The influence of resistance training on neuromuscular function in middle-aged and older adults: a systematic review and meta-analysis of randomised controlled trials.

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Review

The influence of resistance training on neuromuscular function in middle-aged and older adults: A systematic review and meta-analysis of randomised controlled trials.

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ABSTRACT

Background: Deterioration of neuromuscular function is a major mechanism of age-related strength loss. Resistance training (RT) improves muscle strength and mass. However, the effects of RT on neuromuscular adaptations in middle-aged and older adults are unclear.
Methods: Randomised controlled RT interventions (≥2 weeks) involving adults aged ≥50 years were identified. Primary outcome measures were voluntary activation (VA), electromyographic (EMG) activity during maximal voluntary contraction (MVC), and antagonist coactivation. Data were pooled using a weighted random-effect model. Sub-analyses were conducted by muscle or muscle group and health status of participants. Sensitivity analysis was based on study quality. $P < 0.05$ indicated statistical significance.
Results: Twenty-seven studies were included. An effect was found for VA (standardised mean difference [SMD] 0.54, 0.01 to 1.07, $P = 0.04$), This result remained significant following sensitivity analysis involving only studies that were low risk of bias. Subgroup analyses showed an effect for plantar flexor VA (SMD 1.13, 0.20 to 2.06, $P = 0.02$) and VA in healthy participants (SMD 1.04, 0.32 to 1.76, $P = 0.004$). There was no effect for EMG activity or antagonist coactivation of any muscle group ($P > 0.05$).
Discussion: Resistance training did not alter EMG activity or antagonist coactivation in older adults. Sensitivity analysis resulted in the effect for VA remaining significant, indicating that this finding was not dependent on study quality. Studies predominantly involved healthy older adults (78%), limiting the generalisability of these findings to clinical cohorts. Future research should determine the effects of RT on neuromuscular function in people with sarcopenia and age-related syndromes.

1. Introduction

Skeletal muscle strength (SMS) is essential for physical function but declines with biological ageing at a rate of 1.5–5% per year after 50 years of age (Keller and Engelhardt, 2013). Low SMS is associated with increased risk of mortality, morbidity (Leong et al., 2015), falling, functional impairment (Menant et al., 2017), and higher hospitalisation costs (Antunes et al., 2017). The predictive capacity of low SMS for adverse outcomes has recently led to its adoption as the primary diagnostic criteria for sarcopenia (Cruz-Jentoft et al., 2019). To prevent loss in SMS and/or treat sarcopenia, the impact of targeted interventions on the underlying mechanisms of age-related SMS decline needs to be explored.

Impaired neural function is proposed as a major contributor to SMS loss (Clark, 2019; Carson, 2018), and appears to precede age-related reductions in SMS and muscle mass [SMM; (Reid et al., 2014; Piasecki et al., 2018)]. Therefore, targeted interventions to promote neuromuscular adaptation in older adults may maintain or improve SMS. Resistance training (RT) is a recommended intervention to manage sarcopenia (Dent et al., 2018). Neural adaptations in the early stages of RT increase SMS (without hypertrophy) in young men (Akima et al., 1999). It is unclear whether this plasticity of the neuromuscular system is retained in older adults. Arnold and Bautmans (2014) showed that in six studies (three non-randomised) of older adults performing RT

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interventions, voluntary activation (VA) was increased in the plantar flexors (PF) and knee extensors (KE). Several randomised controlled trials (RCTs) have since been published (Aas et al., 2020; Wei and Ng, 2018; Kobayashi et al., 2014; van Leeuwen et al., 2014; Beijersbergen et al., 2017; Hvid et al., 2016; Kobayashi et al., 2016; Toien et al., 2018), thus an up to date and robust review of the literature is required.

New consensus guidelines emphasising low SMS as a major health concern in older adults (Cruz-Jentoft et al., 2019), have coincided with a shift in the conceptualisation of strength decline to a function of neuromuscular, rather than solely musculoskeletal, impairment (Clark, 2019; Carson, 2018). Accordingly, quantifying the effect of RT on the neuromuscular system is important. This systematic review and meta-analysis aims to provide an up-to-date evaluation of RCTs investigating the influence of RT on neuromuscular function in middle-aged and older adults.

2. Methods

This prospectively registered systematic review and meta-analysis (PROSPERO: CRD42019157139) adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols 2015 statement (Moher et al., 2015).

2.1. Objectives

To assess the influence of RT compared to no exercise or usual care on neuromuscular function in middle-aged and older adults, using available RCTs.

2.2. Inclusion and exclusion criteria

Table 1 summarises study inclusion criteria. Cohorts aged older than 50 years were selected because considerable losses in SMS (1.5–5% per year) and SMM (1–2% per year) occur after 50 years of age (Keller and Engelhardt, 2013). Training duration ≥2 weeks was chosen because increases in CAR (Knight and Kamen, 2001) and the number of active motor units (Patten et al., 2001), occur in older adults after two weeks of RT. We excluded; studies involving participants with neurodegenerative disorders or acute neurodegenerative impairment, non-RCTs, studies comparing older versus younger participants, conference abstracts, study protocols, grey literature and studies duplicating data.

Table 1
Inclusion criteria defined using the population, intervention, comparison, outcome, and study type (PICOS).

PICOS	Description
Population	• Community-dwelling or care institution residents that were: o Sarcopenic (defined by authors according to low SMS and/or SMM criteria); or o Mean age ≥50 years across study groups
Intervention	• Resistance training, as a sole or combined intervention, ≥2 weeks in duration, including: o Exercises for whole body or specific muscles o Body-weight exercises, free-weights, resistance bands, isokinetic machines, or vibration training o Any prescribed number of exercise sets, repetitions and intensity, or training frequency
Comparison	• No exercise, usual care
Outcome	• Primary: EMG activity, VA (% or CAR) and/or antagonist muscle co-activation (%) during MVC of the upper or lower limbs • Secondary: SMS, safety, attrition, adherence, and cost effectiveness
Study type	• Peer-reviewed RCTs • All languages

Notes: CAR = central activation ratio; EMG = electromyographic; MVC = maximal voluntary contraction; RCT = randomised controlled trial; SMM = skeletal muscle mass; SMS = skeletal muscle strength; VA = voluntary activation.

2.3. Search strategy

PubMed, Medline, CINAHL and Cochrane Review databases were searched by EJ, from database inception onwards (final search: 25th March 2020). Search terms associated with "sarcopenia", "RT", "muscle activation" and "RCT" were combined (see Appendix A in Supplementary File 1). Independent screening of records (EJ and AO) was performed firstly of titles and abstracts, followed by full-text screening of the selected papers to confirm eligibility. Hand-searching of reference lists of a systematic review (Arnold and Bautmans, 2014) and eligible papers was performed to identify additional studies. Consensus on disagreements was met through discussion with a third reviewer if needed.

2.4. Data extraction

Studies were exported to reference management software (Endnote, Clarivate Analytics, Philadelphia, USA). Data were extracted and recorded (Excel, Microsoft, Washington) independently by two authors (EJ & AO; agreement confirmed by EJ), including: participant characteristics; intervention characteristics; muscles assessed; and outcome measures (as defined above). Two attempts within four weeks were made to contact authors by email to request any missing primary outcome data. Data were excluded from the meta-analysis if a response was not received. Outcomes reported as mean with standard error (SE) were converted to mean with standard deviation [SD; (Higgins and Deeks, 2011)]:

$$SD = SE \times \sqrt{N}$$

To prevent unit-of-analysis error, where studies compared multiple eligible RT interventions to a single control group, intervention groups were combined to create a single pair-wise comparison, using formulae recommended by the Cochrane Collaboration (Higgins et al., 2011):

$$\text{Sample size (N)} = \text{N}_\text{a} + \text{N}_\text{b}$$

$$\text{Mean} = \frac{N_a Mean_a + N_b Mean_b}{N_a + N_{b.}}$$

$$\text{SD} = \sqrt{\frac{(N_a - 1)SD_a^2 + (N_b - 1)SD_b^2 + \frac{N_a N_b}{N_a + N_b}\left(Mean_a^2 + Mean_b^2 - 2Mean_a Mean_b\right)}{N_a + N_b - 1}}$$

where a is group one and b is group two.

Where available, RT as the sole intervention was selected for inclusion if multiple intervention groups were presented (i.e., a RT group was preferred over a combined aerobic and RT group from the same study).

2.5. Quality assessment

Risk of bias was assessed by two authors independently (EJ and AO) using the Cochrane Risk of Bias (RoB2) tool (Sterne et al., 2019). Disagreements were resolved through consensus (EJ and AO). Due to the nature of the intervention, studies were not downgraded based on lack of participant blinding. We visually assessed funnel plots for publication bias. For sensitivity analysis, meta-analyses were re-run to include studies with low risk of bias only.

