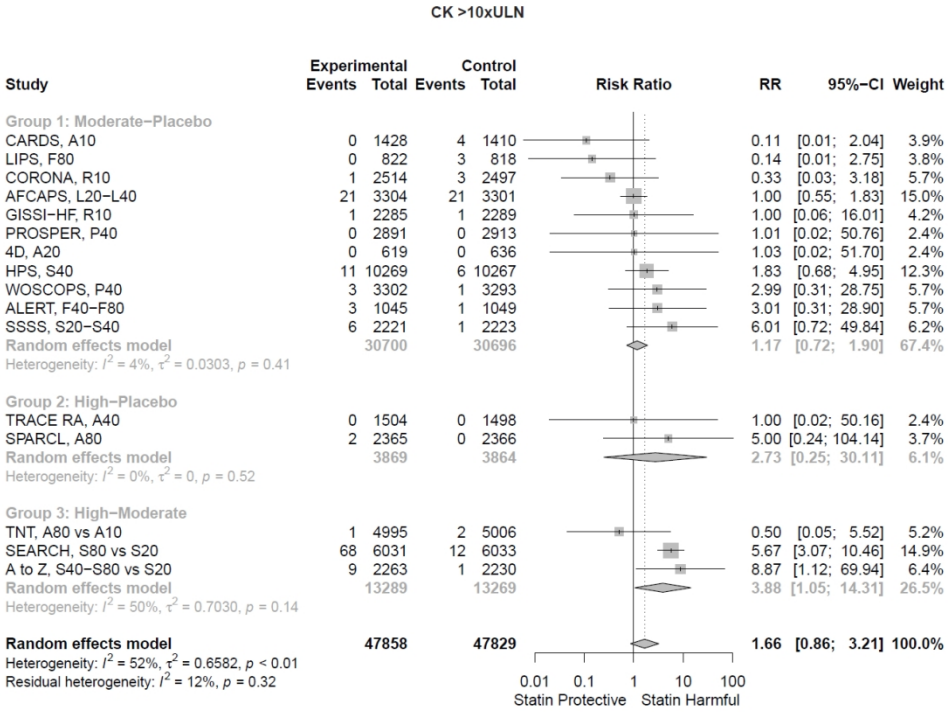

Figure 5

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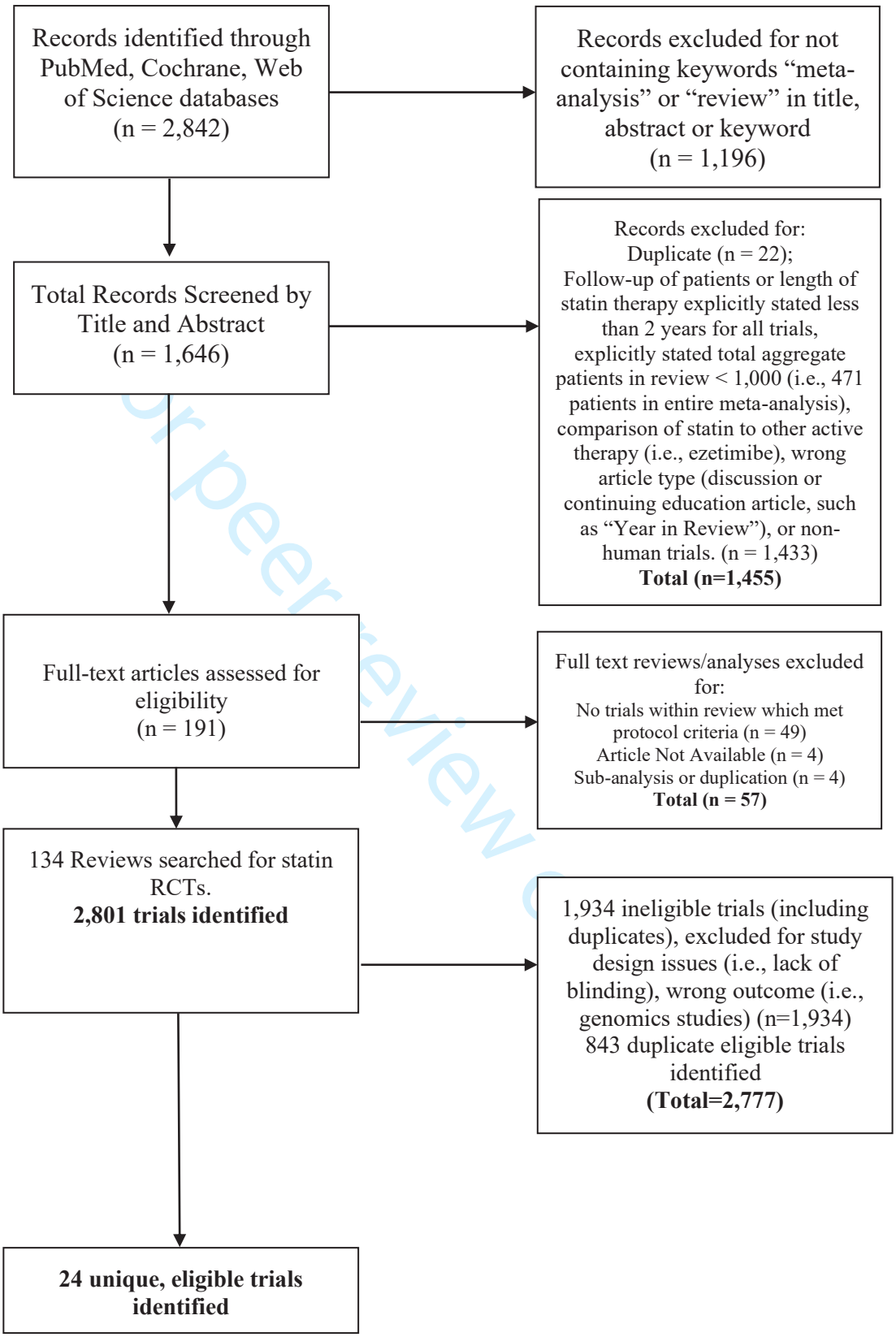
eFigure 1: PRISMA Flow Sheet



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.

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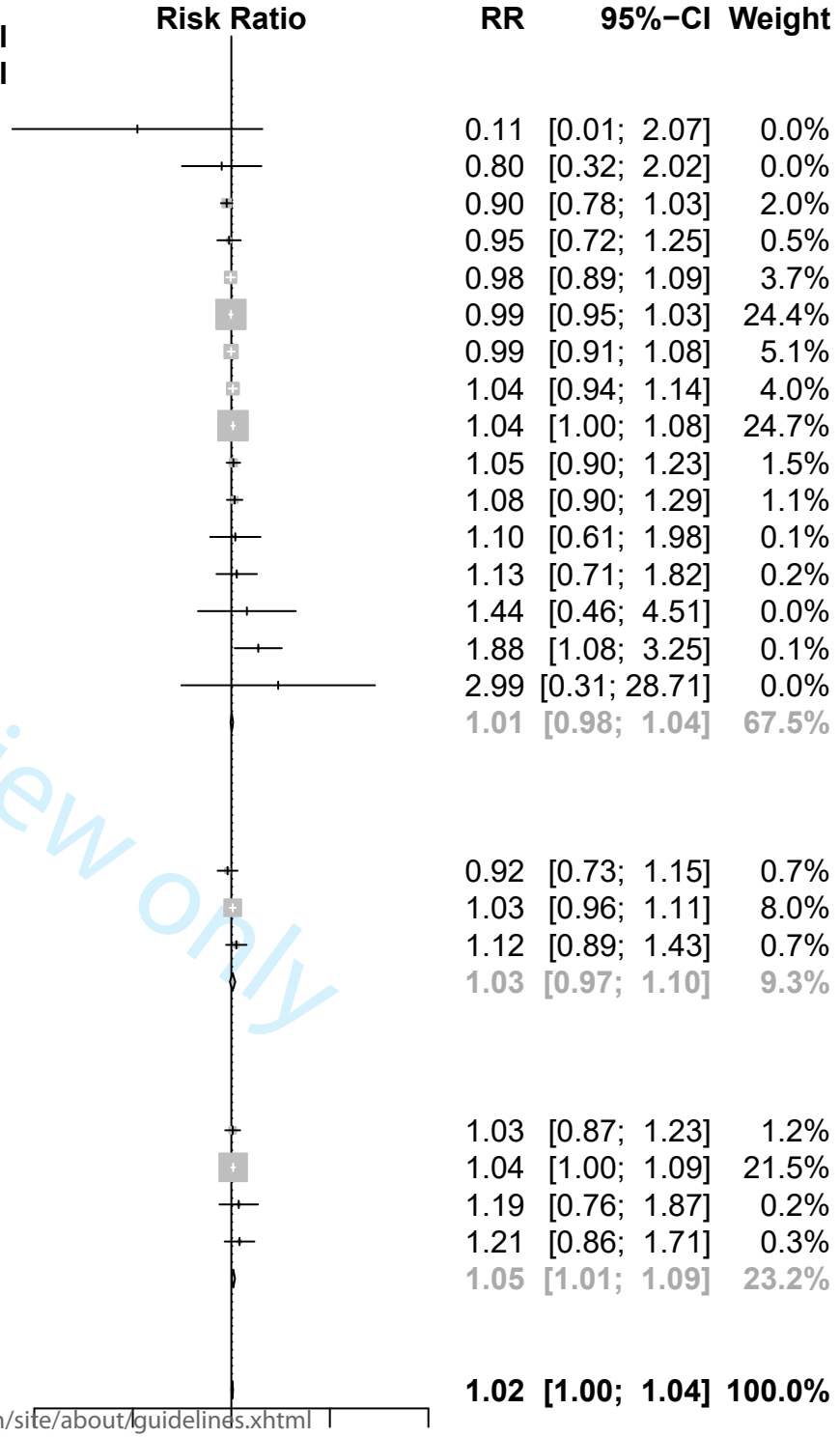
eFigure 2 - GENERAL MUSCLE PROBLEMS. Full forest plot.



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							

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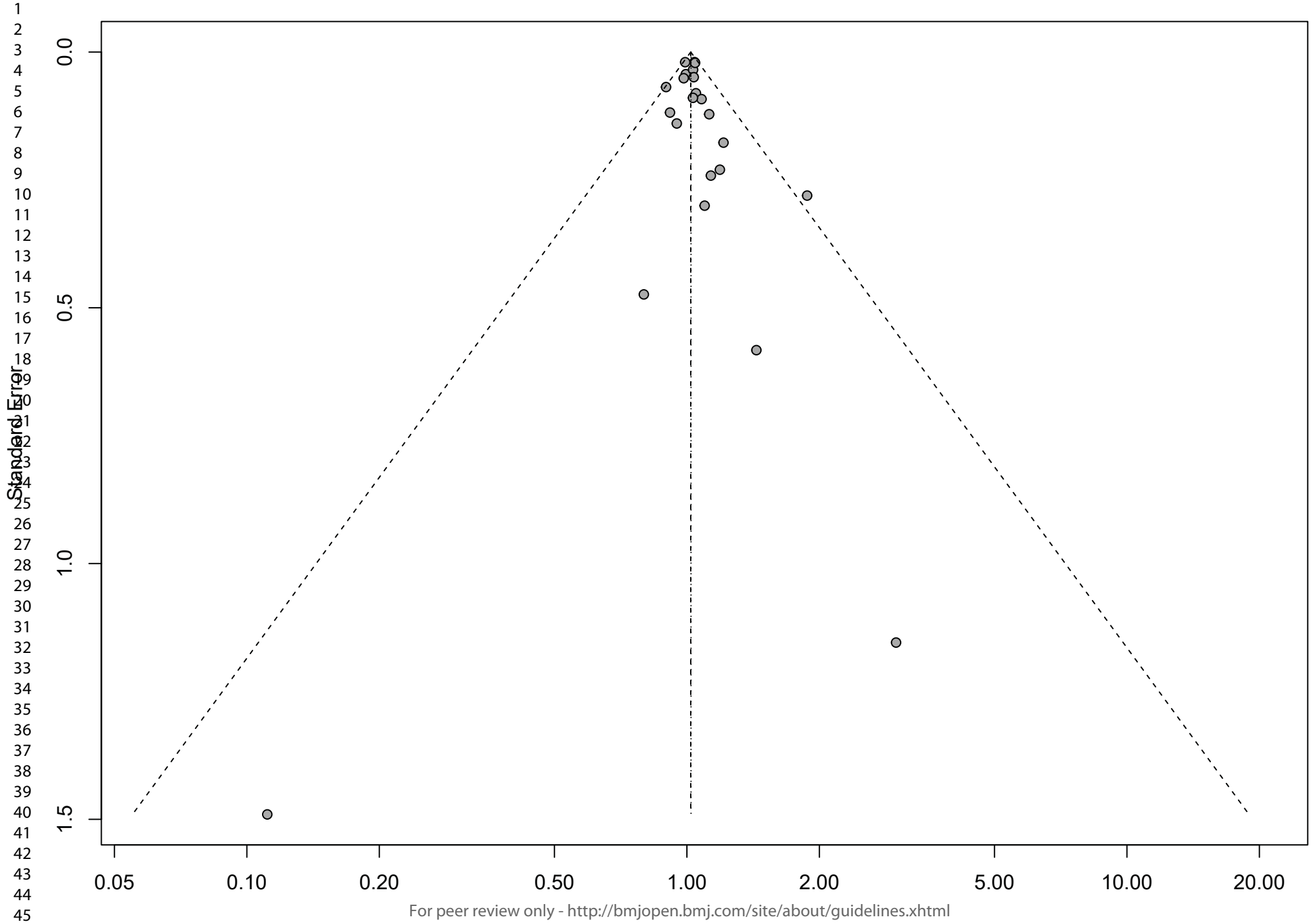
eFigure 3 - GENERAL MUSCLE PROBLEMS. Full funnel plot.



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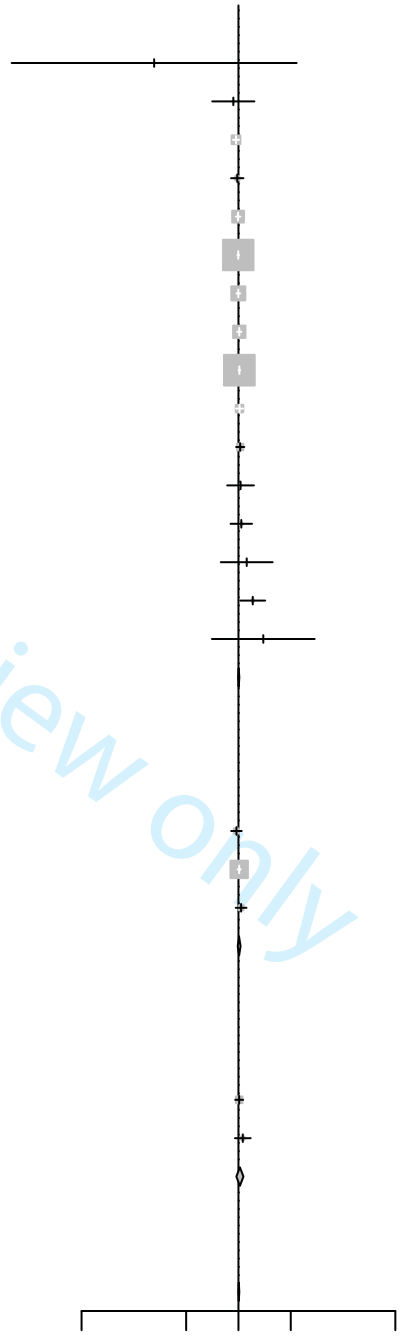
eFigure 4 - GENERAL MUSCLE PROBLEMS. Continuity Correction = 0.1. Forest plot.



Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	Weight
Group 1: Moderate−Placebo							
CARE, P40	0	2078	4	2081	0.02	[0.00; 12.94]	0.0%
LIPID, P40	8	4512	10	4502	0.80	[0.32; 2.02]	0.1%
AURORA, R10	310	1389	343	1378	0.90	[0.78; 1.03]	2.6%
WOSCOPS, P40	97	3302	102	3293	0.95	[0.72; 1.25]	0.6%
CARDS, A10	495	1428	497	1410	0.98	[0.89; 1.09]	4.7%
HPS, S40	3380	10269	3410	10267	0.99	[0.95; 1.03]	31.1%
ALERT, F40−F80	526	1045	531	1049	0.99	[0.91; 1.08]	6.6%
SSSS, S20−S40	613	2221	592	2223	1.04	[0.94; 1.14]	5.1%
AFCAPS, L20−L40	2053	3304	1971	3301	1.04	[1.00; 1.08]	31.6%
ASCOT, A10	298	5101	283	5079	1.05	[0.90; 1.23]	1.9%
CORONA,R10	225	2514	207	2497	1.08	[0.90; 1.29]	1.4%
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]	0.2%
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]**	**86.2%**
Heterogeneity: I^2 = 6%, τ^2 = 0.0002, p = 0.39							
Group 2: High−Placebo							
SPARCL, A80	129	2365	141	2366	0.92	[0.73; 1.15]	0.9%
JUPITER, R20	1421	8869	1375	8864	1.03	[0.96; 1.11]	10.2%
TRACE RA, A40	132	1504	117	1498	1.12	[0.89; 1.43]	0.8%
Random effects model		**12738**		**12728**	**1.03**	**[0.97; 1.10]**	**11.9%**
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]	1.5%
PROVE−IT, A80 vs P40	69	2099	56	2063	1.21	[0.86; 1.71]	0.4%
Random effects model		**7094**		**7069**	**1.07**	**[0.91; 1.25]**	**1.9%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.42							
Random effects model		**67182**		**67082**	**1.02**	**[0.99; 1.04]**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.55							
Residual heterogeneity: I^2 = 0%, p = 0.45							

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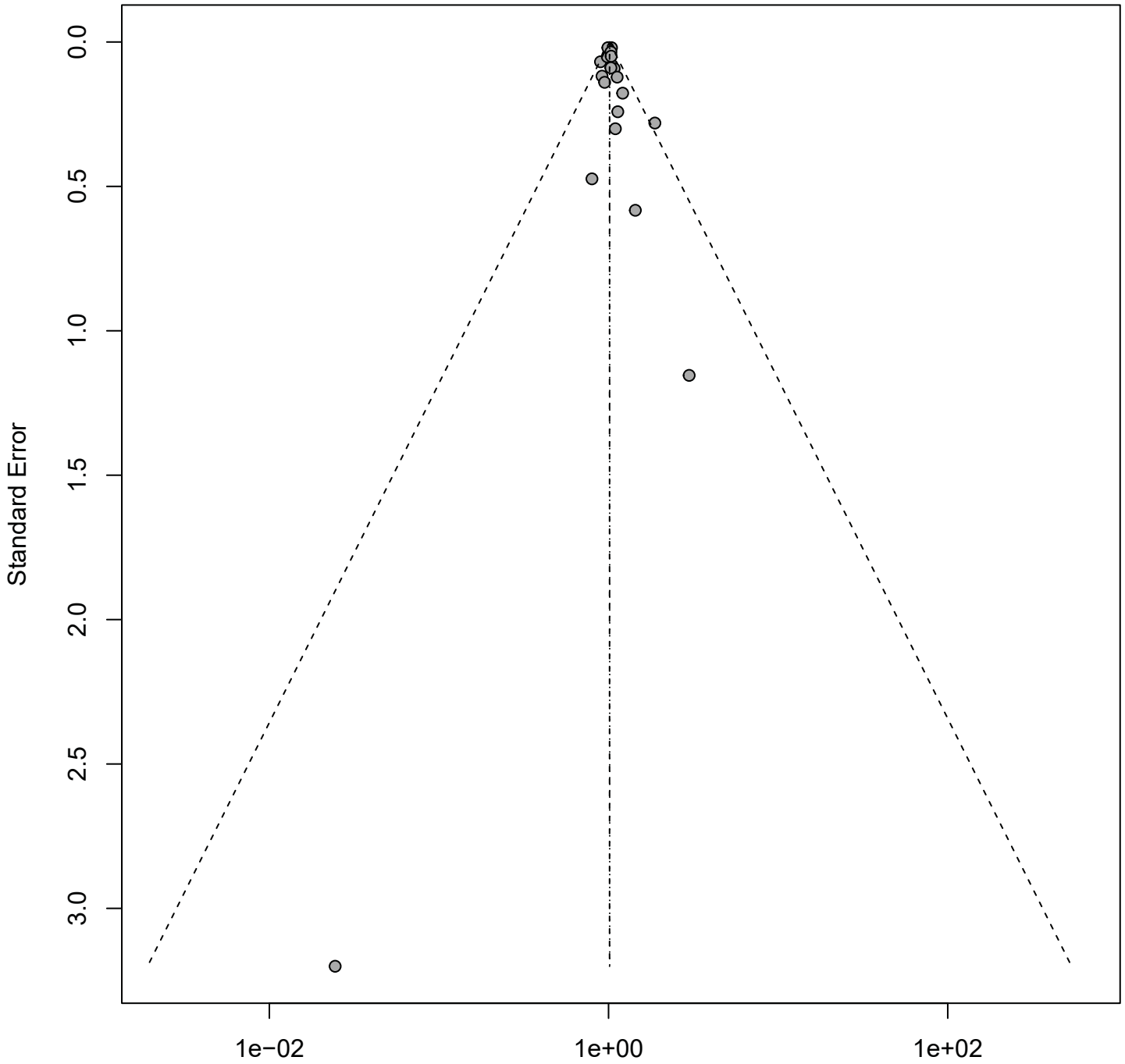
eFigure 3 (continued) - Traditional Meta-Analysis, General Muscle Problems. Sensitivity Analysis, Continuity Correction = 0.1.



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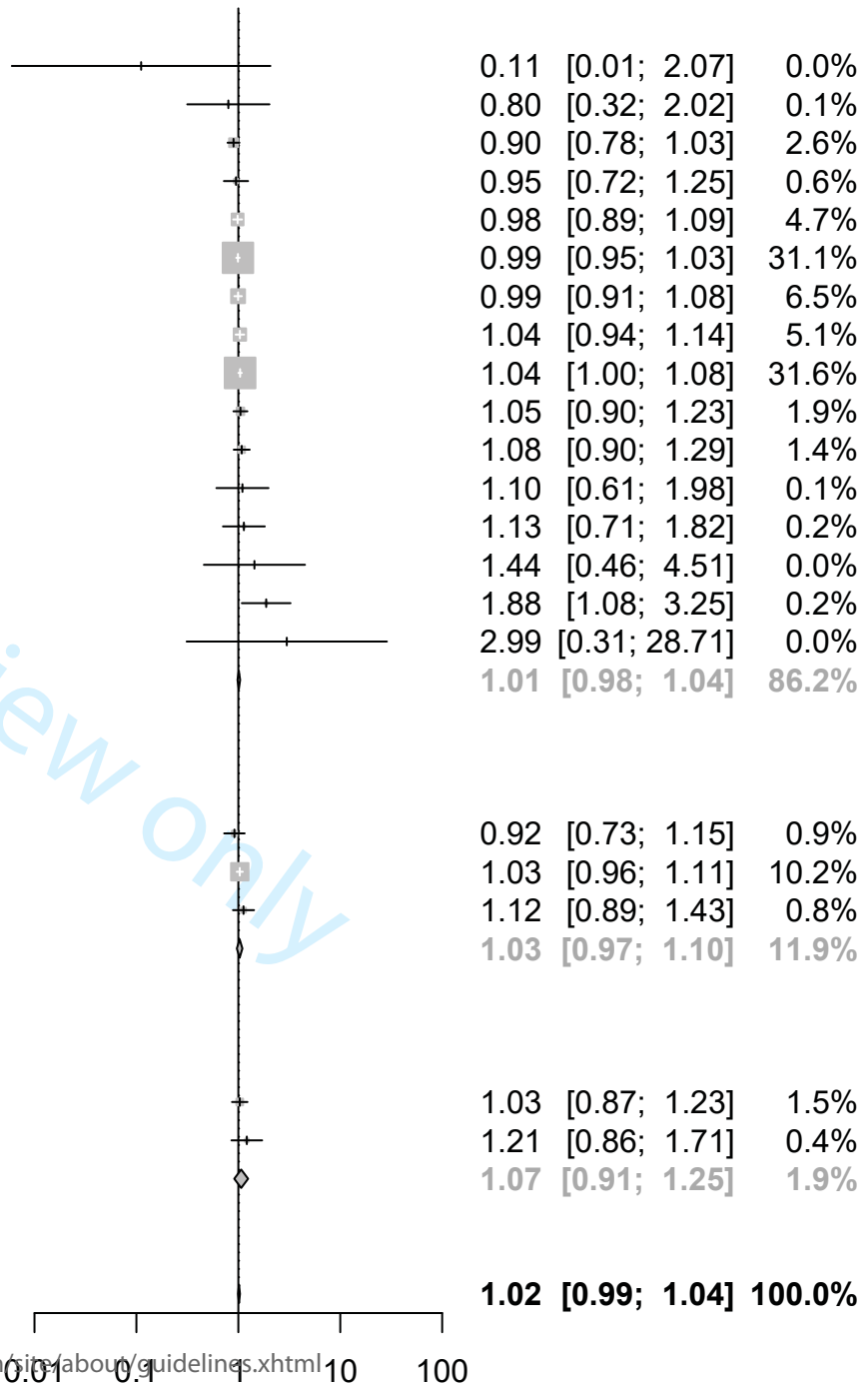
eFigure 4 - GENERAL MUSCLE PROBLEMS. Outliers excluded. Forest plot.



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]	0.1%
AURORA, R10	310	1389	343	1378	0.90	[0.78; 1.03]	2.6%
WOSCOPS, P40	97	3302	102	3293	0.95	[0.72; 1.25]	0.6%
CARDS, A10	495	1428	497	1410	0.98	[0.89; 1.09]	4.7%
HPS, S40	3380	10269	3410	10267	0.99	[0.95; 1.03]	31.1%
ALERT, F40−F80	526	1045	531	1049	0.99	[0.91; 1.08]	6.5%
SSSS, S20−S40	613	2221	592	2223	1.04	[0.94; 1.14]	5.1%
AFCAPS, L20−L40	2053	3304	1971	3301	1.04	[1.00; 1.08]	31.6%
ASCOT, A10	298	5101	283	5079	1.05	[0.90; 1.23]	1.9%
CORONA,R10	225	2514	207	2497	1.08	[0.90; 1.29]	1.4%
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]	0.2%
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]**	**86.2%**
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]	0.9%
JUPITER, R20	1421	8869	1375	8864	1.03	[0.96; 1.11]	10.2%
TRACE RA, A40	132	1504	117	1498	1.12	[0.89; 1.43]	0.8%
Random effects model		**12738**		**12728**	**1.03**	**[0.97; 1.10]**	**11.9%**
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]	1.5%
PROVE−IT, A80 vs P40	69	2099	56	2063	1.21	[0.86; 1.71]	0.4%
Random effects model		**7094**		**7069**	**1.07**	**[0.91; 1.25]**	**1.9%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.42							
Random effects model		**67182**		**67082**	**1.02**	**[0.99; 1.04]**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.49							
Residual heterogeneity: I^2 = 5%, p = 0.40							

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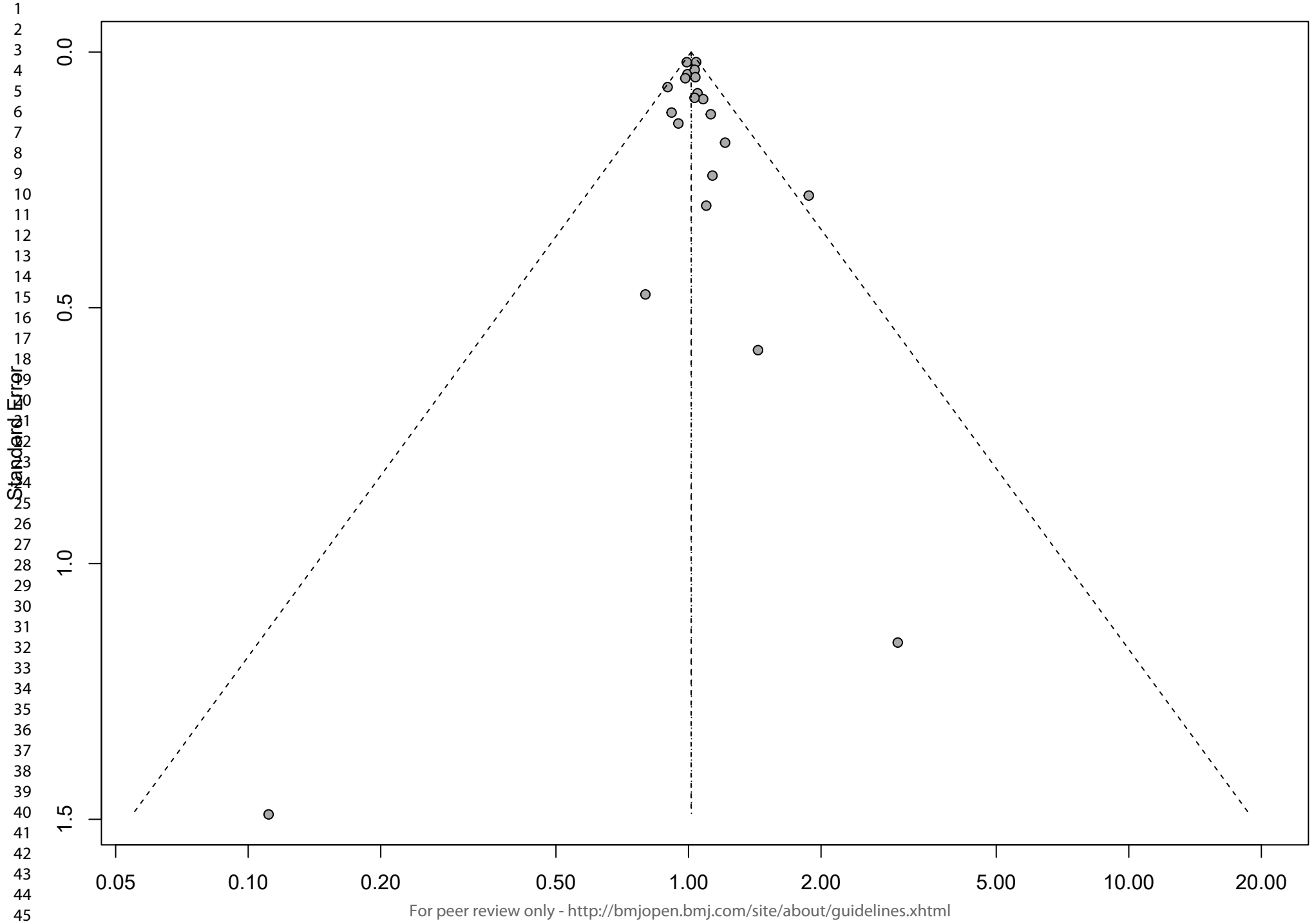
eFigure 5 - GENERAL MUSCLE PROBLEMS. Outliers excluded. Funnel plot.



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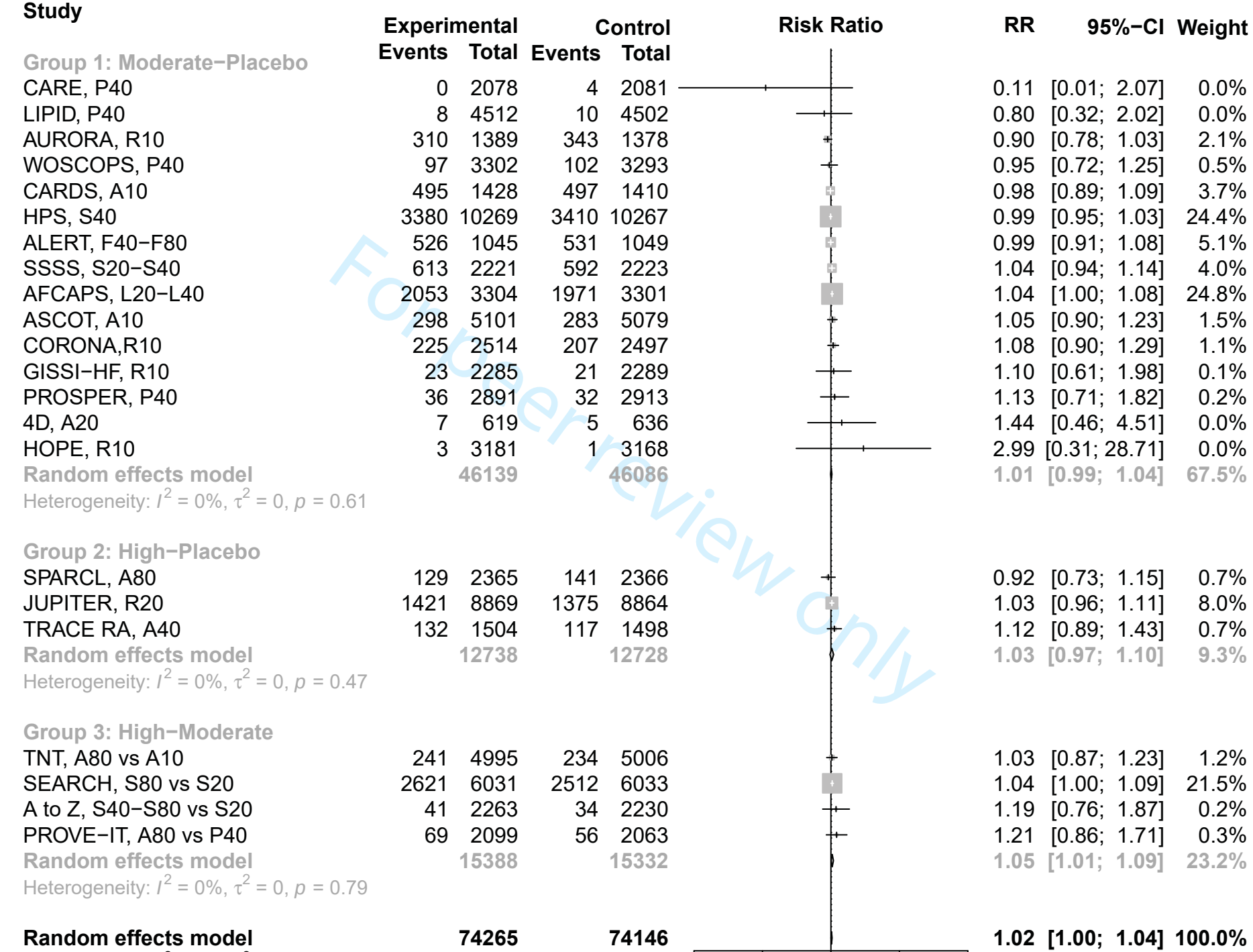
eFigure 6 - GENERAL MUSCLE PROBLEMS. Continuity Correction = 0.1. Forest plot.



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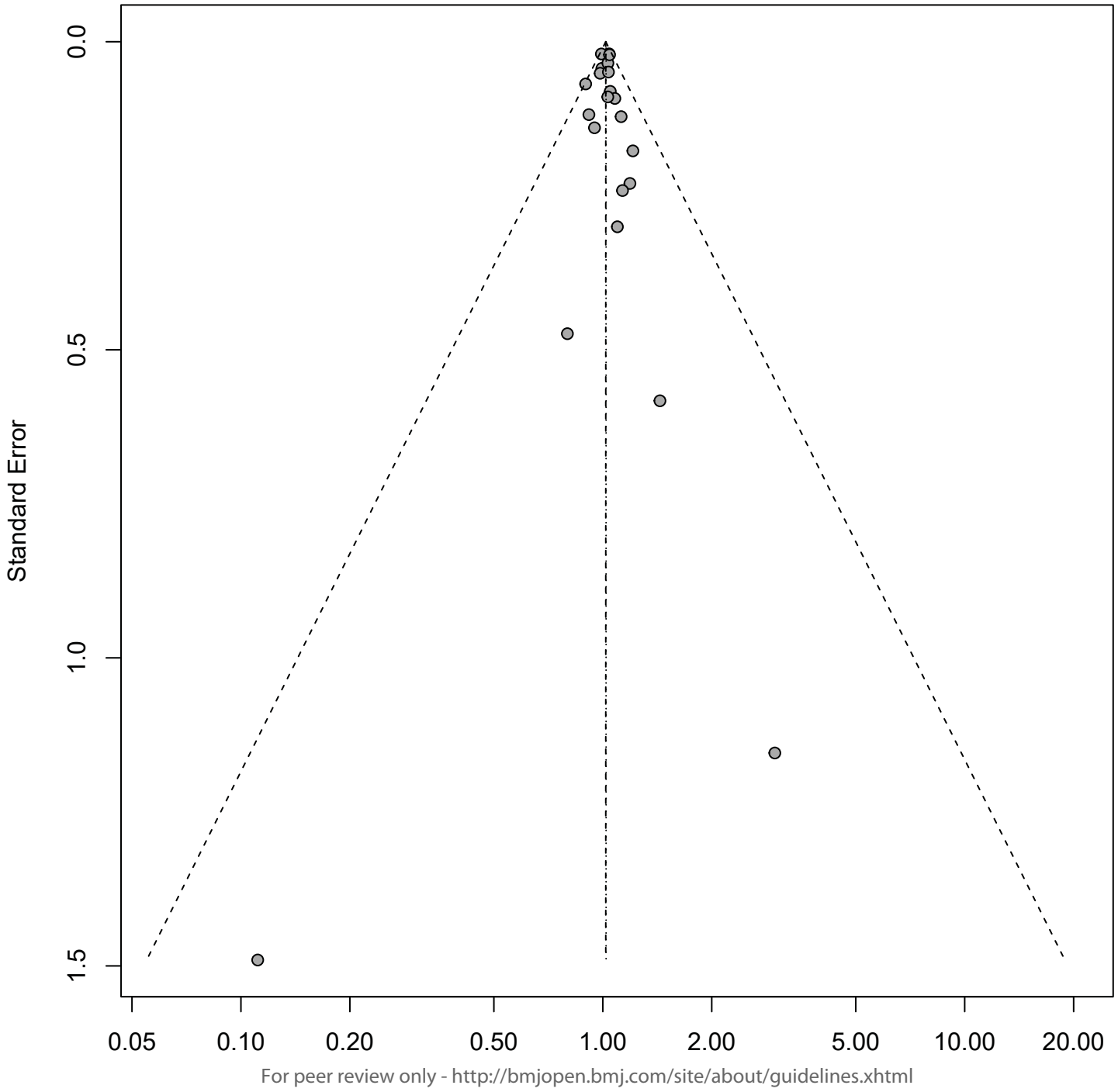
eFigure 7 - GENERAL MUSCLE PROBLEMS. Continuity Correction = 0.1. Funnel plot.



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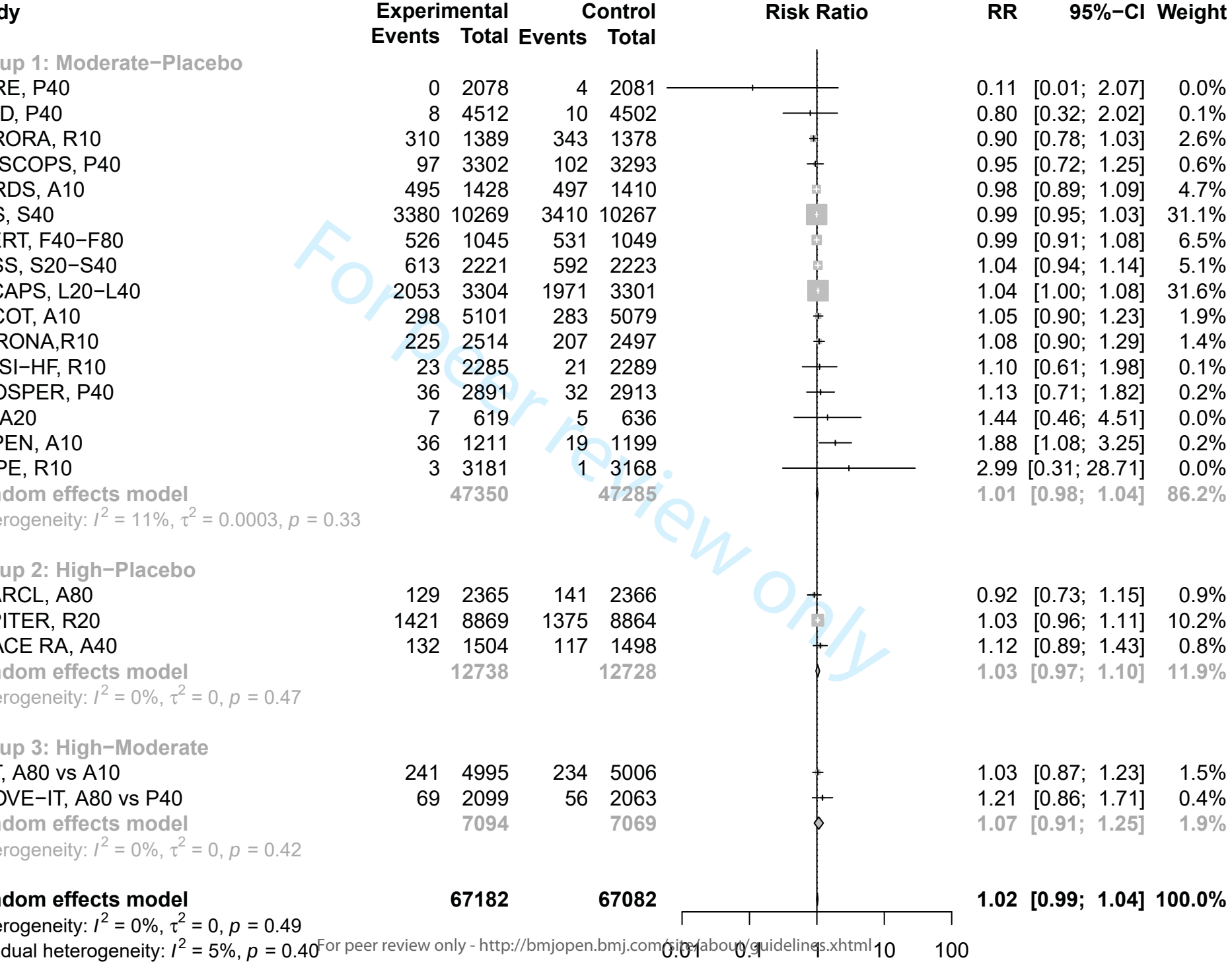
eFigure 8 - GENERAL MUSCLE PROBLEMS. Exclusions of studies testing simvastatin 80 mg. Forest plot.



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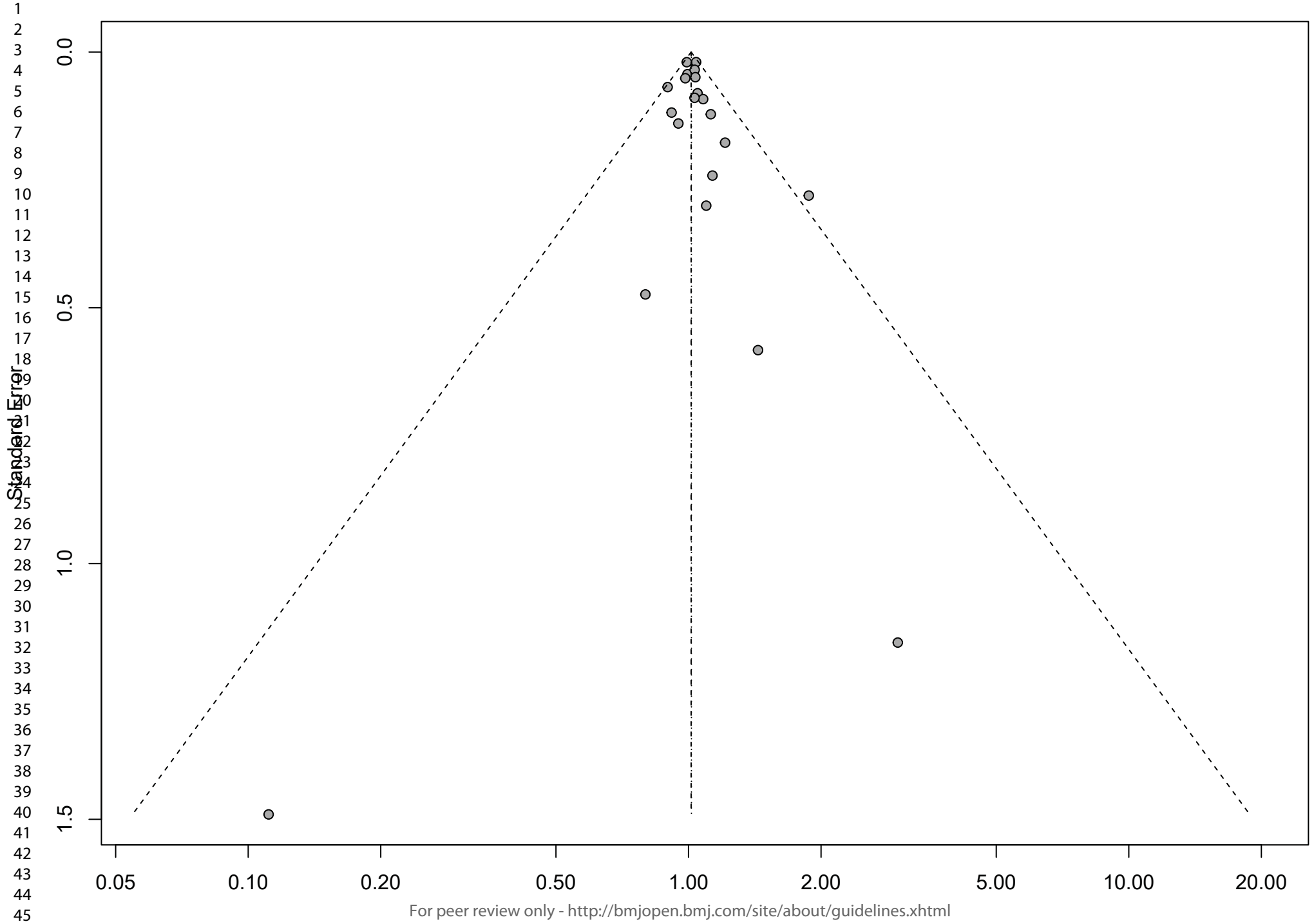
eFigure 9 - GENERAL MUSCLE PROBLEMS. Exclusions of studies testing simvastatin 80 mg. Funnel plot.



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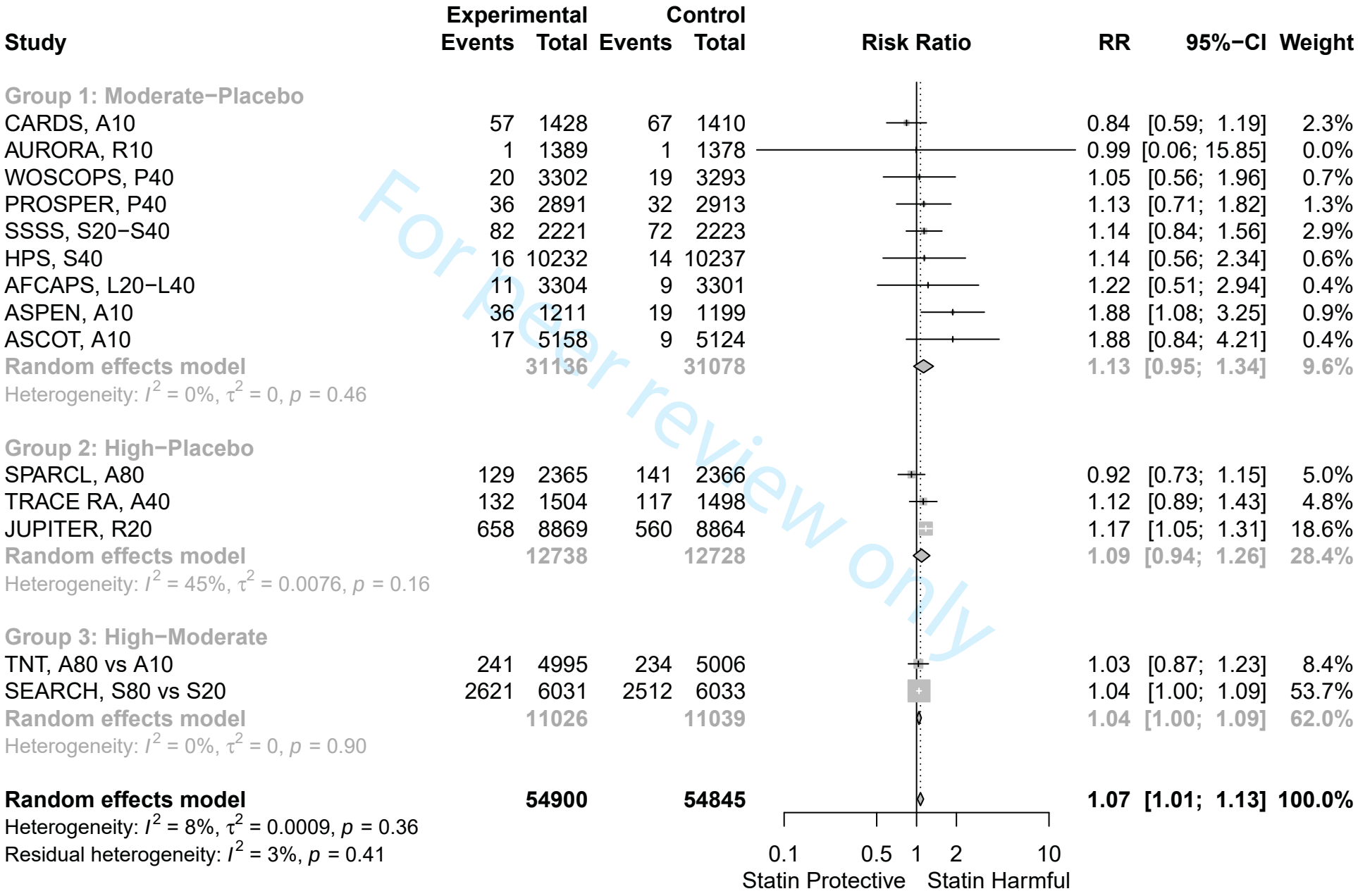
eFigure 10 - MYALGIA. Full forest plot.



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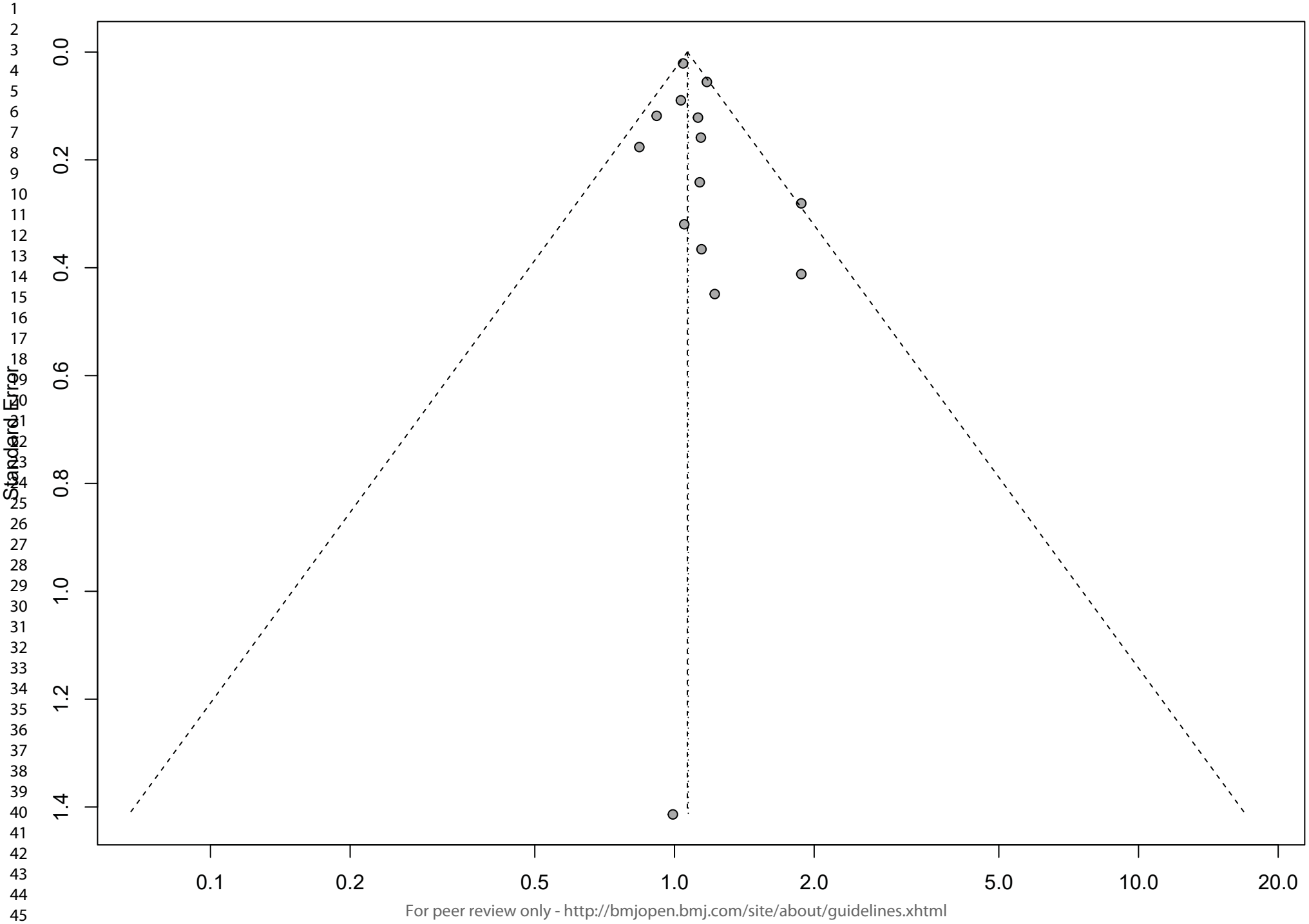
eFigure 11 - MYAGLIA. Full funnel plot.



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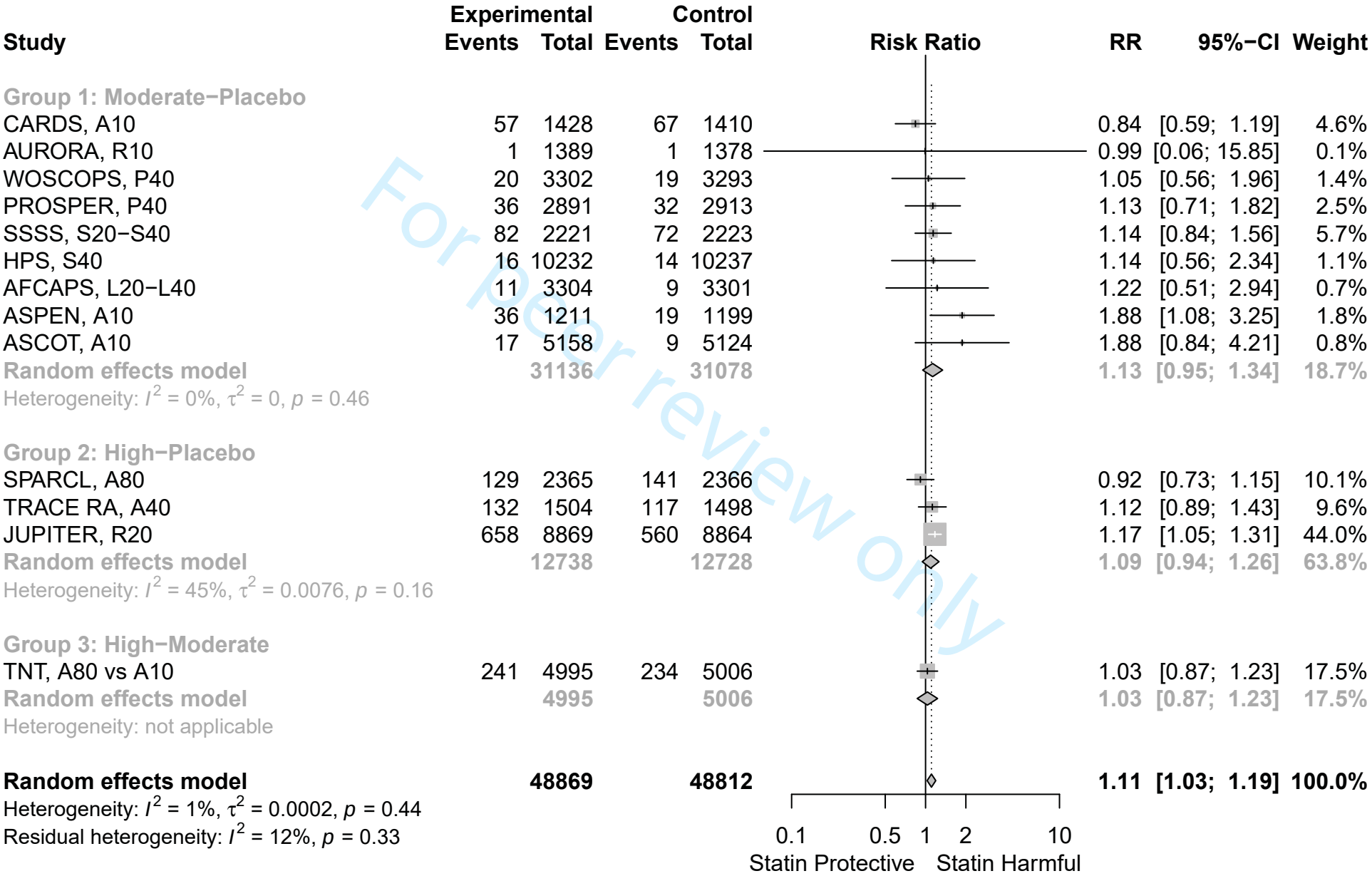
eFigure 12 - MYALGIA. Exclusions of studies testing simvastatin 80 mg. Forest plot.



