Wirkung von Bewegungstraining auf den Knochenmineralgehalt bei postmenopausalen Frauen: Eine systematische Übersicht und Meta-Analyse von Interventionsstudien

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EINFÜHRUNG

Osteoporose

Osteoporose ist eine fortschreitende systemische Skeletterkrankung, die durch eine geringe Knochenmasse und eine mikroarchitektonische Verschlechterung des Knochengewebes gekennzeichnet ist, mit einer daraus folgenden Zunahme der Knochenfragilität und Frakturrisiko (Kanis et al., 1994; Consensus Development Conference, 1993). Die von der Weltgesundheitsorganisation (WHO) vorgeschlagene operationelle Definition der Osteoporose ist ein geringer Knochenmineralgehalt (bzw. eine geringe Knochenmineraldichte; bone mineral density, BMD), gemessen mit der Dual-Energie-Röntgenabsorptiometrie (DEXA). Liegt der erfasste Wert 1 - <2,5 Standardabweichungen (SD) unter dem statistischen Mittelwert für junge gesunde Frauen (T-Score), so liegt eine Osteopenie vor, überschreitet der T-Score -2,5 SD so liegt eine Osteoporose vor (Kanis et al., 2008).

Die Krankheit Osteoporose stellt ein wichtiges globales Problem mit starker Belastung der öffentlichen Gesundheitssysteme (Compston et al., 2019) dar. Die Prävalenz und ihre Folgen (d.h. Fragilitätsfrakturen) erhöhen sich weltweit parallel zur globalen Bevölkerungsalterung. Weltweit wurde bei etwa 200 Millionen Frauen Osteoporose diagnostiziert (Kamienski et al., 2011). In den entwickelten Ländern liegt die Osteoporose-Prävalenz je nach Diagnosemethode zwischen 2 bis 8% bei Männern und 9 bis 38% bei Frauen (Wade et al., 2014). Es wurde berichtet, dass in den USA bei etwa 2 Millionen Männern und 8 Millionen Frauen über 50 Jahren Osteoporose diagnostiziert wurde, und es wird geschätzt, dass 34 Millionen Menschen an Osteopenie leiden (OSG , 2004). In den 27 Ländern der EU wird bei etwa 21% der Frauen im Alter von 50-84 Jahren und somit mehr als 22 Millionen Frauen eine Osteoporose diagnostiziert (Hernlund et al., 2013). Bis zum Jahr 2025 werden allein in der Europäischen Union schätzungsweise mehr als 30 Millionen Männer und Frauen im Alter von 65 Jahren und darüber betroffen sein (Cramer et al., 2013).

Osteoporose führt zu einem signifikant erhöhten Risiko von Knochenbrüchen (Schmitt et al., 2009). Nach einer initialen Fraktur verdoppelt sich das Risiko für eine weitere Fraktur in den nächsten 6 bis 12 Monaten – insbesondere bei vertebralen Frakturen (Sobolev et al., 2015; Bliuc et al., 2015). Diese Frakturen – nicht die Osteoporose per se sind verantwortlich für erhöhte Mortalität, Morbidität, Verringerung der Lebensqualität und chronische Schmerzen (Papaioannou et al., 2010) durch die Osteoporose-Erkrankung. Chronische (Rücken-)Schmerzen, die durch Osteoporose verursacht werden können, nehmen negativen Einfluss auf die Aktivitäten des täglichen Lebens (ADLs) und schränken die Selbstständigkeit des Individuums ein (Cauley, 2013). Durch den Verlust der Selbstständigkeit und erhöhter Frakturinzidenz korreliert die Osteoporose-Erkrankung mit einem Anstieg stationärer Behandlungen sowie häuslicher Pflege und trägt erheblich zu den Gesundheits- und Sozialpflegekosten bei (Papaioannou et al., 2010; Budhia et al., 2012; Yang et al., 2015).

Die hohen Kosten der Osteoporose stellen das öffentliche Gesundheitswesen vor enorme Herausforderungen (Kanis et al., 2013). Im Jahr 2011 wurden mehr als 1,7 Millionen Menschen wegen eines osteoporose-induzierten Knochenbruchs ins Krankenhaus eingeliefert. Die direkten Kosten im Zusammenhang mit einer Osteoporose-Behandlung überstiegen in den USA 70 Milliarden Dollar (BMUS, 2015). In Europa entfielen auf osteoporotische Frakturen mehr verlorene Lebensjahre (disability-adjusted life years, DALYs) als auf rheumatoide Arthritis (Johnell und Kanis, 2006). Die Kosten der Osteoporose, einschließlich der pharmakologischen Interventionen in der EU im Jahr 2010, wurden auf 37 Milliarden Euro geschätzt. Die Kosten für die direkte Behandlung von Osteoporose-induzierten Frakturen machten 66% dieser Kosten aus, pharmakologische Prävention 5% und langfristige Frakturversorgung 29% (Hernlund et al., 2013). In Deutschland wurden die Kosten der Osteoporose im Jahr 2010 auf ca. 9,0 Milliarden Euro geschätzt. Die Kosten für das erste Jahr, die Kosten für das Folgejahr und die Kosten für die pharmakologische Frakturprävention beliefen sich je auf € 6,6 Mrd, € 2,1 Mrd und € 336 Mill. Es wird geschätzt, dass die Kosten die in Zusammenhanmg mit der Osteoporose-Erkrankung stehen bis 2025 auf € 11 Milliarden ansteigen werden (Svedbom et al., 2013).

Postmenopausale Osteoporose und Osteoporose-Erkrankung

Die Menopause wird von der WHO als die dauerhafte Unterbrechung der Menstruation (Monatsblutung) durch den Verlust der Follikelaktivität der Eierstöcke definiert. Sie liegt nach mindestens 12 aufeinanderfolgenden Monaten ohne Regelblutung vor, sofern keine anderen pathologischen oder physiologischen Ursachen für die Amenorrhoe vorliegen (WHO, 1996). Die Menopasuae tritt im Durchschnitt im Alter von etwa 51 Jahren auf, wobei die Altersspanne weltweit zwischen 40 und 60 Jahren liegt (WHO, 1996; Treloar et al., 1967).

Durch die abrupte und signifikante menopausale Reduktion des Östradiols als wichtigstem Östrogen, kommt es insbesondere in der Peri- und frühen Postmenopause zu erheblichen Veränderungen ostrogenabhängiger Gewebe und so auch des Knochens (Overlie et al., 1999).

Im Laufe des Lebens wird der Knochen umgebaut. Je nach Knochenan- oder umbauprozess wird Knochenmasse durch die Osteoklasten resorbiert und durch neuen, von Osteoblasten gebildeten Knochen ersetzt (Florencio-Silva et al., 2015). Die Gesamtmasse des Knochens nimmt ab, wenn - wie in der Menopause – überwiegend mehr Knochen resorbiert als produziert wird. Diese negative Knochenbilanz führt zu den pathophysiologischen Veränderungen die für die Entstehung der Osteoporose (Raisz, 2005; Lerner, 2006) verantwortlich sind.

Von der sogenannten „postmenopausalen Osteoporose“ sind ca. 50% der Frauen in der Menopause betroffen sind, sie gilt zusammen mit der senilen Osteoporose als die mit am häufigsten vorkommende Erkrankung des älteren Menschen (Satpathy et al., 2015). In den ersten fünf Jahren nach der Menopause verlieren Frauen bis zu 10 Prozent ihrer Knochenmasse (AMS, 2020). Bis zum Alter von 70 Jahren ist die Knochenmasse um 30-40% im Vergleich zur „Peak Bone Mass“ des 25.-30. Lebensjahres zurückgegangen (Greendale et al., 2012).

Bewegungstraining

Bewegungstraining oder körperliches Training ist definiert als geplante, organisierte und sich wiederholende körperliche Aktivität, die zur Verbesserung oder Erhaltung der körperlichen Fitness, der körperlichen Leistungsfähigkeit oder bestimmter gesundheitlicher Ergebnisse eingesetzt wird (Horlick et al., 2004). Neben dem Einsatz von pharmazeutischen Wirkstoffen, die auf den BMD abzielen, stellt das Bewegungstraining eine etablierte Säule der Osteoporosetherapie dar. Es gilt als eine preisgünstige, eigenverantwortlich durchführbare und sichere Behandlungsstrategie zur positiven Beeinflussung der Knochenfestigkeit, Sturzreduktion und somit zur umfassenden Frakturprophylaxe (Kemmler et al., 2015; Beck et al., 2017; Daly et al., 2019). Daneben trägt ein Bewegungstraining neben vielfältigen anderen positiven Effekten auf Gesundheitsgrössen (Börjesson et al., 2010) zur Prävention von Morbidität (Kemmler et al., 2016) und zur Verbesserung der Lebensqualität von Frauen mit postmenopausaler Osteoporose (Caputo und Kostka, 2014; Kostka et al, 2017) bei.

Bewegungstraining stimuliert die mechanische Belastung des Knochens, und steigert die Osteoblastenaktivität (Oh et al., 2014; Fleg, 2012; Palombaro et al., 2013; Troy et al., 2018). Allerdings muss das Bewegungstraining physiologische Grundsätze des Knochenumbaus berücksichtigen um Effekte zu generieren. Nicht alle Formen Bewegungstrainings sind gleichermassen wirksam, um eine positive Reaktion des Skeletts hervorzurufen. Neben der Wahl des Belastungsinhalts, ist die Komposition der Belastungsparameter erfolgreicher Bewegungsprotokolle nicht trivial. Problematisch ist zudem, dass die Intervention vom Autor vielfach nicht nachvollziehbar beschrieben wird. Dies erschwerte in der vorliegenden Arbeit vielfach die exakte Klassifikation der Bewegungsprotokolle und eine Analyse mit ausreichender Trennschärfe.

Gewichtstragende/nicht- Gewichtstragende axiale Belastung

Gewichttragendes (überwiegend) aerobes Training (WB-AE)**:** Die axiale Kompression erzeugt die höchste mechanische Belastung der Knochensegmente (Papaioannou et al., 2010; Korpelainen et al., 2006). Sie wird meist über gewichtstragende Belastungsformen wie Gehen, Laufen oder Springen generiert (Huang et al., 2003; Brown und Josse, 2002; Mishra et al., 2011).

Die Evidenz aus randomisierten kontrollierten Studien (RCTs) für die Wirksamkeit dieses Trainingsinhaltes für die Knochendichte von PMW variiert zwischen den Untersuchungen allerdings deutlich (Marques et al., 2012; Martyn-St James und Carroll, 2009). Viele Studien haben einen mäßigen bis hohen positiven Einfluss von WB-AE auf Veränderungen der BMD beobachtet (Gómez-Cabello et al.,2012; Moreira et al., 2014), andere haben berichtet, dass bspw. zügiges Gehen bei Intensitäten von 75% VO_2max (Borer et al., 2007), Gehen mit einer Gewichtweste (Nelson et al., 1991) oder Gehen in Kombination mit anderen Bewegungsformen (Joggen, Treppensteigen, Steppen) (Heinonen et al., 1998; Chien et al., 2000) in Bezug auf die Erhöhung und/oder Erhaltung der BMD effektiv sein könnten. Im Gegensatz dazu wurde in einer 12-monatigen Studie, in der PMW an 6 Tagen pro Woche 50 vertikale Sprünge mit Bodenreaktionskräfte des 4-fachen Körpergewicht ausführten, kein signifikanter Effekt auf die BMD der proximalen Femur- (PF) oder Lendenwirbelsäule (LS) beobachtet (Bassey et al., 1998).

In ähnlicher Weise zeigte eine Meta-Analyse, welche den Effekt von zügligem Gehen („Walking“) auf die Knochendichte evaluierte, keine signifikante, Auswirkungen auf die BMD an LWS oder Oberschenkelhals (FN) (Nikander et al., 2010). Es zeigte sich jedoch, dass Parameter wie die Gehgeschwindigkeit, -dauer und Häufigkeit modifizierenden Charakter auf die Effekte ausübten (Benedetti, 2018).

Auch wenn WB-AE als Trainingsinhalt regelmäßig in Empfehlungen zur Vorbeugung von Osteoporose durch körperliches Training genannt wird (Cosman et al., 2014; NOF, 2020; NIAMS, 2020), sind die Belastungsparameter, die letztlich für die optimierte Effektivität des WB-AE Training entscheidend sind, derzeit nicht immer hinlänglich bekannt (Kanis et al., 2019).

- Nicht-gewichttragendes (überwiegend) aerobes Training (non-WB-AE)**:** Non-WB-AE wie Radfahren und Schwimmen haben erwiesenermaßen wenig oder keinen Einfluss auf die Verhinderung des altersbedingten Knochenabbaus bei PMW (Greenway et al., 2012; Guadalupe-Grau et al., 2009). So zeigen bspw. weibliche Radrennfahrerinnen während einer 12-monatigen Interventionsdauer Veränderungen der BMD an der Hüft- und Lendenwirbelsäule von -1,4% und -1,1% (Sherk et al., 2014). Eine Meta-Analyse von 11 randomisierten, nicht-randomisierten und prospektiven Beobachtungsstudien an Männern und Frauen im Alter von 45 Jahren oder älter berichtete, dass wasserbasiertes Bewegungstraining den altersbedingten Knochendichteverlust an der Hüft- und LS zwar verringerte, aber Übungen an Land wirksamer zur Verbesserung der BMD waren (Simas et al., 2017). Darüber hinaus wurden in einem sechsmonatigen RCT, in der PMW ein hochintensives Wassergymnastikprogramm durchführten, keine BMD-Veränderungen innerhalb der Trainingsgruppe bzw. Unterschiede zur Kontrollgruppe an LS oder FN beobachtet (Moreira et al., 2014).

Tai Chi (TC)

TC ist ein traditionelles chinesisches Training mit einer Reihe verschiedener Bewegungen die Stabilisierungs-, Kraft- und Gleichgewichtsaspekte beeinhalten. Es betont die Kombination von körperlichem Training mit mentalem Training, Tonusreduktion und Entspannungstechniken sowie Atemtechniken auf harmonische Weise (Lou et al., 2017). Innerhalb der Frakturprohylaxe wird TC insbesondere im Spannungsfeld der Sturzprophylaxe sowie damit verbundener Risikofaktoren eingesetz (Leung et al., 2011; Logghe et al., 2010). Die Effekte von TC im Bereich der Verbesserung der Knochenfestigkeit wurden bislang weniger addressiert, einige RCTs liegen indess vor.

So wurde zum Beispiel in einer 12-monatigen Studie die Wirkung von TC auf BMD untersucht. Das Ergebnis zeigte an allen gemessenen Skelettstellen einen generellen Knochenverlust sowohl bei den TC- als auch bei den Kontrollprobanden, jedoch mit einer langsameren Rate in der TC-Gruppe (Chan et al., 2004). Zu ähnlichem Ergebnis kam eine Meta-Analyse, die sechs Artikel mit 182 Teilnehmern in der TC-Interventionsgruppe und 168 Teilnehmern in der Kontrollgruppe einschloss. Die Gesamtanalyse mit Fixed-Effect-Modell zeigte in diesem Fall keinen signifikanten Unterschied der Veränderung von BMD an der LS und am FN zwischen der Interventions- und der Kontrollgruppe (Liu und Wang, 2017).

Einige neuere Studien (Chow et al., 2017; Sun et al., 2016; Zou et al., 2017; Lee et al., 2008; Blake und Hawley, 2012) belegen einen positiven Effekt der auf einer Reduktion des alters- bzw. menopasualen BMD-Verlusts an Lendenwirbelsäule, proximaler Oberschenkelhals weiteren Hüftregionen basiert. Möglicherweise bedingt durch den Remodellingprozess als TC-induzierten Adaptationspfad muss das Training jedoch mindestens 12 Monate anhalten (Chow et al., 2017) um positive Effekte auf die Knochendichte erfassen zu können.

Dynamisches Krafttraining (DRT)

Dynamisches Krafttraining (DRT), ist als Bewegung gegen höhere machanische Widerstände mit einer konzentrischen (überwindenden) einer isometrischen (haltenden) und einer exzentrischen (nachgebenden) Belastungsphasen definiert. DRT gilt als wesentlicher Bestandteil der Osteoporose-Prävention und –Therapie und ist Inhalt aller massgeblichen Trainingsempfehlungen (Beck et al., 2017; Daly et al., 2019; Kemmler und Stengel, 2019).

Dynamisches Krafttraining (DRT) ist die am besten untersuchten Trainingsmethode zur Erhöhung der Knochendichte bei älteren Menschen. Während des DRT wird eine komplexe Vielzahl von muskulären Belastungen auf den Knochen ausgeübt. Die gelenksübergreifende direkte Zugwirkung der Muskeln (Gelenkreaktionskräfte) führt zu komplexen mechanischen Belastungen wie Kompression-, Biege-, Torsions- und Zugbelastung (Hingorjo et al., 2018; Taaffe et al., 2013). Überschwelligkeit der Belastung, also eine Reizintensität (deutlich) über dem habituellen Gebrauch, kann zu einer osteogenen Reaktion des Knochens und dadurch zu einer Verbesserung der Knochenfestigkeit führen (Turner und Robling, 2005; Gómez-Cabello et al., 2012; Hingorjo et al., 2018; Cheung und Giangregorio, 2012). RCTs, die positive Effekte auf die BMD bei älteren Frauen zeigten, beinhalteten in der Regel drei Trainingseinheiten pro Woche mit zwei - drei Sätze von 8-12 Wiederholungen mit 70-85% der maximalen Muskelkraft für alle großen Muskelgruppen. Die Mehrzahl der Untersuchung steigerte dabei die Reizhöhe im Verlauf der Intervention (Zehnacker und Bemis-Dougherty, 2007; Taaffe et al., 2013; Beck et al., 2017).

Kombinierte Trainingsprogramme zur Frakturprophylaxe

Eine Kombination verschiedener Trainingstypen (WB, non-WB, DRT, Koordination, TC) wird entweder in derselben Trainingseinheit oder in unterschiedlichen dedizierten Trainingsphasen appliziert. Ziel ist die Vorbeugung von Osteoporose und Frakturen, da sie möglicherweise einen positiven Einfluss sowohl auf die BMD an FN und LS haben können und darüber hinaus Risikofaktoren mit negativem Effekt auf Sturzhäufigkeit und -ausmaß positiv beeinflussen können (Taaffe et al., 2013; Beck et al., 2017; Nuti et al., 2019).

Ein Überblick über 12 systematische Reviews und Metaanalysen, die über kombinierten Trainingsprogrammen (WB mit RT) durchgeführt wurden, zeigt, dass diese besonders effectiv sind um die Knochedichte bei prä- und postmenopausalen Frauen positiv zu beeinflussen (Xu et al., 2016).

Dieses Ergebnis stimmt mit dem Resultat eines systematischen Reviews überein, wonach die Mehrzahl der Forschungsstudien mit kombiniertem Bewegungstraining eine Verbesserung der BMD bei PMW zeigt (Gómez-Cabello et al., 2012). Es besteht allerdings kein Konsens hinsichtlich des effektivsten Trainingsprotokolls da die ideale Komposition der Belastungsnormativa, also Grössen wie Reizintensität, Bewegungsgeschwindigkeit Reizdauer, Reizhäufigkeit Trainingshäufigkeit des DRT nicht hinreichend bekannt sind (Benedetti et al., 2018).

In Bezug auf die Vielfalt von Trainingstypen und ihre kontroversen Auswirkungen auf die BMD, ist die Durchführung eines systematischen Reviews und einer Metaanalyse von entscheidender Bedeutung, um die verschiedenen Arten von Trainingsinterventionen zu kategorisieren und ihre Auswirkungen auf die BMD im LS und PF bei PMW zu untersuchen.

Daher zielen wir in der vorliegenden systematischen Übersicht und Meta-Analyse darauf ab, (1) den allgemeinen Effekt von körperlichem Training auf die BMD an der LS und am PF durch meta-analytische Techniken zu quantifizieren, (2) Teilnehmer und Trainingsmerkmale zu identifizieren, die die Effekte eines körperlichen Trainings auf die BMD erklären und (3) optimierte Empfehlungen für Trainingsprogramm zur Verbesserung der Knochendichte bei PMW vorzulegen.

Projekt 1

Effect of exercise training on bone mineral density in postmenopausal women: A systematic review and meta-analysis of intervention studies

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ZUSAMMENFASSUNG

Hintergrund und Ziele

Osteoporose ist ein wichtiges Thema für PMW. Bewegungstraining ist eine günstige und sichere nicht-pharmazeutische Strategie zur Osteoporose-Prävention bei Menschen mittleren Alters. Daher war es unser Ziel, in einer Meta-Analyse die Wirkung von Bewegung auf die BMD bei PMW zusammenzufassen.

Methoden und Material

Eine umfassende Suche in elektronischen Datenbanken wurde über PubMed, Scopus, Web of Science, Cochrane, Science Direct, Eric, ProQuest und Primo durchgeführt. BMD-Veränderungen (standardisierte Mittelwertunterschiede: SMD) der LS, des FN und/oder der tHip wurden als Ergebnismessung berücksichtigt. Nach der Kategorisierung der Untergruppen wurden statistische Methoden verwendet, um die Daten zu kombinieren und die Untergruppen zu vergleichen.

Ergebnisse

In die vorliegende Meta-Analyse wurden fünfundsiebzig Studien eingeschlossen. Die Gesamtzahl der Teilnehmer betrug 5.300 (Interventionsgruppe: n = 2.901, Kontrollgruppe: n = 2.399). Der gepoolte Schätzwert der Random-Effekt-Analyse lautete: SMD = 0,37, 95%-CI: 0,25-0,50; SMD = 0,33, 95%-CI: 0,23-0,43 und SMD = 0,40, 95%-CI: 0,28-0,51 für LS, FN und die tHip-BMD. Wir fanden einen signifikanten Effekt (SMD = 0,33-0,40, $p < 0{,}001$) des Trainings auf die BMD an LS und PF.