2.6. Data synthesis

End of intervention values for primary outcome data were pooled using meta-analysis software (RevMan v5.3.5, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Low and high statistical heterogeneity were defined as I^2 <30% and >50%, respectively (Higgins and Thompson, 2002). Due to high heterogeneity, a weighted random-effects model was used (Borenstein et al., 2010). Antagonist coactivation data are presented as mean difference (MD) with 95% confidence intervals (95%CI). Standardised mean difference

(SMD) with 95%CI is presented where units of measurement could not be converted (i.e., CAR or percentage for VA, or various standardisations of EMG activity). For VA, an overall analysis was performed followed by sub-group analyses based on the muscles assessed. Muscle groups were defined using the muscle action i.e., KE, PF, knee flexors (KF), dorsiflexors (DF). For EMG activity and antagonist coactivation, some authors reported multiple results for different muscles. Therefore, separate meta-analyses were performed by muscle or muscle group in the first instance to avoid over-representation of studies with multiple results in a single analysis. Subgroup analyses were also performed to determine the effect of RT on VA and EMG during MVC in healthy and clinical cohorts (defined as patient groups or people with age-related syndromes). Absolute r values of 0.2, 0.5 and 0.8 were considered small, moderate and large effect sizes, respectively (Coolican, 2017). $P < 0.05$ indicated statistical significance.

3. Results

3.1. Results of the search

The database search identified 869 records, including 272 duplicates. After duplicates were removed, 65 of 597 records were accepted from screening titles and abstracts. After review of the 65 full-text articles, 27 were selected for inclusion, including three publications identified from hand searching (Fig. 1).

Outcome data were provided by the authors of six studies (Beijersbergen et al., 2017; Cristea et al., 2008; Gurjao et al., 2012; LaRoche et al., 2008; Simoneau et al., 2006; Simoneau et al., 2007). Four studies met inclusion criteria but did not report participant mean age (Brentano et al., 2008), or group allocation method (de Boer et al., 2007; Jiang et al., 2016; Rice et al., 1993). After attempts to contact the authors these data were not provided, and the four studies were excluded.

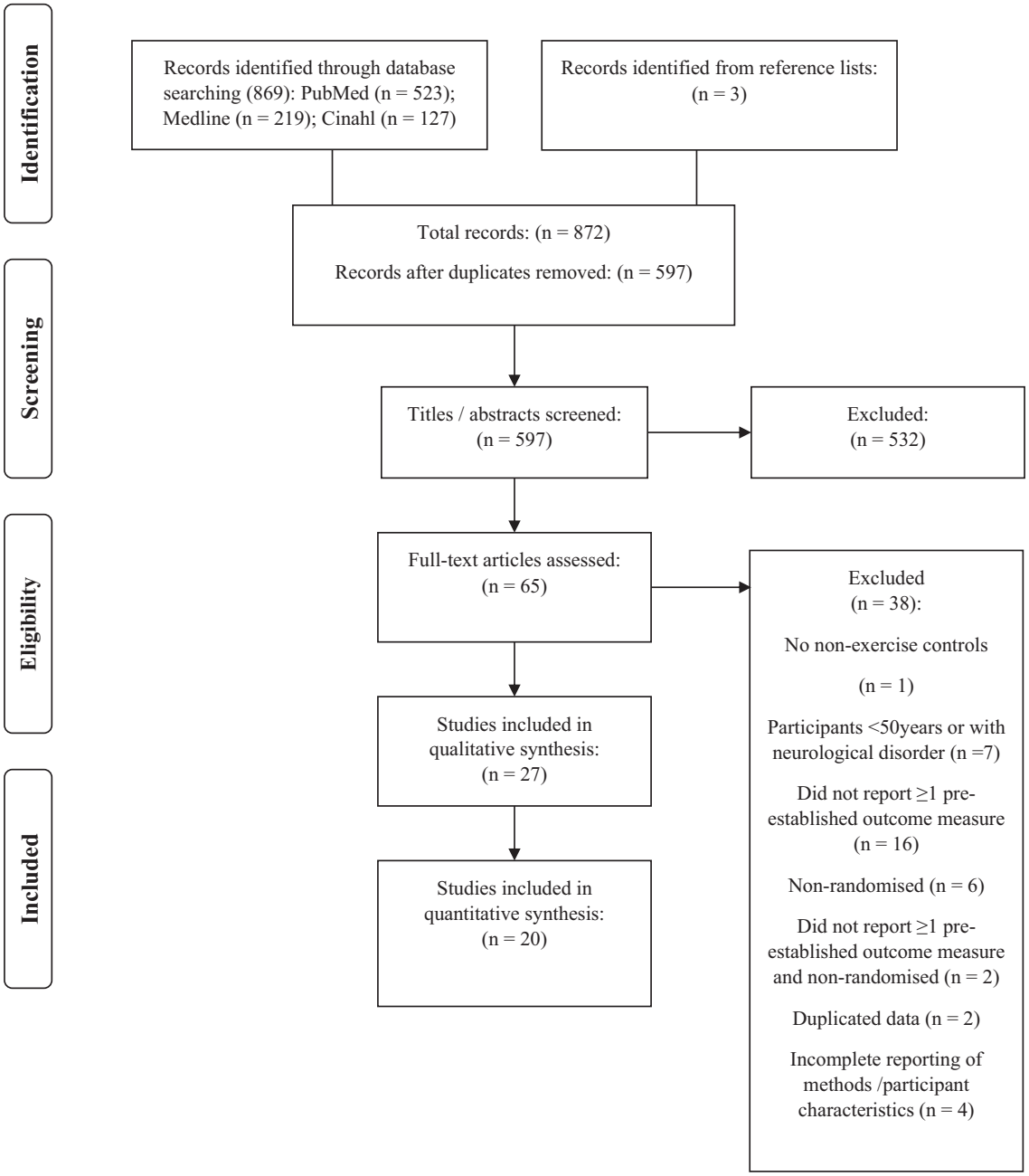

Fig. 1. Schematic diagram of the literature search.

Outcome data were not obtained for six studies due to the data no longer being available (Kobayashi et al., 2016; Karavirta et al., 2011; Ochala et al., 2005) or lack of response from the authors (Kobayashi et al., 2014; Holsgaard-Larsen et al., 2011; Tracy et al., 2004), and were excluded from the meta-analysis. One study compared a vibration training intervention group to a control group performing progressive RT as part of their usual care. This study was excluded from the meta-analysis because we considered this control activity to be too similar to the intervention activity assessed in the remainder of the included studies (Johnson et al., 2010). Antagonist coactivation data for the control group could not be obtained for one study (Cristea et al., 2008). Four studies had multiple intervention groups (Karavirta et al., 2011; Correa et al., 2012; Holviala et al., 2010; Wallerstein et al., 2012), which were approached with the following methods. Two studies compared multiple RT intervention groups with a single control group. A two-phase RCT (Correa et al., 2012) compared a "traditional training" group with a control group in phase one. Phase two involved the sub-division of "traditional training" into three intervention groups: traditional, power, and rapid strength training. For the meta-analysis phase one, prior to the subdivision of the intervention group into multiple groups, was included (i.e., "traditional training"). Wallerstein et al. (2012) compared two intervention groups, "strength training" and "power training", to a single control group. For the meta-analysis, the strength and power training groups were combined to create a single pairwise comparison. Two studies allocated participants to strength, endurance, combined strength and endurance, and control groups (Karavirta et al., 2011; Holviala et al., 2010). Strength as the sole intervention and no – exercise control groups were selected for inclusion.

3.2. Participants and included studies

Table 2 summarises 27 RCTs included in this review. Primary outcome data were assessed in 382 intervention and 284 control participants (mean 70.6 ± 8.8 years). The larger participant number allocated to intervention groups is partially due to three studies comparing multiple intervention groups to a single control group. Six studies included participants with age-related SMM loss, frailty, mobility-limitations, patients post-primary hip replacement, and patients awaiting or post- total knee arthroplasty. The remaining 21 studies involved apparently healthy older adults. Cohorts were female only (n = 5 studies), male only (n = 6 studies) or male and female (n = 16 studies). Intervention group mean age was >50 and ≤60 years (n = 2 studies), >60 and ≤70 years (n = 7 studies), >70 and ≤80 years (n = 16 studies) and >80 years (n = 2 studies). Physical activity status ranged between sedentary (n = 2 studies) and elite trained (n = 1 study).