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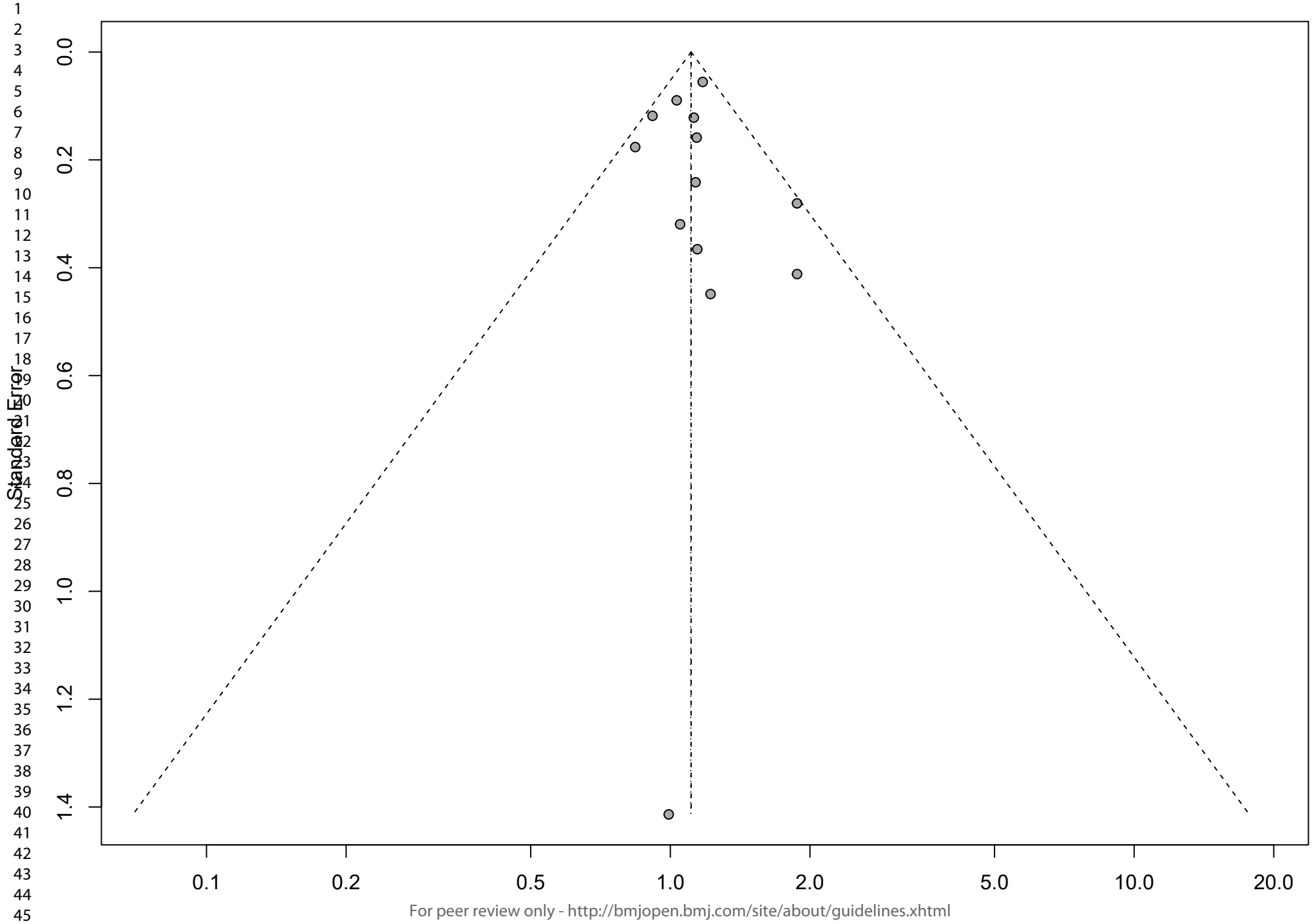
eFigure 13 - MYALGIA. Exclusions of studies testing simvastatin 80 mg. Funnel plot.



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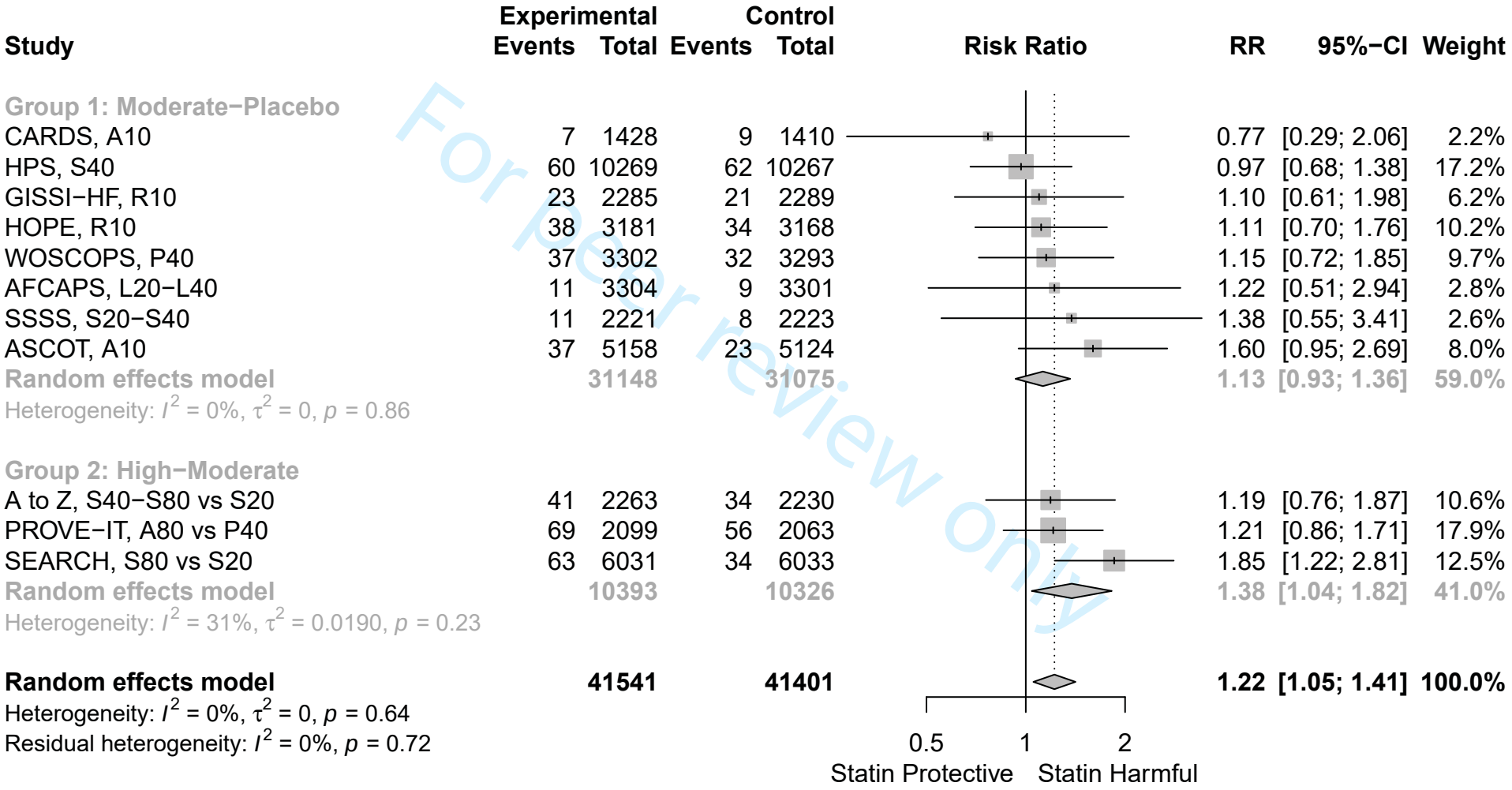
eFigure 14 - ATTRITION DUE TO MUSCLE SYMPTOMS. Full forest plot.



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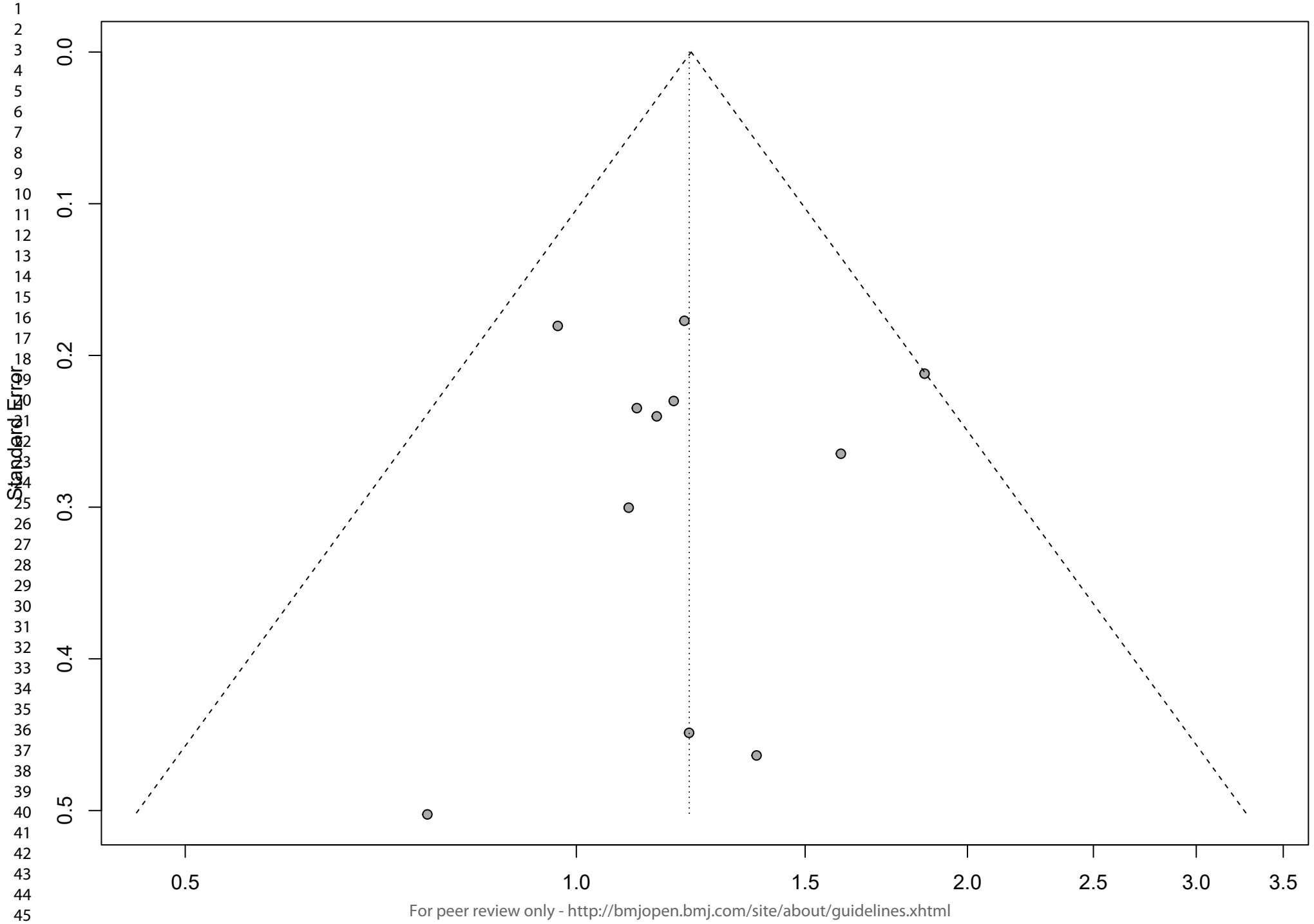
eFigure 15 - ATTRITION DUE TO MUSCLE SYMPTOMS. Full funnel plot.



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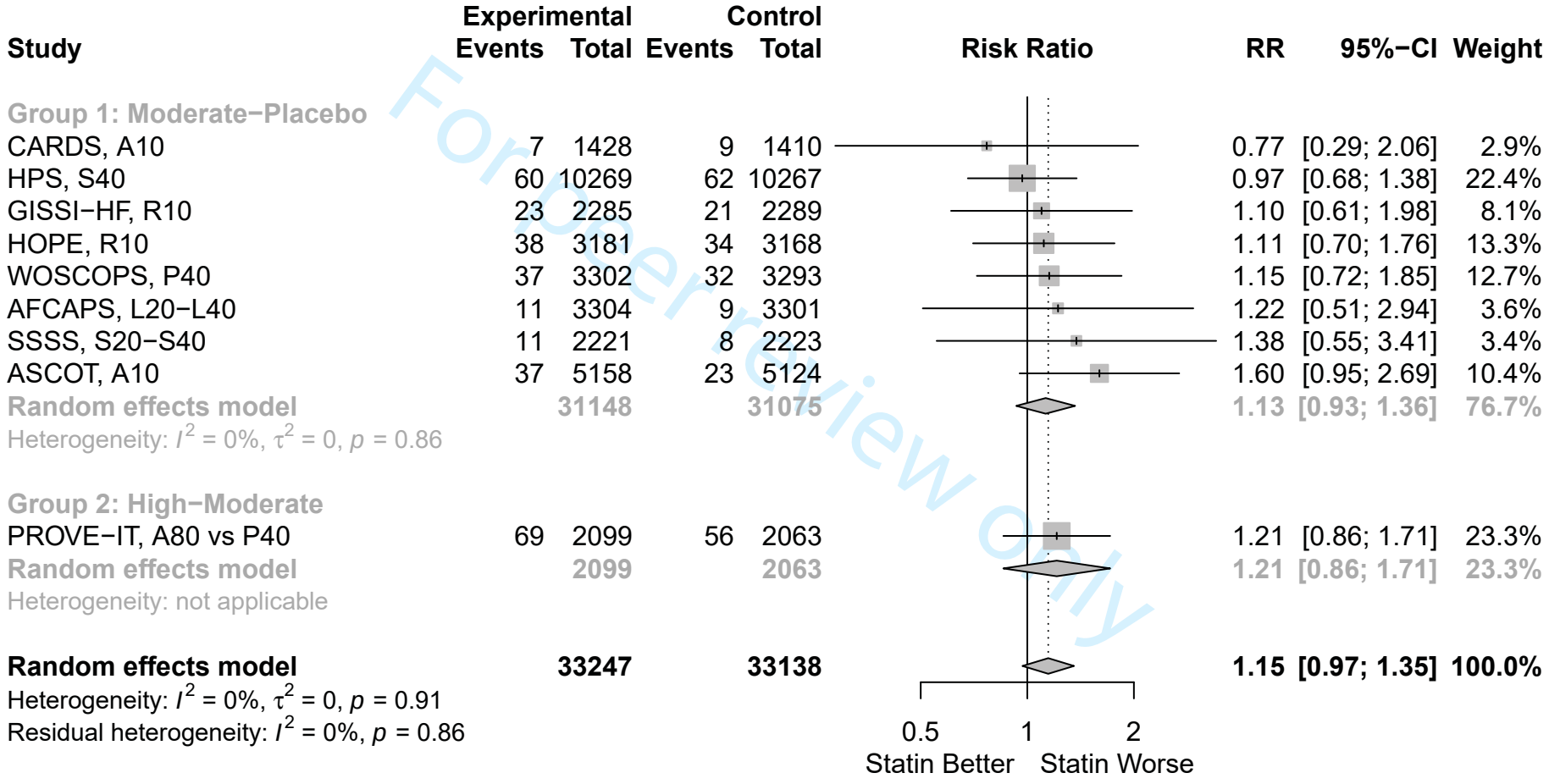
eFigure 16 - ATTRITION DUE TO MUSCLE SYMPTOMS. Exclusions of studies testing simvastatin 80 mg. Forest plot.



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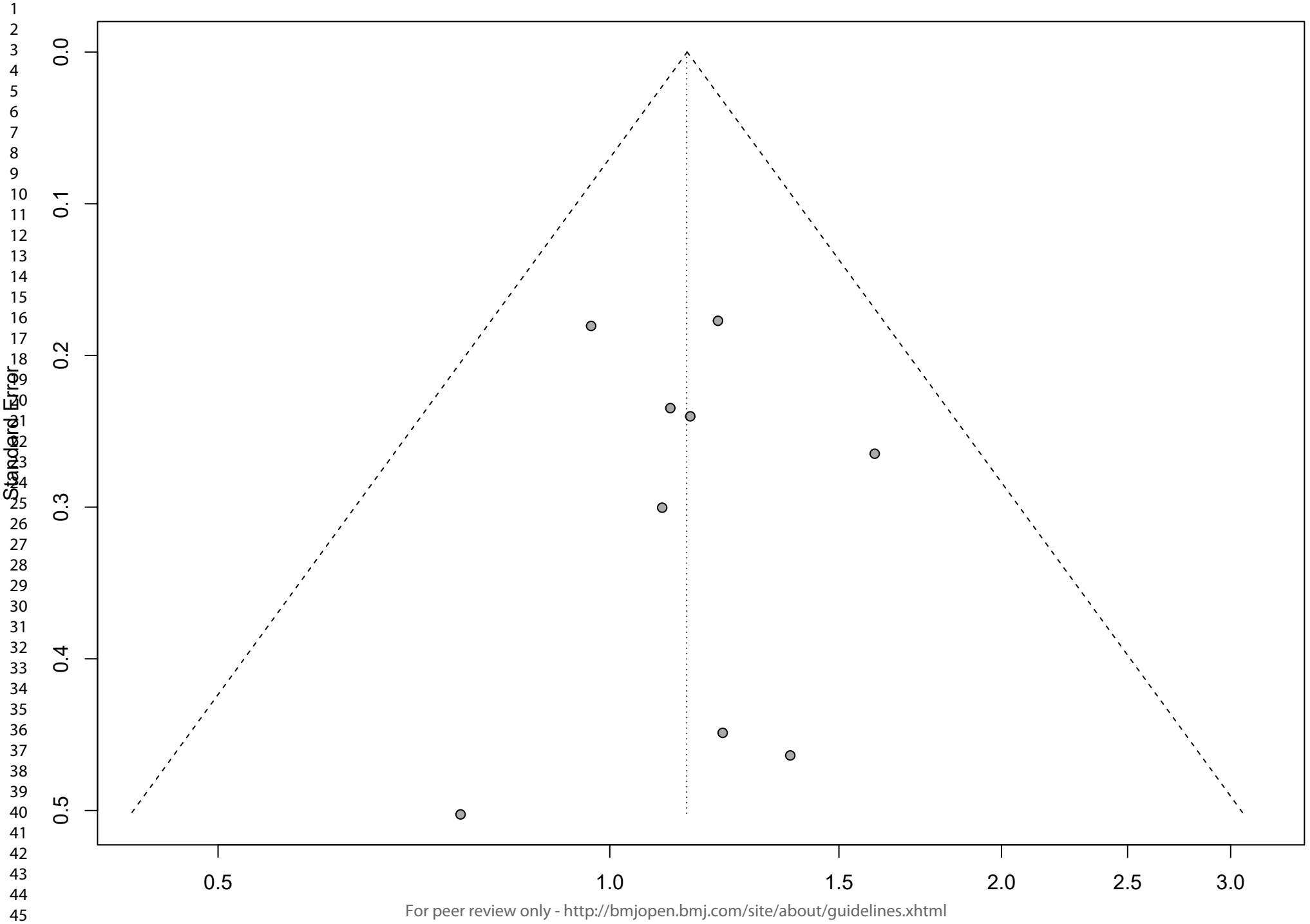
eFigure 17 - ATTRITION DUE TO MUSCLE SYMPTOMS. Exclusions of studies testing simvastatin 80 mg. Funnel plot.



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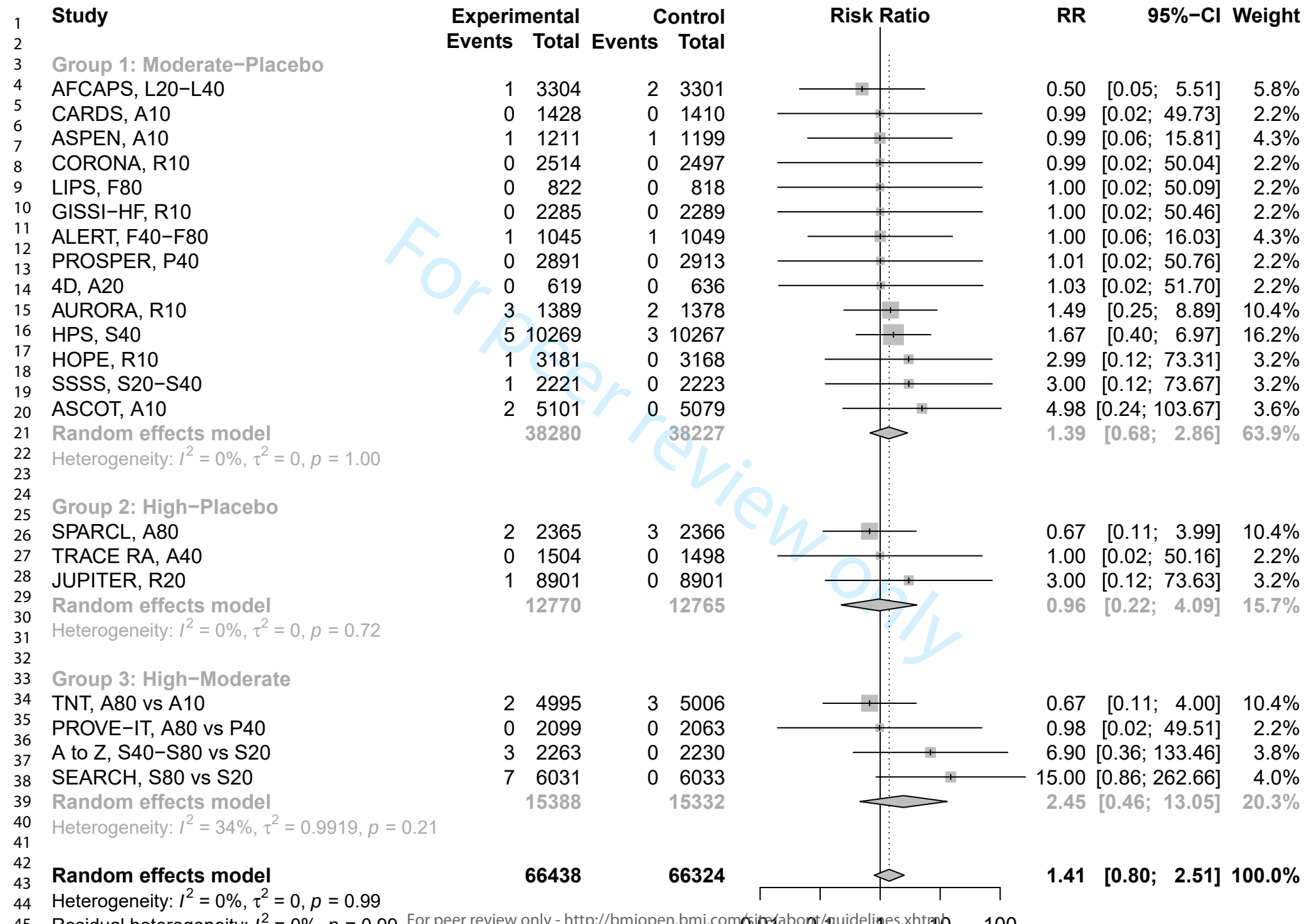
eFigure 18 - RHABDOMYOLYSIS. Full forest plot.



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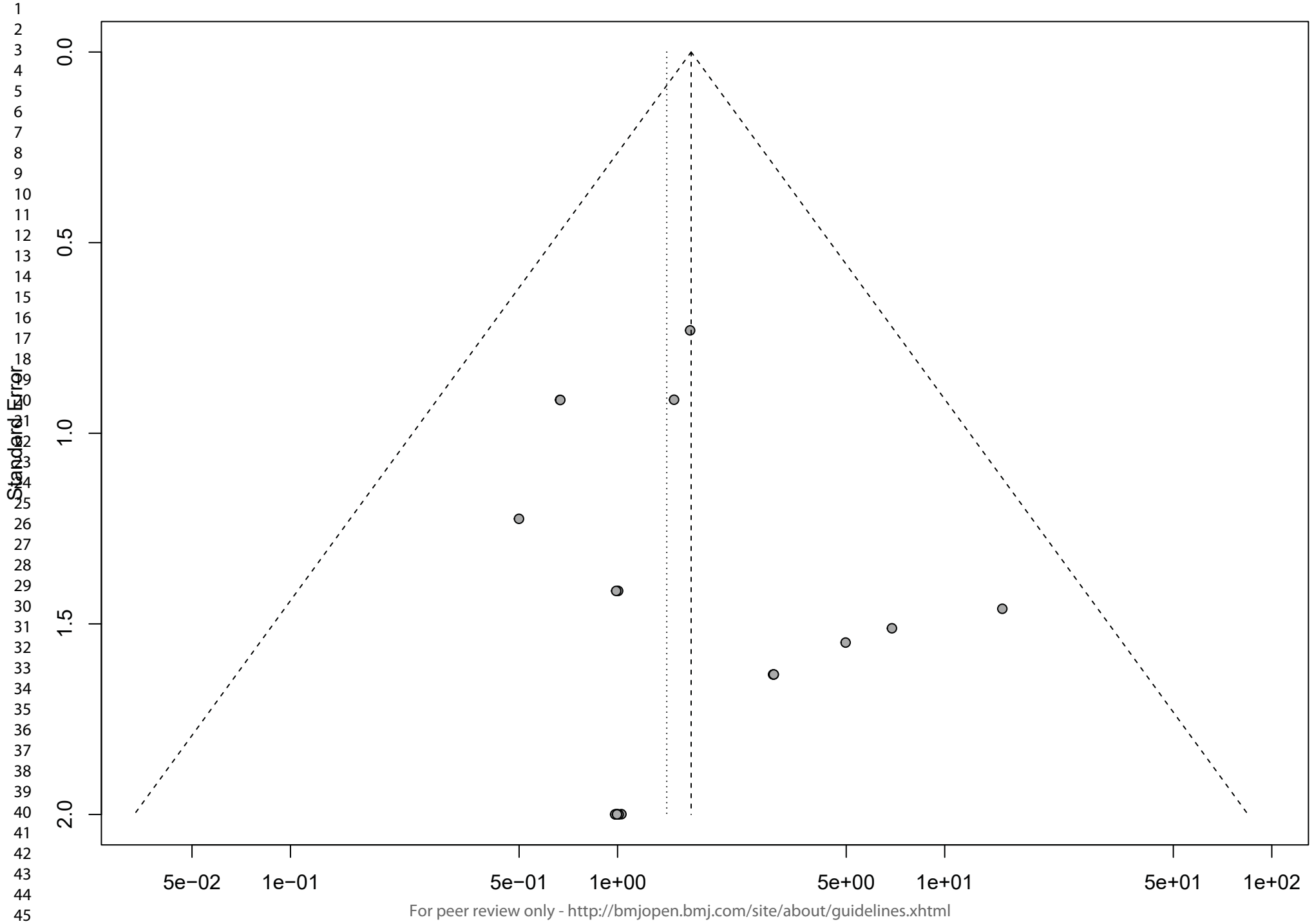
eFigure 19 - RHABDOMYOLYSIS. Full funnel plot.



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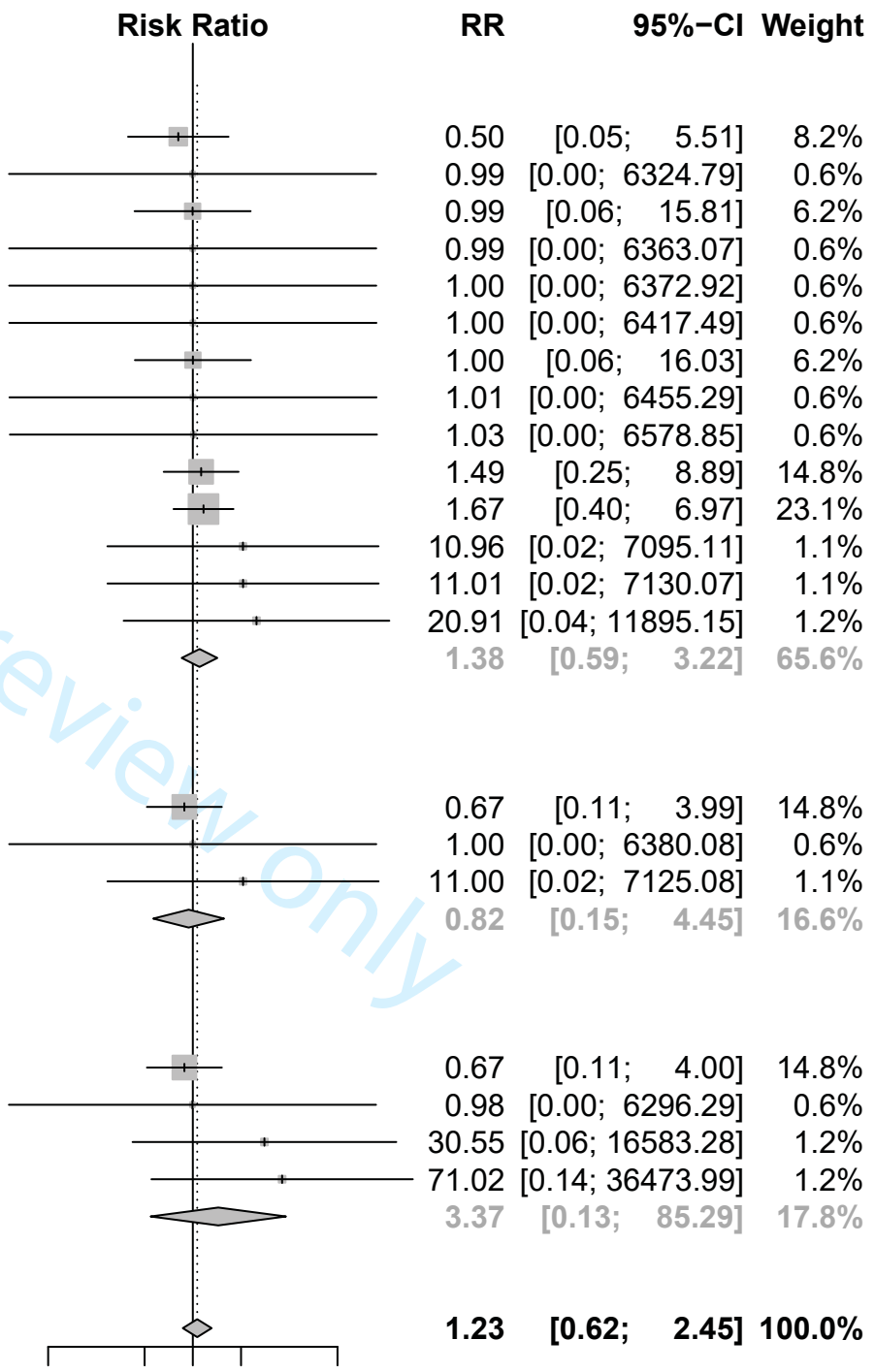
eFigure 20 - RHABDOMYOLYSIS. Continuity Correction = 0.1. Forest plot.



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]	8.2%
CARDS, A10	0	1428	0	1410	0.99	[0.00; 6324.79]	0.6%
ASPEN, A10	1	1211	1	1199	0.99	[0.06; 15.81]	6.2%
CORONA, R10	0	2514	0	2497	0.99	[0.00; 6363.07]	0.6%
LIPS, F80	0	822	0	818	1.00	[0.00; 6372.92]	0.6%
GISSI−HF, R10	0	2285	0	2289	1.00	[0.00; 6417.49]	0.6%
ALERT, F40−F80	1	1045	1	1049	1.00	[0.06; 16.03]	6.2%
PROSPER, P40	0	2891	0	2913	1.01	[0.00; 6455.29]	0.6%
4D, A20	0	619	0	636	1.03	[0.00; 6578.85]	0.6%
AURORA, R10	3	1389	2	1378	1.49	[0.25; 8.89]	14.8%
HPS, S40	5	10269	3	10267	1.67	[0.40; 6.97]	23.1%
HOPE, R10	1	3181	0	3168	10.96	[0.02; 7095.11]	1.1%
SSSS, S20−S40	1	2221	0	2223	11.01	[0.02; 7130.07]	1.1%
ASCOT, A10	2	5101	0	5079	20.91	[0.04; 11895.15]	1.2%
Random effects model		**38280**		**38227**	**1.38**	**[0.59; 3.22]**	**65.6%**
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]	14.8%
TRACE RA, A40	0	1504	0	1498	1.00	[0.00; 6380.08]	0.6%
JUPITER, R20	1	8901	0	8901	11.00	[0.02; 7125.08]	1.1%
Random effects model		**12770**		**12765**	**0.82**	**[0.15; 4.45]**	**16.6%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.70							
Group 3: High−Moderate							
TNT, A80 vs A10	2	4995	3	5006	0.67	[0.11; 4.00]	14.8%
PROVE−IT, A80 vs P40	0	2099	0	2063	0.98	[0.00; 6296.29]	0.6%
A to Z, S40−S80 vs S20	3	2263	0	2230	30.55	[0.06; 16583.28]	1.2%
SEARCH, S80 vs S20	7	6031	0	6033	71.02	[0.14; 36473.99]	1.2%
Random effects model		**15388**		**15332**	**3.37**	**[0.13; 85.29]**	**17.8%**
Heterogeneity: I^2 = 39%, τ^2 = 4.4154, p = 0.18							
Random effects model		**66438**		**66324**	**1.23**	**[0.62; 2.45]**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.99							
Residual heterogeneity: I^2 = 0%, p = 0.98							

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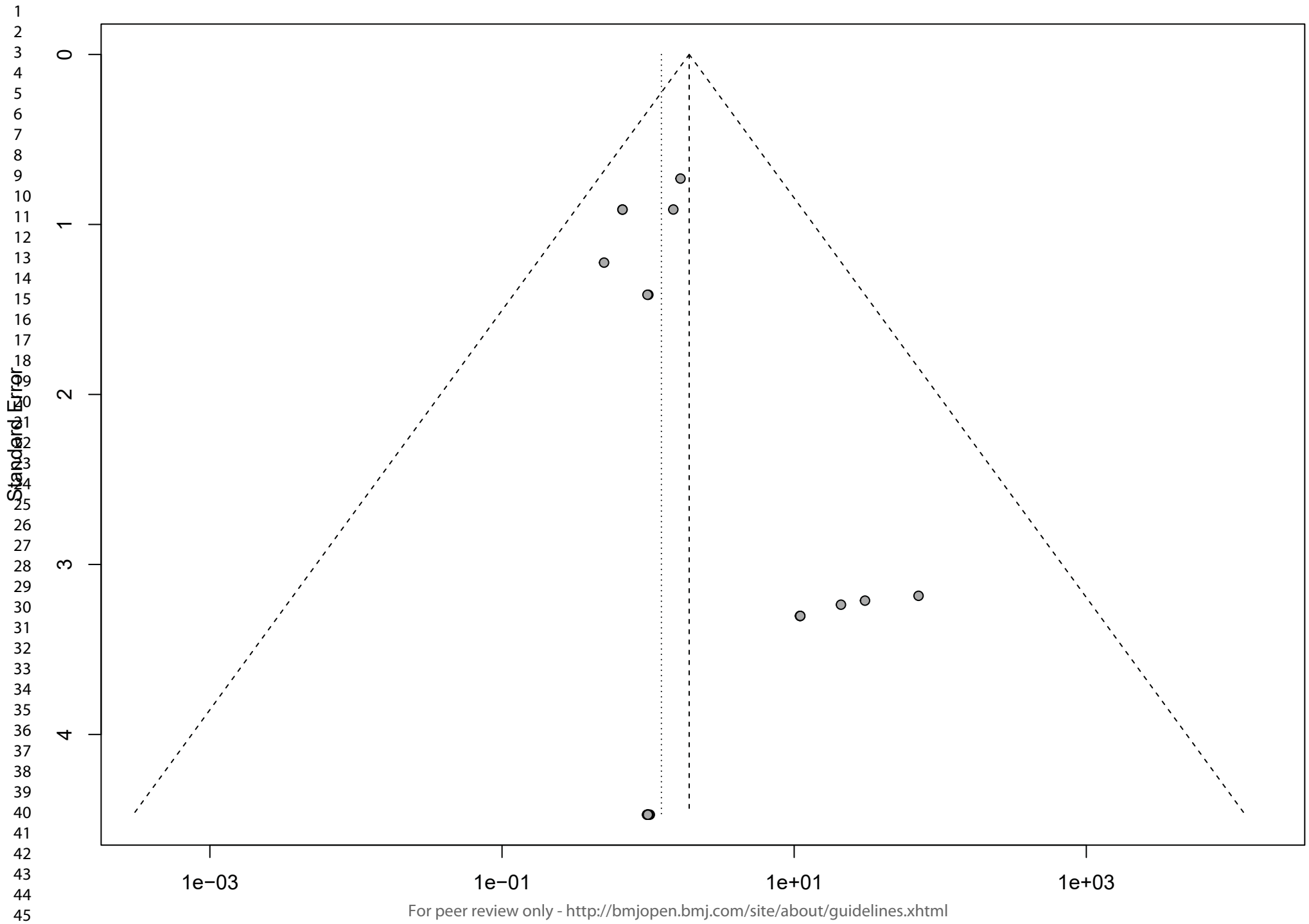
eFigure 21 - RHABDOMYOLYSIS. Continuity Correction = 0.1. Funnel Plot.



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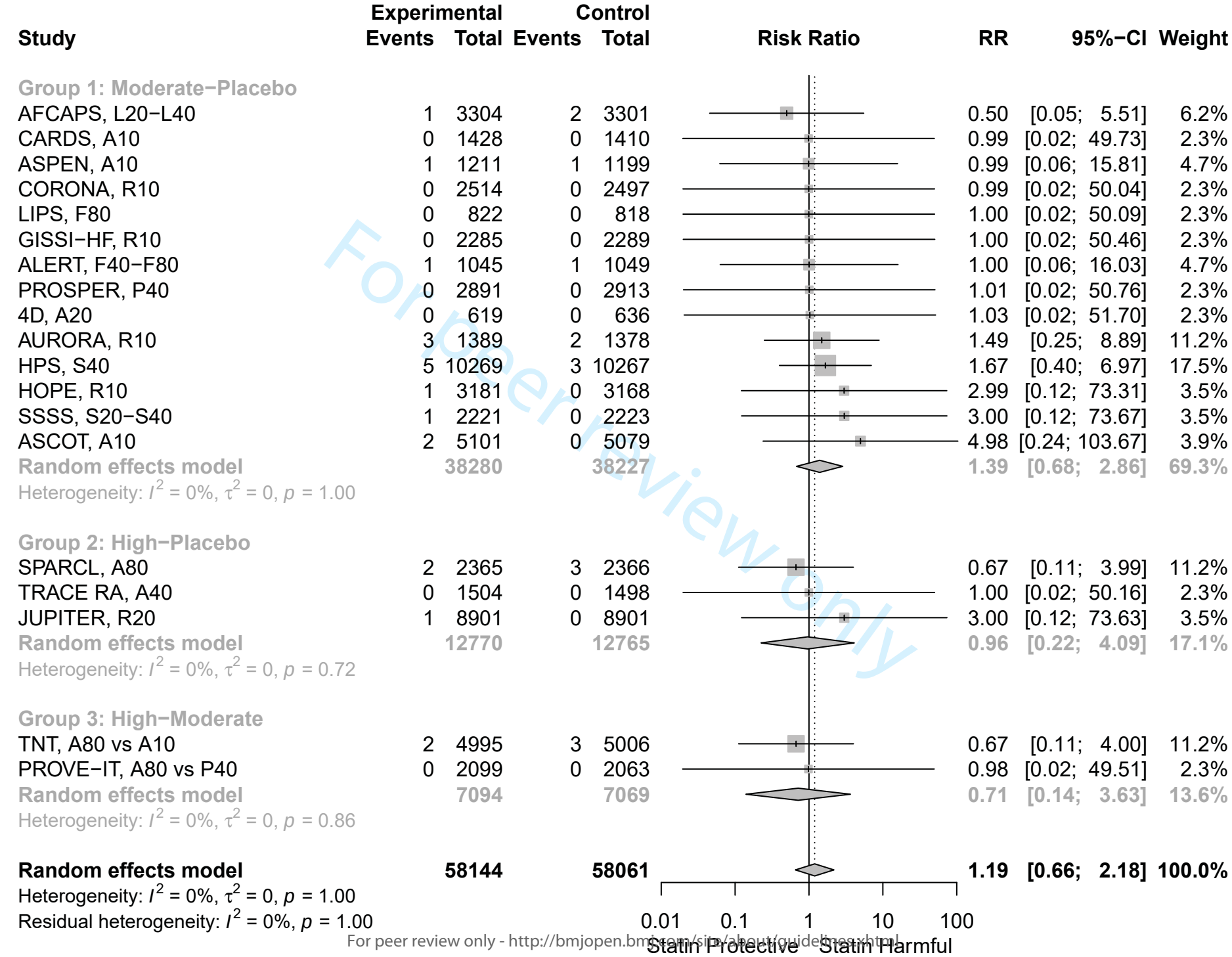
eFigure 22 - RHABDOMYOLYSIS. Exclusions of studies testing simvastatin 80 mg. Forest plot.



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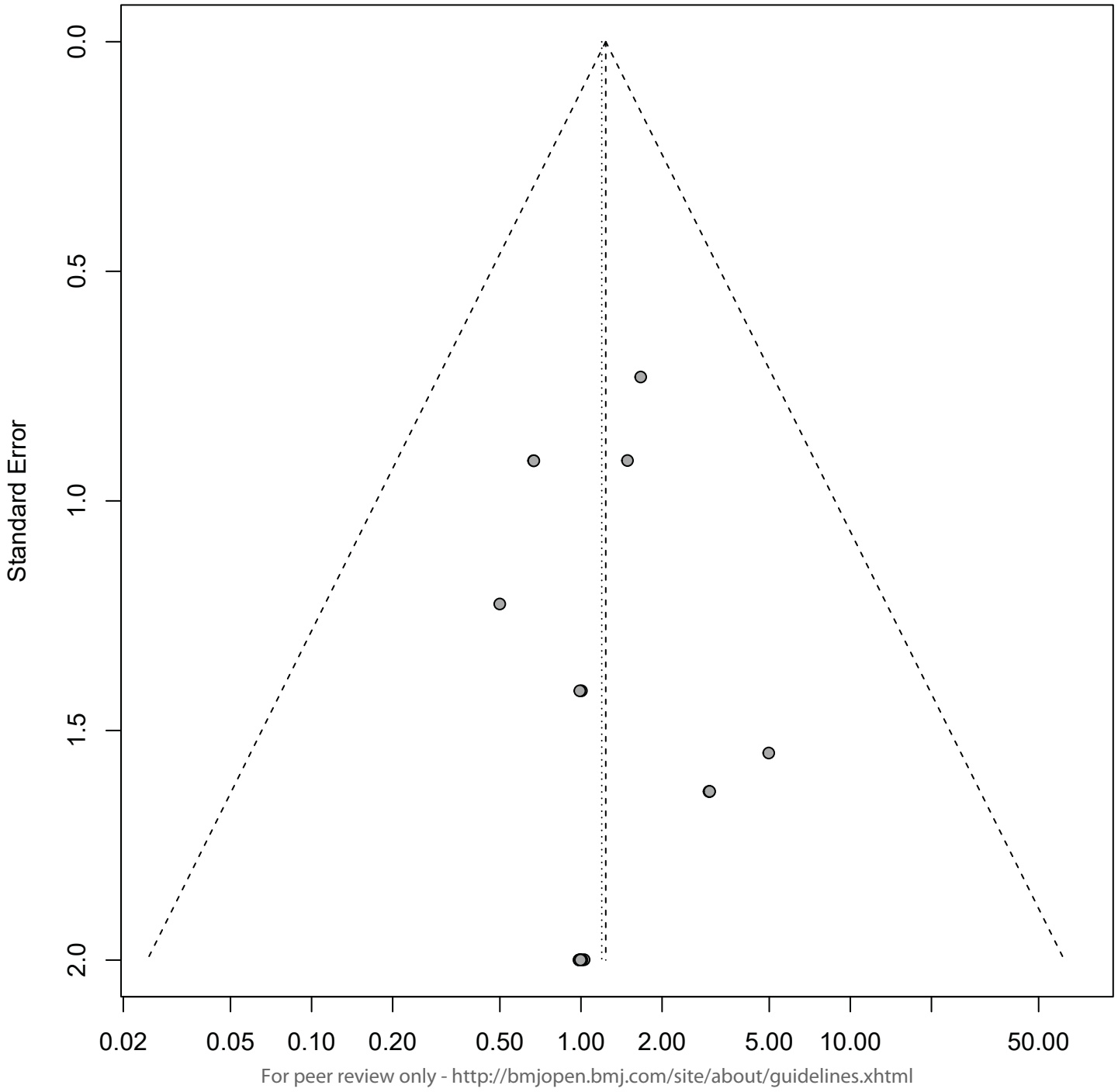
eFigure 23 - RHABDOMYOLYSIS. Exclusions of studies testing simvastatin 80 mg. Funnel plot.



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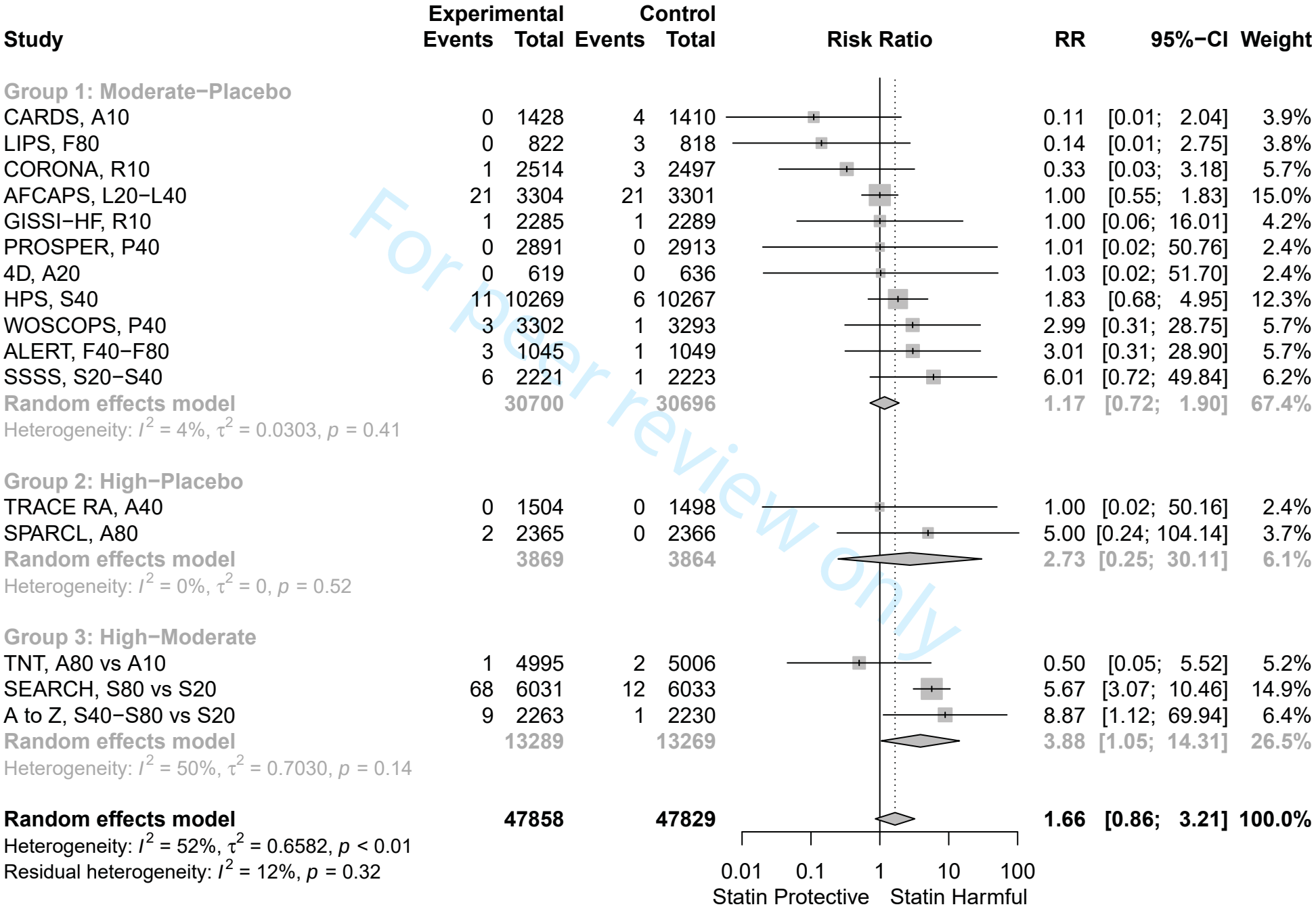
eFigure 24 - CK >10xULN. Full forest plot.



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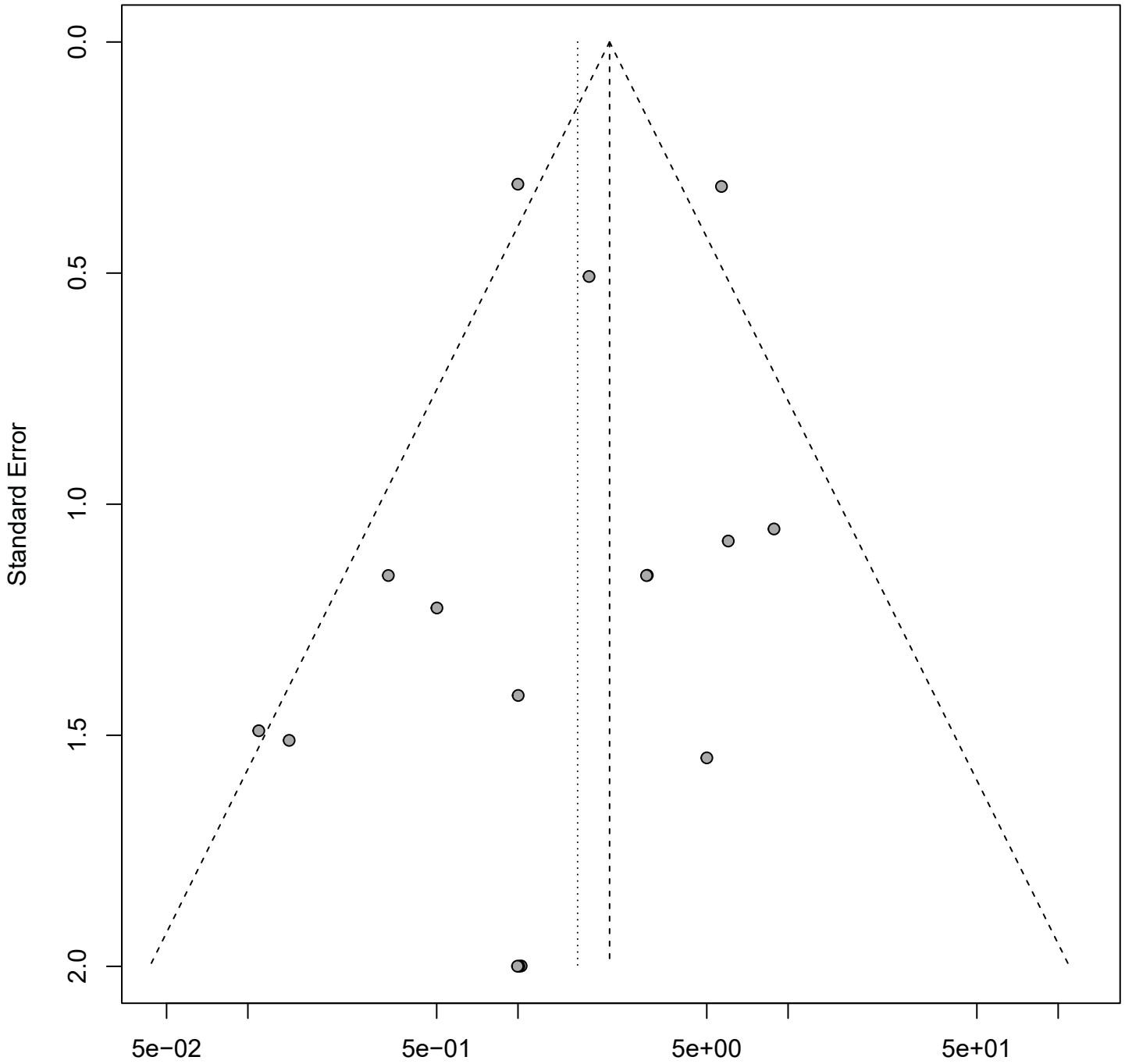
eFigure 25 - CK > 10xULN. Full funnel plot.



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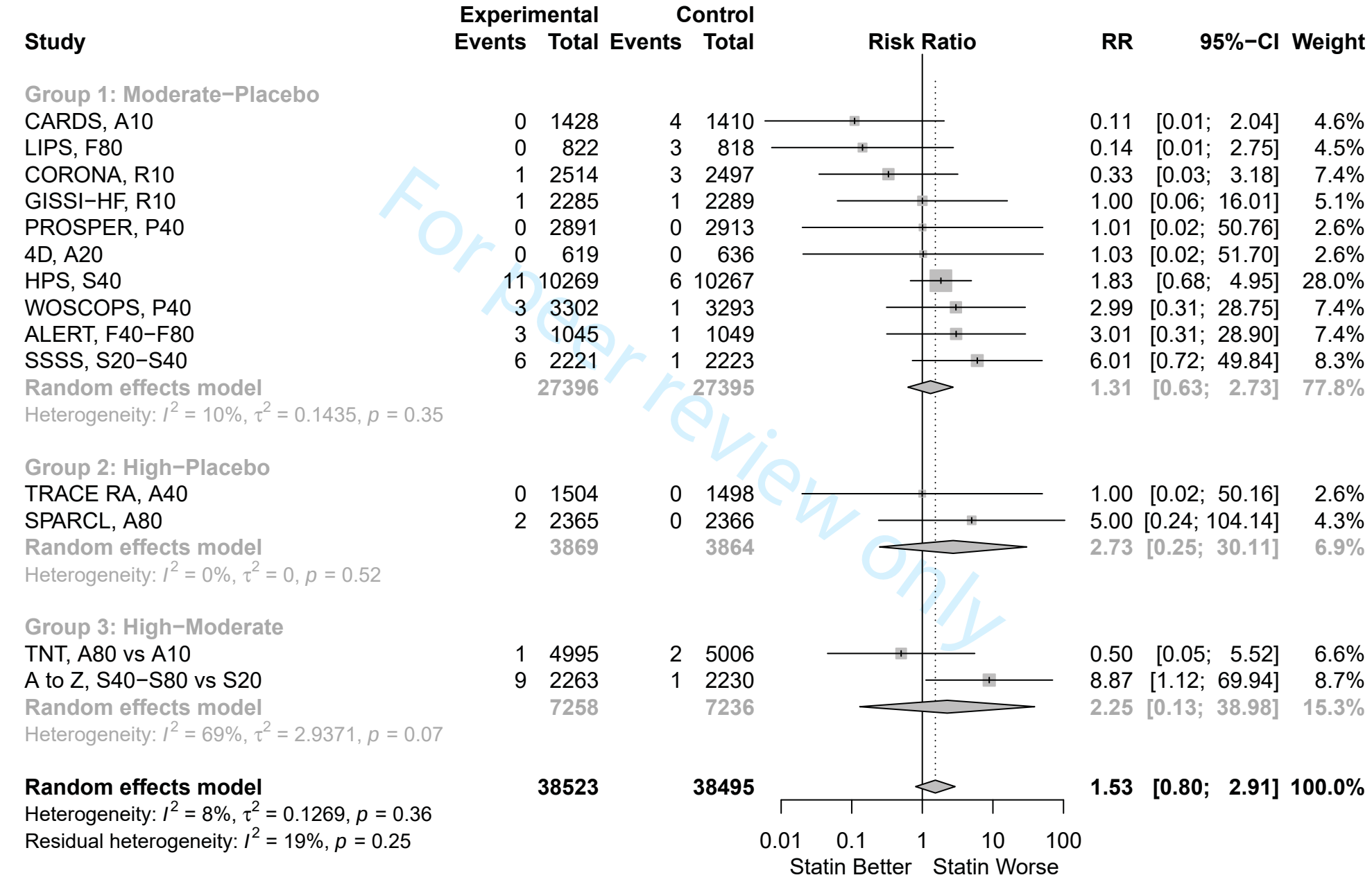
eFigure 26 - CK >10xULN. Outliers excluded. Forest plot.



