國立臺灣大學公共衛生學院流行病學與預防醫學研究所

碩士論文

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Master Thesis

以系統性回顧與網絡統合分析比較阻力訓練、耐力訓練與全身震動系統於治療老年人肌少症之成效

Comparative Effectiveness Analysis of Resistance Training, Endurance Training and Whole Body Vibration in Treating Sarcopenia in Elderly: Systematic Review and Network Meta-Analysis

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論文中文題目：以系統性回顧與網絡統合分析比較阻力訓練、耐力訓練與全身震動系統於治療老年人肌少症之成效

論文英文題目：Comparative Effectiveness Analysis of Resistance Training, Endurance Training and Whole Body Vibration in Treating Sarcopenia in Elderly: Systematic Review and Network Meta-Analysis

本論文係賴芝錦君（R03849040）在國立臺灣大學流行病學與預防醫學研究所完成之碩士學位論文，於民國 105 年 6 月 24 日承下列考試委員審查通過及口試及格，特此證明

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中文摘要

背景與目標：肌少症是因年齡增加導致的肌肉質量減少、肌肉力量衰退與身體活動功能限制的疾病。若特別針對肌少症的三項診斷指標：肌肉質量、肌力與身體活動功能表現，目前仍缺乏各種運動療效之間的比較文獻。本篇研究的目的即採用系統性回顧與網絡統合分析，比較阻力訓練、耐力訓練與全身震動系統於治療老年人肌少症之成效。

方法：收集並分析阻力訓練、耐力訓練與全身震動系統的隨機對照試驗，摘錄其中訓練前與訓練後之肌肉質量、肌力與身體活動功能之數據，對象為六十歲以上的老人。以廣義線性混合模型進行網絡統合分析，並以直接證據與間接證據呈現混合治療型比較之結果。

結果：共收錄 31 篇隨機對照試驗，1405 名六十歲以上老人被收錄(年齡介於 60 歲與 92 歲)。肌力在阻力訓練組與無運動介入組之間達到顯著差異，經由阻力訓練後的肌力較無運動組別增加 12.8 公斤 (95% 信賴區間 8.54 至 17.0 公斤)。身體活動功能則在阻力訓練組與無運動介入組、全身震動系統與無運動介入組達到顯著差異[平均值分別是 2.63 次 (95% 信賴區間 1.34 至 3.93 次) 與 2.07 次 (95% 信賴區間 0.49 至 3.65 次)]。但肌肉質量在各組的直接比較或間接比較皆無顯著差異。

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結論：若使用肌少症的診斷指標來評估老人的運動效益，阻力訓練可顯著增加老人的肌力與身體活動功能，而全身震動系統可顯著改善老人的身體活動功能。但研究結果卻顯示三種運動介入方式無法顯著增加肌肉質量。

關鍵字：肌少症、阻力訓練、耐力訓練、全身震動系統、系統性回顧、網絡統合分析。

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英文摘要

Background and Objectives: Sarcopenia is an age-related loss of muscle mass, muscle strength, and physical performance. Few studies have examined the relative benefits of resistance training, endurance training, and whole-body vibration through the simultaneous consideration of three diagnostic criteria: muscle mass, muscle strength, and physical performance. The purpose of this systemic review and network meta-analysis was to analyze the effects of resistance training, endurance training, and whole-body vibration on changes in muscle mass, muscle strength, and physical performance through the evaluation of lean body mass, leg extension strength, and chair-stand tests in elderly people.

Methods: We combined evidence from all randomized controlled trials comparing resistance training, endurance training, and whole-body vibration with usual care among adults aged at least 60 years. The effects of exercises and usual care on muscle mass, muscle strength, and physical performance were examined. We performed a mixed treatment comparison by using generalized linear mixed models for the network meta-analysis.

Results: Thirty-one randomized controlled trials involving 1405 participants were

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included (age range, 60–92 years). Muscle strength enhancement was greater for resistance training compared with usual care [12.8 (95% CI 8.54 to 17.0)]. Physical performance enhancement was greater for resistance training compared with usual care, and whole-body vibration was greater compared with usual care [2.63 (95% CI 1.34 to 3.93), and 2.07 (95% CI 0.49 to 3.65)]. No significant difference was observed regarding changes in lean body mass.

Conclusion: Resistance training is beneficial for elderly people with outcome indicators of sarcopenia; specifically, it enhances muscle strength and physical performance. Resistance training and whole-body vibration were the two most effective exercise interventions in terms of physical performance. However, no statistically significant results were observed for resistance training, endurance training, and whole-body vibration concerning increases in muscle mass.

Keywords: sarcopenia, resistance training, endurance training, whole body vibration, systemic review, network meta-analysis.

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目　錄 Table of Contents

doi:10.6342/NTU201602158

doi:10.6342/NTU201602158

doi:10.6342/NTU201602158

Figures

doi:10.6342/NTU201602158

doi:10.6342/NTU201602158

Tables

doi:10.6342/NTU201602158

Chapter 1 Introduction

1.1 Sarcopenia

1.1.1 Definition, prevalence and causes of sarcopenia

According to the clinical definition and consensus on diagnostic criteria for sarcopenia specified by the European Working Group on Sarcopenia in Older People (EWGSOP), sarcopenia is defined as an aging-associated condition involving a progressive decline in skeletal muscle mass, resulting in the deterioration of muscle function (muscle strength and physical activity) [1].

The prevalence of sarcopenia has increased with the rapid growth in the number and proportion of elderly people. According to the United Nations World Population Aging 2013, the proportion of the world population aged at least 60 years is projected to increase from 12% in 2013 to 21% in 2050. People aged at least 60 years in the 2010–2015 period are expected to live an additional 20 years [2]. The overall prevalence of sarcopenia was estimated to be 5%–13% for elderly people aged 60–70 years in Europe and the United States [3]. The prevalence of sarcopenia in Taiwan was found to be 18.6% for elderly women and 23.6% for elderly men [4].

Sarcopenia is an age-related condition that leads to a 1%–2% reduction in skeletal

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muscle mass for both men and women over the age of 50 [5]. A reduction in muscle mass and strength in elderly people is caused by the etiologies of sarcopenia. As shown in Figure 1, sarcopenia is a multifactorial process in which aging is the major cause [6]. Primary sarcopenia is caused only by age-related factors such as a reduction in sex hormones, apoptosis, mitochondrial dysfunction, satellite cell dysfunction, and motor neuron loss. Cachexia and vitamin D deficiency contribute to sarcopenia. In addition, sarcopenia is associated with disease states such as neurodegenerative diseases, advanced organ failure, inflammation diseases, malignancies, and endocrine diseases.

Most endocrine diseases, such as diabetes, hypogonadism, and hypercortisolism, as well as obesity and chronic kidney disease are associated with age-related muscle loss [7, 8]. Seven factors are related to loss of muscle mass and strength: humoral, genetic, nervous system, hormonal, nutritional, insulin resistance, and lifestyle. Lifestyle factors consist of sedentary lifestyles, high-fat diets, obesity, smoking, and immobility. Lifestyle factors are more controllable than the other six factors; therefore, they have attracted public attention for the prevention of sarcopenia [1, 9, 10].

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1.1.2 Consequences of sarcopenia

Public health concerns of sarcopenia include higher healthcare costs, diminished quality of life, and mortality [11]. Age- and disease-related muscle loss and comorbidities among elderly people lead to poorer health conditions, suggesting longer periods of hospitalization. Comorbidities of sarcopenia include cognitive decline, cerebrovascular disease, insulin resistance, chronic kidney disease stage three, and osteoporosis at the femur neck in elderly men [7, 12]. Regarding medical procedures, sarcopenia is associated with high costs and poor outcomes after major surgery [13]. Higher mortality is strongly correlated with sarcopenia after liver transplantation [14]. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer [15].

Muscle weakness in the lower extremities (quadriceps, iliopsoas, tibialis anterior or posterior peroneus, and hip or knee) increases the risk for falling in elderly people [16]. A study reported that among elderly women who had fallen in the past year, women who exhibited prolonged chair-rise time (time to stand up from a sitting position) were three times as likely to have a serious injury as were those with shorter chair-rise time [17]. Compared with those without sarcopenia, participants with sarcopenia had a significantly higher number of falls and fractures [18]. Falls threaten

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the independence of elderly people and account for many hospital and nursing home admissions. Functional ability is significantly reduced at 1 year after initial presentation to the emergency department because of a fall [19].

Lower muscle mass, greater fat infiltration into the muscle, and lower knee extensor muscle strength are associated with increased risk of mobility loss in elderly men and women [20]. Severe sarcopenia is a risk factor for the development of physical disabilities, and consequently, disability is associated with increased hospitalization, nursing home placement, home health care, and health care expenditure [11, 21]. In the United States, the estimated direct health care cost attributable to sarcopenia in 2000 was $18.5 billion ($11.8 - $26.2 billion) [22].

1.1.3 Interventions of sarcopenia

Resistance training is a form of physical activity that is designed to improve muscular fitness by exercising a muscle or a muscle group against external resistance [23]. Pharmacological interventions have shown limited efficacy in counteracting skeletal muscle wasting resulting from sarcopenia; therefore, exercise interventions represent a critical approach for preventing and treating sarcopenia [24, 25].

doi:10.6342/NTU201602158

1.2 Resistance training

Resistance training is a form of physical activity that is designed to improve muscular fitness by exercising a muscle or a muscle group against external resistance [26]. The American College of Sports Medicine (ACSM) recommends that resistance training should be performed a minimum of 2–3 days per week. The resistance training intensity and number of repetitions performed in each set are inversely related. Elderly and deconditioned people who are susceptible to musculotendinous injury should begin a resistance training program by conducting a high number of repetitions at moderate and light intensities. Moderate intensity signifies a 60%–70% repetition maximum (1-RM). Light intensity signifies 40%–50% of 1-RM. When 1-RM is not measured, moderate (5–6) and vigorous (7–8) intensity can be distinguished according to a 10-point scale for rating perceived exertion (RPE). With 1-RM and RPE measurements, people can calculate quantitative volume while maintaining an appropriate lifting technique. Repetitions of resistance training can be defined as follows: one set of 8–12 repetitions for healthy adults or 10–15 repetitions for middle-aged and elderly people. No specific duration of training has been identified for effectiveness. For general muscular fitness, a person should perform resistance training for each major muscle group (i.e., chest, shoulders, upper and lower back,

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abdomen, hips, and legs). A total of 8–10 exercises targeting the major muscle groups should be performed. Typical resistance exercises for major muscle groups can be performed using body weight or a variety of exercise equipment such as sand bags and resistance bands. Resistance training causes neural adaptation because of an increase in motor unit synchronization, concentric contraction of synergist muscles, and increased inhibition of antagonist muscles.

1.3 Endurance training

Endurance training has been called aerobic training and cardiorespiratory endurance exercise [26]. Rhythmic, aerobic exercise of at least moderate intensity involving large muscle groups and requiring little skill to perform is recommended for all adults. For example, walking, leisurely cycling, aqua-aerobics, and slow dancing are recommended modes of endurance training for all adults. The ACSM recommends any modality that does not impose excessive orthopedic stress, such as walking, which is the most common type of activity. For elderly people with a limited tolerance for weight-bearing activities, aquatic exercise and stationary cycle exercise may be advantageous. The ACSM recommends an endurance training intensity of 40%–60% heart rate reserve (%HRR), 3–6 metabolic equivalents (MET), and a 5–6 rating of perceived exertion (RPE) to moderate intensity for elderly people. Moderate aerobic

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exercise is recommended for most adults, and light to moderate intensity aerobic exercise can be beneficial for deconditioned people. Endurance training is recommended 3–5 days per week for most adults, with the frequency varying with the intensity of exercises. For moderate-intensity exercises, an accumulated 30–60 min per day in periods of at least 10 min each for a total of 150–300 min per week is recommended.

Endurance training can enhance maximal voluntary contraction in isometric knee extension in elderly people. For elderly people, endurance training increases the cross-sectional area of both type I and type II muscle fibers by 12% and 10%, respectively. When the number of capillaries in contact with each fiber increases, endurance training programs result in a 23% increase in maximal O2 consumption [27].

