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ORIGINAL ARTICLE

The Role of Exercise in Statin-Associated Muscle Symptoms Outcomes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Objective: To provide a synthesis of randomized controlled trials (RCTs) investigating statin-associated muscle symptoms (SAMS) in adults who underwent exercise training intervention.

Patients and Methods: We systematically searched 5 electronic databases for placebo-controlled RCTs through January 31, 2023. We included short-term and long-term exercise interventions that compared the efficacy and safety of exercise+statin vs exercise+placebo in healthy adults and reported SAMS preintervention and postintervention. Publication bias and methodological study quality assessments were performed.

Results: Five of 454 potentially qualifying RCTs met the inclusion criteria, all short-term exercise RCTs. Participants were predominantly physically inactive young to middle-aged (M=37.2 y) men (57%), 252 (49%) who were on statin therapy, and 271 (53%) on placebo. Of the 3 RCTs providing qualitative SAMS results, 19 (9%) out of 220 participants reported SAMS on exercise+statin and 10 (4%) out of 234 reported SAMS on exercise+placebo. There was no difference between exercise+statin vs exercise+placebo for maximal oxygen consumption (d=−0.18; 95% CI, −0.37 to 0.00; P=.06) or creatine kinase after short-term exercise (d=0.59; 95% CI, −0.06 to 1.25; P=.08). Participants in the exercise+statin group reduced low-density lipoprotein cholesterol vs exercise+placebo (d=−1.84; 95% CI, −2.28 to −1.39; P<.001). Most of the RCTs exhibited low levels of risk of bias (k=4, 80%) and achieved moderate methodological study quality (75.0%±5.2%).

Conclusion: Self-reported SAMs tended to be 5% greater after short-term exercise in statin users compared with placebo, although this difference did not achieve statistical significance. There remains an important need for placebo-controlled RCTs investigating the prevalence of statin-induced SAMS during exercise training.

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Approximately 30% of US adults have elevated low-density lipoprotein cholesterol (LDL-C), and there has been a 19% increase in the total number of deaths caused by elevated LDL-C since 2010.[1] Statins (3-hydroxy 3-methylglutaryl-coenzyme A reductase inhibitor) are the most effective drugs for lowering LDL-C; for each 1 mmol/L of LDL-C reduction achieved with statin therapy, there is an ∼22% reduction in cardiovascular disease (CVD) events.[2] Consequently, statins are the most commonly prescribed class of pharmaceuticals to treat elevated LDL-C, and thus, the primary and secondary prevention of CVD.[3] Furthermore, the synergistic effects of exercise and statins may provide optimal CVD event reductions.[4]

Discontinuation and nonadherence to statin therapy persist despite the drug's effectiveness in lowering LDL-C.[5] A major reason for statin discontinuation is the development of statin-associated adverse events, predominantly muscle-related effects known as statin-associated muscle symptoms

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(SAMS).[5] However, disinformation and confusion among patients about statin safety result from conclusions made by nonrandomized, nonplacebo controlled trials, and routine health care records of high SAMS prevalence rates ranging from 7%-29%.[6] By contrast, the Cholesterol Treatment Trialists' Collaboration[6] recently performed a meta-analysis of large-scale, randomized, double-blind trials and documented that statins produce a small 7% increase in SAMS. Interestingly, more than 90% of muscle symptoms reported by statin-treated patients are attributed to nocebo or drucebo effects.[6-9] Unfortunately, due to observational reports suggesting that physical activity (PA) induces or exacerbates SAMS, PA levels may be reduced among some statin-treated patients.[10,11]

Despite PA being a cornerstone lifestyle therapy, the role of PA in SAMS remains inconclusive. Previous systematic reviews and meta-analyses[12-14] have evaluated the safety and efficacy of combining statins and exercise, but their findings are largely based on longitudinal and cross-sectional trials that fail to assess changes in PA before vs after drug treatment. Bytyçi et al[14] recently performed a meta-analysis to assess statin intolerance in 4.2 million patients from 176 studies and found that exercise increases the risk of statin intolerance by 23.2%. Of importance, only 11 studies provided data on PA and the prevalence of statin intolerance in the RCTs (∼5%) was significantly lower than in the cohort (17%) studies.[14] Regardless, these meta-analyses do not suggest that combining statin therapy with exercise decreases exercise performance, but they do suggest that statins may increase the incidence of exercise-related muscle complaints. In fact, the International Lipid Expert Panel (ILEP) provides recommendations on how to proceed with statin therapy in patients who are regular exercisers.[15]

Observational studies are valuable; however, the lack of a placebo comparator limits the ability to establish a causal relationship between statins and muscle complaints with exercise.[16] Because of the limitations and controversy in the literature about the role of PA and exercise training on SAMS outcomes, the present systematic review and meta-analysis sought to provide a detailed synthesis of RCTs that investigated SAMS outcomes in adults who underwent short-term and more long-term exercise training interventions while on statin therapy vs placebo.