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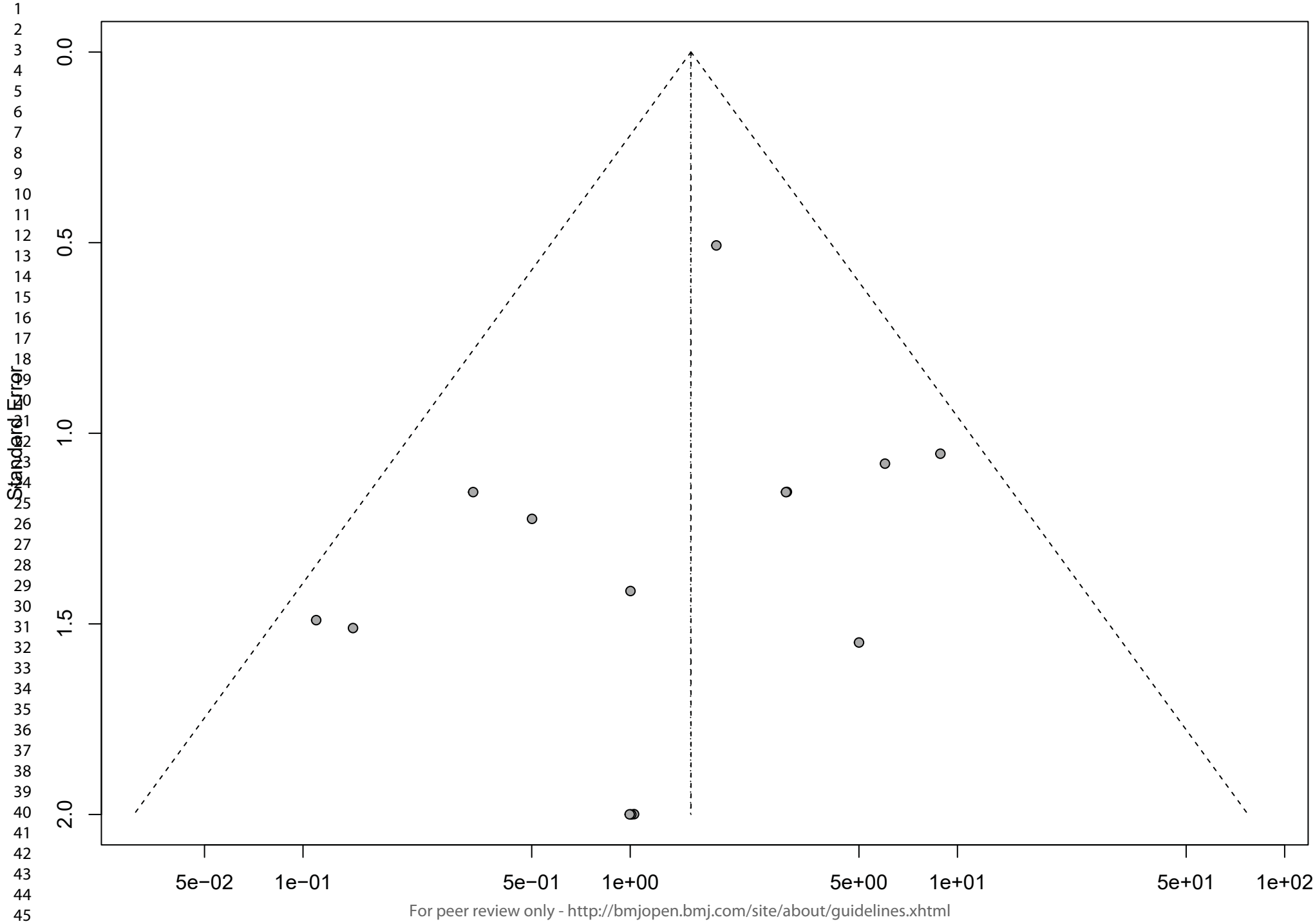
eFigure 27 - CK >10xULN. Outliers excluded. Funnel plot.



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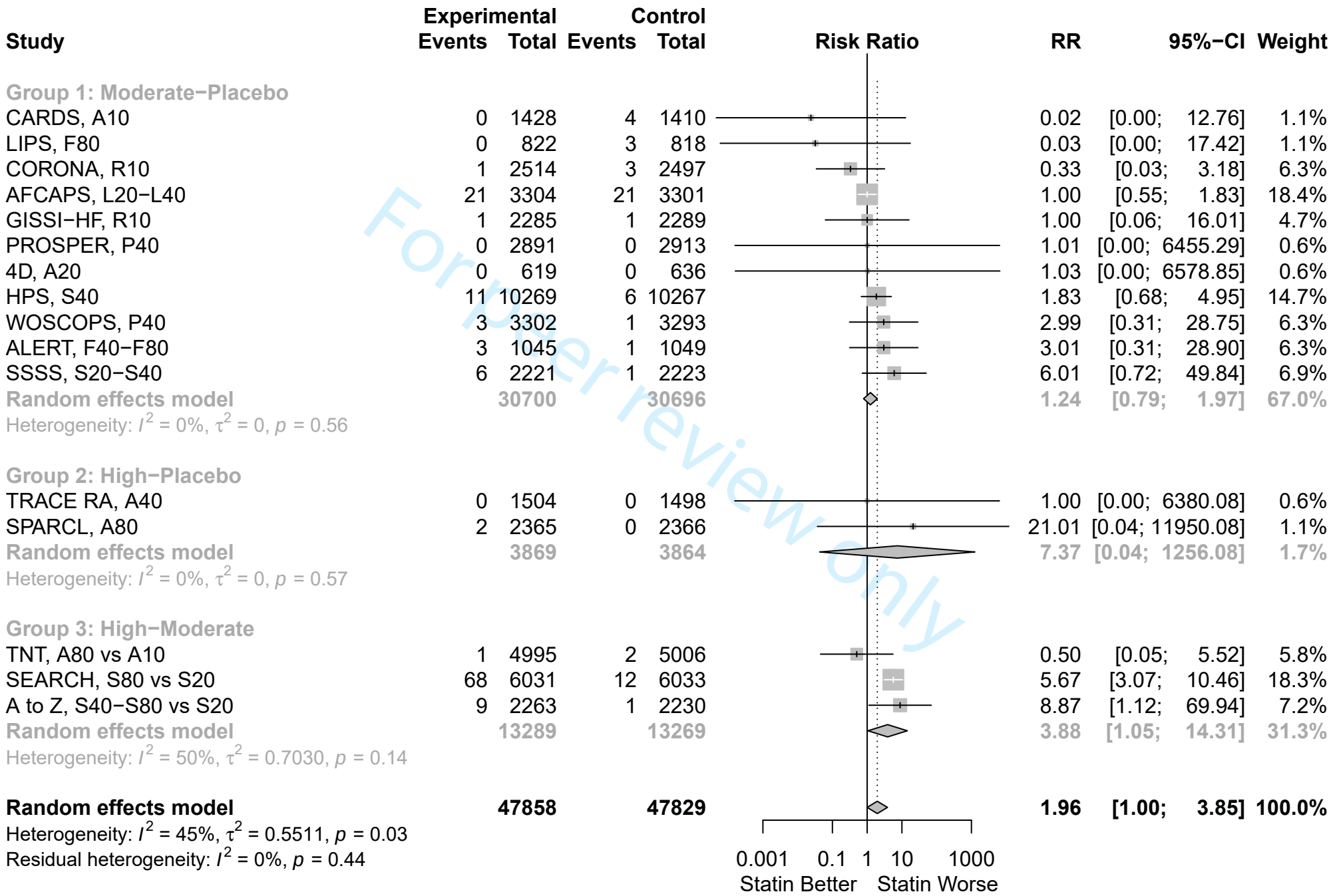
eFigure 28 - CK >10xULN. Continuity Correction = 0.1. Forest plot.



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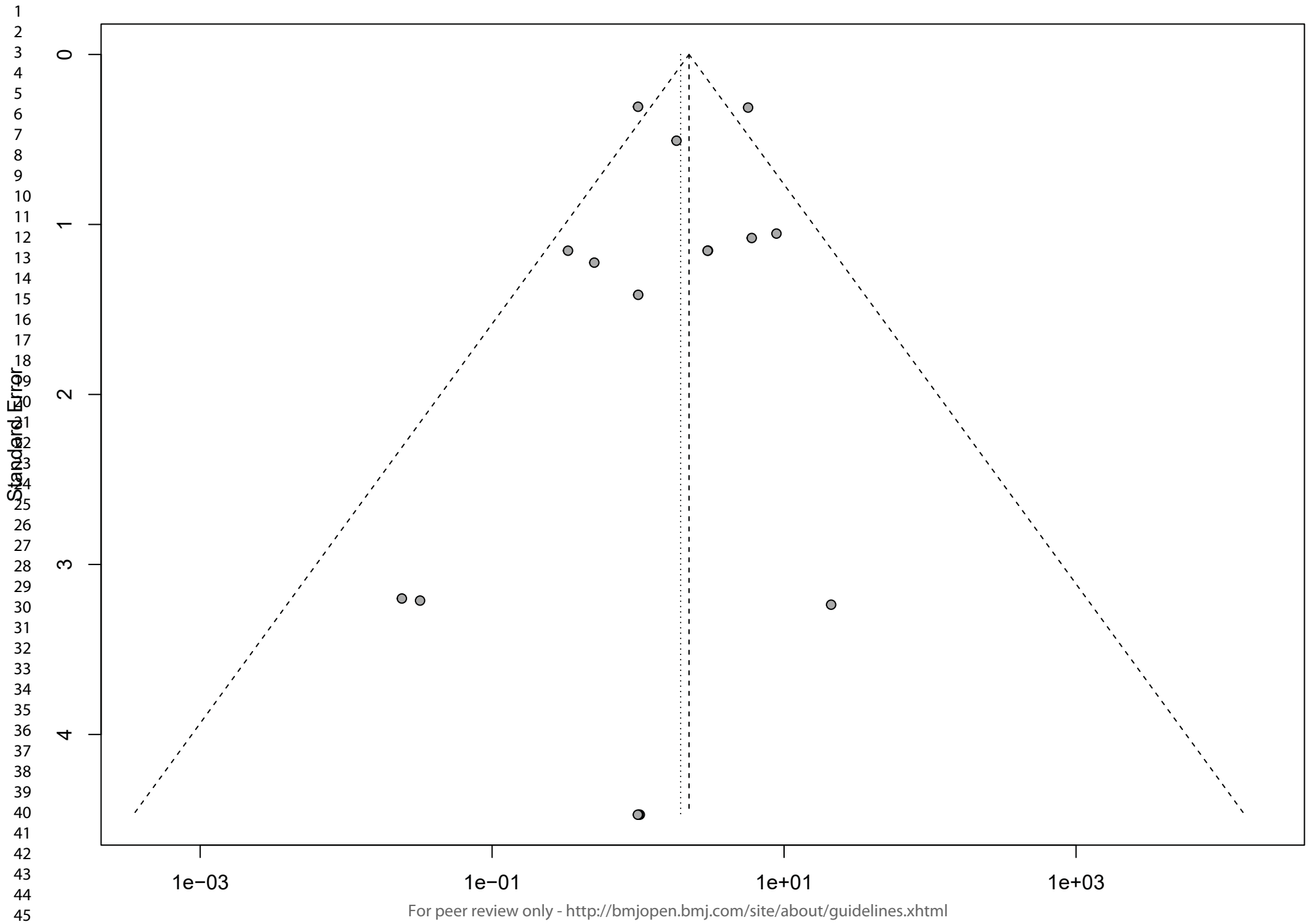
eFigure 29 – CK >10xULN. Continuity Correction = 0.1. Funnel plot.



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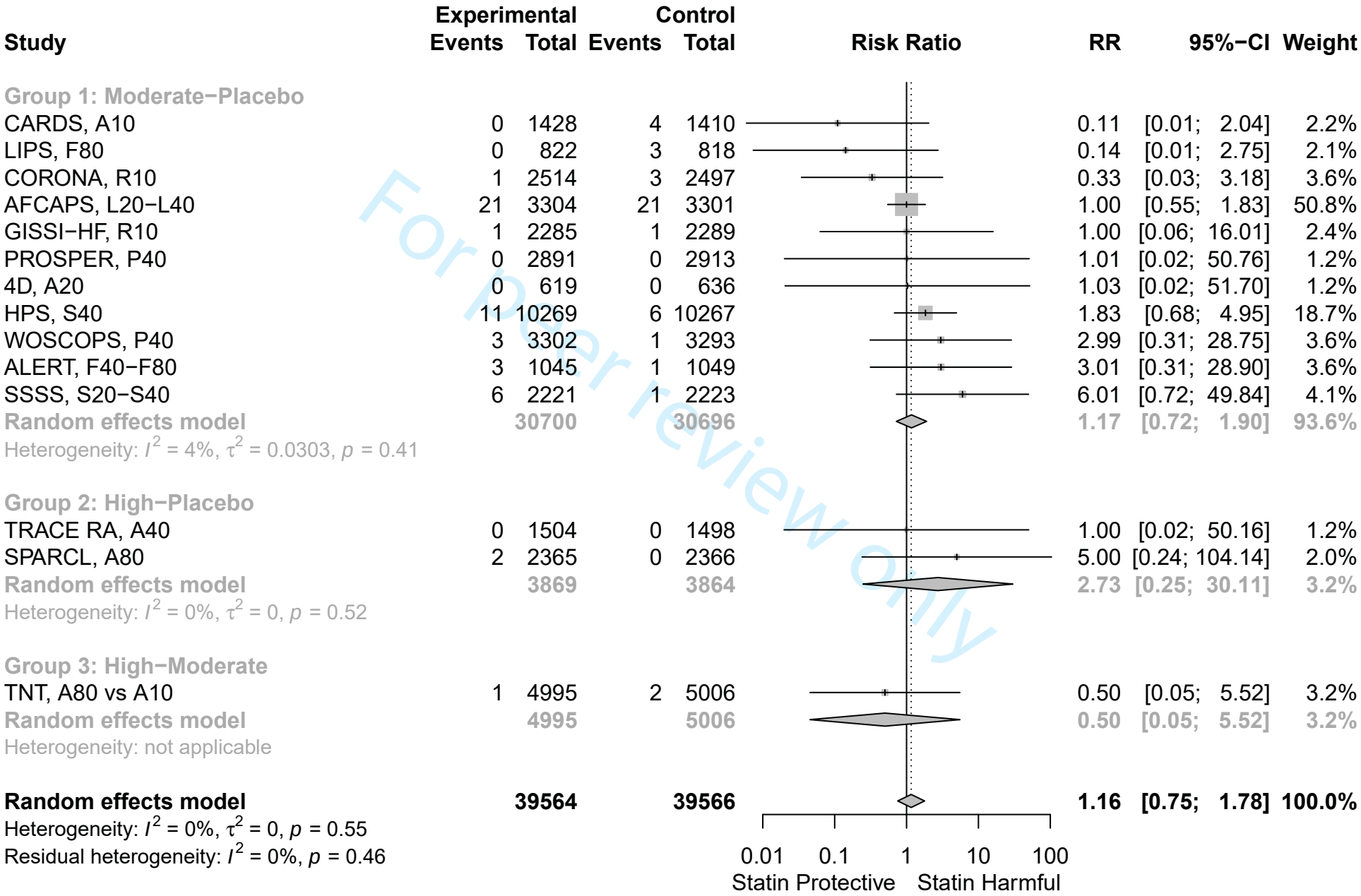
eFigure 30 - CK >10xULN. Exclusions of studies testing simvastatin 80 mg. Forest plot.



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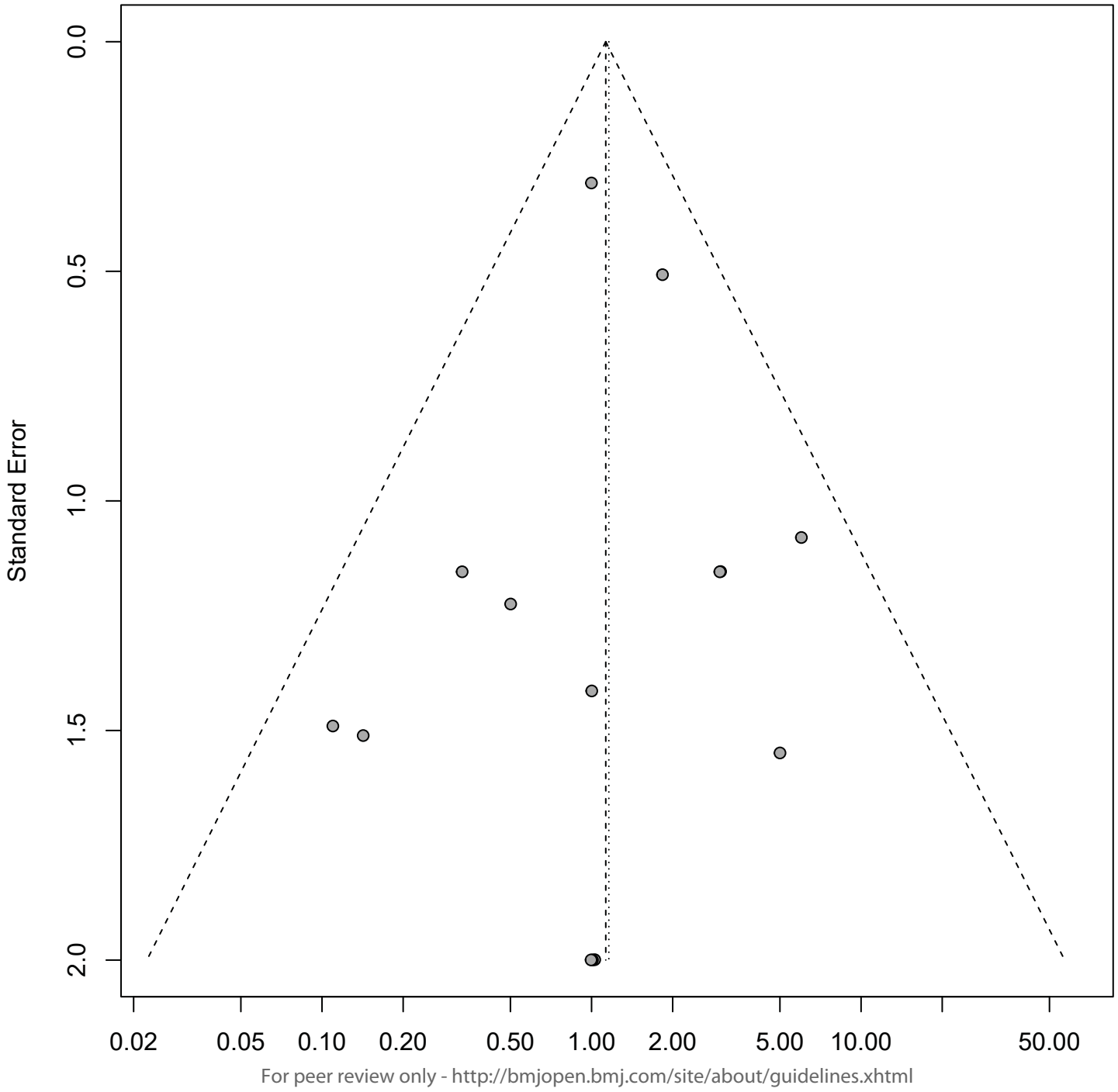
eFigure 31 - CK >10xULN. Exclusions of studies testing simvastatin 80 mg. Funnel plot.



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	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 ($p>0.05$)

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eTABLE 2: NMA RESULTS WITHOUT A-Z[42] and SEARCH[44] TRIALS

	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
Any Probs	1.01 (0.99,1.04)	0.000 (-0.001,0.001)	--	1.02 (0.96,1.09)	0.003 (-0.002,0.007)	--	1.04 (0.98, 1.10)	0.003 (-0.002, 0.007)	--
Myalgia	1.11 (0.97,1.27)	0.001 (-0.000,0.001)	--	1.01 (0.88-1.16)	0.005 (-0.000, 0.009)	--	1.12 (1.02-1.23)	0.006 (0.000, 0.010)	182
Attrition	1.13 (0.93,1.36)	0.001 (-0.000,0.001)	--	1.21 (0.86,1.71)	0.006 (-0.005, 0.016)	--	1.36 (0.92,2.03)	0.006 (-0.004, 0.016)	--
Rhabdo.	1.39 (0.70,2.75)	0.000 (-000,0.001)	--	0.70 (0.22,2.21)	-0.000 (-0.000,0.000)	--	0.97 (0.32,3.00)	0.000 (-0.001, 0.001)	--
CK>10ULN	1.19 (0.77,1.85)	-0.000 (-0.004,0.000)	--	1.07 (0.19, 5.94)	-0.000 (-0.000, 0.000)	--	1.28 (0.23,7.06)	0.000 (-0.000, 0.000)	--

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1 (Title)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5 (Intro)
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3 (abstract)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	With Prospero reg.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8

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Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-11, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results section
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Results section
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Title page

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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**. Page 2 of 2

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BMJ Open

INTENSITY OF STATIN THERAPY AND MUSCLE SYMPTOMS: A NETWORK META-ANALYSIS OF 153,000 PATIENTS

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Complete List of Authors:	Davis, John; University of Texas Medical Branch at Galveston, Preventive Medicine and Population Health Weller, Susan; The University of Texas Medical Branch at Galveston, Departments of Preventive Medicine and Community Health; and Family Medicine
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Epidemiology, Evidence based practice, Pharmacology and therapeutics, Health services research, Medical management
Keywords:	Cardiac Epidemiology < CARDIOLOGY, Coronary heart disease < CARDIOLOGY, CLINICAL PHARMACOLOGY, GENERAL MEDICINE (see Internal Medicine), Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Cardiology < INTERNAL MEDICINE

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INTENSITY OF STATIN THERAPY AND MUSCLE SYMPTOMS: A NETWORK META-ANALYSIS OF 153,000 PATIENTS

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ABSTRACT

Objective: To estimate relative risk of statin-associated musculoskeletal symptoms (SAMS) by statin therapy intensity.

Setting: Network meta-analysis assessing multi-center RCTs across several countries.

Participants: Pubmed, Web of Science, Cochrane database, and clinicaltrials.gov were searched through January 2021 for doubled-blinded RCTs testing the effect of statin therapy on lipids with at least 1000 participants and two years of intended treatment. Two coders assessed articles for final inclusion, quality, and outcomes. Treatment intensity was categorized according to American Heart Association definitions.

Outcomes: Pairwise and network meta-analysis (NMA) estimated relative risk (RR) and risk difference (RD) with random effects modeling. Heterogeneity was evaluated with the I^2 statistic. Outcomes included muscle symptoms (any, myalgia, and attrition due to muscle symptoms), rhabdomyolysis, and elevated creatine kinase (>10x upper limit of normal).

Results: Of 2919 RCTs, 24 (N=152,461) met inclusion criteria. NMA results indicated risk was significantly greater for high compared to moderate intensity statin therapy for any muscle problem (RR=1.04, 95% CI: 1.00,1.07; I^2=0%), myalgia (RR=1.04, 95% CI: 1.00,1.08; I^2=0%, NNH=173), attrition due to muscle problems (RR=1.37, 95% CI: 1.09,1.73, I^2=0%, NNH=218), and elevated CK (RR=4.69, CI: 2.50, 8.80; I^2=7%, NNH=527). Risk also was significantly higher for high intensity compared to placebo for any muscle problem (RR=1.05, 95% CI: 1.01,1.09, I^2=0%), myalgia (RR=1.13, 95% CI: 1.05,1.23; I^2=0%, NNH=182), attrition due to muscle problems (RR=1.55, 95% CI: 1.15,2.08, I^2=0%, NNH=187), and elevated CK (RR=5.37, CI: 2.48, 11.61; I^2=7%,

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NNH=589). Due to inconsistency of results across sensitivity analyses, estimates were inconclusive for rhabdomyolysis and CK. There were no significant differences in risk between moderate intensity therapy and placebo for all outcomes.

Conclusions: For approximately each 200 patients on high intensity statins, one additional patient may experience myalgia or discontinue therapy due to muscle problems compared to moderate intensity therapy.

Trial Registration: Prospero #CRD42019112758

Article Summary:

Strengths

- High-quality, large RCTs analyzed with low risk of heterogeneity bias
- Novel use of network meta-analysis to compare treatment intensities allows for large analysis of dose-dependent effect
- Coding of outcome terms directly as reported by investigators to minimize bias

Weaknesses

- Study-level data precludes meta-analysis with regression for relevant covariables affecting risk of outcome
- Heterogeneity of terms across trials prevented analysis of full trial set for each outcome.

Key Words: Statins, myalgia, nocebo, rhabdomyolysis, network meta-analysis

Abbreviations:

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Network Meta-Analysis (NMA) and pair-wise meta-analysis (MA), Risk Ratio (RR), Risk Difference (RD), Cholesterol Treatment Trialists' Collaboration (CTT), Statin Associated Muscle Symptoms (SAMS), Creatine Kinase (CK) & Upper Limit of Normal (ULN), End Stage Renal Disease (ESRD), Number Needed to Harm (NNH), Hazard Ratio (HR)

Ethical Approval: N/A

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INTRODUCTION

The Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis on patient-level data from large RCTs demonstrated that statin therapy is efficacious in reducing major vascular events.[1,2] Statin therapy is now prominent in cholesterol management guidelines. [3–8] Statin-associated muscle symptoms (SAMS), however, may lead to non-adherence or discontinuation with therapy and ultimately to poorer cardiovascular outcomes.[7] Most RCTs have shown small, insignificant increases in risk for SAMS, although patients taking statins may complain of muscle problems and may discontinue therapy due to muscle problems.[3] For example, a 2016 meta-analysis found a non-significant increase in myopathy. However, it did not report on the more mundane myalgias that often cause statin attrition.[3] These milder symptoms are the major public health concern, as statin non-adherence can lead to significant increases in risk of major adverse cardiovascular events.[3] Observational studies suggest that these mild SAMS may occur as often as 7-29% of patients.[7] One review[9] suggested that clinical observations of increased muscle problems with statin therapy may be due to patient expectations.

SAMS also may be more likely with higher intensity therapy. Although this is assumed to be true, especially with the evidence against simvastatin 80 mg,[10,11] few RCTs have examined high intensity therapy[12,13]. This study used a network meta-analysis (NMA) to combine evidence across trials to estimate the risk of SAMS by treatment intensity. In contrast to pair-wise meta-analysis (MA) that directly estimates causal effects, a NMA can indirectly estimate risk between placebo and moderate, moderate and high, and

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between placebo and high intensity treatment – even though placebo, moderate, and high intensity treatment levels were not compared within a single trial. Results contribute to the debate about whether muscle adverse events are due solely to patient expectations or whether statins might have an independent effect on symptoms. Finally, this study contributes to the ongoing debate as to whether statins cause myalgias and attrition due to muscle problems without marked creatine kinase (CK) elevations.

METHODS

The Trials. PubMed, Cochrane Database, Web of Science, and clinicaltrials.gov were searched for "systematic reviews" and "meta-analysis" in the title, abstract, or keywords prior to January 31, 2021to identify eligible trials (Prospero #CRD42019112758; see online supplement for search terms and strategy). Double-blinded RCTs to improve lipid levels comparing statin therapy to placebo or higher-lower dose statin therapy were selected. In order to detect most adverse events, RCTs were selected that had at least 1,000 participants with two years of intended follow-up, where statin treatment was not given with other prescription drug therapies, and results contained reports on muscle-related adverse events. Both authors independently reviewed trials for final inclusion and coded each for quality with Oxford Center for Evidence-based Medicine ratings[14] and a five-point Jadad quality score.[15] Any disagreements were reconciled by joint review and discussion.

Patient and Public Involvement. Patients were not involved in design or implementation of this study.

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Exposure Variable. Studies were classified by intensity of statin treatment ("high" or "moderate") according to American Heart Association definitions for potency in reduction of lipid levels.[16] High intensity signifies an expected 50% or greater reduction in LDL-C levels when taking that statin (i.e., 80 mg atorvastatin) and moderate signifies 30-50% reduction in LDL-C.[16]

Outcome Variables. Adverse muscle-related events were coded into five main outcomes. The first outcome was for any patient-reported muscle complaint coded from reports of "muscle aches", "pains", "cramps", "stiffness," "musculoskeletal disorders," etc. The second focused on only myalgia or muscle pain. The third focused on attrition due to musculoskeletal complaints. A fourth captured explicit reporting of rhabdomyolysis, with or without a trial definition. The fifth was elevated creatine kinase, greater than ten times the upper limit of normal (CK >10x ULN). This threshold was used to distinguish this outcome from less meaningful CK increases and also because CK>10xULN is commonly reported in RCTs. All outcomes were coded as reported by original investigators in published and online reports, and were independently coded by both authors. Ambiguities were resolved by contacting trial investigators.

Analysis. Published aggregate data from each trial were used. A crude estimate of incidence was calculated from the total number of cases observed divided by the total person-years (using the median or mean follow-up time for each study) and a chi square test was used to test for homogeneity in the proportion of incident cases across studies, within each arm, although these crude estimates ignored randomization. To

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facilitate interpretation and comparison of results to the original trials, risk of adverse effects was estimated with pooled relative risk (RR). A 0.50 continuity correction was added to aggregate frequencies for trials that observed zero cases of an outcome in either treatment arm. A pairwise meta analysis (MA) was used to estimate the RR (Mantel-Haenszel method, random effects)[17] for a statin effect by treatment intensity from direct (head-head comparison) trials in the meta package in R.[18] Because aggregations across studies are only meaningfully interpreted when results are consistent across studies, heterogeneity among RCTs was assessed with an index of consistency across trials (I^2, Q)[19,20] and funnel plots. When $I^2 \leq 25\%$, results are considered to be at low risk of bias due to heterogeneity; high values (>75%) indicate high risk of bias due to heterogeneity. [19,20] Residual I^2 represents the heterogeneity remaining after accounting for sub-groups of treatment intensity. Cochrane's Q (a sub-component of I^2) indicates the probability that the observed heterogeneity is due to chance. Sensitivity analyses included omitting outliers identified in funnel plots and using a 0.10 as a "continuity correction". In addition, analyses were conducted excluding the simvastatin 80 mg studies because of US FDA muscle-related safety warnings.[21]

A network meta-analysis (NMA), conducted in R,[22] used *all* available pairs of comparisons for each outcome to estimate increased risk between the three levels of treatment exposure. Prespecified comparisons were between placebo and moderate intensity, between moderate and high intensity therapy, and between placebo and high intensity. The RR was used to estimate effect size (frequentist, inverse variance method, random effects), so that results would be comparable across original studies

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and the pairwise meta-analysis above. In contrast to a MA which provides a direct estimate of the RR, a NMA provides estimates by combining direct and indirect evidence from all data. A ratio test was used to test for consistency between NMA direct and indirect estimates.[23] Heterogeneity was assessed with and I^2 and Q statistics.[19,20] Number needed to harm (NNH, the inverse of the absolute difference in incidence) was estimated when the pooled RR was significantly greater than 1.0 and the pooled absolute risk reduction (risk difference, RD) was significantly greater than 0.0. Sensitivity analyses included replacement of zeros with 0.10 and with 0.0001.

RESULTS

Searches yielded 134 relevant reviews, including 2919 RCTs that reduced to 24 unique RCTs that met eligibility requirements (see online supplement). Of the 24 RCTs: 17 were placebo-moderate intensity comparisons,[24–44] 3 were placebo-high intensity comparisons,[45–47] and 4 were moderate-high intensity comparisons[10–13] (Table 1). The active blood pressure treatment arm of the HOPE trial[37] was excluded, but the statin only and placebo only arms were retained, allowing for a statin and placebo comparison. Two trials compared moderate and high intensity therapy using 80 mg/day of simvastatin.[10,11] All 24 RCTs scored the highest quality (1) on the Oxford rating and on the Jadad scale 18 scored 5/5 and 6 scored 4/5 (missing detail on random assignment). The RCTs included heterogenous patient populations, e.g., healthy middle-aged adults[26,37,43,46] to ESRD patients. Sample sizes ranged from 1,255[24] to 20,536[40] with follow-up periods from 1.9[46] to 6.7[10] years. Of the 24 RCTs, six were included in the 2006 meta-analysis,[48] 17 in the 2014 systematic review,[49] 23 in the 2016

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meta-analysis,[3] and 18 in the 2013 NMA.[50] None of the previous analyses separated trials into sub-groups by treatment intensity. Crude estimates of incidence increased with intensity of treatment from placebo to moderate intensity to high intensity therapy, but with heterogeneity across trials (online supplement).

Any Muscle Symptoms. Twenty-three trials reported some type of muscle symptom[10,13,25–29,31,35,39,40,46,47] myositis,[34] myalgia,[12,24,30,32,33,42,45] myopathy,[24,38] or discontinuation due to muscle-related symptoms.[11,13,36] The pairwise meta-analysis pooled across subsets of trials indicated consistent trial results with a 1% non-significant increase in risk between placebo and moderate intensity therapy, a 3% non-significant increase between placebo and high intensity therapy (Figure 1), and a 5% significant increase between moderate and high intensity therapy (RR=1.05, 95% CI: 1.01, 1.09; p=0.027, 4 RCTs, N=30,720; I^2=0%). Sensitivity analyses indicated that RRs were essentially unchanged without an outlier[30] identified on the funnel plot, with a 0.10 correction, or without the simvastatin 80 mg trials. (online supplement).

The NMA pooled direct and indirect evidence from all 23 trials and suggested increased risk with higher intensity therapy. Results (Table 2) indicated a 1% non-significant increase in risk between placebo and moderate intensity therapy, a 4% significant increase between moderate and high intensity therapy (RR=1.04, 95% CI: 1.00, 1.08; p=0.031), and a 5% significant increase between placebo and high intensity therapy (RR=1.05, 95% CI: 1.01, 1.09; p=0.012). The RRs were consistent across studies (I^2=0%; Q, p=0.54), were not significantly different between direct and indirect estimates (p=0.48), and were not sensitive to substitutions for zero values. Pooled RDs between

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pairs of treatment groups were not significantly different from zero. There were no outliers in the NMA analysis. Exclusion of the two simvastatin 80mg trials did not meaningfully change risk, but comparisons with high intensity were not statistically significant, likely due to the decreased sample size (online supplement).

Myalgia or pain. Thirteen RCTs reported cases of myalgia,[25,29–32,42,44–47] attrition due to myalgia,[26,28] or pain and/or weakness.[40] The pairwise meta-analysis indicated (Figure 2) a 13% non-significant increase in myalgia between placebo and moderate intensity, a 9% non-significant increase between placebo and high intensity, and a 4% significant increase between moderate and high intensity (RR=1.04, 95% CI: 1.00;1.09, p=0.040, 2 RCT, n=22065; I^2=0%). The three trials comparing placebo and high intensity therapies suggested moderate heterogeneity in results (I^2=45%). Funnel plots did not suggest bias by any of the studies and there were no zero cells (Figures 10-11). Exclusion of the simvastatin 80 mg trial did not meaningfully change the magnitude of risk, although results were non-significant for high intensity compared to moderate intensity therapy possibly due to decreased sample size (online supplement).

The NMA results combining evidence for all 13 trials suggested an increase in myalgia with increased therapy intensity (Table 2). There was a 9% non-significant increase in risk between placebo and moderate intensity therapy, a 4% significant increase between moderate and high intensity therapy (RR=1.04, 95% CI: 1.00, 1.08; p=0.046), and a 13% significant increase in risk for high intensity therapy compared to placebo without heterogeneity (RR=1.13, 95% CI: 1.05, 1.23; p=0.002). The RRs were

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consistent across studies (I^2=0%, Q, p=0.48) and direct and indirect estimates were not significantly different (p=0.63). The pooled RD was significant between high and moderate intensity (NNH=173) and between high intensity and placebo (NNH=154) with low heterogeneity (I^2=20%; Q, p=0.25). Exclusion of the simvastatin 80 mg trial did not change the magnitude of risk although results were not significant for high intensity compared to moderate intensity therapy (online supplement).

Attrition. Attrition due to muscle problems was reported by eight RCTs that compared moderate intensity statin therapy with placebo,[25,26,28,32,36–38,40,44] three that compared moderate with high intensity therapy,[10,11,13] and none that directly compared high intensity to placebo. In the pairwise meta-analysis (Figure 3), patients on moderate intensity statin therapy had a 13% non-significant increase in attrition due to muscle problems compared to placebo. Patients on high intensity therapy had a 38% significantly higher attrition rate than those on moderate intensity (RR=1.38, 95% CI: 1.04, 1.82; p=0.024, 3 RCTs, N=20,719) with moderate heterogeneity across trials (I^2=31%). Funnel plots did not suggest bias and there were no zero cells. Exclusion of the two simvastatin 80 mg trials left only one moderate-high intensity comparison RCT (online supplement).

The NMA results for the 11 trials suggested that risk for attrition increased with intensity of therapy. There was a 13% non-significant increase in risk between placebo and moderate intensity therapy (Table 2), a 37% significant increase in risk between moderate and high intensity (RR=1.37, 95% CI: 1.09, 1.73; p=0.007), and a 16%

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significant increase in risk between placebo and high intensity therapy (RR=1.16, 95% CI: 1.15, 2.08; p=0.004). The RRs were consistent across studies (I^2=0%; Q p=0.72) and closely paralled direct results provided by the meta-analysis, but the NMA provided an estimate for the placebo-high intensity comparison for which there were no head-to-head trials. The pooled RD between moderate and high intensity therapy was significant and the NNH was 218. The pooled RD between high intensity therapy and placebo also was significant and the NNH was 186. Exclusion of the two simvastatin 80 mg trials resulted in a slightly lower risk estimate for the moderate to high comparison and a slightly higher estimate for the placebo to high comparison, and both were non-significant (online supplement).

Rhabdomyolysis. Rhabdomyolysis was reported on by 14 moderate intensity-placebo comparison RCTs,[24–28,30–32,35,36,39–42] four moderate-high intensity comparison RCTs,[10–13] and three high intensity-placebo comparison RCTs.[45–47] Incidence of rhabdomyolysis was very low and statistical comparisons were not conclusive. Pairwise meta-analysis indicated a 39% non-significant increase in rhabdomyolysis incidence between placebo and moderate intensity therapy, 145% non-significant increase between moderate and high intensity, and a 4% non-significant decrease between placebo and high intensity therapy (Figure 4). Results were inconclusive as estimates were not robust across sensitivity analyses. Approximately half (22/42) of the cells were zeros and RR increased for the moderate-high intensity comparison with a smaller correction and removal of the simvastatin 80 mg trials meaningfully changed effect sizes (online supplement).

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NMA results based on all 21 trials indicated increased risk for rhabdomyolysis with increased intensity of therapy (Table 2). There was a 22% non-significant increase in risk between placebo and moderate intensity therapy, a 33% non-significant increase between moderate and high intensity, and a 66% non-significant increase between placebo and high intensity therapy with consistency across trials (I^2=0%, Q p=0.99). Direct and indirect RR estimates were not significantly different (p=0.31). Results were not consistent after exclusion of simvastatin 80 mg trials or replacement of zeros, but remained nonsignificant (online supplement).

Elevated CK. Of 16 RCTs, 11 compared rates of elevated creatine kinase (CK>10xULN) between placebo and moderate intensity therapy,[24–27,32,35,36,39–43] three compared moderate to high intensity therapy[10–12] and two compared high intensity therapy with placebo.[45,47] Incidence of elevated CK was low. Pairwise meta-analysis indicated (Figure 5) a 17% non-significant increase in CK elevation between placebo and moderate intensity therapy, a 173% non-significant increase between placebo and high intensity therapy, and a 288% significantly higher risk for high compared to moderate intensity (RR=3.88, 95% CI: 1.05,14.31; p=0.042, 3 RCTs, n=26,558) with some heterogeneity among the three trials (I^2=50%). Estimates were not stable across sensitivity analyses. Removal of two possible outliers,[10,26] exclusion of simvastatin 80 mg trials, and adjustment for cells with zeros (9/32) meaningfully changed RR estimates (online supplement) .

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Using evidence from all 16 trials, the NMA estimates indicated increased risk with increased intensity. NMA results indicated a 14% non-significant increase between placebo and moderate intensity therapy (Table 2), a 359% significant increase in CK elevation between moderate and high intensity (RR=4.59, 95% CI: 2.32,9.10; p<0.0001), and a 425% significant increase between placebo and high intensity (RR=5.25, 95% CI: 2.29,12.03; p<0.0001). Results were consistent across trials (I^2=7%, Q p=0.37) and direct and indirect RR estimates were not significantly different (p=0.57). The pooled RD between moderate and high intensity therapy was significantly different from zero and the NNH was 527. The pooled RD between high intensity therapy and placebo also was significant and the NNH was 589. There were no outliers in the NMA analysis. Although results were homogeneous with the simvastatin 80 mg trials, exclusion of these trials meaningfully reduced risk associated with statin therapy between moderate and high intensity and between placebo and high intensity therapy; and smaller zero replacement values increased risk estimates (online supplement).

DISCUSSION

A novel contribution of this study was the application of NMA to estimate the dose-response effect of statin therapy on muscle symptoms using clinically-meaningful categories of treatment intensity. The NMA RR estimates closely paralleled the direct estimates, indicating reliability of estimates and increased risk with high intensity statin therapy. The network meta-analyses provide information about risk by utilizing all available evidence, whereas traditional meta-analyses are limited only to direct, head-to-head comparisons. For patient-reported symptoms, there were non-significant

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increases in SAMS between placebo and moderate intensity therapy and significant increases between moderate and high intensity therapy. Because simvastatin 80mg therapy is now restricted because of muscle injury,[51] analyses also were run with and without those trials. This did not meaningfully affect results for patient-reported outcomes. Rhabdomyolysis and elevated CK also showed increased risk with higher intensity, but because of low incidence (with 25-50% zero cells) and inconsistency across sensitivity analyses, results were inconclusive.

Double-blinded RCTs and traditional meta-analyses[3,48,49] suggest no significant increase in risk of muscle adverse events with statin therapy. Since most evidence comes from moderate intensity trials, possible adverse effects of high intensity therapy may be masked in aggregate estimates. In this study, high intensity therapy and focused definitions of patient-reported muscle problems detected higher risk. However, the absolute excess of SAMS was less than 1% for all outcomes. In previous meta-analyses, absolute excess of muscle problems also was small, but non-significant.[3,49] The 2016 meta-analysis estimated risk for extreme outcomes (myopathy and rhabdomyolysis), but did not analyze patient reports of milder SAMS that we present and that concern patients. We did not code for myopathy as an outcome, because we did not have access to patient-level data and could not determine if elevated CK co-occurred with myalgia.

Direct lower-higher dose comparisons in individual RCTs were not consistent, e.g., the SEARCH[10] and A to Z trials found a significant increase in CK and the TNT trial[12] did

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not. A NMA that compared dosage increments within brands[50] suggested no systematic increase in risk for myalgia or discontinuation with higher dosages. These negative findings may have been due to smaller sample sizes, smaller dosage increments in restricted comparisons, or exclusion of the simvastatin 80 mg trials.[50] In this study, results were homogeneous including the simvastatin 80mg trials and indicated high intensity therapy significantly increased myalgia compared to placebo even after their exclusion. The previous NMA did identify a dose-response relationship between statin dose and mildly elevated CK (2-3x ULN), but only for lovastatin and simvastatin.[50] CK>10xULN may be more interpretable than modest elevations, and in this study it was significantly increased with high-intensity statin therapy. While removal of 80mg simvastatin trials had little effect on patient-reported symptoms, their exclusion resulted in smaller non-significant increases in risk for elevated CK. It is unclear if simvastatin 80mg was responsible for the significant increases in CK.

A practical question concerns how large an excess of cases might be observed with statin therapy for myalgia/pain, attrition due to muscle problems, and elevated CK or rhabdomyolysis. Although estimates based on observational studies suggest that incidence of mild SAMS might be as high as 30% among statin users,[52] RCTs suggest a much lower rate. In this study, pooled risk estimates suggested that for each 173 patients on high intensity therapy one additional patient will experience statin-caused myalgia and for each 218 patients one additional patient will discontinue therapy due to muscle problems compared to those on moderate intensity therapy. This represents numerous patients who are at greatest risk for major vascular events, as these are often

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higher risk patients. Discontinuation of statins in the elderly (>75 yrs) may result in 33% increased risk of a cardiovascular event within 3 months [53] and adherence to statins in those 65 and older may reduce mortality by a third.[54]

Myalgias and attrition due to SAMS are important outcomes for the average patient, but have not received as much attention as rhabdomyolysis and myopathy. This study provides evidence that while blinded, moderate intensity statin-takers did not report significantly more general muscle problems or myalgias, but those on high intensity therapy did. Because many myalgia cases occurred without CK elevation increases, this also serves as evidence that SAMS occur in the absence of large elevations in CK. Clinicians with patients who are "statin intolerant" may consider encouraging the patient to first decrease intensity of statin therapy, rather than discontinuing it, in light of these findings.

This analysis also contributes to the "nocebo" debate. A large, unblinded follow-up of RCT patients suggested SAMS are expectation-related.[29] They observed an incidence of 2.03% and 2.00% muscle-related adverse events in statin and placebo groups, respectively, when double-blinded (HR=1.03) and 1.26% and 1.00% in the statin and usual care groups when unblinded (HR=1.41).[29] Both comparisons indicate absolute differences less than 1%. A recent N-of-1 trial[55]also found minimal differences in muscle symptoms when patients took statin versus placebo (blinded), but significantly more muscle symptoms when taking a placebo versus taking nothing (unblinded). Both nocebo and causal effects are small, although they can result in increased SAMS. In a

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clinical setting, SAMS with moderate intensity therapy may be the result of patient expectations, but with high intensity therapy SAMS may be due to expectations and statin therapy. Intensity of treatment and patient expectations may need to be considered before making changes in statin therapy in the absence of CK elevations.

A limitation of study-level meta-analyses is that definitions,[56] assessment, and variable reporting of muscle-related outcomes may differ across studies. Aggregation of heterogeneous outcomes and estimated outcomes (e.g., myopathy) not explicitly reported by investigators can mask an effect. Protocol differences may partially explain incidence disparities across studies. However, use of the RR to estimate effect size minimizes bias due to between-study variations in protocol (e.g., using a symptom checklist versus recording spontaneous mention of symptoms and then categorizing responses).

Estimates in this analysis may have under-estimated SAMS by excluding patients with statin hypersensitivity, as four studies[12,37,40,45] (n=48,950) employed statin "washout" phases and eight trials[24,25,30,32,34–37,47] (n=34,042) excluded patients with known statin hypersensitivity. Collins et al. noted that "statin hypersensitivity" exclusion was a rare occurrence across these trials, as almost all patients enrolled were statin-naïve at screening.[3] The risk of attrition due to SAMS and rhabdomyolysis was actually highest in SEARCH, where an eight week long, active run-in phase was conducted,[3,10] although no patients were excluded for elevated muscle enzymes.[10] Also,an N-of-1 trial in patients who were considering stopping or who had stopped statin therapy because of

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muscle symptoms found no difference in severity of patient-reported muscle symptoms between statin and placebo groups.[57] Because simvastatin 80 mg trials comprise a high proportion of high intensity treatment evidence, this may limit interpretation of CK and rhabdomyolysis risk. Also, adverse events may have been increased due to the presence of co-morbidities; only three trials studied healthy adults (n=30,756).[26,37,46] A final limitation is that although risk estimates are based on the best available evidence and should provide relatively unbiased estimates, confidence intervals and alpha significance levels may be approximate due to multiple comparisons.

Conclusion

Statins likely cause SAMS, but at much lower rates than observational data suggest. We found significant increases in risk for patient-reported muscle problems on high-intensity statins. Clinically-reported SAMS likely represent a combination of expectation bias and true adverse effects.

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Contributorship Statement:

The first author (JD) was responsible for the design and implementation of the study analyses. He was one coder in selecting studies for inclusion, compiled the data for the outcomes of interest, analyzed the data in R, and is responsible for the final manuscript in its entirety. SW (Faculty PI) was responsible for the oversight and implementation of the project. She was the second coder for all trials and offered guidance and support in all decisions regarding design and implementation of the analysis.

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Competing Interests:

None to disclose

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Data Sharing Statement:

All data used in this analysis is available in the online supplement.

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Figure Legend:

Figure 1: Any Muscle Problems

Figure 2: Myalgia or Pain

Figure 3: Attrition Due to Muscle Symptoms

Figure 4: Rhabdomyolysis

Figure 5: CK >10x Upper Limit of Normal

TABLE 1: DESCRIPTION OF THE TRIALS

TABLE 2: RELATIVE RISK AND RISK DIFFERENCE RESULTS FOR COMPARISONS OF TREATMENT INTENSITY PAIRS

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TABLE 1: DESCRIPTION OF THE TRIALS

Trial Name	Total sample size	Special Population	Permit Prior statin†	Ave age	Run-in Period	Median Yrs F/U
Placebo-Moderate						
4D, A20[24]	1,255	DM II, ESRD	Y, -HS	66	Placebo	4.0
4S, S20-S40[25]	4,444	MI or angina	Y, -HS	59	Placebo	5.4
AFCAPS, L20-L40[26]	6,605	Healthy adults	N	58	Placebo+diet	5.2
ALERT, F40-F80[27]	2,094	Renal Trans	N	50	None	5.4
ASCOT, A10[28,29]	10,810	HTN+CVD risk	N	63	Not statin	3.3
ASPEN, A10[30]	2,410	DM II	Y, -HS	61	Placebo	4.0
AURORA, R10[31]	2,767	ESRD	N	64	Placebo	3.2
CARDS, A10[32,33]	2,838	DM II	Y, -HS	62	Placebo	4.0
CARE, P40[34]	4,159	MI	Y, -HS	59	Placebo	5.0
CORONA, R10[35]	5,011	ESRD	Y, -HS	73	Placebo	2.7
GISSI-HF, R10[36]	4,574	CHF	Y, -HS	68	None	3.9
HOPE-3, R10[37]	6,349	Healthy, CVD Risk	Y, -HS	66	Statin	5.6
LIPID, P40[38]	9,014	MI or angina	Y	62*	Placebo+diet	6.0 (*mean*)
LIPS, F80[39]	1,640	Coronary percut. intervention	Y	60	None	3.9
MRC/BHF (HPS), S40[40,41]	20,536	CHD/CHD Risk	N	64	Placebo, then statin	5 (*mean*)
PROSPER, P40[42]	5,804	Elderly, CHD risk	Y	75	Placebo	3.2 (*mean*)
WOSCOPS, P40[43,44]	6,604	Healthy males	Y	55	None	4.9 (*mean*)
Placebo-High						
JUPITER, R20[46]	17,802	Healthy adults	N	66	Placebo	1.9††
SPARCL, A80[45]	4,731	CVA/TIA	Y	63	None	4.9
TRACE, A40[47]	3,002	RA	N, -HS	61	None	2.5
Moderate-High						
A to Z, S40-S80 vs 0-S20[11]	4,497	Acute Coronary Syndrome	N	61	None	1.98
PROVE-IT, A80 vs P40[13]	4,162	Acute Coronary Syndrome	Y, if <80mg	58	None	2.0 (mean)
SEARCH, S80 vs S20[10]	12,064	MI	Y	64	Statin+ Placebo	6.7
TNT, A80 vs A10[12]	10,001	CHD	Y	61	Statin	4.9

*Median

†Y=Yes, N=No, -HS=statin hypersensitivity exclusion

†† Trial was designed for two years of follow-up, but met study end points and terminated the blinded portion of the study earlier.