Schlussfolgerung

Es zeigte sich eine große Heterogenität zwischen den einzelnen Studienergebnissen, von hoch effektiven Studien bis hin zu kleinen signifikanten negativen Ergebnissen. Diese Unterschiede sind größtenteils auf Unterschiede zwischen den Trainingsprotokollen in verschiedenen Studien

zurückzuführen. Die Ergebnisse zeigen, dass der tatsächliche Effekt von Bewegung auf die Knochendichte durch eine signifikante Anzahl von Studien mit ungeeigneten Trainingsprotokollen beeinflusst wird.

SUMMARY

Background and Aims

Osteoporosis is an important concern for PMW. Exercise training is a low cost and safe non-pharmaceutical strategy for osteoporosis prevention in middle aged-older people. Therefore, our aim was summarizing the effect of exercise on BMD among PMW.

Material and Methods

A comprehensive search of electronic databases was conducted through PubMed, Scopus, Web of Science, Cochrane, Science Direct, Eric, ProQuest, and Primo. BMD changes (standardized mean differences: SMD) of the LS, FN and/or tHip were considered as outcome measures. After subgroup categorization, statistical methods were used to combine data and compare subgroups.

Results

In the present meta-analysis, seventy-five studies were included. The pooled number of participants was 5,300 (intervention group: n = 2,901, control group: n = 2,399). The pooled estimate of random effect analysis was SMD = 0.37, 95%-CI: 0.25–0.50, SMD = 0.33, 95%-CI: 0.23–0.43, and SMD = 0.40, 95%-CI: 0.28–0.51 for LS, FN, and tHip-BMD, respectively. We found a small significant effect (SMD = 0.33–0.40, $p < 0.001$) of exercise on BMD at LS and PF.

Conclusions

A large heterogeneity among the single trial findings was seen, from high effective studies to small significant negative results. These differences largely stem from differences between exercise protocols in various studies. Findings show that the real effect of exercise on bone density is influenced by a significant number of studies with inappropriate exercise protocols.

EINLEITUNG Projekt 1

Durch die vorab genannten Argumente haben sich viele Studien auf die Auswirkungen von Bewegung auf die BMD bei PMW konzentriert (Bonaiuti et al., 2002; Howe et al., 2011; Marques et al., 2011; Zhao et al., 2017; Rahimi et al., 2020). Die aufgezeigten Effekte auf die BMD, als dem am häufigsten bewerteten Parameter für die Knochenfestigkeit, variieren jedoch stark. Einige Studien berichten sogar von einem negativen Effekt (vs. Kontrolle) auf die BMD (Bassey und Ramsdale, 1995; Nichols et al., 1995; Choquette et al., 2011). In Anbetracht der großen Vielfalt von Interventionsprotokollen, die durch die Kombination verschiedener Trainingstypen, Belastungsparameter und Trainingsprinzipien erstellt werden können, besteht kein Zweifel daran, dass einige Belastungsprotokolle günstige, andere hingegen negative Effekte auf die BMD zeigen.

Darüber hinaus variieren die Teilnehmercharakteristika der Studien insbesondere für Parameter wie z.B. Alter, Menopausen-, Knochen- und Trainingsstatus, also Grössen die den Effekt der Bewegung auf die BMD modulieren und somit zu unterschedlichen Effektstärken eines körperlichen Trainings beitragen können – ein Aspekt der die z.T. deutlich varierenden Ergebnisse vorliegender Meta-Analysen (mit) zu erklären vermag (Kelley, 1998; Martyn-St James und Carroll, 2010; Marques et al., 2011; Zhao et al., 2017).

Eine weitere Motivation für die vorgelegte Arbeit liegt in der Aktualität der Tematik begründet. Die vorliegenden Meta-Analysen, ausgenommen die Arbeit von Rahimi et al. (2020) mit 16 RCTs, beziehen sich auf Studien, die vor mehr als 8 Jahren veröffentlicht wurden (Howe et al., 2011; Kelley, 1998; Marques et al., 2011; Kelley et al., 2012). Aufgrund der fortgesetzten Forschung in diesem Bereich wurden inzwischen weitere RCTs Ergebnissen veröffentlicht (Basat et al., 2013; Bello et al., 2014; Bolton et al., 2012; Chilibeck et al., 2013; de Oliveira et al., 2019; Duff et al., 2016; Karakiriou et al., 2012; Kemmler et al., 2013; Liu et al., 2015; Moreira et al., 2014; Nicholson et al., 2015; Orsatti et al., 2013; Wang et al., 2015) die für die vorliegende Arbeit von Relevanz waren.

Zur Durchführung der aktuellen systematischen Übersicht und Meta-Analyse wurde eine umfassende Suche in elektronischen Datenbanken über PubMed, Scopus, Web of Science, Cochrane, Science Direct, Eric, ProQuest und Primo für alle bis zum 01. März 2019 veröffentlichten Artikel durchgeführt. Studien wurden einbezogen, wenn sie die folgenden Kriterien erfüllten: (a) randomisierte oder nicht-randomisierte kontrollierte Studien mit mindestens einer Trainingsgruppe als Intervention vs. einer Kontrollgruppe mit habitueller (sedentärer) Lebensweise oder „sham“-Intervention; (b) die Teilnehmer waren zu Beginn der Studie postmenopausal; (c) das Trainingsprogramm dauerte mindestens 6 Monate; (d) BMD der LS oder/und der proximalen Femurregionen "tHip" und/oder "FN" wurden als Ergebnismessung verwendet; (e) Basis- und abschließende BMD-Bewertung für mindestens eine gewünschte Region berichtet; (f) BMD-Messung bewertet durch DXA oder Dual-Photonen-Absorptiometrie (DPA); (g) Studien mit ≤10% der Teilnehmer mit HRT, Hormontherapie (HT), adjuvante endokrine Therapie, antiresorptive oder osteoanabolische Pharmazeutika (z.B. Bisphosphonat, Denosumab, Strontiumranelat) oder Medikamente mit dedizierter osteokatabolischer Wirkung auf den Knochenstoffwechsel (Glukokortikoide), allerdings nur, wenn die Anzahl der Nutzer zwischen Trainings und Kontrollgruppe ähnlich war.

Folgende Studien wurden von der Analyse ausgeschlossen: Studien mit (a) Interventionen mit neuartigen Trainingstechnologien (z. B. Ganzkörpervibration), (b) gemischten Geschlechtern oder gemischten prä- und postmenopausalen Kohorten ohne separate BMD-Analyse für PMW, (c) PMW unter Chemo- und/oder Strahlentherapie, (d) PMW mit Erkrankungen, die den Knochenstoffwechsel beeinflussen, (e) synergistischen/additiven Wirkung von Bewegung und pharmazeutischer Therapie oder (f) Doppelstudien oder vorläufige Daten, Fallberichte, Editorials, Konferenzabstracts und Briefe.

Von 1.757 ursprünglich abgerufenen Artikeln konnten 1.743 Studien aus allen einbezogenen Datenbanken und von anderen Ressourcen gefunden werden. Doppelte Artikel wurden entfernt, die Titel und Abstracts der verbliebenen Artikel wurden gesichtet und anhand der Auswahlkriterien überprüft. Anschließend wurde der Volltext von 153 potenziell relevanten Artikeln überprüft und bei 78 von ihnen festgestellt, dass sie die Einschlusskriterien nicht erfüllten. Insgesamt wurden somit 75 Artikel, die im Zeitraum von 1989 bis 2019 veröffentlicht wurden (Abbildung 1), in diese Studie eingeschlossen.

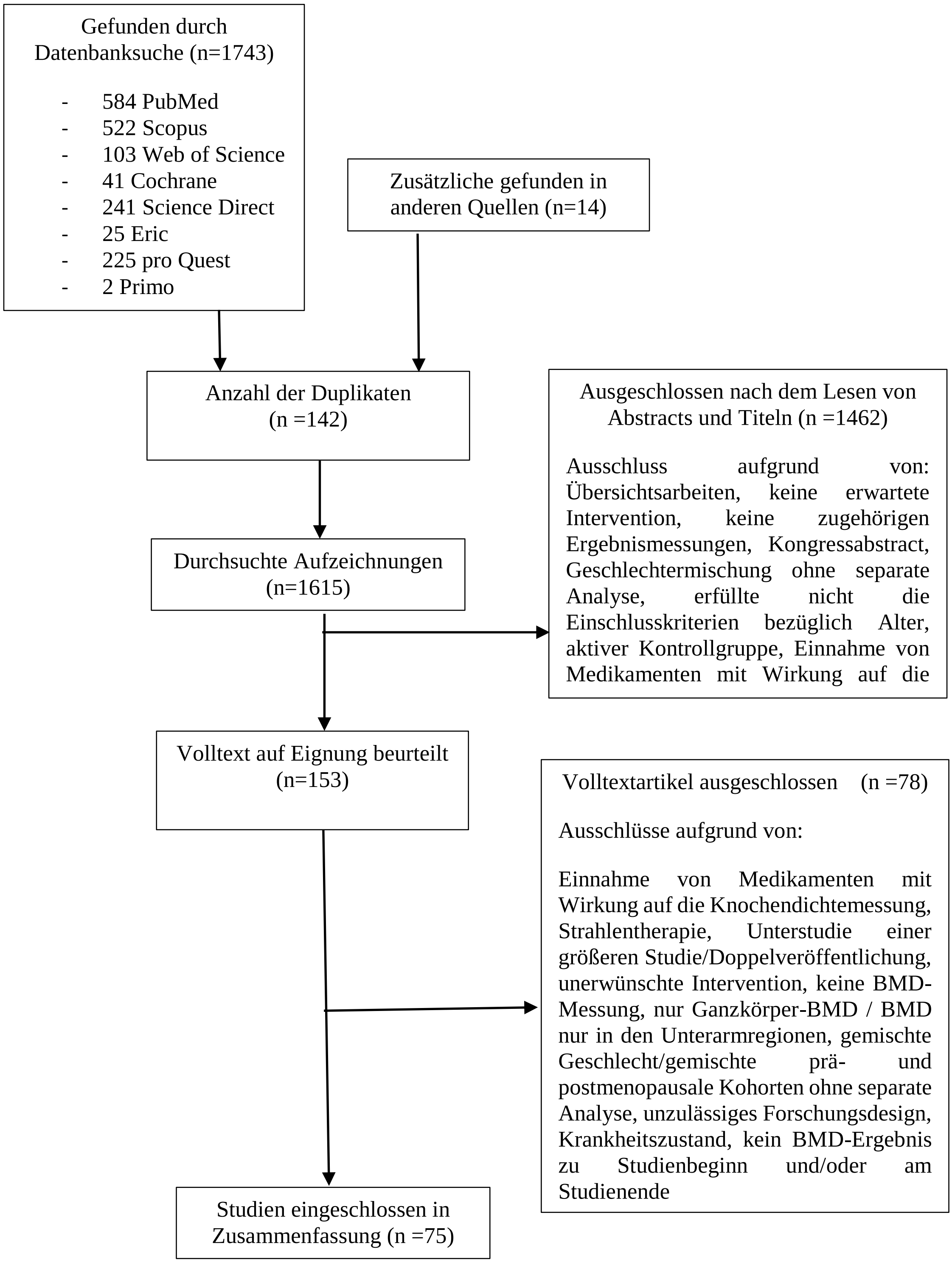
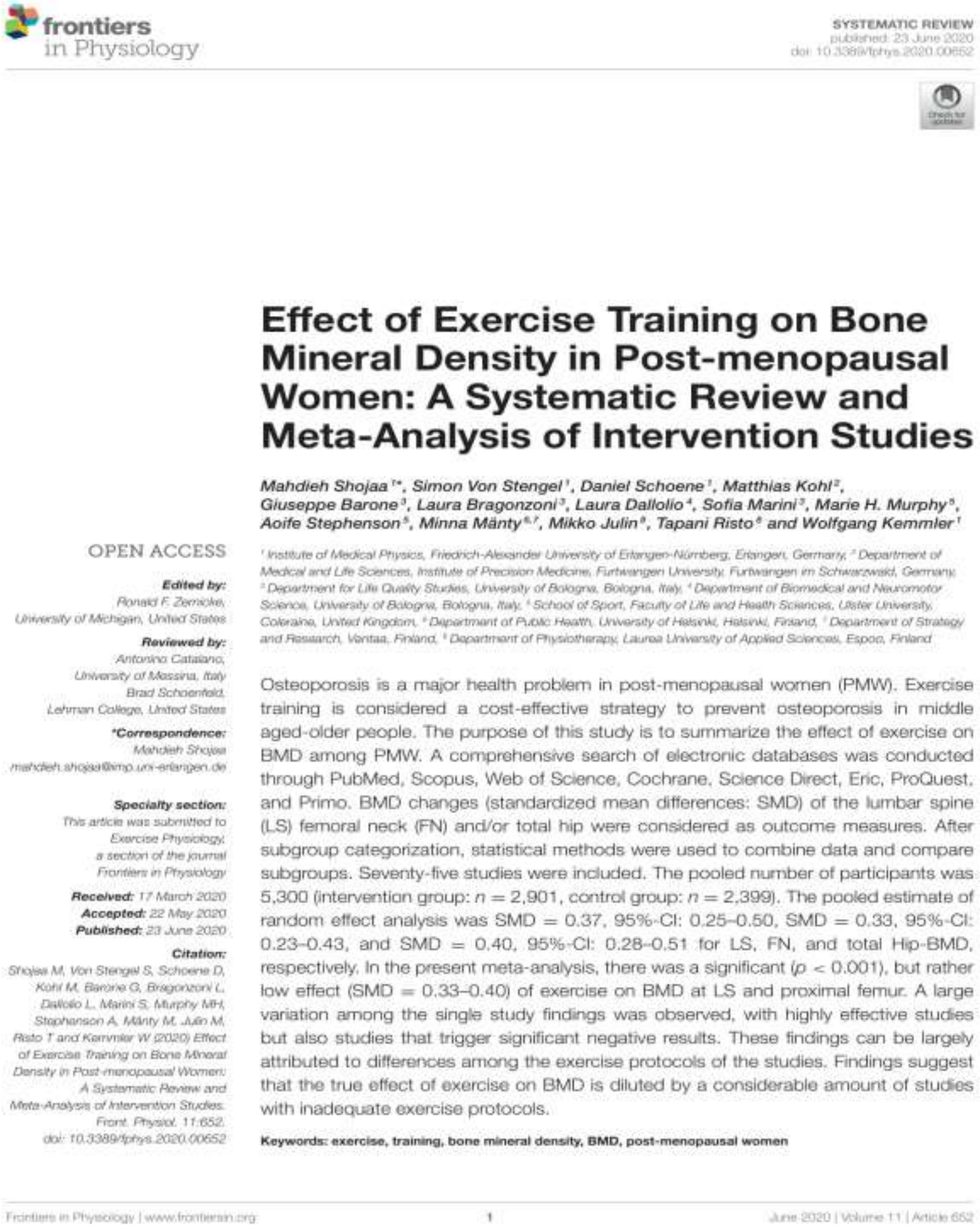


Abb.1: Flussdiagramm zum Verlauf der Studienauswahl

ARTIKEL Projekt 1



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Effect of Exercise Training on Bone Mineral Density in Post-menopausal Women: A Systematic Review and Meta-Analysis of Intervention Studies

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Osteoporosis is a major health problem in post-menopausal women (PMW). Exercise training is considered a cost-effective strategy to prevent osteoporosis in middle aged-older people. The purpose of this study is to summarize the effect of exercise on BMD among PMW. A comprehensive search of electronic databases was conducted through PubMed, Scopus, Web of Science, Cochrane, Science Direct, Eric, ProQuest, and Primo. BMD changes (standardized mean differences: SMD) of the lumbar spine (LS) femoral neck (FN) and/or total hip were considered as outcome measures. After subgroup categorization, statistical methods were used to combine data and compare subgroups. Seventy-five studies were included. The pooled number of participants was 5,300 (intervention group: $n = 2{,}901$, control group: $n = 2{,}399$). The pooled estimate of random effect analysis was SMD = 0.37, 95%-CI: 0.25–0.50, SMD = 0.33, 95%-CI: 0.23–0.43, and SMD = 0.40, 95%-CI: 0.28–0.51 for LS, FN, and total Hip-BMD, respectively. In the present meta-analysis, there was a significant ($p < 0.001$), but rather low effect (SMD = 0.33–0.40) of exercise on BMD at LS and proximal femur. A large variation among the single study findings was observed, with highly effective studies but also studies that trigger significant negative results. These findings can be largely attributed to differences among the exercise protocols of the studies. Findings suggest that the true effect of exercise on BMD is diluted by a considerable amount of studies with inadequate exercise protocols.

Keywords: exercise, training, bone mineral density, BMD, post-menopausal women

INTRODUCTION

Osteoporosis is a disease characterized by low bone mass, microarchitectural deterioration of bone tissue, leading to enhanced bone fragility, and a consequent increase in fracture risk (1991). The disease is an important global public health problem (Compston et al., 2019). Due to the menopausal transition, and the corresponding decline of estrogen, post-menopausal women (PMW) in particular, are at high risk of osteoporosis (Christenson et al., 2012). Exercise training is considered to be a low cost and safe non-pharmaceutical treatment strategy for the protection of musculoskeletal health and fracture prevention (Kemmler et al., 2015; Beck et al., 2017; Daly et al., 2019), thus, many studies have focused on the effects of exercise on bone mineral density (BMD) in PMW (Bonaiuti et al., 2002; Howe et al., 2011; Marques et al., 2011a; Zhao et al., 2017). However, their effects on BMD, as the most frequently assessed parameter for bone strength, vary widely. Some studies even report a negative effect (vs. control) on BMD (Bassey and Ramsdale, 1995; Nichols et al., 1995; Choquette et al., 2011). Considering the large variety of intervention protocols that can be created when combining different types of exercise, exercise-parameters, and training-principles, there is no doubt that some loading protocols demonstrate favorable, while others trigger negative effects, on BMD. Additionally, participant characteristics vary considerably for parameters (e.g., menopausal status, bone status, training status) that might modulate the effect of exercise on BMD and thus may contribute to the low effect size of exercise reported by most meta-analyses (Kelley, 1998a,b; Martyn-St James and Carroll, 2011; Marques et al., 2011a; Zhao et al., 2017).

In the present systematic review and meta-analysis, we aimed to; (1) quantify the general effect of exercise on BMD at lumbar spine (LS) and proximal femur (PF) regions of interest (ROI) by meta-analytic techniques, (2) identify participants and exercise characteristics that explain the effect of exercise on BMD and (3) propose exercise recommendations to favorably affect BMD at the LS, femoral neck (FN) and total hip (tHip) ROI in PMW.

MATERIALS AND METHODS

Literature Search

This review and meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2015) and was registered in advance in the International prospective register of systematic reviews (PROSPERO) (ID: CRD42018095097). A comprehensive search of electronic databases was conducted through PubMed, Scopus, Web of Science, Cochrane, Science Direct, Eric, ProQuest, and Primo for all articles published up to March 01, 2019, with no language restrictions. The search strategy utilized the population, intervention and outcome approach. The literature search was constructed around search terms for "bone mineral density," exercise," and "post-menopausal."

A standard protocol for this search was developed and controlled vocabulary (Mesh term for MEDLINE) was used. Key words and their synonymous were used by applying the following queries, ("Bone" or "Bone mass" or "Bone status" or "Bone structure" or "Bone turnover" or "Bone metabolism" or "Bone mineral content" or "Skeleton" or "Bone Mineral Density" or "BMD" or "Bone Density" or "Osteoporoses" or "Osteoporosis" or "Osteopenia") AND ("Postmenopause" or "Post-Menopause" or "Post-menopausal") AND ("Exercise" or "Training" or "Athletic" or "Sport" or" "physical activity") AND ("Clinical trial" or "Randomized clinical trial"). Furthermore, reference lists of the included articles were searched manually to locate additional relevant studies. Unpublished reports or articles for which only abstracts were available were not considered. Duplicate publications were identified by comparing author names, treatment comparisons, publication dates, sample sizes, intervention, and outcomes. In the case of unclear eligibility criteria or when the confirmation of any data or additional information was needed, the authors were contacted by e-mail.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: (a) randomized or non-randomized controlled trials with at least one exercise group as an intervention vs. one control group with habitual (sedentary) lifestyle or sham exercises; (b) participants were post-menopausal at study onset; (c) the training program lasted a minimum of 6 months; (d) BMD of the LS or/and the proximal femur regions "total hip" and/or "FN" were used as outcome measures; (e) baseline and final BMD assessment reported at least for one desired regions; (f) BMD measurement assessed by dual-energy X-ray absorptiometry (DXA) or dual-photon absorptiometry (DPA); (g) studies with $\leq$10% of participants on hormone replacement therapy (HRT), hormone therapy (HT), adjuvant endocrine therapy, antiresorptive, or osteoanabolic pharmaceutic agents (e.g., Bisphosphonate, Denosumab, Strontiumranelate) or drugs with a dedicated osteo-catabolic effect on bone metabolism, (glucocorticoids), albeit only if the number of users was similar between exercise and control.

Studies addressing (a) interventions applying novel exercise technologies (e.g., whole-body vibration) (b) mixed gender or mixed pre- and post-menopausal cohorts without separate BMD analysis for PMW; (c) PMW under chemo- and/or radiotherapy; (d) PMW with diseases that affect bone metabolism; (e) the synergistic/additive effect of exercise and pharmaceutic therapy, or (f) duplicate studies or preliminary data from the subsequently published study and review articles, case reports, editorials, conference abstracts, and letters were excluded from the analysis.

Data Extraction

Titles and abstracts were screened by an independent reviewer (MS) to exclude irrelevant studies. Two reviewers (SV and MS) separately and independently evaluated full-text articles and extracted data from the included studies. Disagreement was resolved by discussion between the two reviewers; if they could not reach a consensus a third reviewer was consulted (WK). An extraction form was designed to record the relevant data regarding publication details (i.e., the first author's name, title, country and publication year), details of the study (i.e., design, objectives, sample size for each group), participants' characteristics (i.e., age, weight, BMI, years since menopause), description of intervention (i.e., type of exercise, intervention period, frequency, intensity, duration, sets and repetition), compliance (including number of withdrawals), risk assessment, BMD assessment tool and evaluated region, BMD values at baseline and study completion.

Outcome Measures

Outcomes of interest were BMD at the LS and the proximal femur (FN and/or tHip) as assessed by Dual Energy X-Ray Absorptiometry (DXA) or Dual Photon Absorptiometry (DPA) at least at baseline and study end.