3.3. Intervention characteristics

Intervention characteristics are reported in Table 2. Training interventions ranged between three (n = 1 study) and 52 weeks (n = 3 studies); including ≤10 weeks (n = 11 studies), >10 and ≤20 weeks (n = 9 studies), >20 and ≤30 weeks (n = 4 studies), or >50 weeks (n = 3 studies). Training frequency was predominantly two (n = 10 studies) or three (n = 11 studies) sessions per week. Alternatively, studies prescribed two gym-based and one home-based session per week (n = 4 studies), two to three gym-based and two to three home-based sessions per week (n = 1 study). One study increased training frequency from three to five sessions per week over the trial period.

Interventions targeted the lower body (n = 15 studies), or whole body (n = 12 studies), using resistance machines (n = 17 studies), vibration platforms (n = 3 studies), free weights (n = 1 study), or a mixture of resistance machines and free weights, sandbags, or resistance bands (n = 6 studies). Interventions involved; one periodised strength and sprint program, one Beginning Movement Load protocol where the muscle is passive during lengthening, power, or explosive training (n = 5 studies), and traditional strength training (n = 17 studies). Studies with multiple intervention groups included strength training or power training (n = 1 study), and heavy load training at a self-selected or predetermined velocity (n = 1 study). In a two-phase study, traditional strength training was first performed by the entire intervention cohort, followed by their division into three intervention sub-groups (traditional strength, rapid strength, and power training) for phase two. Fifteen interventions were supervised, four used a mix of supervised and unsupervised sessions, and eight studies did not report supervision level.

3.3.1. Training intensity

Some training protocols used a percentage of a pre-determined maximal effort (e.g., percent of 1RM), or the maximal load that a participant could lift for a specified number of repetitions (e.g., 15RM signifies the maximal load that can be lifted 15 times). Progressive training intensities ranged between 30 and 90% 1RM (n = 7 studies), 4-20RM (n = 8 studies), 40–75% 3RM (n = 4 studies) or 60–80% 5RM (n = 2 studies). One intervention maintained the same training load throughout (30% 1RM).

Resistance band protocols progressively increased the band resistance throughout the study period (n = 2 studies). Vibration training studies used progressively increased (n = 2 studies) or maintained the same (n = 1 study) vibration amplitude, frequency, and training volume throughout. Explosive maximal (n = 1 study) and explosive high velocity/low load and low velocity/high load protocols (n = 1 study) were also reported.

3.4. Control characteristics

Control allocations prescribed "no training" or "no intervention" (n = 5 studies). Some participants were instructed to maintain their habitual activity (n = 14 studies), including one study involving elite athletes that maintained their usual run-based training. "Usual care" allocations included progressive RT as standard care (n = 1 study), and rehabilitation or therapy programmes using no external resistance (n = 2 studies). Four studies did not specify the control activity.

3.5. Primary outcomes

3.5.1. VA

There was a moderate intervention effect (SMD 0.54, 0.01 to 1.07, P = 0.04), with high statistical heterogeneity (I^2 = 65%), in nine studies that reported the effects of RT on agonist VA. Subgroup analysis by muscle group showed a large intervention effect for the PF (SMD 1.13, 0.20 to 2.06, P = 0.02) and no effect for the KE (SMD 0.14, −0.37 to 0.65, P = 0.60). I^2 values were 72% and 37% for the PF and KE, respectively (Fig. 2). Sub-group analysis by health status showed a large intervention effect in healthy adults (SMD 1.04, 0.32 to 1.76, P = 0.004) and no effect in clinical cohorts (SMD –0.01, −0.55 to 0.54, P = 0.99). I^2 values were 63% and 33%, respectively (Fig. 3). Studies reported agonist VA as CAR (n = 1 study) or percent (n = 8 studies). One study involved patients awaiting total knee arthroplasty reported VA for the affected and unaffected leg in the intervention and control group (van Leeuwen et al., 2014). The affected leg was chosen for analysis.

3.5.2. EMG activity during MVC

Analysis based on muscle group was initially performed. There was no effect on EMG activity of the vastus lateralis (VL; SMD 0.38, −0.30 to 1.06, P = 0.27, I^2 = 80%, Fig. 4A), vastus medialis (VM; SMD 0.61, −0.04 to 1.25, P = 0.07, I^2 = 74%, Fig. 4B), rectus femoris (RF; SMD 1.06, −0.24 to 2.37, P = 0.11, I^2 = 84%, Fig. 4C) or biceps femoris (BF; SMD 0.52, −0.04 to 1.08, P = 0.07, I^2 = 0%, Fig. 4D). There was no effect on the KE (SMD −0.01, −0.67 to 0.65, P = 0.98, I^2 = 0%, Fig. 4E) or PF (SMD 0.14, −0.43 to 0.71, P = 0.63, I^2 = 0%, Fig. 4F), when grouped by the authors. Results could not be pooled for the DF due to insufficient data. One study reported EMG during MVC in patients following hip replacement surgery (Suetta et al., 2004). Removal of this

Table 2
Characteristics of included RCTs.

Study details	Participants			Study characteristics			Outcome	
Author (year)	N	Age (yrs) ± SD	Sample	Intervention (I) control (C)	Frequency duration	Volume intensity	Muscles assessed	Measure
Aas et al. (2020)[a]	I: 10 C: 9	I: 86.6 ± 6.9 C:84.5 ± 7.2	M and F; frail	I: Supervised lower-extremity RT C: Not specified	2 x/week 10 weeks	2–4 × 6–12 reps 6-12RM	KE	VA (%)
Beijersbergen et al. (2017)[a]	I: 12 C: 13	I: 72.1 ± 5.4 C:69.7 ± 5.0	M and F; non-mobility limited	I: Lower-extremity power training C: Usual activity	3 x/week 10 weeks	3 × 6–10 reps 40–60% 3RM	KE, KF, PF	rmsEMG (mV)
Correa et al. (2012)[ab]	Wks 1–6 I: 41 CG: 17 Wks 7–12 I (TG): 14 I (PG): 13 I (RG): 14 C: 17	67 ± 5	F; no regular RT for ≥1 year	I: Wks 1–6 (Phase 1) Lower-extremity strength training Wks 7–12 (Phase 2) Lower-extremity traditional (TG), power (PG) or rapid strength (RG) training C: No RT	2 x/week 12 weeks	Phase 1: 2–3 × 12–20 reps 12-20RM Phase 2: 3–4 × 8–12 reps 8-12RM	KE	rmsEMG (μV)
Cristea et al. (2008)[a]	I: 7 C: 4	I: 66 ± 7.9 C: 71 ± 10	M; elite sprinters; no RT experience	I: Periodised whole-body strength and sprint training C: Usual training	2 x/week 20 weeks	Strength: 2–4 × 3–12 reps 35–85% 1RM Sprint: 2–5 × 30-250 m 75–98% max. Speed	KE	iEMG (μV·s)
Gurjao et al. (2012)[a]	I: 10 C: 7	I: 61.7 ± 4.8 C:65.0 ± 5.1	F; no systemic exercise participation	I: Supervised whole-body strength training C: Usual activity	3 x/week 8 weeks	3 × 10–12 reps 10-12RM	KE	iEMG (μV·s)
Holsgaard-Larsen et al. (2011)	I: 10 C: 9	69.7 ± 3.4	F; physically active; no RT participation	I: Supervised explosive lower-extremity strength training C: No training	2 x/week 12 weeks	4 × 8–20 reps 50–80% 1RM	KE, KF	rmsEMG
Holviala et al. (2010)[a]	I: 9 C: 9	I: 56 ± 2 C: 54 ± 9	M; physically active; no systemic endurance or RT participation	I: Supervised whole-body strength training C: Usual activity	2 x/week 21 weeks	2–5 × 5–20 reps 40–85% 1RM	KE	iEMG (μV)
Hvid et al. (2016)[a]	I: 16 C: 21	I: 82.3 ± 5.2 C:81.6 ± 5.0	M and F; mobility-limited	I: Supervised whole-body power training C: Not specified	2 x/week 12 weeks	3 × 8–10 reps 70–80% 1RM	KE	VA (%)
Johnson et al. (2010)	I: 8 C: 8	I:67.0 ± 10.0 C:68.5 ± 6.0	M and F; post-total knee arthroplasty	I: Supervised WBV training C: Progressive RT (usual care)	3 x/week 4 weeks	1–3 × 30–60s	KE	VA (CAR)
Karavirta et al. (2011)	I: 25 C: 16	I:56.6 ± 6.0 C:55.0 ± 8.0	M; untrained	I: Supervised whole-body strength training C: Not specified	2 x/week 21 weeks	2–4 × 5–20 reps 40–85% 1RM	KE, EE	iEMG
Kobayashi et al. (2014)	I: 17 C: 7	I: 67.5 ± 5.2 C: 67.5 ± 5.8	M and F; no recent RT or high intensity exercise participation	I: Supervised whole-body Beginning Movement Load training C: Usual activity	3 x/week 8 weeks	5–7 × 15 reps 30% 1RM	KE, KF, EF, EE	rmsEMG (mV)
Kobayashi et al. (2016)	I: 30 C: 23	I (F):70 ± 7 I (M): 73 ± 5 C (F): 70 ± 5 C (M):72 ± 5	M and F; no recent systemic RT participation	I: Lower-extremity explosive strength training C: Not specified	2 x/week 4 weeks	3 × 10 reps Maximal	PF	rmsEMG (mV)
LaRoche et al. (2008)[a]	I: 12 C: 12	I: 71.3 ± 6.3 C: 73.7 ± 4.6	F; functionally independent; no structured exercise participation	I: Explosive lower-extremity RT at two angular velocities C: Usual activity	3 x/week 8 weeks	3 × 8 reps per velocity 45 deg.·s^{-1} and 200 deg.·s^{-1}	KE, KF	Antagonist coactivation (%)
Machado et al. (2010)[a]	I: 13 C: 13	I: 79.3 ± 7.3 C: 76.2 ± 8.4	F; ≤2 h moderate exercise weekly	I: Lower-extremity static and dynamic WBV training C: Usual activity	[Weeks 1–4: 3; Weeks 5–8: 4; Weeks 9–10: 5] x/week 10 weeks	1–2 × 30–60s 20-40 Hz 2-4 mm amplitude	KE, KF	rmsEMG (μV)