1.4 Whole body vibration

Whole-body vibration has recently been proposed as a mild approach to improve neuromuscular performance. Whole-body vibration is an oscillatory motion delivered to the entire body from a platform. Oscillatory motion is a mechanical stimulus characterized by a lineal pivotal platform, depending on the type of equipment. The

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intensity of oscillation is set at biomechanical variables of frequency and amplitude. The extent of the oscillatory motion reflects the amplitude (measured in millimeters) of the vibration. The repetition rate of the cycles of vibration per second reflects the frequency of the vibration (measured in hertz) [28]. The frequencies of vibration studied in elderly people have varied from 12.6 to 60 Hz, with reported amplitudes varying from 55 μm to 8 mm [29]. In elderly people with fragile musculoskeletal systems, amplitudes >0.5 mm have been reported to have greater effects on the body, causing discomfort [30]. A review of Rittweger [31] revealed that vibration frequencies ranging between 20 and 45 Hz shows adaptive neuromuscular effects. However, Rittweger reported that at frequencies above 50 Hz, severe muscle soreness and hematoma may emerge in untrained subjects [32]. Low-intensity whole-body vibration can induce muscle activity as effectively as higher-intensity protocols do, and it may thus be the preferred choice for frail elderly people [33].

Vibration-induced enhancements in muscular performance have been suggested to be similar to those after several weeks of power training [34]. Standing on oscillating platforms induces an enhanced refectory response of the leg and postural muscles through the so-called “tonic vibration reflex” [35]. Tonic vibration reflex is a mechanical vibration that induces the stretch reflex of muscle spindles and activates I-

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α afferents, which initiates impulses in the polysynaptic excitatory pathway, causing tonic contraction of the muscle. Skin mechanoreceptors such as Pacinian corpuscles activate muscle spindles and induce a flexion reflex during vibration stimulation. This causes wider spreading effects compared with those of the tonic vibration reflex and evoked muscle contractions [36].

1.5 Review of three exercises

1.5.1 Resistance training

Recent studies have suggested that physical activity and exercises such as resistance training can be used to slow down the progression of sarcopenia effectively [37-39]. Charette reported an increase in the cross-sectional area of type II muscle fibers, but not type I fibers, after a 12-week resistance training program. High-intensity exercises are necessary for the development of type II muscle fibers. However, elderly people typically have a reduced frequency of high-intensity activities, which leads to type II muscle fiber-selective atrophy, but the preservation of type I muscle fibers. Therefore, high-intensity exercise (e.g., resistance training) can increase muscle mass [40]. In Peterson's meta-analysis on resistance training designed for elderly people [41], 49 randomized and nonrandomized controlled trials were analyzed. Trials were included if the mean age of participants was over 50 years. Results revealed that muscle mass

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was effectively increased because of the resistance training protocol. The weighted pooled estimate of the mean change in lean body mass was 1.1 kg (95%CI 0.9–1.2). Kelley's meta-analysis involved two randomized controlled trials and six nonrandomized controlled trials to determine the effects of resistance training in 225 men aged 18–70 [42]. Compared with the control group, lean body mass increase was reported to be statistically significant in men conducting resistance training (weighted mean difference 0.3 kg (95%CI -0.2–0.6). However, three randomized controlled trials involving 143 premenopausal women aged 18–47 were included in another meta-analysis by Kelley [43]. Results showed no statistically significant difference in muscle mass within or between the resistance training groups and control groups. In a meta-analysis by Silva [44], 15 randomized controlled trials involving 528 participants aged 66 years or older were conducted. Muscle strength was significantly enhanced in the resistance training group compared with the control group (weighted mean difference 23.1%, 95% CI 15.4–30.8).

1.5.2 Endurance training

Endurance training has been considered minimally effective on muscle mass and muscle strength, but moderately effective on aerobic capacity. However, a review by Konopka indicated that endurance training increased muscle hypertrophy by

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improving muscle molecular regulation and protein metabolism. In sedentary men and women, muscle and myofiber size increased after endurance training [45]. Endurance training changed the muscle fiber distribution. In patients with chronic heart failure, a regular bicycle exercise improved exercise tolerance, which was associated with a shift in fiber type distribution from fast-twitch type II fibers to slow-twitch type I fibers [46].

1.5.3 Whole body vibration

Osawa conducted a meta-analysis comprising 10 studies to determine the effects of whole-body vibration on knee extension muscle strength. Data collected from four trials that included elderly people showed a significant increase in knee extensor muscle strength for exercises in the whole-body vibration group [47]. Sitjà-Rabert performed a meta-analysis to evaluate the efficacy of whole-body vibration in an elderly population compared with conventional exercise in control groups. A total of 16 randomized controlled trials were pooled, which indicated that whole-body vibration significantly enhanced muscle strength (weighted mean difference 18.3 newton meters [95%CI 8.0-28.6])[48].

Recent evidence from systemic reviews and meta-analyses shows that resistance

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training, endurance training, and whole-body vibration are crucial for increasing muscle mass and muscle strength and improving physical performance. However, because of limitations in traditional meta-analysis, evidence regarding comparisons of different types of exercise intervention is insufficient. Recent studies have not identified the most effective option for mitigating the indicators of sarcopenia.

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Chapter 2 Study gap

When considering the diagnostic criteria of sarcopenia (muscle mass, muscle strength, and physical performance), it is difficult to conduct a well-designed randomized controlled trial for all competing exercise interventions. Furthermore, traditional meta-analysis was used in the comparison of two arms (i.e., one intervention group compared with one control group). The disadvantage of traditional meta-analysis is that multiple interventions are tested according to difficulties; traditional analysis does not enable adequate assessment of the comparative effectiveness of all exercise interventions. To mitigate the multi-arm analysis problem, a network meta-analysis was conducted to compare direct and indirect evidence.

In this study, we conducted a network meta-analysis to synthesize direct and indirect evidence and estimate the relative efficacy between a pair of exercise interventions. After the rank and the effect of interventions are determined, the exercise can become a nonpharmacological intervention strategy for preventing sarcopenia in elderly people.

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Chapter 3 Materials and methods

3.1 Identification of studies

We searched the databases in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), the Physiotherapy Evidence Database (PEDro) using the keywords including *sarcopenia, physical activity, muscle atrophy, resistance training, endurance training, whole body vibration, lean body mass, body composition, body fat distribution , and muscle strength or physical performance* or other related terms. We limited the search to English language studies. We conducted a literature search to identify relevant studies published from 1989 until 15 February 2016. The term 'sarcopenia' was proposed by Irwin Rosenberg in 1989 [49].

3.2 Selection of sample studies

Systemic reviews and meta-analyses were followed by the PRISMA (Preferred Reporting Items for Systemic Reviews and Meta-analyses) guidelines, and used a predetermined protocol. To be included in this study for higher quality, the studies should be designed as randomized control trials involving the comparison between the intervention of resistance training, endurance training, whole body vibration and the usual-care control group in elderly people (average age ≥ 60 years). In addition, the inclusion criteria should be met by including at least one of the three following data

doi:10.6342/NTU201602158

results: muscle mass, muscle strength and physical performance. The muscle mass, muscle strength and physical performance refer to lean body mass, leg extension strength, chair-stand test, respectively.

The intervention protocols of resistance trainings are classified in accordance with the American College of Sports Medicine (ACSM). The resistance trainings for the elderly is a dynamic exercise performed by multi-joint use. In the resistance training protocol for the elderly to perform a complete movement of a given exercise, the duration of each exercise is set as a range of approximately 20–45 minutes per session and no less than 20 minutes, the intensity is at least 60% one-repetition maximum (1RM), and the repetition requires at least 10 times[26].

The National Institute on Aging (NIA) recommend older adult's progress to at least 30 minutes of moderate to vigorous endurance exercises. The 30-minute goal can accomplished by accumulating time in shortening sessions of at least 10 minutes each[50]. ACSM recommends accumulating 20-60 minutes at that level three to five days a week[26].

Whole body vibration system was characterized oscillatory motion delivered to the entire body from a platform. The biomechanical variables that determine its intensity

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are the frequency and amplitude. The extent of the oscillatory motion determines the amplitude (peak to peak displacement, in mm) of the vibration. The repetition rate of the cycles of oscillation determines the frequency of the vibration (measured in Hz)[28].

The usual-care control group was used in comparison with the resistance trainings group, endurance training group and whole body vibration group. In the usual-care control group, the trials incorporating a placebo-based intervention are also included (education, stretching, etc.).

3.3 Data extraction and bias assessment

The muscle mass is categorized as the primary outcome while the muscle strength and physical performance are secondary outcome. The primary outcome is the change of lean body mass that can be assessed by the imaging techniques (CT, MRI, dual energy x-ray absorptiometry (DXA)), bio-impedance analysis and anthropometric measurement. The secondary outcomes are the evaluation of the muscle strength by the leg extension strength [51], and the physical performance on the chair-stand test [52]. Maximal concentric leg extension strength is assessed by one-repetition maximum test (1RM) [51]. Chair-stand test was chosen to evaluate the physical

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performance for the muscular strength and endurance in the elderly's legs [52]. The participants were instructed to perform a sit-to-stand by rising to a full stand from a complete sitting position, repeated as many times as possible within 30 seconds, and the total number of times was counted.

The data are extracted from the same independent extractor from full-text articles. The publication bias is assessed with funnel plots and egger's test of effect size (mean difference) against its standard error. The risk of potential bias assessments is conducted by Cochrane Collaboration's tool[53]. By using the Cochrane Risk of Bias Tool, studies were classified as being at low risk, at high risk or unclear. This study is not funded or sponsored by any special interest.

3.4 Data synthesis and analysis

3.4.1 Relative treatment effects

The primary and secondary outcomes are represented as the mean change from baseline in lean body mass (kilogram), leg extension strength (kilogram) and chair-stand performance (frequency), respectively. All the outcomes are continuous variables. Because of not only different sample of participants but differences in the way studies were conducted, random effect model was conducted for pairwise meta-

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analysis comparisons from trials with the same interventions (i.e. resistance training vs. usual care, resistance training vs. endurance training, endurance training vs. whole body vibration and so on). We estimated the pairwise relative treatment effects of the competing interventions using weighted mean differences for outcomes (lean body mass, leg extension strength and chair stand test) and the mean difference with 95% confidential intervals (CI). Change of standard deviation was calculated using the formula [54, 55]:

$$Change\ of\ standard\ deviation\ (SD) = \sqrt{{SD_{pre}}^2 + SD_{post}^2 - 2 \times Corr(pre, post) \times SD_{pre} \times SD_{post}}$$

Within-participant correlation was imputed 0.5 if correlation was not reported. All tests were two-tailed and a p value of less than 0.05 was determined statistically significant. The heterogeneity was estimated by restricted maximum likelihood. The data were analyzed with Stata version 14 (StataCorp LP, Texas, USA).

3.4.2 Methods for direct and indirect comparisons

We performed a mixed treatment comparison using generalized linear mixed models for network meta-analysis to analyze direct and indirect comparisons of different exercise interventions. For example, for conducting the direct comparison of

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resistance training and endurance training, direct evidence is provided by trials directly comparing these two exercise training. For conducting the indirect comparisons of resistance training and endurance training, each has been compared with a common comparator, say usual care, indirect evidence is based on the direct comparison of resistance training and usual care and the direct comparison of endurance training and usual care. We performed network meta-analysis in Stata using the mvmeta command and self-programmed. The between-study variance can be estimated using restricted maximum likelihood method and DerSimonian-Laird method [56].

3.4.3 Relative treatment ranking

The relative ranking probabilities for four arms were estimated by using “network rank max” command. Rankogram of the effects of usual care, resistance training, endurance training and whole body vibration on lean body mass, leg extension strength and chair-stand test were used for showing the hierarchy of the competing interventions. The surface under the cumulative ranking curve (SUCRA) is a percentage of the mean rank of each treatment relative to an imaginary treatment that is the best without uncertainty. The larger area under the curve, the better the rank of the exercise intervention [57].