METHODS

Selection Criteria

This systematic review of RCTs reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines[17] and to fulfill high methodological standards (Figure 1). Included studies were placebo-controlled RCTs that: (1) enrolled adults aged 18 years or older; (2) included an exercise group with statins (exercise+statin); (3) had an exercise group put on placebo (exercise+placebo); (4) included objective or subjective measurements of SAMS preintervention and postintervention; (5) reported the intensity, time, or type of the short-term (single bout of exercise) or the frequency, intensity, time, or type of the long-term (training) exercise intervention; and (6) were peer-reviewed and published in English. Trials were excluded if they: (1) reported the use of diet and nutraceutical modifications (vitamin D, coq10, l-carnitine) in addition to exercise; or (2) included populations with known chronic disease other than dyslipidemia (eg, CVD, cancer, and HIV/AIDS).

Search Strategy

After consultation with a health science librarian, we systematically searched 5 electronic databases, including PubMed, Cochrane Library, Sports Discus, Cumulated Index to Nursing and Allied Health Literature, and Scopus (including EMBASE) using MeSH terms of *statin* and *exercise* and *myalgia* in English from inception through January 31, 2023 (see Supplemental Table 1, available online at http://www.mcpiqojournal.org, for full search strategy for each of the electronic database queried). The 454 potentially qualifying trials that emerged from the search were screened by title, abstract, and full text in duplicate by trained coders (LM, OK, and SN). Reference lists of qualifying reports were manually searched for additional trials.

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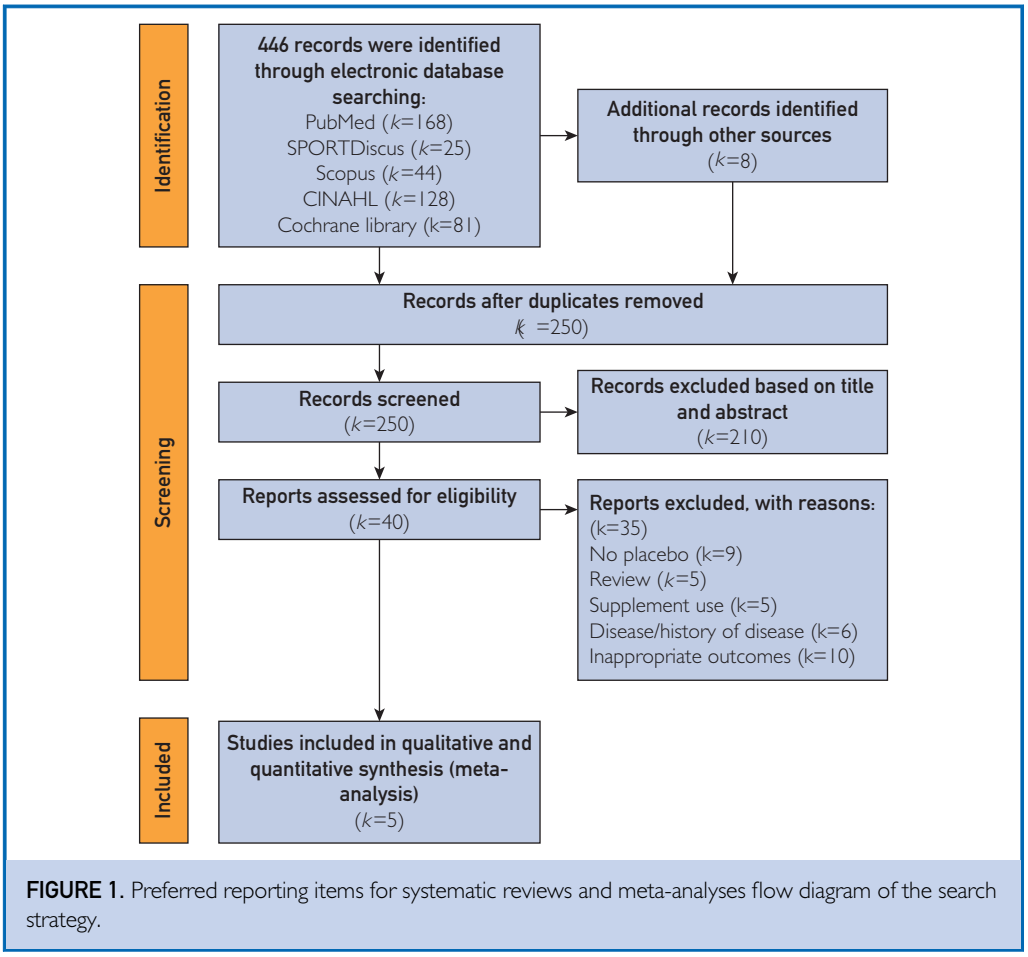

FIGURE 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram of the search strategy.