(continued on next page)

Table 2 (*continued*)

Study details	Participants			Study characteristics			Outcome	
Author (year)	N	Age (yrs) ± SD	Sample	Intervention (I) control (C)	Frequency duration	Volume intensity	Muscles assessed	Measure
Morse et al. (2007)[a]	I: 11 C: 8	I: 72.7 ± 3.3 C: 73.9 ± 4.0	M; physically active; no structured training participation	I: Whole-body supervised gym- and unsupervised home-based strength training C: Usual activity	[2 gym-based; 1 home-based] x/ week 52 weeks	2–3 × 8–10 reps 8-10RM	PF, DF	VA (%); Antagonist co-activation (%)
Morse et al. (2005)[a]	I: 13 C: 8	I: 73.1 ± 12 C: 74.0 ± 4.7	M; physically active; no structured training participation	I: Whole-body supervised gym- and unsupervised home-based strength training C: Usual activity	[2 gym-based; 1 home-based] x/ week 52 weeks	2–3 × 8–10 reps 8-10RM	PF, DF	VA (%); Antagonist co-activation (%)
Ochala et al. (2005)	I: 14 C: 7	I:75.4 ± 8.2 C:77.2 ± 5.0	M and F; sedentary	I: Supervised lower-extremity strength training C: Usual activity	2 x/week 24 weeks	3 × 10 reps 50–75% 3RM	PF	rmsEMG
Reeves et al. (2003)[a]	I: 7 C: 7	I: 73.6 ± 3.4 C: 66.4 ± 1.7	M and F; no RT experience	I: Supervised whole-body strength training C: Usual activity	3 x/week 14 weeks	1–2 × 10–15 reps 45–80% 5RM	KE, KF	rmsEMG (mV·s); Antagonist co-activation (%)
Reeves et al. (2004)[a]	I: 9 C:9	I: 74.3 ± 3.5 C: 67.1 ± 2.0	M and F; physically active; no RT experience	I: Supervised whole-body strength training C: No training	3 x/week 14 weeks	1–2 × 10–15 reps 45–80% 5RM	KE, KF	VA (CAR); rmsEMG (mV·s); Antagonist co-activation (%)
Simoneau et al. (2006)[a]	I: 11 C: 9	I: 78.1 ± 3.1 C: 75.9 ± 3.4	M and F; moderately active	I: Lower-extremity supervised gym- and unsupervised home-based strength training C: Usual activity	[2 gym-based; 1 home-based] x/ week 26 weeks	Gym-based: 3 × 10 reps 50–75% 3RM Home-based: 3 × 8 reps (resistance band)	PF, DF	VA (%)
Simoneau et al. (2007)[a]	I: 12 C: 11	I: 78.5 ± 2.9 C: 76.2 ± 4.3	M and F; moderately active	I: Lower-extremity supervised gym- and unsupervised home-based strength training C: Usual activity	[2 gym-based; 1 home-based] x/ week 52 weeks	Gym-based: 3 × 10 reps 50–75% 3RM Home-based: 3 × 8 reps (resistance band)	PF, DF	rmsEMG/Mmax; Antagonist coactivation (%)
Suetta et al. (2004)[a]	I: 11 C: 9	I: 71 (61–86) C: 69 (62–78)	M and F; patients post-primary hip replacement	I: Standard rehabilitation + supervised unilateral lower-extremity strength training C: Standard rehabilitation	3 x/week 12 weeks	3–5 × 8–10 reps 8-20RM	KE	rmsEMG (μV)
Toien et al. (2018)[a]	I: 11 C: 12	I: 75 ± 5 C:72 ± 3	M; moderately to highly active; no systemic RT participation	I: Supervised lower-extremity maximal concentric velocity strength training C: No training	3 x/week 3 weeks	4 × 4 reps 4RM	PF	VA (%)
Tracy et al. (2004)	I (HLS): 6 I (HL): 11 C: 9	I (HLS): 69.7 ± 3.7 I (HL): 73.1 ± 4.9 C:74.2 ± 4.9	M and F; moderately active; no RT participation	I: Supervised lower-extremity strength training. Heavy load (HL) or heavy load steady (HLS) training C: No training	3 x/week 16 weeks	3 × 10 reps 80% 1RM	KE, KF	rmsEMG (mV)
van Leeuwen et al. (2014)[a]	I: 10 C: 8	I: 71.8 ± 7.5 C: 69.5 ± 7.1	M and F; patients awaiting total knee arthroplasty; no RT experience	I: Usual care + lower-extremity strength training C: Usual care	[2–3 gym-based; 2–3 home-based] x/week 6 weeks	3–4 × 8–15 reps 8-15RM	KE	VA (%)
Wallerstein et al. (2012)[a]	I: Strength 14 I: Power 16 C: 13	I: Strength 63.6 ± 4.0 I: Power 64.9 ± 3.9 C: 63.0 ± 4.0	M and F; sedentary or lightly active	I: Whole-body strength or power training C: No intervention	2 x/week 16 weeks	Strength: 1–4 × 4–10 reps 70–90% 1RM Power: 1–4 × 4–7 reps 30–50% 1RM	KE	rmsEMG (μV)
Wei and Ng (2018)[a]	I: 6 C: 6	I: 73.6 ± 4.0 C: 74.8 ± 6.0	M and F; with age-related muscle atrophy	I: Supervised lower-extremity static WBV training C: Usual activity	3 x/week 12 weeks	4 × 3600 vibration cycles 40 Hz Amplitude 4 mm	KE	VA (%)

Notes: sample sizes refer to participants involved in primary outcome analysis. CAR = central activation ratio; C = control; DF = dorsiflexors; EE = elbow extensors; EF = elbow flexors; EMG = electromyographic; F = females; HL = heavy load; HLS = heavy load steady; iEMG = integrated EMG; I = intervention; KE = knee extensors;

KF = knee flexors; M = males; Mmax = maximal M-wave; PF = plantar flexors; PG = power group; RG = rapid group; RM = repetition maximum; RMS = root mean square; RT = resistance training; TG = traditional group; VA = voluntary activation; WBV = whole-body vibration.

[a] Included in meta-analysis.

[b] Phase 1 of the intervention included in the meta-analysis only.