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TABLE 2: RELATIVE RISK AND RISK DIFFERENCE RESULTS FOR COMPARISONS OF TREATMENT INTENSITY PAIRS

	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
Any Probs	1.010 (0.988,1.033)	0.000 (-0.001,0.001)	--	1.039 (1.004,1.075)	0.004 (-0.000,0.008)	--	1.049 (1.010,1.089)	0.004 (-0.001, 0.008)	--
Myalgia	1.090 (.9997,1.188)	0.001 (-0.000,0.001)	--	1.041 (1.001,1.083)	0.006 (0.001, 0.010)	173	1.134 (1.046,1.230)	0.007 (0.002, 0.011)	182
Attrition	1.127 (0.931,1.364)	0.001 (-000,0.001)	--	1.372 (1.091,1.726)	0.005 (0.002, 0.007)	218	1.155 (1.147,2.084)	0.005 (0.002, 0.008)	187
Rhabdo.	1.225 (0.624,2.405)	-0.000 (-0.001,0.001)	--	1.326 (0.487,3.614)	0.002 (0.001,0.003)	--	1.624 (0.579,4.553)	0.002 (0.000, 0.003)	--
CK> 10xULN	1.143 (0.686,1.905)	-0.000 (-0.001,0.001)	--	4.594 (2.320,9.098)	0.002 (0.001, 0.003)	527	5.252 (2.293,12.028)	0.002 (0.000, 0.003)	589

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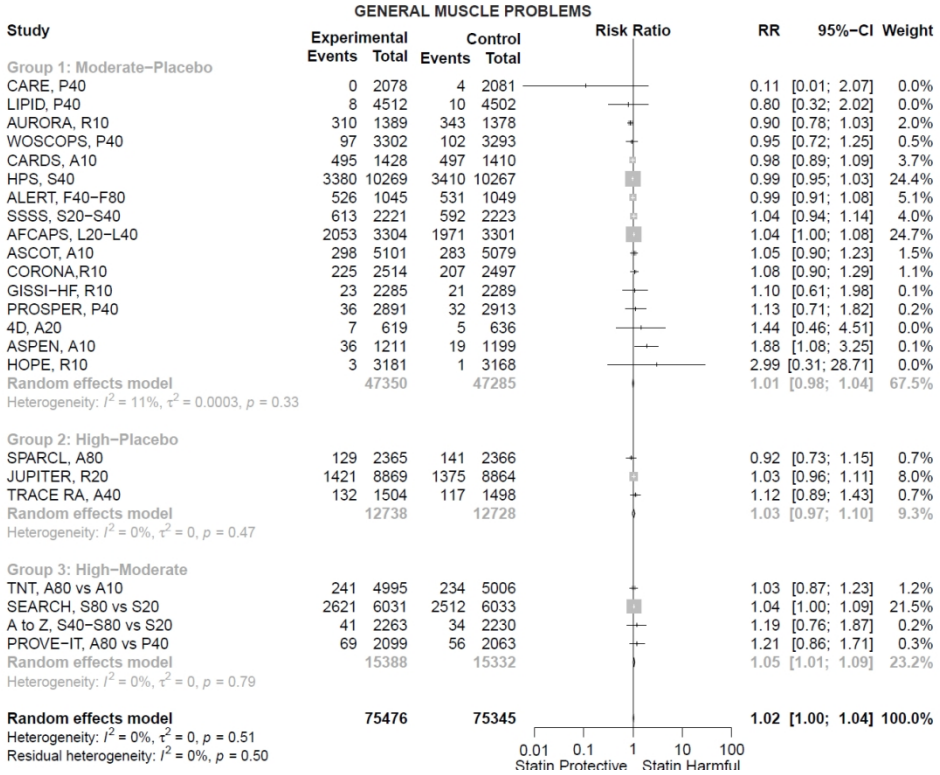

Figure 1

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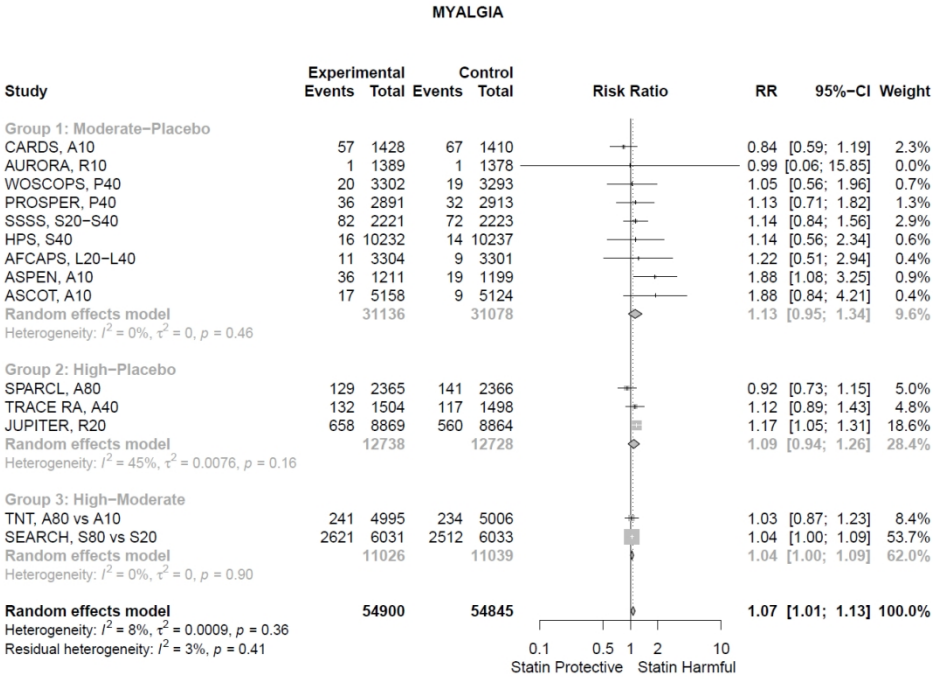

Figure 2

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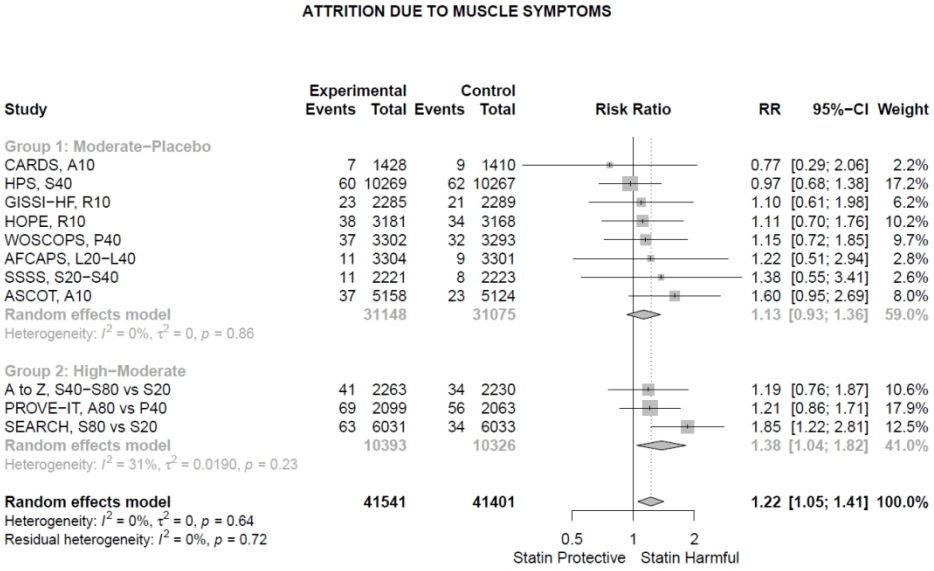

Figure 3

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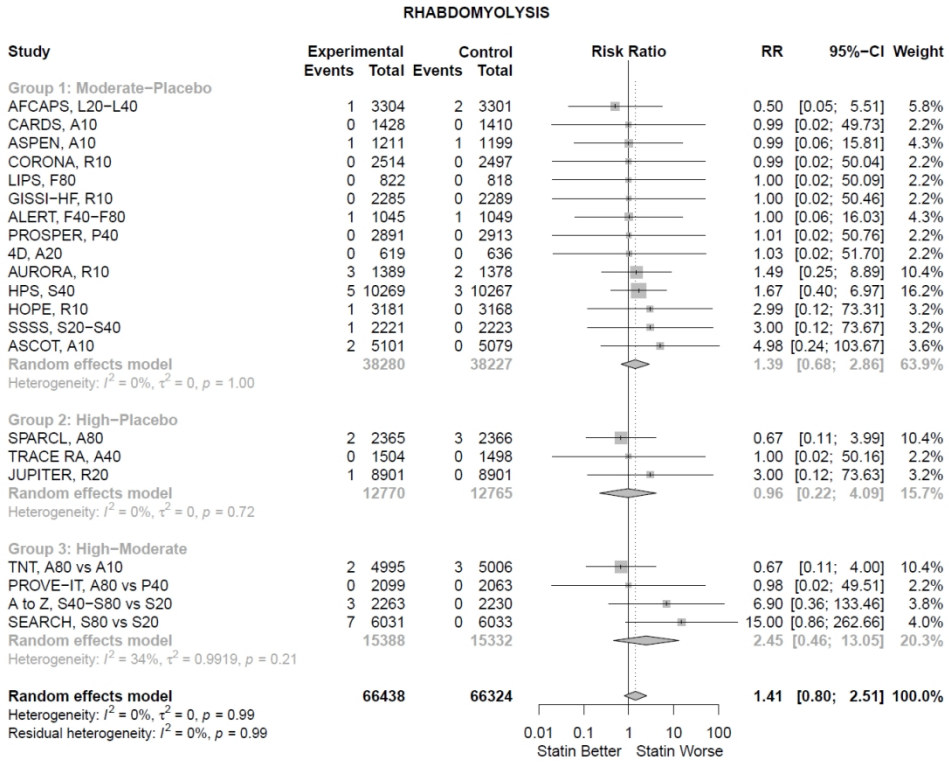

Figure 4

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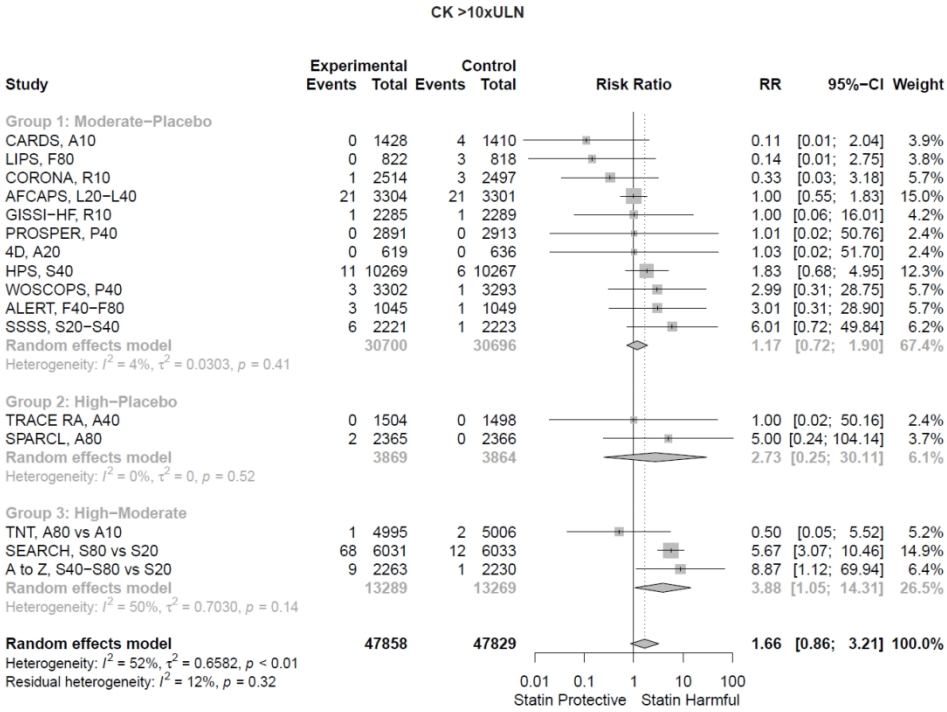

Figure 5

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INTENSITY OF STATIN THERAPY AND MUSCLE SYMPTOMS:

A NETWORK META-ANALYSIS OF 153,000 PATIENTS

J.W. Davis & S.C. Weller

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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

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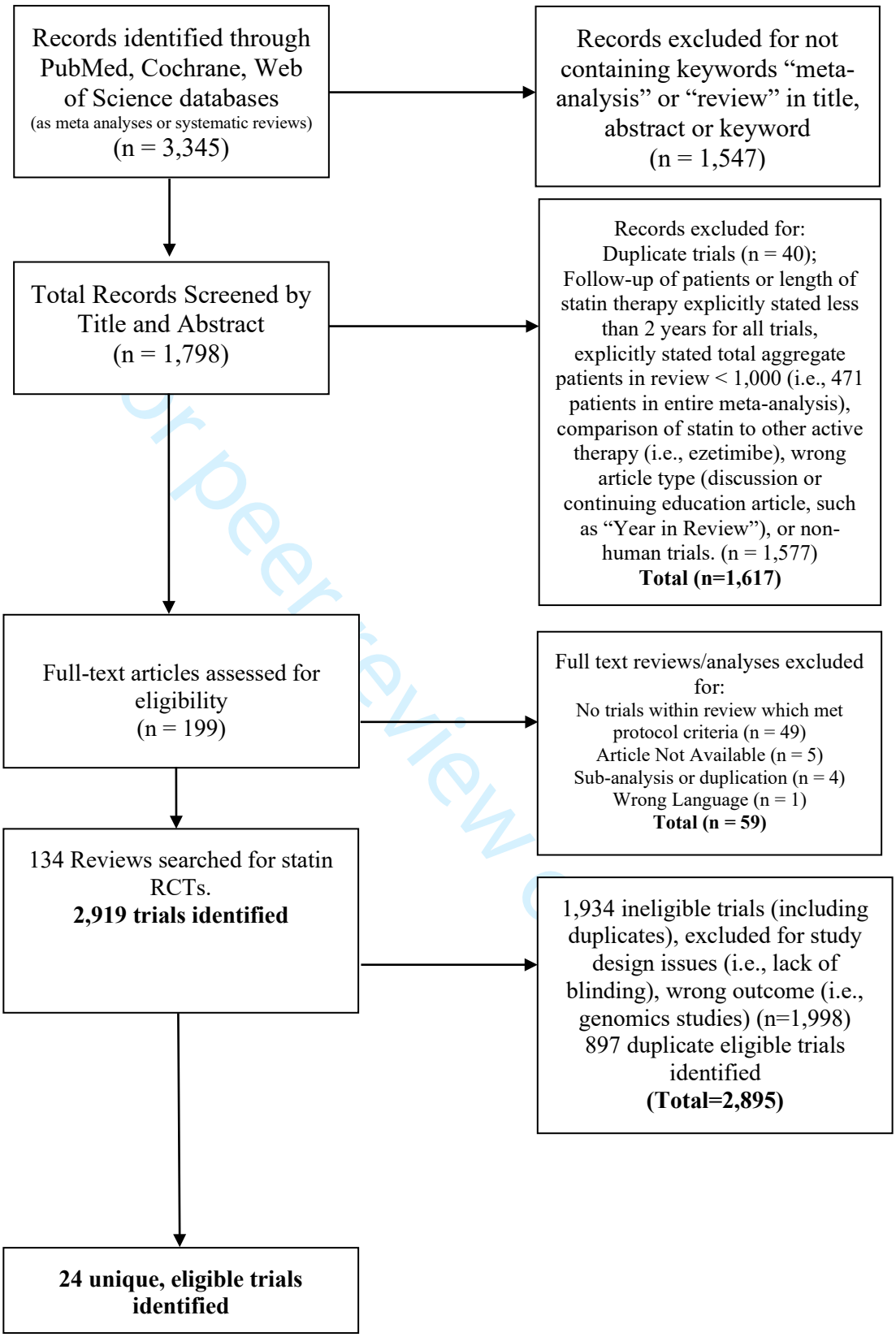
PRISMA FLOW SHEET



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.

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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.

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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	(ci 981 or ci981 or liptonorm).mp.	123	Advanced
24	(6 methylcompactin or mk 803 or mk803 or mevinolin or monacolin k).mp.	602	Advanced
25	(mevalotol 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 ellsor or eptastatin or lipemol or lipiat or llostat 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	(201801* or 201802* or 201803* or 201804* or 201805* or 201806* or 201807* or 201808* or 201809* or 201810* or 201811*).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

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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 ($p>0.05$)

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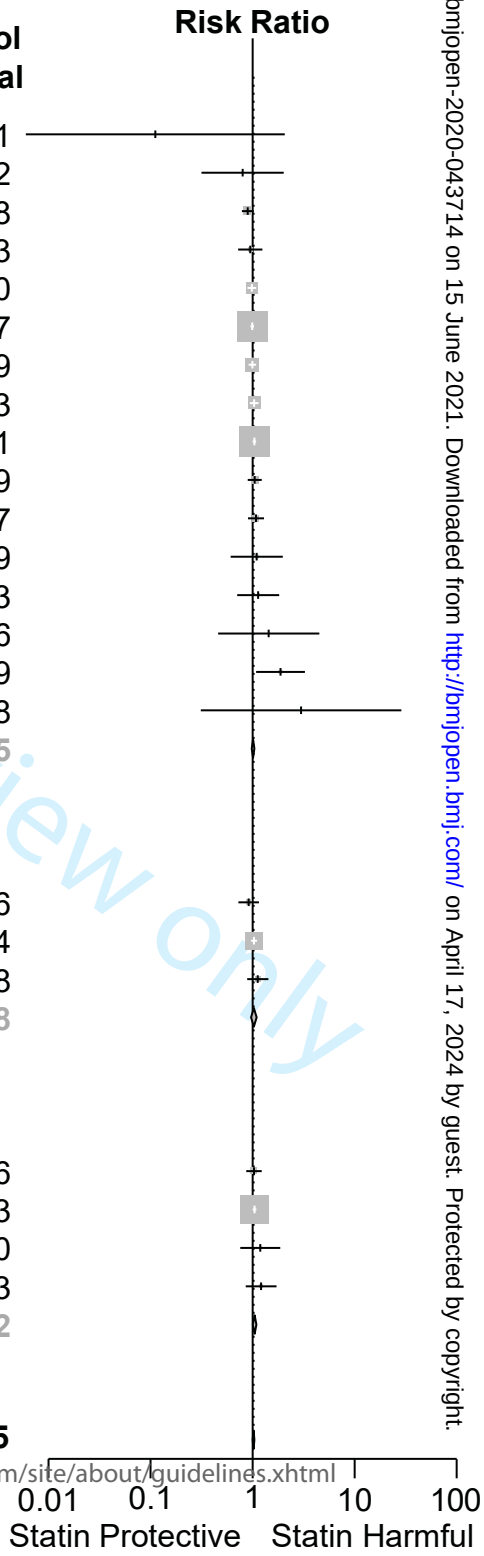
ANY MUSCLE PROBLEMS: Meta-Analysis Forest plot with data.

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							



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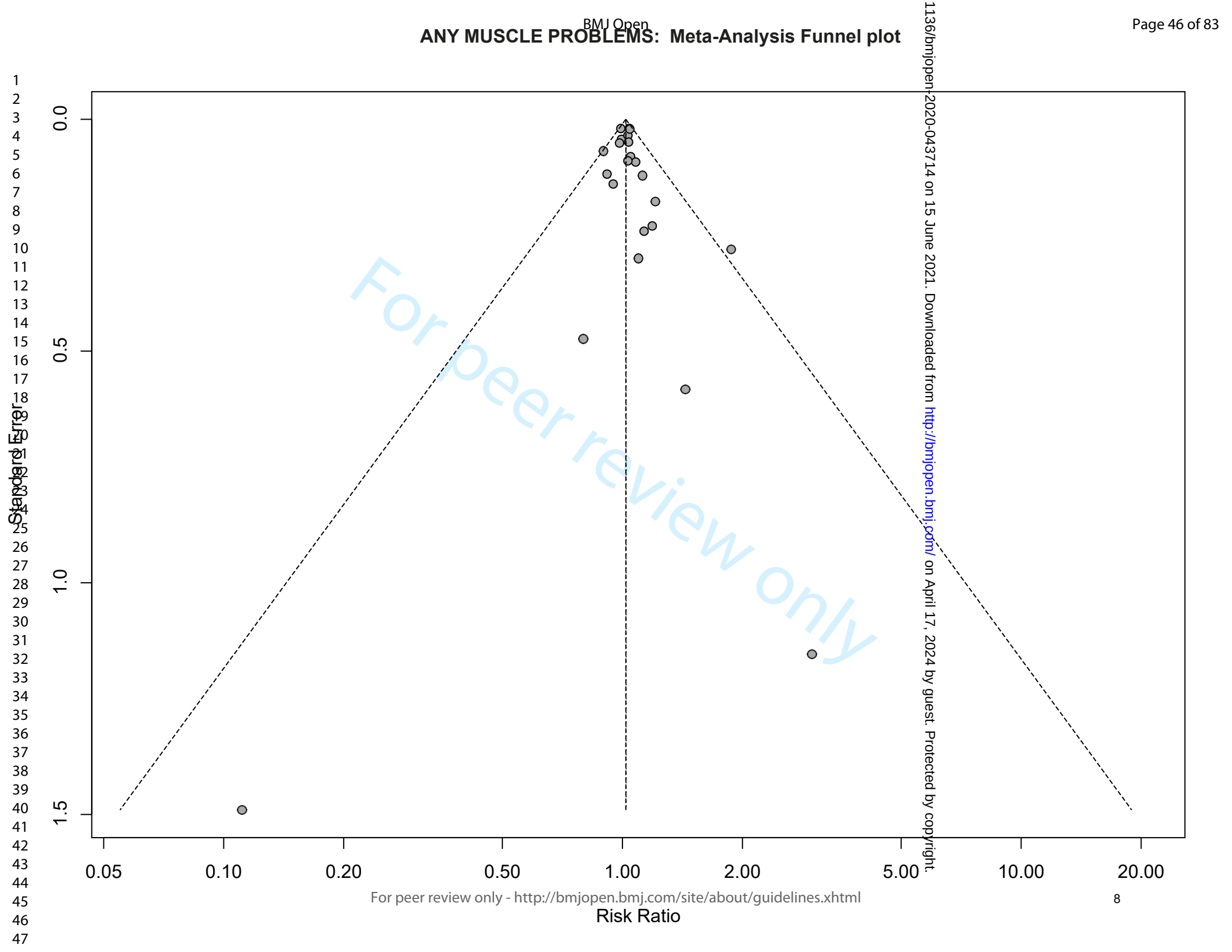

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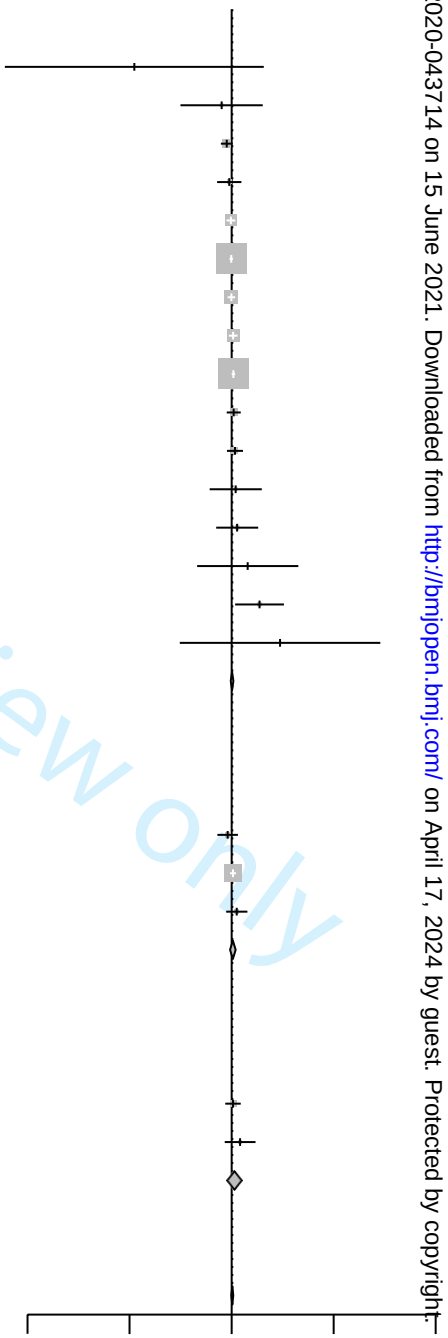
GENERAL MUSCLE PROBLEMS. Outliers excluded. Forest plot.

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]	0.1%
AURORA, R10	310	1389	343	1378	0.90	[0.78; 1.03]	2.6%
WOSCOPS, P40	97	3302	102	3293	0.95	[0.72; 1.25]	0.6%
CARDS, A10	495	1428	497	1410	0.98	[0.89; 1.09]	4.7%
HPS, S40	3380	10269	3410	10267	0.99	[0.95; 1.03]	31.1%
ALERT, F40−F80	526	1045	531	1049	0.99	[0.91; 1.08]	6.5%
SSSS, S20−S40	613	2221	592	2223	1.04	[0.94; 1.14]	5.1%
AFCAPS, L20−L40	2053	3304	1971	3301	1.04	[1.00; 1.08]	31.6%
ASCOT, A10	298	5101	283	5079	1.05	[0.90; 1.23]	1.9%
CORONA,R10	225	2514	207	2497	1.08	[0.90; 1.29]	1.4%
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]	0.2%
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]**	**86.2%**
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]	0.9%
JUPITER, R20	1421	8869	1375	8864	1.03	[0.96; 1.11]	10.2%
TRACE RA, A40	132	1504	117	1498	1.12	[0.89; 1.43]	0.8%
Random effects model		**12738**		**12728**	**1.03**	**[0.97; 1.10]**	**11.9%**
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]	1.5%
PROVE−IT, A80 vs P40	69	2099	56	2063	1.21	[0.86; 1.71]	0.4%
Random effects model		**7094**		**7069**	**1.07**	**[0.91; 1.25]**	**1.9%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.42							
Random effects model		**67182**		**67082**	**1.02**	**[0.99; 1.04]**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.49							
Residual heterogeneity: I^2 = 5%, p = 0.40							



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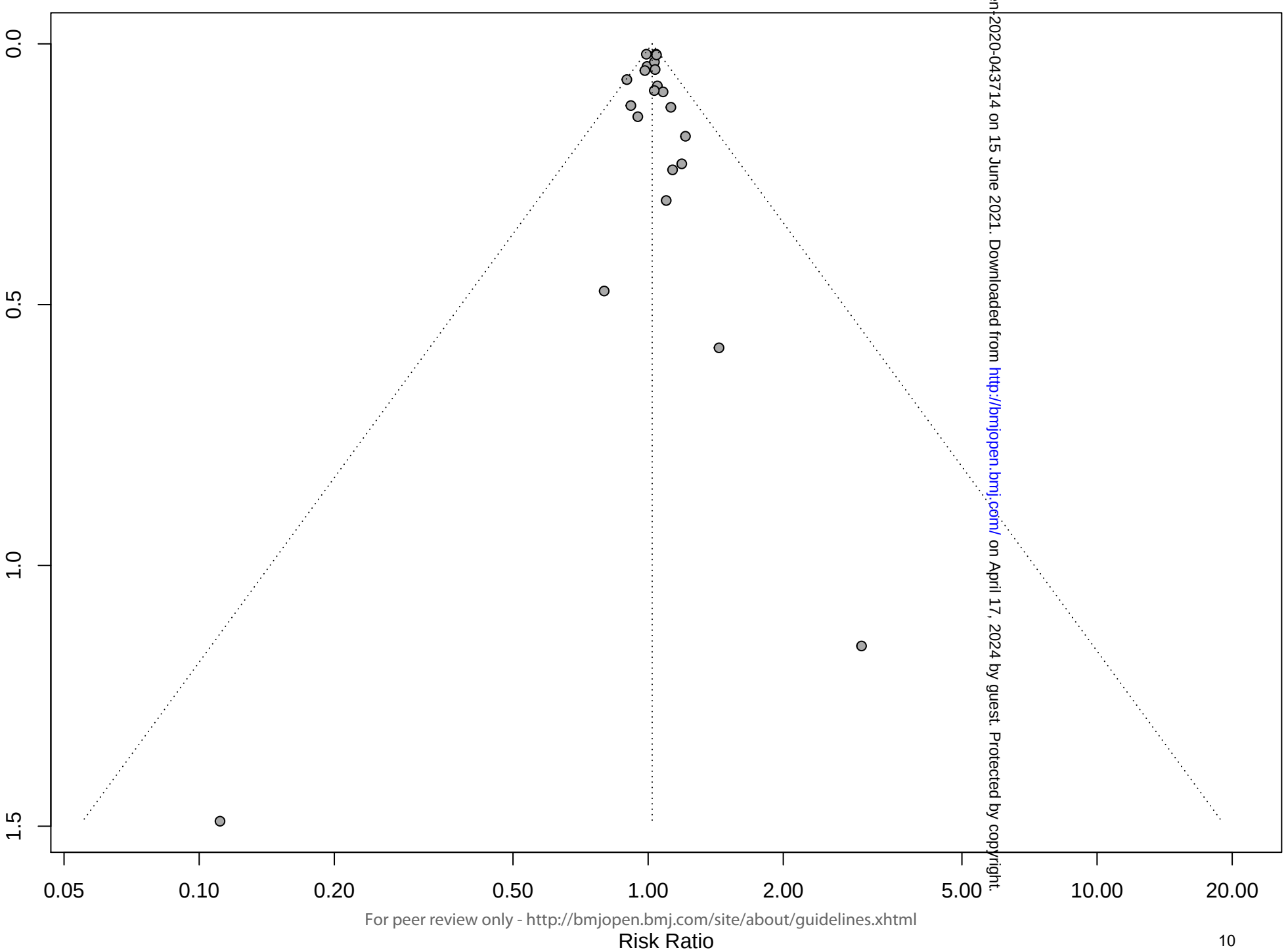
GENERAL MUSCLE PROBLEMS. Outliers excluded. Funnel plot.



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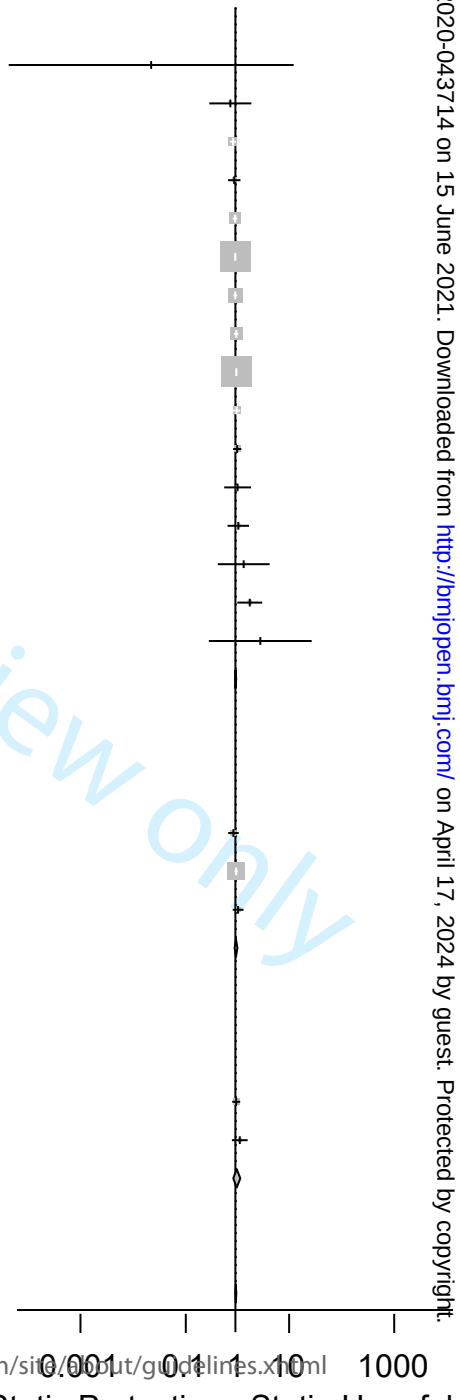
GENERAL MUSCLE PROBLEMS. Continuity Correction = 0.1. Forest plot.

Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	Weight
Group 1: Moderate−Placebo							
CARE, P40	0	2078	4	2081	0.02	[0.00; 12.94]	0.0%
LIPID, P40	8	4512	10	4502	0.80	[0.32; 2.02]	0.1%
AURORA, R10	310	1389	343	1378	0.90	[0.78; 1.03]	2.6%
WOSCOPS, P40	97	3302	102	3293	0.95	[0.72; 1.25]	0.6%
CARDS, A10	495	1428	497	1410	0.98	[0.89; 1.09]	4.7%
HPS, S40	3380	10269	3410	10267	0.99	[0.95; 1.03]	31.1%
ALERT, F40−F80	526	1045	531	1049	0.99	[0.91; 1.08]	6.6%
SSSS, S20−S40	613	2221	592	2223	1.04	[0.94; 1.14]	5.1%
AFCAPS, L20−L40	2053	3304	1971	3301	1.04	[1.00; 1.08]	31.6%
ASCOT, A10	298	5101	283	5079	1.05	[0.90; 1.23]	1.9%
CORONA,R10	225	2514	207	2497	1.08	[0.90; 1.29]	1.4%
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]	0.2%
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]**	**86.2%**
Heterogeneity: I^2 = 6%, τ^2 = 0.0002, p = 0.39							
Group 2: High−Placebo							
SPARCL, A80	129	2365	141	2366	0.92	[0.73; 1.15]	0.9%
JUPITER, R20	1421	8869	1375	8864	1.03	[0.96; 1.11]	10.2%
TRACE RA, A40	132	1504	117	1498	1.12	[0.89; 1.43]	0.8%
Random effects model		**12738**		**12728**	**1.03**	**[0.97; 1.10]**	**11.9%**
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]	1.5%
PROVE−IT, A80 vs P40	69	2099	56	2063	1.21	[0.86; 1.71]	0.4%
Random effects model		**7094**		**7069**	**1.07**	**[0.91; 1.25]**	**1.9%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.42							
Random effects model		**67182**		**67082**	**1.02**	**[0.99; 1.04]**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.55							
Residual heterogeneity: I^2 = 0%, p = 0.45							



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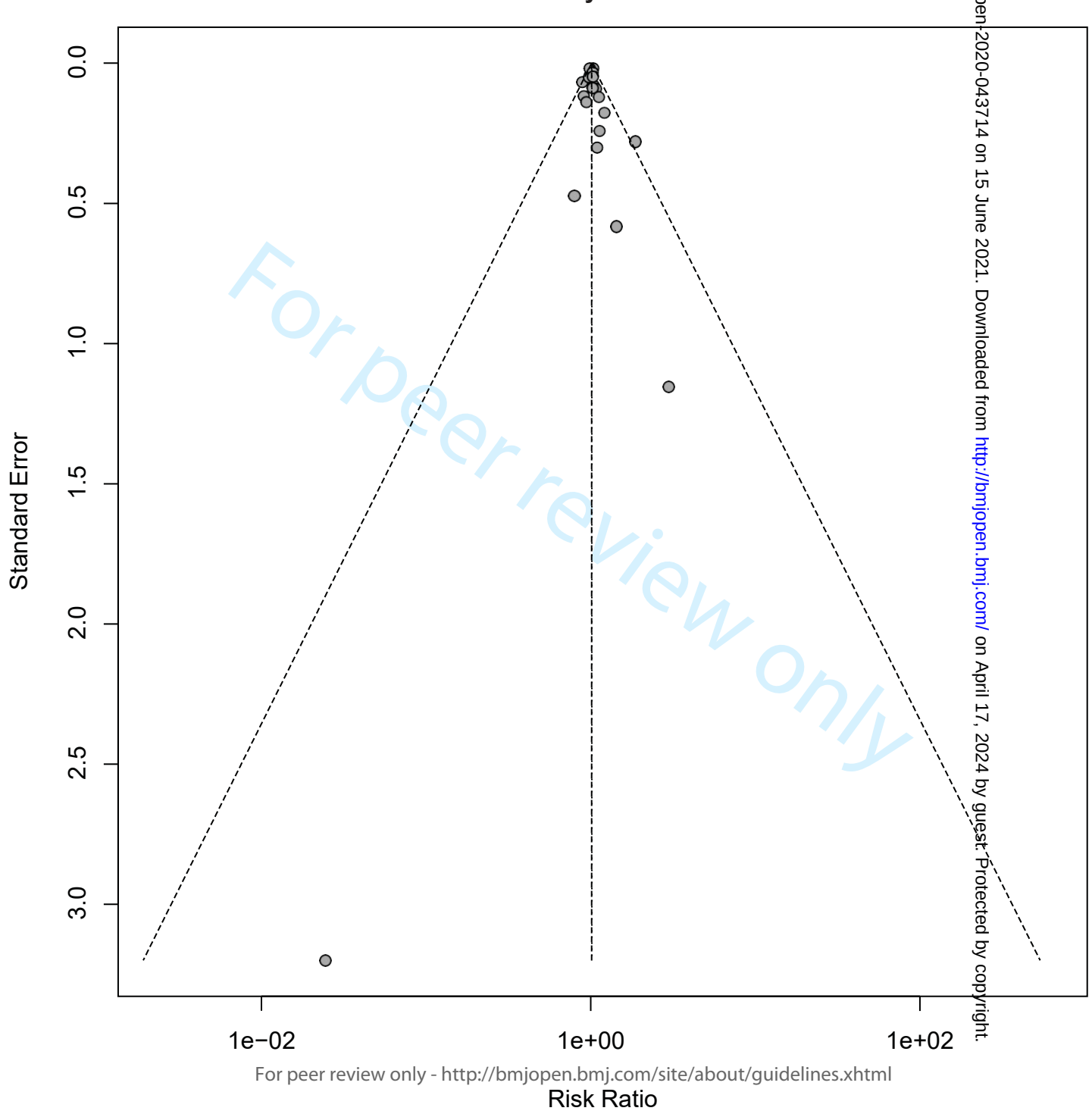

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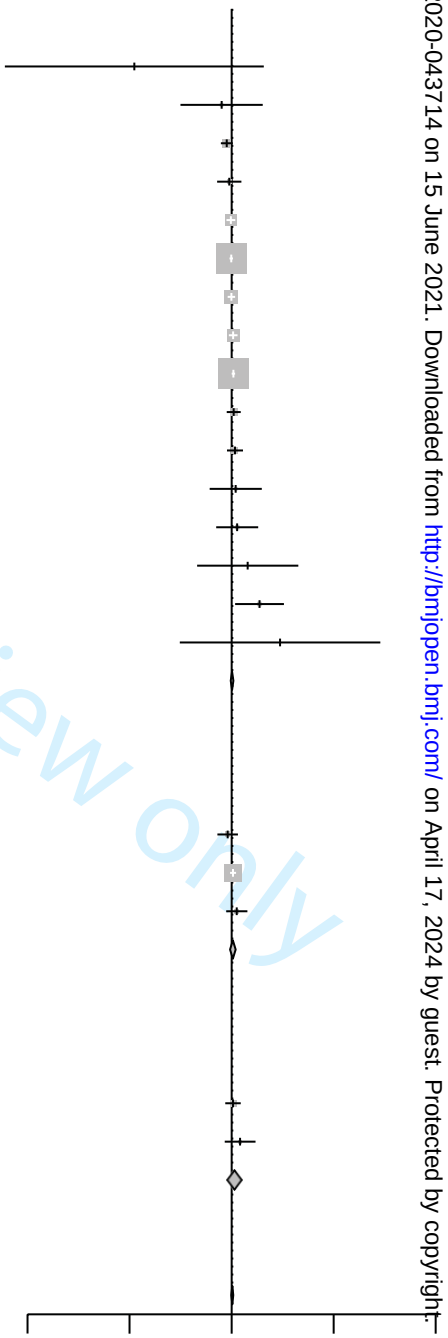
ANY MUSCLE PROBLEMS: Meta-Analysis Forest plot excluding simvastatin 80 mg trials.

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]	0.1%
AURORA, R10	310	1389	343	1378	0.90	[0.78; 1.03]	2.6%
WOSCOPS, P40	97	3302	102	3293	0.95	[0.72; 1.25]	0.6%
CARDS, A10	495	1428	497	1410	0.98	[0.89; 1.09]	4.7%
HPS, S40	3380	10269	3410	10267	0.99	[0.95; 1.03]	31.1%
ALERT, F40−F80	526	1045	531	1049	0.99	[0.91; 1.08]	6.5%
SSSS, S20−S40	613	2221	592	2223	1.04	[0.94; 1.14]	5.1%
AFCAPS, L20−L40	2053	3304	1971	3301	1.04	[1.00; 1.08]	31.6%
ASCOT, A10	298	5101	283	5079	1.05	[0.90; 1.23]	1.9%
CORONA,R10	225	2514	207	2497	1.08	[0.90; 1.29]	1.4%
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]	0.2%
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]**	**86.2%**
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]	0.9%
JUPITER, R20	1421	8869	1375	8864	1.03	[0.96; 1.11]	10.2%
TRACE RA, A40	132	1504	117	1498	1.12	[0.89; 1.43]	0.8%
Random effects model		**12738**		**12728**	**1.03**	**[0.97; 1.10]**	**11.9%**
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]	1.5%
PROVE−IT, A80 vs P40	69	2099	56	2063	1.21	[0.86; 1.71]	0.4%
Random effects model		**7094**		**7069**	**1.07**	**[0.91; 1.25]**	**1.9%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.42							
Random effects model		**67182**		**67082**	**1.02**	**[0.99; 1.04]**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.49							
Residual heterogeneity: I^2 = 5%, p = 0.40							



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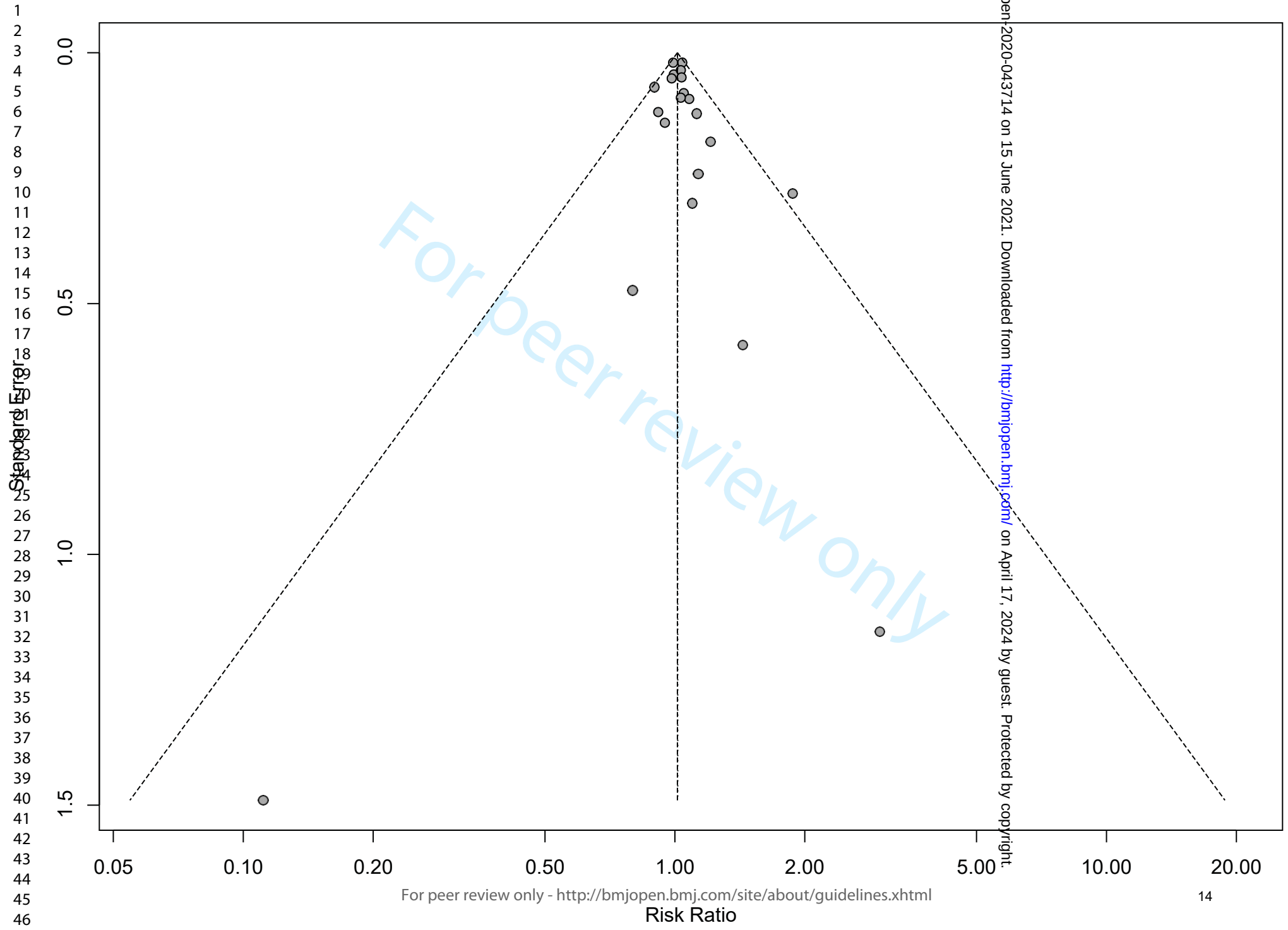
ANY MUSCLE PROBLEMS: Meta-Analysis Funnel plot excluding simvastatin 80 mg trials



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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)	--

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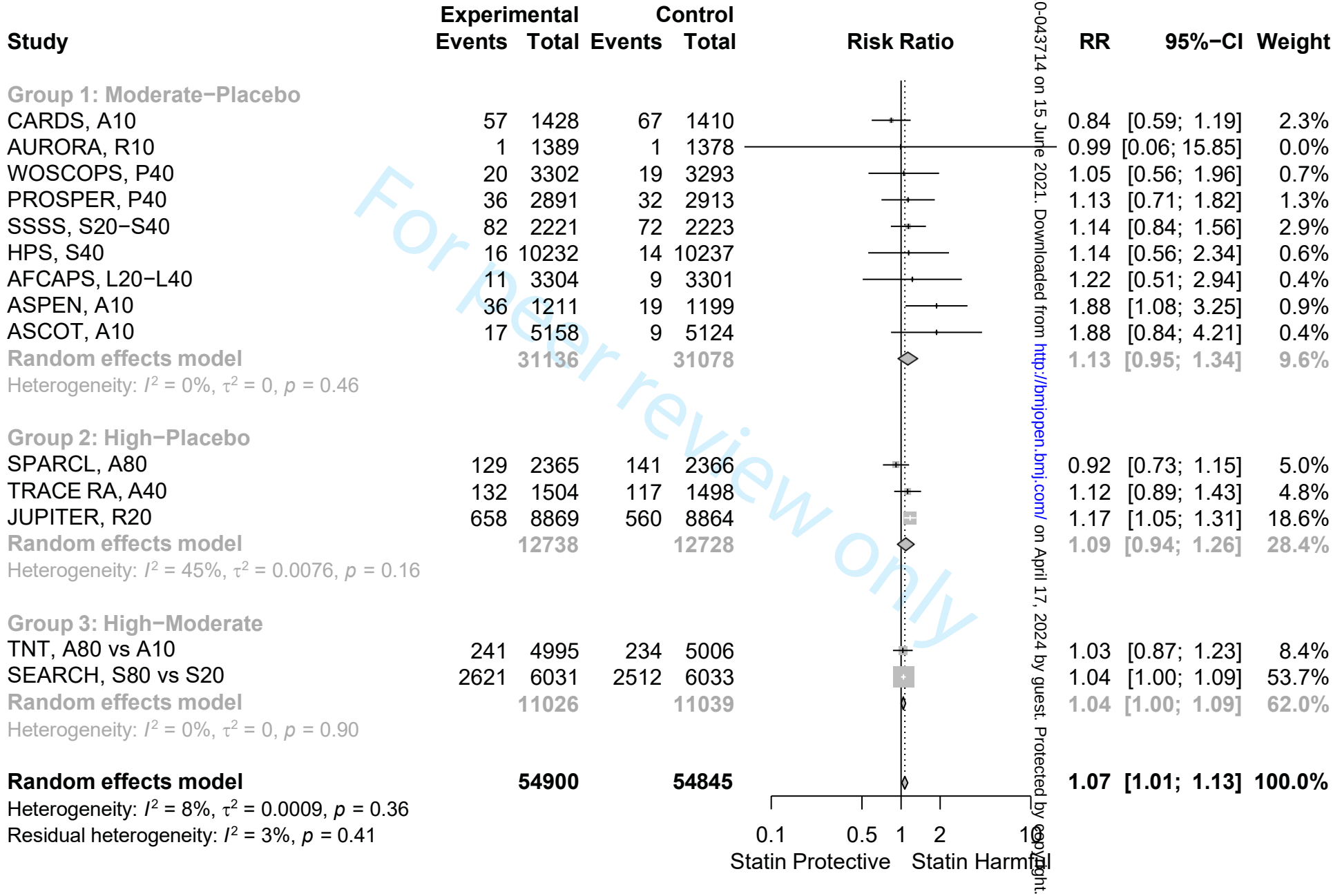
MYALGIA OR PAIN : Meta-Analysis Forest plot with data



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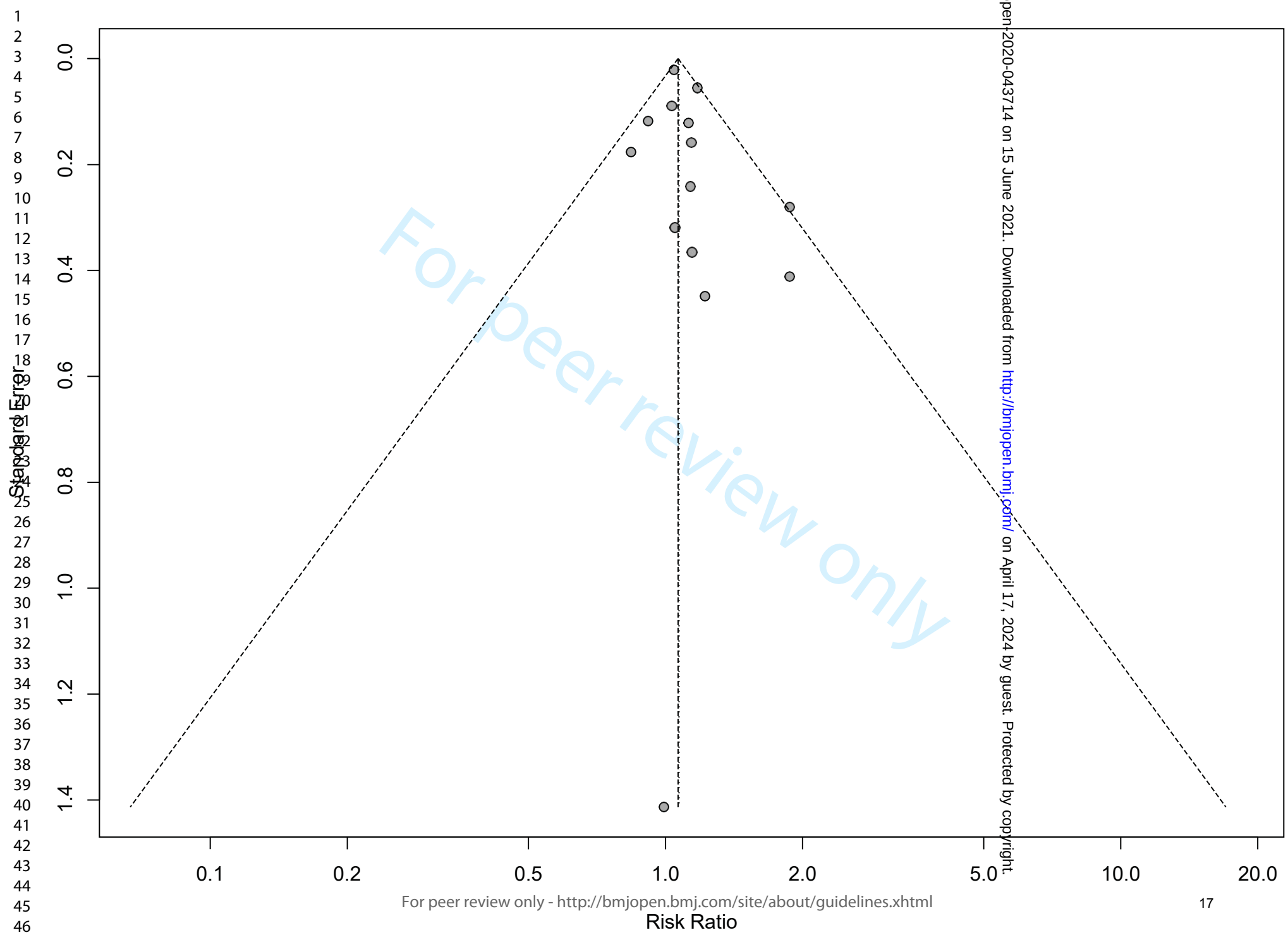

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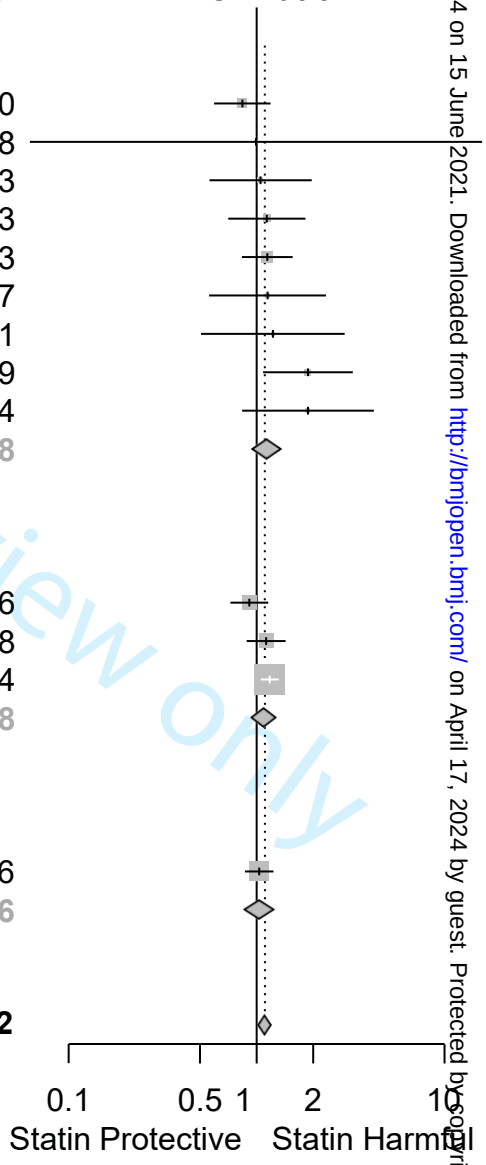
MYALGIA OR PAIN: Meta-Analysis Forest plot excluding simvastatin 80 mg trials.



Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	Weight
Group 1: Moderate−Placebo							
CARDS, A10	57	1428	67	1410	0.84	[0.59; 1.19]	4.6%
AURORA, R10	1	1389	1	1378	0.99	[0.06; 15.85]	0.1%
WOSCOPS, P40	20	3302	19	3293	1.05	[0.56; 1.96]	1.4%
PROSPER, P40	36	2891	32	2913	1.13	[0.71; 1.82]	2.5%
SSSS, S20−S40	82	2221	72	2223	1.14	[0.84; 1.56]	5.7%
HPS, S40	16	10232	14	10237	1.14	[0.56; 2.34]	1.1%
AFCAPS, L20−L40	11	3304	9	3301	1.22	[0.51; 2.94]	0.7%
ASPEN, A10	36	1211	19	1199	1.88	[1.08; 3.25]	1.8%
ASCOT, A10	17	5158	9	5124	1.88	[0.84; 4.21]	0.8%
Random effects model		**31136**		**31078**	**1.13**	**[0.95; 1.34]**	**18.7%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.46							
Group 2: High−Placebo							
SPARCL, A80	129	2365	141	2366	0.92	[0.73; 1.15]	10.1%
TRACE RA, A40	132	1504	117	1498	1.12	[0.89; 1.43]	9.6%
JUPITER, R20	658	8869	560	8864	1.17	[1.05; 1.31]	44.0%
Random effects model		**12738**		**12728**	**1.09**	**[0.94; 1.26]**	**63.8%**
Heterogeneity: I^2 = 45%, τ^2 = 0.0076, p = 0.16							
Group 3: High−Moderate							
TNT, A80 vs A10	241	4995	234	5006	1.03	[0.87; 1.23]	17.5%
Random effects model		**4995**		**5006**	**1.03**	**[0.87; 1.23]**	**17.5%**
Heterogeneity: not applicable							
Random effects model		**48869**		**48812**	**1.11**	**[1.03; 1.19]**	**100.0%**
Heterogeneity: I^2 = 1%, τ^2 = 0.0002, p = 0.44							
Residual heterogeneity: I^2 = 12%, p = 0.33							

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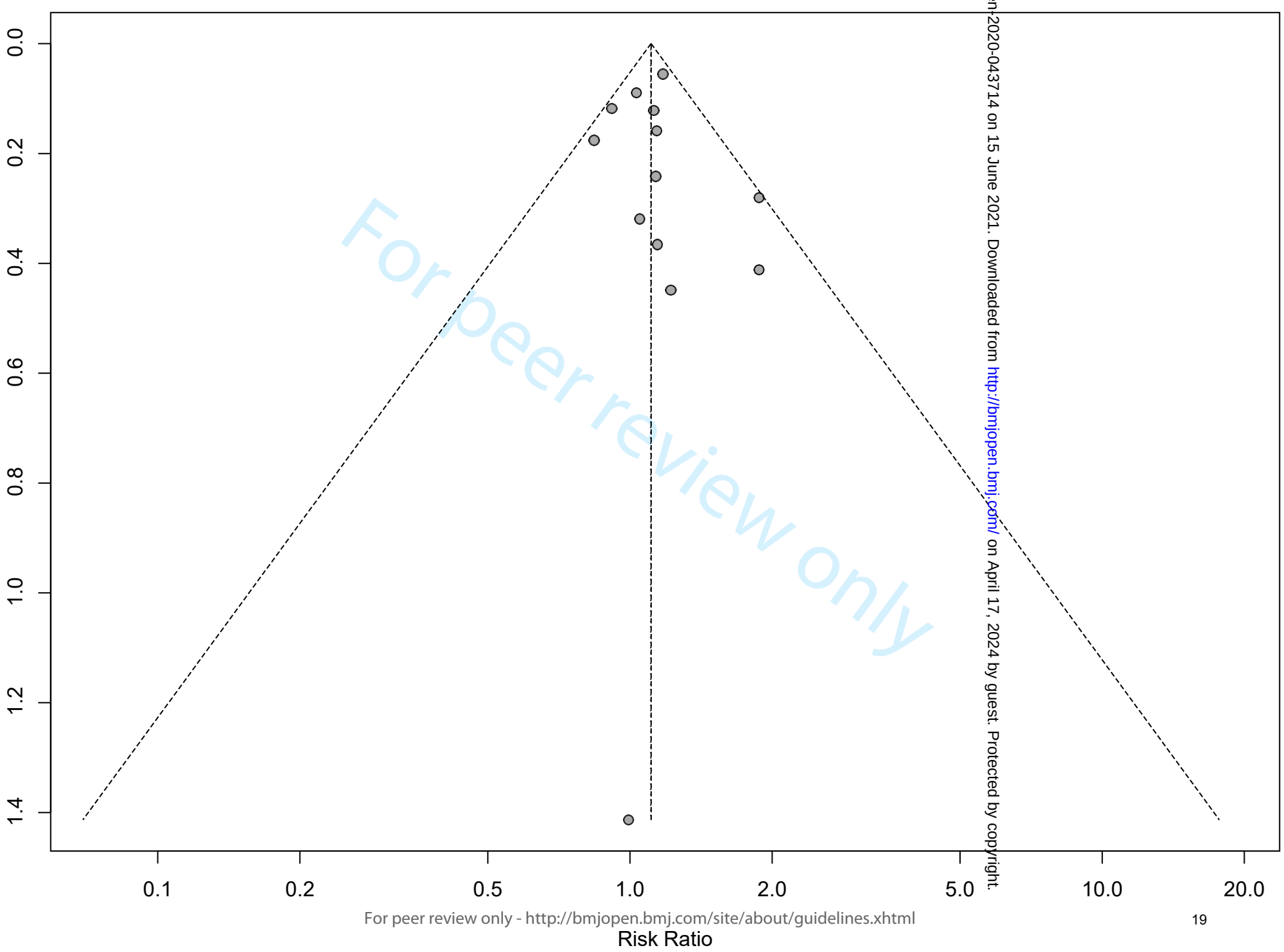
MYALGIA OR PAIN. Meta-Analysis Funnel plot excluding simvastatin 80 mg trials



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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

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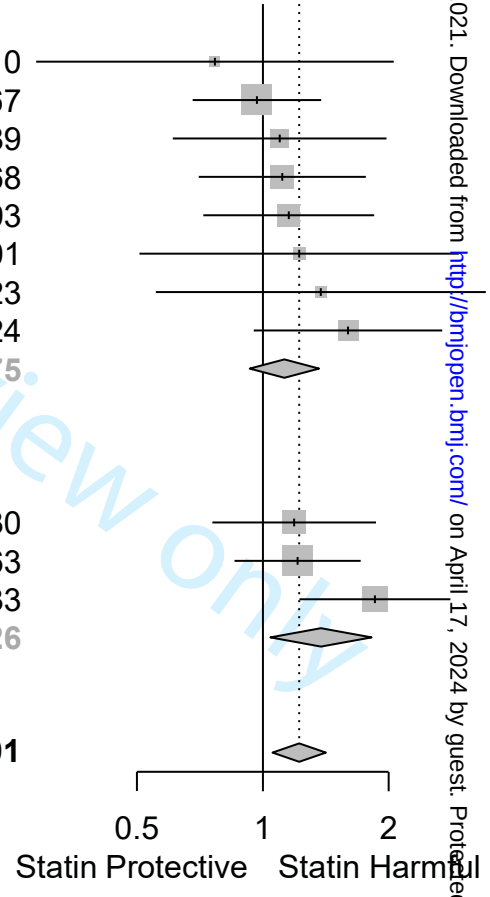
ATTRITION: Meta-Analysis Forest plot with data

Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	Weight
Group 1: Moderate−Placebo							
CARDS, A10	7	1428	9	1410	0.77	[0.29; 2.06]	2.2%
HPS, S40	60	10269	62	10267	0.97	[0.68; 1.38]	17.2%
GISSI−HF, R10	23	2285	21	2289	1.10	[0.61; 1.98]	6.2%
HOPE, R10	38	3181	34	3168	1.11	[0.70; 1.76]	10.2%
WOSCOPS, P40	37	3302	32	3293	1.15	[0.72; 1.85]	9.7%
AFCAPS, L20−L40	11	3304	9	3301	1.22	[0.51; 2.94]	2.8%
SSSS, S20−S40	11	2221	8	2223	1.38	[0.55; 3.41]	2.6%
ASCOT, A10	37	5158	23	5124	1.60	[0.95; 2.69]	8.0%
Random effects model		31148		31075	1.13	[0.93; 1.36]	59.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.86							
Group 2: High−Moderate							
A to Z, S40−S80 vs S20	41	2263	34	2230	1.19	[0.76; 1.87]	10.6%
PROVE−IT, A80 vs P40	69	2099	56	2063	1.21	[0.86; 1.71]	17.9%
SEARCH, S80 vs S20	63	6031	34	6033	1.85	[1.22; 2.81]	12.5%
Random effects model		10393		10326	1.38	[1.04; 1.82]	41.0%
Heterogeneity: I^2 = 31%, τ^2 = 0.0190, p = 0.23							
Random effects model		**41541**		**41401**	**1.22**	**[1.05; 1.41]**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.64							
Residual heterogeneity: I^2 = 0%, p = 0.72							



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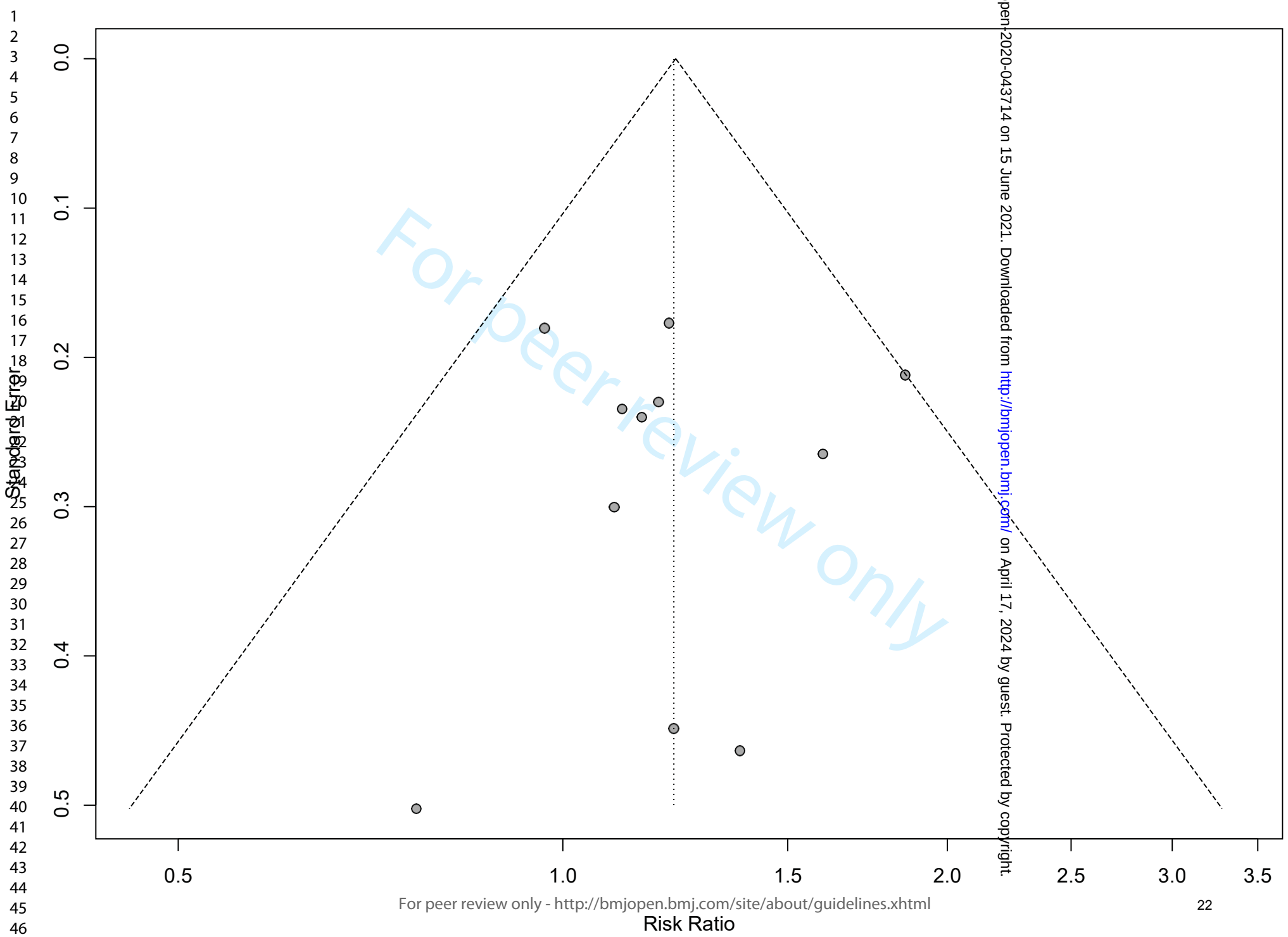
ATTRITION: Meta-Analysis Funnel plot



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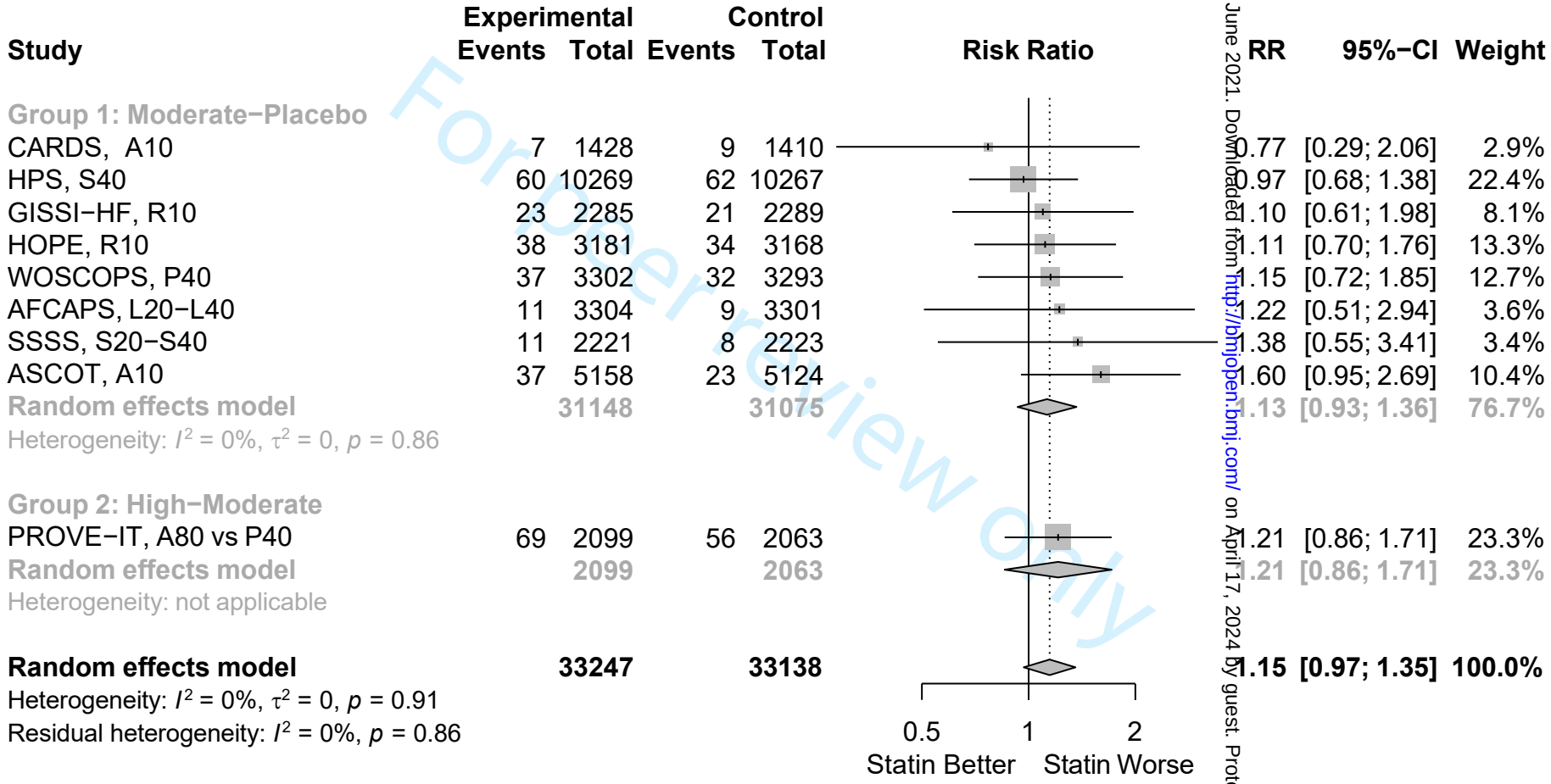
ATTRITION: Meta-Analysis Forest plot excluding simvastatin 80 mg trials.



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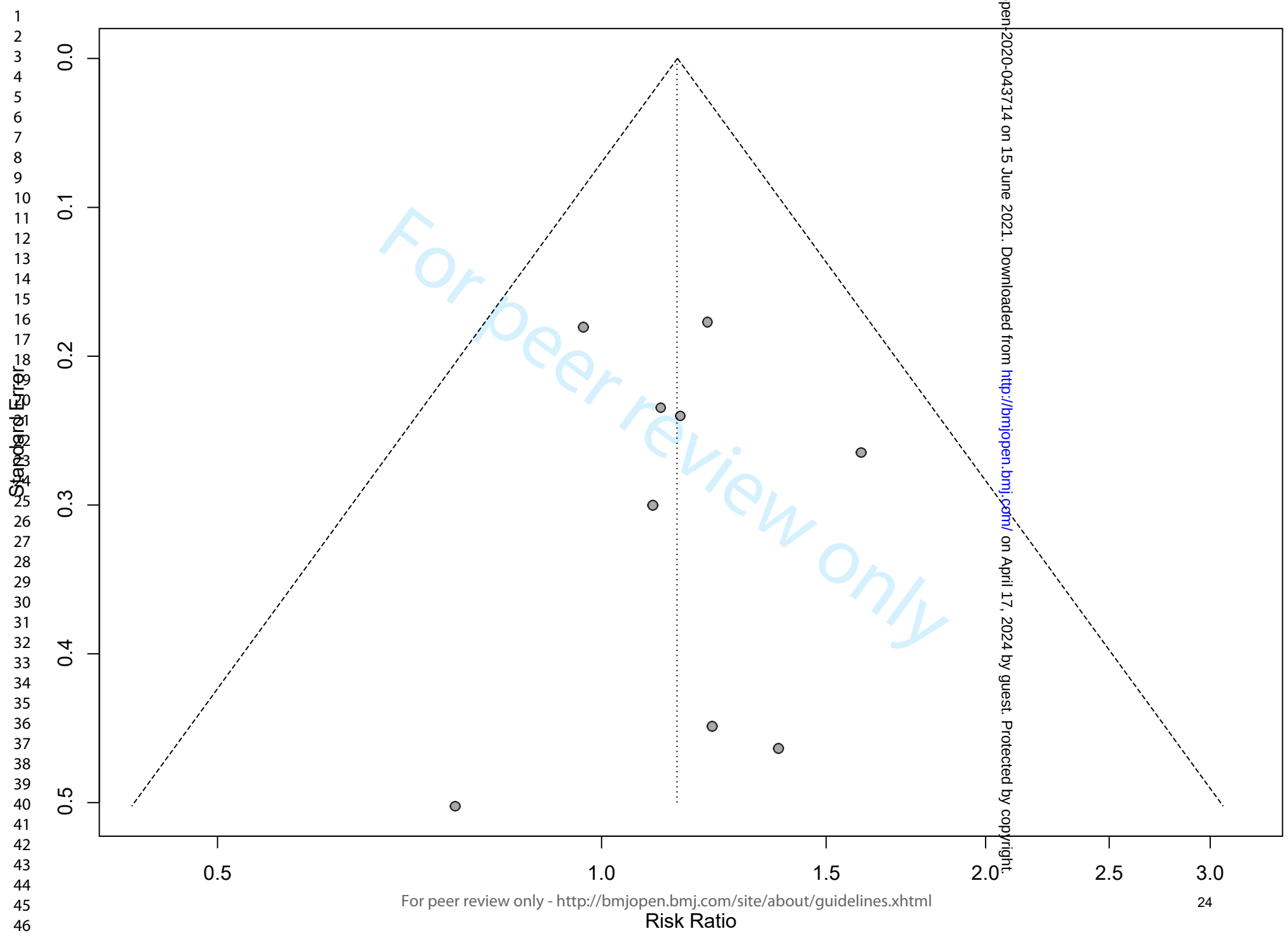
ATTRITION: Meta-Analysis Funnel plot excluding simvastatin 80 mg trials



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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*

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RHABDOMYOLYSIS: Meta-Analysis Forest Plot with Data

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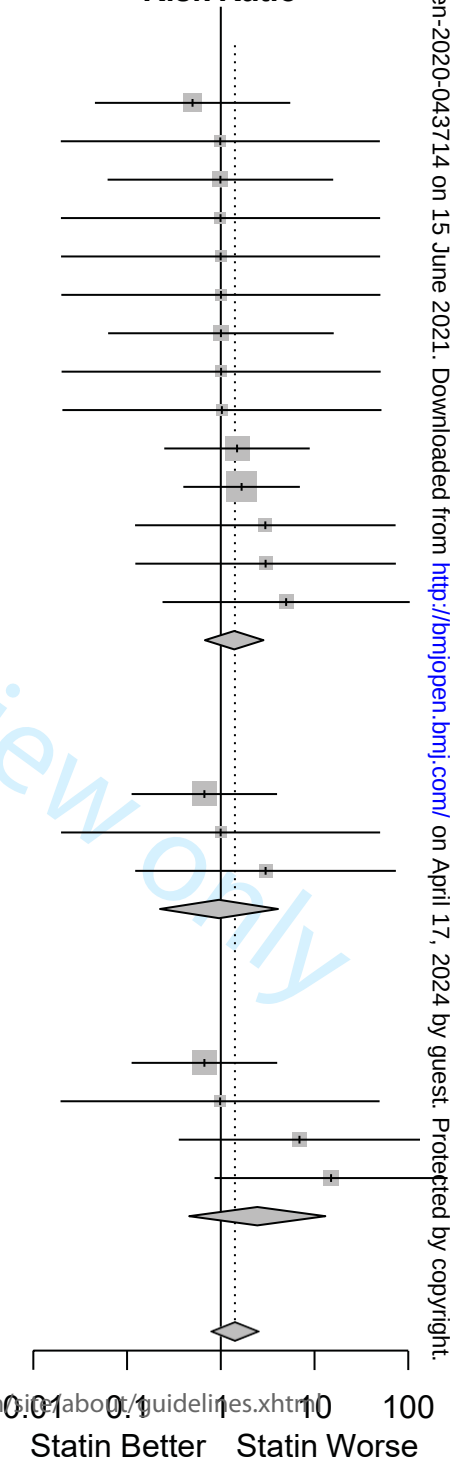
Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	Weight
Group 1: Moderate−Placebo							
AFCAPS, L20−L40	1	3304	2	3301	0.50	[0.05; 5.51]	5.8%
CARDS, A10	0	1428	0	1410	0.99	[0.02; 49.73]	2.2%
ASPEN, A10	1	1211	1	1199	0.99	[0.06; 15.81]	4.3%
CORONA, R10	0	2514	0	2497	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							



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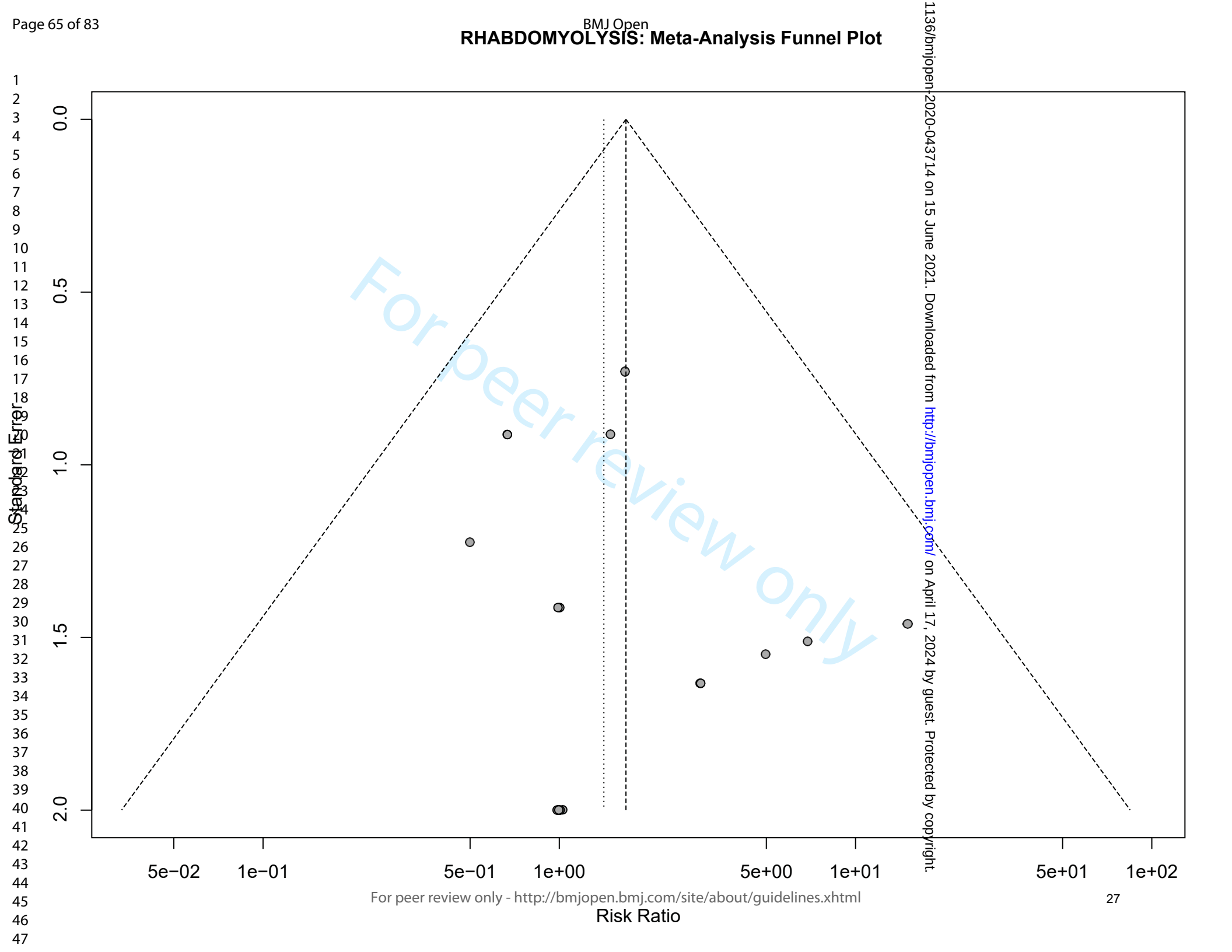

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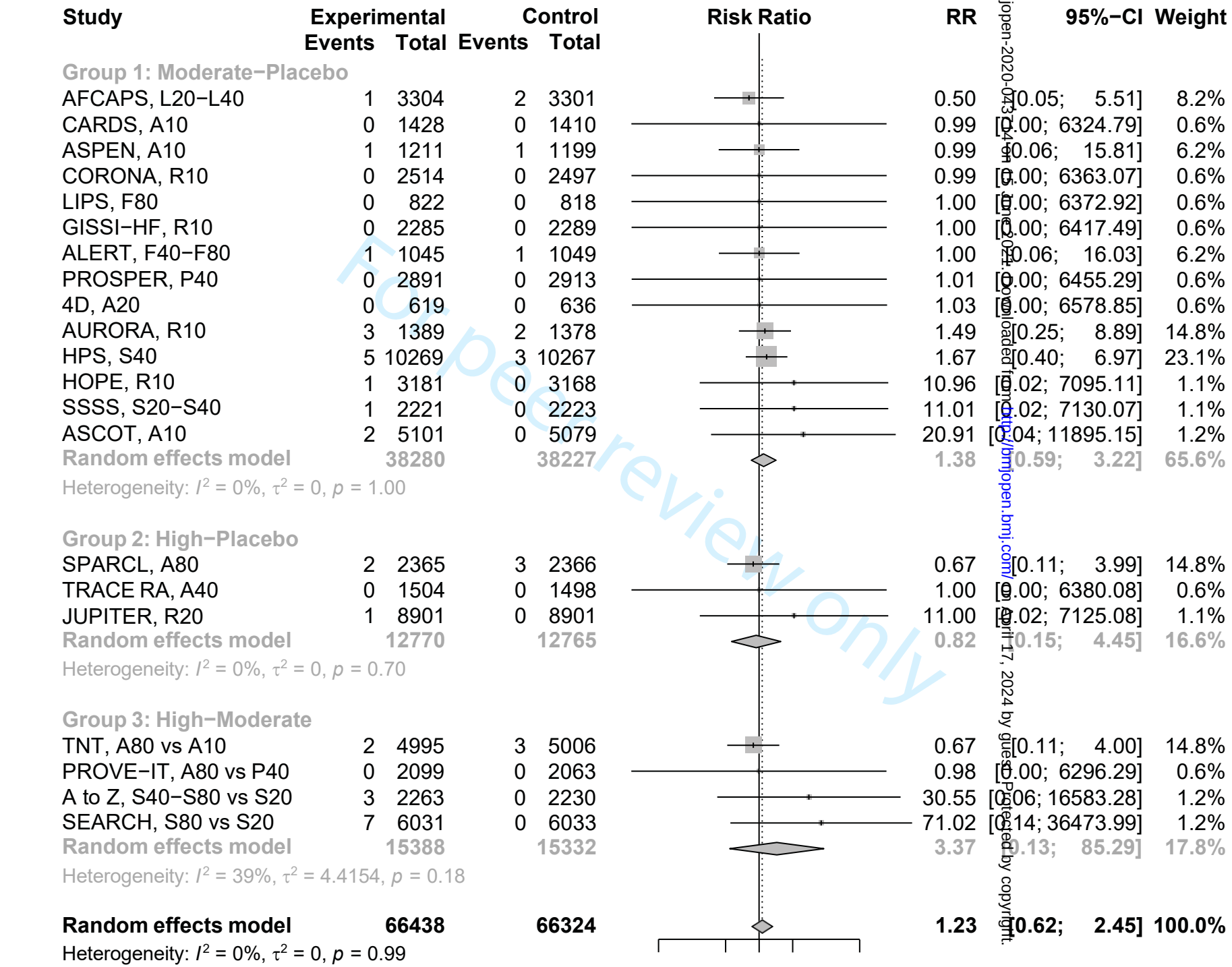
RHABDOMYOLYSIS: Meta-Analysis Forest Plot with Continuity Correction = 0.1.



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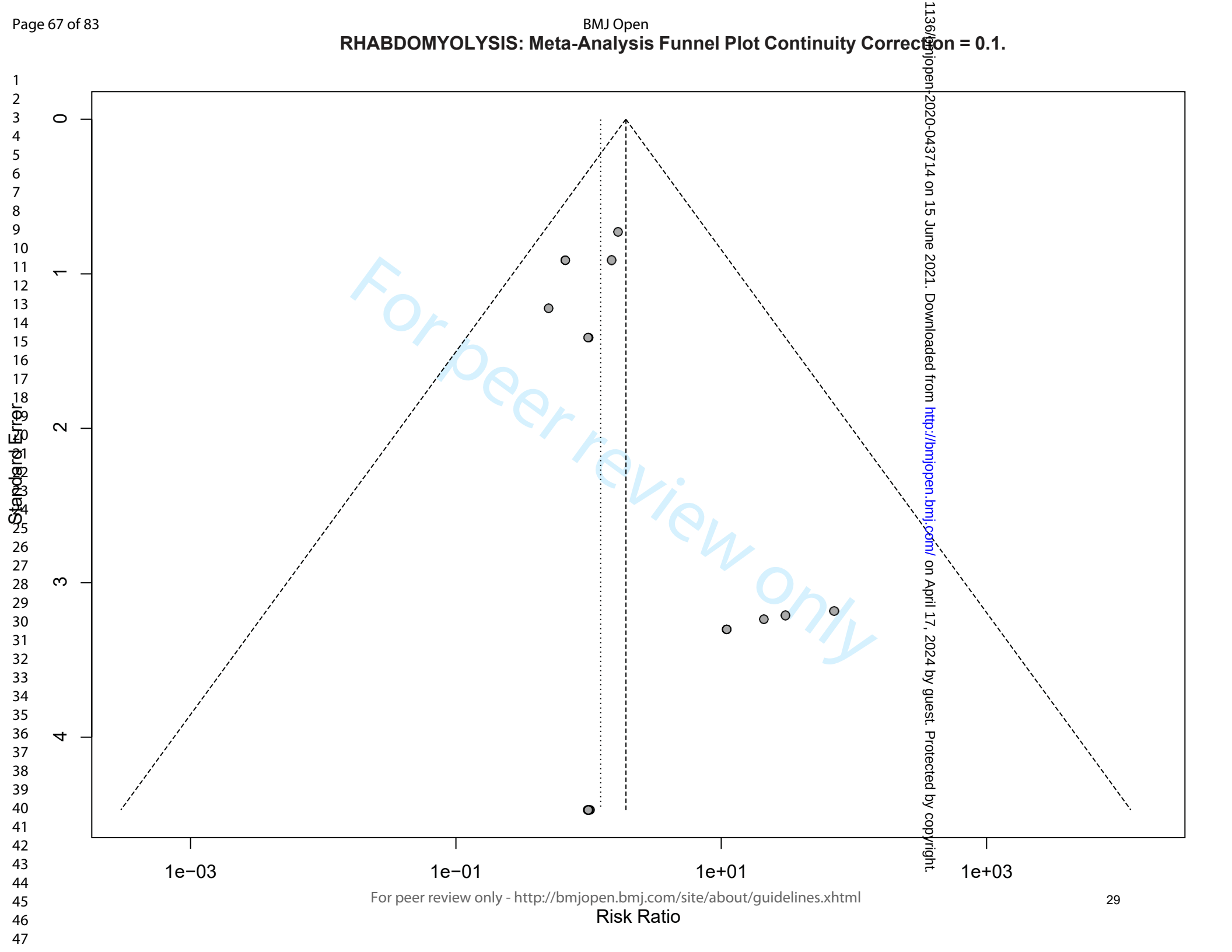

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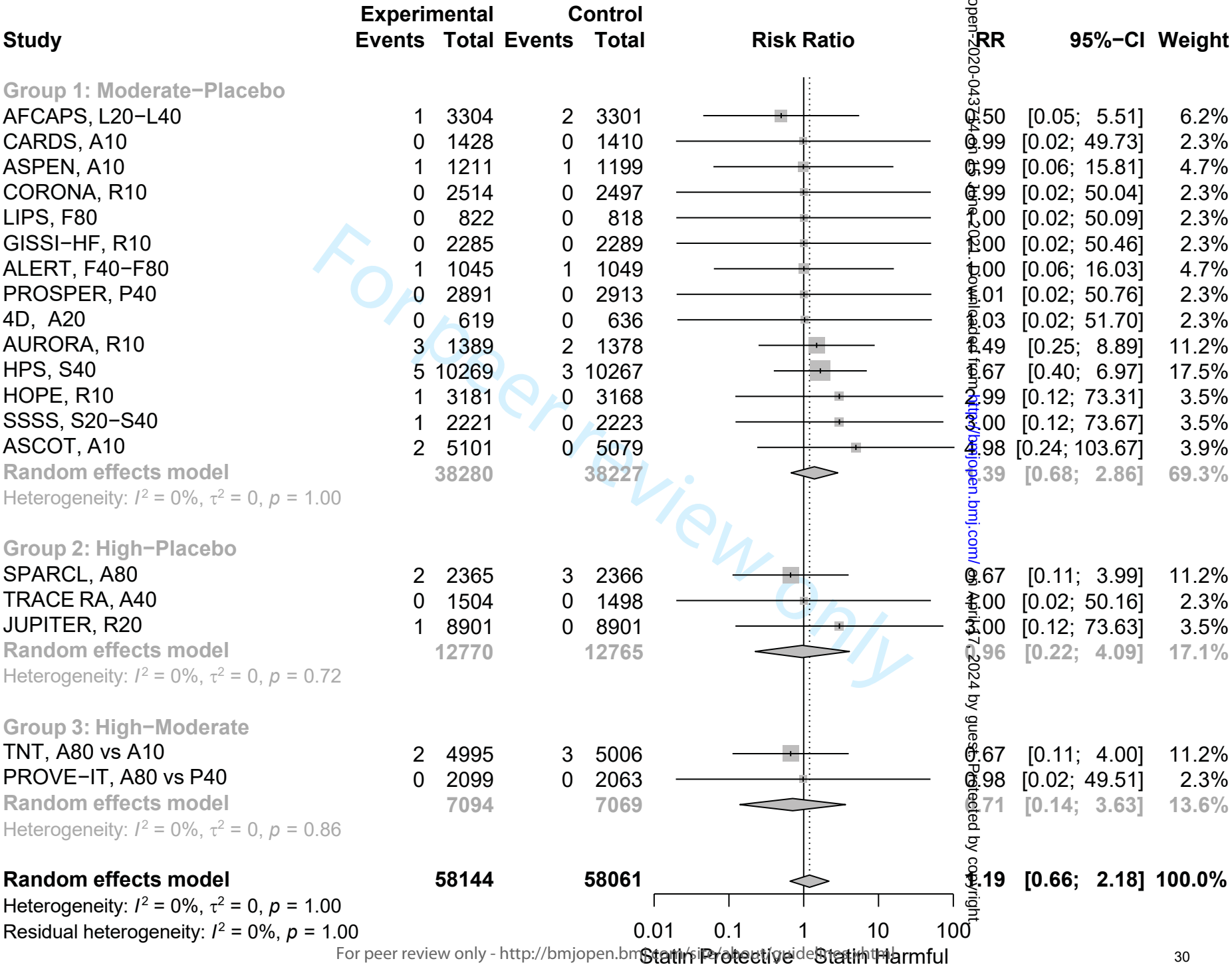
RHABDOMYOLYSIS: Meta-Analysis Forest plot excluding simvastatin 80 mg trials.



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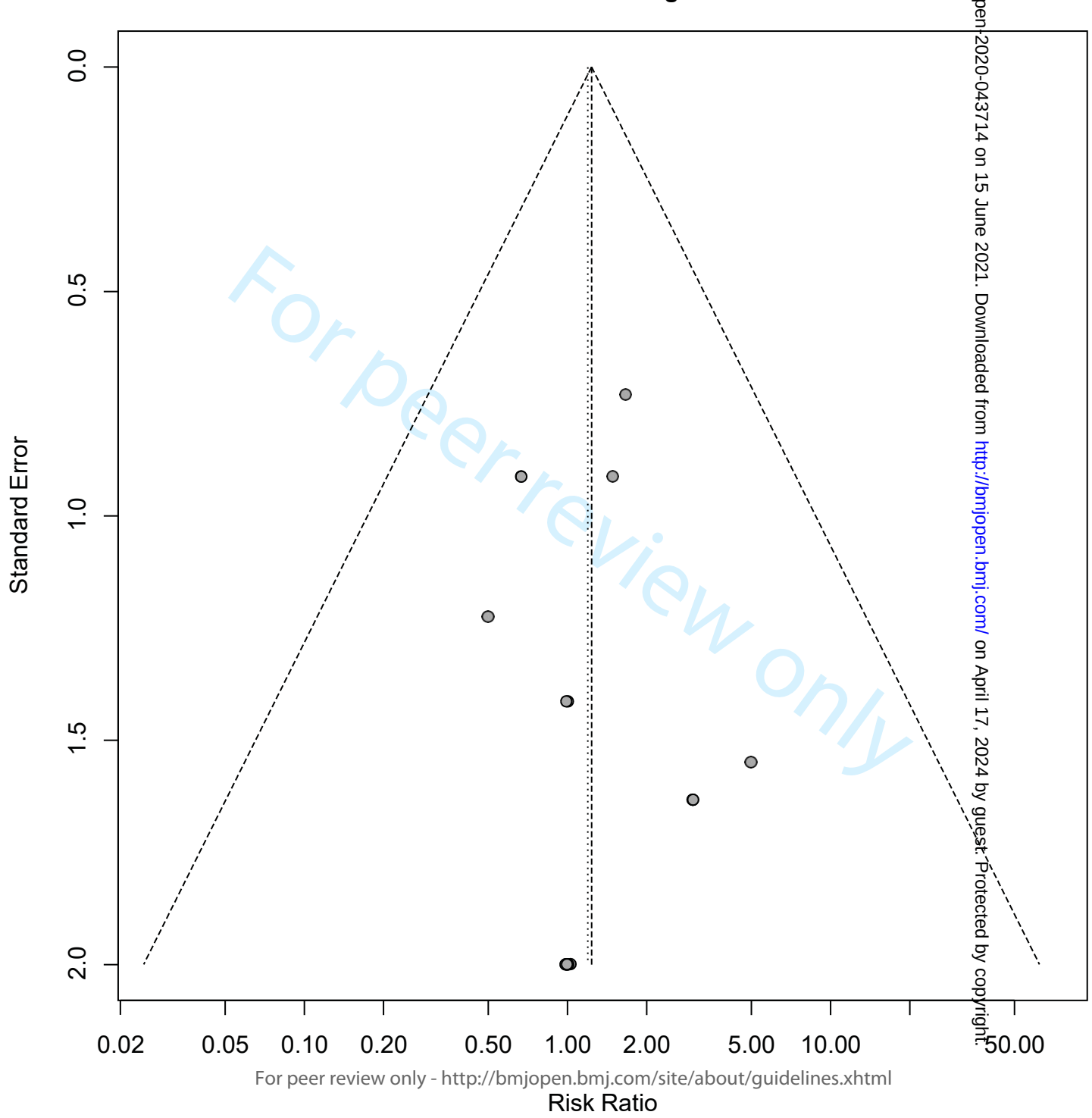

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RHADOMYOLYSIS SUMMARY: PAIRWISE AND NETWORK META-ANALYSIS RESULTS

	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)	--

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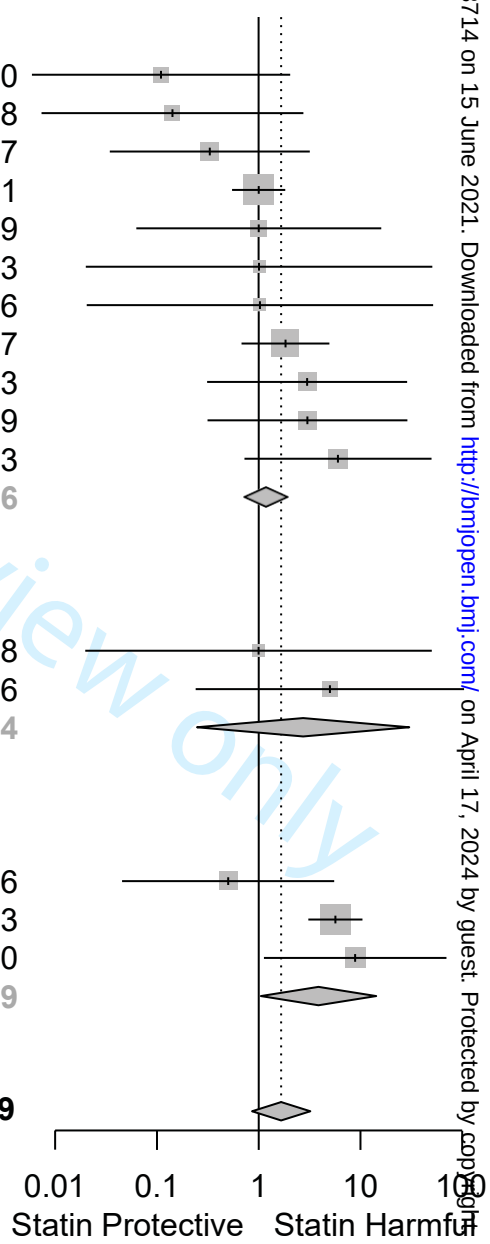
CK >10x ULN: Meta-Analysis Forest Plot with Data



Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	Weight
Group 1: Moderate−Placebo							
CARDS, A10	0	1428	4	1410	0.11	[0.01; 2.04]	3.9%
LIPS, F80	0	822	3	818	0.14	[0.01; 2.75]	3.8%
CORONA, R10	1	2514	3	2497	0.33	[0.03; 3.18]	5.7%
AFCAPS, L20−L40	21	3304	21	3301	1.00	[0.55; 1.83]	15.0%
GISSI−HF, R10	1	2285	1	2289	1.00	[0.06; 16.01]	4.2%
PROSPER, P40	0	2891	0	2913	1.01	[0.02; 50.76]	2.4%
4D, A20	0	619	0	636	1.03	[0.02; 51.70]	2.4%
HPS, S40	11	10269	6	10267	1.83	[0.68; 4.95]	12.3%
WOSCOPS, P40	3	3302	1	3293	2.99	[0.31; 28.75]	5.7%
ALERT, F40−F80	3	1045	1	1049	3.01	[0.31; 28.90]	5.7%
SSSS, S20−S40	6	2221	1	2223	6.01	[0.72; 49.84]	6.2%
Random effects model		**30700**		**30696**	**1.17**	**[0.72; 1.90]**	**67.4%**
Heterogeneity: I^2 = 4%, τ^2 = 0.0303, p = 0.41							
Group 2: High−Placebo							
TRACE RA, A40	0	1504	0	1498	1.00	[0.02; 50.16]	2.4%
SPARCL, A80	2	2365	0	2366	5.00	[0.24; 104.14]	3.7%
Random effects model		**3869**		**3864**	**2.73**	**[0.25; 30.11]**	**6.1%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.52							
Group 3: High−Moderate							
TNT, A80 vs A10	1	4995	2	5006	0.50	[0.05; 5.52]	5.2%
SEARCH, S80 vs S20	68	6031	12	6033	5.67	[3.07; 10.46]	14.9%
A to Z, S40−S80 vs S20	9	2263	1	2230	8.87	[1.12; 69.94]	6.4%
Random effects model		**13289**		**13269**	**3.88**	**[1.05; 14.31]**	**26.5%**
Heterogeneity: I^2 = 50%, τ^2 = 0.7030, p = 0.14							
Random effects model		**47858**		**47829**	**1.66**	**[0.86; 3.21]**	**100.0%**
Heterogeneity: I^2 = 52%, τ^2 = 0.6582, p < 0.01							
Residual heterogeneity: I^2 = 12%, p = 0.32							

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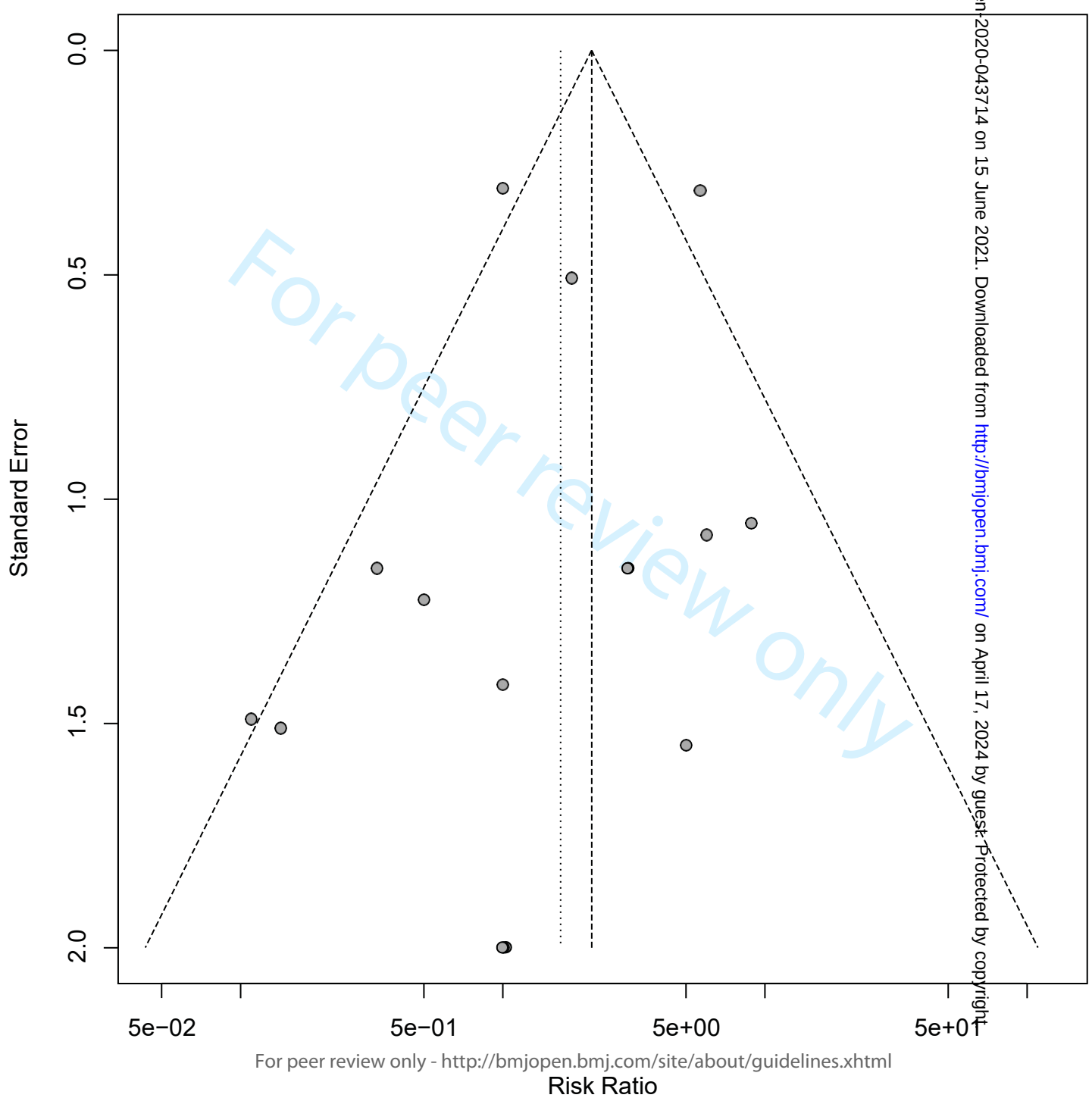

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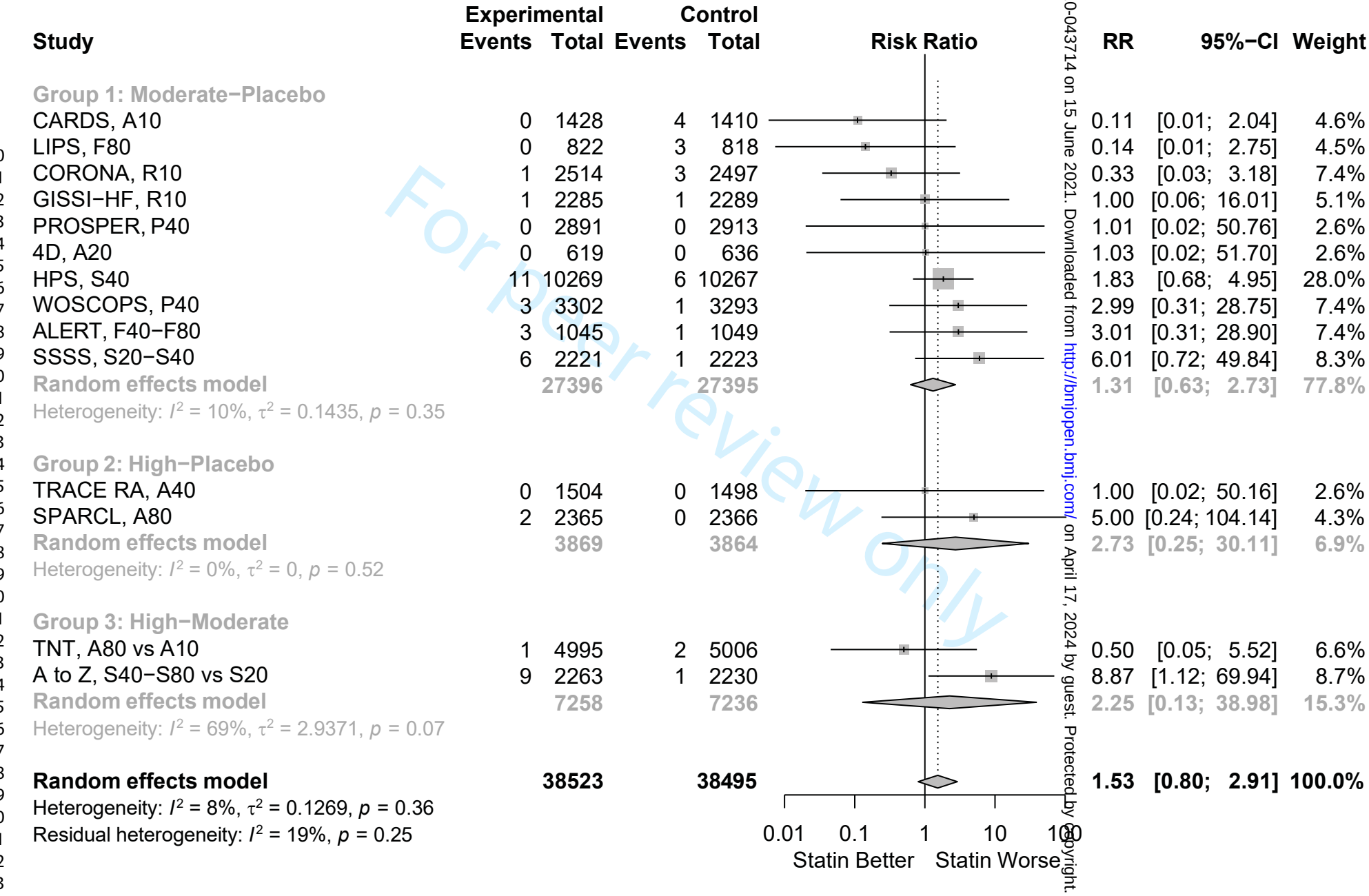
CK >10x ULN: Meta-Analysis Forest Plot with outliers excluded.



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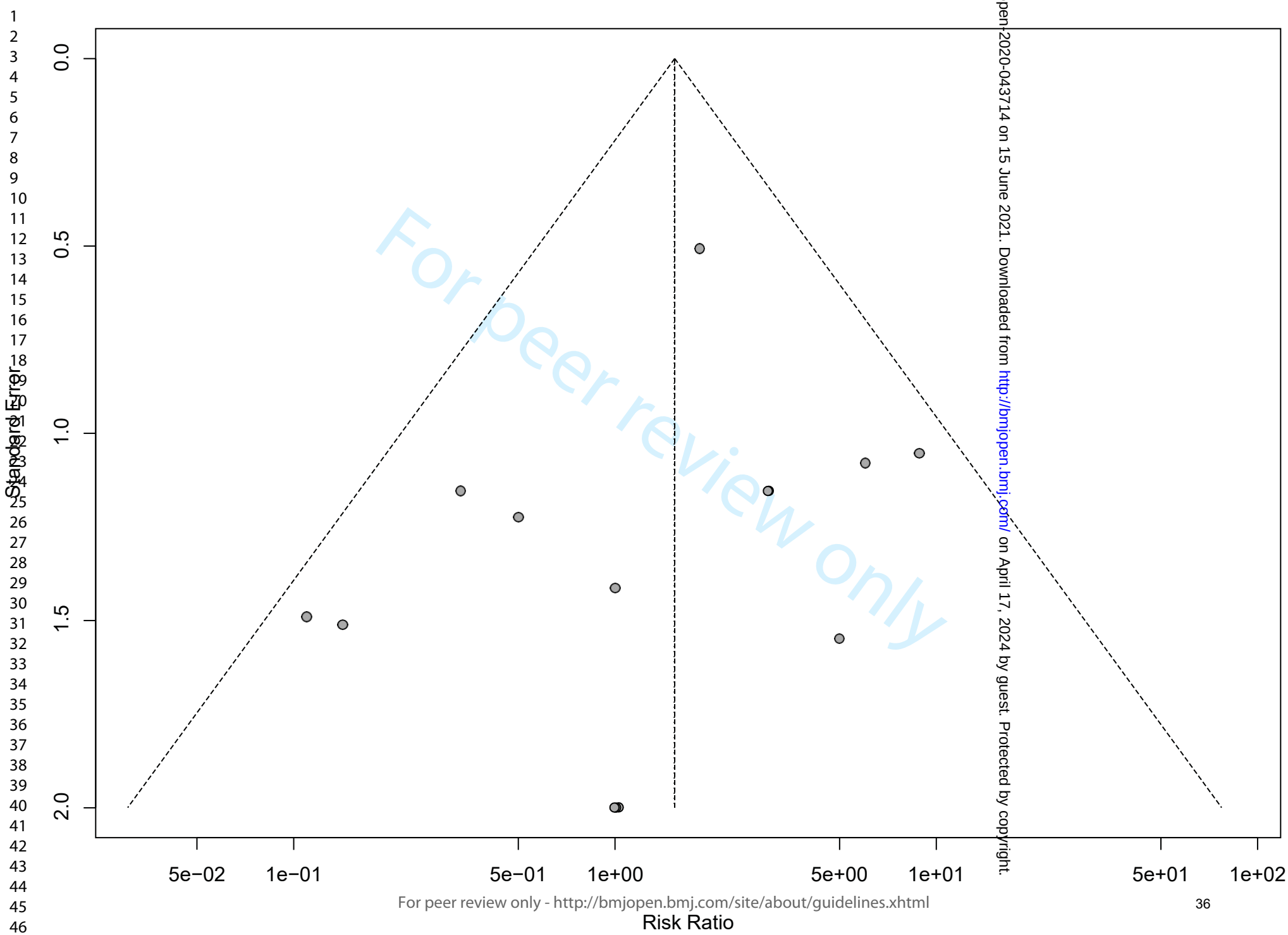
CK >10x ULN: Meta-Analysis Funnel Plot with outliers excluded.



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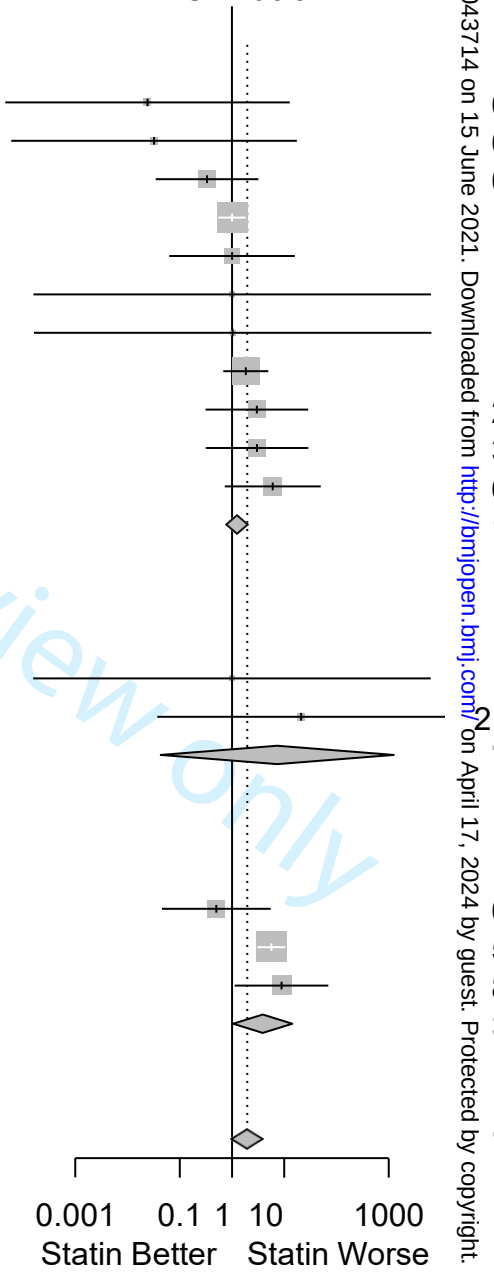
CK >10x ULN: Meta-Analysis Forest Plot with Continuity Correction = 0.1.



Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	Weight
Group 1: Moderate−Placebo							
CARDS, A10	0	1428	4	1410	0.02	[0.00; 12.76]	1.1%
LIPS, F80	0	822	3	818	0.03	[0.00; 17.42]	1.1%
CORONA, R10	1	2514	3	2497	0.33	[0.03; 3.18]	6.3%
AFCAPS, L20−L40	21	3304	21	3301	1.00	[0.55; 1.83]	18.4%
GISSI−HF, R10	1	2285	1	2289	1.00	[0.06; 16.01]	4.7%
PROSPER, P40	0	2891	0	2913	1.01	[0.00; 6455.29]	0.6%
4D, A20	0	619	0	636	1.03	[0.00; 6578.85]	0.6%
HPS, S40	11	10269	6	10267	1.83	[0.68; 4.95]	14.7%
WOSCOPS, P40	3	3302	1	3293	2.99	[0.31; 28.75]	6.3%
ALERT, F40−F80	3	1045	1	1049	3.01	[0.31; 28.90]	6.3%
SSSS, S20−S40	6	2221	1	2223	6.01	[0.72; 49.84]	6.9%
Random effects model		**30700**		**30696**	**1.24**	**[0.79; 1.97]**	**67.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.56							
Group 2: High−Placebo							
TRACE RA, A40	0	1504	0	1498	1.00	[0.00; 6380.08]	0.6%
SPARCL, A80	2	2365	0	2366	21.01	[0.04; 11950.08]	1.1%
Random effects model		**3869**		**3864**	**7.37**	**[0.04; 1256.08]**	**1.7%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.57							
Group 3: High−Moderate							
TNT, A80 vs A10	1	4995	2	5006	0.50	[0.05; 5.52]	5.8%
SEARCH, S80 vs S20	68	6031	12	6033	5.67	[3.07; 10.46]	18.3%
A to Z, S40−S80 vs S20	9	2263	1	2230	8.87	[1.12; 69.94]	7.2%
Random effects model		**13289**		**13269**	**3.88**	**[1.05; 14.31]**	**31.3%**
Heterogeneity: I^2 = 50%, τ^2 = 0.7030, p = 0.14							
Random effects model		**47858**		**47829**	**1.96**	**[1.00; 3.85]**	**100.0%**
Heterogeneity: I^2 = 45%, τ^2 = 0.5511, p = 0.03							
Residual heterogeneity: I^2 = 0%, p = 0.44							

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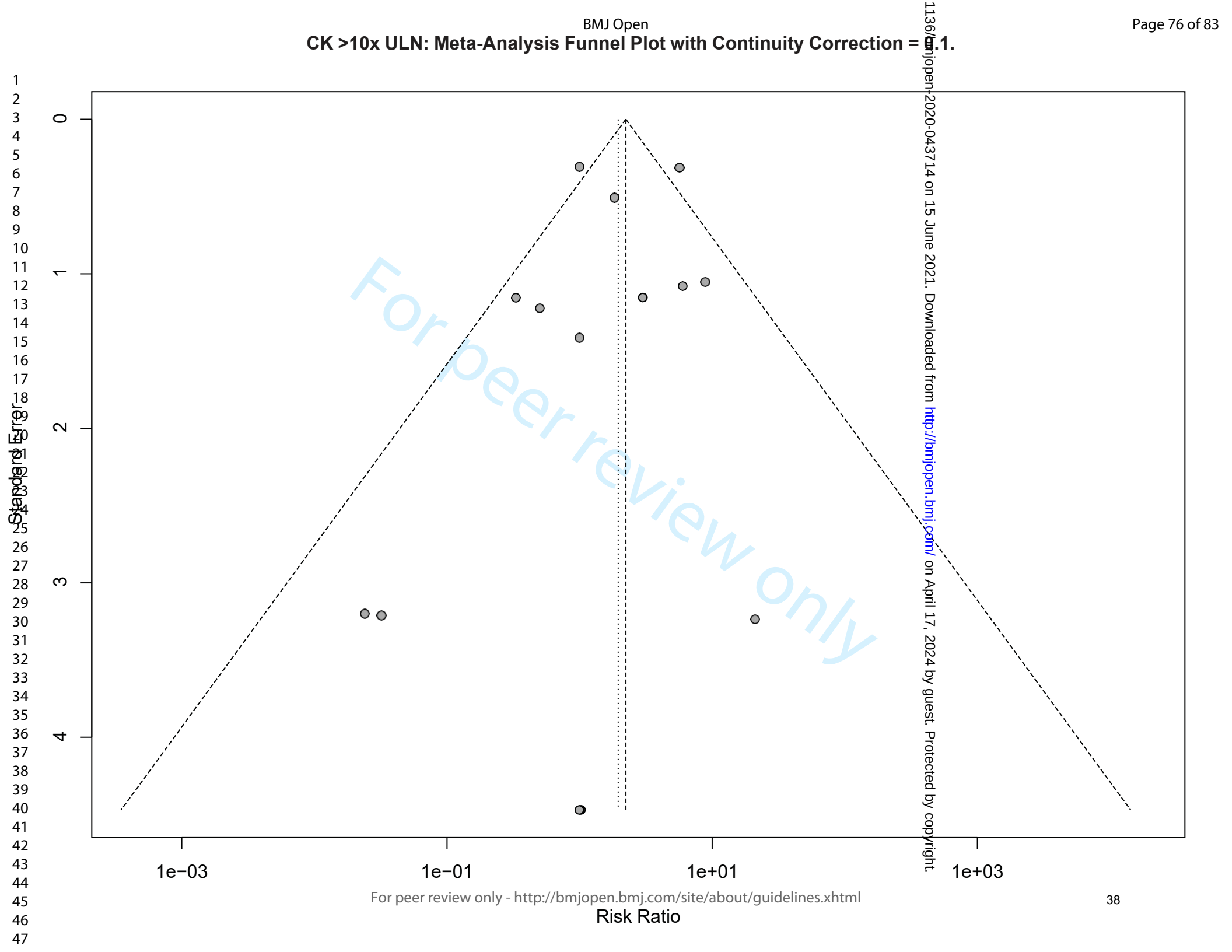

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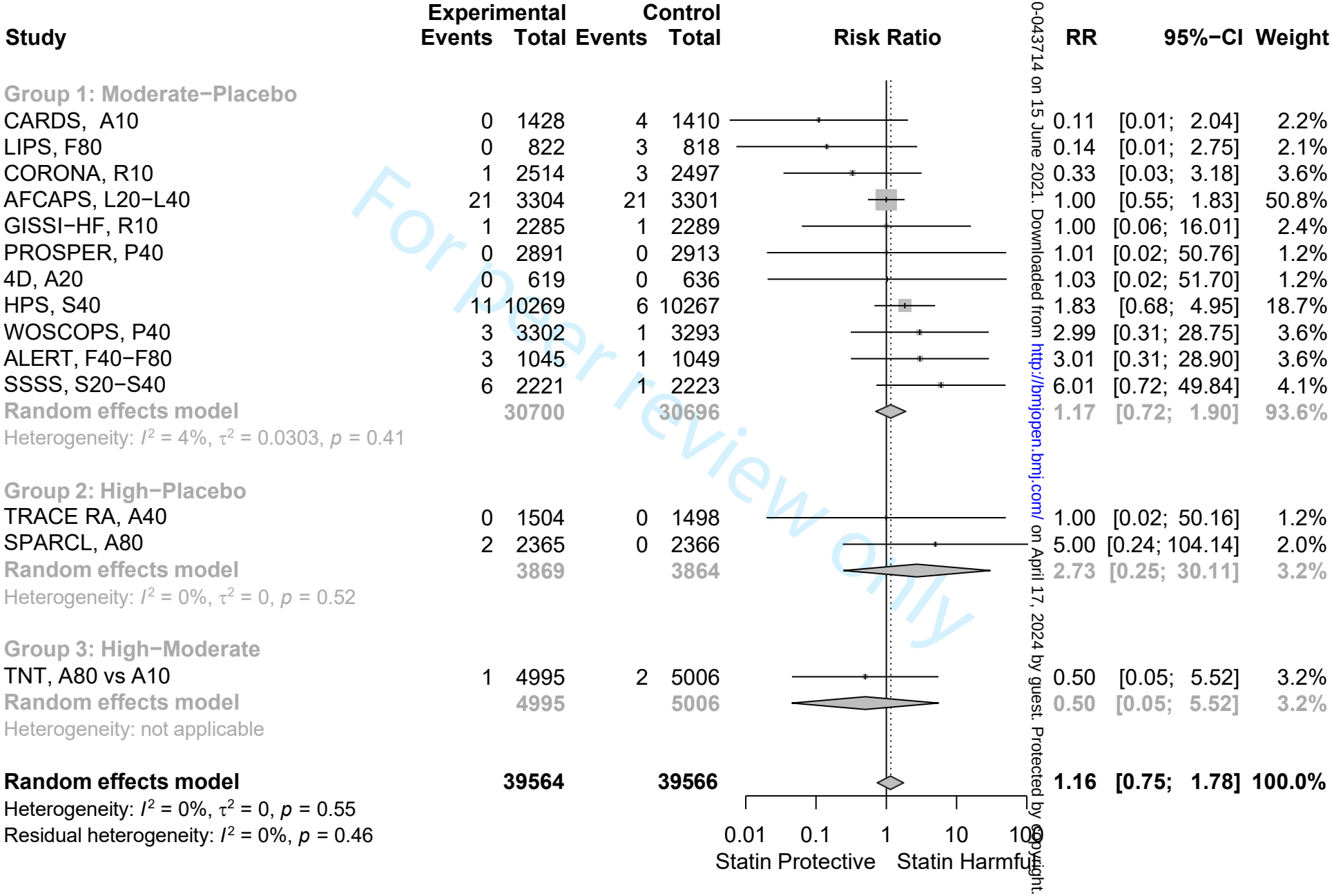
CK >10x ULN: Meta-Analysis Forest Plot excluding simvastatin 80 mg trials.



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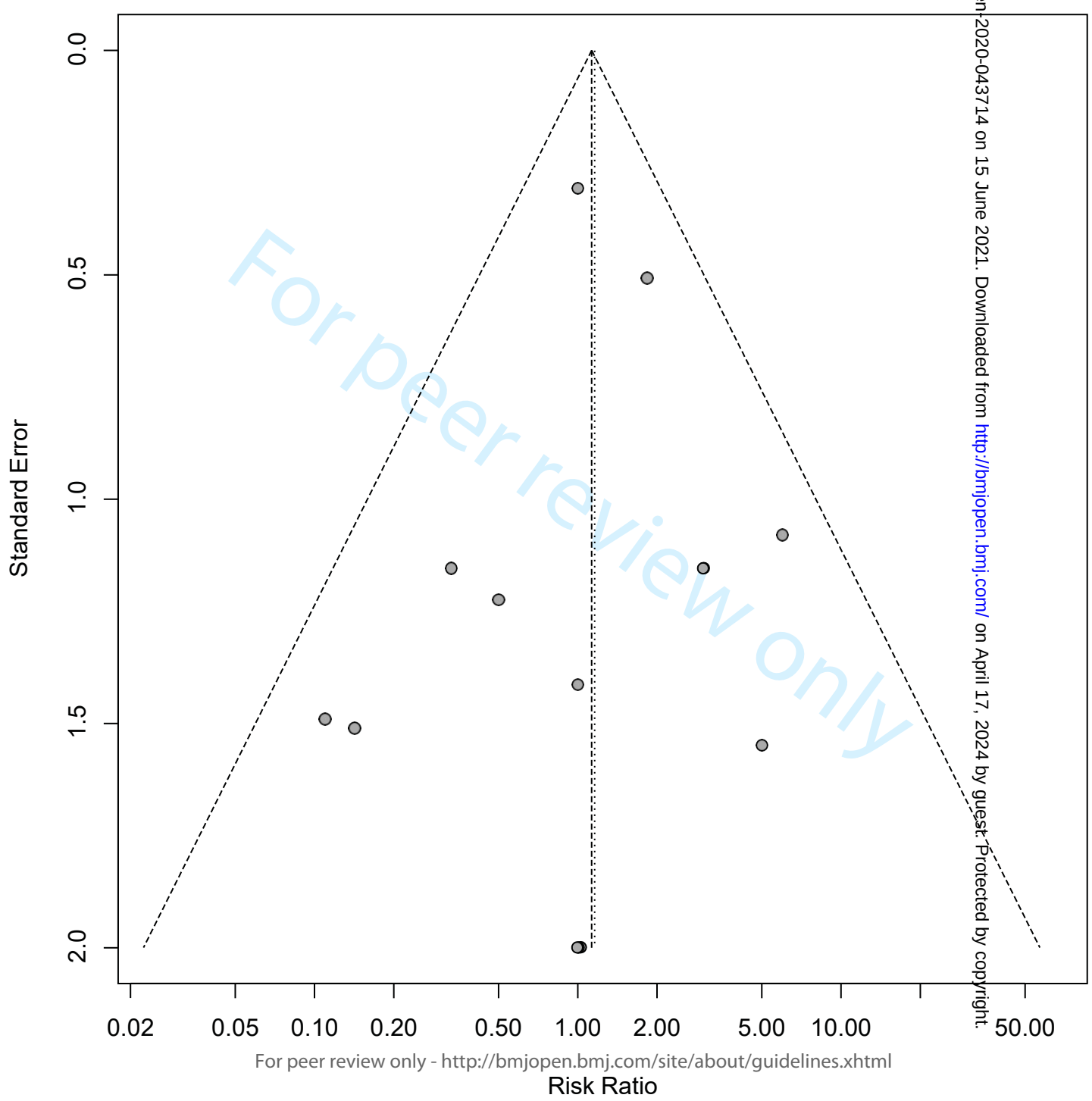

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CK>10XULN SUMMARY: PAIRWISE AND NETWORK META-ANALYSIS RESULTS

	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)	--

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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)
```

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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
```

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1 (Title)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5 (Intro)
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3 (abstract)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	With Prospero reg.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8

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PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-11, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results section
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Results section
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Title page

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PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**. Page 2 of 2

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BMJ Open

INTENSITY OF STATIN THERAPY AND MUSCLE SYMPTOMS: A NETWORK META-ANALYSIS OF 153,000 PATIENTS

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Manuscript ID	bmjopen-2020-043714.R2
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Date Submitted by the Author:	17-May-2021
Complete List of Authors:	Davis, John; University of Texas Medical Branch at Galveston, Preventive Medicine and Population Health Weller, Susan; The University of Texas Medical Branch at Galveston, Departments of Preventive Medicine and Community Health; and Family Medicine
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Epidemiology, Evidence based practice, Pharmacology and therapeutics, Health services research, Medical management
Keywords:	Cardiac Epidemiology < CARDIOLOGY, Coronary heart disease < CARDIOLOGY, CLINICAL PHARMACOLOGY, GENERAL MEDICINE (see Internal Medicine), Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Cardiology < INTERNAL MEDICINE

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INTENSITY OF STATIN THERAPY AND MUSCLE SYMPTOMS: A NETWORK META-ANALYSIS OF 153,000 PATIENTS

By

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Word count: 3893

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ABSTRACT

Objective: To estimate relative risk of statin-associated musculoskeletal symptoms (SAMS) by statin therapy intensity.

Setting: Network meta-analysis assessing multi-center RCTs across several countries.

Participants: Pubmed, Web of Science, Cochrane database, and clinicaltrials.gov were searched through January 2021 for doubled-blinded RCTs testing the effect of statin therapy on lipids with at least 1000 participants and two years of intended treatment. Two coders assessed articles for final inclusion, quality, and outcomes. Treatment intensity was categorized according to American Heart Association definitions.

Outcomes: Pairwise and network meta-analysis (NMA) estimated relative risk (RR) and risk difference (RD) with random effects modeling. Heterogeneity was evaluated with the I^2 statistic. Outcomes included muscle symptoms (any, myalgia, and attrition due to muscle symptoms), rhabdomyolysis, and elevated creatine kinase (>10x upper limit of normal).

Results: Of 2919 RCTs, 24 (N=152,461) met inclusion criteria. NMA results indicated risk was significantly greater for high compared to moderate intensity statin therapy for any muscle problem (RR=1.04, 95% CI: 1.00,1.07; I^2=0%), myalgia (RR=1.04, 95% CI: 1.00,1.08; I^2=0%, NNH=173), attrition due to muscle problems (RR=1.37, 95% CI: 1.09,1.73, I^2=0%, NNH=218), and elevated CK (RR=4.69, CI: 2.50, 8.80; I^2=7%, NNH=527). Risk also was significantly higher for high intensity compared to placebo for any muscle problem (RR=1.05, 95% CI: 1.01,1.09, I^2=0%), myalgia (RR=1.13, 95% CI: 1.05,1.23; I^2=0%, NNH=182), attrition due to muscle problems (RR=1.55, 95% CI: 1.15,2.08, I^2=0%, NNH=187), and elevated CK (RR=5.37, CI: 2.48, 11.61; I^2=7%,

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NNH=589). Due to inconsistency of results across sensitivity analyses, estimates were inconclusive for rhabdomyolysis and CK. There were no significant differences in risk between moderate intensity therapy and placebo for all outcomes.

Conclusions: For approximately each 200 patients on high intensity statins, one additional patient may experience myalgia or discontinue therapy due to muscle problems compared to moderate intensity therapy.

Trial Registration: Prospero #CRD42019112758

Article Summary:

Strengths

- High-quality, large RCTs analyzed with low risk of heterogeneity bias
- Novel use of network meta-analysis to compare treatment intensities allows for large analysis of dose-dependent effect
- Coding of outcome terms directly as reported by investigators to minimize bias

Weaknesses

- Study-level data precludes meta-analysis with regression for relevant covariables affecting risk of outcome
- Heterogeneity of terms across trials prevented analysis of full trial set for each outcome.

Key Words: Statins, myalgia, nocebo, rhabdomyolysis, network meta-analysis

Abbreviations:

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Network Meta-Analysis (NMA) and pair-wise meta-analysis (MA), Risk Ratio (RR), Risk Difference (RD), Cholesterol Treatment Trialists' Collaboration (CTT), Statin Associated Muscle Symptoms (SAMS), Creatine Kinase (CK) & Upper Limit of Normal (ULN), End Stage Renal Disease (ESRD), Number Needed to Harm (NNH), Hazard Ratio (HR)

Ethical Approval: N/A

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INTRODUCTION

The Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis on patient-level data from large RCTs demonstrated that statin therapy is efficacious in reducing major vascular events.[1,2] Statin therapy is now prominent in cholesterol management guidelines. [3–8] Statin-associated muscle symptoms (SAMS), however, may lead to non-adherence or discontinuation with therapy and ultimately to poorer cardiovascular outcomes.[7] Most RCTs have shown small, insignificant increases in risk for SAMS, although patients taking statins may complain of muscle problems and may discontinue therapy due to muscle problems.[3] For example, a 2016 meta-analysis found a non-significant increase in myopathy. However, it did not report on the more mundane myalgias that often cause statin attrition.[3] These milder symptoms are the major public health concern, as statin non-adherence can lead to significant increases in risk of major adverse cardiovascular events.[3] Observational studies suggest that these mild SAMS may occur as often as 7-29% of patients.[7] One review[9] suggested that clinical observations of increased muscle problems with statin therapy may be due to patient expectations.

SAMS also may be more likely with higher intensity therapy. Although this is assumed to be true, especially with the evidence against simvastatin 80 mg,[10,11] few RCTs have examined high intensity therapy[12,13]. This study used a network meta-analysis (NMA) to combine evidence across trials to estimate the risk of SAMS by treatment intensity. In contrast to pair-wise meta-analysis (MA) that directly estimates causal effects, a NMA can indirectly estimate risk between placebo and moderate, moderate and high, and

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between placebo and high intensity treatment – even though placebo, moderate, and high intensity treatment levels were not compared within a single trial. Results contribute to the debate about whether muscle adverse events are due solely to patient expectations or whether statins might have an independent effect on symptoms. Finally, this study contributes to the ongoing debate as to whether statins cause myalgias and attrition due to muscle problems without marked creatine kinase (CK) elevations.

METHODS

The Trials. PubMed, Cochrane Database, Web of Science, and clinicaltrials.gov were searched for "systematic reviews" and "meta-analysis" in the title, abstract, or keywords prior to January 31, 2021to identify eligible trials (Prospero #CRD42019112758; see online supplement for search terms and strategy). Double-blinded RCTs to improve lipid levels comparing statin therapy to placebo or higher-lower dose statin therapy were selected. In order to detect most adverse events, RCTs were selected that had at least 1,000 participants with two years of intended follow-up, where statin treatment was not given with other prescription drug therapies, and results contained reports on muscle-related adverse events. Both authors independently reviewed trials for final inclusion and coded each for quality with Oxford Center for Evidence-based Medicine ratings[14] and a five-point Jadad quality score.[15] Any disagreements were reconciled by joint review and discussion.

Patient and Public Involvement. Patients were not involved in design or implementation of this study.

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Exposure Variable. Studies were classified by intensity of statin treatment ("high" or "moderate") according to American Heart Association definitions for potency in reduction of lipid levels.[16] High intensity signifies an expected 50% or greater reduction in LDL-C levels when taking that statin (i.e., 80 mg atorvastatin) and moderate signifies 30-50% reduction in LDL-C.[16]

Outcome Variables. Adverse muscle-related events were coded into five main outcomes. The first outcome was for any patient-reported muscle complaint coded from reports of "muscle aches", "pains", "cramps", "stiffness," "musculoskeletal disorders," etc. The second focused on only myalgia or muscle pain. The third focused on attrition due to musculoskeletal complaints. A fourth captured explicit reporting of rhabdomyolysis, with or without a trial definition. The fifth was elevated creatine kinase, greater than ten times the upper limit of normal (CK >10x ULN). This threshold was used to distinguish this outcome from less meaningful CK increases and also because CK>10xULN is commonly reported in RCTs. All outcomes were coded as reported by original investigators in published and online reports, and were independently coded by both authors. Ambiguities were resolved by contacting trial investigators.

Analysis. Published aggregate data from each trial were used. A crude estimate of incidence was calculated from the total number of cases observed divided by the total person-years (using the median or mean follow-up time for each study) and a chi square test was used to test for homogeneity in the proportion of incident cases across studies, within each arm, although these crude estimates ignored randomization. To

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facilitate interpretation and comparison of results to the original trials, risk of adverse effects was estimated with pooled relative risk (RR). A 0.50 continuity correction was added to aggregate frequencies for trials that observed zero cases of an outcome in either treatment arm. A pairwise meta-analysis (MA) was used to estimate the RR (Mantel-Haenszel method, random effects as implemented in the meta package in R)[17,18] for a statin effect by treatment intensity from direct (head-head comparison) trials (online supplement contains detailed results for random effects with Mantel-Haenszel and inverse variance methods). Because aggregations across studies are only meaningfully interpreted when results are consistent across studies, heterogeneity among RCTs was assessed with an index of consistency across trials (I^2, Q)[19,20] and funnel plots. When $I^2 \leq 25\%$, results are considered to be at low risk of bias due to heterogeneity; high values (>75%) indicate high risk of bias due to heterogeneity. [19,20] Residual I^2 represents the heterogeneity remaining after accounting for sub-groups of treatment intensity. Cochrane's Q (a sub-component of I^2) indicates the probability that the observed heterogeneity is due to chance. Sensitivity analyses included omitting outliers identified in funnel plots and using a 0.10 as a "continuity correction". In addition, analyses were conducted excluding the simvastatin 80 mg studies because of US FDA muscle-related safety warnings.[21]

A network meta-analysis (NMA), conducted in R,[22] used *all* available pairs of comparisons for each outcome to estimate increased risk between the three levels of treatment exposure. Prespecified comparisons were between placebo and moderate intensity, between moderate and high intensity therapy, and between placebo and high

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intensity. The RR was used to estimate effect size (frequentist, inverse variance method, random effects), so that results would be comparable across original studies and the pairwise meta-analysis above. In contrast to a MA which provides a direct estimate of the RR, a NMA provides estimates by combining direct and indirect evidence from all data. A ratio test was used to test for consistency between NMA direct and indirect estimates.[23] Heterogeneity was assessed with and I^2 and Q statistics.[19,20] Number needed to harm (NNH, the inverse of the absolute difference in incidence) was estimated when the pooled RR was significantly greater than 1.0 and the pooled absolute risk reduction (risk difference, RD) was significantly greater than 0.0. Sensitivity analyses included replacement of zeros with 0.10 and with 0.0001.

RESULTS

Searches yielded 134 relevant reviews, including 2919 RCTs that reduced to 24 unique RCTs that met eligibility requirements (see online supplement). Of the 24 RCTs: 17 were placebo-moderate intensity comparisons,[24–44] 3 were placebo-high intensity comparisons,[45–47] and 4 were moderate-high intensity comparisons[10–13] (Table 1). The active blood pressure treatment arm of the HOPE trial[37] was excluded, but the statin only and placebo only arms were retained, allowing for a statin and placebo comparison. Two trials compared moderate and high intensity therapy using 80 mg/day of simvastatin.[10,11] All 24 RCTs scored the highest quality (1) on the Oxford rating and on the Jadad scale 18 scored 5/5 and 6 scored 4/5 (missing detail on random assignment). The RCTs included heterogenous patient populations, e.g., healthy middle-aged adults[26,37,43,46] to ESRD patients. Sample sizes ranged from 1,255[24] to

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20,536[40] with follow-up periods from 1.9[46] to 6.7[10] years. Of the 24 RCTs, six were included in the 2006 meta-analysis,[48] 17 in the 2014 systematic review,[49] 23 in the 2016 meta-analysis,[3] and 18 in the 2013 NMA.[50] None of the previous analyses separated trials into sub-groups by treatment intensity. Crude estimates of incidence increased with intensity of treatment from placebo to moderate intensity to high intensity therapy, but with heterogeneity across trials (online supplement).

Any Muscle Symptoms. Twenty-three trials reported some type of muscle symptom[10,13,25–29,31,35,39,40,46,47] myositis,[34] myalgia,[12,24,30,32,33,42,45] myopathy,[24,38] or discontinuation due to muscle-related symptoms.[11,13,36] The pairwise meta-analysis pooled across subsets of trials indicated consistent trial results with a 1% non-significant increase in risk between placebo and moderate intensity therapy, a 3% non-significant increase between placebo and high intensity therapy (Figure 1), and a 5% significant increase between moderate and high intensity therapy (RR=1.05, 95% CI: 1.01, 1.09; p=0.027, 4 RCTs, N=30,720; I^2=0%). Sensitivity analyses indicated that RRs were essentially unchanged without an outlier[30] identified on the funnel plot, with a 0.10 correction, or without the simvastatin 80 mg trials. (online supplement).

The NMA pooled direct and indirect evidence from all 23 trials and suggested increased risk with higher intensity therapy. Results (Table 2) indicated a 1% non-significant increase in risk between placebo and moderate intensity therapy, a 4% significant increase between moderate and high intensity therapy (RR=1.04, 95% CI: 1.00, 1.08; p=0.031), and a 5% significant increase between placebo and high intensity therapy (RR=1.05, 95% CI: 1.01, 1.09; p=0.012). The RRs were consistent across studies

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(I^2=0%; Q, p=0.54), were not significantly different between direct and indirect estimates (p=0.48), and were not sensitive to substitutions for zero values. Pooled RDs between pairs of treatment groups were not significantly different from zero. There were no outliers in the NMA analysis. Exclusion of the two simvastatin 80mg trials did not meaningfully change risk, but comparisons with high intensity were not statistically significant, likely due to the decreased sample size (online supplement).

Myalgia or pain. Thirteen RCTs reported cases of myalgia,[25,29–32,42,44–47] attrition due to myalgia,[26,28] or pain and/or weakness.[40] The pairwise meta-analysis indicated (Figure 2) a 13% non-significant increase in myalgia between placebo and moderate intensity, a 9% non-significant increase between placebo and high intensity, and a 4% significant increase between moderate and high intensity (RR=1.04, 95% CI: 1.00;1.09, p=0.040, 2 RCT, n=22065; I^2=0%). The three trials comparing placebo and high intensity therapies suggested moderate heterogeneity in results (I^2=45%). Funnel plots did not suggest bias by any of the studies and there were no zero cells (online supplement). Exclusion of the simvastatin 80 mg trial did not meaningfully change the magnitude of risk, although results were non-significant for high intensity compared to moderate intensity therapy possibly due to decreased sample size (online supplement).

The NMA results combining evidence for all 13 trials suggested an increase in myalgia with increased therapy intensity (Table 2). There was a 9% non-significant increase in risk between placebo and moderate intensity therapy, a 4% significant increase between moderate and high intensity therapy (RR=1.04, 95% CI: 1.00, 1.08; p=0.046),

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and a 13% significant increase in risk for high intensity therapy compared to placebo without heterogeneity (RR=1.13, 95% CI: 1.05, 1.23; p=0.002). The RRs were consistent across studies (I^2=0%, Q, p=0.48) and direct and indirect estimates were not significantly different (p=0.63). The pooled RD was significant between high and moderate intensity (NNH=173) and between high intensity and placebo (NNH=154) with low heterogeneity (I^2=20%; Q, p=0.25). Exclusion of the simvastatin 80 mg trial did not change the magnitude of risk although results were not significant for high intensity compared to moderate intensity therapy (online supplement).

Attrition. Attrition due to muscle problems was reported by eight RCTs that compared moderate intensity statin therapy with placebo,[25,26,28,32,36–38,40,44] three that compared moderate with high intensity therapy,[10,11,13] and none that directly compared high intensity to placebo. In the pairwise meta-analysis (Figure 3), patients on moderate intensity statin therapy had a 13% non-significant increase in attrition due to muscle problems compared to placebo. Patients on high intensity therapy had a 38% significantly higher attrition rate than those on moderate intensity (RR=1.38, 95% CI: 1.04, 1.82; p=0.024, 3 RCTs, N=20,719) with moderate heterogeneity across trials (I^2=31%). Funnel plots did not suggest bias and there were no zero cells. Exclusion of the two simvastatin 80 mg trials left only one moderate-high intensity comparison RCT (online supplement).

The NMA results for the 11 trials suggested that risk for attrition increased with intensity of therapy. There was a 13% non-significant increase in risk between placebo and

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moderate intensity therapy (Table 2), a 37% significant increase in risk between moderate and high intensity (RR=1.37, 95% CI: 1.09, 1.73; p=0.007), and a 16% significant increase in risk between placebo and high intensity therapy (RR=1.16, 95% CI: 1.15, 2.08; p=0.004). The RRs were consistent across studies (I^2=0%; Q p=0.72) and closely paralled direct results provided by the meta-analysis, but the NMA provided an estimate for the placebo-high intensity comparison for which there were no head-to-head trials. The pooled RD between moderate and high intensity therapy was significant and the NNH was 218. The pooled RD between high intensity therapy and placebo also was significant and the NNH was 186. Exclusion of the two simvastatin 80 mg trials resulted in a slightly lower risk estimate for the moderate to high comparison and a slightly higher estimate for the placebo to high comparison, and both were non-significant (online supplement).

Rhabdomyolysis. Rhabdomyolysis was reported on by 14 moderate intensity-placebo comparison RCTs,[24–28,30–32,35,36,39–42] four moderate-high intensity comparison RCTs,[10–13] and three high intensity-placebo comparison RCTs.[45–47] Incidence of rhabdomyolysis was very low and statistical comparisons were not conclusive. Pairwise meta-analysis indicated a 39% non-significant increase in rhabdomyolysis incidence between placebo and moderate intensity therapy, 145% non-significant increase between moderate and high intensity, and a 4% non-significant decrease between placebo and high intensity therapy (Figure 4). Results were inconclusive as estimates were not robust across sensitivity analyses. Approximately half (22/42) of the cells were zeros and RR increased for the moderate-high intensity comparison with a smaller correction and

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removal of the simvastatin 80 mg trials meaningfully changed effect sizes (online supplement).

NMA results based on all 21 trials indicated increased risk for rhabdomyolysis with increased intensity of therapy (Table 2). There was a 22% non-significant increase in risk between placebo and moderate intensity therapy, a 33% non-significant increase between moderate and high intensity, and a 66% non-significant increase between placebo and high intensity therapy with consistency across trials (I^2=0%, Q p=0.99). Direct and indirect RR estimates were not significantly different (p=0.31). Results were not consistent after exclusion of simvastatin 80 mg trials or replacement of zeros, but remained nonsignificant (online supplement).

Elevated CK. Of 16 RCTs, 11 compared rates of elevated creatine kinase (CK>10xULN) between placebo and moderate intensity therapy,[24–27,32,35,36,39–43] three compared moderate to high intensity therapy[10–12] and two compared high intensity therapy with placebo.[45,47] Incidence of elevated CK was low. Pairwise meta-analysis indicated (Figure 5) a 17% non-significant increase in CK elevation between placebo and moderate intensity therapy, a 173% non-significant increase between placebo and high intensity therapy, and a 288% significantly higher risk for high compared to moderate intensity (RR=3.88, 95% CI: 1.05,14.31; p=0.042, 3 RCTs, n=26,558) with some heterogeneity among the three trials (I^2=50%). Estimates were not stable across sensitivity analyses. Removal of two possible outliers,[10,26] exclusion of simvastatin 80

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mg trials, and adjustment for cells with zeros (9/32) meaningfully changed RR estimates (online supplement) .

Using evidence from all 16 trials, the NMA estimates indicated increased risk with increased intensity. NMA results indicated a 14% non-significant increase between placebo and moderate intensity therapy (Table 2), a 359% significant increase in CK elevation between moderate and high intensity (RR=4.59, 95% CI: 2.32,9.10; p<0.0001), and a 425% significant increase between placebo and high intensity (RR=5.25, 95% CI: 2.29,12.03; p<0.0001). Results were consistent across trials (I^2=7%, Q p=0.37) and direct and indirect RR estimates were not significantly different (p=0.57). The pooled RD between moderate and high intensity therapy was significantly different from zero and the NNH was 527. The pooled RD between high intensity therapy and placebo also was significant and the NNH was 589. There were no outliers in the NMA analysis. Although results were homogeneous with the simvastatin 80 mg trials, exclusion of these trials meaningfully reduced risk associated with statin therapy between moderate and high intensity and between placebo and high intensity therapy; and smaller zero replacement values increased risk estimates (online supplement).

DISCUSSION

A novel contribution of this study was the application of NMA to estimate the dose-response effect of statin therapy on muscle symptoms using clinically-meaningful categories of treatment intensity. The NMA RR estimates closely paralleled the direct estimates, indicating reliability of estimates and increased risk with high intensity statin

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therapy. The network meta-analyses provide information about risk by utilizing all available evidence, whereas traditional meta-analyses are limited only to direct, head-to-head comparisons. For patient-reported symptoms, there were non-significant increases in SAMS between placebo and moderate intensity therapy and significant increases between moderate and high intensity therapy. Because simvastatin 80mg therapy is now restricted because of muscle injury,[51] analyses also were run with and without those trials. This did not meaningfully affect results for patient-reported outcomes. Rhabdomyolysis and elevated CK also showed increased risk with higher intensity, but because of low incidence (with 25-50% zero cells) and inconsistency across sensitivity analyses, results were inconclusive.

Double-blinded RCTs and traditional meta-analyses[3,48,49] suggest no significant increase in risk of muscle adverse events with statin therapy. Since most evidence comes from moderate intensity trials, possible adverse effects of high intensity therapy may be masked in aggregate estimates. In this study, high intensity therapy and focused definitions of patient-reported muscle problems detected higher risk. However, the absolute excess of SAMS was less than 1% for all outcomes. In previous meta-analyses, absolute excess of muscle problems also was small, but non-significant.[3,49] The 2016 meta-analysis estimated risk for extreme outcomes (myopathy and rhabdomyolysis), but did not analyze patient reports of milder SAMS that we present and that concern patients. We did not code for myopathy as an outcome, because we did not have access to patient-level data and could not determine if elevated CK co-occurred with myalgia.

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Direct lower-higher dose comparisons in individual RCTs were not consistent, e.g., the SEARCH[10] and A to Z trials found a significant increase in CK and the TNT trial[12] did not. A NMA that compared dosage increments within brands[50] suggested no systematic increase in risk for myalgia or discontinuation with higher dosages. These negative findings may have been due to smaller sample sizes, smaller dosage increments in restricted comparisons, or exclusion of the simvastatin 80 mg trials.[50] In this study, results were homogeneous including the simvastatin 80mg trials and indicated high intensity therapy significantly increased myalgia compared to placebo even after their exclusion. The previous NMA did identify a dose-response relationship between statin dose and mildly elevated CK (2-3x ULN), but only for lovastatin and simvastatin.[50] CK>10xULN may be more interpretable than modest elevations, and in this study it was significantly increased with high-intensity statin therapy. While removal of 80mg simvastatin trials had little effect on patient-reported symptoms, their exclusion resulted in smaller non-significant increases in risk for elevated CK. It is unclear if simvastatin 80mg was responsible for the significant increases in CK.

A practical question concerns how large an excess of cases might be observed with statin therapy for myalgia/pain, attrition due to muscle problems, and elevated CK or rhabdomyolysis. Although estimates based on observational studies suggest that incidence of mild SAMS might be as high as 30% among statin users,[52] RCTs suggest a much lower rate. In this study, pooled risk estimates suggested that for each 173 patients on high intensity therapy one additional patient will experience statin-caused

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myalgia and for each 218 patients one additional patient will discontinue therapy due to muscle problems compared to those on moderate intensity therapy. This represents numerous patients who are at greatest risk for major vascular events, as these are often higher risk patients. Discontinuation of statins in the elderly (>75 yrs) may result in 33% increased risk of a cardiovascular event within 3 months [53] and adherence to statins in those 65 and older may reduce mortality by a third.[54]

Myalgias and attrition due to SAMS are important outcomes for the average patient, but have not received as much attention as rhabdomyolysis and myopathy. This study provides evidence that while blinded, moderate intensity statin-takers did not report significantly more general muscle problems or myalgias, but those on high intensity therapy did. Because many myalgia cases occurred without CK elevation increases, this also serves as evidence that SAMS occur in the absence of large elevations in CK. Clinicians with patients who are “statin intolerant” may consider encouraging the patient to first decrease intensity of statin therapy, rather than discontinuing it, in light of these findings.

This analysis also contributes to the “nocebo” debate. A large, unblinded follow-up of RCT patients suggested SAMS are expectation-related.[29] They observed an incidence of 2.03% and 2.00% muscle-related adverse events in statin and placebo groups, respectively, when double-blinded (HR=1.03) and 1.26% and 1.00% in the statin and usual care groups when unblinded (HR=1.41).[29] Both comparisons indicate absolute differences less than 1%. A recent N-of-1 trial[55]also found minimal differences in muscle

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symptoms when patients took statin versus placebo (blinded), but significantly more muscle symptoms when taking a placebo versus taking nothing (unblinded). Both nocebo and causal effects are small, although they can result in increased SAMS. In a clinical setting, SAMS with moderate intensity therapy may be the result of patient expectations, but with high intensity therapy SAMS may be due to expectations and statin therapy. Intensity of treatment and patient expectations may need to be considered before making changes in statin therapy in the absence of CK elevations.

A limitation of study-level meta-analyses is that definitions,[56] assessment, and variable reporting of muscle-related outcomes may differ across studies. Aggregation of heterogeneous outcomes and estimated outcomes (e.g., myopathy) not explicitly reported by investigators can mask an effect. Protocol differences may partially explain incidence disparities across studies. However, use of the RR to estimate effect size minimizes bias due to between-study variations in protocol (e.g., using a symptom checklist versus recording spontaneous mention of symptoms and then categorizing responses).

Estimates in this analysis may have under-estimated SAMS by excluding patients with statin hypersensitivity, as four studies[12,37,40,45] (n=48,950) employed statin “washout” phases and eight trials[24,25,30,32,34–37,47] (n=34,042) excluded patients with known statin hypersensitivity. Collins et al. noted that “statin hypersensitivity” exclusion was a rare occurrence across these trials, as almost all patients enrolled were statin-naïve at screening.[3] The risk of attrition due to SAMS and rhabdomyolysis was actually highest

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in SEARCH, where an eight week long, active run-in phase was conducted,[3,10] although no patients were excluded for elevated muscle enzymes.[10] Also,an N-of-1 trial in patients who were considering stopping or who had stopped statin therapy because of muscle symptoms found no difference in severity of patient-reported muscle symptoms between statin and placebo groups.[57] Because simvastatin 80 mg trials comprise a high proportion of high intensity treatment evidence, this may limit interpretation of CK and rhabdomyolysis risk. Also, adverse events may have been increased due to the presence of co-morbidities; only three trials studied healthy adults (n=30,756).[26,37,46] A final limitation is that although risk estimates are based on the best available evidence and should provide relatively unbiased estimates, confidence intervals and alpha significance levels may be approximate due to multiple comparisons.

Conclusion

Statins likely cause SAMS, but at much lower rates than observational data suggest. We found significant, but small increases in risk for patient-reported muscle problems on high-intensity statins. Complaints of SAMS in observational studies may be related to statin therapy or patient expectations, but more likely may be due to methodological biases or the generally high prevalence of muscle problems.

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Contributorship Statement:

The first author (JD) was responsible for the design and implementation of the study analyses. He was one coder in selecting studies for inclusion, compiled the data for the outcomes of interest, analyzed the data in R, and is responsible for the final manuscript in its entirety. SW (Faculty PI) was responsible for the oversight and implementation of the project. She was the second coder for all trials and offered guidance and support in all decisions regarding design and implementation of the analysis.

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Competing Interests:

None to disclose

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Data Sharing Statement:

Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi.org/10.5061/dryad.kprr4xh2q

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Figure Legend:

Figure 1: Any Muscle Problems

Figure 2: Myalgia or Pain

Figure 3: Attrition Due to Muscle Symptoms

Figure 4: Rhabdomyolysis

Figure 5: CK >10x Upper Limit of Normal

TABLE 1: DESCRIPTION OF THE TRIALS

TABLE 2: RELATIVE RISK AND RISK DIFFERENCE RESULTS FOR COMPARISONS OF TREATMENT INTENSITY PAIRS

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TABLE 1: DESCRIPTION OF THE TRIALS

Trial Name	Total sample size	Special Population	Permit Prior statin†	Ave age	Run-in Period	Median Yrs F/U
Placebo-Moderate						
4D, A20[24]	1,255	DM II, ESRD	Y, -HS	66	Placebo	4.0
4S, S20-S40[25]	4,444	MI or angina	Y, -HS	59	Placebo	5.4
AFCAPS, L20-L40[26]	6,605	Healthy adults	N	58	Placebo+diet	5.2
ALERT, F40-F80[27]	2,094	Renal Trans	N	50	None	5.4
ASCOT, A10[28,29]	10,810	HTN+CVD risk	N	63	Not statin	3.3
ASPEN, A10[30]	2,410	DM II	Y, -HS	61	Placebo	4.0
AURORA, R10[31]	2,767	ESRD	N	64	Placebo	3.2
CARDS, A10[32,33]	2,838	DM II	Y, -HS	62	Placebo	4.0
CARE, P40[34]	4,159	MI	Y, -HS	59	Placebo	5.0
CORONA, R10[35]	5,011	ESRD	Y, -HS	73	Placebo	2.7
GISSI-HF, R10[36]	4,574	CHF	Y, -HS	68	None	3.9
HOPE-3, R10[37]	6,349	Healthy, CVD Risk	Y, -HS	66	Statin	5.6
LIPID, P40[38]	9,014	MI or angina	Y	62*	Placebo+diet	6.0 (*mean*)
LIPS, F80[39]	1,640	Coronary percut. intervention	Y	60	None	3.9
MRC/BHF (HPS), S40[40,41]	20,536	CHD/CHD Risk	N	64	Placebo, then statin	5 (*mean*)
PROSPER, P40[42]	5,804	Elderly, CHD risk	Y	75	Placebo	3.2 (*mean*)
WOSCOPS, P40[43,44]	6,604	Healthy males	Y	55	None	4.9 (*mean*)
Placebo-High						
JUPITER, R20[46]	17,802	Healthy adults	N	66	Placebo	1.9††
SPARCL, A80[45]	4,731	CVA/TIA	Y	63	None	4.9
TRACE, A40[47]	3,002	RA	N, -HS	61	None	2.5
Moderate-High						
A to Z, S40-S80 vs 0-S20[11]	4,497	Acute Coronary Syndrome	N	61	None	1.98
PROVE-IT, A80 vs P40[13]	4,162	Acute Coronary Syndrome	Y, if <80mg	58	None	2.0 (mean)
SEARCH, S80 vs S20[10]	12,064	MI	Y	64	Statin+ Placebo	6.7
TNT, A80 vs A10[12]	10,001	CHD	Y	61	Statin	4.9

*Median

†Y=Yes, N=No, -HS=statin hypersensitivity exclusion

†† Trial was designed for two years of follow-up, but met study end points and terminated the blinded portion of the study earlier.

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TABLE 2: RELATIVE RISK AND RISK DIFFERENCE RESULTS FOR COMPARISONS OF TREATMENT INTENSITY PAIRS

	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
Any Probs	1.010 (0.988,1.033)	0.000 (-0.001,0.001)	--	1.039 (1.004,1.075)	0.004 (-0.000,0.008)	--	1.049 (1.010,1.089)	0.004 (-0.001, 0.008)	--
Myalgia	1.090 (.9997,1.188)	0.001 (-0.000,0.001)	--	1.041 (1.001,1.083)	0.006 (0.001, 0.010)	173	1.134 (1.046,1.230)	0.007 (0.002, 0.011)	182
Attrition	1.127 (0.931,1.364)	0.001 (-000,0.001)	--	1.372 (1.091,1.726)	0.005 (0.002, 0.007)	218	1.155 (1.147,2.084)	0.005 (0.002, 0.008)	187
Rhabdo.	1.225 (0.624,2.405)	-0.000 (-0.001,0.001)	--	1.326 (0.487,3.614)	0.002 (0.001,0.003)	--	1.624 (0.579,4.553)	0.002 (0.000, 0.003)	--
CK> 10xULN	1.143 (0.686,1.905)	-0.000 (-0.001,0.001)	--	4.594 (2.320,9.098)	0.002 (0.001, 0.003)	527	5.252 (2.293,12.028)	0.002 (0.000, 0.003)	589

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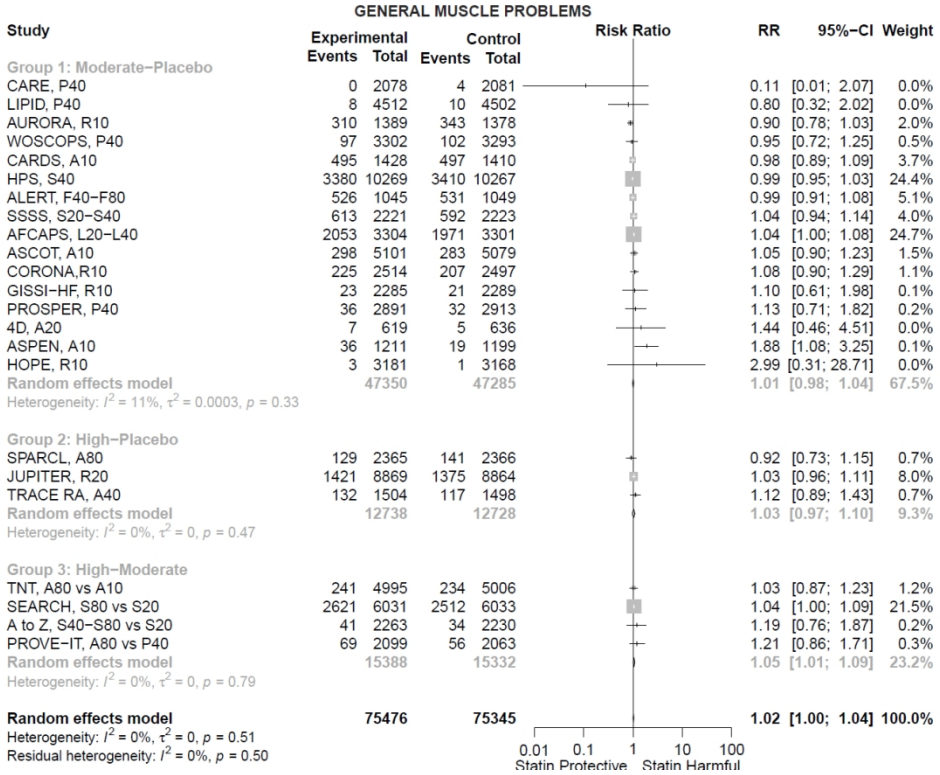

Figure 1

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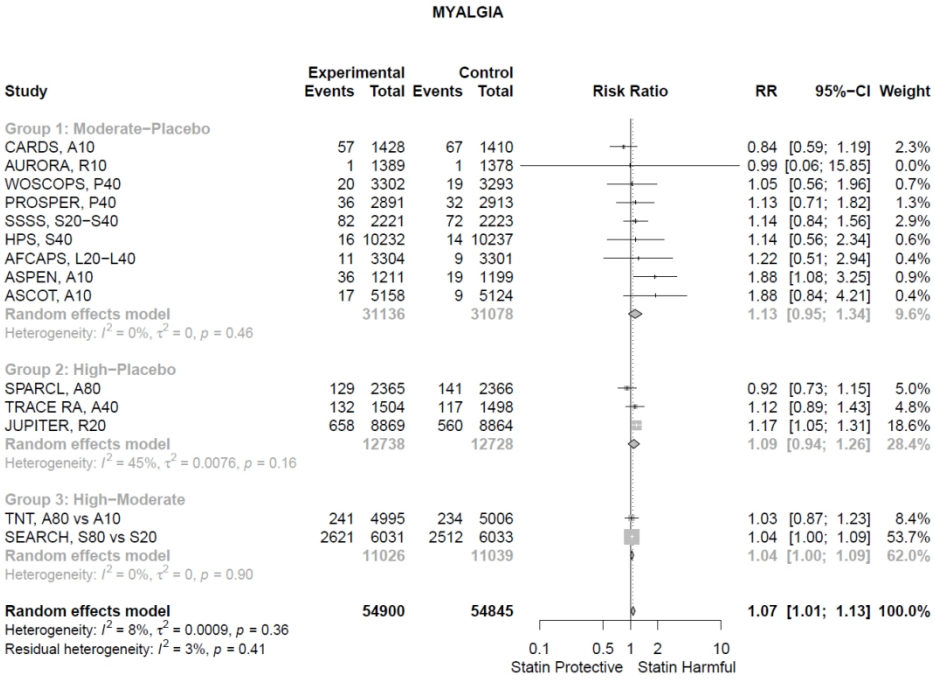

Figure 2

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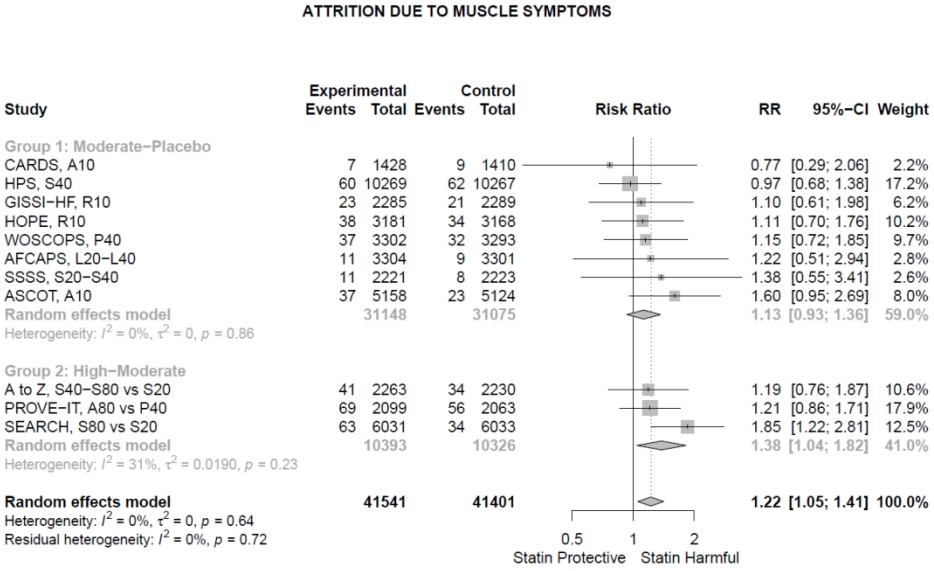

Figure 3

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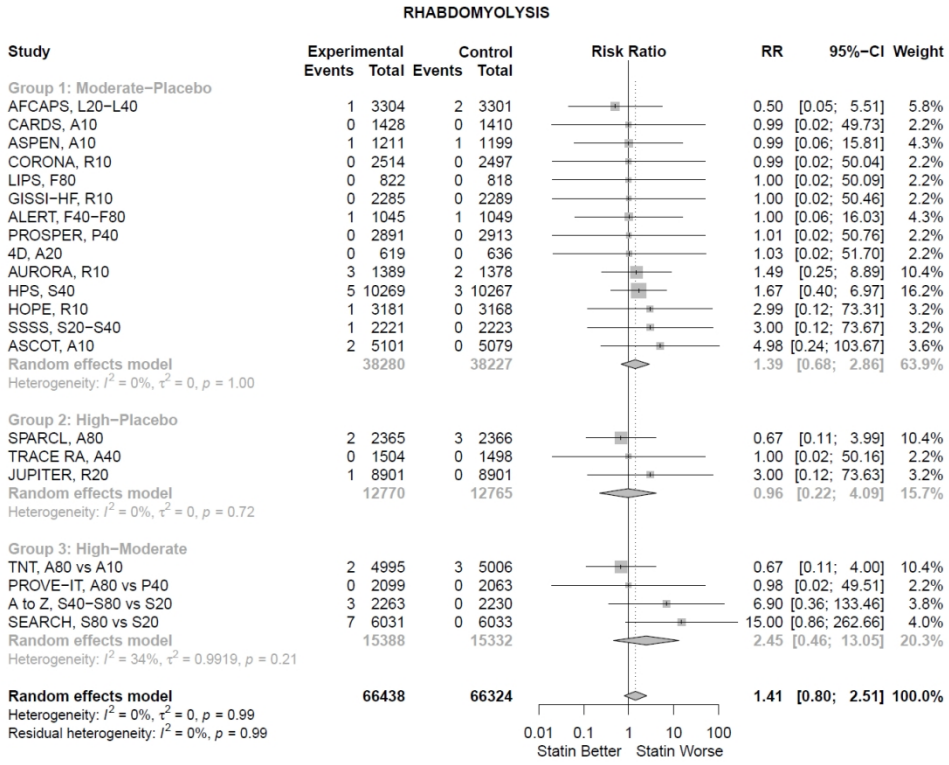

Figure 4

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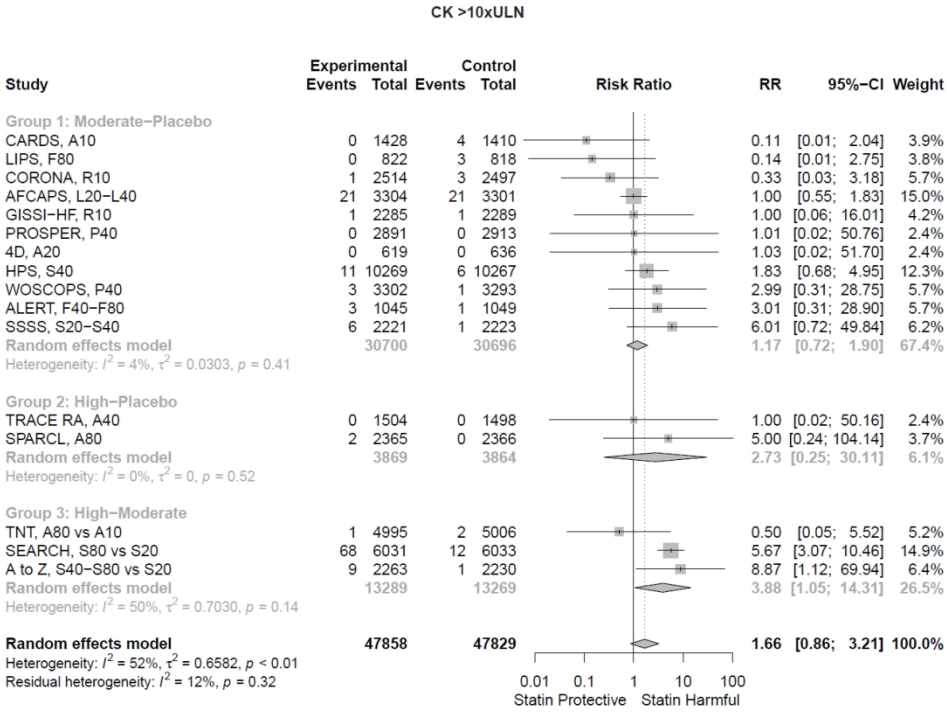

Figure 5

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INTENSITY OF STATIN THERAPY AND MUSCLE SYMPTOMS:

A NETWORK META-ANALYSIS OF 153,000 PATIENTS

J.W. Davis & S.C. Weller

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27 RHABDOMYOLYSIS: Meta-Analysis Funnel Plot

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

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

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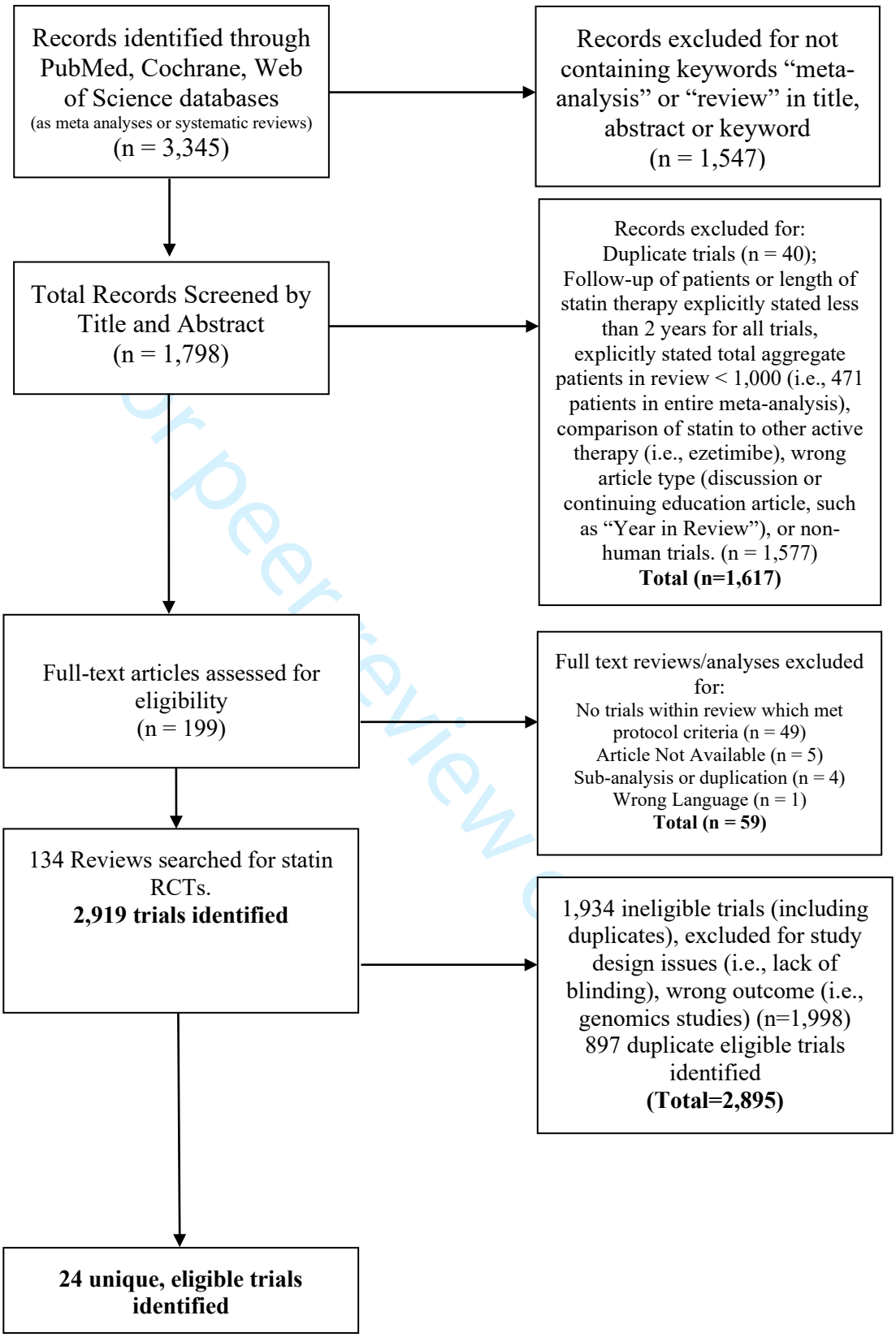
PRISMA FLOW SHEET



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.