Data Extraction and Coded Variables

Coded variables were extracted using a standardized data extraction sheet and coder manual our laboratory previously developed.[18,19] Two trained coders (LM and SN) independently extracted and coded information. Disagreements were resolved through discussion with a third independent party (OK) if needed. Data extracted included study (eg, methodological study quality, and trial location), sample (eg, age, baseline LDL-C, and body mass index), and intervention characteristics (eg, frequency, intensity, time, and type of exercise).

Effect Size Calculations

The standardized mean difference effect sizes (d) were calculated for each study sample (k) for the between-group effects as the mean difference between the exercise+statin and exercise+placebo by subtracting the postintervention mean from the preintervention mean for the exercise and placebo arms and dividing by the pooled standard deviation, correcting for small sample size bias.[20] If necessary, the standard error of the mean was converted into a standard deviation (ie, $s = se\sqrt{n-1}$). The primary outcome of the current meta-analysis was the SAMS response to exercise as reflected by creatine kinase (CK) levels because CK is the most commonly used biomarker of SAMS.[21] When trials measured CK postexercise at multiple time points, we treated the CK value taken at the time point closest to the end of the exercise bout as the postintervention CK value. Secondary analyses were performed for the exercise performance outcome of maximal oxygen consumption (VO_2 max) and LDL-C. Moderator analyses were not performed given the insufficient amount of patient-level data

available. When reaching statistical significance ($P<.05$), d values were interpreted as insufficient (0 to −0.19), small (−0.20 to −0.49), medium (−0.50 to −0.79), and large (≤−0.80).[22] Negative d values indicated exercise+statin was more effective at reducing SAMS outcomes, VO_2 max and LDL-C than exercise+placebo. Statistical heterogeneity was evaluated with the Q statistic and quantified by τ^2 and I^2 and its 95% CIs.[23] To determine the influence that each RCT had on the overall summary effect in the primary meta-analysis models, 1-study removed sensitivity analyses were undertaken.

Risk of Bias and Methodological Study Quality

We performed a risk of bias (RoB) assessment with the revised Cochrane risk of bias tool for RCTs (RoB 2.0).[24] The overall RoB was classified as low risk, some concern, or high risk. Methodological study quality was assessed using an adapted version of the Downs and Black[25] checklist (27 items) for randomized controlled and noncontrolled trials and was scored as the percentage of items satisfied out of a possible 32-point total. Overall methodological study quality scores were classified as low (≤16 points, <50%), moderate (>16-25 points, 50%-79%), or high (>25 points, ≥80%) of the 27 items on the checklist.[26] We also evaluated the potential for publication and other reporting biases for each treatment arm by visually examining the distribution and asymmetry of the LDL-C funnel plots[27] and performing Egger's regression asymmetry test.[28]

Statistical Computing

Analyses incorporating random-effects assumptions were performed using Stata/SE 17.0 (Stata Corp) with macros for meta-analysis (list the macro names).[29] Descriptive statistics are reported as mean ± SD. The 2-sided significance level was P value of <.05.

RESULTS

RCT Search and Characteristics

There were 454 potentially qualifying full-text reports. Of these, 5 RCTs qualified (Figure 1). All 5 RCTs were conducted in the United States between 1991 and 2013 and involved short-term exercise only sample, study, and intervention characteristics of the 5 RCTs are summarized in the Table.[30-34]

Sample Characteristics

The included RCTs had a total of 513 participants (43% female) with a mean of 105±158 subjects per RCT ranging from 8-420 participants, 252 (49%) of whom were on statin therapy and 271 (53%) on placebo. The participants were predominantly physically inactive, young to middle-aged adults. When reported (k=2, 40%)[30,34], participants were predominantly identified as white (96%) males (57%). Baseline LDL-C was between 83 mg/dL and 160 mg/dL for the total sample. Thompson et al[31] and Chung et al[33] enrolled samples (n=75) with elevated LDL-C (≥130 mg/dL), Parker et al[34] and Urso et al[32] enrolled samples (n=428) with normal LDL-C (<130 mg/dL), and Reust et al[30] failed to report LDL-C but reported enrolling a sample (n=10) with normal total cholesterol (<200 mg/dL). In the qualifying RCTs, no participant had baseline CK levels >10 times the upper limit of normal, and no participant had a previous history of muscle complaints. Chung et al[33] enrolled a sample with fair baseline cardiorespiratory fitness, whereas Parker et al[34] enrolled a sample with poor baseline cardiorespiratory fitness.[35] No other trials assessed cardiorespiratory fitness.