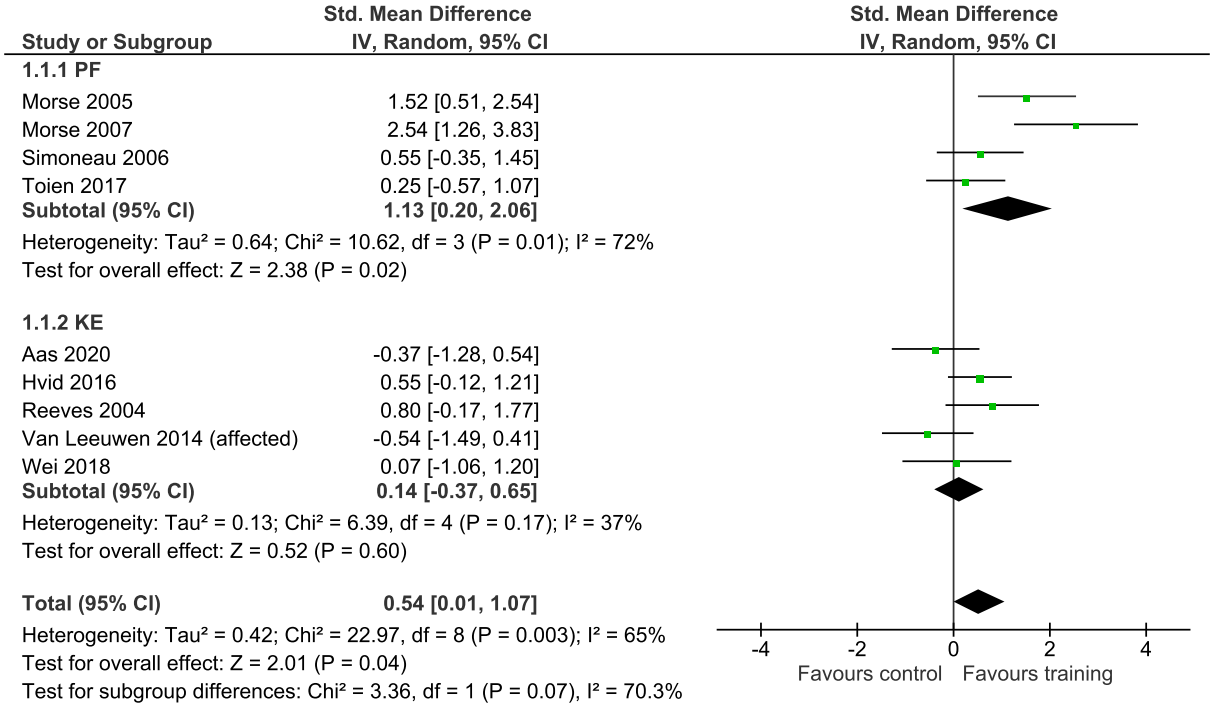

Fig. 2. Forest plot of nine trials investigating the effect of RT on VA in middle-aged and older adults. Overall effect size and subgroup analyses by muscle group are presented. KE = knee extensors; PF = plantar flexors; VA = voluntary activation.

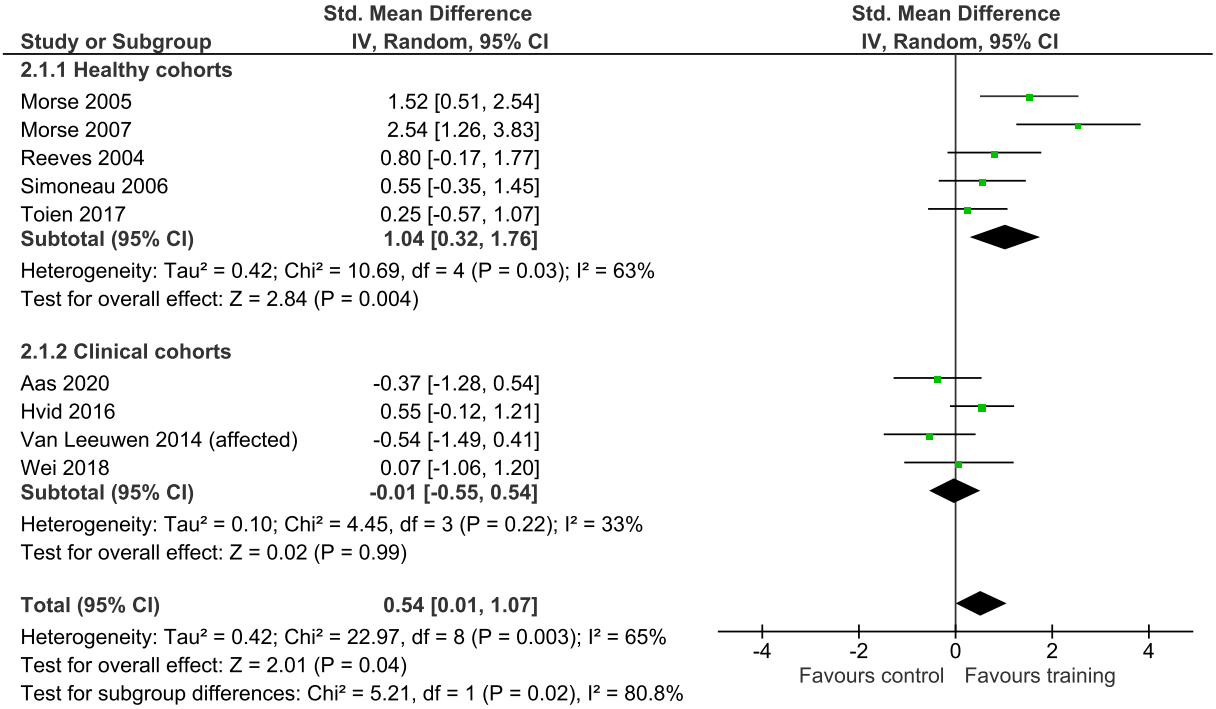

Fig. 3. Forest plot of nine trials investigating the effect of RT on VA in middle-aged and older adults. Overall effect size and subgroup analyses by health status are presented. KE = knee extensors; PF = plantar flexors; VA = voluntary activation.

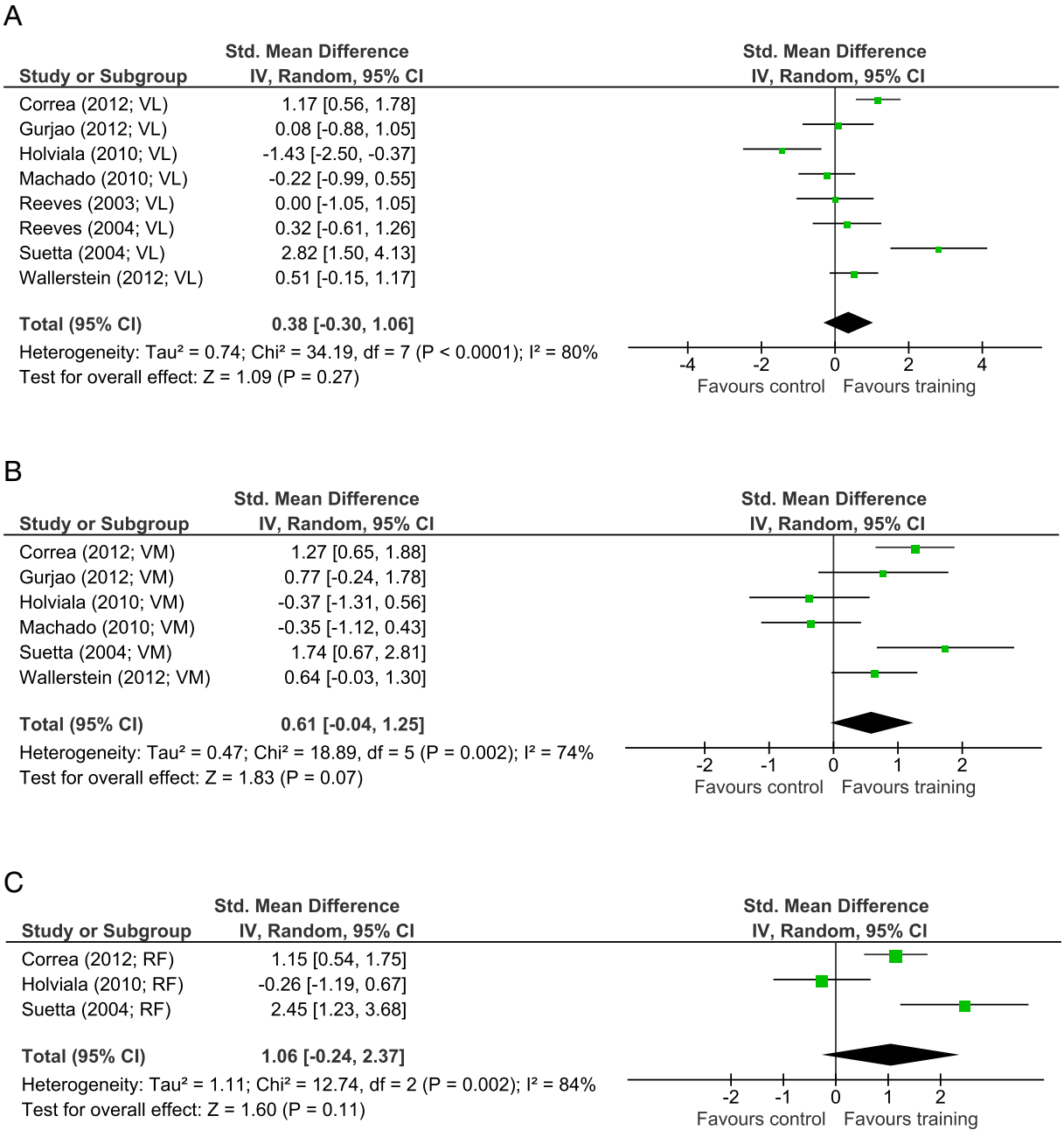

Fig. 4. Forest plots of 11 trials investigating the effect of RT on EMG activation in middle-aged and older adults during MVC, for the A) vastus lateralis [VL]; B) vastus medialis [VM]; C) rectus femoris [RF]; D) biceps femoris [BF]; E) knee extensors [KE] combined; and F) plantar flexors [PF] combined.

study did not result in a significant effect on EMG activity in the VL, VM, or RF ($P \geq 0.21$; figures not shown). EMG parameters during MVC were reported in 11 studies for a single ($n = 3$ studies) or multiple ($n = 8$ studies) muscle or muscle groups.