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3.4.4 Statistical heterogeneity and inconsistency

Heterogeneity refers to between-study variance within a comparison[58]. For the pairwise comparisons (i.e. direct comparisons), statistical heterogeneity was assessing by the forest plot, I-squared and its 95% confidence interval.

Inconsistency refers to differences between direct and indirect evidence in the network [58]. For the network comparison, loop-specific approach and "node-splitting" method were conducted to assess inconsistency locally. Design-by-treatment model was conducted to evaluate inconsistency globally

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Chapter 4 Results

The PRISMA flow chart of the included trials and the assessment of the risk of bias of the included randomized control trials are given in figure 2, 3 and 4. Figure 2 outlines the searching strategy, identifying 234 publications. The titles and abstracts were screened for inclusion. The full texts of 138 articles were retrieved, of which 31 met the inclusion criteria. One-hundred seven were excluded: 38 studies were participants for the age only 60 years or younger, 1 was not written in English, 2 did not incorporate the primary and secondary outcomes, and 60 did not use usual-care control group or other exercise interventions for comparison.

The findings with respect to random sequence generation, allocation concealment, blinding of participants, personnel and outcome measurement, completeness of outcome data and slective reporting were demonstreated on figure 3 and 4. Most studies were low risk of concealment of allocation, blinding of particants and personnel, incomplete outcomes data and selective reporting. All studies were rated low risk of bias of random seqence generation exept for Emerson's study [59], in which group randomization was based upon the participant's availability and willingness to attend the training sessions. Many trials did not address insufficient information of blinding of outcome assessment were rated "unclear risk of bias".

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Because of the characteristics of intervention study, no study blinded participants and personnels to the intervention exept for Bautmans' study [60], in this study usual care group standed on identical whole body system with intervention group but with switched-off plates.

Table 2, 3 and 4 showed the selected characteristics of the 31 studies that met the inclusion criteria. All studies involved comparisons on at least of two or three of four arms (usual care, resistance training, endurance training and whole body vibration). The studies recruited 1405 participants, of which female accounts for 58.5% while four studies did not provide detailed information for the female percentage[59, 61-63]. The age for the 31 randomized control trials was 60 to 92 years. The physical conditions of participants in 23 studies were healthy older adults, while those physical conditions of participants in 8 studies were type 2 diabetes[64], coronary artery disease[65, 66], frailty[67, 68], and lower extremity weakness [69, 70], hospitalized[71], respectively. The time period of 31 studies was 6 weeks to 48 weeks.

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4.1 Muscle mass: Lean body mass

The results of traditional meta-analysis on the primary outcome in terms of lean body mass was shown in figure 5A. Six trials compared resistance training with usual care were included in our studies [59, 64, 65, 72-74], the result showed no significant difference in the change of lean body mass, it still showed a difference by an increase of 1.12 kg of lean body mass in comparison between resistance training and the control group (95%CI -2.53–0.29).

Eight studies of the 31 studies reported the outcome of lean body mass [64, 65, 72-77], as shown in figure 6A. One of the eight trials was multi-arm. As shown in table 5 and figure 7, no significant difference was observed regarding changes in lean body mass. Table 5 showed a greater difference by an increase of 0.82 kg of lean body mass of comparison between resistance training versus whole body vibration (95%CI -3.43 to 5.08). And the difference of resistance training versus usual care (mean 0.49 [95%CI, -0.12–1.11]) is slight lower than that of endurance training versus whole body vibration (mean 0.60 [95%CI -3.64 to 4.85]). However it showed a trend of a slightly decrease in whole body vibration versus usual care (mean change-0.33 [95%CI -4.54–3.88]).

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Figure 12A and 13A showed a rank from high to low, there is a 38% probability that resistance training ranked 1st, 42% that endurance training ranked 2nd, 49% that usual care ranked 3rd and 55% whole body vibration ranked 4th.

4.2 Muscle strength: Leg extension strength

Figure 5B displayed the results of the traditional meta-analysis on the assessment of the secondary outcome based on the leg extension strength. Seventeen trials reported outcome of leg extension strength were included in this meta-analysis [59, 62, 65, 66, 69, 70, 72, 73, 78-86]. We reported significant effect of resistance training on leg extension strength. The comparison between resistance training and usual care regarding leg extension strength was 12.6 kg (95%CI 7.98–17.2).

Twenty-one studies of the 31 studies reported the outcome of leg extension strength, as shown in figure 6B [59, 60, 62, 65, 66, 69, 70, 72, 73, 77-88]. Two of the 21 trials were multi-arms. As shown in table 5 and figure 8, no significant difference was observed regarding changes in lean body mass. Compared with usual care, leg extension strength was significantly increased with resistance training, with mean difference 12.75 kg (95%CI 8.54–16.97). There were no statistically significance between other pairwise comparisons.

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Resistance training was ranked first according to the estimated surface under the cumulative ranking curve values. Endurance training was more effective than were usual care and whole body vibration (figure 12B and 13B)

Subgroup analyses were undertaken to investigate whether there was evidence of a differential effect of measurement of 1-RM test in predefined subgroups of the elderly. We analyzed data based on data collected from knee extension machine (7 trials) and leg press machine (15 trials) separately, as shown in table 6. The leg extension strength assessed by knee extension machine and leg press machine were both significantly increased in resistance training compared with usual care, with mean difference 10.05 kg (95%CI 5.68–14.41) and 18.45 kg (95%CI 9.63–27.28), separately.

4.3 Physical performance: chair-stand test

Figure 5C showed the results of the traditional meta-analysis on the assessment of the secondary outcome based on the chair-stand test. Five studies reported outcome of chair-stand test were included in this meta-analysis [62, 71, 86, 89, 90]. We reported significant effect of resistance training on chair-stand test. The comparison between resistance training and usual care regarding chair stand test was 2.64 times (95%CI

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1.17–4.11).

As shown in table 5 and figure 9, the results of the network meta-analysis on the assessment of outcome based on chair-stand test. Eight studies reported outcome of chair-stand test were included in this analysis [60, 62, 68, 71, 86, 89-91]. Chair-stand test was significantly improved with resistance training and whole body vibration, comparing with usual care, with mean difference of 2.63 times (95% CI 1.34–3.93) and 2.07 times (95%CI 0.49–3.65), respectively.

The result of ranking probability showed the most effective exercise intervention for the elderly endpoint was resistance training. The second choice was whole body vibration (figure 12C and 13C).

4.4 Publication bias

Examination of the Begg's funnel plot of lean body mass (fig. 10A) and chair-stand test (fig. 10C) were demonstrated considerable symmetry, suggesting that there was no significant publication bias. However, funnel plot of leg extension strength (fig. 10B) showed asymmetry in a sample of 21 trials.

The Egger's regression plot of lean body mass (fig. 11A) of leg extension strength

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(fig. 11B) and chair stand test (fig. 11C) was graphically demonstrated. More the intercept deviates from zero, the more pronounced the asymmetry. If the p-value of the intercept is smaller than 0.05, the asymmetry is considered to be statistically significant. The coefficient of bias of lean body mass and chair stand test were -0.27 and -0.48 (95%CI, -0.76–0.22 and -5.28–4.32, p = 0.25 and 0.82, separately). The Egger's test showed there were small study effects in leg extension strength (coefficient of bias: -1.84, 95% CI-3.42–-0.26, p=0.024)

4.5 Statistical heterogeneity and Inconsistency

For muscle mass and physical performance, there were no statistically significance of I squared between pair-wise comparison. But for muscle strength, there were statistically significance of resistance training versus usual care (I squared=86.0%, p=0.00). (Figure 7, 8 and 9)

For assessing inconsistency locally, we conducted loop-specific approach and "node-splitting" method. We did not note any inconsistencies between evidence derived from direct and indirect comparisons in these two methods. For assessing inconsistency globally, we applied the design-by-treatment inconsistency model, we did not find significant differences in relative effects.

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Chapter 5 Discussion

This systemic review and network meta-analysis provides evidence of an overall benefit of resistance training for muscle strength and physical performance among elderly people. The pair-wise comparison suggested benefits of whole-body vibration on physical performance. However, three exercise interventions showed a nonsignificant increase of muscle mass.

5.1 Comparison with previous studies

5.1.1 Muscle mass

Two meta-analyses have considered the effectiveness of resistance training in nonelderly participants [42, 43]; however, one meta-analysis was published concerning the benefits of resistance exercises in lean body mass among elderly people [41]. A total of 49 randomized and nonrandomized controlled trails and 81 cohorts were included; the analysis revealed that after 20.5 weeks of resistance training, a significant increase in lean body mass of 1.1 kg was recorded among elderly people (95%CI 0.9–1.2kg, $p<0.001$). The average age in our study is much higher than that of Peterson's study (age range of our study: 64.8 to 91.9 years vs. 65.5±7 years); this difference between the two meta-analyses imply that exercise effects among elderly people may attenuate, although no statistically significance

doi:10.6342/NTU201602158

results were found in our study.

Among functionally limited elderly people, lower extremity muscle mass was a critical determinant of physical performance, and a strong association was also observed between lower extremity lean mass and muscle strength [92].

5.1.2 Muscle strength

Studies included in our network meta-analysis have indicated a significant enhancement in leg extension strength. In a meta-analysis by Silva [44], 15 studies (84 effect-sizes) were included, the pooled data of which revealed that resistance training causes strength gains in adults over 55 years old (standard mean difference 2.00, 95%CI 1.76–2.23). However, our meta-regression analysis showed that strength increases only if the training duration is sufficient. Compared with meta-analysis by Osawa[47], four studies were included, the pooled data of which showed significant enhancements in muscle strength of the knee extensor in the whole-body vibration group. Our pooled effect also showed significant strength enhancements in the resistance training group, but no significant enhancements were observed among the endurance training, whole-body vibration, and usual care groups. Resistance loading inhibits myostatin, which inhibits myoblast proliferation and differentiation in

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developing muscle. By performing a muscle biopsy before and 24-hour after a series of resistance training exercises, our study revealed that resistance training downregulates myostatin expression and alters genes that are key to cell cycle progression [93]. Through the increase in myofibrillar and mitochondrial protein synthesis rates, resistance training improves the expression of myosin-heavy chains and increases the quantity and improves the quality of muscle protein [94].

A recent Cochrane review included 121 trials with 6700 participants who received progressive resistance training and were assessed according to physical functionality. A modest improvement in gait speed and a moderate to large effect in chair-rise time were observed [95].

5.1.3 Physical performance

The present study reports significant enhancement in physical performance in whole-body vibration and resistance training. However, in a meta-analysis by Tschopp [96], which comprised 11 trials and 377 elderly people, a small advantage over strength training was observed for various functional outcomes (Short Physical Performance Battery, chair-stand test, 5-time chair rise, box stepping). The difference between this and our study is the different function tests applied.

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5.2 Preservation of muscle mass and improvement of muscle strength

In a cross-sectional study, changes in muscle mass and strength during a 3-year period were examined in 1880 elderly people. The knee extensor strength decline was much more rapid than the concomitant loss of muscle mass, suggesting a decline in muscle quality [97]. Why did muscle strength improve significantly in the resistance training group, but not muscle mass? Additionally, why was physical performance in the resistance training group and whole-body vibration group significantly improved? Resistance training strengthens muscles that are involved in the exercise, but the enhancement in strength may reflect an increase in fiber tissue or an improved synchronization of contractions, rather than an increase in lean muscle mass [98]. Mechanisms of resistance exercise training appear to enhance muscle strength without necessarily increasing muscle mass [99]. Furthermore, a Framingham Heart Study revealed that total body and lower extremity muscle mass were not associated with physical functionality in either men or women [100].

5.3 Improvement of muscle strength and physical performance

Resistance training significantly enhanced both muscle strength and physical performance. These results imply that the performance in the chair stand test was similar to that of the leg extension exercise. In Hardy's study, improved leg extensor

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power was correlated with improved chair-rise performance among 174 people aged 53 years [101]. However, improved performance in the chair-rise test was not correlated with favorable performance in the muscle strength test. The improved chair-rise performance was associated with improved standing balance performance [101]. Furthermore, whole-body vibration was effective in improving balance ability according to the Tinetti total score [102], Tinetti body balance score, and timed up-and-go test. Our study also reveals that whole-body vibration significantly improved performance in the chair-stand test, compared with the usual care group.