Reust et al,[30] Urso et al,[32] Chung et al,[33] and Parker et al[34] recruited statin-naïve participants. Thompson et al[30] reported previous use of statins and required a 6-week discontinuation period before study entry. Only Chung et al[33] and Parker et al[34] reported information regarding medication use other than statins. Parker et al[34] included patients who were on pain (n=63), antihypertensives (n=24), or thyroid and hormone medications (n=49). Chung et al[33] excluded participants who required more than 1 antihypertensive medication.

Intervention Characteristics

Of the 5 qualifying RCTs, Thompson et al,[31] Urso et al,[32] Chung et al,[33] and Parker et al[34] used a short-term double-blinded, placebo-controlled random-assignment design. Reust et al[30] used a short-term double-blind, placebo-controlled cross-over

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TABLE. Baseline Sample, Study, and Intervention Characteristics of the Included RCTs (n=5)[a]

Reference, Year	Participant Characteristics: Exercise+Statin	Participant Characteristics: Exercise+Placebo	Statin Naive	Statin Type /Duration	Short-Term Exercise Intervention	SAMS Diagnosis	Results
Reust et al,[30] 1991	n=10 Age=27.5 y Female (%)=0 Ethnicity: 100% White BMI (kg/m^2)=NA TC=195.6±21 mg/dL [b]Physically inactive	n=10 Age=27.5 y Female (%)=0 Ethnicity: 100% White BMI (kg/m^2)=NA TC=195.6±21 mg/dL [b]Physically inactive	Y	Lovastatin 40 mg, 4 wk	Treadmill;-14% incline; 3 km/h (1 h)	CK	↔ CK when compared with placebo (P=.90)
Thompson et al,[31] 1997	n=22 Age=39.4±2.4 y Female (%)=0 Ethnicity: NA BMI (kg/m^2)=28.6±1.1 [b]LDL (mg/dL)=152±4 [b]Physically inactive	n=27 Age=37.7±1.7 y Female (%)=0 Ethnicity: NA BMI (kg/m^2)=27±0.6 [b]LDL (mg/dL)=160±4 [b]Physically inactive	N	Lovastatin 40 mg, 5 wk	Treadmill; -15% incline; 64 % HR_{max} (45 min)	CK	Downhill treadmill: ↑ CK when compared with placebo (P<.05) 24 and 48 h after exercise and adjusted initial CK differences. Biceps exercise: ↔ CK when compared with placebo.
Urso et al,[32] 2005	n=4 Age=24.50±1.57 y Female (%)=0 Ethnicity: NA BMI (kg/m^2)=25.4 LDL (mg/dL)=83.1±25.1 [b]Physically inactive	n=4 Age=22.75±0.53 y Female (%)=0 Ethnicity: NA BMI (kg/m^2)=24 LDL (mg/dL)=119.1±37.1 [b]Physically inactive	Y	Atorvastatin 80 mg, 4 wk	300 eccentric 1-leg contractions (30 min)	CK Skeletal Muscle Response (UPP). Self-reported muscle symptoms	↔ CK between placebo or statin (P<.05) Statin treatment plus eccentric exercise had the greatest effect on transcription factors and genes involved in the UPP. No myalgia in either group.