3.5.3. Antagonist coactivation

Antagonist coactivation was reported in seven RCTs. No overall effect for RT was found on antagonist coactivation of the KF during knee extension (MD -2.28%, −9.57 to 5.00%, $P = 0.54$, $I^2 = 0\%$, Fig. 5A) or DF during plantar flexion (MD 0.31%, −3.00 to 3.62%, $P = 0.85$, $I^2 = 0\%$, Fig. 5B). Antagonist coactivation results from Simoneau et al. (2006) were excluded from this analysis, in favour of data from the same participant cohort at the final timepoint in the same study [i.e. to avoid "double counting" the data; (Simoneau et al., 2007)]. No clinical cohorts were involved in these studies. Therefore, sub-group analysis by health status was not performed. Data for two muscle groups (PF and DF) are reported in one study (Simoneau et al., 2007).

3.6. Secondary outcomes

3.6.1. Muscle strength

Twenty-five studies reported at least one SMS assessment for intervention and control groups. Eighteen studies reported a significant improvement in SMS in the intervention group post-training in all assessed muscles. Where a pre- to post-intervention strength increase is reported, the mean improvement was between 6 and 85%, 15 and 40%, 10 and 93%, and 12 and 30% for the KE, KF, PF, and EE, respectively, and 7.6% for the DF (see Appendix B in Supplementary File 2).

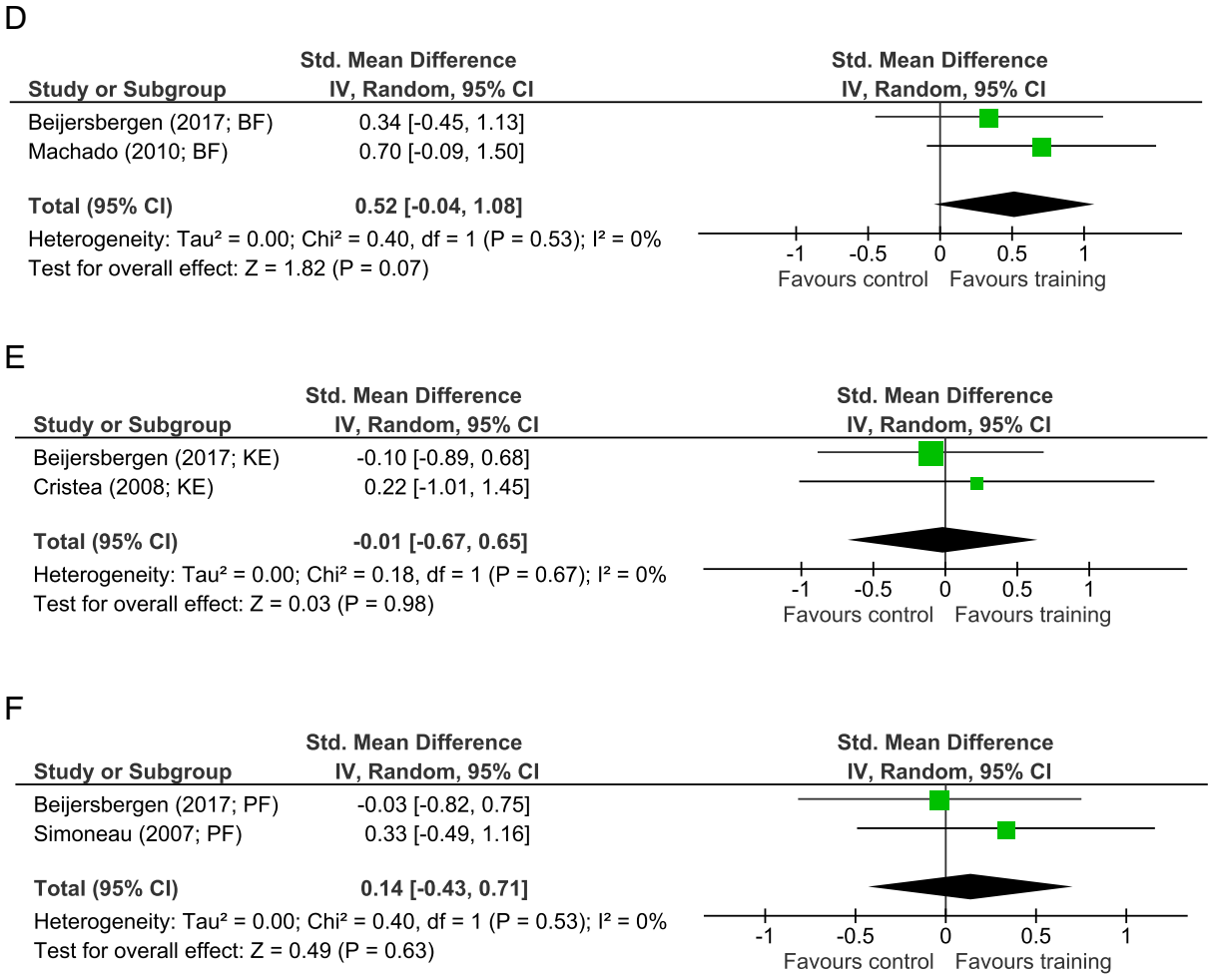

Fig. 4. (*continued*).

3.6.2. Attrition

Participant attrition rates of ≤10% ($n = 7$ studies), >10% and ≤ 20% (n = 7 studies), >20% and ≤30% ($n = 3$ studies) and 32% were reported ($n = 1$ study). No loss of participants was reported in nine studies.

3.6.3. Adherence

Adherence to the intervention (defined as; percentage of prescribed training completed) was: 100% in two studies; ≥90% and <100% in six studies; and 86% in one study. Four studies set a minimum level of training adherence (≥80%, ≥83% or 100%) for participant data to be included in the analysis. Three studies extended the intervention period as necessary, to ensure all prescribed exercise sessions were completed by all participants. Participant adherence was not reported in eleven studies.

3.6.4. Safety

Adverse events (defined as; injury or illness in participants allocated to intervention groups occurring in the study period) included incidence of muscle or tendon pain or injury (n = 3 studies), incidence of illness unrelated to RT ($n = 4$ studies), and pain or discomfort during the interpolated twitch protocol ($n = 2$ studies). There were no adverse events in five studies. The occurrence or lack of adverse events was not reported in 16 studies.

3.6.5. Cost effectiveness

No studies reported the cost effectiveness of the intervention.

3.7. Quality assessment

Based on five areas of potential bias, one trial was at high risk of bias overall, 12 had "some concerns", and the remaining were low risk (Fig. 6). There were too few studies in each meta-analysis to allow for accurate identification of asymmetry through visual funnel plot assessment.

3.8. Sensitivity analysis

After removal of studies with high risk of bias and "some concerns" the effect of RT on VA remained significant (SMD 0.92, 0.36 to 1.48, $P = 0.001$, $I^2 = 2\%$). The effect of RT on EMG activity for the VL (SMD 0.02, −0.84 to 0.88, $P = 0.97$, $I^2 = 80\%$), VM (SMD 0.21, −0.95 to 1.38, $P = 0.72$, $I^2 = 86\%$) and RF (SMD 0.49, −0.89 to 1.87, $P = 0.49$, $I^2 = 84\%$) remained non-significant after removal of studies with high risk of bias or "some concerns". Removal of studies with high risk of bias or "some concerns" resulted in too few studies to pool for EMG activity of the KE, BF or PF. The same sensitivity analysis did not alter the statistical outcome of RT on antagonist coactivation of the DF (MD 0.71%, −2.96 to 4.38%, $P = 0.71$, $I^2 = 0\%$). No studies were removed from the analysis of antagonist coactivation for the KF.