Quality Assessment

Included articles were independently assessed for risk of bias using the Physiotherapy Evidence Database (PEDro) scale risk of bias tool (Sherrington et al., 2000; de Morton, 2009). This was completed by two reviewers from Germany (MS, SvS). Partners from Finland (MM, MJ, TR), Italy (LB, LD, SM, GB) or Northern Ireland (MHM, AS) acted as a third reviewer. Potential biases in studies were selection bias, performance bias, detection bias, attrition bias, and reporting bias using 11 criteria, however, the scale scores 10 items. The categories assessed were randomization, allocation concealment, similarity at baseline, blinding of participants and staff, assessor blinding, incomplete outcome data, intention-to-treat analysis, between groups comparison, and measure of variability. Scores ranged from 0 to 10 and points were awarded when a criterion was clearly explained; otherwise, a point was not awarded. Discrepancies were discussed with a review author from Germany (WK) until a consensus was reached. The methodological quality of the included studies was classified as follows: ≥ 7, high; 5–6, moderate; <5, low (Ribeiro de Avila et al., 2018).

Data Synthesis

For sub-analyses, the intervention period was stratified as ≤ 8, 9–18, and >18 months by considering the remodeling cycle for cancellous and cortical bone (Eriksen, 2010). Post-menopausal status was categorized as early (≤ 8 years) and late (>9 years) (Harlow et al., 2012). We also classified the type of exercise into seven sub-groups including weight-bearing aerobic exercise (WB-AE), dynamic resistance training (DRT), Jumping+[resistance training (RT) and/or WB], WB+RT, Jumping, non-WB+RT and Tai Chi. Type of mechanical forces was categorized as joint reaction force (JRF), ground reaction force (GRF), and mix of JRF+GRF (Daly et al., 2019; Kemmler and von Stengel, 2019).

If the studies presented a confidence interval (CI) or standard errors (SE), they were converted to standard deviation (SD) by using standardized formulae (Higgins and Green, 2008). Where standard deviation was not given, authors were contacted to provide the missing data. When no reply was received or data were not available, the exact *p*-value of the absolute change of BMD was obtained to compute the SD of the change. In the case of unreported *p*-value, we calculated the SDs using pre and post SDs, and correlation coefficients with the following formula:

$$\sqrt{}\mathrm{SD}_{\mathrm{pre}}^2 + \mathrm{SD}_{\mathrm{post}}^2 - (2 \times \mathrm{corr} \times \mathrm{SD}_{\mathrm{pre}} \times \mathrm{SD}_{\mathrm{post}}),$$

where "*corr*" is the correlation coefficient which was imputed using the mean of the correlations available for some included studies. $\mathrm{SD}_{\mathrm{pre}}$ and $\mathrm{SD}_{\mathrm{post}}$ are the baseline and final standard deviation, respectively (Higgins and Green, 2008). This resulted in using a within-participant correlation of $r = 0.95$ and $r = 0.94$ in exercise and control groups at LS, respectively. At FN, the mean correlation was computed $r = 0.82$ among exercise groups and $r = 0.85$ for control groups. Finally, at the total hip, $r = 0.97$ and $r = 0.98$ were considered for intervention and control groups, respectively. When the absolute mean difference was not available, it was imputed by calculation of the difference between post- and pre-intervention. For those studies which measured BMD at multiple times, only the baseline and final values were included in the analysis.

Statistical Analysis

The meta-analyses were performed using the package metaphor in the statistical software R (R Development Core Team, 2019). Effect size (ES) values were considered as the standardized mean differences (SMDs) combined with the 95% confidence interval (CI).

Random-effects meta-analysis was conducted by using the meta for package (Viechtbauer, 2010). Heterogeneity for between-study variability was implemented using the Cochran Q test and considered statistically significant if p-value < 0.05. The extent of heterogeneity was examined with the I^2 statistics. I^2 0 to 40% is considered as low heterogeneity, 30 to 60%, and 50 to 90% represent moderate and substantial heterogeneity, respectively (Higgins and Green, 2008). For those studies with two different intervention groups, the control group was split into 2 smaller groups for comparison against each intervention group (Higgins and Green, 2008).

To explore potential publication biases, a funnel plot with regression test and the rank correlation between effect estimates and their standard errors (SEs), using the *t*-test and Kendall's τ statistic were conducted, respectively. The p-value < 0.05 was defined as the significant level for all tests.

Subgroup analyses were performed for menopausal status, intervention duration, type of exercise, and type of mechanical forces. Sensitivity analysis was conducted to try different values of the correlation coefficient (minimum, mean or maximum) to determine whether the overall result of the analysis is robust to the use of the imputed correlation coefficient.

RESULTS

Study Selection

Of 1,757 articles initially retrieved, 1,743 studies were found from all included databases and other resources. Duplicate articles were removed and the title and abstract of the remaining articles were screened and checked based on the eligibility criteria. The full-text of 153 potentially relevant articles were then checked, and 78 of them were found not to meet the inclusion criteria. A total of 75 articles were thus included in this study, published from 1989 to 2019 (**Figure 1**). Three included studies contained English abstracts but with Italian (Tolomio et al., 2009), Portuguese (Orsatti et al., 2013), and German (Kemmler, 1999) full texts, which were translated by native speakers.

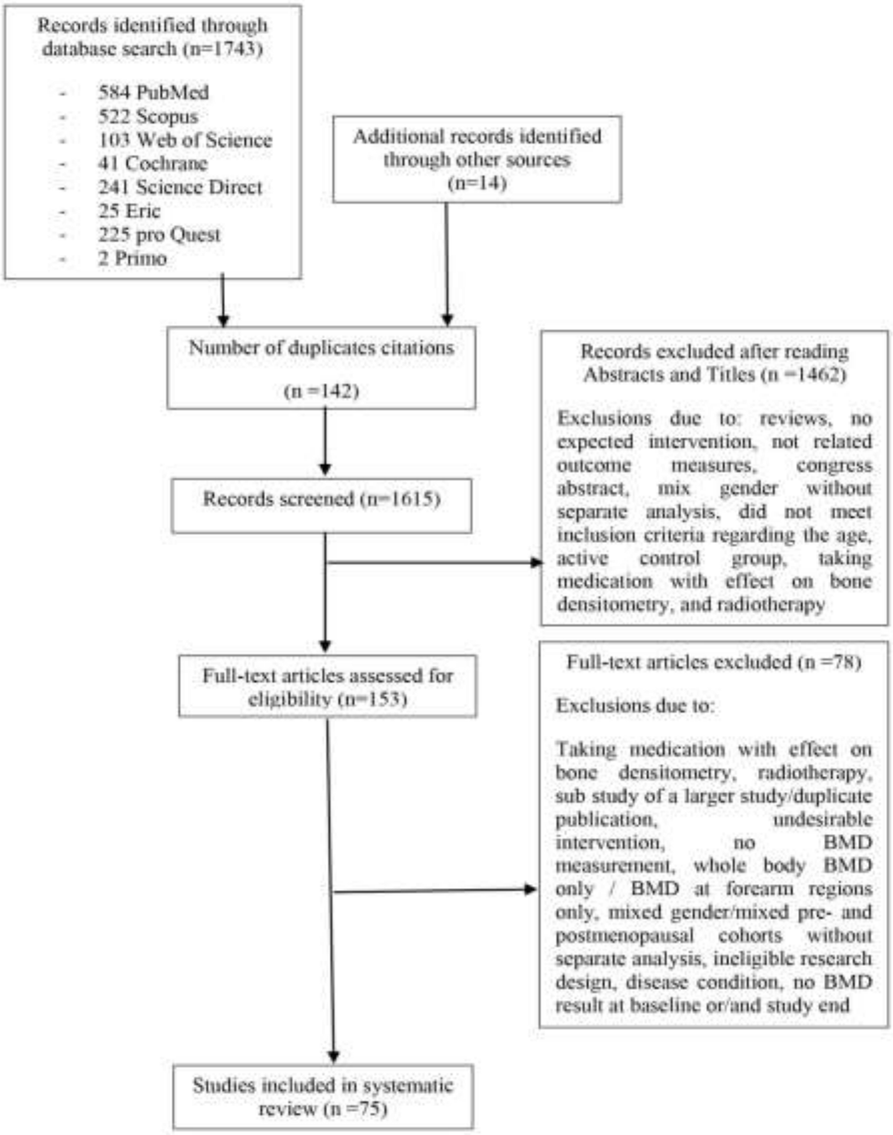


FIGURE 1 | Flow diagram of search process.

Study and Participants' Characteristic

Seventy-five studies were included in this systematic review and meta-analysis, comprising 88 individual training groups based on our eligibility criteria (Sinaki et al., 1989; Nelson et al., 1991, 1994; Grove and Londeree, 1992; Lau et al., 1992; Pruitt et al., 1992, 1995; Bloomfield et al., 1993; Caplan et al., 1993; Hatori et al., 1993; Martin and Notelovitz, 1993; Bassey and Ramsdale, 1995; Kohrt et al., 1995, 1997; Nichols et al., 1995; Prince et al., 1995; Hartard et al., 1996; Kerr et al., 1996, 2001; Lord et al., 1996; Brooke-Wavell et al., 1997, 2001; Ebrahim et al., 1997; Bassey et al., 1998; Ryan et al., 1998; Adami et al., 1999; Kemmler, 1999; Bemben et al., 2000, 2010; Rhodes et al., 2000; Iwamoto et al., 2001; Chilibeck et al., 2002, 2013; Hans et al., 2002; Sugiyama et al., 2002; Going et al., 2003; Jessup et al., 2003; Milliken et al., 2003; Chan et al., 2004; Kemmler et al., 2004, 2010, 2013; Verschueren et al., 2004; Yamazaki et al., 2004; Englund et al., 2005; Korpelainen et al., 2006; Wu et al., 2006; Evans et al., 2007; Maddalozzo et al., 2007; Woo et al., 2007; Bergstrom et al., 2008; Kwon et al., 2008; Park et al., 2008; Bocalini et al., 2009; Chuin et al., 2009; de Matos et al., 2009; Deng, 2009; Silverman et al., 2009; Tolomio et al., 2009; Sakai et al., 2010; Choquette et al., 2011; Marques et al., 2011b,c; Tartibian et al., 2011; Bolton et al., 2012; Karakiriou et al., 2012; Basat et al., 2013; Orsatti et al., 2013; Bello et al., 2014; Moreira et al., 2014; Liu et al., 2015; Nicholson et al., 2015; Wang et al., 2015; Duff et al., 2016; de Oliveira et al., 2019). The pooled number of participants was 5,300 (intervention group: $n = 2,901$, control group: $n = 2,399$) and sample size in individual studies ranged from five (Grove and Londeree, 1992) to 125 (Adami et al., 1999) participants per group. **Table 1** presents a summary of included study characteristics. The mean menopausal age ranged from at least 0.5 (according to eligibility criteria) (Sinaki et al., 1989; Wang et al., 2015) to 24 years (Jessup et al., 2003), and the range of mean ages was between 50 (Bemben et al., 2000) and 79 (Lau et al., 1992; Tella and Gallagher, 2014) years. The mean body mass index (BMI, kg/m^2) of individual studies varied from 19.7 (Iwamoto et al., 2001) to 32.6 kg/m^2 (Silverman et al., 2009) (**Table 1**).

Twenty-seven studies recruited participants with sedentary life style (Nelson et al., 1991, 1994; Grove and Londeree, 1992; Bloomfield et al., 1993; Kohrt et al., 1995, 1997; Brooke-Wavell et al., 1997, 2001; Ryan et al., 1998; Adami et al., 1999; Rhodes et al., 2000; Iwamoto et al., 2001; Jessup et al., 2003; Yamazaki et al., 2004; Wu et al., 2006; Woo et al., 2007; Bocalini et al., 2009; Kemmler et al., 2010; Choquette et al., 2011; Marques et al., 2011b,c; Tartibian et al., 2011; Karakiriou et al., 2012; Orsatti et al., 2013; Bello et al., 2014; Moreira et al., 2014; de Oliveira et al., 2019), 33 trials involved participants with some kinds of exercises activities (Pruitt et al., 1992, 1995; Martin and Notelovitz, 1993; Bassey and Ramsdale, 1995; Nichols et al., 1995; Prince et al., 1995; Hartard et al., 1996; Kerr et al., 1996, 2001; Lord et al., 1996; Ebrahim et al., 1997; Bassey et al., 1998; Kemmler, 1999; Bemben et al., 2000, 2010; Chilibeck et al., 2002, 2013; Going et al., 2003; Milliken et al., 2003; Chan et al., 2004; Kemmler et al., 2004, 2013; Bergstrom et al., 2008; Kwon et al., 2008; Park et al., 2008; Deng, 2009; Silverman et al., 2009; Sakai et al., 2010; Bolton et al., 2012; Basat et al., 2013; Nicholson et al., 2015; Wang et al., 2015; Duff et al., 2016), while the remaining studies did not provide any information with respect to the life style status of participants (Sinaki et al., 1989; Lau et al., 1992; Caplan et al., 1993; Hatori et al., 1993; Hans et al., 2002; Sugiyama et al., 2002; Verschueren et al., 2004; Englund et al., 2005; Korpelainen et al., 2006; Evans et al., 2007; Maddalozzo et al., 2007; Chuin et al., 2009; de Matos et al., 2009; Tolomio et al., 2009; Liu et al., 2015).

Sixty-one studies comprised healthy participants (Sinaki et al., 1989; Nelson et al., 1991; Grove and Londeree, 1992; Lau et al., 1992; Pruitt et al., 1992, 1995; Bloomfield et al., 1993; Caplan et al., 1993; Hatori et al., 1993; Martin and Notelovitz, 1993; Bassey and Ramsdale, 1995; Kohrt et al., 1995, 1997; Nichols et al., 1995; Prince et al., 1995; Kerr et al., 1996, 2001; Lord et al., 1996; Brooke-Wavell et al., 1997, 2001; Ebrahim et al., 1997; Bassey et al., 1998; Ryan et al., 1998; Adami et al., 1999; Kemmler, 1999; Bemben et al., 2000, 2010; Rhodes et al., 2000; Chilibeck et al., 2002, 2013; Sugiyama et al., 2002; Going et al., 2003; Jessup et al., 2003; Milliken et al., 2003; Chan et al., 2004; Verschueren et al., 2004; Englund et al., 2005; Wu et al., 2006; Evans et al., 2007; Maddalozzo et al., 2007; Woo et al., 2007; Kwon et al., 2008; Park et al., 2008; Bocalini et al., 2009; Chuin et al., 2009; Deng, 2009; Silverman et al., 2009; Kemmler et al., 2010, 2013; Sakai et al., 2010; Choquette et al., 2011; Marques et al., 2011b,c; Tartibian et al., 2011; Orsatti et al., 2013; Bello et al., 2014; Moreira et al., 2014; Nicholson et al., 2015; Wang et al., 2015; Duff et al., 2016; de Oliveira et al., 2019), and the remaining studies recruited participants with osteopenia, osteoporosis, or with a history of spinal fracture(s) (Nelson et al., 1994; Hartard et al., 1996; Iwamoto et al., 2001; Hans et al., 2002; Kemmler et al., 2004; Yamazaki et al., 2004; Korpelainen et al., 2006; Bergstrom et al., 2008; de Matos et al., 2009; Tolomio et al., 2009; Bolton et al., 2012; Karakiriou et al., 2012; Basat et al., 2013; Liu et al., 2015) (**Table 2**).

Exercise Characteristic Description

Table 2 outlines the exercise prescription characteristics. The program duration ranged from six (Hartard et al., 1996; Ryan et al., 1998; Adami et al., 1999; Bemben et al., 2000; Sugiyama et al., 2002; Verschueren et al., 2004; Kwon et al., 2008; Bocalini et al., 2009; Chuin et al., 2009; Silverman et al., 2009; Sakai et al., 2010; Choquette et al., 2011; Tartibian et al., 2011; Karakiriou et al., 2012; Basat et al., 2013; Moreira et al., 2014; Nicholson et al., 2015; de Oliveira et al., 2019) to 30 months (Korpelainen et al., 2006).

Eleven studies applied an intervention period of ≥ 18 months (Sinaki et al., 1989; Caplan et al., 1993; Prince et al., 1995; Ebrahim et al., 1997; Iwamoto et al., 2001; Kerr et al., 2001; Hans et al., 2002; Kemmler et al., 2004, 2010; Korpelainen et al., 2006; Chilibeck et al., 2013), 39 trials used an intervention period between 9 and 18 months (Nelson et al., 1991, 1994; Grove and Londeree, 1992; Lau et al., 1992; Pruitt et al., 1992, 1995; Martin and Notelovitz, 1993; Bassey and Ramsdale, 1995; Kohrt et al., 1995, 1997; Nichols et al., 1995; Kerr et al., 1996; Lord et al., 1996; Brooke-Wavell et al., 1997, 2001; Bassey et al., 1998; Kemmler, 1999; Rhodes et al., 2000; Chilibeck et al., 2002; Going et al., 2003; Milliken et al., 2003; Chan et al., 2004; Yamazaki et al., 2004; Englund et al., 2005; Wu et al., 2006; Evans et al., 2007; Maddalozzo et al., 2007; Woo et al., 2007; Bergstrom et al., 2008; Park et al., 2008; de Matos et al., 2009; Deng, 2009; Tolomio et al., 2009; Bolton et al., 2012; Kemmler et al., 2013; Orsatti et al., 2013; Liu et al., 2015; Wang et al., 2015; Duff et al., 2016), and 25 scheduled a short intervention period of ≤ 8 months (Bloomfield et al., 1993; Hatori et al., 1993; Hartard et al., 1996; Ryan et al., 1998; Adami et al., 1999; Bemben et al., 2000, 2010; Sugiyama et al., 2002; Jessup et al., 2003; Verschueren et al., 2004; Kwon et al., 2008; Bocalini et al., 2009; Chuin et al., 2009; Silverman et al., 2009; Sakai et al., 2010; Choquette et al., 2011; Marques

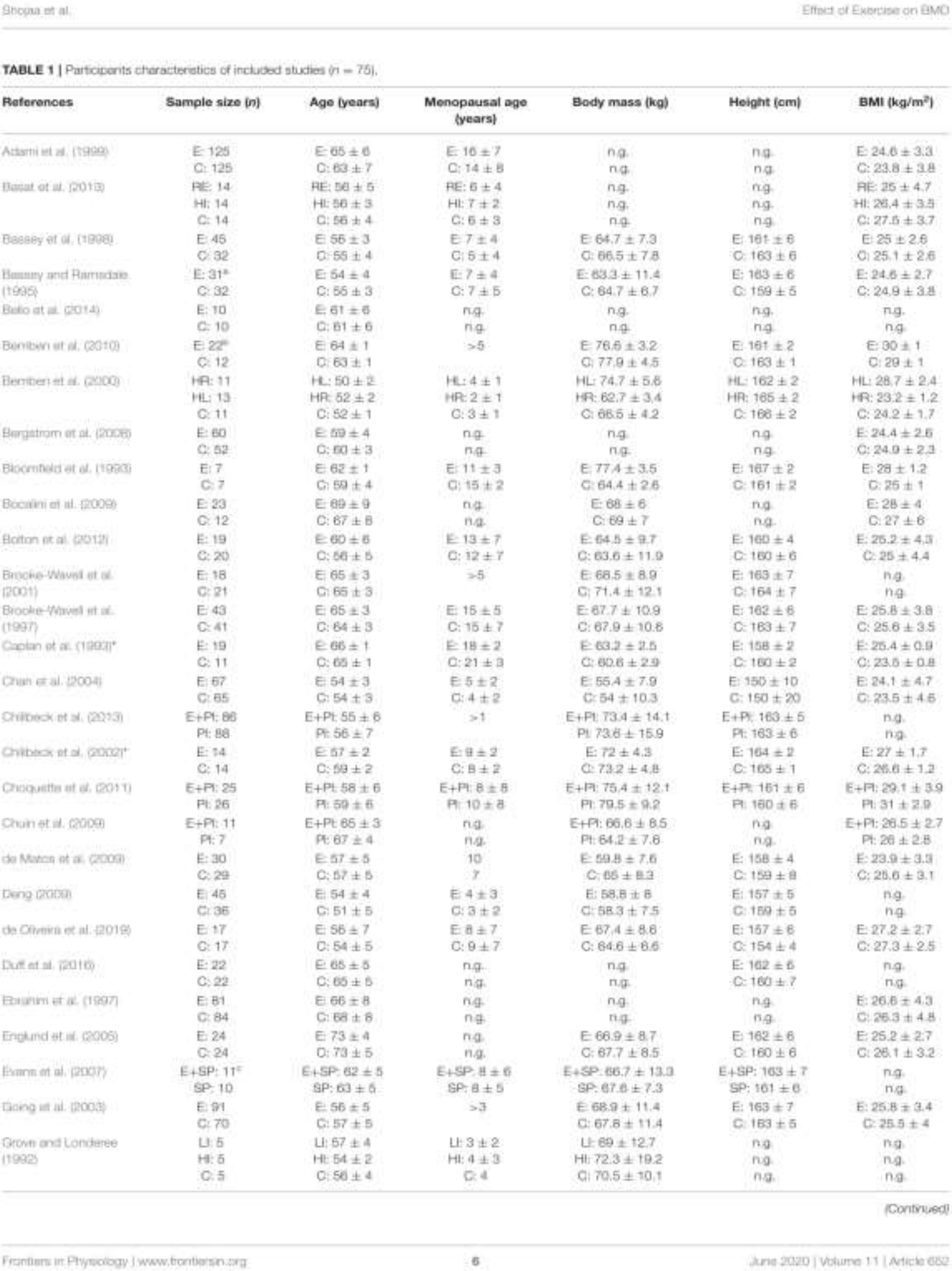


TABLE 1 | Participants characteristics of included studies ($n = 75$).