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TABLE. Continued

Reference, Year	Participant Characteristics: Exercise+Statin	Participant Characteristics: Exercise+Placebo	Statin Naive	Statin Type /Duration	Short-Term Exercise Intervention	SAMS Diagnosis	Results
Chung et al,[33] 2008	n=13 Age=51.8±5.5 y Female (%)=46 Ethnicity: NA BMI (kg/m^2)=25.6±3.6 [b]LDL (mg/dL)=142±24	n=13 Age=53.6±4.8 y Female (%)=38 Ethnicity: NA BMI (kg/m^2)=25.4±2.8 [b]LDL (mg/dL)=136±18	Y	Atorvastatin 40 mg, 8 wk	Bicycle ergometry (16 min)	CK VO_2 Self-reported muscle Symptoms	↔ CK in either group. ↔ in VO_2, substrate oxidation, or anaerobic threshold between groups. No myalgia in either group.
Parker et al,[34] 2013	n=203 Age=43.6±0.08 y Female (%)=51 Ethnicity: 95% White BMI (kg/m^2)=26.3±5.1 LDL (mg/dL)=119±35.6	n=217 Age=44.6±0.08 y Female (%)=52 Ethnicity: 93% White BMI (kg/m^2)=26.5±5.3 LDL (mg/dL)=116±32.6	Y	Atorvastatin 80 mg, 26 weeks	Isometric and isokinetic strength Knee endurance fatigue	CK Muscle strength VO_2 Muscle Symptoms: Study definition for myalgia	↑ CK in statin compared with placebo (P<0.01). ↔ In muscle strength or VO_2. PA decreased (P=.007) regardless of drug treatment. More atorvastatin than placebo subjects developed myalgia (19 vs 10; P=.05).
Total	Mean n=104.6±158.2 Mean Age=37.2 y Mean (%) Female=43 Mean Ethnicity=96% White		Y:90%	NA	NA	CK: *k*=5 VO_2: *k*=2 Strength: *k*=1 Symptoms: *k*=3 UPP: *k*=1	NA

[a]Abbreviations: BMI, body mass index; CVD, cardiovascular disease; CK, creatine kinase; F, female; HRmax, maximum heart rate; LDL, low-density lipoprotein; PA, physical activity; TC, total cholesterol; UPP, ubiquitin proteosome pathway; VO_2max, maximal oxygen uptake; *k*, number of RCTs, ↑, increase; ↔, no change

[b]Positive CVD risk factors.

design. Urso et al[32] and Parker et al[34] administered high-intensity statin therapy (Atorvastatin, 80 mg) and Reust et al[30] (Lovastatin, 40 mg), Thompson et al[31] (Lovastatin, 40 mg), and Chung et al[33] (Atorvastatin, 40 mg) administered moderate-intensity statin therapy. The shortest duration of statin therapy was 16 days[30,32] and the longest was 6 months.[31] Three of the RCTs (60%) involved an eccentric component to the short-term exercise intervention with Reust et al[30] and Thompson et al[32] using a downhill treadmill walking protocol and Urso et al[34] a 300-eccentric leg contraction short-term protocol. Parker et al[34] administered a maximal exercise test and assessed hand-grip isometric strength and elbow and knee extension or flexion isometric and isokinetic strength. Chung et al[33] administered a bicycle ergometer of 16 minute submaximal, as a constant-load exercise test.

SAMS outcomes (CK and Muscle Symptoms)

Urso et al,[32] Parker et al,[34] Reust et al,[30] and Thompson et al[31] found CK levels were not different between exercise+statin vs exercise+placebo (d=0.59; 95% CI, −0.06 to 1.25; P=.08 and I^2=76.59%, τ^2=0.30) (Figure 2A). Although Chung et al[33] did not provide CK data, they concluded CK did not differ between exercise+statin vs exercise+placebo. CK responses to exercise+statin vs exercise+placebo exhibited high heterogeneity likely because of expected intraindividual variability in CK responses and the various short-term exercise interventions.[36]

Urso et al,[32] Parker et al,[34] and Chung et al[33] (n=456) provided qualitative results for muscle symptoms. Urso et al[32] and Chung et al[33] (n=36) reported no muscle pain with exercise+statin or exercise+placebo. Parker et al[34] found that 19 exercise+statin and 10 exercise+placebo participants met the study definition for myalgia (χ^2=3.74; P=.05). By contrast, Urso et al[32] and Chung et al[33] did not provide a study definition for myalgia. In the 3 RCTs that assessed muscle symptoms,[32-34] 19 (9%) out of 220 participants reported that they experienced pain on exercise+statin and 10 (4%) out of 234 participants reported that they experienced pain on exercise+placebo (χ^2=3.61; P=.06), a difference not achieving statistical significance.

VO_2 Max and LDL-C

Chung et al[33] and Parker et al[34] (n=445) found no difference in VO_2 max between exercise+statin vs exercise+placebo (d=−0.18; 95% CI, −0.37 to 0.00; P=.06, I^2=0.00% and τ^2=0.00). Parker et al[29] (n=420) additionally measured muscle strength and endurance and PA levels and found no difference in these outcomes between the groups (P=.17).