4. Discussion

4.1. Summary of results

This systematic review and meta-analysis aimed to evaluate the

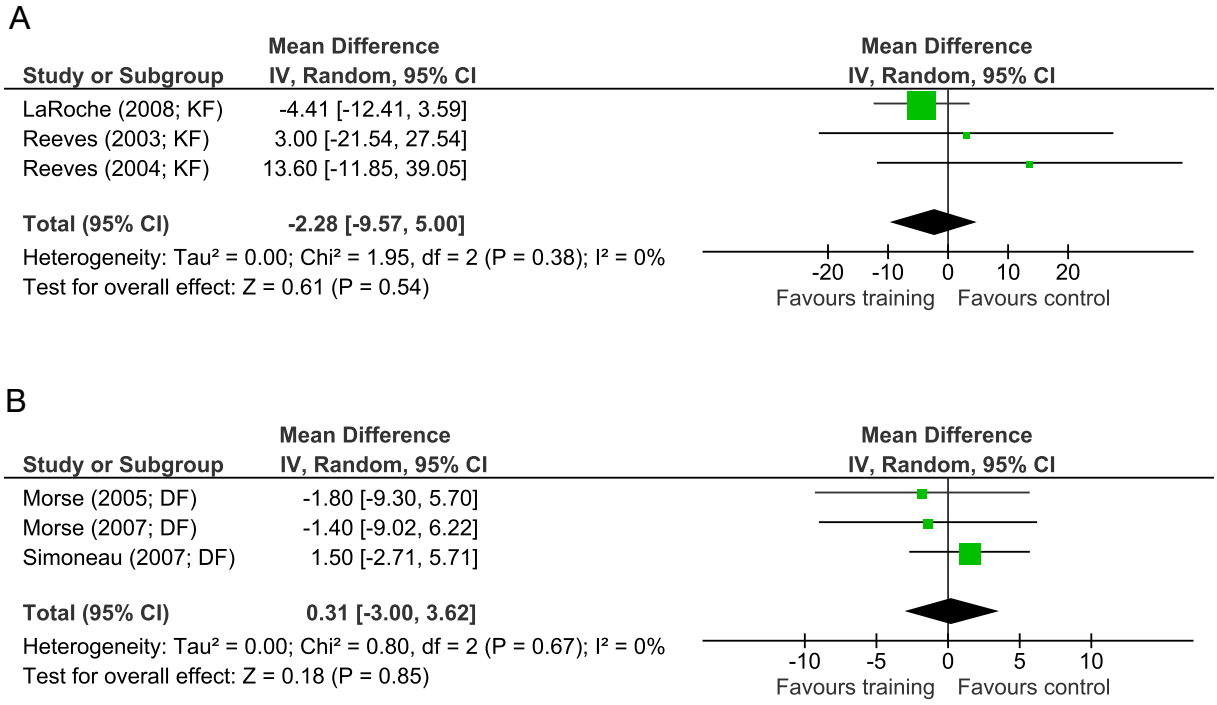

Fig. 5. Forest plot of six trials investigating the effect of RT on antagonist coactivation (%) in middle-aged and older adults, for the A) knee flexors [KF]; and B) dorsiflexors [DF].

influence of RT on strength-related neuromuscular function in middle-aged and older adults. The findings demonstrate that RT improves VA, in particular of the PF and in healthy cohorts. There was no effect of RT on EMG activity during MVC, or antagonist coactivation for any assessed muscle or muscle group, in middle-aged and older adults.

4.2. Agonist muscle activation

There was an effect of RT on VA (Figs. 2 and 3) but not EMG activity of the agonist muscles during MVC (Fig. 4). Several mechanisms might underpin training-induced neuromuscular adaptations, including: expansion of the neuromuscular junction (Deschenes et al., 2015); increased motor unit discharge rate (Kamen and Knight, 2004); and lowering of the motor unit recruitment threshold (Van Cutsem et al., 1998). Within the current review, lower intensity training [progressive from 20RM; (Correa et al., 2012; Suetta et al., 2004)], shorter intervention periods [≤6 weeks; (Toien et al., 2018; Johnson et al., 2010; Correa et al., 2012)] and partially home-based training (Morse et al., 2007; Morse et al., 2005) had improved agonist muscle activation. Considering the low uptake of RT among older adults (Merom et al., 2012), and the suggestion that short, low intensity, or unsupervised training interventions might be more appealing for older adults unfamiliar with RT (Fisher et al., 2017), our findings suggest that these preferred training modes may elicit improved muscle activation and should therefore be considered when prescribing exercise for older adults.

4.3. Antagonist coactivation

No effect was found on antagonist coactivation (Fig. 5). The desirability of modifying antagonist coactivation in older adults is debated. Coordination of agonist- antagonist muscle activity is modulated by disynaptic reciprocal inhibition (Hortobágyi and DeVita, 2006). An age-related reduction of spinal inhibition might contribute to an increase in antagonist coactivity (Hortobágyi and DeVita, 2006), which subsequently decreases net force production (Baratta et al., 1988). This is because total muscle force is a product of the simultaneous activation of opposing muscles (Carolan and Cafarelli, 1992). However, reductions in coactivation might be detrimental in older adults because antagonist muscles provide joint stability (Baratta et al., 1988), a factor associated with recurrent falls (Nevitt et al., 2016). Alternatively, others report no relationship between antagonist coactivation and joint stability in older adults (Segal et al., 2015). Therefore, more research is needed to determine the training effect on antagonist coactivation in older people and the importance of this measure. It is notable that antagonist coactivation was seldom reported, and few of the eight recent studies, published since the previous review (Arnold and Bautmans, 2014), reported this variable.

4.4. Subgroup analyses

After sub-analysis by muscle group, an effect remained for VA of the PF (Fig. 2). Increases in SMS in the PF ranged 10 to 93% (see Appendix B in Supplementary File 2). This is potentially important because increased activation and SMS in the PF reduces incidence of falling in older people (Cattagni et al., 2018). However, sub-analysis showed no effect for VA of the KE despite reports of increased KE SMS in most studies (6 to 85%; see Appendix B in Supplementary File 2). It is therefore likely that increases in KE SMS are explained by non-neural mechanisms.

It is unclear why a significant effect for VA remained in the PF but not KE. Baseline VA was inversely associated with gains in VA following six months of RT (Simoneau et al., 2006). Therefore, greater capacity for adaptation might exist in participants with lower initial activation, which is proposed to be <90% (Hvid et al., 2016). However, baseline measures in the intervention groups reporting VA for KE (71 to 90%, or 0.9 to 0.95 CAR) and for PF (80 to 88%) were not considerably different. Therefore, low initial activation might not consistently determine adaptation capacity.

Predominant muscle fibre type of the tested muscle may explain neuromuscular adaptation (Deschenes et al., 2015; Deschenes et al., 2011). Training-related neuromuscular junction adaptation in ageing rats occurred in type 2 muscle fibres only (Deschenes et al., 2015; Deschenes et al., 2011). Ageing is associated with a relative increase in