References	Sample size (n)	Age (years)	Menopausal age (years)	Body mass (kg)	Height (cm)	BMI (kg/m²)
Adami et al. (1999)	E: 125 C: 125	E: 65 ± 6 C: 63 ± 7	E: 16 ± 7 C: 14 ± 8	n.g. n.g.	n.g. n.g.	E: 24.6 ± 3.3 C: 23.8 ± 3.8
Basat et al. (2013)	RE: 14 HI: 14 C: 14	RE: 56 ± 5 HI: 56 ± 3 C: 56 ± 4	RE: 6 ± 4 HI: 7 ± 2 C: 6 ± 3	n.g. n.g. n.g.	n.g. n.g. n.g.	RE: 25 ± 4.7 HI: 26.4 ± 3.5 C: 27.5 ± 3.7
Bassey et al. (1998)	E: 45 C: 32	E: 56 ± 3 C: 55 ± 4	E: 7 ± 4 C: 5 ± 4	E: 64.7 ± 7.3 C: 66.5 ± 7.8	E: 161 ± 6 C: 163 ± 6	E: 25 ± 2.6 C: 25.1 ± 2.6
Bassey and Ramsdale (1995)	E: 31[a] C: 32	E: 54 ± 4 C: 55 ± 3	E: 7 ± 4 C: 7 ± 5	E: 63.3 ± 11.4 C: 64.7 ± 6.7	E: 163 ± 6 C: 159 ± 5	E: 24.6 ± 2.7 C: 24.9 ± 3.8
Bello et al. (2014)	E: 10 C: 10	E: 61 ± 6 C: 61 ± 6	n.g. n.g.	n.g. n.g.	n.g. n.g.	n.g. n.g.
Bemben et al. (2010)	E: 22[b] C: 12	E: 64 ± 1 C: 63 ± 1	>5	E: 76.6 ± 3.2 C: 77.9 ± 4.5	E: 161 ± 2 C: 163 ± 1	E: 30 ± 1 C: 29 ± 1
Bemben et al. (2000)	HR: 11 HL: 13 C: 11	HL: 50 ± 2 HR: 52 ± 2 C: 52 ± 1	HL: 4 ± 1 HR: 2 ± 1 C: 3 ± 1	HL: 74.7 ± 5.6 HR: 62.7 ± 3.4 C: 66.5 ± 4.2	HL: 162 ± 2 HR: 165 ± 2 C: 166 ± 2	HL: 28.7 ± 2.4 HR: 23.2 ± 1.2 C: 24.2 ± 1.7
Bergstrom et al. (2008)	E: 60 C: 52	E: 59 ± 4 C: 60 ± 3	n.g. n.g.	n.g. n.g.	n.g. n.g.	E: 24.4 ± 2.6 C: 24.9 ± 2.3
Bloomfield et al. (1993)	E: 7 C: 7	E: 62 ± 1 C: 59 ± 4	E: 11 ± 3 C: 15 ± 2	E: 77.4 ± 3.5 C: 64.4 ± 2.6	E: 167 ± 2 C: 161 ± 2	E: 28 ± 1.2 C: 25 ± 1
Bocalini et al. (2009)	E: 23 C: 12	E: 69 ± 9 C: 67 ± 8	n.g. n.g.	E: 68 ± 6 C: 69 ± 7	n.g. n.g.	E: 28 ± 4 C: 27 ± 6
Bolton et al. (2012)	E: 19 C: 20	E: 60 ± 6 C: 56 ± 5	E: 13 ± 7 C: 12 ± 7	E: 64.5 ± 9.7 C: 63.6 ± 11.9	E: 160 ± 4 C: 160 ± 6	E: 25.2 ± 4.3 C: 25 ± 4.4
Brooke-Wavell et al. (2001)	E: 18 C: 21	E: 65 ± 3 C: 65 ± 3	>5	E: 68.5 ± 8.9 C: 71.4 ± 12.1	E: 163 ± 7 C: 164 ± 7	n.g. n.g.
Brooke-Wavell et al. (1997)	E: 43 C: 41	E: 65 ± 3 C: 64 ± 3	E: 15 ± 5 C: 15 ± 7	E: 67.7 ± 10.9 C: 67.9 ± 10.6	E: 162 ± 6 C: 163 ± 7	E: 25.8 ± 3.8 C: 25.6 ± 3.5
Caplan et al. (1993)*	E: 19 C: 11	E: 66 ± 1 C: 65 ± 1	E: 18 ± 2 C: 21 ± 3	E: 63.2 ± 2.5 C: 60.6 ± 2.9	E: 158 ± 2 C: 160 ± 2	E: 25.4 ± 0.9 C: 23.5 ± 0.8
Chan et al. (2004)	E: 67 C: 65	E: 54 ± 3 C: 54 ± 3	E: 5 ± 2 C: 4 ± 2	E: 55.4 ± 7.9 C: 54 ± 10.3	E: 150 ± 10 C: 150 ± 20	E: 24.1 ± 4.7 C: 23.5 ± 4.6
Chilibeck et al. (2013)	E+PI: 86 PI: 88	E+PI: 55 ± 6 PI: 56 ± 7	>1	E+PI: 73.4 ± 14.1 PI: 73.6 ± 15.9	E+PI: 163 ± 5 PI: 163 ± 6	n.g. n.g.
Chilibeck et al. (2002)*	E: 14 C: 14	E: 57 ± 2 C: 59 ± 2	E: 9 ± 2 C: 8 ± 2	E: 72 ± 4.3 C: 73.2 ± 4.8	E: 164 ± 2 C: 165 ± 1	E: 27 ± 1.7 C: 26.6 ± 1.2
Choquette et al. (2011)	E+PI: 25 PI: 26	E+PI: 58 ± 6 PI: 59 ± 6	E+PI: 8 ± 8 PI: 10 ± 8	E+PI: 75.4 ± 12.1 PI: 79.5 ± 9.2	E+PI: 161 ± 6 PI: 160 ± 6	E+PI: 29.1 ± 3.9 PI: 31 ± 2.9
Chuin et al. (2009)	E+PI: 11 PI: 7	E+PI: 65 ± 3 PI: 67 ± 4	n.g. n.g.	E+PI: 66.6 ± 8.5 PI: 64.2 ± 7.6	n.g. n.g.	E+PI: 26.5 ± 2.7 PI: 26 ± 2.6
de Matos et al. (2009)	E: 30 C: 29	E: 57 ± 5 C: 57 ± 5	10 7	E: 59.8 ± 7.6 C: 65 ± 8.3	E: 158 ± 4 C: 159 ± 8	E: 23.9 ± 3.3 C: 25.6 ± 3.1
Deng (2009)	E: 45 C: 36	E: 54 ± 4 C: 51 ± 5	E: 4 ± 3 C: 3 ± 2	E: 58.8 ± 8 C: 58.3 ± 7.5	E: 157 ± 5 C: 159 ± 5	n.g. n.g.
de Oliveira et al. (2019)	E: 17 C: 17	E: 56 ± 7 C: 54 ± 5	E: 8 ± 7 C: 9 ± 7	E: 67.4 ± 8.6 C: 64.6 ± 6.6	E: 157 ± 6 C: 154 ± 4	E: 27.2 ± 2.7 C: 27.3 ± 2.5
Duff et al. (2016)	E: 22 C: 22	E: 65 ± 5 C: 65 ± 5	n.g. n.g.	n.g. n.g.	E: 162 ± 6 C: 160 ± 7	n.g. n.g.
Ebrahim et al. (1997)	E: 81 C: 84	E: 66 ± 8 C: 68 ± 8	n.g. n.g.	n.g. n.g.	n.g. n.g.	E: 26.6 ± 4.3 C: 26.3 ± 4.8
Englund et al. (2005)	E: 24 C: 24	E: 73 ± 4 C: 73 ± 5	n.g. n.g.	E: 66.9 ± 8.7 C: 67.7 ± 8.5	E: 162 ± 6 C: 160 ± 6	E: 25.2 ± 2.7 C: 26.1 ± 3.2
Evans et al. (2007)	E+SP: 11[c] SP: 10	E+SP: 62 ± 5 SP: 63 ± 5	E+SP: 8 ± 6 SP: 8 ± 5	E+SP: 66.7 ± 13.3 SP: 67.6 ± 7.3	E+SP: 163 ± 7 SP: 161 ± 6	n.g. n.g.
Going et al. (2003)	E: 91 C: 70	E: 56 ± 5 C: 57 ± 5	>3	E: 68.9 ± 11.4 C: 67.8 ± 11.4	E: 163 ± 7 C: 163 ± 5	E: 25.8 ± 3.4 C: 25.5 ± 4
Grove and Londeree (1992)	LI: 5 HI: 5 C: 5	LI: 57 ± 4 HI: 54 ± 2 C: 56 ± 4	LI: 3 ± 2 HI: 4 ± 3 C: 4	LI: 69 ± 12.7 HI: 72.3 ± 19.2 C: 70.5 ± 10.1	n.g. n.g. n.g.	n.g. n.g. n.g.

(Continued)

TABLE 1 | Continued

References	Sample size (*n*)	Age (years)	Menopausal age (years)	Body mass (kg)	Height (cm)	BMI (kg/m^2)
Hans et al. (2002)	E: 110 C: 35	E: 68 ± 5 C: 66 ± 5	>5	E: 63 ± 7.3 C: 59.5 ± 7.5	E: 161 ± 8 C: 159 ± 8	n.g. n.g.
Hartard et al. (1996)	E: 18 C: 16	E: 64 ± 6 C: 67 ± 10	>2	E: 67 ± 7.7 C: 63.8 ± 11.2	E: 162 ± 7 C: 158 ± 6	n.g. n.g.
Hatori et al. (1993)	E: 23[d] C: 12	H: 56 ± 4 M: 58 ± 5 C: 58 ± 8	H: 7 ± 5 M: 6 ± 4 C: 9 ± 8	H: 54 ± 5 M: 53.4 ± 6.8 C: 53.9 ± 6	H: 151 ± 3 M: 151 ± 5 C: 151 ± 5	H: 23.3 ± 2.3 M: 23.5 ± 2.4 C: 24.6 ± 3.3
Iwamoto et al. (2001)	E: 8 C: 20	E: 65 ± 5 C: 65 ± 6	E: 16 ± 6 C: 15 ± 6	E: 45.5 ± 6.5 C: 45.8 ± 4	E: 152 ± 8 C: 152 ± 6	E: 19.7 ± 1.3 C: 19.9 ± 2.1
Jessup et al. (2003)	E: 10 C: 10	E: 69 ± 3 C: 69 ± 4	E: 24 ± 11 C: 22 ± 11	E: 78 ± 9.2 C: 84.2 ± 17.7	n.g. n.g.	n.g. n.g.
Karakiriou et al. (2012)*	E: 10 C: 9	E: 53 ± 1 C: 53 ± 1	E: 5 ± 1 C: 3 ± 1	E: 71.2 ± 2.8 C: 75.4 ± 2	E:159 ± 1 C:157 ± 2	E: 28.1 ± 1.1 C: 30.4 ± 0.8
Kemmler et al. (2013)	E: 43 C: 42	E: 52 ± 2 C: 52 ± 3	E: 2 ± 1 C: 2 ± 1	E: 69.5 ± 9.6 C: 70.9 ± 16.8	E: 165 ± 5 C: 165 ± 6	n.g. n.g.
Kemmler et al. (2010)	E: 123 C: 123	E: 69 ± 4 C: 69 ± 4	n.g. n.g.	E: 68.1 ± 10.9 C: 69.5 ± 12	E: 162 ± 6 C: 160 ± 6	n.g. n.g.
Kemmler et al. (2004)	E: 86 C: 51	E: 55 ± 3 C: 56 ± 3	>1	E: 67.6 ± 9.7 C: 64.8 ± 13.6	E: 164 ± 6 C: 162 ± 7	E: 25.1 ± 3.3 C: 24.7 ± 3.9
Kemmler (1999)	E-PM: 15 L-PM: 17 C: 18	EPM: 54 ± 5 LPM: 65 ± 6 C: 56 ± 8	EPM ≤ 8 LPM > 8 C >1	n.g. n.g. n.g.	n.g. n.g. n.g.	EPM: 25.5 ± 4.2 LPM: 26.2 ± 3.8 C: 27.4 ± 5.3
Kerr et al. (2001)	RE: 42 Fit: 42 C: 42	RE: 60 ± 5 Fit: 59 ± 5 C: 62 ± 6	RE: 11 ± 6 Fit: 9 ± 5 C: 12 ± 6	RE: 72.2 ± 12 Fit: 69 ± 11.4 C: 69.3 ± 14.6	RE: 163 ± 5 Fit: 165 ± 6 C: 162 ± 7	n.g. n.g. n.g.
Kerr et al. (1996)	En: 28[e] S: 28	En: 56 ± 5 S: 58 ± 4	En: 6 ± 4 S: 8 ± 3	En: 70.8 ± 10 S: 69.4 ± 11.4	En: 165 ± 6 S: 165 ± 7	n.g. n.g.
Kohrt et al. (1997) *	JRF: 15 GRF: 18 C: 15	JRF: 65 ± 1 GRF: 66 ± 1 C: 68 ± 1	n.g. n.g. n.g.	JRF: 72.6 ± 2.3 GRF: 70.9 ± 4.2 C: 71.6 ± 1.8	JRF: 164 ± 2 GRF: 163 ± 1 C: 163 ± 2	n.g. n.g. n.g.
Kohrt et al. (1995)	E: 8[f] C: 8	E: 65 ± 3 C: 66 ± 3	>10	E: 63.4 ± 11.9 C: 63.4 ± 8.1	E: 161 ± 5 C: 161 ± 5	n.g. n.g.
Korpelainen et al. (2006)	E: 84 C: 76	E: 73 ± 1 C: 73 ± 1	n.g. n.g.	E: 61.2 ± 7.9 C: 62.2 ± 9.2	E: 154 ± 5 C: 156 ± 5	E: 25.7 ± 3.4 C: 25.5 ± 3.5
Kwon et al. (2008)	E: 20 C: 20	E: 77 ± 2 C: 77 ± 3	n.g. n.g.	E: 56.4 ± 3.8 C: 58.1 ± 5.6	E: 149 ± 6 C: 152 ± 3	E: 25.9 ± 1.9 C: 25.2 ± 2.8
Lau et al. (1992)	E+PI: 15 PI: 15	E+PI: 79 PI: 75	n.g. n.g.	n.g. n.g.	n.g. n.g.	n.g. n.g.
Liu et al. (2015)	E: 50 C: 48	E: 63 ± 7 C: 62 ± 8	E: 14 ± 6 C: 13 ± 7	n.g. n.g.	E: 154 ± 4 C: 157 ± 4	n.g. n.g.
Lord et al. (1996)	E: 90 C: 89	E: 72 ± 5 C: 71 ± 5	n.g. n.g.	E: 66 ± 11.4 C: 64.7 ± 14.4	E: 157 ± 6 C:157 ± 7	n.g. n.g.
Maddalozzo et al. (2007)	E: 35 C: 34	E: 52 ± 3 C: 52 ± 3	E: 2 ± 1 C: 2 ± 1	E: 70 ± 8.7 C: 67.1 ± 12.6	n.g. n.g.	n.g. n.g.
Marques et al. (2011b)	E: 30 C: 30	E: 70 ± 5 C: 68 ± 5	n.g. n.g.	n.g. n.g.	n.g. n.g.	E: 28.4 ± 3.7 C: 28.2 ± 3.7
Marques et al. (2011c)	RE: 23 AE: 24 C: 24	RE: 67 ± 5 AE: 70 ± 5 C: 68 ± 6	n.g. n.g. n.g.	n.g. n.g. n.g.	n.g. n.g. n.g.	RE: 28.8 ± 4.6 AE: 27.5 ± 3.8 C: 28.1 ± 3.5
Martin and Notelovitz (1993)	45^{min}E: 25 30^{min}E: 27 C: 24	45^{min}E: 58 ± 7 30^{min}E: 60 ± 8 C: 57 ± 7	45^{min} E: 9 ± 9 30^{min}E: 13 ± 9 C: 8 ± 7	45^{min} E: 65.6 ± 11.9 30^{min} E: 68.9 ± 11.5 C: 72.9 ± 15.5	45^{min} E: 159 ± 5 30^{min}E: 162 ± 7 C: 162 ± 4	n.g. n.g. n.g.
Milliken et al. (2003)	E: 26 C: 30	E: 57 ± 5 C: 57 ± 5	E: 6 ± 3 C: 6 ± 3	E: 68.4 ± 10.6 C: 68.4 ± 10.6	E: 162 ± 6 C: 162 ± 6	n.g. n.g.
Moreira et al. (2014)	E: 64 C: 44	E: 59 ± 7 C: 59 ± 6	>5	E: 73 ± 15.8 C: 74 ± 12.6	E: 157 ± 6 C: 156 ± 6	n.g. n.g.

(Continued)

TABLE 1 | Continued

References	Sample size (*n*)	Age (years)	Menopausal age (years)	Body mass (kg)	Height (cm)	BMI (kg/m^2)
Nelson et al. (1994)	E: 21 C: 19	E: 61 ± 4 C: 57 ± 6	E: 12 ± 5 C: 10 ± 5	E: 64.7 ± 7.7 C: 62.2 ± 8.9	E: 163 ± 6 C: 164 ± 8	E: 24.4 ± 2.5 C: 23.1 ± 2.2
Nelson et al. (1991)*	E: 21[g] C: 20	E: 60 ± 1 C: 60 ± 1	E: 11 ± 1 C: 11 ± 1	E: 64 ± 1.4 C: 64 ± 1.4	E: 162 ± 1 C: 162 ± 1	E: 24.4 ± 0.5 E: 24.4 ± 0.5
Nichols et al. (1995)*	E: 17 C: 17	E: 68 ± 2 C: 65 ± 1	E: 18 ± 1 C: 18 ± 1	E: 68.8 ± 2.8 C: 72 ± 13.5	E: 163 ± 1 C: 164 ± 1	n.g. n.g.
Nicholson et al. (2015)	E: 28 C: 29	E: 66 ± 4 C: 66 ± 5	>5	E: 70.6 ± 9.1 C: 66.8 ± 10.7	E: 164 ± 4 C: 163 ± 5	E: 26 ± 3.2 C: 24.5 ± 2.9
Orsatti et al. (2013)	E+Pl: 20 Pl: 20	E+Pl: 56 ± 9 Pl: 55 ± 8	E+Pl: 9 ± 6 Pl: 8 ± 6	n.g. n.g.	n.g. n.g.	E+Pl: 26 ± 3 Pl: 30.4 ± 5.3
Park et al. (2008)	E: 25 C: 25	E: 68 ± 4 C: 68 ± 3	E: 18 ± 2 C: 19 ± 3	n.g. n.g.	E: 153 ± 4 C: 152 ± 4	n.g. n.g.
Prince et al. (1995)	E+Ca: 42 Ca: 42	E+Ca: 63 ± 5 Ca: 62 ± 5	E+Ca: 16 ± 5 Ca: 16 ± 6	n.g. n.g.	n.g. n.g.	n.g. n.g.
Pruitt et al. (1995)	H-int: 15 L-int: 13 C: 12	H-int: 67 L-int: 68 ± 1 C: 70 ± 4	n.g. n.g. n.g.	H-int: 64.5 ± 9.2 L-int: 61.5 ± 4.6 C: 63.8 ± 9.1	H-int: 162 ± 7 L-int: 160 ± 5 C: 160 ± 9	H-int: 24.5 ± 3.4 L-int: 23.9 ± 1.6 C: 25.1 ± 3.1
Pruitt et al. (1992)*	E: 17 C: 10	E: 54 ± 1 C: 56 ± 1	E: 3 C: 4 ± 1	E: 64.2 ± 1.9 C: 65.5 ± 2.9	E: 162 ± 1 C: 163 ± 2	n.g. n.g.
Rhodes et al. (2000)	E: 22 C: 22	E: 69 ± 3 C: 68 ± 3	n.g. n.g.	E: 68.4 ± 12 C: 61.7 ± 12.9	E: 161 ± 5 C: 159 ± 4	n.g. n.g.
Ryan et al. (1998)	E: 18 C: 18	E: 62 ± 6 C: 63 ± 6	>2	E: 79.3 ± 8 C: 83.1 ± 11.3	n.g. n.g.	E: 30.5 ± 2.8 C: 30.9 ± 3
Sakai et al. (2010)*	E: 49 C: 45	E: 68 ± 1 C: 68	n.g. n.g.	E: 51.4 ± 1.1 C: 51.7 ± 0.9	E: 151 ± 1 C: 151 ± 1	E: 22.4 ± 0.4 C: 22.6 ± 0.4
Silverman et al. (2009)	E: 46 C: 40	E: 60 ± 5 C: 58 ± 5	E: 12 ± 8 C: 11 ± 7	E: 84.6 ± 11.3 C: 87.4 ± 14.4	n.g. n.g.	E: 32.1 ± 4.2 C: 32.6 ± 4.6
Sinaki et al. (1989)	E: 34 C: 34	E: 56 ± 4 C: 56 ± 4	>0.5	E: 66.2 ± 9.3 C: 66.1 ± 10.6	E: 163 ± 6 C: 161 ± 5	n.g. n.g.
Sugiyama et al. (2002)*	E: 13[h] C: 13	E: 52 ± 1 C: 53 ± 1	E: 3 C: 2	E: 54.7 ± 3.4 C: 50.9 ± 1.7	E: 155 ± 2 C: 153 ± 1	E: 22.7 ± 1.2 C: 21.7 ± 0.7
Tartibian et al. (2011)	E: 20 C: 18	E: 61 ± 7 C: 59 ± 8	>8	E: 77.5 ± 10.4 C: 75.9 ± 17.2	E: 167 ± 8 C: 168 ± 16	E: 25.1 ± 7.1 C: 28.5 ± 3.7
Tolomio et al. (2009)	E: 81 C: 79	E: 62 ± 5 C: 64 ± 5	n.g. n.g.	E: 66 ± 10.9 C: 63 ± 9.7	E: 161 ± 10 C: 159 ± 10	n.g. n.g.
Verschueren et al. (2004)	E: 22 C: 24	E: 64 ± 4 C: 64 ± 3	E: 15 ± 6 C: 15 ± 7	E: 70.5 ± 9.6 C: 68.6 ± 14.5	E: 161 ± 6 C: 160 ± 6	E: 27.4 ± 3.5 C: 26.5 ± 5.8
Wang et al. (2015)	TC: 40 TC+RT: 40 C: 39	TC: 58 ± 3 TCRT: 58 ± 3 C: 58 ± 3	>0.5	TC: 60.5 ± 8.3 TCRT: 60 ± 6 C: 60.5 ± 8.3	TC: 159 ± 5 TCRT: 161 ± 4 C: 159 ± 5	n.g. n.g. n.g.
Woo et al. (2007)	TC: 30 RE: 30 C: 30	TC: 70 ± 3 RE: 70 ± 3 C: 69 ± 3	n.g. n.g. n.g.	n.g. n.g. n.g.	n.g. n.g. n.g.	TC: 24.4 ± 4.3 RE: 24.6 ± 4 C: 24.9 ± 3
Wu et al. (2006)	E+Pl: 34 Pl: 34	E+Pl: 55 ± 3 Pl: 55 ± 3	E+Pl: 4 ± 2 Pl: 4 ± 2	E+Pl: 54.1 ± 7.3 Pl: 51.4 ± 7.1	E+Pl: 155 ± 6 Pl: 157 ± 6	E+Pl: 22.4 ± 2.9 Pl: 20.9 ± 2.2
Yamazaki et al. (2004)*	E: 32 C: 18	E: 64 ± 3 C: 66 ± 3	E: 17 ± 2 C: 15 ± 2	E: 51.2 ± 1.4 C: 50.1 ± 1.6	E: 155 ± 1 C: 156 ± 1	E: 21.2 ± 0.7 C: 21.1 ± 1.1

[a] *According to the text, 63 women were randomized equally.*

[b] *It is not stated, seven drop out belong to which groups.*

[c] *It is not stated, nine drop out belong to which groups.*

[d] *It is not clear to which exercise groups two persons who failed to complete the program belong.*

[e] *One side of body is considered as control and the other side as intervention.*

[f] *No data concerning participants/group; we assumed an equal allocation.*

[g] *Exercise with or without 831 mg/d Ca vs. sedentary control with or without 831 mg/d Ca.*

[h] *According to the baseline table in the article, there are 13 PMW in the exercise group, however, the text said that six persons in exercise groups were excluded due to low compliance with exercise but it is not clear whether these participants are in the pre- or post-menopausal group.*

*AE, aerobic exercise; C, control; Ca,calcium; E, exercise; En, Endurance; EPM, early post-menopausal; Fit, fitness; GRF, ground-reaction forces (i.e., walking); H, High; HI, high impact; H-int, high intensity; HL, high load; HR, high repetition; JRF, joint-reaction forces; LI, low impact; L-int, Low intensity; LPM, late post-menopausal; M, Moderate; n.g., not given; Pl, Placebo; RE, resistance exercise; S, Strength; SP, soy protein; TCRT, Tai Chi resistance training; TC, Tai Chi; All values are presented as mean ± SD, otherwise it is stated; *Numbers are presented as mean ± SE. Eligibility criteria with respect to post-menopausal age were utilized, if the studies provided no information regarding this item.*

TABLE 2 | Exercise prescription characteristics of included studies ($n = 75$).