Patients in the exercise+statin group reduced LDL-C compared with exercise+placebo (−57.2±18.3 mg/dL vs −1.27±19.6 mg/dL, d=−1.84; 95% CI, −2.28 to −1.39; P<.001, I^2=46.12%, τ^2=0.11). In Figure 2B, LDL-C responses to exercise+statin compared with exercise+placebo groups exhibited a high heterogeneity likely because of expected intraindividual variability in baseline LDL-C levels and various statin dosages or types.[37]

Risk of Bias and Publication Bias

The RoB ratings for the RCTs are shown in Supplemental Table 2. available online at http://www.mcpiqojournal.org. Most RCTs exhibited low levels of RoB (k=4, 80%). On average, the included RCTs achieved moderate methodological study quality on the augmented Downs and Black[25] checklist (75.0%±5.2%).

The tests of Begg and Egger were not suggestive of the possibility of publication or other reporting bias for the LDL-C response to exercise+statin vs exercise+placebo (Begg: z=−0.24, P=.90; Egger: z=−0.32, P=.75) or CK (Begg: z=0.34, P=.73; Egger: z=1.65, P=.10). Visual inspection of the distribution and asymmetry of the funnel plot for CK revealed that 25% of the studies fell outside of the inverted triangle, indicating there was between-study heterogeneity in CK (Supplemental Figure 1) responses to exercise+statin and exercise+placebo but not in LDL-C (Supplemental Figure 2). Results remained robust after sensitivity analysis was conducted.

DISCUSSION

We performed the present systematic review and meta-analysis to provide a detailed synthesis of RCTs that investigated SAMS outcomes in adults who underwent short-term and more long-term exercise

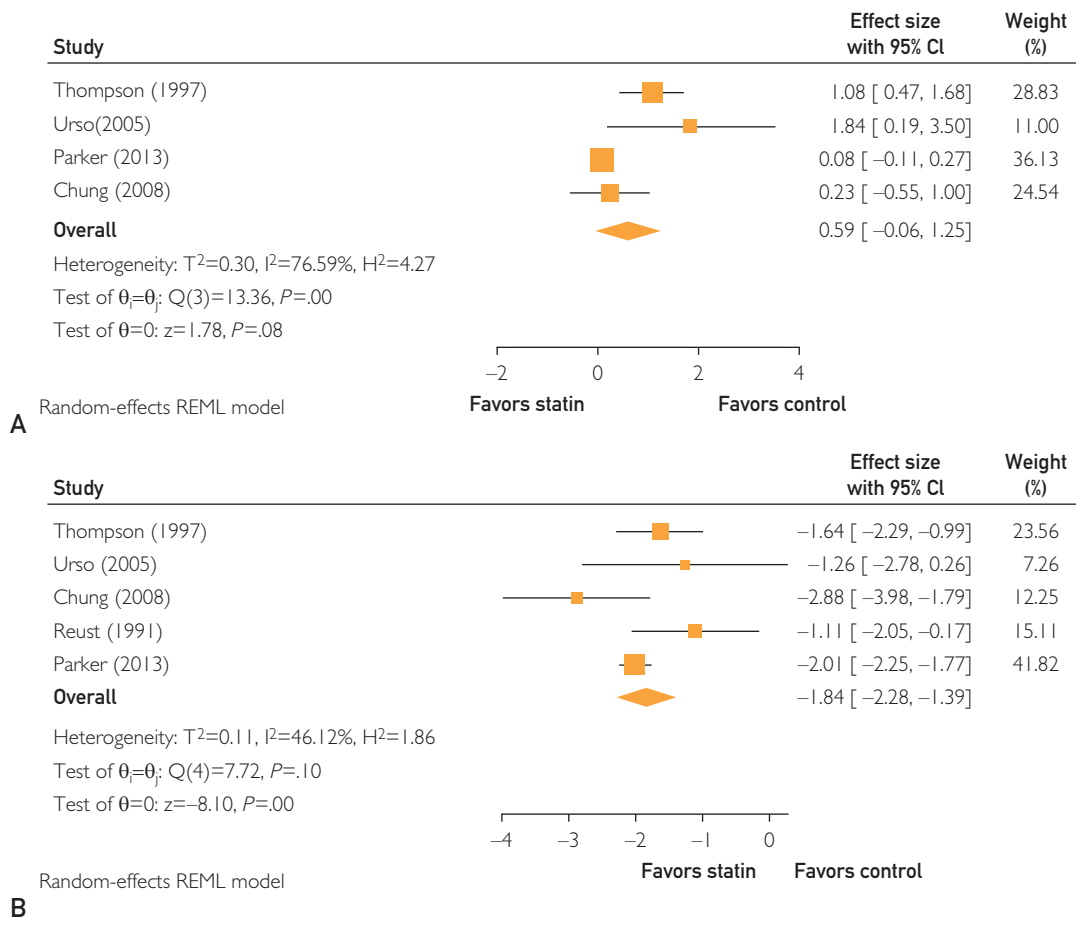

FIGURE 2. Forest plots derived from random-effects meta-analysis models depicting the between-group effects as the mean difference between the exercise+statin and exercise+placebo for (A) Creatine kinase (CK), and (B) Low-density lipoprotein cholesterol (LDL-C). Negative *d* values indicate exercise+statin was more effective at reducing SAMS outcomes, VO_2 max, and LDL-C than exercise+placebo. SAMS, statin-associated muscle symptoms; VO_2 max, maximal oxygen consumption.