5.4 Improvement of muscle strength in the elderly with heart disease

In the healthy control group (aged older than 60 years), a significant reduction in leg extensors strength in cardiac patients was observed [103], despite the fact that cardiac diseases lead to calcium leak mechanisms in skeletal muscles, causing age-related loss of muscle function and muscle weakness [104, 105]. In our study, the muscle strength in elderly people with coronary heart disease was no poorer than that of the healthy elderly participants [65, 66]. This can be explained by two possible reasons: 1. Resistance training may delay this adverse mechanism. 2. In the two trials, participants with stable angina, coronary heart disease, post revascularization status, and myocardial infarction were included; participants with severe conditions (e.g.,

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uncontrolled hypertension, very low threshold angina (<3 METs workload), and hospitalization for an acute coronary syndrome within 6 months) were excluded.

5.5 Estimation the benefits of endurance training on physical performance

No scientific evidence exists to support that improvement in the chair-stand test because of endurance training is a measure of physical performance. However, we extracted data from Davidson's study for a similar comparison [106]. A total of 136 sedentary, abdominally obese elderly men and women were recruited and randomized to 1 of the following 4 groups for 6 months: resistance training, endurance training, combined exercise, and nonexercise control. This study was excluded from our network meta-analysis because all participants received dietary intervention. However, when we extracted data from the resistance training group and the endurance training group to pool with our network meta-analysis of physical performance, the results indicate that endurance training was the most effective exercise intervention. Resistance training was considered the second most effective option, and whole-body vibration was the third treatment option for the obese participants, as shown in table 7. The trend in physical performance implies that endurance training is an acceptable exercise intervention for elderly people.

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5.6 Public health issue and clinical implication

In the current systemic review and network meta-analysis, we present available evidence regarding the effectiveness of the three exercise interventions on the indicators of sarcopenia and as treatment for sarcopenia. The roles of the three indicators of sarcopenia prevention after exercise training are also presented in our study. Muscle mass (lean body mass) was considered as an indicator. By examining muscle mass, we observed that the participants who accepted exercise intervention did not lose muscle mass with age. Muscle strength and physical performance were the two appropriate indicators for preventing sarcopenia. The improvements after exercise intervention were easily measured according to muscle strength and physical performance.

Building muscle as a result of exercise intervention is crucial for successful aging. Performing appropriate exercises to prevent and treat sarcopenia can considerably benefit the prevention of the consequences attributed to falling and immobility, help avoid hospitalization, and contribute to healthy aging. Our study reveals how key indicators change after exercising, which may influence recommendations for elderly people.

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5.7 Strength and limitation

The strengths of this study are as follows: (1) This study is the first network meta-analysis to investigate the relative efficacy between a pair of exercise interventions (2) It possesses more restrictive inclusion criteria than those of other randomized controlled trials; (3) It exhibits more robust outcomes and reveals relevant indicators of sarcopenia; and (4) It has higher generalizability, including not only the healthy elderly population, but also elderly people with frailty, type 2 DM, and cardiovascular disease. The study limitations are variability in training characteristics and outcome measurements.

5.8 Direction of future research

Translating research into clinical practice is challenging. With regard to the clinical practice of resistance training, endurance training, and whole-body vibration, more research must be conducted to create a structured guideline. This guideline would provide practical information on increasing muscle mass and enhancing strength and physical performance. To effectively enhance muscle attributes, the benefits of exercises combined with other remedies (i.e., nutrition interventions, behavioral modification technique, medicine) may be investigated in future research. Because many elderly people are unwilling or simply unable to engage in exercise training,

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future research is necessary to develop structural programs for preventing sarcopenia.

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Chapter 6 Conclusion

Resistance training is beneficial for elderly people with outcome indicators of sarcopenia; specifically, it enhances muscle strength and physical performance. Resistance training and whole-body vibration were the two most effective exercise interventions in terms of physical performance. However, no statistically significant results were observed for resistance training, endurance training, and whole-body vibration concerning increases in muscle mass.

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Figure 1. Scheme of the different etiological sarcopenia mechanism and their consequences [1, 10]

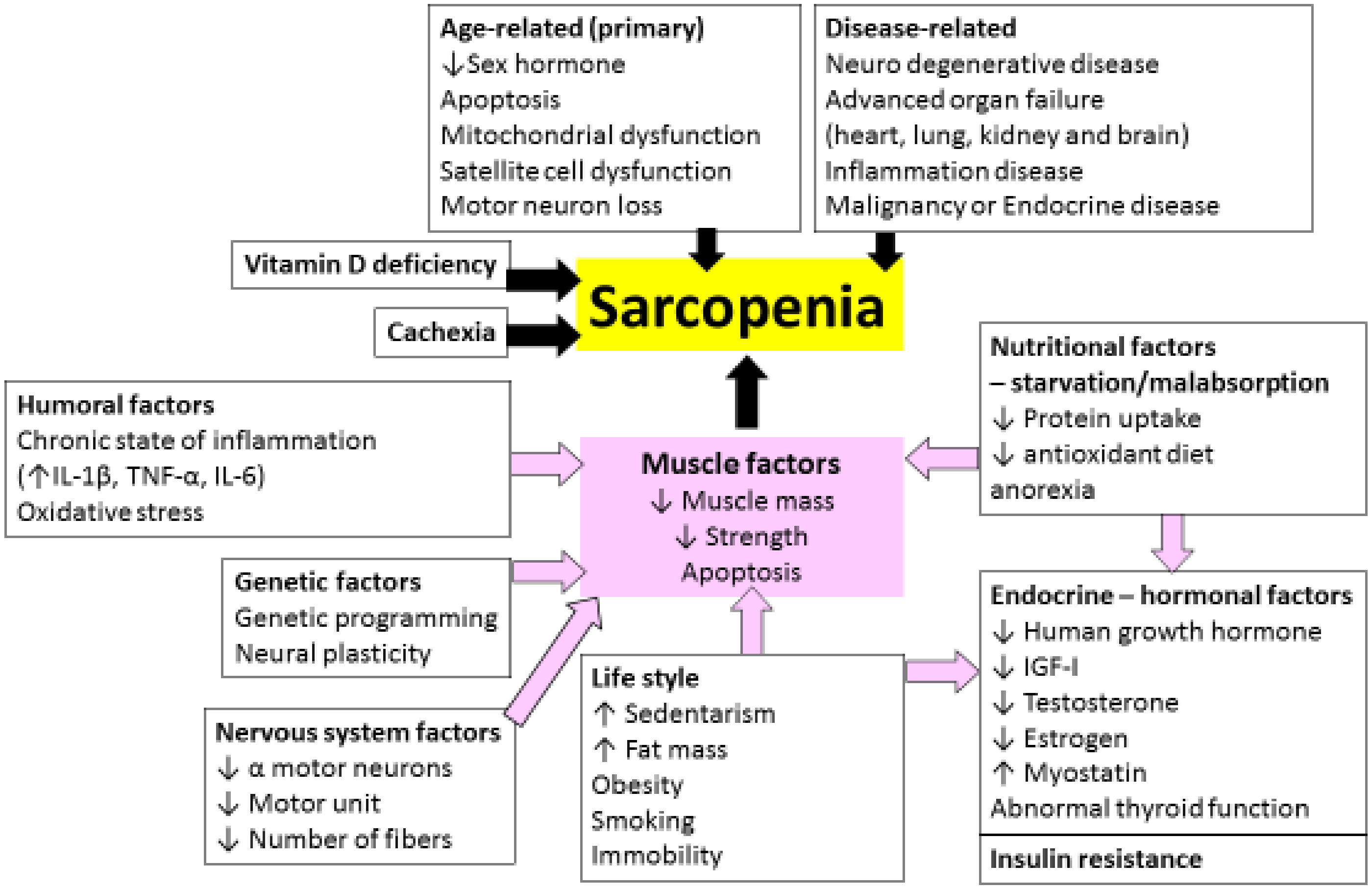

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Table 1. Summary of meta-analysis of studies on muscle mass, muscle strength and physical performance

Study	Intervention group	Length of training (range), week	Enrolled trials number	Participants number	Participants characteristics	Average age (age range)	Outcome[1]
Peterson, 2010	Resistance training	10-52	19 RCTs and 31 non-RCTs	1328	Mean age older than 50 years	50-83	Muscle mass (lean body mass): Weighted mean difference 1.1 kg (95%CI 0.9–1.2)
Silva, 2014	Resistance training	8-52	15 RCTs	528	Mean age older than 55 years	55-97	Muscle strength (leg extension) weighted mean difference 23.1 % (95% CI 15.4–30.8)
Rabert, 2012	Whole body vibration	8-72	16 RCTs	957	Older people (not set specific age range)	57-82	Muscle strength (leg extension): weighted mean difference 18.3 newton meters (95%CI 8.0–28.6)

doi:10.6342/NTU201602158

Osawa, 2013	Whole body vibration	6-72	4 RCTs	154	Older people (not set specific age range)	12-78	Muscle strength (leg extension): standard mean difference 0.76 (95%CI 0.21–1.32)
Orr, 2015	Whole body vibration	6-72	5 RCTs[2]	162	Mean age older than 60 years.	64-85	Timed up and go test: weighted mean difference -1.10 seconds (95%CI -2.97–0.78)

[1]showed outcomes of indicators of sarcopenia (muscle mass, muscle strength and physical performance) only

[2]using whole body vibration only. Three of 5 studies comes from a same study with different frequency of intervention.

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Figure 2. Flowchart of network meta-analysis

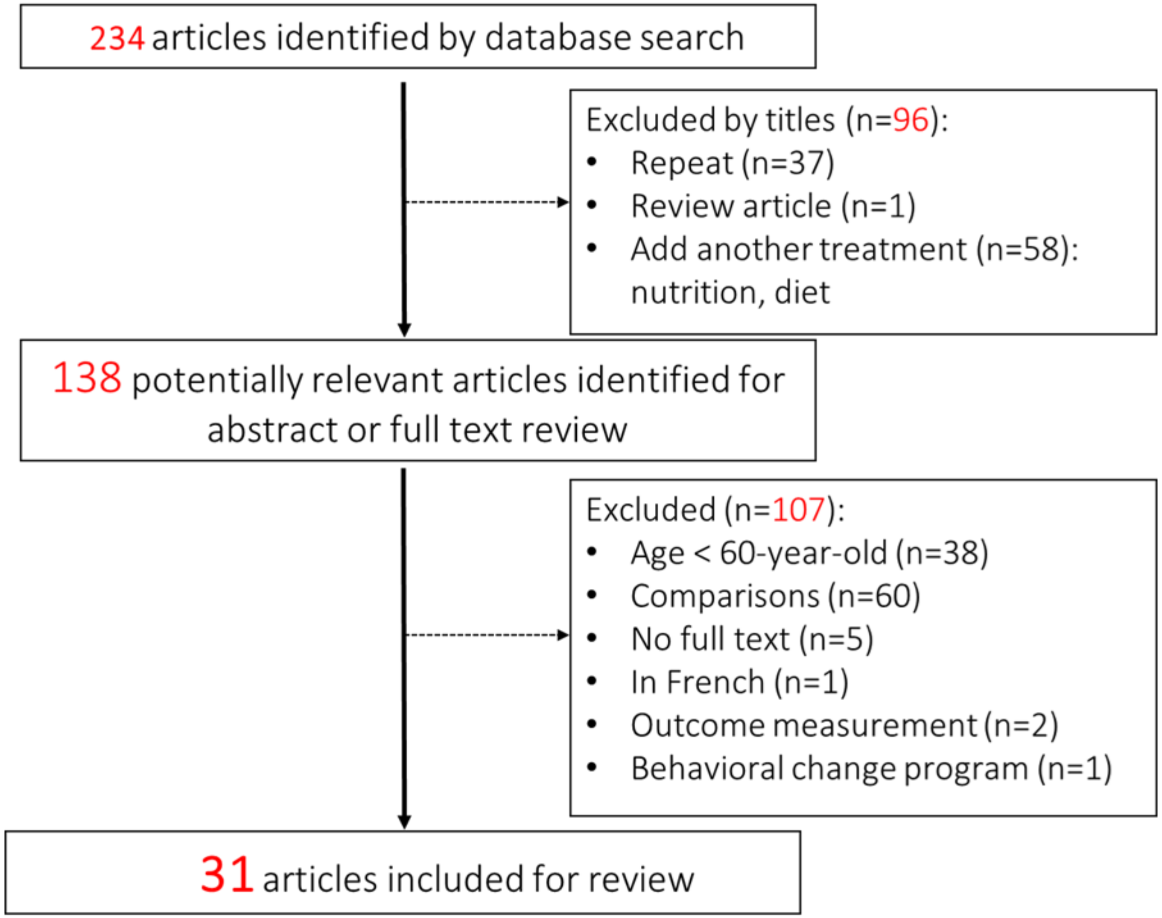

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Figure 3. Risk of bias summary: assessments for studies in a Cochrane review of resistance training, endurance training and whole body vibration