References	Status	Length months	PR-INT	Main part of exercise	SiSp	Volume (min/w), Supervision (Attendance)	Exercise/strain composition	Summary of main part of exercise
Adami et al. (1999)	Healthy 16 ± 7 y post Sedentary	6	No	DRT (focus on forearm sites); volleyball in a sitting/standing position	No Yes	2 × 95–110, SJE (83%) 7 × 30 HE (n.g.)	SJE: 15–30 min warm up (walking), 70 min press-up, volleyball, 10 min DRT for the forearm with a 500 g weight. Number of reps (10–25)/min increased progressively. HE: Repeat all exercise	L-Intensity AET and RT (forearm site)
Basat et al. (2013)	Osteopenia 6 ± 4 y post No-BSE	6	No	DRT (focus on lower body with few trunk exercises)	Yes Yes	3 × 60, S-JE (>60%)	15 min warm up (walking, cycling), 30–40 min RT: ≥9 exercises, one set, 10 reps (more details n.g.)	L/M-intensity DRT
		6	No	Rope skipping	No Yes	7 × 35, S-JE (>60%)	15 min warm up (walking, cycling). Maximum 50 jumps/session (more details n.g.)	M-Impact jumping
Bassey et al. (1998)	Healthy 7 ± 4 y post No vigorous Ex > 1 h/w	12	No	Jumping: counter-movement jumps (CMJ)	No Yes	5 × 10, HE 1 × 10, S-JE (91%)	50 CMJ barefoot with both legs, five sets × 10 reps with ground reaction forces (GRF): 4× body mass	H-Impact jumping
Bassey and Ramsdale (1995)	Healthy 7 ± 4 y post No-BSE	12	No	Heel-drops, jumping, skipping	No Yes	1 × ?, S-JE 7 × ?, HE (84%)	HE: 50 heel-drops barefoot on a thinly covered floor with knee and hip extended. S-JE: jumping and skipping (More details n.g.)	H-Impact heel drop
Bello et al. (2014)	Healthy 61 ± 6 y No-M/H intensity Ex >20 min or 2/w	8	No	Walking; DRT (all main muscle groups); aquatic exercise (RT main muscle groups)	Yes Yes	3 × 40-?, S-JE (85%)	40 min walking 1 × w, WB-circuit training 1 × w with easy loads: six exercises, three sets, 15–20 reps. Aquatic exercise 1 × w: four exercise, three sets, 15–20 reps; all at RPE 12–15 of Borg CR 20. 1× w each type of exercise	L-Intensity WB AET and L-Intensity DRT
Bemben et al. (2010)	Healthy >5 y post No-RT	8	No	DRT (all main muscle groups) with machines	Yes Yes	3× ≈60, S-JE (90%)	5 min warm up (walking, cycling), eight exercises, three sets, 10 reps, 80% 1RM + dumbbell wrist curls and seated abdominal flexion L/M intensity	H-Intensity DRT
Bemben et al. (2000)	Healthy 3 ± 1 y post No-RT	6	Yes	DRT (all main muscle groups) with machines	Yes Yes	3 × 60, S-JE (87%)	DRT:45 min, 8 exercises, three sets, eight reps, 80% 1RM	H-Intensity DRT
		6	Yes	DRT (all main muscle groups) with machines	Yes Yes	3 × 60, S-JE (93%)	DRT: 45 min, eight exercises, three sets, 16 reps, 40% 1RM	L-Intensity DRT
Bergstrom et al. (2008)	Osteopenia (forearm fractures) 59 ± 4 y No-BSE	12	Yes	DRT (all main muscle groups); AET; walking	Yes Yes	1–2 × 60, S-JE 3 × 30, HE HT and S-JE (95%)	S-JE: 25 min DRT, 25 min WB-AET (more details n.g.) HE: fast walking (more details n.g.)	L-Intensity AET and ?-Intensity DRT
Bloomfield et al. (1993)	Healthy 11 ± 3 y post Sedentary	8	Yes	Cycle ergometer	No No	3 × 50, S-JE (82%)	15 min warm up [flexibility and calisthenics (more details n.g.)], 30 min cycling at 60–80% HRmax, 5 min walking (cool down)	H-Intensity Non-WB AET
Bocalini et al. (2009)	Healthy >8 y post Sedentary	6	Yes	DRT (all main muscle groups)	Yes Yes	3 × 60, S-JE (>90%)	10 min warm up (low impact running), 12 exercises, three sets, 10 reps, 85% 1RM with focus on eccentric exercises, 1 min rest (alternate upper and lower body exercises) between ex	H-Intensity DRT
Bolton et al. (2012)	Osteopenia 13 ± 7 y post No-BSE	12	Yes	DRT (muscle groups n.g.: "loading the proximal femur"); jumping	No Yes	3 × 60, S-JE 1/w (88%) Daily HT	S-JE: 40 min (?) exercises, two sets, eight reps, 80% 1RM with slow velocity, one set with reduced load and high velocity (12 rep). HT: Daily three sets, 10 reps of jumps (more details n.g.)	M/H-Impact and H-Intensity DRT
Brooke-Wavell et al. (2001)	Healthy >5 y post Sedentary	12	No	Brisk walking	No Yes	>3 × >20 (140 min/w), non-supervised (>90%)	4–5 × 25–35 min/d ≈ 70% HRmax	M-Intensity WB-AET
Brooke-Wavell et al. (1997)	Healthy 15 ± 6 y post Sedentary	12	No	Brisk walking	No Yes	140 min/w, Non-supervised (100%)	20–50 min long for each walk, ≈ 70% HRmax	M-Intensity WB-AET
Caplan et al. (1993)	Healthy 18 ± 8 y post n.g.	24	No	Aerobic dance, ball games; DRT: floor exercises (more details n.g.)	? Yes	2 × 60, S-JE (n.g.) ≥1 × 20–30, HT (n.g.)	20–25 min AET, 10 min ball games (more details n.g.) 20–30 min DRT (more details n.g.)	L-Impact, ?-Intensity WB-AET and ?-Intensity DRT
Chan et al. (2004)	Healthy 5 ± 2 y post No >0.5 h/w	12	No	Tai Chi: Yang Style [all main muscle groups (more details n.g.)]	? Yes	5 × 50, S-JE (≈84%)	Slow, smooth movements with constant velocity	Tai Chi (Yang Style)

(Continued)

TABLE 2 | Continued

References	Status	Length months	PR-INT	Main part of exercise	SiSp	Volume (min/w), Supervision (Attendance)	Exercise/strain composition	Summary of main part of exercise
Chilibeck et al. (2013)	Healthy >1 y post No-BSE	24	Yes	Walking; DRT (all main muscle groups) on machines	Yes Yes	2 × n.g., S-JE 4 × 20–30, HT and S-JE (77%)	S-JE: 15 exercises, two sets, eight reps, 80% 1RM HT and S-JE: walking at 70% HRmax	M-Intensity WB-AET and H-Intensity DRT
Chilibeck et al. (2002)	Healthy 9 ± 2 y post No-vigorous Ex	12	Yes	DRT (all main muscle groups) on machines	Yes Yes	3 × ?, S-JE (78%)	12 exercises, two sets, 8–10 reps, ≈70% 1RM	H-Intensity DRT
Choquette et al. (2011)	Healthy 8 ± 8 y post Sedentary	6	Yes	Treadmill and cycling; DRT (all main muscle groups) on machines and with free weights	Yes Yes	3 × 60, S-JE (≥85%)	AET: 30 min at 40–85% HRmax; after 3 months H-intensity intervals of 4 × 4 min ≥90% HRmax, 3 min rest at 50–65% HRmax. RT: 30 min, ?exercise, one set, 12–15 rep increased to four sets 4–6 reps, at 60–85%1RM	H-Intensity AET and H-Intensity DRT
Chuin et al. (2009)	Healthy >8 y post n.g.	6	Yes	DRT (most main muscle groups) on machines	Yes Yes	3 × 60, S-JE (>90%)	15 min warm up (treadmill/cycle ergometer), DRT: 45 min, eight exercises, three sets, eight reps at 80% 1RM, rest between sets 90–120 s, 1RM-test each 4 weeks	H-Intensity DRT
de Matos et al. (2009)	≥Osteopenia 10 y post n.g.	12	Yes	DRT (all main muscle groups) on machines or free weights; AET (Bike, Treadmill)	Yes Yes	3 × 45–65, n.g. (presumably S-JE) (n.g.)	WB-/non-WB-AET (Bike, treadmill, Stepper): 5–20 min (RPE 4–6 on Borg CR 10). DRT: 30–40 min, nine exercises,? sets, 10–15 reps, ? 1RM, TUT: three s conc-3 s eccentric; 1 min rest between sets and exercise	L/M-Intensity DRT and M-Intensity AET
Deng (2009)	Healthy 4 ± 3 y post No-BSE	12	Yes	Brisk walking, stepping, jumping; DRT (all main muscle groups) on machines with free weights	Yes Yes	2 × 60, S-JE 3–5 × 60, HE (82%)	S-EJ: 45 min DRT, nine exercises, 2–5 sets, 12–40 reps, at 50–60% 1RM, self-selected rest (more details n.g.). HE: 30 min walking, at 50–80% HRmax, 15 min step routine, 50–300 jumps from a 4 inch bench	H-Impact, H-Intensity WB-AET, M-Intensity DRT
de Oliveira et al. (2019)	Healthy 8 ± 7 y post Sedentary	6	Yes	Pilates (all main muscle groups) on machines	Yes Yes	3 × 60, S-JE (93%)	21 exercises (strengthening and flexibility), one set, 10 reps, 1 min rest between exercises, 5–6 at Borg CR10	M-Intensity DRT
Duff et al. (2016)	Healthy >8 y post No-RT	9	Yes	DRT (all main muscle groups) on machines and with free weights	Yes Yes	3 × ?, S-JE (84%)	12 exercises, two sets, 8–12 reps to muscular fatigue, ? 1RM (more details n.g.)	?-Intensity DRT
Ebrahim et al. (1997)	Healthy (upper limb fractures) 66 ± 8 y No limit	24	No	Brisk walking	No Yes	3 × 40, HE (100%)	40 min walking, "faster than usual, but not so fast as to be uncomfortable"	L-Intensity WB-AET
Englund et al. (2005)	Healthy >8 y post n.g.	12	Yes	Walking/jogging; DRT (all main muscle groups)	Yes Yes	2 × 50, S-JE (67%)	WB-AET: 10 min warm up, 15 min walking/jogging. DRT: 12 min, two sets, 8–12 reps., ? 1RM (more details n.g.)	L/M-Intensity WB-AET and ?-Intensity DRT
Evans et al. (2007)	Healthy ≈8 ± 6 y post n.g.	9	Yes	Walking/running, rowing, stair-climbing (machines)	Yes Yes	3 × 45, S-JE (n.g.)	WB and Non-WB AET (machines) at 55–80% VO_2peak. Rest by changing exercise mode	H-Intensity WB-AET
Going et al. (2003)	Healthy 3–11 y post No-RT, <120 min Ex	12	Yes	Walking, Jogging, skipping, hopping, stepping with weighted vests; DRT (all main muscle groups) on machines with free weights	Yes Yes	3 × ≈60, S-JE (72%)	10 min warm up (walking), 20–25 min WB-AET at 60% HRmax, 120–300 stair/steps with 5–13 kg weighted vest. DRT: 7 exercises, two sets, 6–8 reps 70–80% 1 RM	L-Intensity WB-AET and H-Intensity DRT
Grove and Londeree (1992)	Healthy 4 ± 3 y post Sedentary	12	No	Jumping variations, heel drops (GRF≥2x body mass)	No Yes	3 × 60, S-JE (83%)	20 min of high impact exercises. 15 min cool down (RT with abdominal and leg adduction/abduction exercises)	H-Impact intensity WB-AET
		12	No	Walking, charleston, heel jacks (GRF<1.5 × body mass)	No Yes	3 × 60, S-JE (80%)	20 min of low impact exercises. 15 min cool down (RT with abdominal and leg adduction/abduction exercises)	L-Impact intensity WB-AET
Hans et al. (2002)	≥Osteopenia >5 y post n.g.	24	Yes (?)	Heel-drops: barefoot on a force measuring platform (osteocare)	No Yes	5 × 3-5, HE (65%)	Impact loading: strength or height 25–50% above the estimated resting force, daily 120 correct force impacts	L-Impact intensity WB-AET
Hartard et al. (1996)	Osteopenia >2 y post <1 h/w, No-BSE	6	Yes	DRT (all main muscle groups) on machines	Yes Yes	2 × ?, S-JE (>83%)	14 exercises, 1–2 sets, 8–12 reps, 70% 1RM, TUT: concentric: 3–4 s-eccentric 3–4s. ≥2 min rest between sets	M-Intensity DRT
Hatori et al. (1993)	Healthy ≈7 ± 5 y post n.g.	7	No	Walking below the anaerobic threshold at "flat grass covered ground"	No Yes	3 × 30, n.g. (n.g.)	30 min walking at 90% anaerobic threshold HR (6.2 km/h)	L/M-Intensity WB-AET

(Continued)

TABLE 2 | Continued

References	Status	Length months	PR-INT	Main part of exercise	SiSp	Volume (min/w), Supervision (Attendance)	Exercise/strain composition	Summary of main part of exercise
		7	No	Walking above the anaerobic threshold at "flat grass covered ground"	No Yes	3 × 30, n.g. (n.g.)	30 min walking at 110% anaerobic threshold HR (7.2 km/h)	H-Intensity WB-AET
Iwamoto et al. (2001)	Osteoporosis 16 ± 6 y post Sedentary	24	Yes	Walking; DRT ("Gymnastics": lower limbs and trunk exercises)	Yes Yes	Daily (walking) × ?, HE 2× daily RTx?,HE (n.g.)	Additionally (to basic activity walking) ≈3,000 steps/d, RT: ≥ 4 exercises, two sets, 15 reps, ?% 1RM	L-Intensity WB-AET and ?-Intensity DRT
Jessup et al. (2003)	Healthy >8 y post Sedentary	8	Yes	Walking, stairclimbing; DRT (most main muscle groups) on machines	Yes Yes	3 × 60–90, S-JE (n.g.)	DRT: 20–35 min, eight exercises, ? sets, 8–10 reps, 50–75% 1RM. WB-AET: 30–45 min with weighted vest (increased up to 10% body-mass)	?-Intensity WB-AE and M-Intensity DRT
Karakiriou et al. (2012)	Osteopenia 5 ± 2 y post Sedentary	6	No	Step aerobic exercise; DRT (all main muscle groups)	Yes Yes	2 × ? RT, S-JE 1 × 45 min AET (80%)	15 min warm up (walking on treadmill/cycling ergometer and jumping). Abdominal and back extension exercises (one exercise for each muscle group, 2–4 sets of 16 repetitions). RT:11 exercises, 2–3 sets, 10–12 reps at 70% 1RM, 30 s rest between exercises, 3 min between sets. AET: 20 min, nine exercise, two circuits of 40 s; rest: 20 s between exercises, 2 min between circuits, 70–85% HRmax	M/H-Impact WB-AET and H-Intensity DRT
Kemmler et al. (2013)	Healthy 2 ± 1 y post No-BSE	12	Yes	Block periodized AET, jumping; isometric and DRT (all main muscle groups) exercise on machines with free weight, body mass	Yes Yes	3 × 45–60, S-JE (67%)	Block I: 1 × 45 min/w H-Impact aerobic 75–85% HRmax, 2 × 20 min/w aerobic 75–85% HRmax, 4 × 15–20 jumps, 90 s rest. RT: 15 min, 8–12 floor exercises (trunk, hip, legs), 1–2 sets, rep?, 30 s rest. RT: 20 min, eight exercises, two sets, 8–9 rep, 45 s rest up, TUT: 2s concentric, 2 s eccentric. to 80% 1RM	H-Impact; H-Intensity WB-AET and H-Intensity DRT
Kemmler et al. (2010)	Healthy >8 y post Sedentary	18	Yes	Aerobic dance; DRT (all main muscle groups)	Yes Yes	2 × 60, S-JE (76%) 2 × 20, HE (42%)	AET: 20 min at 70–85% HRmax. RT: 10–15 exercises, 1–3 sets of 6–10 s maximum isometric contractions, 20–30 s rest, 3 upper body exercises, 2–3 sets 10–15 reps, TUT: 2s concentric, 2s eccentric at 65–70% 1RM; three lower extremity exercises, two sets eight reps, 1 min rest at 80% 1RM. HT: RT 1–2 sets, 6–8 exercise, 10–15 rep. 2–3 belt exercises, two sets, 10–15 rep	H-Intensity WB-AET and H-Intensity DRT
Kemmler et al. (2004)	Osteopenia 1–8 y post No-BSE	26	Yes	Fast walking and running, jumping; DRT (all main muscle groups) on machines with free weight, body mass	Yes Yes	2 × 60–70, S-JE (79%) 2 × 25, HT (61%)	AET: 20 min at 65–85% HRmax. Jumping started after 5–6 months with 4x 15 multi-lateral jumps. DRT: 30–40 min, 1/w. The first 6 month: 13 ex, two sets, 20–12 rep, TUT: 2 s concentric, 2 s eccentric at 50–65% RM, 90 s rest between sets and exercises. Then, 12 w blocks of H-intensity at 70–90% 1RM interleaved by 4 w at 55–79% 1RM. Isometric RT: 30–40 min, 1/w, 12–15 exercises (trunk and femur), 2–4 sets, 15–20 rep, 15–20 s rest. HT: rope skipping (three set, 20 rep), RT	H-Impact, H-Intensity WB-AET, and H-Intensity DRT
Kemmler (1999)	Healthy 1–15 y post No-BSE	9	Yes	Running, gaming, jumping; DRT (all main muscle groups)	Yes Yes	2 × 90, S-JE (82%) 2 × 35, HT (59%)	AET: 25 min at 70–80% HRmax. RT: 65 min, 12–15 exercises, 2–4 sets of 8 s maximum isometric contractions; six trunk, upper back, lower extremity exercises, 20–25 reps at 60–65% 1 RM. HT: resistance exercises	H-Impact, H-Intensity WB-AET and M-Intensity DRT
Kerr et al. (2001)	Healthy ≈10 ± 6 y post <2 h/w	24	Yes	DRT (all main muscle groups)	Yes Yes	3 × 60, S-JE (74%)	≈30 min brisk walking and stretching, RT: 30 min, nine exercises, three sets at 8 RM (≈75–80% 1RM)	H-Intensity DRT
		24	No	DRT (all main muscle groups); Stationary cycling	Yes Yes	3 × 60, S-JE (77%)	≈30 min brisk walking and stretching. RT: 30 min, nine exercises, three set, eight rep, 40 s/exercise with "minimal load"; 10 s rest between the exercises (more details n.g.). Stationary cycling 40 s, HR < 150 beats/min	L-Intensity DRT and Non-WB-AET

(Continued)