training interventions while on statin vs placebo therapy. Surprisingly, only short-term exercise interventions emerged from our literature search. Self-reported SAMs tended to be 5% greater after performing a short-term bout of exercise after 1-6 months of statin therapy when compared with placebo; however, this difference was not statistically significant. There was a small exercise-induced CK increase in statin and placebo (89.2 vs 35.4 U/L), without impairing aerobic capacity as assessed by VO_2 max. Furthermore, exercise and statin combination therapy markedly improved the LDL-C compared with exercise and placebo (−57.2 vs −1.27 mg/dL). The risk of SAMS in response to short-term exercise is small compared with the many cardiovascular benefits of statin therapy[2,3,38] and PA[39] and calls into question the exaggerated claims about SAMS risks.

Our finding that self-reported SAMS tended to be 5% greater in statin users compared with placebo aligns with SAMS outcomes in other double-blinded, RCTs[6,8,9,40] who documented that on average, statins produce up to a 7% increase in SAMS. In contrast, our results conflict with those of large observational studies[10,11] and meta-analyses of such studies[12-14]; observational studies report higher levels of SAMS and increased levels of

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SAMS induced by PA than our double-blinded, RCT. Observational studies are valuable however, their lack of a placebo comparator limits the ability to establish a causal relationship between statin and muscle complaints with exercise. Thus, many of the muscle symptoms reported by statin-treated patients in such studies are attributed to nocebo or drucebo effects,[6-9] and may lead to an overestimation of SAMS.[6-9] Furthermore, individuals on statins initiating an exercise program may experience aches and pains due to exercise per se rather than SAMS, which may cause them to erroneously discontinue statin use.[14] Our observation that participants experienced pain on a placebo is one plausible explanation for the considerably higher (7%-29%) reports of SAMS in observational studies.[16] These findings highlight the limitations of relying on self-reported muscle symptoms and elucidate the importance of using a double-blind trial to examine the incidence and characteristics of SAMS.

An additional challenge is that there is no gold standard measure for identifying SAMS in clinical practice, which makes it difficult to confirm patient self-report of muscle symptoms.[41] Reliance on self-reported SAMS is challenging given the variability in the type of complaints, severity of symptoms, and onset of symptoms. Only 1 trial in our review[34] used a statin challenge-dechallenge protocol as a diagnostic tool for SAMS, whereas the other trials used CK, clinical criteria, or exercise testing. The most commonly used biomarker is CK, an indicator of muscle damage.[21] Creatine kinase however, is universally recognized as providing little diagnostic help in most patients with possible SAMS.[16,42] In our review, we found that statins resulted in a small but nonsignificant increase in the postexercise-induced rise in CK levels. Another meta-analysis[12] failed to perform CK analyses due to the high heterogeneity of their included intervention types. Other nonrandomized trials[43-46] assessed exercise-associated elevations in CK in statin users, and of these trials, 2[45,46] reported that statin use significantly increased CK from baseline following exercise. Similar to our findings, the other 2 trials[43,44] found no significant adverse effects of statin treatment on the CK response to exercise.

Creatine kinase varies by factors, such as race, gender, age, and recent exercise,[47] and there is large intersubject variability in serum CK response after eccentric exercise.[36] We, similar to other studies[43,46] documented significant variability in peak postexercise CK responses across trials, and most trials used a large eccentric component as an extreme model of exercise-induced muscle injury. However, the findings of Parker et al[34] that asymptomatic and symptomatic individuals on statins reported increases in CK levels after short-term exercise, in addition to the findings of Thompson et al[31] that exercise-associated elevations in CK levels were greater in asymptomatic patients on statins than those not on statins, illustrate the limitation of using CK levels to identify SAMS. Notably, the ILEP provides recommendations on the diagnosis, prevention, and treatment of statin-related adverse effects with a special focus on muscle symptoms and creatine kinase (CK) elevations.[15] Future studies investigating SAMS should also implement a rigorous step-by-step approach that has been suggested by the ILEP for the management of the nocebo or drucebo effect.[48] Ultimately, management strategies for SAMS involve a patient-centered clinical approach to optimize statin tolerability and improve cardiovascular outcomes.[49]