Zhang, 2014	Yasuda, 2014	Vincent, 2002	Tibaek, 2014	Taaffe, 1999	Strasser, 2009	Seynnes, 2004	Sausa, 2013	Nelson, 2004	Miszko, 2003	Kalapotharakos, 2004	Irving, 2015	Hunter, 2001	Hruda, 2003	Gomez-Cabello, 2014	Gerage, 2013	Fragala, 2014	Fatouros, 2005	Emerson, 2015	Earles, 2001	DeVos, 2005	DeBeliso,2005	Cadore, 2013	Brooks, 2007	Brochu, 2002	Binder, 2005	Bautmans, 2005	Aragao, 2014	Amaral, 2014	Álvarez-Barbosaa, 2014	Ades, 2005	Ades, 1996	
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	Random sequence generation (selection bias)
+	+	+	+	+	?	+	+	+	+	+	+	+	+	+	+	+	+	?	+	+	+	+	+	+	?	+	+	+	+	+	+	Allocation concealment (selection bias)
−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	Blinding of participants and personnel (performance bias)
+	?	?	+	?	+	+	?	?	?	?	+	+	?	+	?	?	+	?	?	+	?	+	?	?	?	?	?	?	+	+	?	Blinding of outcome assessment (detection bias)
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Incomplete outcome data (attrition bias)
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Selective reporting (reporting bias)
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Other bias

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Figure 4. Risk of bias graph: assessments for studies in a Cochrane review of resistance training, endurance training and whole body vibration

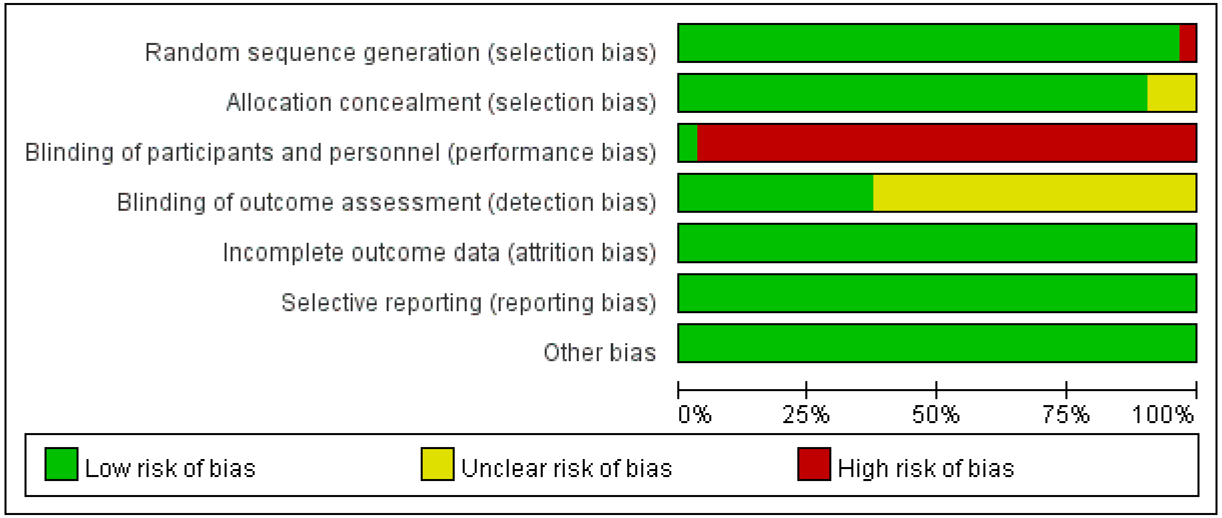

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Table 2. Description of the study participants and the interventions of resistance training

Trials, Year	Age range in year (mean±SD)	Female percent (%)	Physical Condition	Number of Subjects	intervention	Intervention time period in week	Resistance training protocol					Outcome(s) compared with control groups
							set	Repetition time	Intensity 1RM [a] (%) or RPE [b]	Frequency in days per week	Number of Exercise	
Ades, 1996[78]	≥60 (70.4±4)	51.6%	Healthy	24	RT versus UC	12	3	8	50-80[a]	3	7	**Leg extension strength** RT 23.5±1 UC 42.8±4 (p=0.001)
Taaffe, 1999[72]	≥60 (69.4±4)	37.0%	Healthy	47	RT versus UC	24	3	8	80[a]	1-3 RT 1: 1 RT 2: 2 RT 3: 3	8	**Lean body mass** UC< RT 1-3 (p< 0.001) **leg extension strength** UC< RT 1-3 (p< 0.001)
Earles, 2001[87]	>70 (77.6±5)	66.2%	Healthy	40	RT versus ET (walking intervention): 30 min, moderate intensity, 6 days/week)	12	3	10	-	3	5	**Leg extension strength** RT> RT (p< 0.001 time effect, group effect no significant)
Hunter, 2001[79]	>60 (66.4±5)	44.4%	Healthy	36	RT versus UC	25	1	15-25	RT1 50-80 RT2 80[a]	3	10	**Leg extension strength** RT1, RT2> UC (p<0.05)

doi:10.6342/NTU201602158

Brochu, 2002[65]	≥65 (70.6±5)	100%	Coronary heart disease	25	RT versus UC (stretching, breathing, yoga: 30-40 min, 3 days/week)	24	1-2	10	50-80[a]	3	8	**Lean body mass** (% change): RT +0.5 > UC -0.2 (p=0.64) **Leg extension strength** (% change): RT +46 > UC +10 (P=0.0001)
Miszko, 2003[69]	≥65 (72.5±6)	56.4%	Below-average leg extensors power	39	RT versus UC	16	3	6-8	RT1: 50-80 RT2: 40[a] (as fast as possible)	3	8	**Leg extension strength**: RT1> UC (p<0.05)
Hruda, 2003[89]	≥75 (83.7±5)	76.0%	Long term care facility	25	RT versus UC	10	1	4-8	-	3	8	**Chair-stand test** intragroup improve (p<0.05)
Rabelo, 2004[80]	>60 (64.8±5)	100%	Healthy	61	RT versus UC	10	3	8	RT1: 50 RT2: 80[a]	3	8	**Leg extension strength:** RT1>UC, RT2>UC (p<0.001)
Kalapotharakos, 2004[81]	≥60 (64.9±4)	63.6%	Healthy	33	RT versus UC	12	3	15	RT1: 60 RT2: 80[a]	3	6	**Leg extension strength**: RT1>UC, RT2>UC (p<0.001)
Nelson,	≥70	79.2%	Lower body	72	RT versus	24	2	8	7-8[b]	3	6	**Leg extension strength**:

doi:10.6342/NTU201602158

2004[70]	(77.8±5)		functional impairment		UC							RT1>UC, RT2>UC (p<0.001)
Ades, 2005[66]	>60 (72.0±5)	100%	Coronary artery disease	42	RT versus UC	24	1-2	10	50-80[a]	3	8	**Leg extension strength** (% change): RT +47 > UC +11 (P=0.0001)
Binder, 2005[67]	>78 (83.0±3)	54.0%	Frail	91	RT versus UC	12	1-3	6-12	65-100[a]	3	6	**Fat free mass** RT>UC (p<0.05)
DeBeliso, 2005[82]	>60 (72.6±5)	55.0%	Healthy	60	RT versus UC	18	RT1: 3 RT2: 2-4	1	RT1: 9RM RT2: 15-9RM	2	8	**Leg extension strength:** RT1, RT2 > UC (p<0.05)
de Vos, 2005[83]	≥60 (69.0±6)	61.0%	Healthy	112	RT versus UC	12	3	8	RT1: 20 RT2: 50 RT3: 80[a]	2	5	**Leg extension strength:** RT1, RT2, RT3 > UC (p<0.05)
Fatouros, 2005[84]	≥65 (71.2±4)	0%	Healthy	52	RT versus UC	24	2-3	6-8	RT1: 50-55 RT2: 80-85[a]	3	10	**Leg extension strength**: RT1, RT2 > UC (p<0.05)
Brooks, 2007[64]	≥55 (66±2)	35.5%	Type II DM	62	RT versus UC	16	3	8	60-80[a]	3	5	**Lean body mass**: RT>UC (p=0.04)
Cadore, 2013[62]	≥85 (91.9±4)	-	Healthy	24	RT versus UC	12	-	8-10	40-60[a]	2	2	**Leg extension strength**: RT > UC (p<0.01) **Chair stand test:** RT

doi:10.6342/NTU201602158

												versus UC no significance
Gerage, 2013[85]	≥60 (65.9±5)	100%	Healthy	29	RT versus UC	12	2	10-15	Until moderate fatigue	3	8	**Leg extension strength**: RT > UC (p<0.05) **Fat free mass**: RT versus UC no significance
Sausa, 2013[90]	>65 (67.7±5)	0%	Healthy	33	RT versus UC	32	3	8-12	65-75[a]	1	7	**Chair-stand test** intragroup improve, but intergroup no significance
Aragao, 2014[74]	>60 (70.1±5)	100%	Healthy	158	RT versus UC	48	1-4	8-15	40-80[a]	3	6	**Fat free mass** (BIA): RT>US (p<0.001)
Fragala, 2014[73]	>60 (70.1±6)	47.8%	Healthy	23	RT versus UC	6	3	8-15	70-85[a]	2	7-8	**Lean body mass**: RT versus UC (no significance) **Leg extension strength**: RT>UC (p<0.05)
Tibaek, 2014[71]	>60 (79.5±7)	58.9%	Hospitalized (length of stay >7days)	56	RT versus UC	Mean treatment session: 10(SD=7)	3	12-15	60-70[a]	4	5	**Chair-stand test** intragroup improve, but intergroup no significance
Yasuda,	>60	66.7%	Healthy	19	RT versus	12	-	10-30	20-30[a]	-	2	**Leg extension strength**:

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2014[86]	(69.4±7)				UC							RT > UC (p<0.01) **Chair-stand test**: RT > UC (p<0.05)
Emerson, 2015[59]	>60 (71.2±6)	-	Healthy	23	RT versus UC	6	3	8-15	70-85[a]	2	8	**Lean body mass**: RT versus UC (no significance) **Leg extension strength:** RT > UC (p<0.05)

SD, standard deviation; DM, diabetes mellitus; RT, resistance training; UC, usual care; ET, endurance training; 1RM, one repetition maximum; RPE, rated perceived exertion.

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Table 3. Description of the study participants and the interventions of resistance training and endurance training

Trials, Year	Age range in year (mean±SD)	Female percent (%)	Physical Condition	Number of Subjects	Intervention time period in week	Training protocol	Outcome(s) compared with control groups
Irving, 2015[77]	≥65 (70.3±2)	54.2%	Sedentary (exercising < 2 days/wk)	31	8	Endurance training (ET) group: cycling at 65% VO2max for 1 hour, 5 days/week Resistance training (RT) group: 4 sets x 8-10 repetitions (multiple muscle groups), 4 days/week Usual care (UC): no exercise training for 8 weeks → Combined treatment (CT): combined ET and RT for 8wks after UC period	**Lean body mass**: ET pre vs post: increase **leg extension strength:** ET, RT, CT pre vs post: increase
Strasser, 2009[88]	>70 (74.6±5)	76.2%	Healthy	42	24	Endurance training (ET) group: cycle ergometer, at 60% VO_{2max} for 15-30 minutes, 3 days/week Resistance training (RT) group: 3 sets x 10-15 repetitions, 3 days/week, 60-70 1RM Usual care: no change lifestyle	**leg extension strength:** RT pre vs post: increase

SD, standard deviation; DM, diabetes mellitus; RT, resistance training; UC, usual care; ET, endurance training; 1RM, one repetition maximum; RPE, rated perceived exertion.