TABLE 2 | Continued

References	Status	Length months	PR-INT	Main part of exercise	SiSp	Volume (min/w), Supervision (Attendance)	Exercise/strain composition	Summary of main part of exercise
Kerr et al. (1996)	Healthy ≈7 ± 4 y post No-RT, no racquet sports, No-Ex > 3 h/w	12	Yes	Unilateral DRT (all main muscle groups, randomized allocation of the left side or right side to exercise or control group) on machines or free weights	Yes Yes	3 × 45–60, S-JE (89%)	13 exercises, three sets at 20 RM, 3–5 rep (≈60–65% 1RM), 2–3 min rest between sets	M-Intensity DRT
		12	Yes	Unilateral DRT (see above)	Yes Yes	3 × 20–30, S-JE (87%)	13 exercises, three sets at 8 RM, 3–5 rep (≈75–80% 1RM), 2–3 min rest between sets	H-Intensity DRT
Kohrt et al. (1997)	Healthy >8 y post Sedentary	11	Yes	Walking, jogging, stair climbing	No Yes	3–5 × 30–45, n.g. (pre-sumably S-JE) (≈70%)	First 2 months flexibility, 9 months WB at 60–85% HRmax	H-Intensity WB-AET
		11	Yes	DRT (all main muscle groups) with free weights and on machines; rowing	Yes Yes	3–5 × 40–60, n.g. (presumably S-JE) (≈70%)	First 2 months flexibility, DRT: 2/w, ≈20–30 min, eight exercises, 2–3 sets, 8–12 reps "to fatigue" (≈70–80% 1RM). Rowing: 3/w,15–30 min, 2–3 sets × 10 min at 60–85% HRmax	H-Intensity DRT and Non WB-AET
Kohrt et al. (1995)	Healthy >8 y post Sedentary	11	Yes	Walking, jogging, stair climbing	No Yes	3–5 × 45, HE (≈70%)	First 2 months flexibility, 9 months WB: 5–10 min warm up (treadmill 60–70% HRmax), 30 min WB at 65–85% HRmax	H-Intensity WB-AET
Korpelainen et al. (2006)	Osteopenia >8 y post n.g.	30	Yes	Jumping, walking/jogging, dancing, stamping, chair climbing	Yes Yes	1 × 60, S-JE 7 × 20, HE (≈75%)	S-JE: 45 min WB-AET. The first six months: 1× 60 min S-JE and daily × 20 min HE. The second 6 months: HE: daily × 20 min HE applying the same exercise to S-JE	M/H-Impact and H-Intensity WB-AET
Kwon et al. (2008)	Healthy >8 y post No-Ex>2/w	6	Yes RT?	Aerobic dance; DRT (six upper and lower body exercises) with free weights	Yes Yes	3 × 80, n.g. (presumably S-JE) (n.g.)	30 min AET at 40–75% HRmax, 30 min DRT of 6 exercises, 7 sets, 3–10 reps to voluntary fatigue (i.e., 75% 1RM)	M-Intensity WB-AET and M/H-Intensity DRT
Lau et al. (1992)	Healthy >8 y post n.g.	10	No	Stepping up and down, Upper trunk movements	Yes Yes	4 × ≈20–25, S-JE (n.g.)	100 steps on a 23 cm block 15 min upper trunk movements (?) in a standing position with sub-maximum effort (more details n.g.)	M-Intensity WB-AET
Liu et al. (2015)	Osteoporosis 14 ± 6 y post n.g.	12	No	Tai-Chi	No Yes	3 × daily ≈3–5, HE (96%)	Eight exercise brocade, seven rep (raising slowly the arms coming on the toes stretching the back and go back on the heel with arms hanging down)	Tai-Chi
Lord et al. (1996)	Healthy >8 y post No equal intensity with the intervention	12	No	Conditioning period: Brisk walking, multilateral stepping, lunges, heel rises; DRT (all main muscle groups) using owns body mass	Yes Yes	2 × 60, S-JE (73%)	5 min warm up (paced walking), conditioning period 35–40 min: AET and guided functional gymnastics for all main muscle groups (sets?, reps?, intensity?)	L/M-Intensity WB-AET and ?-Intensity DRT
Maddalozzo et al. (2007)	Healthy 1–3 y post n.g.	12	Yes	DRT (back squat, deadlifts) with free weights	Yes Yes	2 × 50, S-JE (85%)	15–20 min warm up (exercise focusing on posture, muscle engagement, abdominal strength, flexibility) two sets, 10–12 reps, 50% 1RM. Main part: 20–25 min, two exercises, three sets, 8–12 reps, 60 s rest between sets at 60–75% 1RM, TUT: 1–2 s concentric, 2–3 s eccentric	M-Intensity DRT
Marques et al. (2011b)	Healthy >8 y post Sedentary	8	Yes	Marching, bench stepping, heel-drops; DRT (most main muscle groups) with weighted vests, elastic bands, free weights	Yes Yes	2 × 60, S-JE (72%)	15 min WB-AET with Peak-GRF up to 2.7× body mass and high strain frequency (120–125 beats/min), 10 min for ≥7 muscle endurance exercises, 1–3 sets, 8–15 reps, 71RM (more details n.g.), 10 min balance and dynamic exercise (walking, playing with ball, rope, sticks, etc.), 10 min agility training (coordination, balance, ball games, dance)	M/H-Intensity WB-AET and L/M-Intensity DRT
Marques et al. (2011c)	Healthy >8 y post Sedentary	8	Yes	Walking, stepping, skipping, jogging, dancing	Yes Yes	3 × 60, S-JE (78%)	Only the first 6 w 10 min DRT (lower body). 35–40 min of WB-AET (50–85% HRR) with Peak-GRF up to 2.7 × body mass with up to 120 beats/min	H-Intensity WB-AET
		8	Yes	DRT (all main muscle groups) on machines	Yes Yes	3 × 60, S-JE (78%)	8–10 min warm up (cycling/rowing ergometer) at low intensity. 30–40 min DRT, 8 exercises, two sets, 15–6 reps, 50–80% 1RM with variable TUT (3-6s/rep.), 120 s rest between sets, 5–10 min cool down (walking and stretching)	H-Intensity DRT

(Continued)

TABLE 2 | Continued

References	Status	Length months	PR-INT	Main part of exercise	SiSp	Volume (min/w), Supervision (Attendance)	Exercise/strain composition	Summary of main part of exercise
Martin and Notelovitz (1993)	Healthy ≈11 ± 9 y post No-BSA	12	Yes	Brisk walking on treadmill	No Yes	3 × 36–40, n.g. (presumably S-JE) (79%)	30 min brisk walking (4–6.2 km/h at 3–7% incline) at 70–85% HRmax	H-intensity WB-AET
		12	Yes	Brisk walking on treadmill	No Yes	3 × 51–55, n.g. (presumably S-JE) (82%)	45 min brisk walking (4–6.2 km/h at 3–7% incline) at 70–85% HRmax	H-intensity WB-AET
Milliken et al. (2003)	Healthy 6 ± 3 y post <2 h/w	12	Yes	Walking, skipping, multilateral stepping, jumping with weighted vests; DRT (all main muscle groups) with free weights, on machines; functional gymnastics	Yes Yes	3 × 75, S-JE (n.g.)	20 min WB-AET at 50–70% HRmax. 35 min DRT: 8 exercises, two sets, 6–8 reps, 70–80% 1 RM. Functional gymnastics for shoulder and abdominals using elastic bands and physio-balls	M-impact, M-intensity WB-AET, H-intensity DRT
Moreira et al. (2014)	Healthy >5 y post Sedentary	6	Yes	Aquatic exercise (RT and AET in 1.1–1.3 m water depth) without equipment	Yes Yes	3 × 50–60, S-JE (66%)	2–5 sets of 30–10 s of four upper and lower body exercise with maximum effort and movement speed (full ROM), 1–1:40 min rest, 16–9 min at 55–90% HRmax	H-intensity aquatic RT and AET
Nelson et al. (1994)	Healthy (6 women with 1 spine fracture) 12 ± 5 y post Sedentary	12	Yes	DRT (most main muscle groups) on machines	Yes Yes	2 × 55, S-JE (88%)	45 min, five exercises, three sets, eight reps, 50–80% 1RM, TUT-6–9 s/rep, 3 s rest between reps, 90–120 s rest between sets	H-intensity DRT
Nelson et al. (1991)	Healthy 11 ± 1 y post Sedentary	12	No	Walking with weighted vest	No Yes	4 × 50, S-JE (90%)	Walking with a 3.1 kg weighted vest at 75–80% HRmax	H-intensity WB-AET
Nichols et al. (1995)	Healthy >8 y post ≥3 × 30min/w	12	Yes	DRT (all main muscle groups) on machines	Yes Yes	3 × ≈45–60, S-JE (82%)	5 min warm up (walking), 8 exercises, 1–3 sets, 10–12 reps, 50–80% 1RM; 30–60s rest between exercises, 60 s rest between sets	H-intensity DRT
Nicholson et al. (2015)	Healthy >5 y post No-RT	6	Yes	DRT (all main muscle groups): "Body Pump Release 83" (i.e., barbell exercises)	Yes Yes	2 × 50, S-JE (89%)	10 × up to 6 min blocks of exercises for all main muscle groups (21 exercises in total); up to 108 reps (squats), ≤30% 1RM	very L-intensity DRT
Orsatti et al. (2013)	Healthy 8 ± 6 y post Sedentary	9	Yes	DRT (all main muscle groups) with free weights and on machines	Yes Yes	3 × 50–60, S-JE (n.g.)	Eight exercises three sets, 8–15 reps at 40–80% 1RM, three sets—20–30 reps for trunk flexion and calf raises, 1–2 min rest between sets	H-intensity DRT
Park et al. (2008)	Healthy >8 y post ≤7 h/w M-Ex	12	No	WB-AET; RT (more details n.g.)	? Yes	3 × 60, n.g. (n.g.)	10 min RT, 23 min of WB exercise at 65–70% HRmax (more details n.g.)	M-intensity WB-AET and ?-intensity RT
Prince et al. (1995)	Healthy >8 y post ≤2 h/w Ex	24	No	WB-AET (more details n.g.)	No Yes	4 × 60, 2 × S-JE/2 × HE (39%)	4 × WB exercise (including 2 × walking) at 60% HRmax (more details n.g.)	L-intensity WB-AET
Pruitt et al. (1995)	Healthy >8 y post No-RT	12	Yes	DRT (all main muscle groups) on machines	Yes Yes	3 × 55–65, S-JE (81%)	50–55 min, 10 exercises, one warm up set, 14 reps, at 40% 1 RM, two sets, seven reps, 80% 1RM	H-intensity DRT
	Healthy >8 y post No-RT	12	Yes	DRT (all main muscle groups) on machines	Yes Yes	3 × 55–65, S-JE (77%)	50–55 min, 10 exercises, three sets, 14 reps, at 40% 1RM	L-intensity DRT
Pruitt et al. (1992)	Healthy 3 ± 1 y post No-BSE	9	Yes	DRT (all main muscle groups) with free weights and on machines	Yes Yes	3 × 60, S-JE (83%)	40 min, 11 exercises, one set, at 10–12 RM for upper body and 10–15 RM for lower body (more details n.g.)	H-intensity DRT
Rhodes et al. (2000)	Healthy >8 y post Sedentary	12	Yes	DRT (all main muscle groups) on machines	Yes Yes	3 × 60, S-JE (85%)	10 min warm up (cycle ergometer), DRT: 40 min, ≥6 exercises, three set, eight reps, 75% 1RM, TUT: 2–3 s concentric–3–4 s eccentric movement/rep applied in a circuit mode	H-intensity DRT
Ryan et al. (1998)	Healthy >2 y post Sedentary	6	Yes	Walking, jogging on treadmill	No Yes	3 × 55, S-E (>90%)	Up to (4th month) 35 min walking/jogging at 50–70% VO_2max, 10 min cool down (cycle ergometer). Energy-intake restriction of 250–350 kcal/d (weight loss study).	H-intensity WB-AET
Sakai et al. (2010)	Healthy >8 y post n.g.	6	No	Unilateral standing on one leg	No Yes	7 × 2, HE (≥70%)	Three sets (early, at noon, in the evening) of unilateral standing for 1 min on each leg with eyes open	WB-AET and Balance

(Continued)

TABLE 2 | Continued

References	Status	Length months	PR-INT	Main part of exercise	SiSp	Volume (min/w), Supervision (Attendance)	Exercise/strain composition	Summary of main part of exercise
Silverman et al. (2009)	Healthy 12 ± 8 y post Sedentary	6	No	Walking	No Yes	3 × 45–60, S-JE >1 session(78%)	walking at 50–75% HRmax, energy-intake restriction of 250–350 kcal/d (weight loss study)	M-Intensity WB-AET
Sinaki et al. (1989)	Healthy >0.5 y post n.g.	24	Yes	DRT (back strengthening exercise in a prone position using a back pack; ≈hyperextensions) with free weights	Yes No	5 × ?, HE (n.g.)	One back strengthening exercise, one set, 10 reps, with a weight equivalent to 30% of the maximum isometric back muscle strength in pounds (maximum 23 kg)	L/M-Intensity DRT
Sugiyama et al. (2002)	Healthy 3 y post n.g.	6	No	Rope skipping (more details n.g.)	No Yes	2–3 × ?, HE (82%)	100 jump/session (more details n.g.)	M/H-Impact jumping
Tartibian et al. (2011)	Healthy >8 y post Sedentary	6	Yes	Walking/jogging on treadmill	No Yes	3–6 × 25–45, S-JE (95%)	First 12 weeks: 3–4 × 25–30 min at 45–55% HRmax, second 12 weeks: 4–6 × 40–45 min at 55–65% HRmax	L/M-Intensity WB-AET
Tolomio et al. (2009)	≥Osteopenia 2–22 y post n.g.	11	No	DRT (joint mobility, elastic bands, balls); aquatic exercise (more details n.g.)	? Yes	3 × 60, S-JE and 1 × HE (n.g.)	The first 11 w only in gym, then two times in gym and once in water. 15 min warm up (brisk walking, stretching), 2 × 30 min/week RT, 1 × 30 min/week water gymnastics (more details n.g.), two periods (6 and 10 w) training at home (more details n.g.)	?-Intensity DRT and aquatic exercise
Verschueren et al. (2004)	Healthy 15 ± 6 y post n.g.	6	Yes	DRT (leg press, leg extension)	No Yes	3 × 60, n.g. (presumably S-JE) (n.g.)	20 min warm up (running, stepping, or cycling) at 60–80% HRmax, DRT:2 exercise, 1–3 set, 20–8 rep	H-Intensity DRT
Wang et al. (2015)	Healthy >0.5 y post No Tai Chi	12	No	Tai Chi (Yang-style)	? Yes	2 × 60, S-JE 2 × 60, Group E with video (n.g.)	40 min: 5 reps × 6 min set, 42 type compositions each, 2 min rest (more details n.g.)	Tai Chi (Yang-Style)
		12	No	Tai Chi-RT (includes 4 Chen style actions)	? Yes	2 × 60, S-JE 2 × 60, Group E with video (n.g.)	40 min: 6 reps × 5min exercise, 2 min rest (more details n.g.)	Tai-Chi-RT (includes 4 Chen style actions)
Woo et al. (2007)	Healthy >8 y post Sedentary	12	No	Tai-Chi (Yang Style)	? Yes	3 × ?, S-JE (81%)	24 forms of Yang-Style Tai Chi	Tai Chi (Yang-style)
		12	No	DRT (arm-lifting, hip abduction, heel raise, hip-flexion,-extension, squat) using elastic bands	Yes Yes	3 × ?, S-JE (76%)	Six exercises, 30 reps (no more information given)	L/M-Intensity DRT
Wu et al. (2006)	Healthy 4 ± 2 y post Sedentary	12	No	Walking	No Yes	3 × 60, S-JE (n.g.)*	45 min of walking with 5–6 km/h	L-Intensity WB-AET
Yamazaki et al. (2004)	≥Osteopenia 17 ± 8 y post Sedentary	12	No	Walking	No Yes	≥4 × 60, n.g. (presumably HE) (100%)	8,000 steps/session at 50% VO_2max	M-Intensity WB-AET

*Obviously low, according to the additional number steps/day compared with the sedentary control group. AET, aerobic exercise training; BSE, Bone specific exercise; DRT, dynamic resistance training; GRF, Ground Reaction Forces; HE, Home Exercise; JE, joint exercise program; PS, Partially supervised; PR-INT, Progression of intensity parameters; PrInt, Progression of Intensity; RPE, rate of perceived exertion; S, Supervised; SiSp, Site specifity (for LS and hip ROI); ?, no clear information; WB, weight bearing; TUT, time under tension; L, low; M, moderate; H, high. Status: We focus on osteoporosis/osteopenia and fractures reported only. Otherwise subjects were considered "healthy"; Period of menopausal status: In the case of no information, the mean age was reported; Physical activity: Predominately we used the characterization of the authors. In some cases (e.g., Martin and Notelovitz, 1993) we summarize the information given to no bone specific exercise (no BSE); Progression: We only consider the progression of exercise intensity; Type of exercise: We subsume the information given in weight-bearing (WB) vs. Non-WB aerobic exercise training (AET); resistance (RT) or dynamic resistance exercise (DRT), jumping, aquatic exercise or Tai Chi; Site specifity (SiSp): First line: Estimated site specific of the exercise type on LS-BMD; Second line: Estimated site specific of the exercise type on FN-BMD. E.g., we considered the effect of walking as site specific for FN but not for LS. Depending on the exercises applied, DRT was considered as site specific for both BMD-ROIs; Exercise volume/week; setting, attendance: Number of sessions per week × minutes per session (e.g., 3 × 60); setting of the exercise application, i.e., either supervised group exercise (S-JE) or home exercise or exercise individually performed without supervision (HE). In parenthesis: Attendance as defined as rate of sessions performed (%); Composition of strain/exercise parameters per session: AET: specific exercise (i.e., walking, jogging, aerobic dance), exercise duration, exercise intensity; DRT: exercises/number of exercises; number of sets, number of repetitions; exercise intensity; jumping: type of jumps, number of jumps, intensity of jumps; Tai-Chi: style, number of forms. ##We did not include warm up in the table, if the authors did not report the duration and type of exercise as warm-up; cycle ergometer ≤ 5 min as warm-up, stretching and balance as cool-down have not been included in the table.

et al., 2011b,c; Tartibian et al., 2011; Karakiriou et al., 2012; Basat et al., 2013; Bello et al., 2014; Moreira et al., 2014; Nicholson et al., 2015; de Oliveira et al., 2019). Of importance, no study reported a delay between the end of the intervention and the control assessments.

Of all 75 included studies, 13 had two intervention groups (based on our eligibility criteria). Five of them assigned various types of exercises between the intervention groups (Grove and Londeree, 1992; Kohrt et al., 1997; Woo et al., 2007; Marques et al., 2011c; Basat et al., 2013), the other 5 trials compared two different training intensities (Hatori et al., 1993; Pruitt et al., 1995; Kerr et al., 1996, 2001; Bemben et al., 2000) whereas, Martin and Notelovitz (1993) categorized intervention groups according to the training duration (Martin and Notelovitz, 1993). Moreover, one study considered two intervention groups with different Tai Chi styles (Wang et al., 2015). Kemmler (1999) classified participants based on the menopausal status, and they were included in the analysis as individual intervention groups.

The majority of the 88 intervention groups employed aerobic exercise as the main component of their intervention, with walking and/or jogging the most common types (Nelson et al., 1991; Grove and Londeree, 1992; Lau et al., 1992; Bloomfield et al., 1993; Hatori et al., 1993; Martin and Notelovitz, 1993; Bassey and Ramsdale, 1995; Kohrt et al., 1995, 1997; Prince et al., 1995; Brooke-Wavell et al., 1997, 2001; Ebrahim et al., 1997; Bassey et al., 1998; Ryan et al., 1998; Hans et al., 2002; Sugiyama et al., 2002; Yamazaki et al., 2004; Korpelainen et al., 2006; Wu et al., 2006; Evans et al., 2007; Silverman et al., 2009; Sakai et al., 2010; Marques et al., 2011c; Tartibian et al., 2011; Basat et al., 2013). Twenty-six training protocols combined aerobic and resistance exercise (Caplan et al., 1993; Lord et al., 1996; Kohrt et al., 1997; Adami et al., 1999; Kemmler, 1999; Iwamoto et al., 2001; Kerr et al., 2001; Going et al., 2003; Jessup et al., 2003; Milliken et al., 2003; Kemmler et al., 2004, 2010, 2013; Englund et al., 2005; Bergstrom et al., 2008; Kwon et al., 2008; Park et al., 2008; de Matos et al., 2009; Deng, 2009; Choquette et al., 2011; Marques et al., 2011b; Bolton et al., 2012; Karakiriou et al., 2012; Chilibeck et al., 2013; Bello et al., 2014; Moreira et al., 2014). Resistance exercise as the predominant component was prescribed by 27 intervention groups (Sinaki et al., 1989; Pruitt et al., 1992, 1995; Nelson et al., 1994; Nichols et al., 1995; Hartard et al., 1996; Kerr et al., 1996, 2001; Kohrt et al., 1997; Bemben et al., 2000, 2010; Rhodes et al., 2000; Chilibeck et al., 2002; Verschueren et al., 2004; Maddalozzo et al., 2007; Woo et al., 2007; Bocalini et al., 2009; Chuin et al., 2009; Marques et al., 2011c; Basat et al., 2013; Orsatti et al., 2013; Nicholson et al., 2015; Duff et al., 2016; de Oliveira et al., 2019), Tai Chi was utilized in 5 training groups (Chan et al., 2004; Woo et al., 2007; Liu et al., 2015; Wang et al., 2015).

Exercise intensities varied considerably between the exercise protocols (very low to high; Garber et al., 2011). With respect to resistance training, most of the studies prescribed a training intensity of 70–80% of one repetition maximum (1-RM). Aerobic exercise was predominately performed in the range between 60 and 80% of the maximum heart rate maximum (HRmax). In 54 intervention groups, the exercise intensity was progressively increased during the intervention period (Sinaki et al., 1989; Pruitt et al., 1992, 1995; Bloomfield et al., 1993; Martin and Notelovitz, 1993; Nelson et al., 1994; Kohrt et al., 1995, 1997; Nichols et al., 1995; Hartard et al., 1996; Kerr et al., 1996, 2001; Ryan et al., 1998; Kemmler, 1999; Bemben et al., 2000; Rhodes et al., 2000; Iwamoto et al., 2001; Chilibeck et al., 2002, 2013; Hans et al., 2002; Going et al., 2003; Jessup et al., 2003; Milliken et al., 2003; Kemmler et al., 2004, 2010, 2013; Verschueren et al., 2004; Englund et al., 2005; Korpelainen et al., 2006; Evans et al., 2007; Maddalozzo et al., 2007; Bergstrom et al., 2008; Kwon et al., 2008; Bocalini et al., 2009; Chuin et al., 2009; de Matos et al., 2009; Deng, 2009; Choquette et al., 2011; Marques et al., 2011b,c; Tartibian et al., 2011; Bolton et al., 2012; Orsatti et al., 2013; Moreira et al., 2014; Nicholson et al., 2015; Duff et al., 2016; de Oliveira et al., 2019).