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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.

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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	(ci 981 or ci981 or liptonorm).mp.	123	Advanced
24	(6 methylcompactin or mk 803 or mk803 or mevinolin or monacolin k).mp.	602	Advanced
25	(mevalotol 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 ellsor or eptastatin or lipemol or lipiat or llostat 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	(201801* or 201802* or 201803* or 201804* or 201805* or 201806* or 201807* or 201808* or 201809* or 201810* or 201811*).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

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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 ($p>0.05$)

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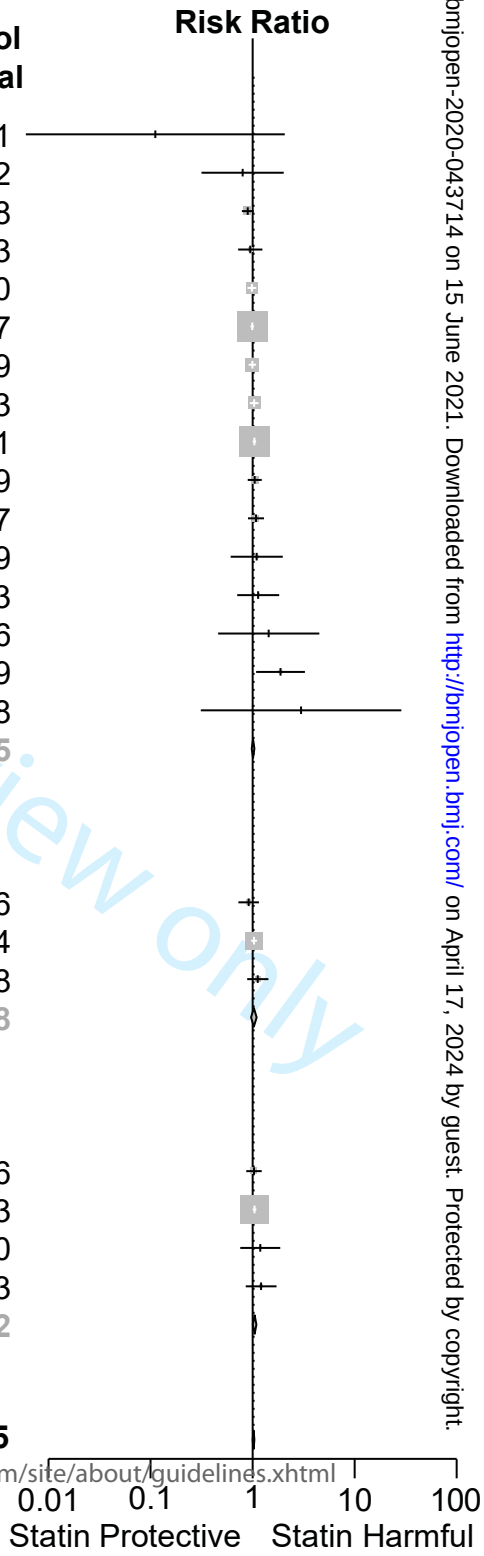
ANY MUSCLE PROBLEMS: Meta-Analysis Forest plot with data.

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							



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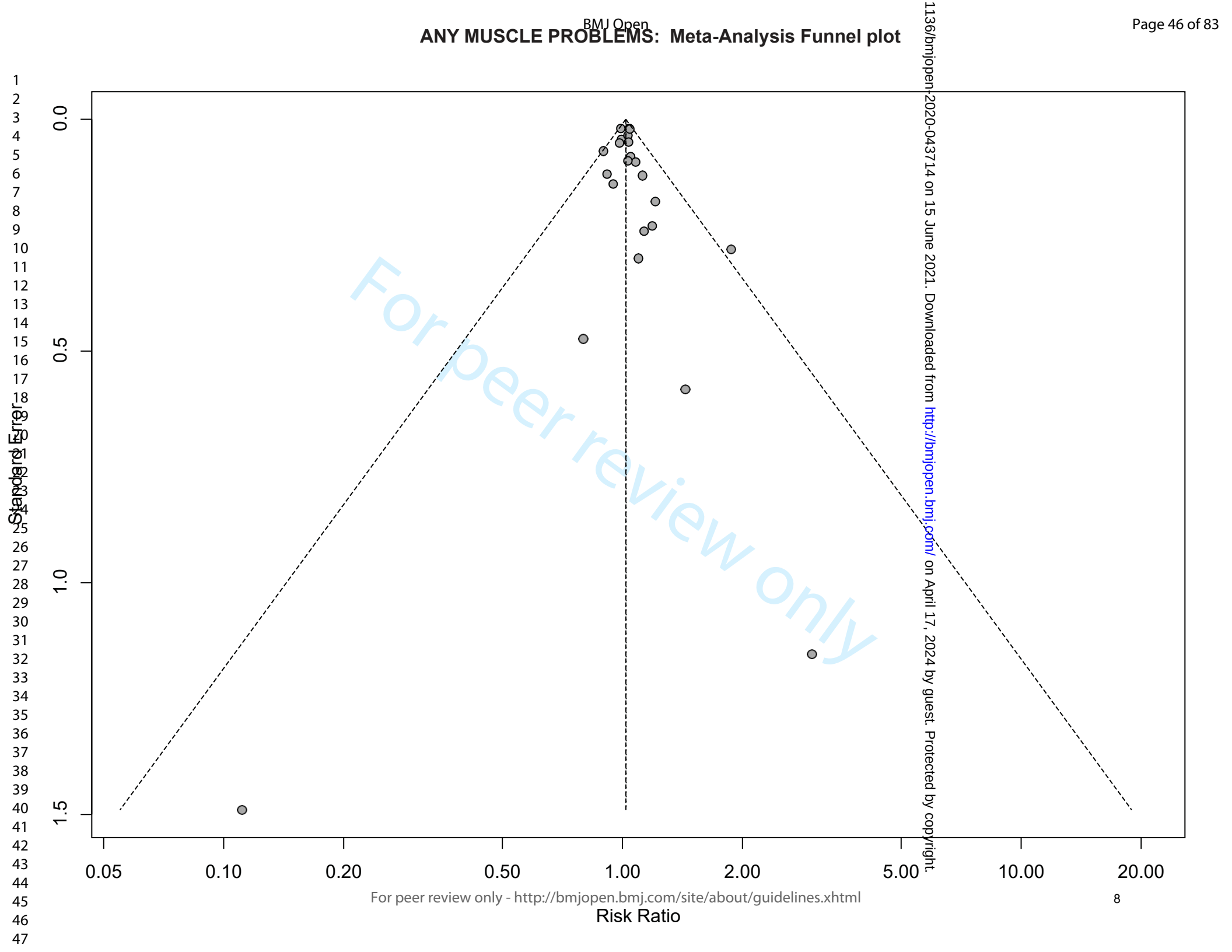

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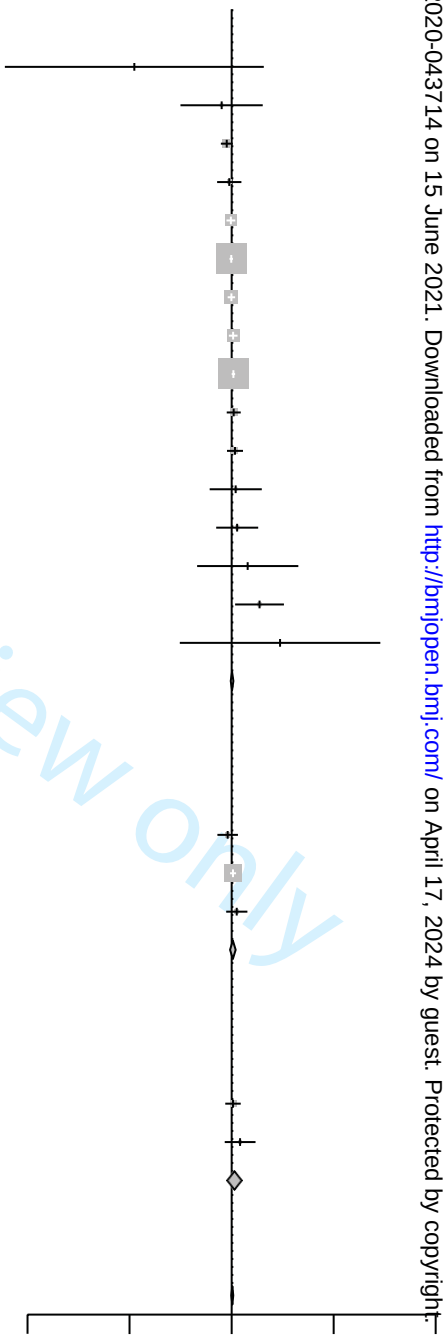
GENERAL MUSCLE PROBLEMS. Outliers excluded. Forest plot.

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]	0.1%
AURORA, R10	310	1389	343	1378	0.90	[0.78; 1.03]	2.6%
WOSCOPS, P40	97	3302	102	3293	0.95	[0.72; 1.25]	0.6%
CARDS, A10	495	1428	497	1410	0.98	[0.89; 1.09]	4.7%
HPS, S40	3380	10269	3410	10267	0.99	[0.95; 1.03]	31.1%
ALERT, F40−F80	526	1045	531	1049	0.99	[0.91; 1.08]	6.5%
SSSS, S20−S40	613	2221	592	2223	1.04	[0.94; 1.14]	5.1%
AFCAPS, L20−L40	2053	3304	1971	3301	1.04	[1.00; 1.08]	31.6%
ASCOT, A10	298	5101	283	5079	1.05	[0.90; 1.23]	1.9%
CORONA,R10	225	2514	207	2497	1.08	[0.90; 1.29]	1.4%
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]	0.2%
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]**	**86.2%**
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]	0.9%
JUPITER, R20	1421	8869	1375	8864	1.03	[0.96; 1.11]	10.2%
TRACE RA, A40	132	1504	117	1498	1.12	[0.89; 1.43]	0.8%
Random effects model		**12738**		**12728**	**1.03**	**[0.97; 1.10]**	**11.9%**
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]	1.5%
PROVE−IT, A80 vs P40	69	2099	56	2063	1.21	[0.86; 1.71]	0.4%
Random effects model		**7094**		**7069**	**1.07**	**[0.91; 1.25]**	**1.9%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.42							
Random effects model		**67182**		**67082**	**1.02**	**[0.99; 1.04]**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.49							
Residual heterogeneity: I^2 = 5%, p = 0.40							



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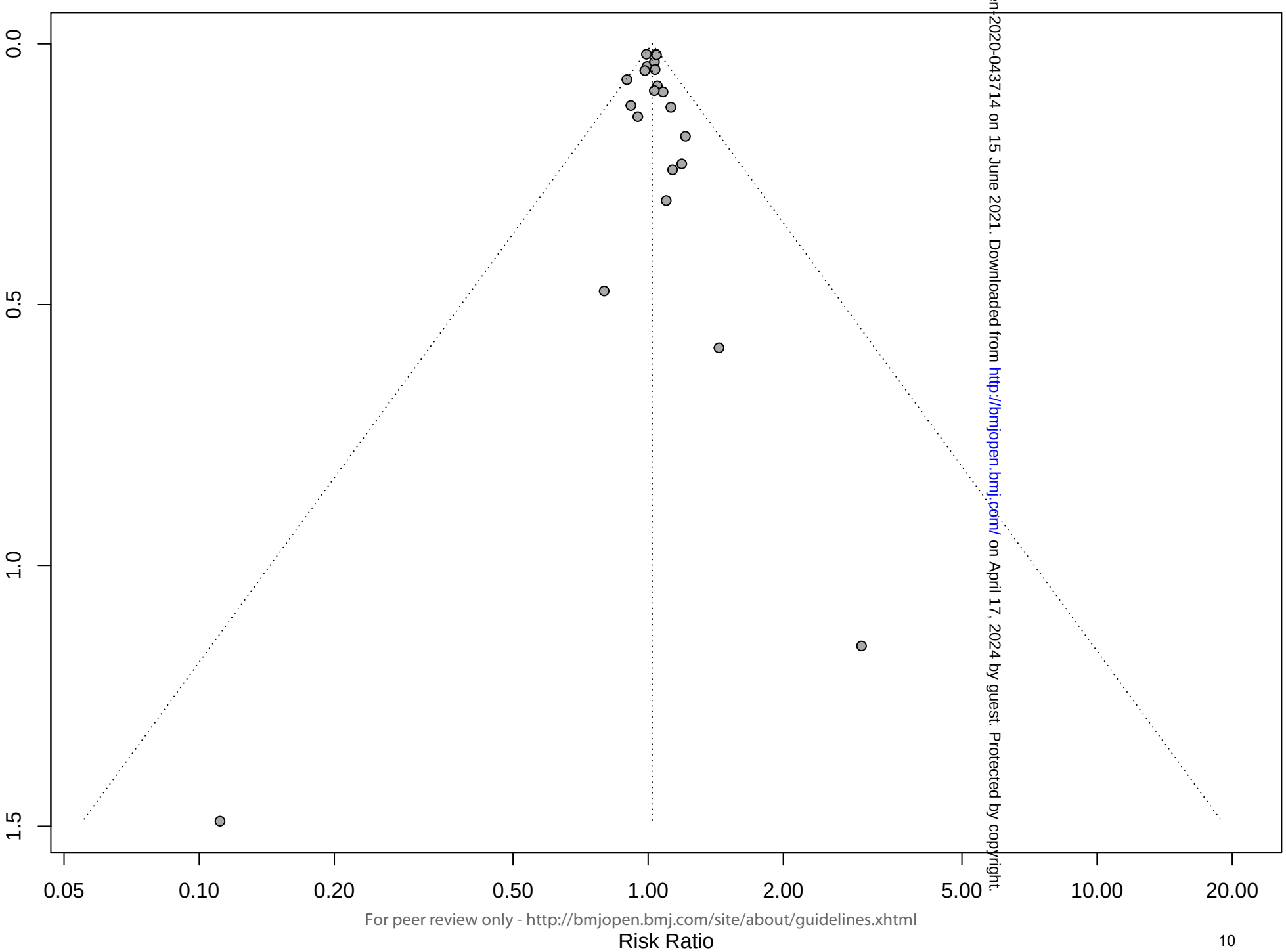
GENERAL MUSCLE PROBLEMS. Outliers excluded. Funnel plot.



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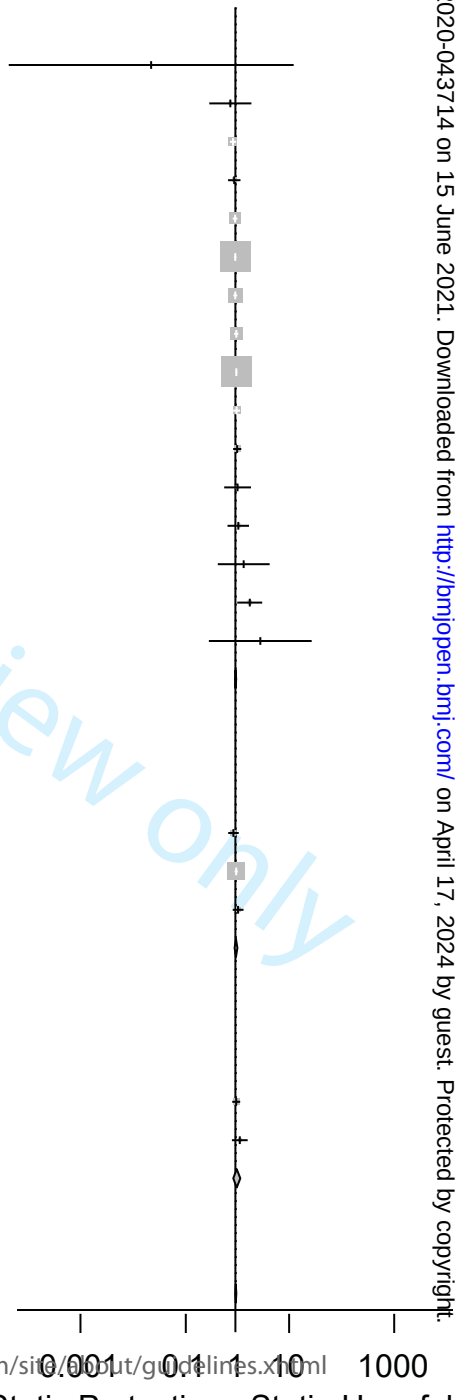
GENERAL MUSCLE PROBLEMS. Continuity Correction = 0.1. Forest plot.

Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	Weight
Group 1: Moderate−Placebo							
CARE, P40	0	2078	4	2081	0.02	[0.00; 12.94]	0.0%
LIPID, P40	8	4512	10	4502	0.80	[0.32; 2.02]	0.1%
AURORA, R10	310	1389	343	1378	0.90	[0.78; 1.03]	2.6%
WOSCOPS, P40	97	3302	102	3293	0.95	[0.72; 1.25]	0.6%
CARDS, A10	495	1428	497	1410	0.98	[0.89; 1.09]	4.7%
HPS, S40	3380	10269	3410	10267	0.99	[0.95; 1.03]	31.1%
ALERT, F40−F80	526	1045	531	1049	0.99	[0.91; 1.08]	6.6%
SSSS, S20−S40	613	2221	592	2223	1.04	[0.94; 1.14]	5.1%
AFCAPS, L20−L40	2053	3304	1971	3301	1.04	[1.00; 1.08]	31.6%
ASCOT, A10	298	5101	283	5079	1.05	[0.90; 1.23]	1.9%
CORONA,R10	225	2514	207	2497	1.08	[0.90; 1.29]	1.4%
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]	0.2%
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]**	**86.2%**
Heterogeneity: I^2 = 6%, τ^2 = 0.0002, p = 0.39							
Group 2: High−Placebo							
SPARCL, A80	129	2365	141	2366	0.92	[0.73; 1.15]	0.9%
JUPITER, R20	1421	8869	1375	8864	1.03	[0.96; 1.11]	10.2%
TRACE RA, A40	132	1504	117	1498	1.12	[0.89; 1.43]	0.8%
Random effects model		**12738**		**12728**	**1.03**	**[0.97; 1.10]**	**11.9%**
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]	1.5%
PROVE−IT, A80 vs P40	69	2099	56	2063	1.21	[0.86; 1.71]	0.4%
Random effects model		**7094**		**7069**	**1.07**	**[0.91; 1.25]**	**1.9%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.42							
Random effects model		**67182**		**67082**	**1.02**	**[0.99; 1.04]**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.55							
Residual heterogeneity: I^2 = 0%, p = 0.45							



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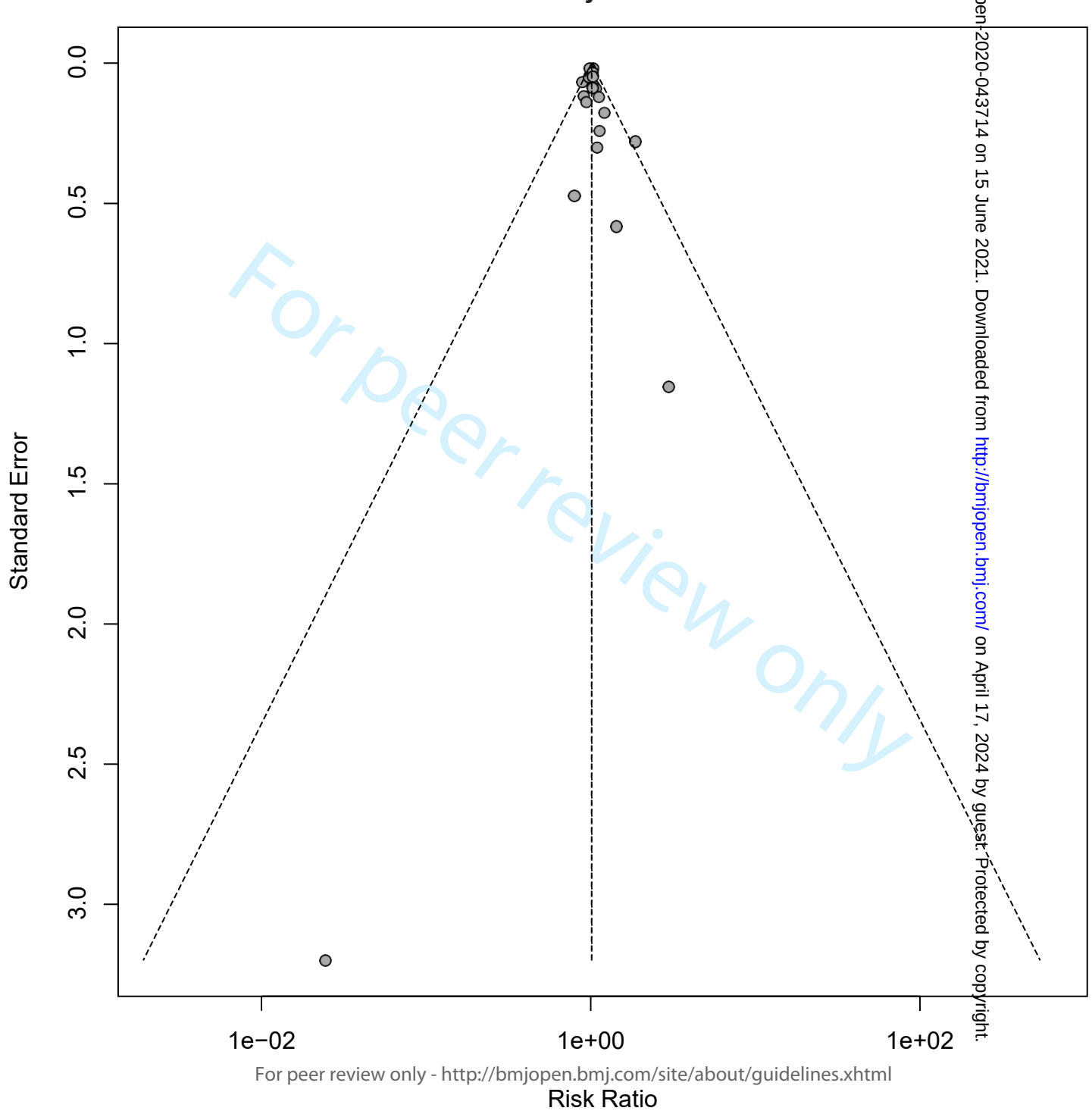

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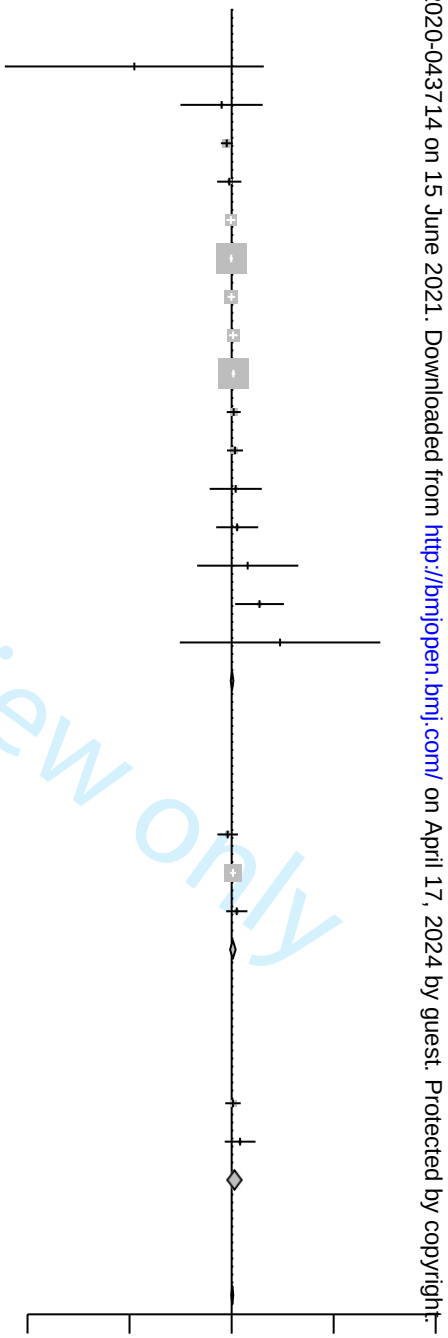
ANY MUSCLE PROBLEMS: Meta-Analysis Forest plot excluding simvastatin 80 mg trials.

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]	0.1%
AURORA, R10	310	1389	343	1378	0.90	[0.78; 1.03]	2.6%
WOSCOPS, P40	97	3302	102	3293	0.95	[0.72; 1.25]	0.6%
CARDS, A10	495	1428	497	1410	0.98	[0.89; 1.09]	4.7%
HPS, S40	3380	10269	3410	10267	0.99	[0.95; 1.03]	31.1%
ALERT, F40−F80	526	1045	531	1049	0.99	[0.91; 1.08]	6.5%
SSSS, S20−S40	613	2221	592	2223	1.04	[0.94; 1.14]	5.1%
AFCAPS, L20−L40	2053	3304	1971	3301	1.04	[1.00; 1.08]	31.6%
ASCOT, A10	298	5101	283	5079	1.05	[0.90; 1.23]	1.9%
CORONA,R10	225	2514	207	2497	1.08	[0.90; 1.29]	1.4%
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]	0.2%
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]**	**86.2%**
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]	0.9%
JUPITER, R20	1421	8869	1375	8864	1.03	[0.96; 1.11]	10.2%
TRACE RA, A40	132	1504	117	1498	1.12	[0.89; 1.43]	0.8%
Random effects model		**12738**		**12728**	**1.03**	**[0.97; 1.10]**	**11.9%**
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]	1.5%
PROVE−IT, A80 vs P40	69	2099	56	2063	1.21	[0.86; 1.71]	0.4%
Random effects model		**7094**		**7069**	**1.07**	**[0.91; 1.25]**	**1.9%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.42							
Random effects model		**67182**		**67082**	**1.02**	**[0.99; 1.04]**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.49							
Residual heterogeneity: I^2 = 5%, p = 0.40							



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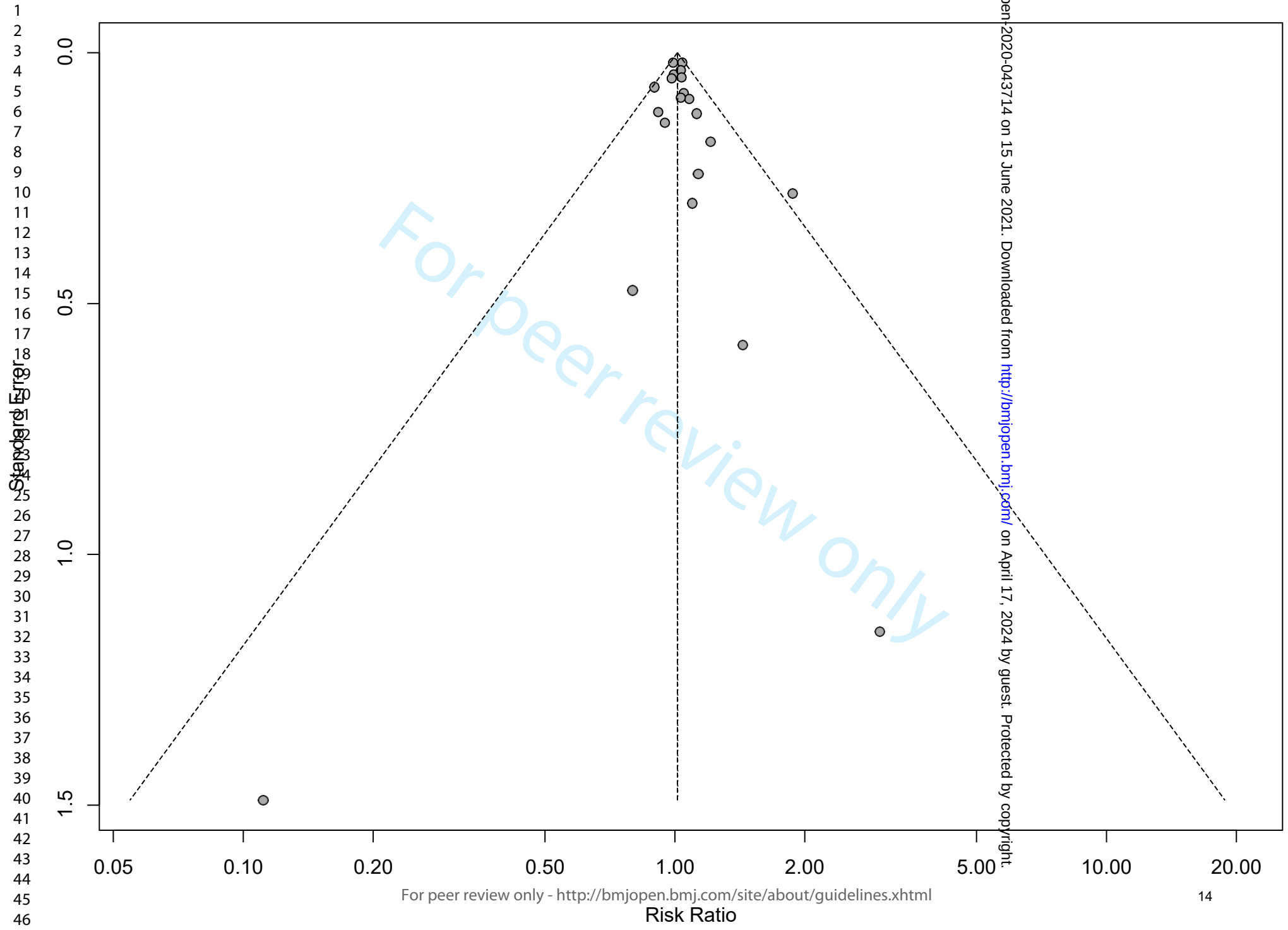
ANY MUSCLE PROBLEMS: Meta-Analysis Funnel plot excluding simvastatin 80 mg trials



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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)	--

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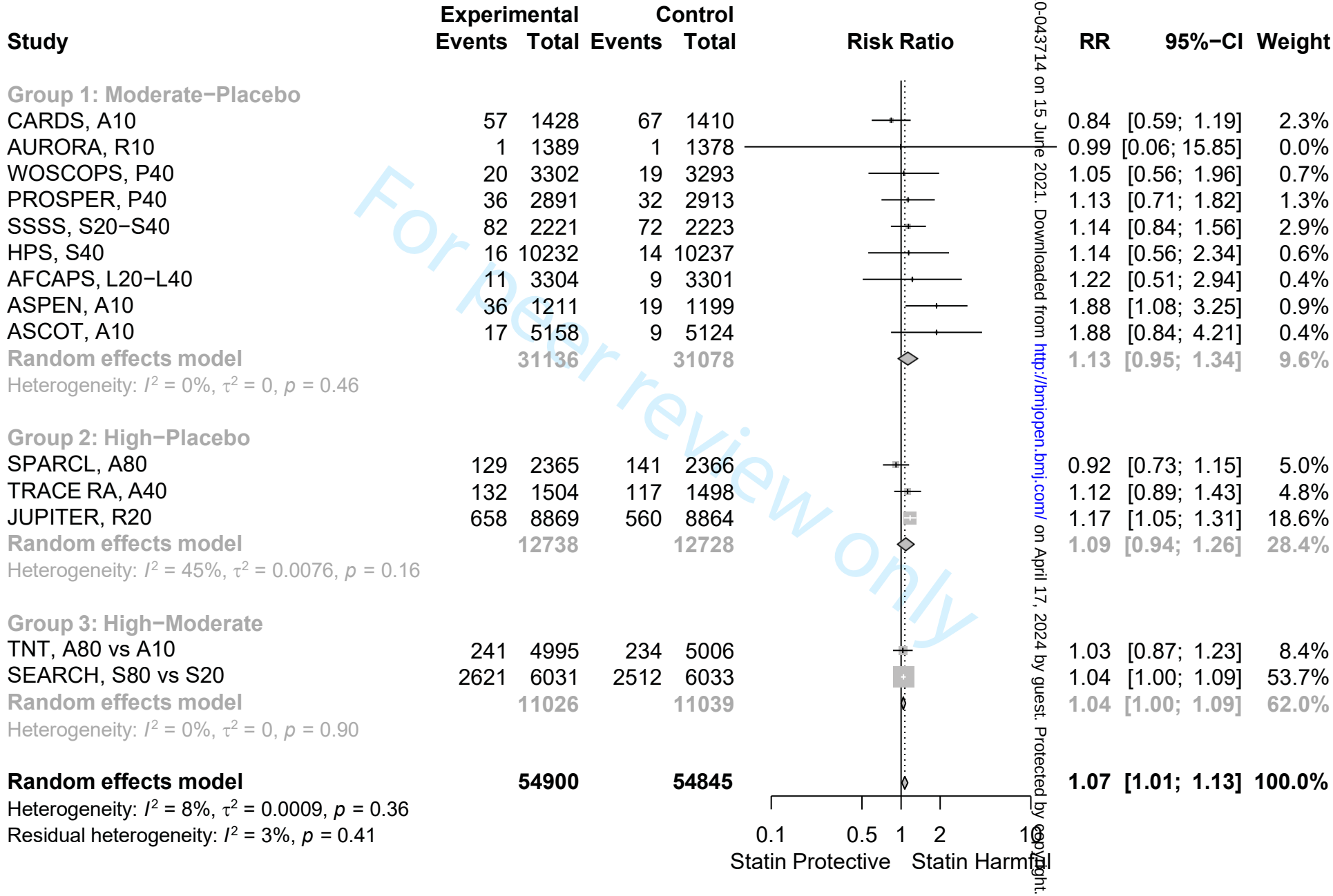
MYALGIA OR PAIN : Meta-Analysis Forest plot with data



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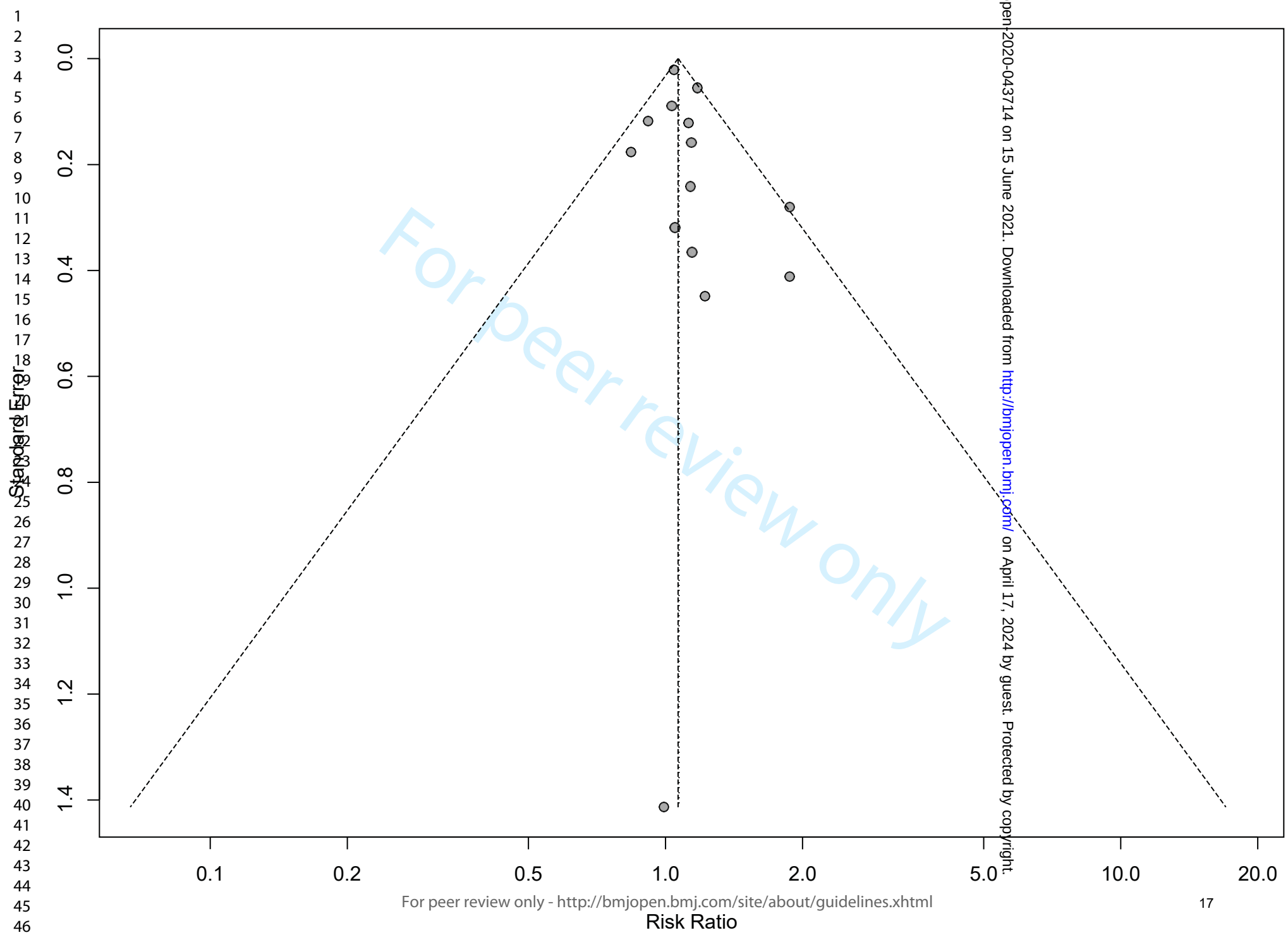

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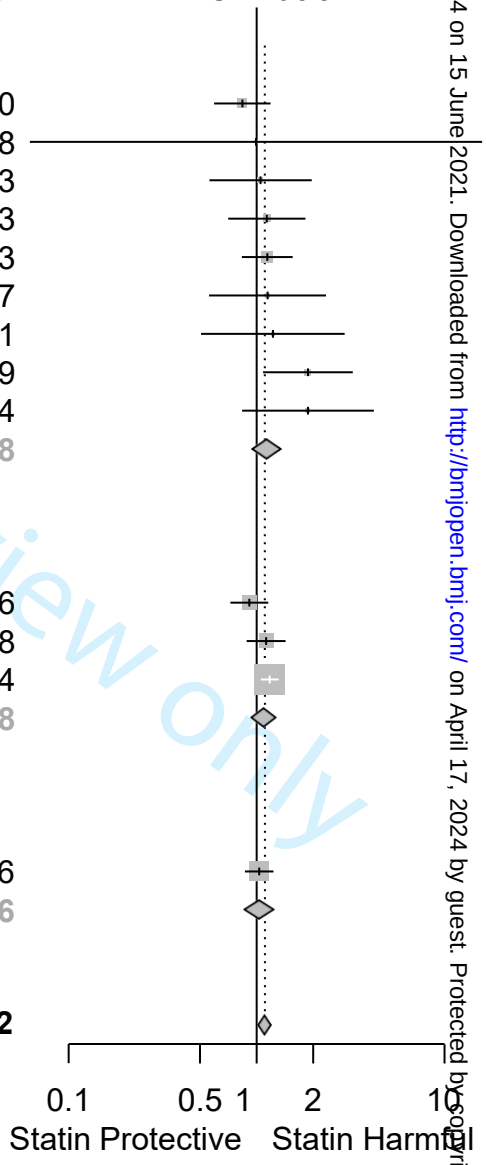
MYALGIA OR PAIN: Meta-Analysis Forest plot excluding simvastatin 80 mg trials.



Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	Weight
Group 1: Moderate−Placebo							
CARDS, A10	57	1428	67	1410	0.84	[0.59; 1.19]	4.6%
AURORA, R10	1	1389	1	1378	0.99	[0.06; 15.85]	0.1%
WOSCOPS, P40	20	3302	19	3293	1.05	[0.56; 1.96]	1.4%
PROSPER, P40	36	2891	32	2913	1.13	[0.71; 1.82]	2.5%
SSSS, S20−S40	82	2221	72	2223	1.14	[0.84; 1.56]	5.7%
HPS, S40	16	10232	14	10237	1.14	[0.56; 2.34]	1.1%
AFCAPS, L20−L40	11	3304	9	3301	1.22	[0.51; 2.94]	0.7%
ASPEN, A10	36	1211	19	1199	1.88	[1.08; 3.25]	1.8%
ASCOT, A10	17	5158	9	5124	1.88	[0.84; 4.21]	0.8%
Random effects model		**31136**		**31078**	**1.13**	**[0.95; 1.34]**	**18.7%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.46							
Group 2: High−Placebo							
SPARCL, A80	129	2365	141	2366	0.92	[0.73; 1.15]	10.1%
TRACE RA, A40	132	1504	117	1498	1.12	[0.89; 1.43]	9.6%
JUPITER, R20	658	8869	560	8864	1.17	[1.05; 1.31]	44.0%
Random effects model		**12738**		**12728**	**1.09**	**[0.94; 1.26]**	**63.8%**
Heterogeneity: I^2 = 45%, τ^2 = 0.0076, p = 0.16							
Group 3: High−Moderate							
TNT, A80 vs A10	241	4995	234	5006	1.03	[0.87; 1.23]	17.5%
Random effects model		**4995**		**5006**	**1.03**	**[0.87; 1.23]**	**17.5%**
Heterogeneity: not applicable							
Random effects model		**48869**		**48812**	**1.11**	**[1.03; 1.19]**	**100.0%**
Heterogeneity: I^2 = 1%, τ^2 = 0.0002, p = 0.44							
Residual heterogeneity: I^2 = 12%, p = 0.33							

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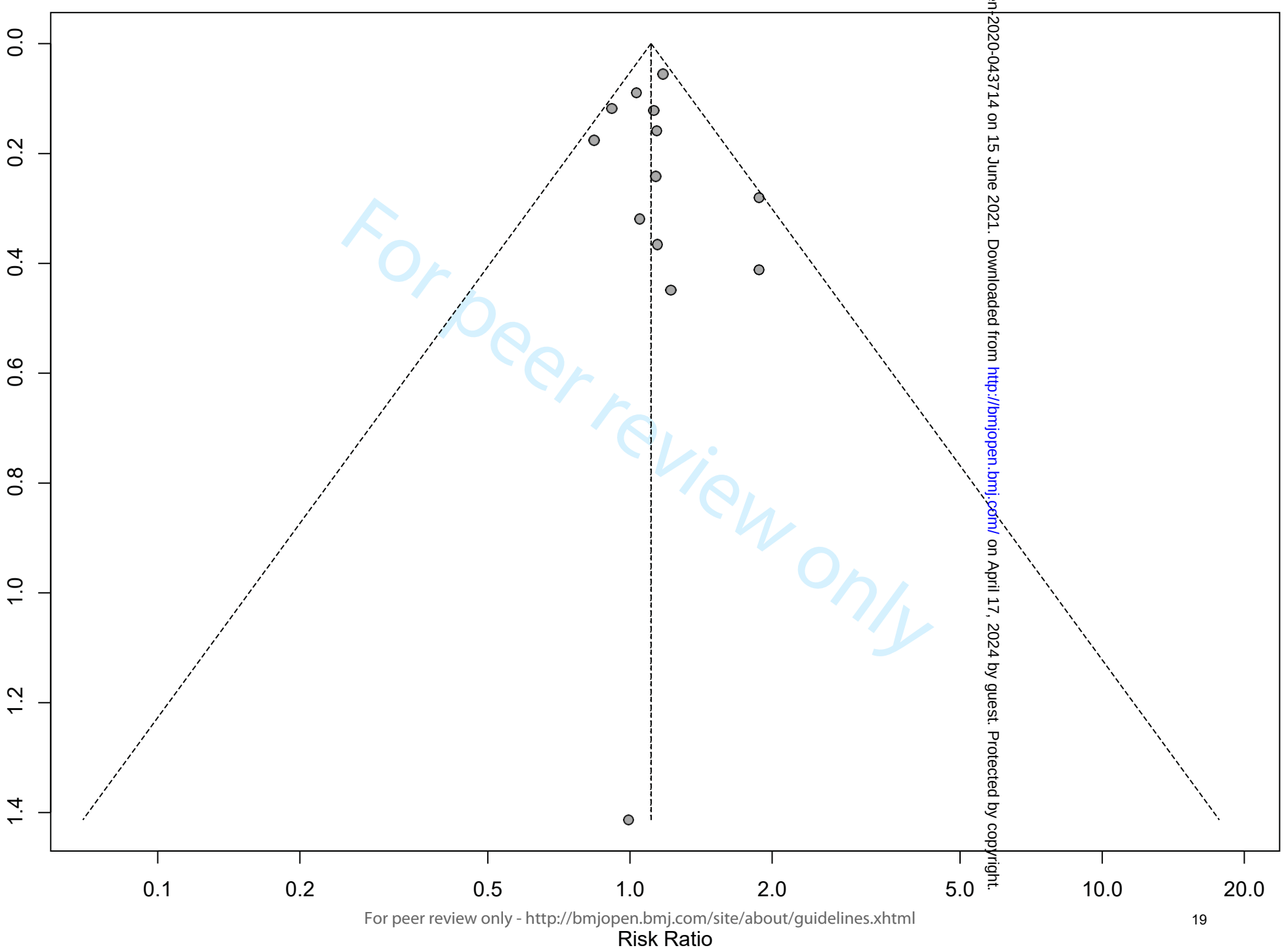
MYALGIA OR PAIN. Meta-Analysis Funnel plot excluding simvastatin 80 mg trials



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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

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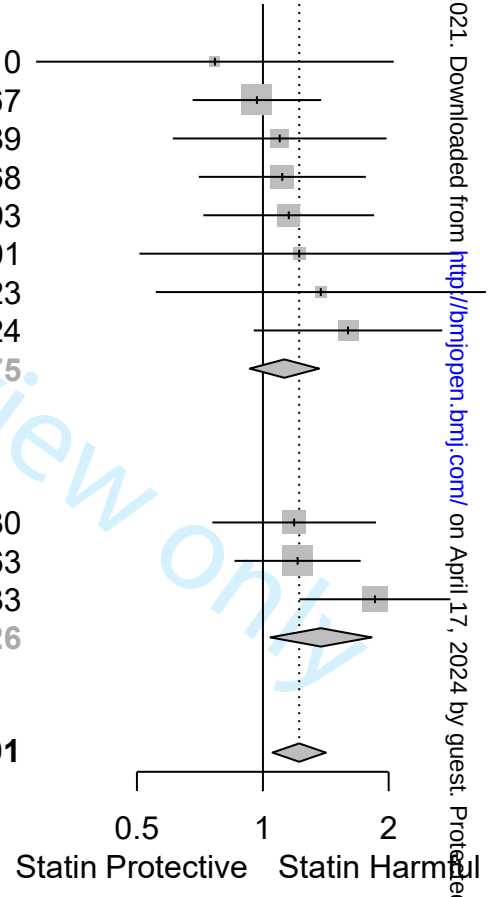
ATTRITION: Meta-Analysis Forest plot with data

Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	Weight
Group 1: Moderate−Placebo							
CARDS, A10	7	1428	9	1410	0.77	[0.29; 2.06]	2.2%
HPS, S40	60	10269	62	10267	0.97	[0.68; 1.38]	17.2%
GISSI−HF, R10	23	2285	21	2289	1.10	[0.61; 1.98]	6.2%
HOPE, R10	38	3181	34	3168	1.11	[0.70; 1.76]	10.2%
WOSCOPS, P40	37	3302	32	3293	1.15	[0.72; 1.85]	9.7%
AFCAPS, L20−L40	11	3304	9	3301	1.22	[0.51; 2.94]	2.8%
SSSS, S20−S40	11	2221	8	2223	1.38	[0.55; 3.41]	2.6%
ASCOT, A10	37	5158	23	5124	1.60	[0.95; 2.69]	8.0%
Random effects model		31148		31075	1.13	[0.93; 1.36]	59.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.86							
Group 2: High−Moderate							
A to Z, S40−S80 vs S20	41	2263	34	2230	1.19	[0.76; 1.87]	10.6%
PROVE−IT, A80 vs P40	69	2099	56	2063	1.21	[0.86; 1.71]	17.9%
SEARCH, S80 vs S20	63	6031	34	6033	1.85	[1.22; 2.81]	12.5%
Random effects model		10393		10326	1.38	[1.04; 1.82]	41.0%
Heterogeneity: I^2 = 31%, τ^2 = 0.0190, p = 0.23							
Random effects model		**41541**		**41401**	**1.22**	**[1.05; 1.41]**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.64							
Residual heterogeneity: I^2 = 0%, p = 0.72							



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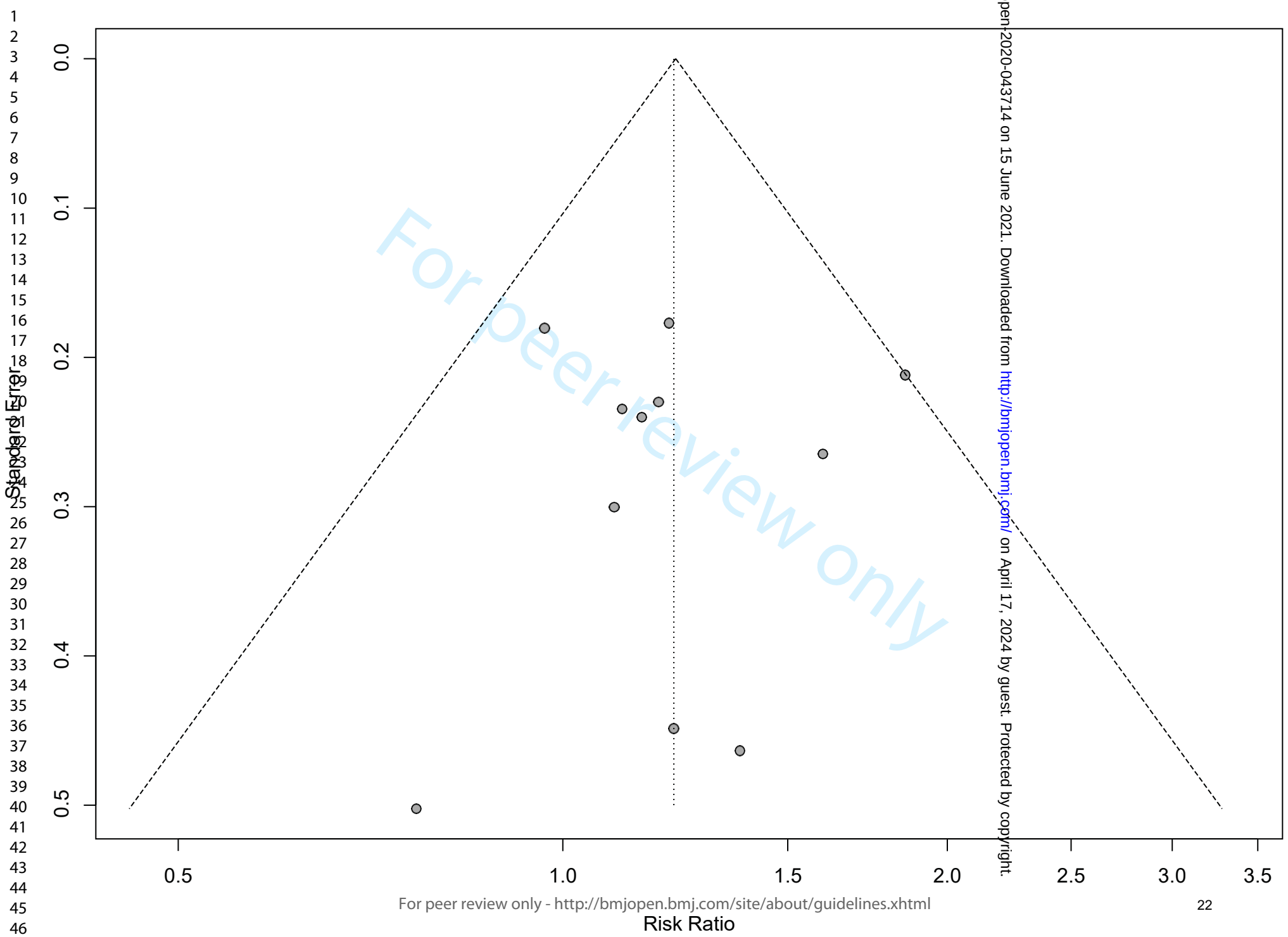
ATTRITION: Meta-Analysis Funnel plot



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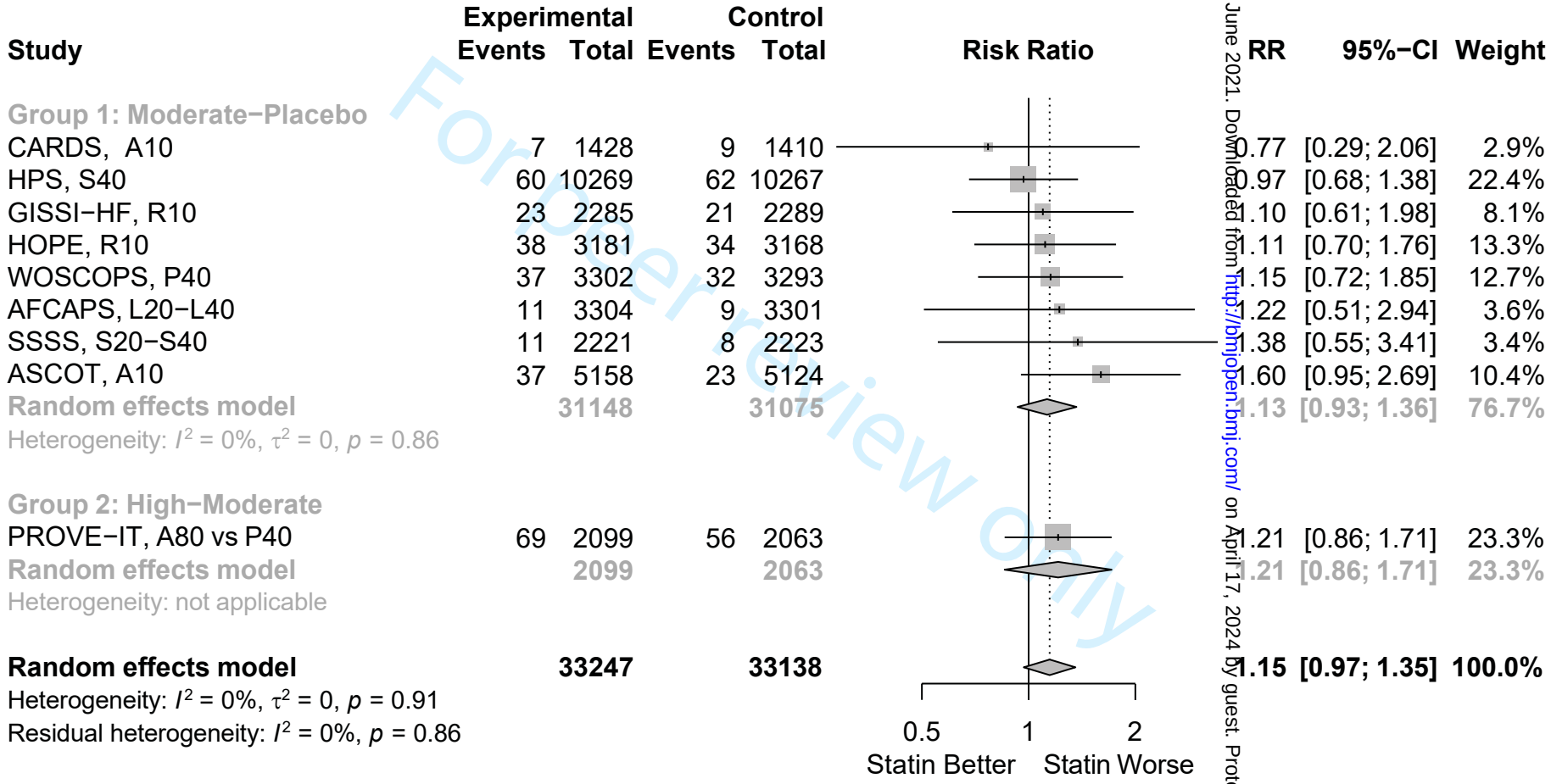
ATTRITION: Meta-Analysis Forest plot excluding simvastatin 80 mg trials.