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Table 4. Description of the study participants and the interventions of whole body vibration training (WBV)

Trials, Year	Age range in year (mean±SD)	Female percent (%)	Physical Condition	Number of Subjects	intervention	Intervention time period in week	Training protocol	Outcome(s) compared with control groups
Álvarez-Barbosaa, 2014[91]	≥80 (85.0±4)	83.0%	Healthy (in nursing home)	29	WBV versus UC	8	WBV gorup: 30-35 Hz, peak to peak displacement of 4mm, 6 exercises(step up and down, lunge, squat, calf rises, left and right pivot in a front and letaral positions) x 6-12 repetitions x 3 times/week	**Chair stand test** (median, IQR): WBV > UC, p<0.001
Amaral, 2014[75]	>60 (70.5±4)	100%	Healthy	18	WBV versus UC	12	WBV group: 30-35 Hz, amplitude 2-4mm, 3 sets of isometric squat x 30-45 seconds x 3 times/week	**Lean body mass** (BIA): WBV versus UC (p=0.32)
Gomez-Cabello, 2014[76]	≥65 (75.0±5)	59.2%	Healthy`	49	WBV versus UC	11	WBV group: 40 Hz, amplitude 2 mm, 10 repetitions x 45 seconds x 3 times/week	**Lean body mass:** WBV versus UC (no significance)
Zhang, 2014[68]	≥75 (85.3±4)	5.4%	Frail	37	WBV versus UC	8	WBV group: 6-26 Hz, amplitude 1-3 mm, 4-5 bouts (60sec/bout) x 3-5 times/week (Galileo machine)	**Leg extension strength**: sig **Chair-stand test**: sig
Bautmans, 2005[60]	>60 (77.5±11.0)	40.0%	Healthy	15	WBV versus UC	6	WBV group: 6 lower extremity exercises, 1.5-3 min, 3 times/wk Usual care (UC): identical with WBC group but with switched-off plates	**Chair-stand test** WBV > UC (p=0.2)

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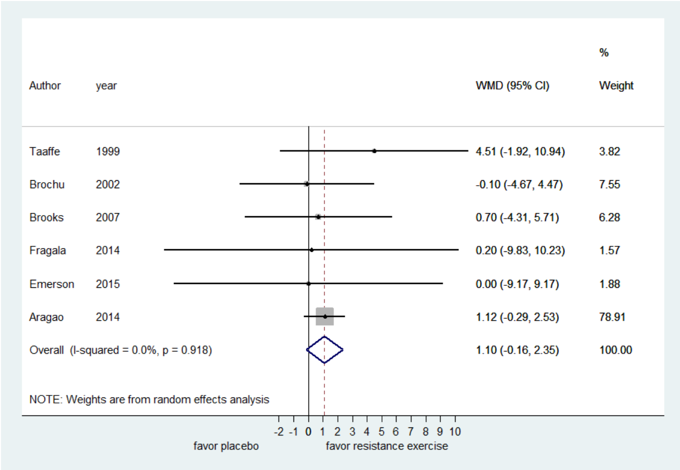
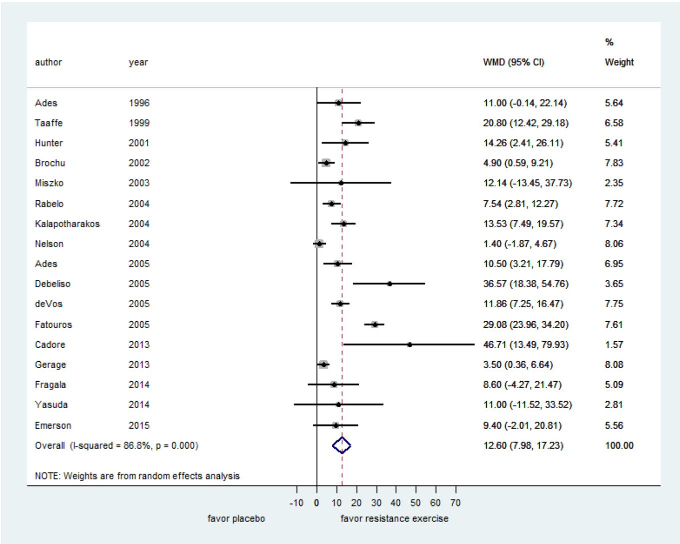
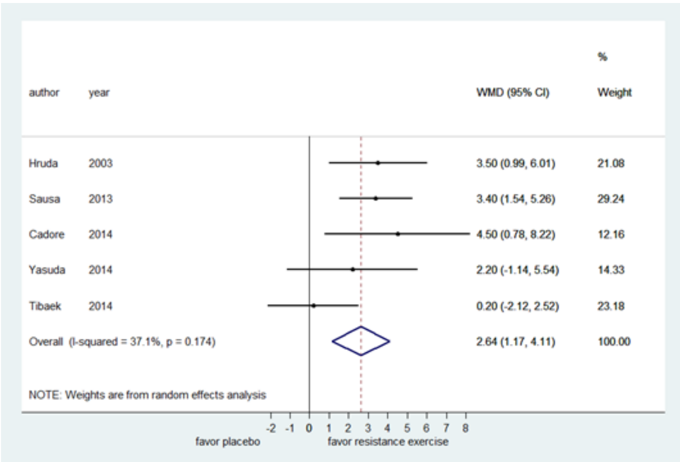
Figure 5 Traditional meta-analysis of the effects of the effects of resistance training (RT) and usual care (CON) on muscle mass (A), muscle strength (B) and physical performance (C)



(A)



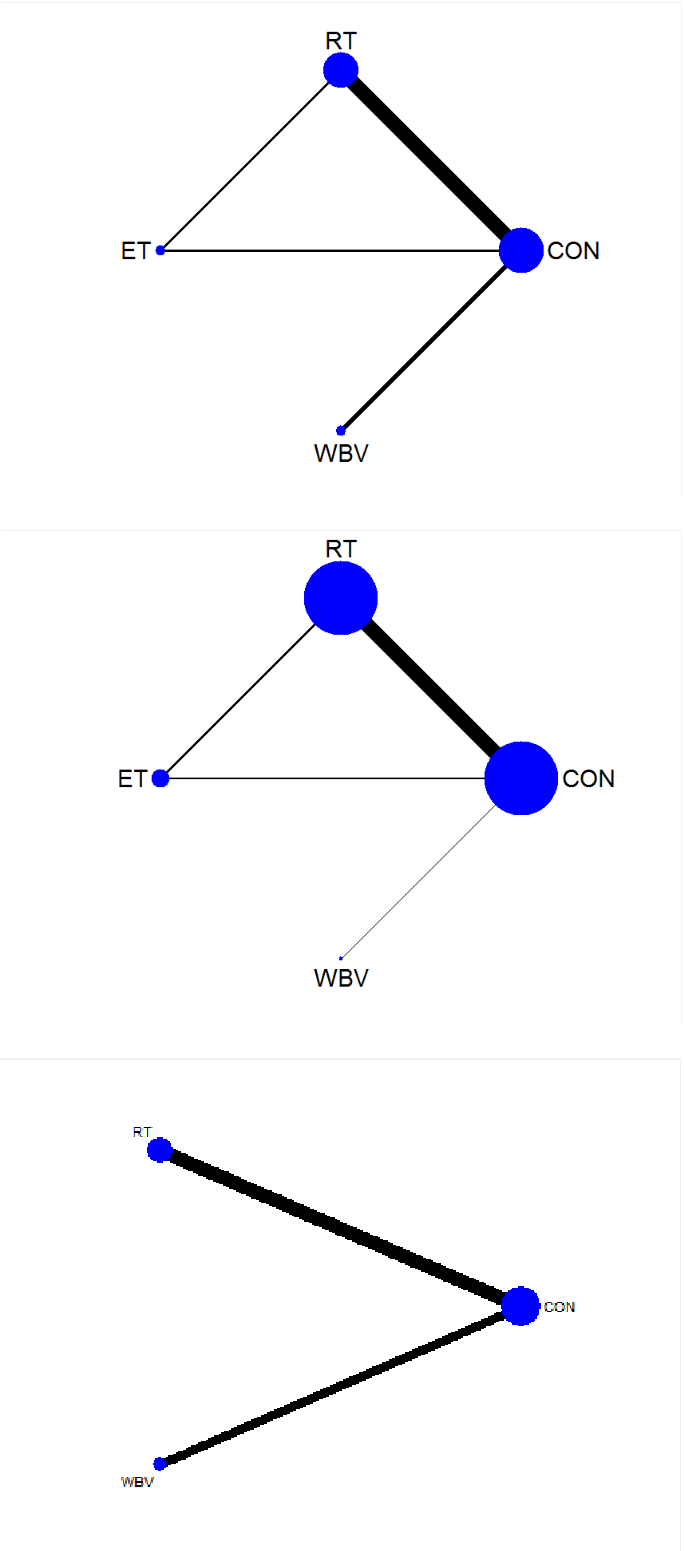
(B)



(C)

doi:10.6342/NTU201602158

Figure 6. Summary of network geometry of muscle mass (A), muscle strength (B) and physical performance (C)



(A)

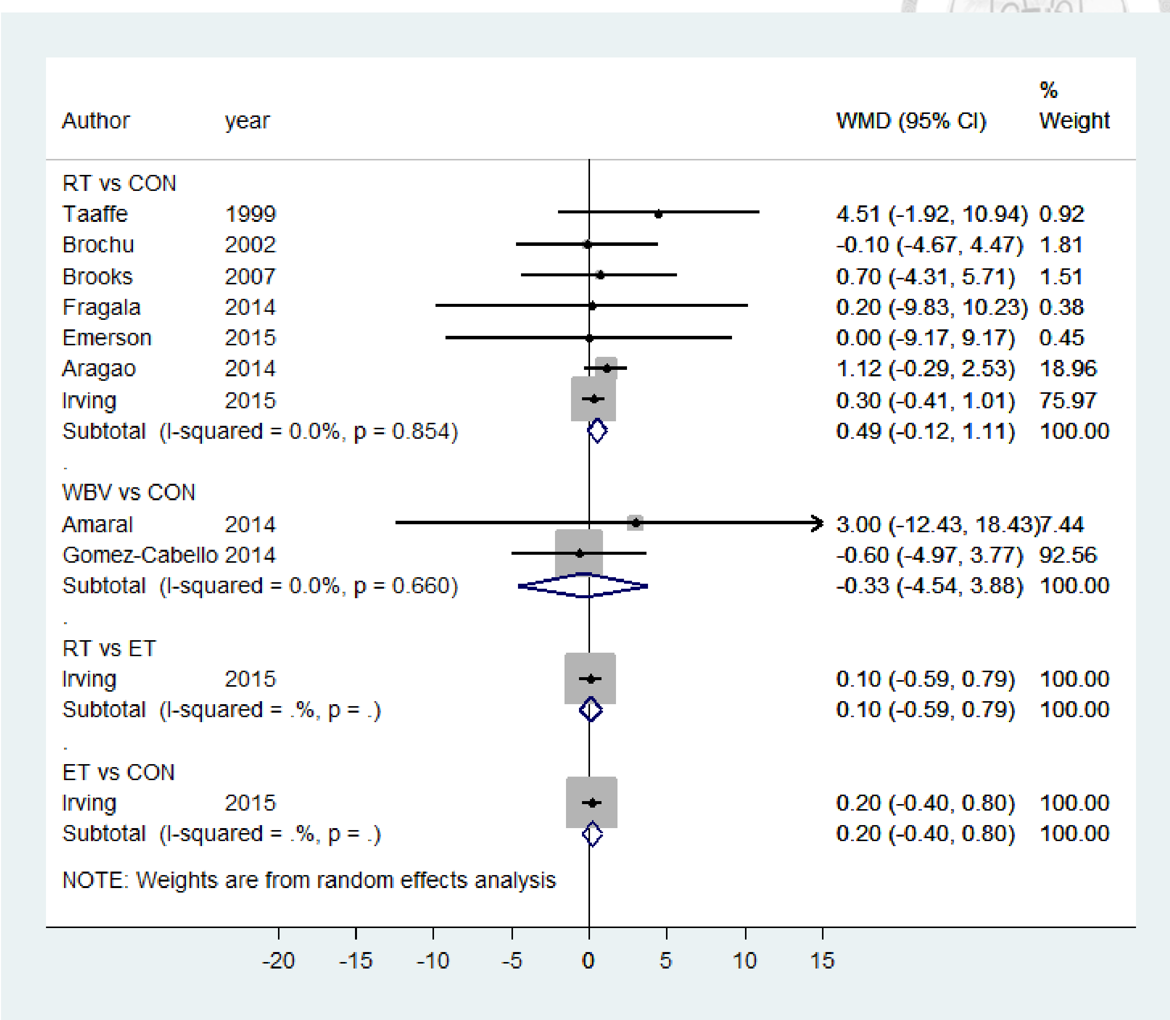
(B)