Fifty-one intervention groups adequately addressed their endpoints LS and/or FN BMD by their exercise protocol (site specificity) (Lau et al., 1992; Pruitt et al., 1992, 1995; Nelson et al., 1994; Nichols et al., 1995; Hartard et al., 1996; Kerr et al., 1996, 2001; Lord et al., 1996; Kohrt et al., 1997; Kemmler, 1999; Bemben et al., 2000, 2010; Rhodes et al., 2000; Iwamoto et al., 2001; Chilibeck et al., 2002, 2013; Going et al., 2003; Jessup et al., 2003; Milliken et al., 2003; Kemmler et al., 2004, 2010, 2013; Englund et al., 2005; Korpelainen et al., 2006; Evans et al., 2007; Maddalozzo et al., 2007; Woo et al., 2007; Bergstrom et al., 2008; Kwon et al., 2008; Bocalini et al., 2009; Chuin et al., 2009; de Matos et al., 2009; Deng, 2009; Choquette et al., 2011; Marques et al., 2011b,c; Karakiriou et al., 2012; Basat et al., 2013; Orsatti et al., 2013; Bello et al., 2014; Moreira et al., 2014; Nicholson et al., 2015; Duff et al., 2016; de Oliveira et al., 2019). Some studies defined BMD at LS and/or FN as a study endpoint—however, the corresponding bone regions were not (or at least not adequately) addressed by their training protocol (**Table 2**).

The majority of studies prescribed an exercise frequency of three times per week (range 2–9 sessions/week) (Nelson et al., 1994; Hartard et al., 1996; Lord et al., 1996; Adami et al., 1999; Iwamoto et al., 2001; Englund et al., 2005; Maddalozzo et al., 2007; Marques et al., 2011b; Nicholson et al., 2015). Exercise session duration ranged from ≈2 to 110 min (Adami et al., 1999; Sakai et al., 2010). During resistance training sessions 1–21 exercises (Sinaki et al., 1989; Nicholson et al., 2015; de Oliveira et al., 2019), with up to 108 repetitions (Nicholson et al., 2015) structured in 1–5 sets (Sinaki et al., 1989; Pruitt et al., 1992; Deng, 2009; Basat et al., 2013; de Oliveira et al., 2019), were applied per session. Sixteen RT studies (Nelson et al., 1994; Nichols et al., 1995; Hartard et al., 1996; Kerr et al., 1996; Kemmler et al., 2004, 2010, 2013; Maddalozzo et al., 2007; Bocalini et al., 2009; Chuin et al., 2009; de Matos et al., 2009; Marques et al., 2011c; Karakiriou et al., 2012; Orsatti et al., 2013; Moreira et al., 2014; de Oliveira et al., 2019) additionally listed rest period between sets and/or exercises (range: 15–180 s). Time under tension (TUT) was reported in nine studies only (Nelson et al., 1994; Hartard et al., 1996; Rhodes et al., 2000; Kemmler et al., 2004, 2010, 2013; Maddalozzo et al., 2007; de Matos et al., 2009; Marques et al., 2011c) and ranged between 3 and 9 s per repetition, with two studies using fast or explosive movements in the concentric part of the exercise.

Exercise sessions were supervised in 59 studies (Nelson et al., 1991, 1994; Grove and Londeree, 1992; Lau et al., 1992; Pruitt et al., 1992, 1995; Bloomfield et al., 1993; Caplan et al., 1993; Martin and Notelovitz, 1993; Bassey and Ramsdale, 1995; Nichols et al., 1995; Prince et al., 1995; Hartard et al., 1996; Kerr et al., 1996, 2001; Lord et al., 1996; Bassey et al., 1998; Ryan et al., 1998; Adami et al., 1999; Kemmler, 1999; Bemben et al., 2000, 2010; Rhodes et al., 2000; Chilibeck et al., 2002, 2013; Going et al., 2003; Jessup et al., 2003; Milliken et al., 2003; Chan et al., 2004; Kemmler et al., 2004, 2010, 2013; Englund et al., 2005;

Korpelainen et al., 2006; Wu et al., 2006; Evans et al., 2007; Maddalozzo et al., 2007; Woo et al., 2007; Bergstrom et al., 2008; Kwon et al., 2008; Bocalini et al., 2009; Chuin et al., 2009; Deng, 2009; Silverman et al., 2009; Tolomio et al., 2009; Choquette et al., 2011; Marques et al., 2011b,c; Tartibian et al., 2011; Bolton et al., 2012; Karakiriou et al., 2012; Basat et al., 2013; Orsatti et al., 2013; Bello et al., 2014; Moreira et al., 2014; Nicholson et al., 2015; Wang et al., 2015; Duff et al., 2016; de Oliveira et al., 2019). **Ten trials used non-supervised home-exercise protocols** (Sinaki et al., 1989; Kohrt et al., 1995; Brooke-Wavell et al., 1997, 2001; Ebrahim et al., 1997; Iwamoto et al., 2001; Hans et al., 2002; Sugiyama et al., 2002; Sakai et al., 2010; Liu et al., 2015). **The remaining studies did not state the corresponding setting comprehensively** (Hatori et al., 1993; Kohrt et al., 1997; Verschueren et al., 2004; Yamazaki et al., 2004; Park et al., 2008; de Matos et al., 2009).

The majority of studies reported attendance rates of more than 70% [minimum: 39% (Prince et al., 1995)**, maximum: 100%** (Brooke-Wavell et al., 1997; Ebrahim et al., 1997; Yamazaki et al., 2004)**]. However, 15 studies did not provide any information regarding the attendance rate** (Sinaki et al., 1989; Lau et al., 1992; Hatori et al., 1993; Iwamoto et al., 2001; Jessup et al., 2003; Milliken et al., 2003; Verschueren et al., 2004; Wu et al., 2006; Evans et al., 2007; Kwon et al., 2008; Park et al., 2008; de Matos et al., 2009; Tolomio et al., 2009; Orsatti et al., 2013; Wang et al., 2015).

Methodological Quality

PEDro scores are listed in Table 3. The methodological quality of 14 trials can be considered as high (Ebrahim et al., 1997; Chilibeck et al., 2002, 2013; Jessup et al., 2003; Korpelainen et al., 2006; Woo et al., 2007; Park et al., 2008; Kemmler et al., 2010, 2013; Bolton et al., 2012; Orsatti et al., 2013; Nicholson et al., 2015; Duff et al., 2016; de Oliveira et al., 2019)**, 44 studies demonstrated moderate** (Sinaki et al., 1989; Nelson et al., 1991, 1994; Grove and Londeree, 1992; Lau et al., 1992; Pruitt et al., 1992, 1995; Caplan et al., 1993; Hatori et al., 1993; Martin and Notelovitz, 1993; Nichols et al., 1995; Prince et al., 1995; Hartard et al., 1996; Kerr et al., 1996, 2001; Brooke-Wavell et al., 1997, 2001; Kemmler, 1999; Rhodes et al., 2000; Iwamoto et al., 2001; Hans et al., 2002; Going et al., 2003; Milliken et al., 2003; Chan et al., 2004; Verschueren et al., 2004; Wu et al., 2006; Evans et al., 2007; Maddalozzo et al., 2007; Bergstrom et al., 2008; Bocalini et al., 2009; Chuin et al., 2009; Tolomio et al., 2009; Bemben et al., 2010; Sakai et al., 2010; Choquette et al., 2011; Marques et al., 2011b,c; Tartibian et al., 2011; Basat et al., 2013; Bello et al., 2014; Moreira et al., 2014; Liu et al., 2015; Wang et al., 2015)**, while the remaining studies ($n = 17$) were classified as being of low quality (Table 3).**

Outcomes Measures

Fourteen of the 75 trials assessed BMD at LS and proximal femur (Prince et al., 1995; Pruitt et al., 1995; Bemben et al., 2000, 2010; Chilibeck et al., 2002, 2013; Sugiyama et al., 2002; Kemmler et al., 2004; Wu et al., 2006; Maddalozzo et al., 2007; Choquette et al., 2011; Nicholson et al., 2015; Duff et al., 2016; de Oliveira et al., 2019)**, 9 studies measured BMD only at LS** (Sinaki et al., 1989; Grove and Londeree, 1992; Hatori et al., 1993; Martin and Notelovitz, 1993; Iwamoto et al., 2001; Verschueren et al., 2004; Yamazaki et al., 2004; Evans et al., 2007; Karakiriou et al., 2012)**, while seven studies focused only on the BMD of at least one proximal femur ROI** (Kerr et al., 1996; Hans et al., 2002; Korpelainen et al., 2006; Tolomio et al., 2009; Sakai et al., 2010; Marques et al., 2011c; Bello et al., 2014).

Meta-Analysis Results

Effect of Exercise on BMD at the LS

Seventy-nine trials evaluated the effect of exercise on BMD at the LS. In summary, the exercise intervention resulted in significant positive effects ($P < 0.001$). The pooled estimate of random effect analysis was 0.37, 95%-CI: 0.25–0.50 with a substantial level of heterogeneity between trials [$I^2 = 73.2\%$, Q = 262.43, degrees of freedom (df) = 78, $P < 0.001$; **Figure 2A**]. Sensitivity analysis revealed the most similar effect, when the mean correlation coefficient (max correlation: SMD = 0.65, 95%-CI: 0.43–0.86; min correlation: SMD = 0.26, 95%-CI: 0.17–0.36) was utilized to impute SD of the absolute change for those studies with missing SDs, and when the analysis was computed among studies with available SDs of the change (25 groups) (SMD = 0.32, 95%-CI: 0.10–0.53, $P = 0.004$). The funnel plot suggested positive evidence of publication bias (**Figure 2B**). The rank correlation test for funnel plot asymmetry further confirmed the significant asymmetry ($P = 0.002$).

Effect of Exercise on BMD at the FN-ROI

Sixty-eight intervention groups evaluated the effect of exercise on BMD of the FN. The random-effect analysis demonstrated a significant pooled difference between the exercise and control groups ($P < 0.0001$). The pooled estimate of random effect analysis was 0.33, 95%-CI: 0.23–0.43. There was a moderate level of heterogeneity in estimates of the exercise effect [$I^2 = 59.8\%$, Q = 166.35, degrees of freedom (df) = 67, $P < 0.001$; **Figure 3A**]. Sensitivity analysis indicated the most similar effect when the mean correlation coefficient (max correlation: SMD = 0.74, 95%-CI: 0.49–1.00; min correlation: SMD = 0.24, 95%-CI: 0.16–0.32) was used to impute SD of the absolute change for those trials with missing SDs, and when the analysis was conducted among studies with available SDs of the change (25 groups) (SMD = 0.36, 95%-CI: 0.19–0.52, $P = 0.0001$). The funnel plot suggested positive evidence of publication bias (**Figure 3B**). The regression test for funnel plot asymmetry presented the significant asymmetry ($P = 0.03$).

Effect of Exercise on BMD of Total Hip-ROI

Twenty-nine intervention groups addressed the effect of exercise on BMD of the total Hip. Our result demonstrated a significant exercise-induced improvement in total Hip BMD ($P < 0.0001$). The pooled estimate of random effect analysis, favoring exercise intervention over the control group, was 0.40, 95%-CI: 0.28–0.51. There was a low level of heterogeneity in estimates of the exercise effect [$I^2 = 21.8\%$, Q = 34.79, degrees of freedom (df) = 28, $P = 0.176$; **Figure 4A**). Sensitivity analysis revealed the most similar effect when the mean correlation coefficient (max correlation: SMD = 0.51, 95%-CI: 0.36–0.66; min correlation:

TABLE 3 | Assessment of risk of bias for included studies ($n = 75$).

References	Eligibility criteria	Random allocation	Allocation concealment	Inter group homogeneity	Blinding subjects	Blinding personnel	Blinding assessors	participation≥ 85% allocation	Intention to treat analysis[a]	Between group comparison	Measure of variability	Total score
Adami et al. (1999)	Y	0	0	1	0	0	0	1	0	1	1	4
Basat et al. (2013)	Y	1	1	1	0	0	0	0	0	1	1	5
Bassey et al. (1998)	Y	1	0	1	0	0	0	0	0	1	1	4
Bassey and Ramsdale (1995)	Y	1	0	1	0	0	0	0	0	1	1	4
Bello et al. (2014)	Y	1	0	1	0	0	0	0	1	1	1	5
Bemben et al. (2010)	Y	0	0	1	0	0	0	1	1	1	1	5
Bemben et al. (2000)	Y	1	0	1	0	0	0	0	0	1	1	4
Bergstrom et al. (2008)	Y	1	1	1	0	0	0	0	1	1	1	6
Bloomfield et al. (1993)	Y	0	0	0	0	0	0	1	1	1	1	4
Bocalini et al. (2009)	Y	1	0	1	0	0	1	0	0	1	1	5
Bolton et al. (2012)	Y	1	1	0	0	0	1	1	1	1	1	7
Brooke-Wavell et al. (2001)	Y	0	0	1	0	0	0	1	1	1	1	5
Brooke-Wavell et al. (1997)	Y	1	0	1	0	0	0	1	0	1	1	5
Caplan et al. (1993)	Y	0	0	1	0	0	0	1	1	1	1	5
Chan et al. (2004)	Y	1	0	1	0	0	0	0	1	1	1	5
Chilibeck et al. (2013)	Y	1	1	1	0	0	1	1	1	1	1	8
Chilibeck et al. (2002)	Y	1	1	1	1	1	0	0	1	1	1	8
Choquette et al. (2011)	Y	1	0	1	0	0	0	0	1	1	1	5
Chuin et al. (2009)	Y	1	0	1	0	0	0	0	1	1	1	5
de Matos et al. (2009)	Y	0	0	1	0	0	0	0	0	1	1	3
Deng (2009)	Y	0	0	1	0	0	0	1	0	1	1	4
de Oliveira et al. (2019)	Y	1	1	1	0	0	1	1	1	1	1	8
Duff et al. (2016)	Y	1	1	1	1	0	1	0	1	1	1	8
Ebrahim et al. (1997)	Y	1	1	1	0	0	1	0	1	1	1	7
Englund et al. (2005)	Y	1	0	1	0	0	0	0	0	1	1	4
Evans et al. (2007)	Y	1	1	1	0	0	0	0	1	1	1	6
Going et al. (2003)	Y	1	0	1	0	0	0	0	1	1	1	5
Grove and Londeree (1992)	Y	1	0	1	0	0	0	1	1	1	1	6
Hans et al. (2002)	Y	1	0	1	0	0	0	0	1	1	1	5
Hartard et al. (1996)	Y	0	0	1	0	0	0	1	1	1	1	5
Hatori et al. (1993)	Y	1	0	1	0	0	1	1	0	1	1	6
Iwamoto et al. (2001)	Y	1	0	1	0	0	0	0	1	1	1	5
Jessup et al. (2003)	Y	1	1	0	0	0	1	1	1	1	1	7

(Continued)

TABLE 3 | Continued

References	Eligibility criteria	Random allocation	Allocation concealment	Inter group homogeneity	Blinding subjects	Blinding personnel	Blinding assessors	participation≥ 85% allocation	Intention to treat analysis[a]	Between group comparison	Measure of variability	Total score
Karakiriou et al. (2012)	Y	1	0	0	0	0	0	0	0	1	1	3
Kemmler et al. (2013)	Y	1	0	1	1	0	1	0	1	1	1	7
Kemmler et al. (2010)	Y	1	1	1	1	0	1	1	1	1	1	9
Kemmler et al. (2004)	Y	0	0	1	0	0	0	0	1	1	1	4
Kemmler (1999)	Y	0	0	1	0	0	0	1	1	1	1	5
Kerr et al. (2001)	Y	1	0	1	0	0	0	0	1	1	1	5
Kerr et al. (1996)	Y	1	0	1	0	0	0	0	1	1	1	5
Kohrt et al. (1997)	Y	0	0	1	0	0	0	0	1	1	1	4
Kohrt et al. (1995)	Y	0	0	1	0	0	0	0	1	1	1	4
Korpelainen et al. (2006)	Y	1	1	1	0	0	1	0	1	1	1	7
Kwon et al. (2008)	Y	0	0	1	0	0	0	0	0	1	1	3
Lau et al. (1992)	Y	1	1	1	0	0	0	0	1	0	1	5
Liu et al. (2015)	Y	1	0	1	0	0	0	1	1	1	1	6
Lord et al. (1996)	Y	1	0	1	0	0	0	0	1	1	1	5
Maddalozzo et al. (2007)	Y	1	0	1	0	0	0	1	1	1	1	6
Marques et al. (2011b)	Y	1	1	1	0	0	0	0	1	1	1	6
Marques et al. (2011c)	Y	1	1	1	0	0	0	0	1	1	1	6
Martin and Notelovitz (1993)	Y	1	0	1	0	0	0	0	1	1	1	5
Milliken et al. (2003)	Y	1	0	1	0	0	0	1	1	1	1	6
Moreira et al. (2014)	Y	1	0	1	0	0	0	1	1	1	1	6
Nelson et al. (1994)	Y	1	0	1	0	0	0	1	1	1	1	6
Nelson et al. (1991)	Y	0	0	1	0	0	0	1	1	1	1	5
Nichols et al. (1995)	Y	1	0	1	0	0	0	0	1	1	1	5
Nicholson et al. (2015)	Y	1	1	1	0	0	0	1	1	1	1	7
Orsatti et al. (2013)	Y	1	1	1	0	0	0	1	1	1	1	7
Park et al. (2008)	Y	1	1	1	0	0	0	1	1	1	1	7
Prince et al. (1995)	Y	1	1	1	0	0	0	0	1	1	1	6
Pruitt et al. (1995)	Y	1	0	1	0	0	0	0	1	1	1	5
Pruitt et al. (1992)	Y	0	0	1	0	0	0	1	1	1	1	5
Rhodes et al. (2000)	Y	1	0	1	0	0	0	1	1	1	1	6
Ryan et al. (1998)	Y	0	0	1	0	0	0	0	1	1	1	4
Sakai et al. (2010)	Y	1	1	1	0	0	0	1	0	1	1	6
Silverman et al. (2009)	Y	0	0	1	0	0	1	0	0	1	1	4
Sinaki et al. (1989)	Y	1	0	1	0	0	0	1	1	1	1	6

(Continued)

TABLE 3 | Continued

References	Eligibility criteria	Random allocation	Allocation concealment	Inter group homogeneity	Blinding subjects	Blinding personnel	Blinding assessors	participation≥ 85% allocation	Intention to treat analysis[a]	Between group comparison	Measure of variability	Total score
Sugiyama et al. (2002)	Y	0	0	1	0	0	0	0	0	1	1	3
Tartibian et al. (2011)	Y	1	0	1	0	0	0	1	1	1	1	6
Tolomio et al. (2009)	Y	1	0	1	0	0	0	1	0	1	1	5
Verschueren et al. (2004)	Y	1	1	1	0	0	1	0	0	1	1	6
Wang et al. (2015)	Y	1	0	1	0	0	0	1	1	1	1	6
Woo et al. (2007)	Y	1	1	1	0	0	1	1	1	1	1	8
Wu et al. (2006)	Y	1	0	1	1	0	0	0	1	1	1	6
Yamazaki et al. (2004)	Y	0	0	1	0	0	0	0	1	1	1	4

[a] The point is awarded not only for intention to treat analysis, but also when "all subjects for whom outcome measures were available received the treatment or control condition as allocated". Mainly higher scores were hindered by the lack of allocation concealment, subject, therapies and assessor blinding, and reporting the key outcomes for ≥85% of subjects as the common limitations.

SMD = 0.32, 95%-CI: 0.21–0.42) was used to impute SD of the absolute change for those studies with missing SDs, and when the analysis was computed among studies with available SDs of the change (11 groups) (SMD = 0.39, 95%-CI: 0.19–0.58, $P <$ 0.0001). The funnel plot provided no evidence of publication bias (**Figure 4B**) which was confirmed by the rank correlation test for funnel plot asymmetry ($P = 0.42$).

Subgroup Analysis

Menopausal Status

LS-BMD: To estimate the effect of menopausal status on LS BMD, we only included studies that listed information concerning the menopausal status (early vs. late) of their cohorts. In summary, forty-nine groups were analyzed and a mixed-effects analysis found no significant difference between the early (≤8 years, 14 groups) and late (> 8 years, 35 groups) ($P = 0.24$) post-menopausal groups. A subgroup analysis that compared the early (Grove and Londeree, 1992; Pruitt et al., 1992; Kemmler, 1999; Bemben et al., 2000; Sugiyama et al., 2002; Chan et al., 2004; Kemmler et al., 2004, 2013; Wu et al., 2006; Maddalozzo et al., 2007; Deng, 2009; Karakiriou et al., 2012) and late-post-menopausal (Nelson et al., 1991; Lau et al., 1992; Bloomfield et al., 1993; Caplan et al., 1993; Kohrt et al., 1995, 1997; Nichols et al., 1995; Prince et al., 1995; Pruitt et al., 1995; Lord et al., 1996; Brooke-Wavell et al., 1997, 2001; Adami et al., 1999; Kemmler, 1999; Rhodes et al., 2000; Iwamoto et al., 2001; Jessup et al., 2003; Verschueren et al., 2004; Yamazaki et al., 2004; Englund et al., 2005; Woo et al., 2007; Kwon et al., 2008; Park et al., 2008; Bocalini et al., 2009; Chuin et al., 2009; de Matos et al., 2009; Bemben et al., 2010; Kemmler et al., 2010; Marques et al., 2011b; Tartibian et al., 2011; Nicholson et al., 2015; Duff et al., 2016) group with their corresponding control-groups indicate comparable effects on LS-BMD (early: SMD = 0.64, 95%-CI: 0.33–0.95 vs. late post-menopausal: 0.39, 0.19–0.59).