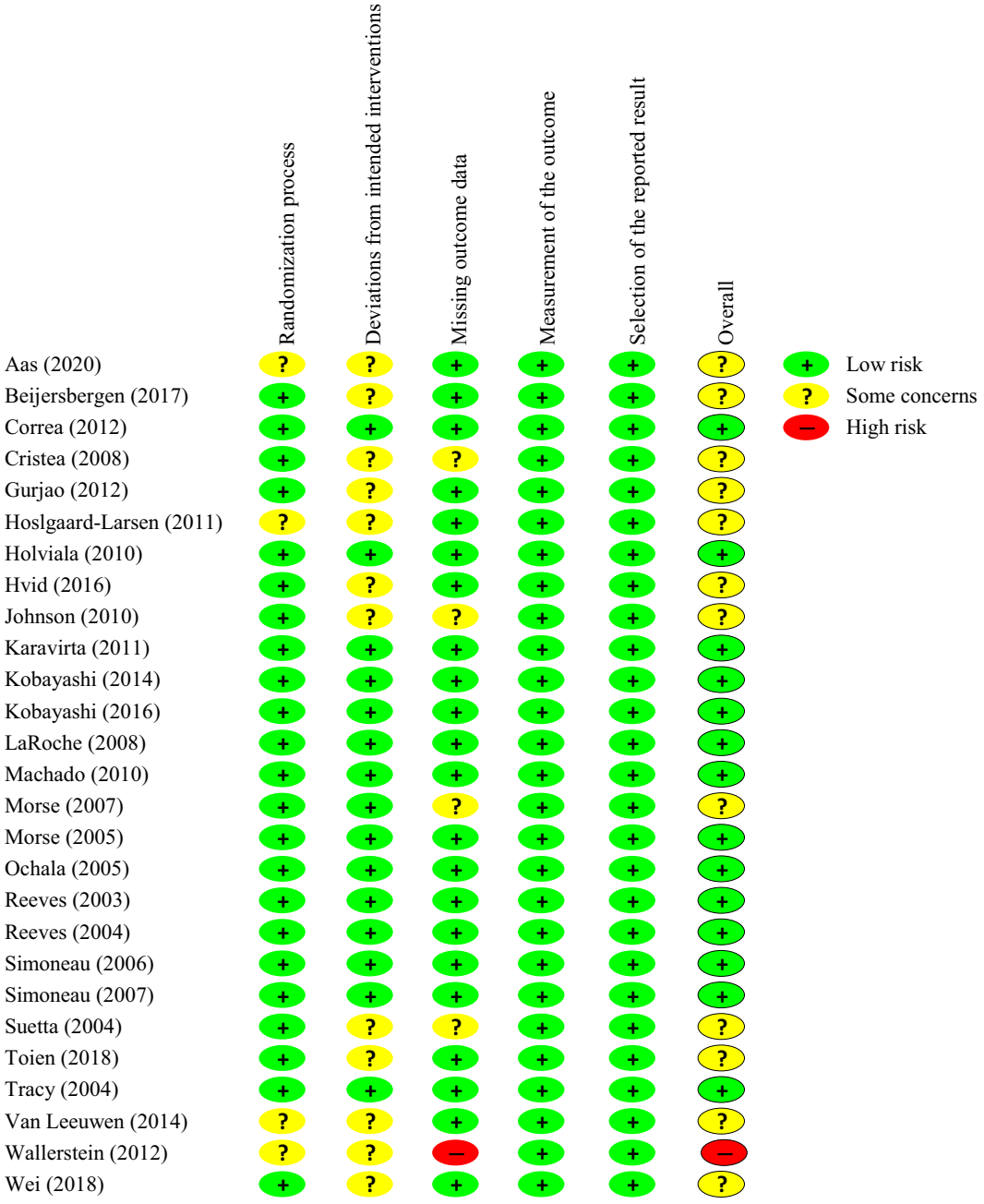

Fig. 6. Study quality using the Cochrane Risk of Bias 2 tool.

the proportion of type 1 muscle fibre content (Kim et al., 2005), which might reduce capacity for neuromuscular training adaptations with age. Our findings indicated that improvements in PF VA occurred in intervention groups with a mean age between 70 and 80 years (Toien et al., 2018; Simoneau et al., 2006; Morse et al., 2007; Morse et al., 2005). However, 12 weeks of power training increased KE VA in older participants (82.3 ± 1.3 years) with mobility limitations (Hvid et al., 2016). Therefore, it is unlikely that our findings are explained by muscle fibre changes associated with old age.

Interestingly, the observed improvements in PF VA occurred in recreationally active, apparently healthy participants (Toien et al., 2018; Simoneau et al., 2006; Morse et al., 2007; Morse et al., 2005). There was no overall effect for KE VA, which was assessed in one physically active, healthy participant group (Reeves et al., 2004) and participants with frailty (Aas et al., 2020), low SMM (Wei and Ng, 2018), mobility limitations (Hvid et al., 2016), and osteoarthritis (van Leeuwen et al., 2014; Johnson et al., 2010). Accordingly, subgroup analysis of VA by health status showed a significant effect for healthy groups and no intervention effect for clinical cohorts (Fig. 3). Although two studies reported post-training improvements in VA in people with total knee arthroplasty (not included in the meta-analysis) and mobility limitations (Hvid et al., 2016; Johnson et al., 2010), initial health and functional status on neuromuscular response to training may be an important factor in the capacity for neuromuscular adaptation. Alternatively, this result might be explained by study quality. No studies involving clinical populations included in this review were considered low risk of bias, thus all four studies assessing VA in clinical cohorts were removed during sensitivity analysis. Conversely, only two of the five studies involving healthy cohorts were removed during the sensitivity analysis, with three studies considered high quality.

4.5. Future research

There is a need for high-quality studies assessing the influence of RT on muscle activation in sedentary and clinical cohorts, including people with sarcopenia. Across 11 European countries, 71% of adults 50 years or older were reported to be physically inactive (Linardakis et al., 2013), precluding the transfer of the present finding to the majority of older adults. "Probable sarcopenia", or low SMS, was identified in 5.3% of adults over 40 years (Dodds et al., 2020). Furthermore, the presence of comorbidity almost doubles the risk of probable sarcopenia (Dodds et al., 2020). Improving neuromuscular function in middle-aged and older adults with sarcopenia or functional decline is important, due to the association between SMS and activation (Aas et al., 2020; Toien et al., 2018; Watanabe et al., 2018). Interventions which improve neuromuscular function might reverse or prevent the onset of sarcopenia, contributing to improved health outcomes for older adults. Studies in this review predominantly included recreationally active, apparently healthy older adults, highlighting the paucity of studies investigating the effects of RT on neuromuscular function in sedentary and clinical cohorts. Future studies should determine the influence of RT on neuromuscular function in previously inactive older adults, particularly those with sarcopenia and other coexisting diseases.

The potential for translation of these findings into clinical practice should also be considered. This review showed that RT positively influences VA. Recent publications have highlighted potential clinical applications of surface EMG (McManus et al., 2020; Medved et al., 2020; Campanini et al., 2020). In rehabilitation settings, potential uses of EMG activity assessment include monitoring of exercise training response, non-invasive diagnosis of neuromuscular disorders and provision of visual biofeedback for goal setting during exercise-based rehabilitation (McManus et al., 2020; Medved et al., 2020; Campanini et al., 2020). The aetiology of age-related SMS decline is multifactorial, as such comprehensive assessment and monitoring of the underlying mechanisms of strength loss in clinical practice, including the use of surface EMG, could inform targeted interventions for patients. Whilst there are potential benefits of widescale adoption of surface EMG techniques into clinical practice, this would require careful consideration of factors including: guideline development by an expert panel, the equipment costs, time costs for training practitioners and performing the measurement, the standardisation of surface EMG measurement protocols, and ensuring that standards and competencies of practitioners are upheld across centres performing the techniques. Therefore, translation of neuromuscular function research into clinical settings requires high-quality multi-centre trials in patient cohorts to support its use, alongside an evaluation of acceptability and cost-effectiveness. Finally, to demonstrate the clinical utility of surface EMG in the context of this review, i.e., to quantify neuromuscular responses to RT in adults >50 years, it should be shown to have independent and/or complementary benefits to existing measures of RT responses, such as strength.

4.6. Strengths and limitations

The strengths of this review are that: (a) a comprehensive literature search with no language, date or geographical restrictions was conducted; (b) a broad definition of RT was used to represent current practice in exercise prescription; and (c) no health conditions other than neurological were considered exclusion criteria, in attempt to identify participant cohorts that are representative of the general population.

Despite a comprehensive search strategy and independent study selection by two authors, it cannot be excluded that relevant references were overlooked. Some relevant trials were excluded due to unsuccessful attempts to contact the authors. Bias in the review process may have been introduced in the subjective appraisal of study quality using the RoB2 tool.

4.7. Comparison with other reviews

These results are in agreement with a previous systematic review and meta-analysis that reported a significant effect for VA of the PF and no effect for antagonist coactivation, in older adults (>60 years) following RT (Arnold and Bautmans, 2014). Arnold and Bautmans (2014) found an effect for the KE (pooled from three non-controlled studies), a finding not supported by our results. The exclusion of non-RCTs, and subsequent lower bias, in the present review may explain this discrepancy.

4.8. Implications

Resistance training interventions of two to six times per week at an intensity ranging from 20RM to maximal training, with three to 20 repetitions and one to seven sets, appear to be well tolerated in older adults with high adherence, low attrition, and few safety concerns. Resistance training has a moderate – to – large effect on VA of the lower limbs in older adults.

5. Conclusion

Lower limb VA improved following RT in middle-aged and older people, particularly in the PF and in healthy participants, coinciding with increased SMS. There was no RT effect on EMG activity during MVC or antagonist coactivation. Studies predominantly involved habitually active, healthy older people, meaning that the present results are not applicable to people with, or most at risk of, sarcopenia. More high quality RCTs are needed to elucidate the influence of RT on neuromuscular function in adults with diagnosed sarcopenia and other coexisting diseases.

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CRediT authorship contribution statement

Emily James: conceptualisation, methodology, investigation, formal analysis, writing – original draft, writing – review and editing
Simon Nichols: methodology, writing – review and editing
Stuart Goodall: methodology, writing – review and editing
Kirsty M Hicks: methodology, writing – review and editing
Alasdair F O'Doherty: conceptualisation, methodology, writing – review and editing, validation

Declaration of competing interest

None.

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