(C)

(RT: resistance training, ET: endurance training, WBV: whole body vibration, CON: usual care)

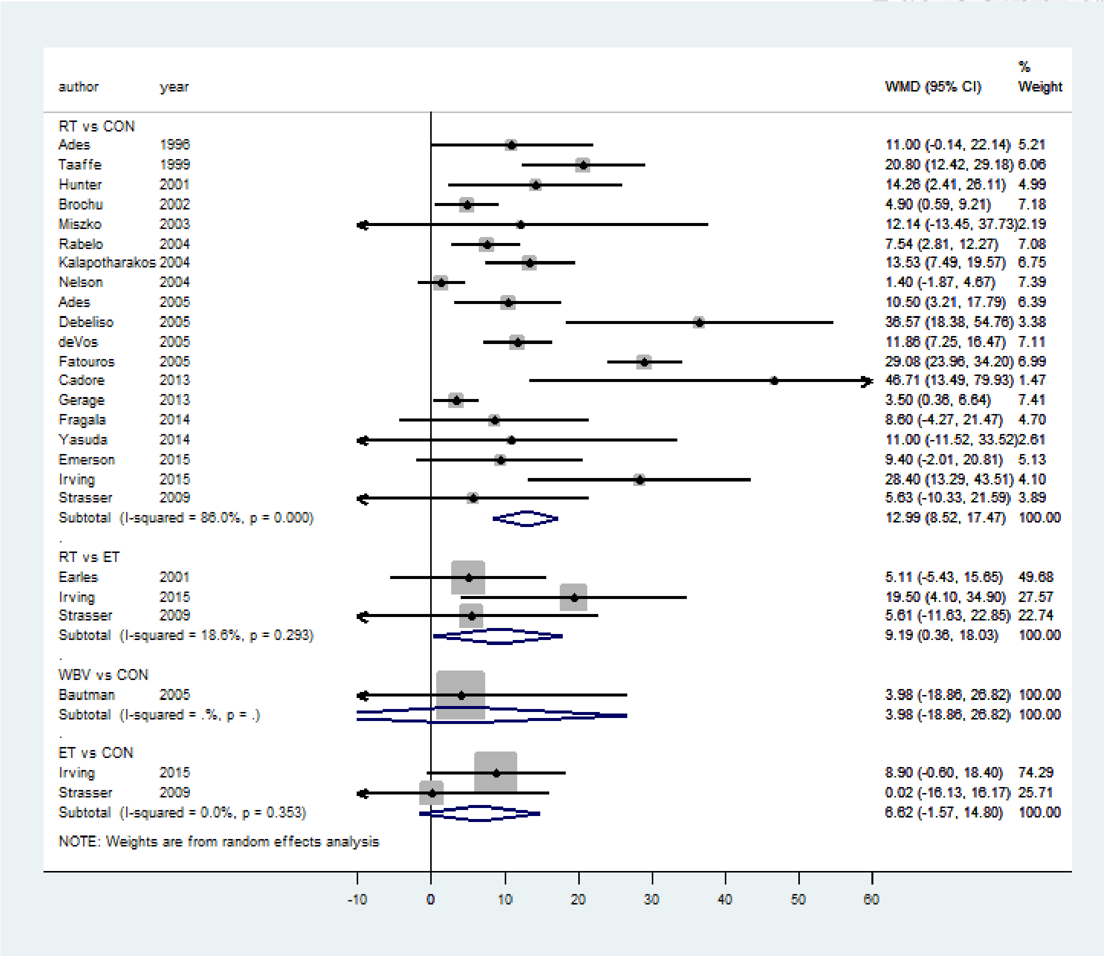
doi:10.6342/NTU201602158

Figure 7. Network meta-analysis of the effects of usual care (CON), resistance training (RT), endurance training (ET) and whole body vibration (WBV) on lean body mass



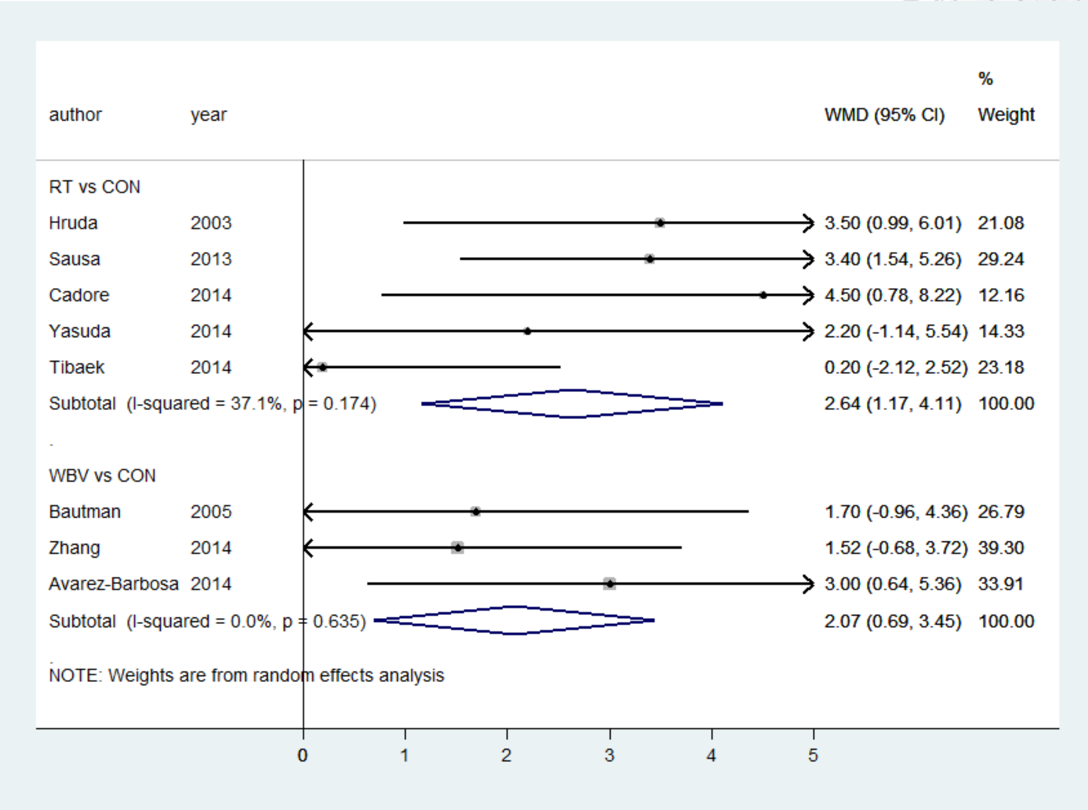
doi:10.6342/NTU201602158

Figure 8. Network meta-analysis of the effects of usual care (CON), resistance training (RT), endurance training (ET) and whole body vibration (WBV) on leg extension strength



doi:10.6342/NTU201602158

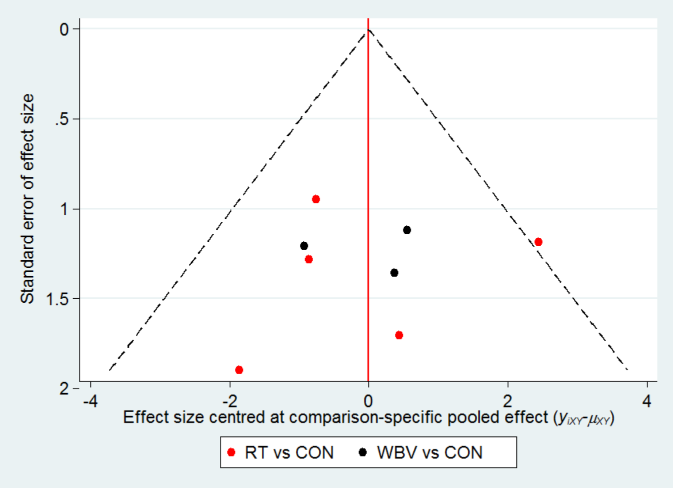
Figure 9. Network meta-analysis of the effects of usual care (CON), resistance training (RT), endurance training (ET) and whole body vibration (WBV) on chair stand test



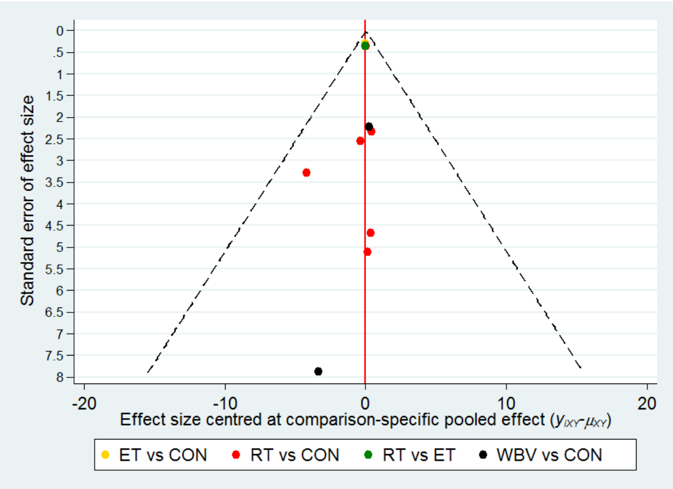
doi:10.6342/NTU201602158

Figure 10. Begg's funnel plots of the effects of usual care (CON), resistance training (RT), endurance training (ET) and whole body vibration (WBV) on lean body mass, leg extension strength, and chair-stand test among older adults

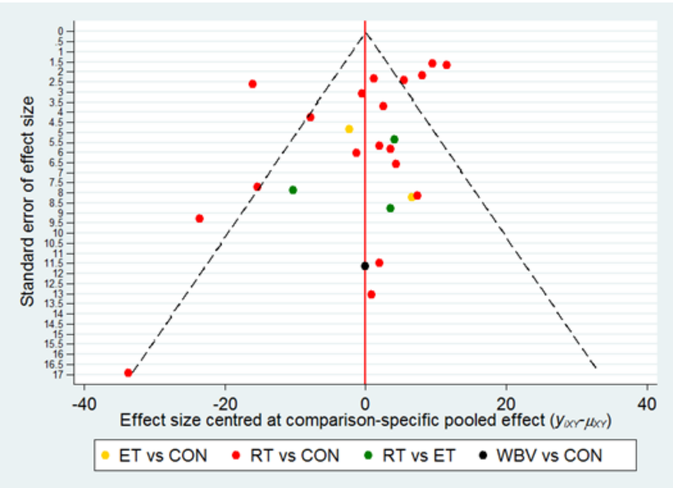
(A) Lean body mass, (B) leg extension strength, (C) chair-stand test



(A)



(B)



(C)