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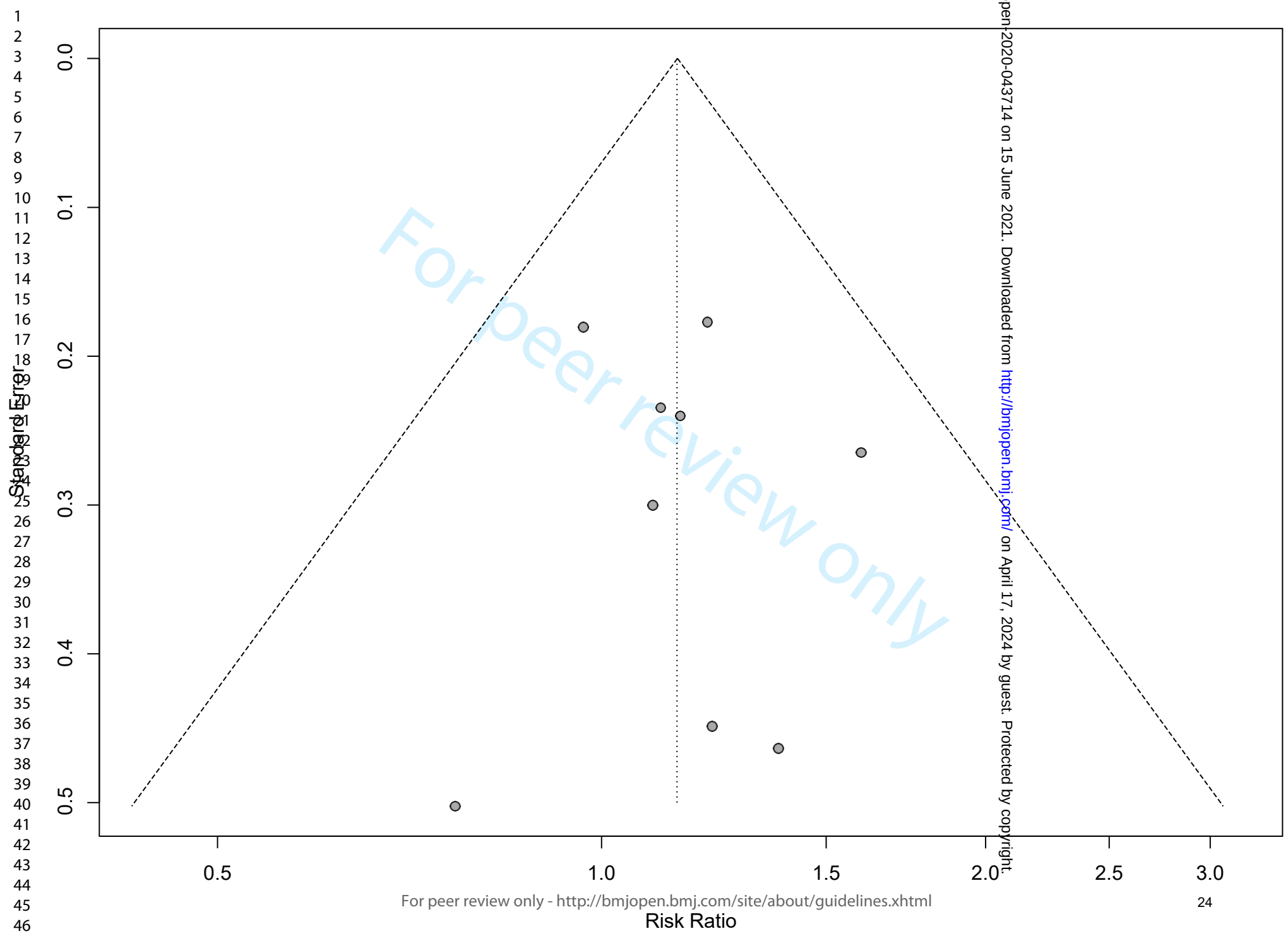
ATTRITION: Meta-Analysis Funnel plot excluding simvastatin 80 mg trials



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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*

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RHABDOMYOLYSIS: Meta-Analysis Forest Plot with Data

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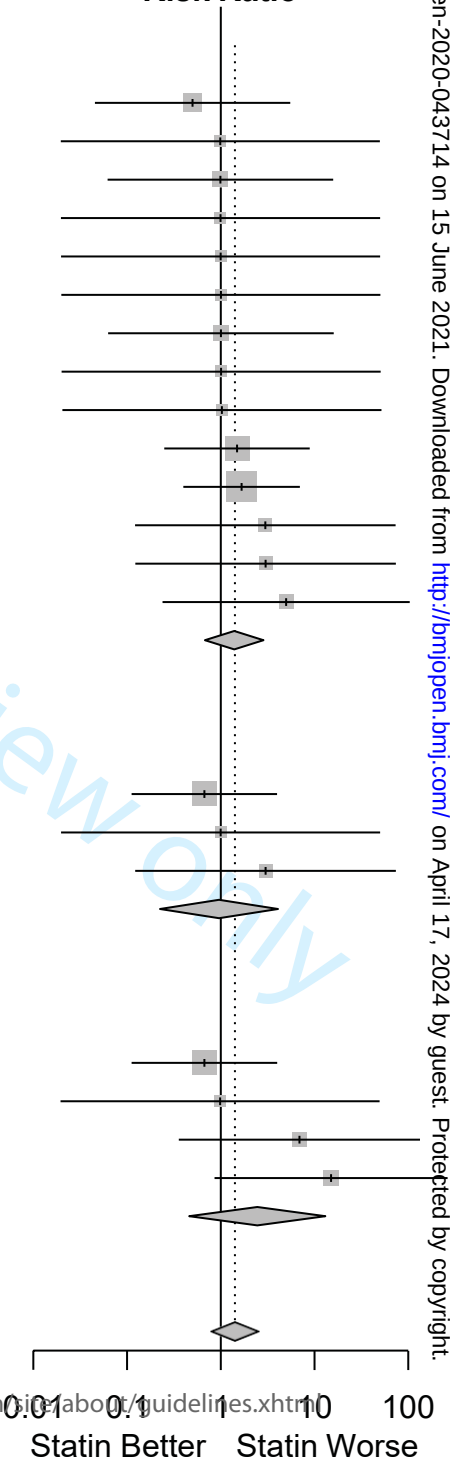
Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	Weight
Group 1: Moderate−Placebo							
AFCAPS, L20−L40	1	3304	2	3301	0.50	[0.05; 5.51]	5.8%
CARDS, A10	0	1428	0	1410	0.99	[0.02; 49.73]	2.2%
ASPEN, A10	1	1211	1	1199	0.99	[0.06; 15.81]	4.3%
CORONA, R10	0	2514	0	2497	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							



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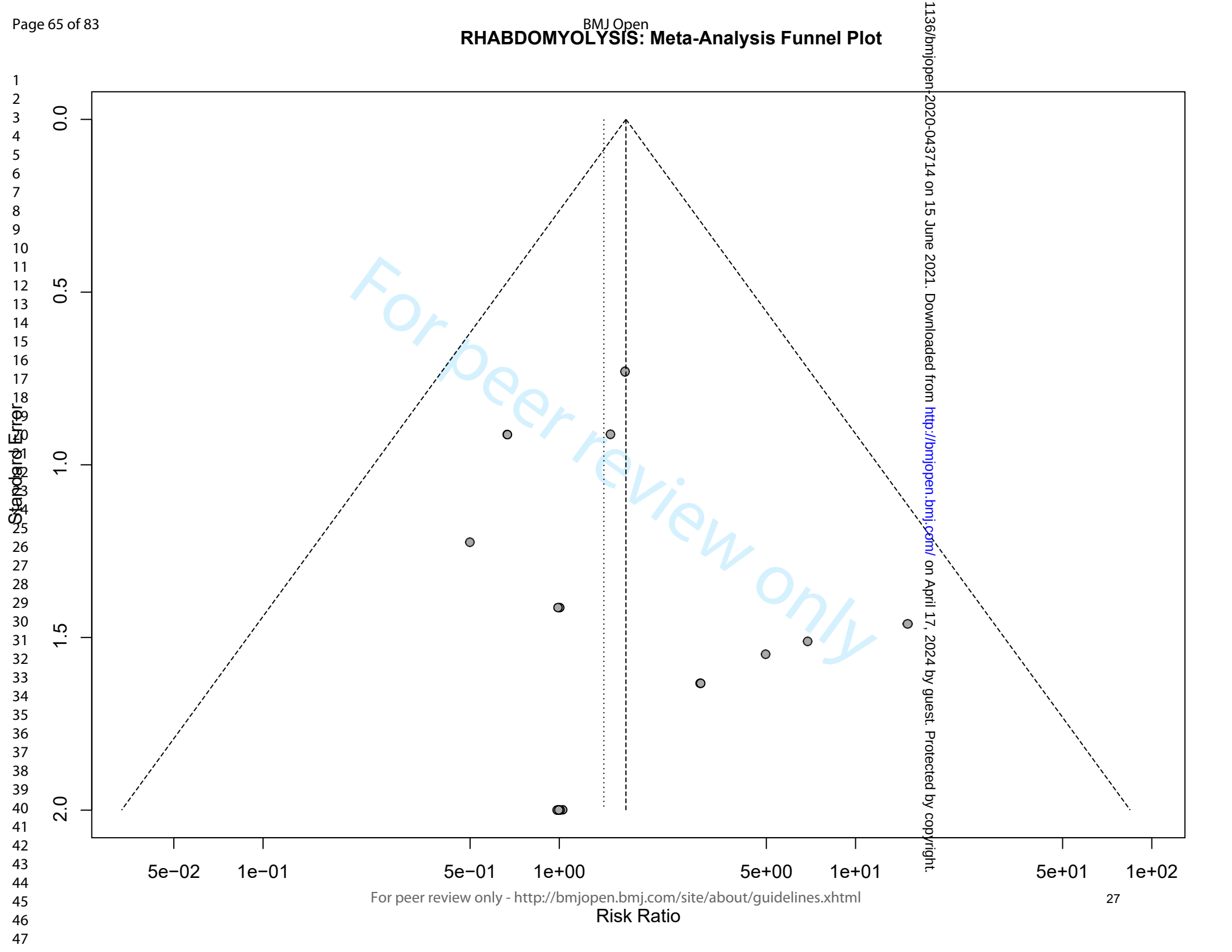

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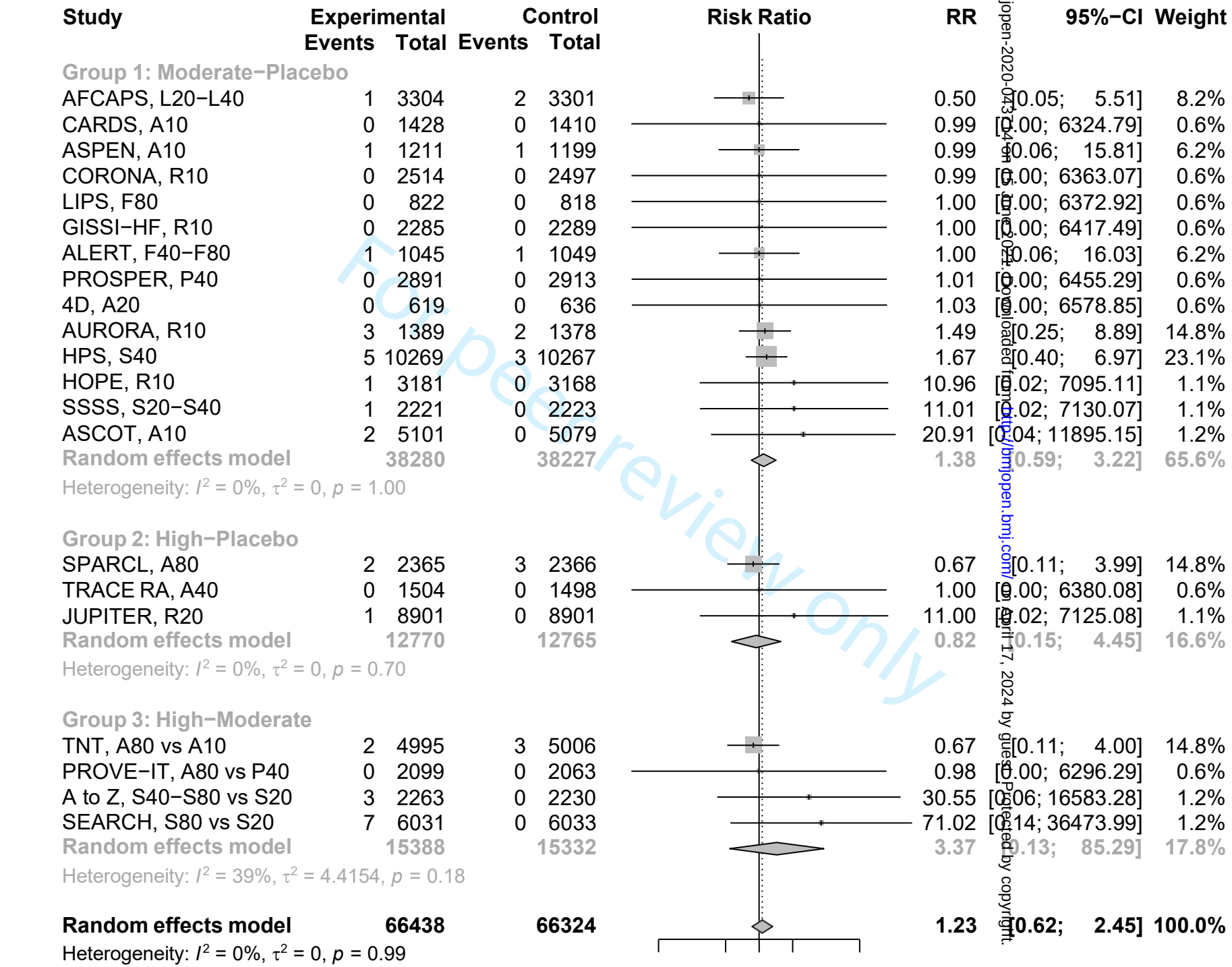
RHABDOMYOLYSIS: Meta-Analysis Forest Plot with Continuity Correction = 0.1.



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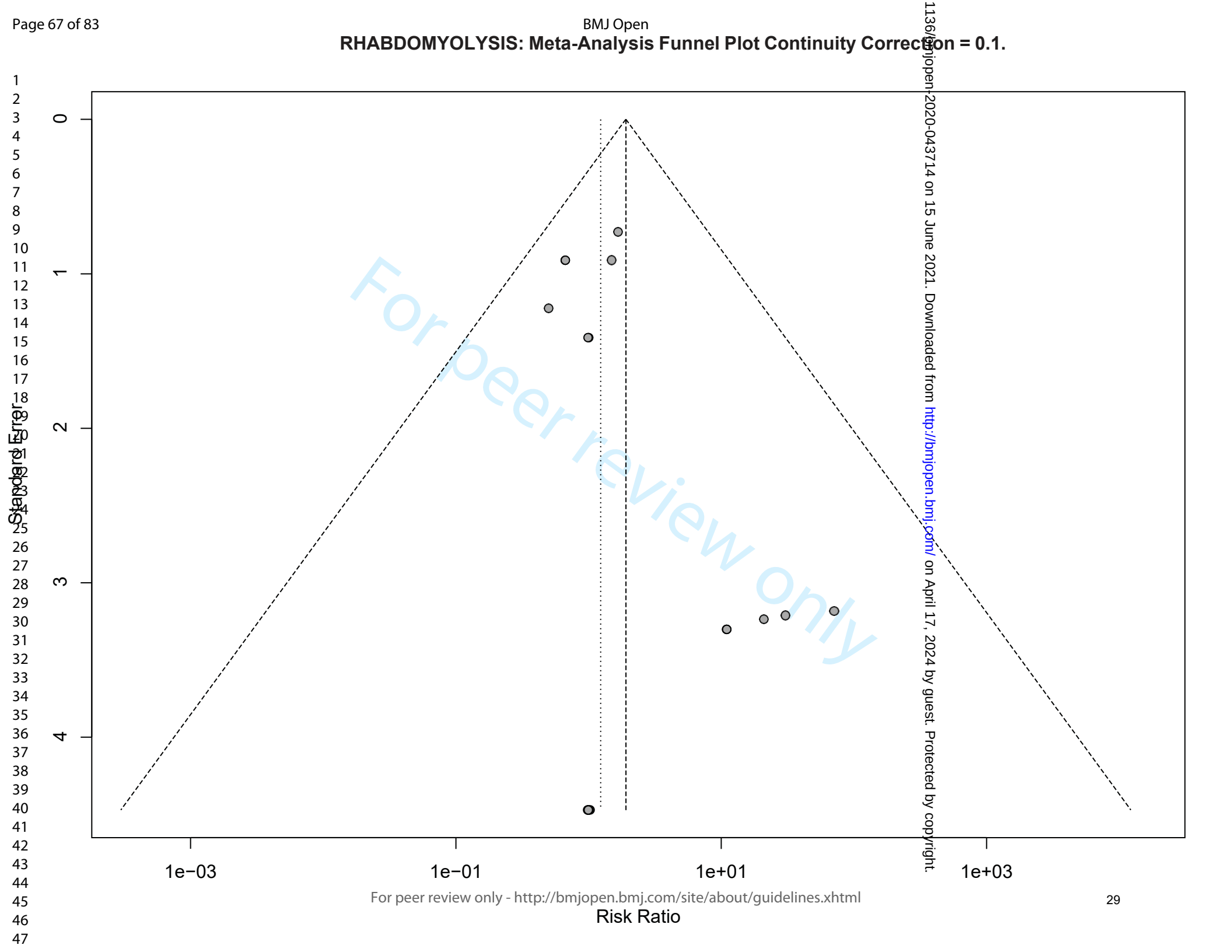

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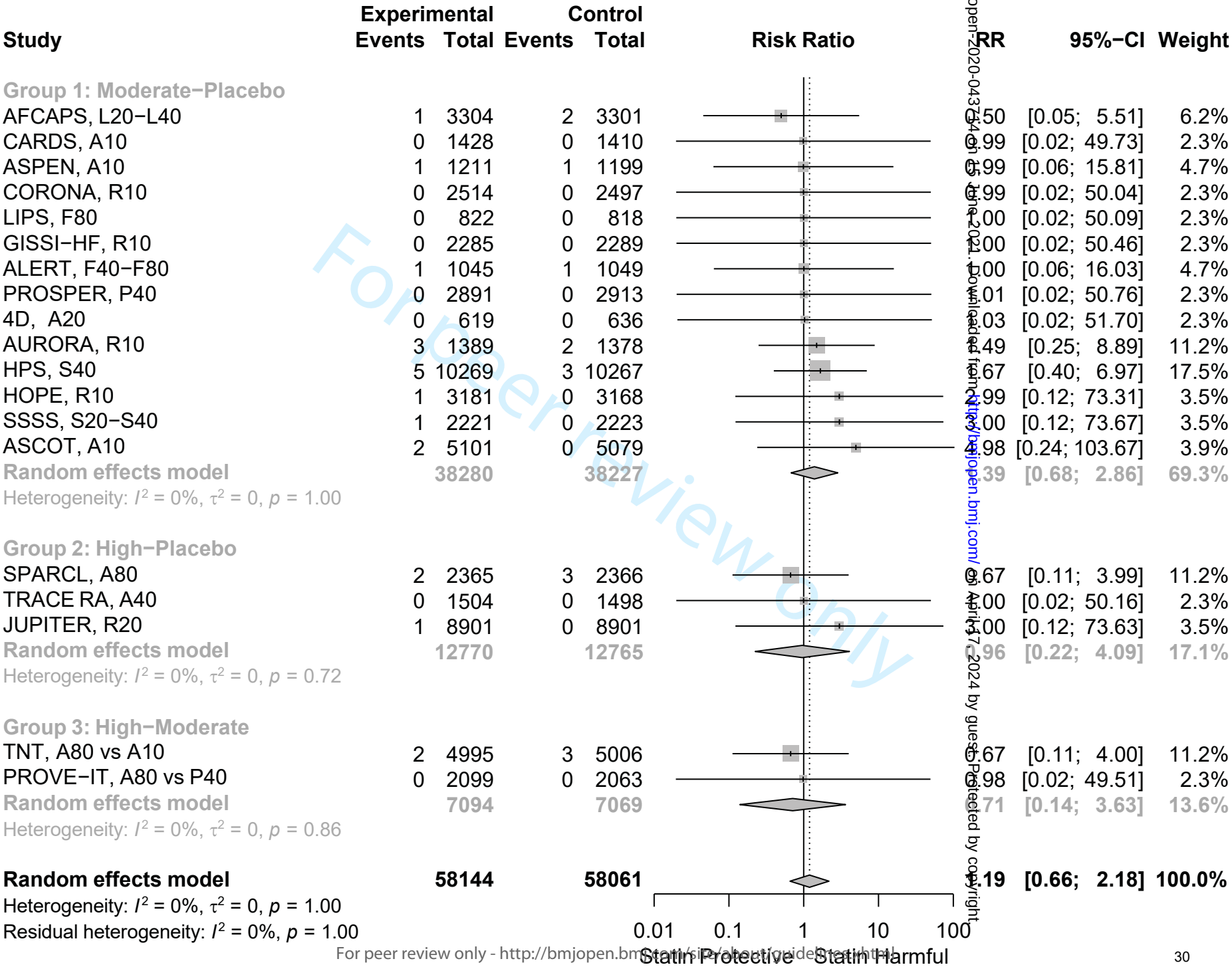
RHABDOMYOLYSIS: Meta-Analysis Forest plot excluding simvastatin 80 mg trials.



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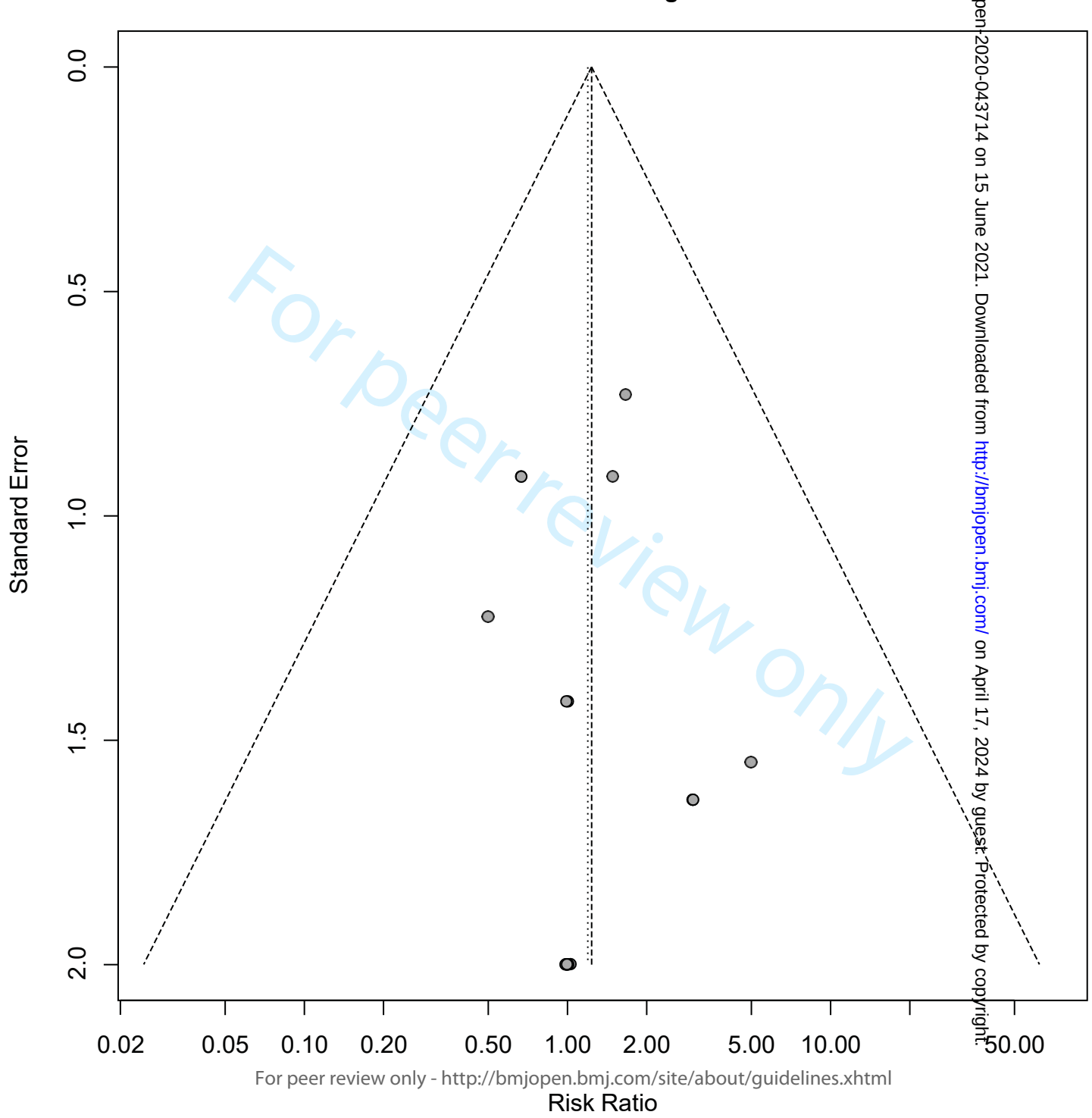

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RHADOMYOLYSIS SUMMARY: PAIRWISE AND NETWORK META-ANALYSIS RESULTS

	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)	--

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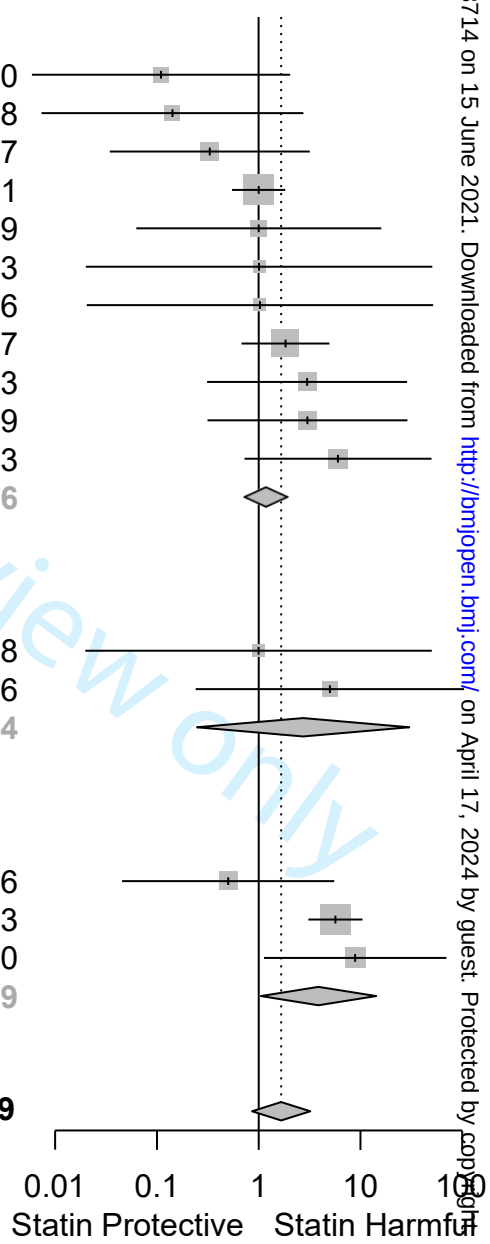
CK >10x ULN: Meta-Analysis Forest Plot with Data



Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	Weight
Group 1: Moderate−Placebo							
CARDS, A10	0	1428	4	1410	0.11	[0.01; 2.04]	3.9%
LIPS, F80	0	822	3	818	0.14	[0.01; 2.75]	3.8%
CORONA, R10	1	2514	3	2497	0.33	[0.03; 3.18]	5.7%
AFCAPS, L20−L40	21	3304	21	3301	1.00	[0.55; 1.83]	15.0%
GISSI−HF, R10	1	2285	1	2289	1.00	[0.06; 16.01]	4.2%
PROSPER, P40	0	2891	0	2913	1.01	[0.02; 50.76]	2.4%
4D, A20	0	619	0	636	1.03	[0.02; 51.70]	2.4%
HPS, S40	11	10269	6	10267	1.83	[0.68; 4.95]	12.3%
WOSCOPS, P40	3	3302	1	3293	2.99	[0.31; 28.75]	5.7%
ALERT, F40−F80	3	1045	1	1049	3.01	[0.31; 28.90]	5.7%
SSSS, S20−S40	6	2221	1	2223	6.01	[0.72; 49.84]	6.2%
Random effects model		**30700**		**30696**	**1.17**	**[0.72; 1.90]**	**67.4%**
Heterogeneity: I^2 = 4%, τ^2 = 0.0303, p = 0.41							
Group 2: High−Placebo							
TRACE RA, A40	0	1504	0	1498	1.00	[0.02; 50.16]	2.4%
SPARCL, A80	2	2365	0	2366	5.00	[0.24; 104.14]	3.7%
Random effects model		**3869**		**3864**	**2.73**	**[0.25; 30.11]**	**6.1%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.52							
Group 3: High−Moderate							
TNT, A80 vs A10	1	4995	2	5006	0.50	[0.05; 5.52]	5.2%
SEARCH, S80 vs S20	68	6031	12	6033	5.67	[3.07; 10.46]	14.9%
A to Z, S40−S80 vs S20	9	2263	1	2230	8.87	[1.12; 69.94]	6.4%
Random effects model		**13289**		**13269**	**3.88**	**[1.05; 14.31]**	**26.5%**
Heterogeneity: I^2 = 50%, τ^2 = 0.7030, p = 0.14							
Random effects model		**47858**		**47829**	**1.66**	**[0.86; 3.21]**	**100.0%**
Heterogeneity: I^2 = 52%, τ^2 = 0.6582, p < 0.01							
Residual heterogeneity: I^2 = 12%, p = 0.32							

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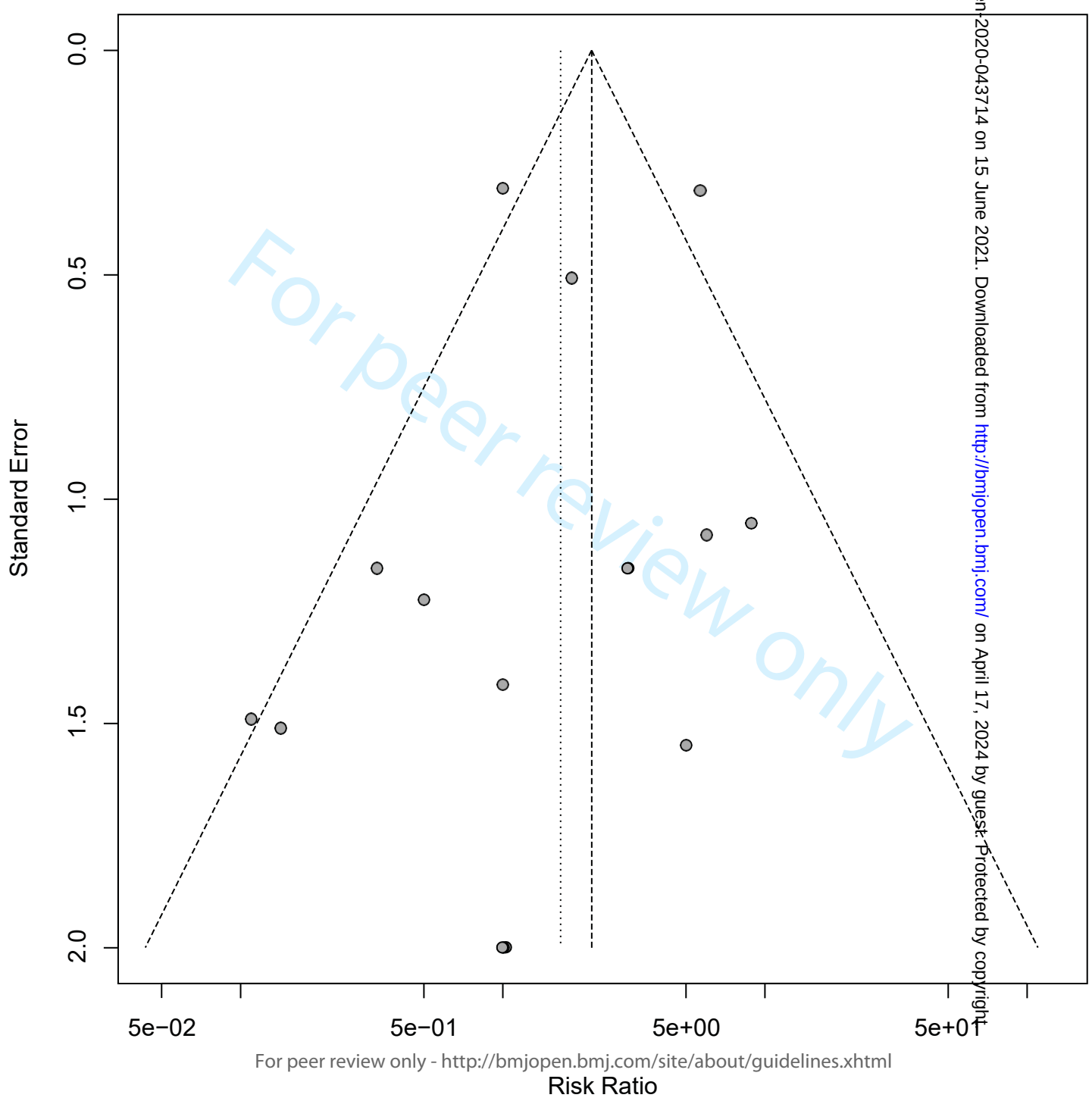

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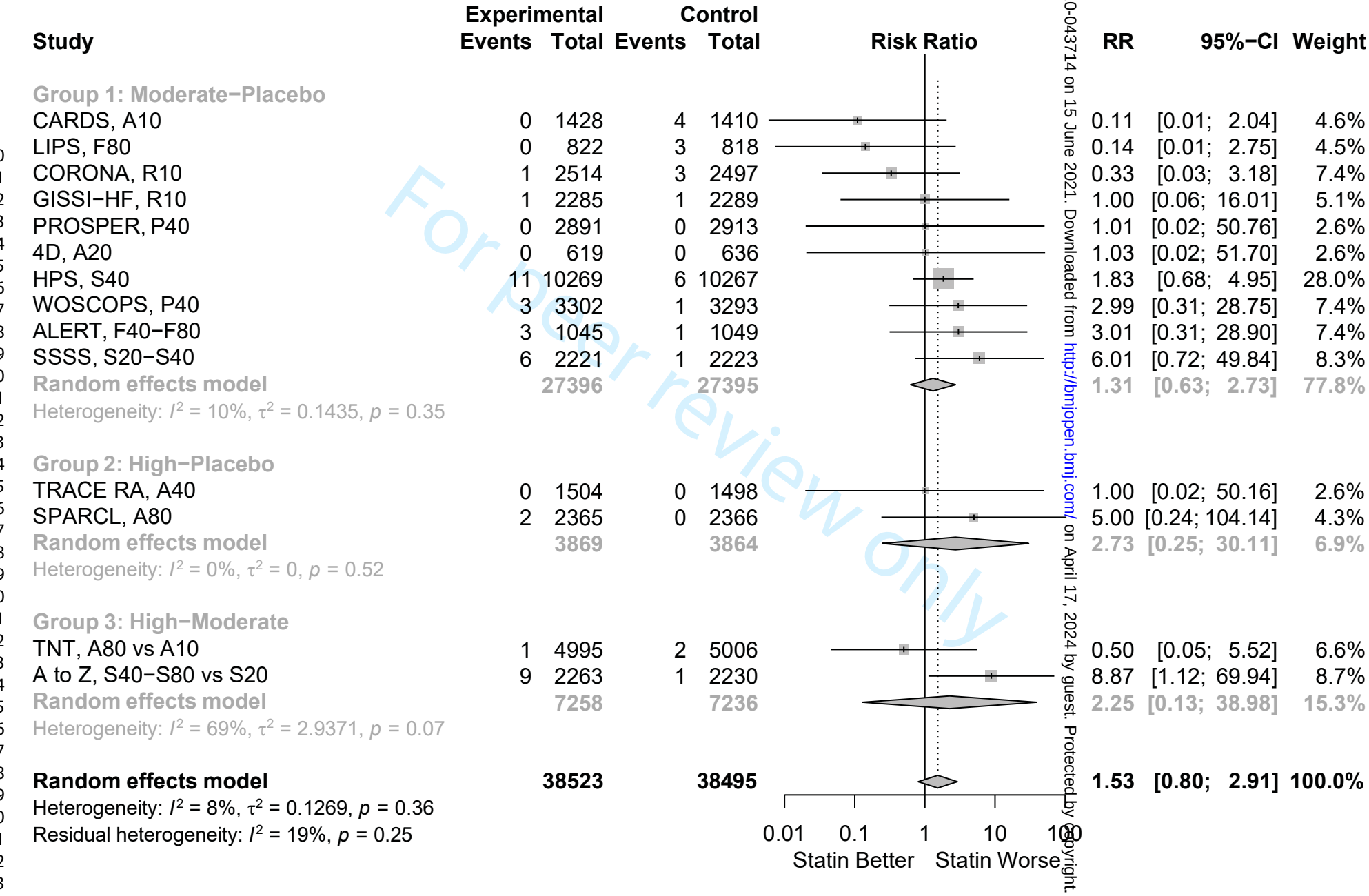
CK >10x ULN: Meta-Analysis Forest Plot with outliers excluded.



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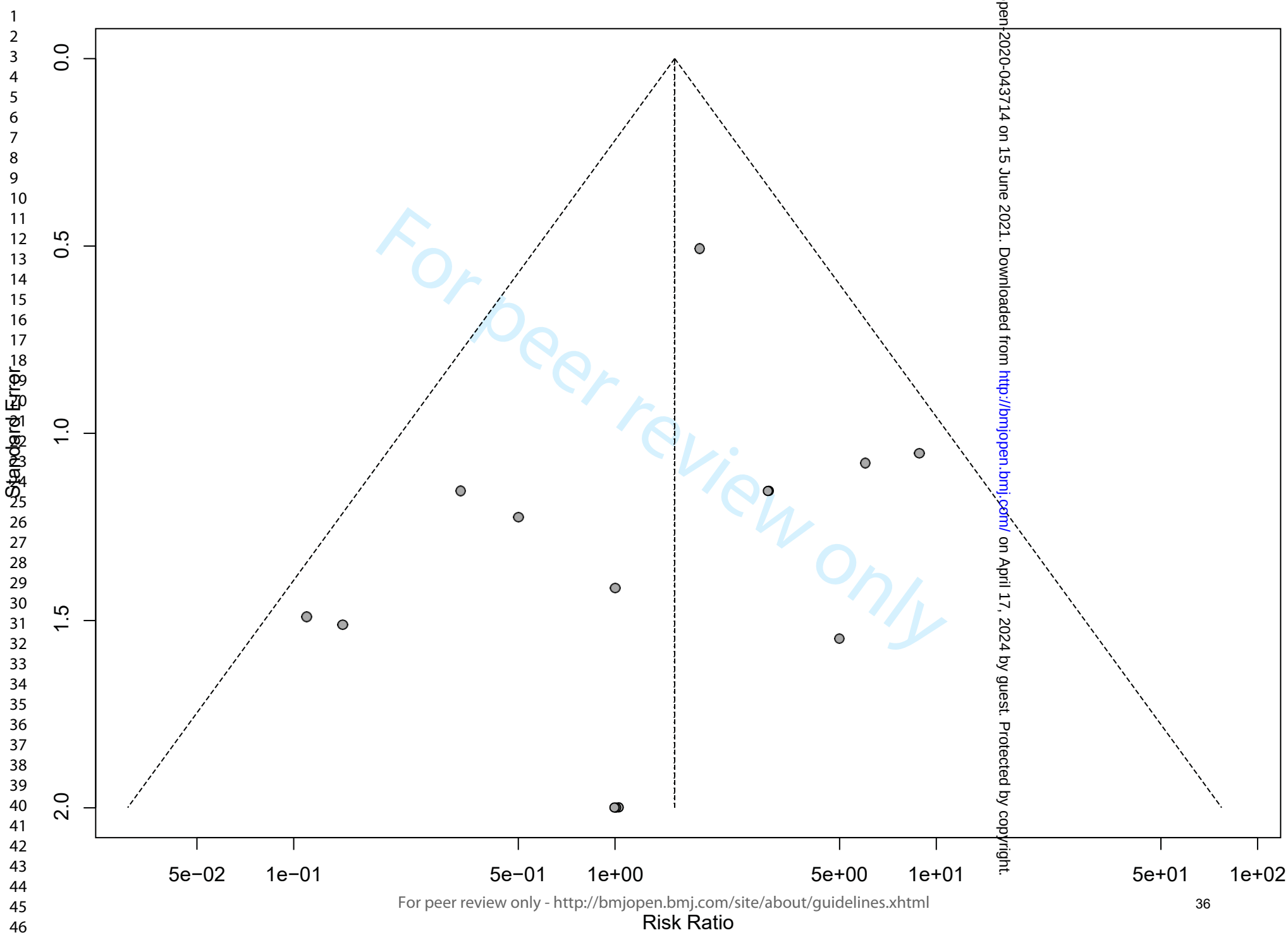
CK >10x ULN: Meta-Analysis Funnel Plot with outliers excluded.



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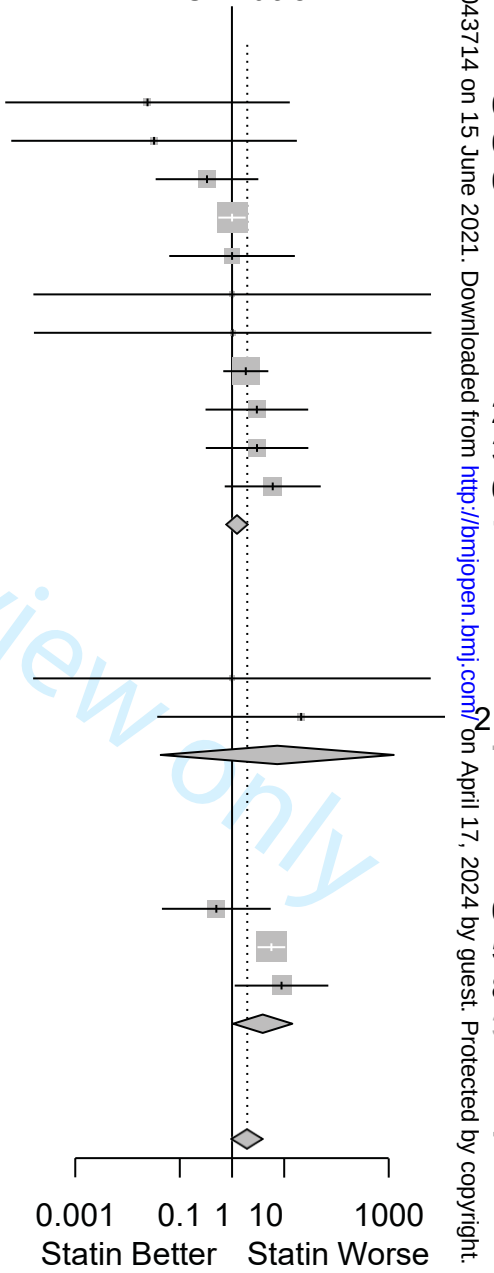
CK >10x ULN: Meta-Analysis Forest Plot with Continuity Correction = 0.1.



Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	Weight
Group 1: Moderate−Placebo							
CARDS, A10	0	1428	4	1410	0.02	[0.00; 12.76]	1.1%
LIPS, F80	0	822	3	818	0.03	[0.00; 17.42]	1.1%
CORONA, R10	1	2514	3	2497	0.33	[0.03; 3.18]	6.3%
AFCAPS, L20−L40	21	3304	21	3301	1.00	[0.55; 1.83]	18.4%
GISSI−HF, R10	1	2285	1	2289	1.00	[0.06; 16.01]	4.7%
PROSPER, P40	0	2891	0	2913	1.01	[0.00; 6455.29]	0.6%
4D, A20	0	619	0	636	1.03	[0.00; 6578.85]	0.6%
HPS, S40	11	10269	6	10267	1.83	[0.68; 4.95]	14.7%
WOSCOPS, P40	3	3302	1	3293	2.99	[0.31; 28.75]	6.3%
ALERT, F40−F80	3	1045	1	1049	3.01	[0.31; 28.90]	6.3%
SSSS, S20−S40	6	2221	1	2223	6.01	[0.72; 49.84]	6.9%
Random effects model		**30700**		**30696**	**1.24**	**[0.79; 1.97]**	**67.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.56							
Group 2: High−Placebo							
TRACE RA, A40	0	1504	0	1498	1.00	[0.00; 6380.08]	0.6%
SPARCL, A80	2	2365	0	2366	21.01	[0.04; 11950.08]	1.1%
Random effects model		**3869**		**3864**	**7.37**	**[0.04; 1256.08]**	**1.7%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.57							
Group 3: High−Moderate							
TNT, A80 vs A10	1	4995	2	5006	0.50	[0.05; 5.52]	5.8%
SEARCH, S80 vs S20	68	6031	12	6033	5.67	[3.07; 10.46]	18.3%
A to Z, S40−S80 vs S20	9	2263	1	2230	8.87	[1.12; 69.94]	7.2%
Random effects model		**13289**		**13269**	**3.88**	**[1.05; 14.31]**	**31.3%**
Heterogeneity: I^2 = 50%, τ^2 = 0.7030, p = 0.14							
Random effects model		**47858**		**47829**	**1.96**	**[1.00; 3.85]**	**100.0%**
Heterogeneity: I^2 = 45%, τ^2 = 0.5511, p = 0.03							
Residual heterogeneity: I^2 = 0%, p = 0.44							

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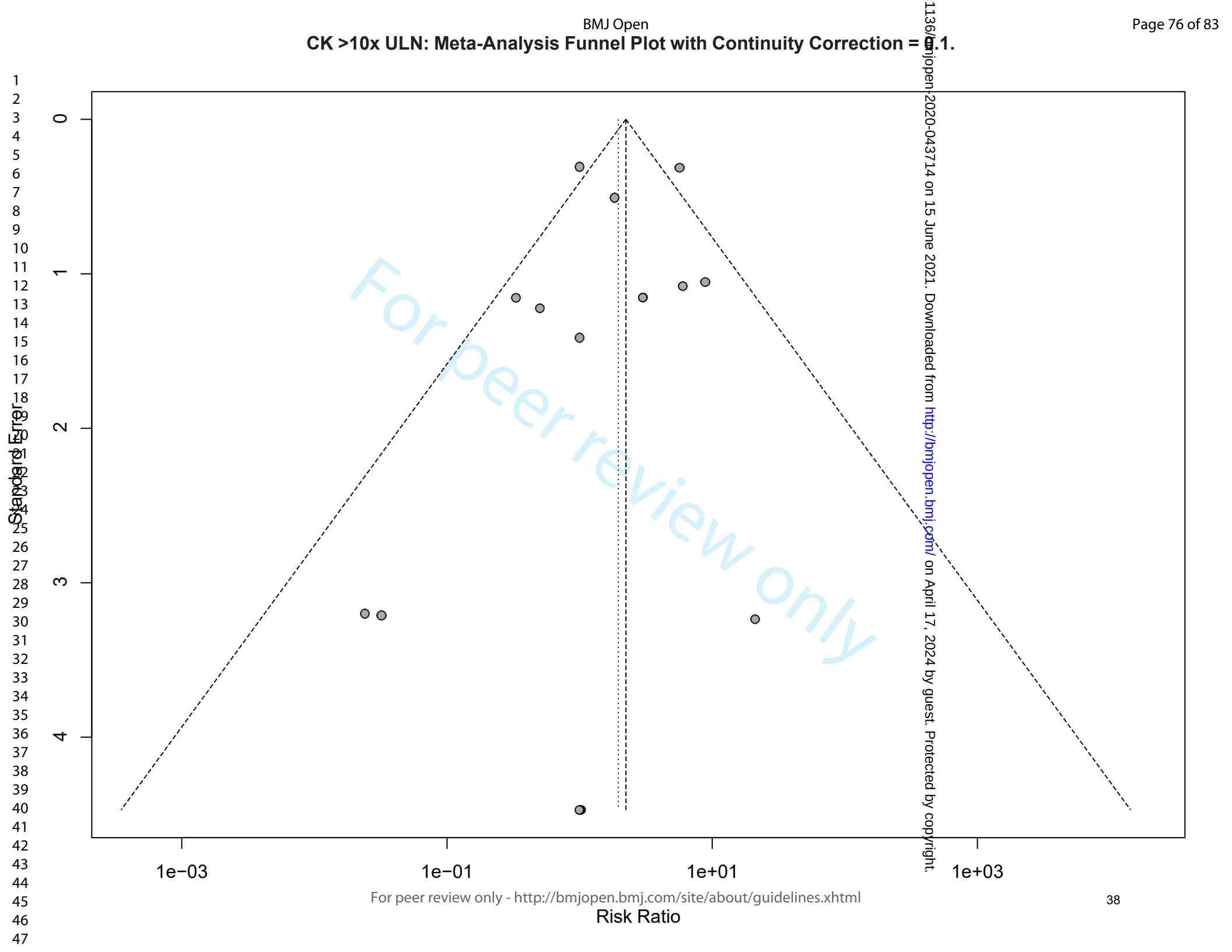

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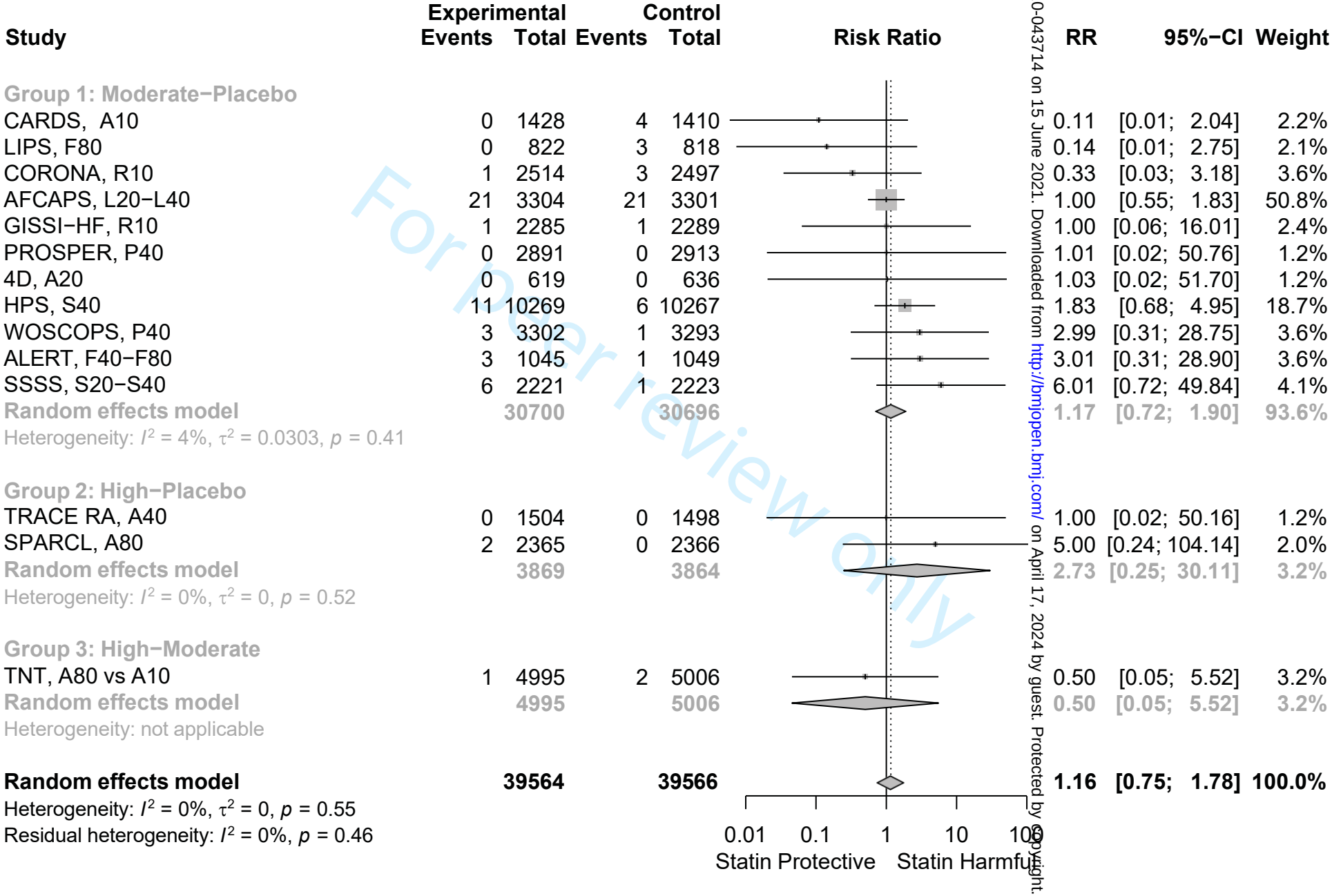
CK >10x ULN: Meta-Analysis Forest Plot excluding simvastatin 80 mg trials.



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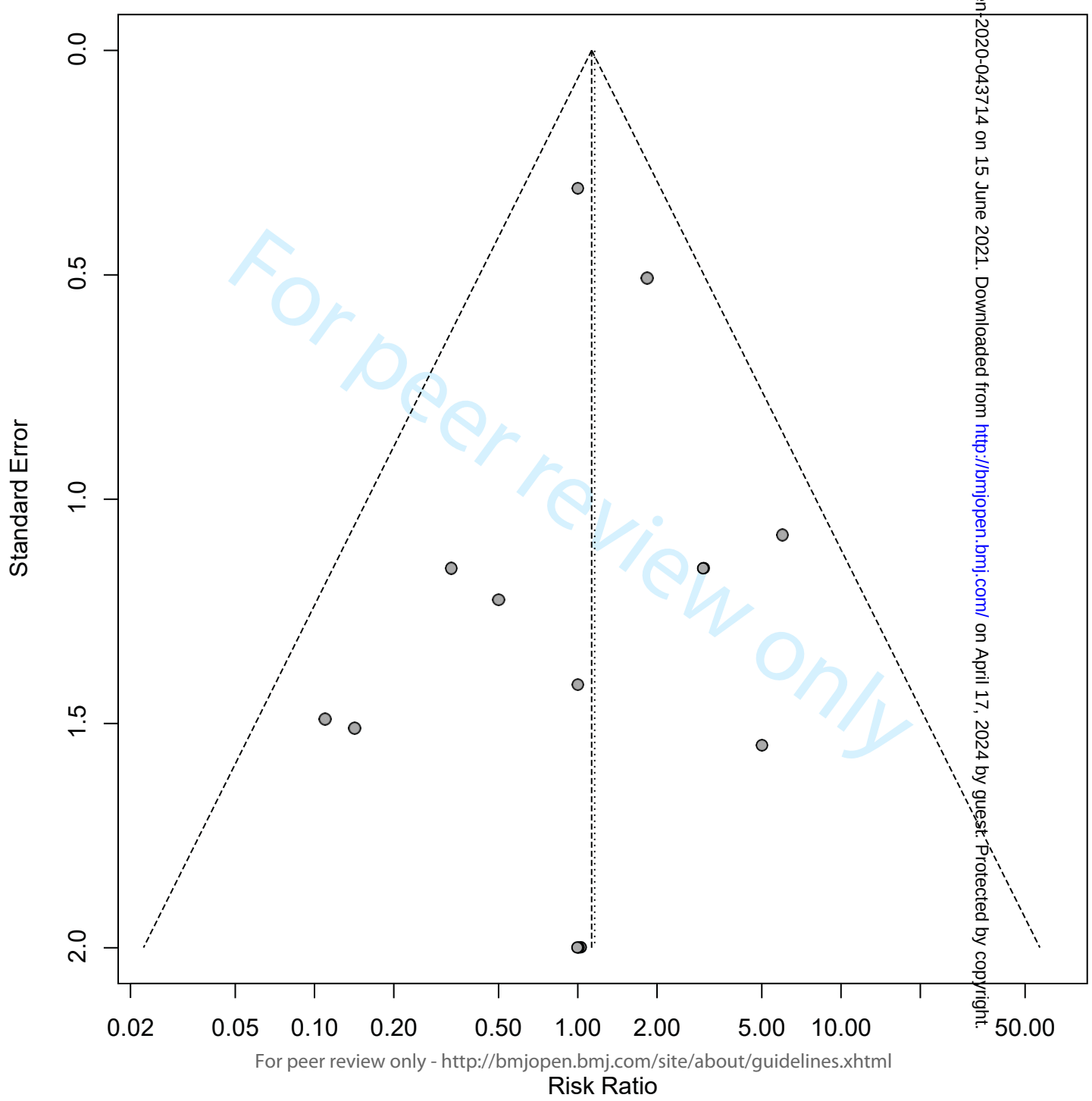

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CK>10XULN SUMMARY: PAIRWISE AND NETWORK META-ANALYSIS RESULTS

	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)	--

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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)
```

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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
```

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1 (Title)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5 (Intro)
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3 (abstract)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	With Prospero reg.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8

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PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-11, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results section
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Results section
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Title page

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PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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