Although there remains an important need for placebo-controlled clinical trials investigating the prevalence of statin-induced SAMS during more long-term exercise training programs, our data are promising in that short-term exercise RCTs found a small increase in SAMS outcomes and these findings are comparable with other large double-blinded, RCTs [6,12] and other nonplacebo controlled RCTs[50-52] that found long-term exercise training does not exacerbate SAMS outcomes. These findings should also urge clinicians to identify a gold standard measure for confirming SAMS in clinical practice in an attempt to reduce instances of exaggerated SAMS reports. The negative press coverage that statins receive could not only lead to reduced medication compliance but also reduced PA. Either consequence is worrisome given each therapy's independent ability to lower mortality risk, and their combined ability to lower mortality risk that is greater than either therapy alone.[4]

We also performed secondary outcome analyses on VO_2 max because it is considered a potential noninvasive diagnostic tool for SAMS,[21] and LDL-C as clinical management of lipids in patients with or at risk of CVD is centered around LDL-C lowering therapies.[53] We did not find any evidence that statins negatively affected aerobic performance, which aligns with other systematic reviews and meta-analyses,[13,54] yet not with observational reports.[55] Regardless, our findings that only 2 RCTs included aerobic performance measures highlight the sparsity of controlled trials investigating the effects of statins on exercise performance. Furthermore, optimal LDL-C reductions occurred with statin and short-term exercise combined compared with short-term exercise interventions alone (−57.2 vs −1.27 mg/dL), which is consistent with our expectations given the previously documented effectiveness of PA and statin therapy on LDL-C reductions.[2,56]

Limitations

We acknowledge that there are limitations to our meta-analysis. First, we did not include the gray literature (eg, conference proceedings and dissertations). We also only used English search terms and databases that feature studies done in Western culture. Our findings are limited by the small number of placebo-controlled short-term exercise RCTs that qualified. Thus, we did not have adequate statistical power to examine important moderators (eg, age, sex, gender, ethnicity, genetic factors, or concurrent drug therapy) that could influence SAMS outcomes. There exists a clinical profile said to be a primary risk factor for SAMS that includes increased age, race, female sex, concomitant medications, statin type, and a history of muscle disease or myopathy, among others.[57,58] Thus, the generalizability of our findings is limited to individuals at low risk of developing SAMS. We cannot be certain that SAMS were causal for those patients treated with statins. Only 1 study[34] used a challenge-dechallenge protocol and provided a study definition of statin-induced myalgia to diagnose SAMS. Furthermore, individuals on statins initiating an exercise program may experience aches and pains due to exercise per se rather than SAMS.[14] However, the strength of this meta-analysis is that to our knowledge, it is the first to evaluate placebo-controlled RCTs that compared the effects of short-term exercise interventions with control groups in healthy adults. Our data provide a promising direction for reducing apprehension toward PA among statin users; however, above all, the methodological limitations we have outlined should encourage future investigators to conduct well-designed, rigorous more long-term exercise training interventions.

CONCLUSION

We performed a meta-analysis to provide a comprehensive synthesis of RCTs that investigated SAMS outcomes in adults who underwent short-term exercise interventions while on statin therapy compared with placebo. Consistent with findings from other double-blinded RCTS, our analysis found that self-reported SAMS tended to be 5% greater after short-term exercise in statin users compared with placebo. This slight increase in the risk of SAMS with exercise should not be a reason for patients who exercise regularly to discontinue exercise or statin therapy without being evaluated by their physician, especially given the well-documented benefits of regular exercise on CVD and all-cause mortality.[15,59] Although there remains an important need for placebo-controlled RCTs investigating the prevalence of statin-induced SAMS during more long-term exercise training programs, the small risks of muscle symptoms compared with the many cardiovascular benefits of statin therapy[2,3,38] and PA[39] call into question the exaggerated claims about side-effect rates with statin therapy.

POTENTIAL COMPETING INTERESTS

LSP is founder and sole proprietor of P3-EX, LLC, which potentially could benefit from this research.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

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Abbreviations and Acronyms: **CVD,** cardiovascular disease; **CK,** creatine kinase; **LDL-C,** low-density lipoprotein cholesterol; **PA,** physical activity; **RCT,** randomized controlled trial; **RoB,** risk of bias; **SAMS,** Statin-associated muscle symptoms; **V02 max,** maximal oxygen consumption

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