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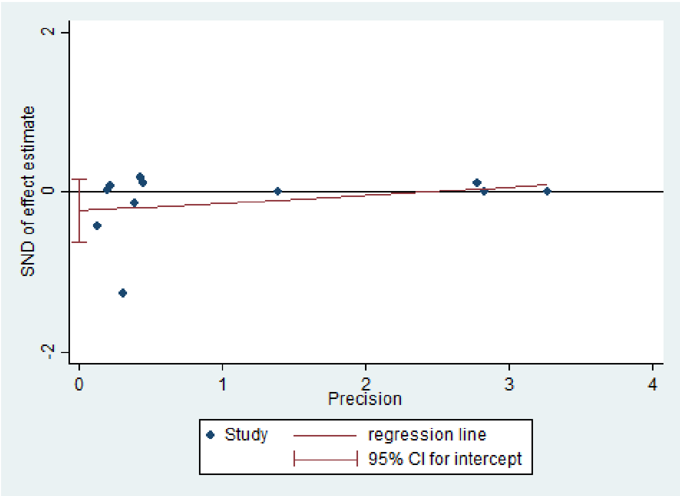
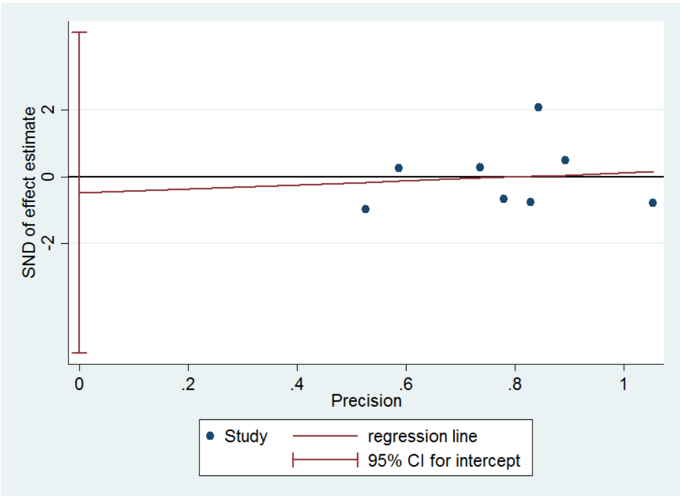
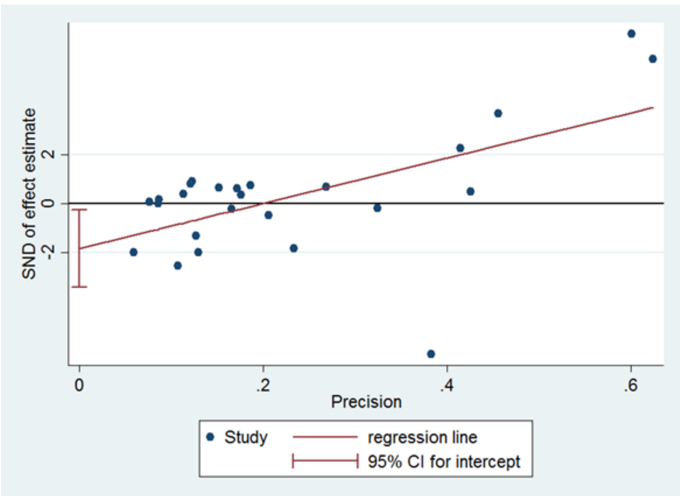
Figure 11. Egger's regression of the effects of usual care (CON), resistance training (RT), endurance training (ET) and whole body vibration (WBV) on lean body mass (A), leg extension strength (B), and chair-stand test (C) among older adults



(A)



(B)



(C)

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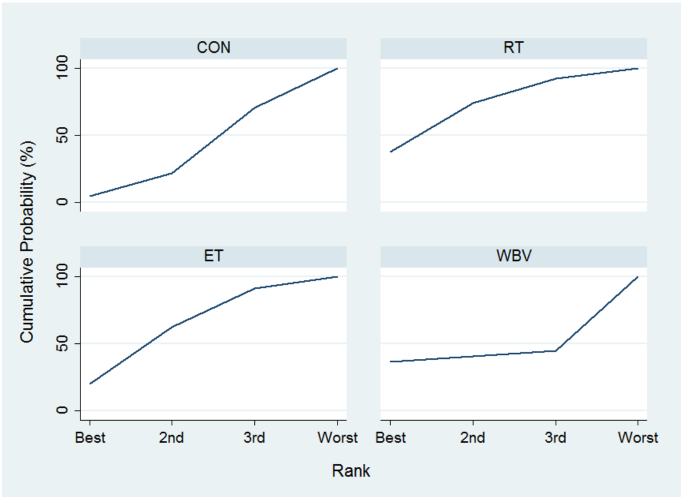
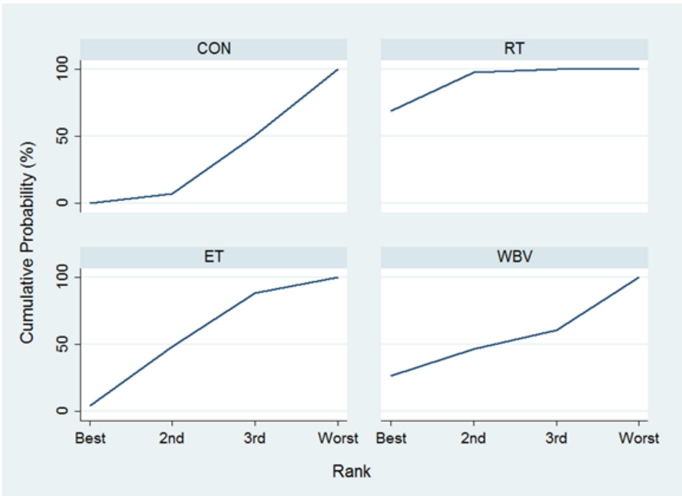
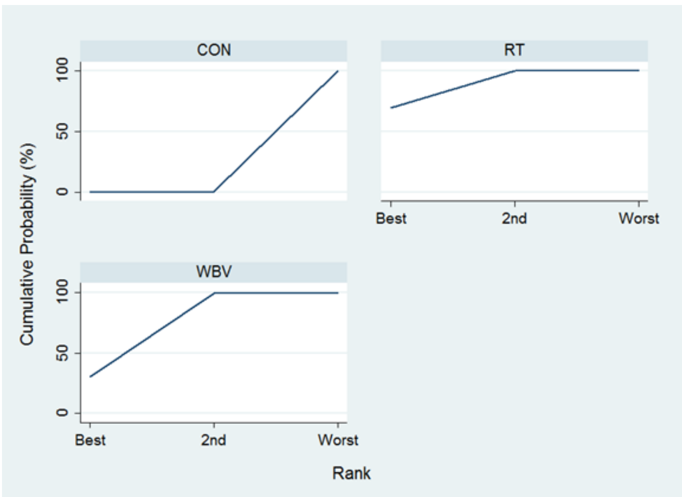
Figure 12. Rankogram of the effects of usual care (CON), resistance training (RT), endurance training (ET) and whole body vibration (WBV) on lean body mass (A), leg extension strength (B), and chair-stand test (C) among older adults



(A)



(B)



(C)

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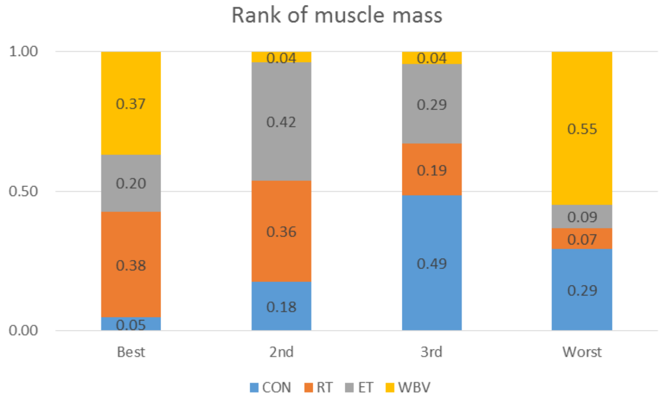
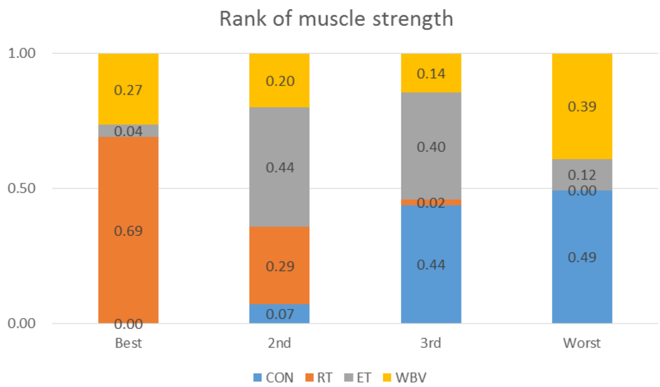
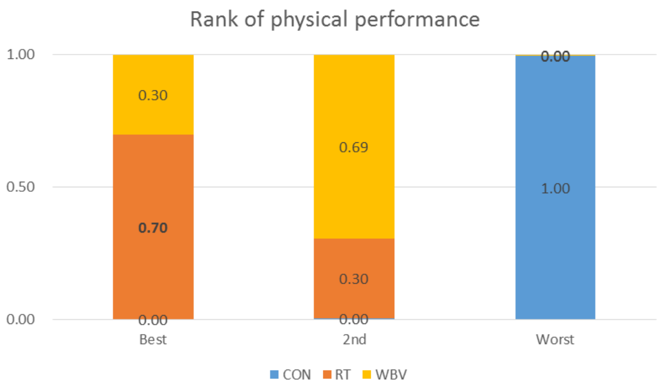
Figure 13. Histogram with percentage bins of the relative ranking probabilities for usual care (CON), resistance training (RT), endurance training (ET) and whole body vibration (WBV) on muscle mass(A), muscle strength (B), and physical performance (C) among older adults



(A)



(B)



(C)

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Table 5. Network meta-analysis of pairwise comparisons: mean change from baseline in lean body mass, leg extension strength and chair-stand test

Mean change from baseline in lean body mass (95% CI), kg			
Resistance training			
0.22 (-0.44, 0.88)	Endurance training		
0.82 (-3.43, 5.08)	0.60 (-3.64, 4.85)	Whole body vibration	
0.49 (-0.12, 1.11)	0.27 (-0.31, 0.86)	-0.33 (-4.54, 3.88)	Usual care
Mean change from baseline in leg extension strength (95% CI), kg			
Resistance training			
7.93 (-2.47, 18.33)	Endurance training		
8.77 (-18.74, 36.28)	0.84 (-28.30, 29.99)	Whole body vibration	
12.75 (8.54, 16.97)	4.82 (-5.68, 15.33)	3.98 (-23.21, 31.17)	Usual care
Mean change from baseline in chair-stand test (95% CI), frequency			
Resistance training			
0.56 (-1.48, 2.60)	Whole body vibration		
2.63 (1.34, 3.93)	2.07 (0.49, 3.65)	Usual care	

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Table 6. Subgroup analysis: network meta-analysis of pairwise comparisons of leg extension strength for knee extension machines and leg press machine

Mean change from baseline in leg extension strength for knee extension machines (95% CI), kg		
Resistance training		
6.07 (-19.64, 31.77)	Whole body vibration	
10.05 (5.68, 14.41)	3.98 (-21.35, 29.31)	Usual care
Mean change from baseline for leg press machine (95% CI), kg		
Resistance training		
9.88 (-2.65, 22.42)	Endurance training	
18.45 (9.63, 27.28)	8.57 (-5.20, 22.34)	Usual care

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Table 7. Network meta-analysis of pairwise comparisons: mean change from baseline in chair-stand test with Davidson's study [106]

Mean change from baseline in physical performance (95% CI), frequency			
Resistance training			
-0.17 (-2.00, 1.66)	Endurance training		
0.93 (-1.03, 2.89)	1.10 (-1.33, 3.53)	Whole body vibration	
3.00 (1.88, 4.13)	3.17 (1.34, 5.00)	2.07 (0.47, 3.67)	Usual care

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