FN-BMD: Of 68 groups that addressed FN-BMD, 44 exercise groups comprised early or late post-menopausal participants. A mixed-effects analysis found no significant difference between early (≤8 years, 10 groups) and late (>8 years, 34 groups) ($P = 0.65$) PMW. The subgroup analysis that compared the early (Pruitt et al., 1992; Kemmler, 1999; Bemben et al., 2000; Sugiyama et al., 2002; Chan et al., 2004; Kemmler et al., 2004; Wu et al., 2006; Maddalozzo et al., 2007; Deng, 2009) vs. the late-post-menopausal exercise-groups (Nelson et al., 1991; Lau et al., 1992; Bloomfield et al., 1993; Caplan et al., 1993; Kohrt et al., 1995, 1997; Nichols et al., 1995; Prince et al., 1995; Pruitt et al., 1995; Lord et al., 1996; Brooke-Wavell et al., 1997, 2001; Adami et al., 1999; Kemmler, 1999; Rhodes et al., 2000; Hans et al., 2002; Jessup et al., 2003; Englund et al., 2005; Korpelainen et al., 2006; Kwon et al., 2008; Park et al., 2008; Bocalini et al., 2009; Chuin et al., 2009; Bemben et al., 2010; Kemmler et al., 2010; Sakai et al., 2010; Marques et al., 2011b,c; Tartibian et al., 2011; Nicholson et al., 2015; Duff et al., 2016) with their corresponding control-groups did not detect different effects of menopausal status on FN-BMD (early: SMD = 0.31; 95%-CI: 0.09–0.52 vs. late-post-menopausal: 0.39, 0.17–0.60).

Total Hip-BMD: Twenty studies with tHip-BMD assessment reported the menopausal status of their cohorts. A mixed-effects analysis indicated no statistically significant difference between the early (≤8 years, 7 groups) and late (> 8 years, 13 groups) post-menopausal group ($P = 0.37$).

The sub-group analysis did not indicate a different effect of varying menopausal status on BMD at the tHip-ROI [early- (Bemben et al., 2000; Sugiyama et al., 2002; Kemmler et al., 2004, 2013; Wu et al., 2006; Maddalozzo et al., 2007): **SMD = 0.51, 95%-CI: 0.27–0.75 vs. late post-menopausal** (Prince et al., 1995; Pruitt et al., 1995; Hans et al., 2002; Woo et al., 2007; de Matos et al., 2009; Bemben et al., 2010; Sakai et al., 2010; Marques et al., 2011c; Nicholson et al., 2015; Duff et al., 2016): **0.38, 0.20–0.56]**.

Intervention Duration

LS-BMD: **Of 79 groups, 25 training groups were included in the short-term intervention (≤8 months) group** (Bloomfield et al., 1993; Hatori et al., 1993; Hartard et al., 1996; Ryan et al., 1998;

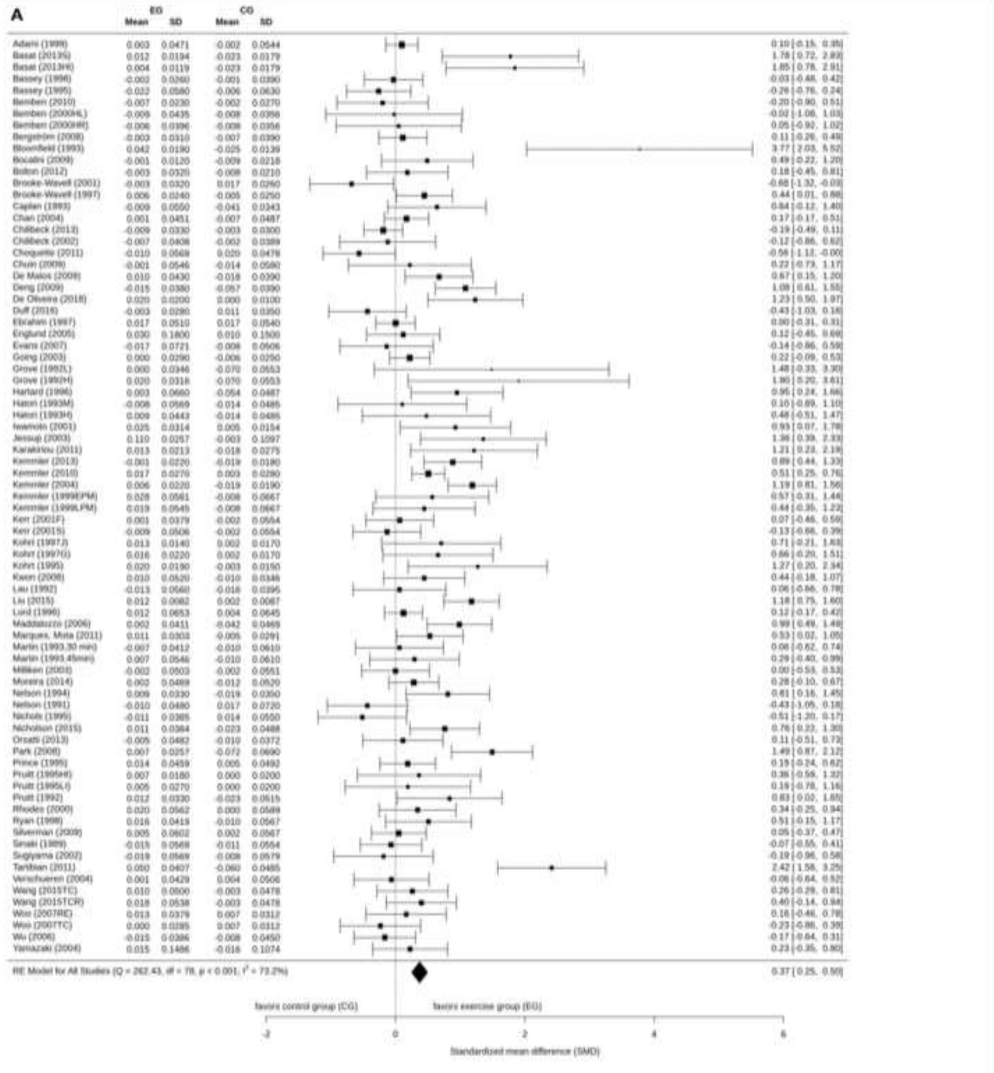


FIGURE 2 | Continued

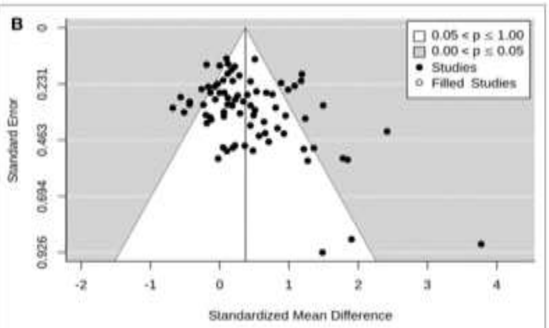


FIGURE 2 | (A) Forest plot of meta-analysis results at the LS. The data are shown as pooled standard mean difference (SMD) with 95% CI for changes in exercise and control groups. **(B)** Funnel plot of LS BMD with Trim and Fill. SE, standard error of standardized mean difference; SMD, standardized mean difference.

Adami et al., 1999; Bemben et al., 2000, 2010; Sugiyama et al., 2002; Jessup et al., 2003; Verschueren et al., 2004; Kwon et al., 2008; Bocalini et al., 2009; Chuin et al., 2009; Silverman et al., 2009; Choquette et al., 2011; Marques et al., 2011b; Tartibian et al., 2011; Karakiriou et al., 2012; Basat et al., 2013; Moreira et al., 2014; Nicholson et al., 2015; de Oliveira et al., 2019), 44 groups were classified as applying a moderate duration (9–18 months) intervention (Nelson et al., 1991, 1994; Grove and Londeree, 1992; Lau et al., 1992; Pruitt et al., 1992, 1995; Martin and Notelovitz, 1993; Bassey and Ramsdale, 1995; Kohrt et al., 1995, 1997; Nichols et al., 1995; Lord et al., 1996; Brooke-Wavell et al., 1997, 2001; Bassey et al., 1998; Kemmler, 1999; Rhodes et al., 2000; Chilibeck et al., 2002; Going et al., 2003; Milliken et al., 2003; Chan et al., 2004; Yamazaki et al., 2004; Englund et al., 2005; Wu et al., 2006; Evans et al., 2007; Maddalozzo et al., 2007; Woo et al., 2007; Bergstrom et al., 2008; Park et al., 2008; de Matos et al., 2009; Deng, 2009; Bolton et al., 2012; Kemmler et al., 2013; Orsatti et al., 2013; Liu et al., 2015; Wang et al., 2015; Duff et al., 2016), and 10 training groups applied a long intervention (≥18 months) (Sinaki et al., 1989; Caplan et al., 1993; Prince et al., 1995; Ebrahim et al., 1997; Iwamoto et al., 2001; Kerr et al., 2001; Kemmler et al., 2004, 2010; Chilibeck et al., 2013). According to a mixed-effects analysis, no significant difference was observed between the sub-groups ($P = 0.26$). However, the short intervention period demonstrated a slightly higher effect (exercise vs. control, SMD = 0.59, 95%-CI: 0.29–0.9) than the moderate (0.30, 0.15–0.45) or the long intervention duration (0.28, −0.15–0.58) that did not significantly differ from control ($P = 0.06$).

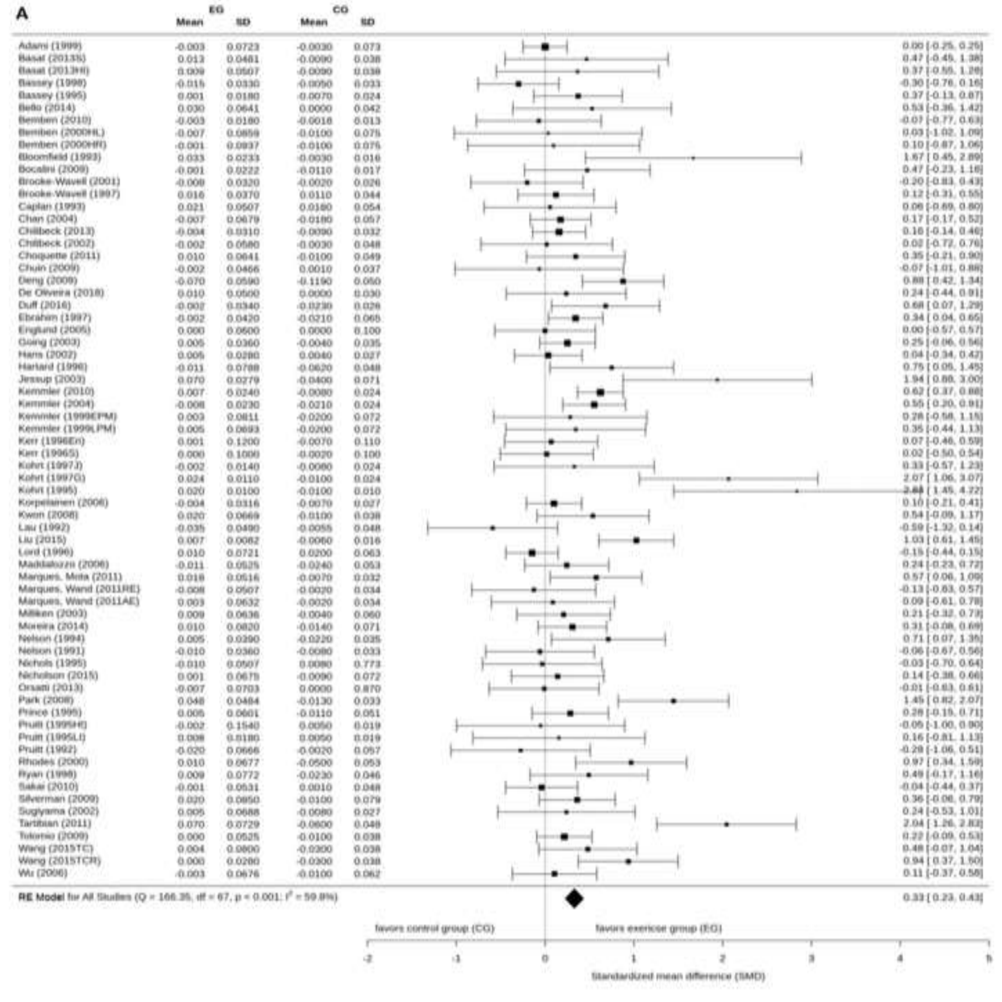
FN-BMD: Of 68 groups, 25 studies applied a short (Bloomfield et al., 1993; Hartard et al., 1996; Ryan et al., 1998; Bemben et al., 2000, 2010; Sugiyama et al., 2002; Jessup et al., 2003; Kwon et al., 2008; Bocalini et al., 2009; Chuin et al., 2009; Silverman et al., 2009; Sakai et al., 2010; Choquette et al., 2011; Marques et al., 2011b,c; Tartibian et al., 2011; Basat et al., 2013; Bello et al., 2014; Moreira et al., 2014; Nicholson et al., 2015; de Oliveira et al., 2019), 35 groups scheduled a moderate (Nelson et al., 1991, 1994; Lau et al., 1992; Pruitt et al., 1992, 1995; Bassey and Ramsdale, 1995; Kohrt et al., 1995, 1997; Nichols et al., 1995; Kerr et al., 1996; Lord et al., 1996; Brooke-Wavell et al., 1997, 2001; Bassey et al., 1998; Kemmler, 1999; Rhodes et al., 2000; Chilibeck et al., 2002; Going et al., 2003; Milliken et al., 2003; Chan et al., 2004; Englund et al., 2005; Wu et al., 2006; Maddalozzo et al., 2007; Park et al., 2008; Deng, 2009; Tolomio et al., 2009; Orsatti et al., 2013; Liu et al., 2015; Wang et al., 2015; Duff et al., 2016), and 8 groups conducted a long duration of the exercise intervention (Caplan et al., 1993; Prince et al., 1995; Ebrahim et al., 1997; Hans et al., 2002; Kemmler et al., 2004, 2010; Korpelainen et al., 2006; Chilibeck et al., 2013). A mixed-effects analysis did not observe significant differences between the sub-groups ($P = 0.83$). The subgroups analysis demonstrated that the short intervention period triggered the highest effects (exercise vs. control, SMD = 0.38, 95%-CI: 0.20–0.56) followed by moderate (0.32, 0.15–0.49), and long intervention duration (0.30, 0.13–0.47).

Total Hip-BMD: Of 29 groups, 11 training groups were classified as short-term (Bemben et al., 2000, 2010; Sugiyama et al., 2002; Sakai et al., 2010; Choquette et al., 2011; Marques et al., 2011c; Bello et al., 2014; Nicholson et al., 2015; de Oliveira et al., 2019), 12 groups were classified as moderate (Pruitt et al., 1995; Chilibeck et al., 2002; Wu et al., 2006; Maddalozzo et al., 2007; Woo et al., 2007; Bergstrom et al., 2008; de Matos et al., 2009; Bolton et al., 2012; Kemmler et al., 2013; Duff et al., 2016), and six training groups were categorized as long-term interventions (Prince et al., 1995; Kerr et al., 2001; Hans et al., 2002; Kemmler et al., 2004; Chilibeck et al., 2013). A mixed-effects analysis indicated no significant difference between the subgroups ($P = 0.50$). In contrast to LS and FN, the subgroup analysis indicated that long-term intervention demonstrated a tendentially more favorable effect on tHip-BMD (exercise vs. control, SMD = 0.48, 95%-CI: 0.27–0.7) than moderate (0.39, 0.23–0.55) or short intervention duration (0.31, 0.06–0.55).

Type of Exercise

LS-BMD: Of 79 groups, 18 training groups were classified as WB-AE (Nelson et al., 1991; Lau et al., 1992; Hatori et al., 1993; Martin and Notelovitz, 1993; Kohrt et al., 1995, 1997; Prince et al., 1995; Brooke-Wavell et al., 1997, 2001; Ebrahim et al., 1997; Ryan et al., 1998; Yamazaki et al., 2004; Wu et al., 2006; Evans et al., 2007; Silverman et al., 2009; Tartibian et al., 2011), 15 as DRT (Pruitt et al., 1992, 1995; Nelson et al., 1994; Hartard et al., 1996; Bemben et al., 2000; Chilibeck et al., 2002; Maddalozzo et al., 2007; Woo et al., 2007; Orsatti et al., 2013; Nicholson et al., 2015; Duff et al., 2016; de Oliveira et al., 2019), 11 as Jumping+RT+WB (Grove and Londeree, 1992; Bassey and Ramsdale, 1995; Kemmler, 1999; Milliken et al., 2003; Kemmler et al., 2004, 2013; Deng, 2009; Bolton et al., 2012; Karakiriou et al., 2012; Basat et al., 2013), 24 as WB+RT (Grove and Londeree, 1992; Caplan et al., 1993; Nichols et al., 1995; Lord et al., 1996; Adami et al., 1999; Iwamoto et al., 2001; Kerr et al., 2001; Going et al., 2003; Jessup et al., 2003; Verschueren et al., 2004; Englund et al., 2005; Bergstrom et al., 2008; Kwon et al., 2008; Park et al., 2008; Bocalini et al., 2009; Chuin et al., 2009; de Matos et al., 2009; Bemben et al., 2010; Kemmler et al., 2010; Choquette et al., 2011; Marques et al., 2011b; Basat et al., 2013; Chilibeck et al., 2013), two groups as jumping (Bassey et al., 1998; Sugiyama et al., 2002), 4 groups as non-WB+RT (Bloomfield et al., 1993; Kohrt et al., 1997; Rhodes et al., 2000; Moreira et al., 2014), and five training groups as Tai Chi intervention (Chan et al., 2004; Woo et al., 2007; Liu et al., 2015; Wang et al., 2015). A mixed-effects analysis did not reveal significant differences between the subgroups ($P = 0.36$). According to the subgroup analysis, Jumping+RT+WB triggered the most favorable (and reliable) effects on LS-BMD (exercise vs. control, SMD = 0.71, 95%-CI: 0.33–1.10), followed by dynamic RT (0.40, 0.13–0.67) and the WB+RT intervention (0.30, 0.10–0.50). There was a considerable variation of study effects in the WB-AE (18 groups, 0.24, −0.03 −0.52), Tai Chi (5 groups, 0.37, −0.08 to 0.83), Non-WB+RT (4 groups, 1.05, −0.31 to 2.50) -groups with no significant differences to control in the three latter groups. Of note, the (two) jumping only studies revealed a slight trend to negative effects on BMD (−0.07, −0.46 to 0.32).

FN-BMD: Of 68 training groups, 15 were classified as WB-AE (Nelson et al., 1991; Lau et al., 1992; Kohrt et al., 1995, 1997; Prince et al., 1995; Brooke-Wavell et al., 1997, 2001; Ebrahim



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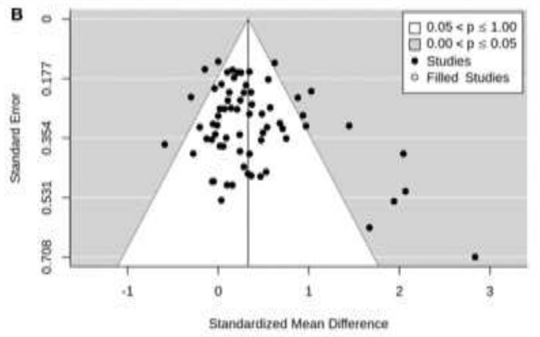

FIGURE 3 | (A) Forest plot of meta-analysis results at the FN. The data are shown as pooled standard mean difference (SMD) with 95% CI for changes in exercise and control groups. **(B)** Funnel plot of FN BMD with Trim and Fill. SE, standard error of standardized mean diffterence; SMD, standardized mean difference.

et al., 1997; Ryan et al., 1998; Hans et al., 2002; Wu et al., 2006; Silverman et al., 2009; Sakai et al., 2010; Marques et al., 2011c; Tartibian et al., 2011), **15 as DRT** (Pruitt et al., 1992, 1995; Nelson et al., 1994; Hartard et al., 1996; Kerr et al., 1996; Bemben et al., 2000; Chilibeck et al., 2002; Maddalozzo et al., 2007; Orsatti et al., 2013; Nicholson et al., 2015; Duff et al., 2016; de Oliveira et al., 2019), **8 as Jumping+RT+WB** (Bassey and Ramsdale, 1995; Kemmler, 1999; Milliken et al., 2003; Kemmler et al., 2004; Korpelainen et al., 2006; Deng, 2009; Basat et al., 2013), **20 as WB+RT** (Caplan et al., 1993; Nichols et al., 1995; Lord et al., 1996; Adami et al., 1999; Going et al., 2003; Jessup et al., 2003; Englund et al., 2005; Kwon et al., 2008; Park et al., 2008; Bocalini et al., 2009; Chuin et al., 2009; Tolomio et al., 2009; Bemben et al., 2010; Kemmler et al., 2010; Choquette et al., 2011; Marques et al., 2011b,c; Basat et al., 2013; Chilibeck et al., 2013; Bello et al., 2014), **2 as jumping** (Bassey and Ramsdale, 1995; Sugiyama et al., 2002), **4 as non-WB+RT** (Bloomfield et al., 1993; Kohrt et al., 1997; Rhodes et al., 2000; Moreira et al., 2014), **and 4 as Tai Chi exercise type** (Chan et al., 2004; Liu et al., 2015; Wang et al., 2015). **A mixed-effects analysis did not result in significant differences between the subgroups (*P* = 0.43). According to the subgroup analysis, the Non-WB+RT (4 groups, SMD = 0.68, 95%-CI: 0.16–1.19) and the Tai Chi (4 groups, 0.64, 0.21–1.05) demonstrated the most favorable effects (vs. corresponding control), followed by WB-AE (0.42, 0.03–0.81), Jumping+RT+WB (0.39, 0.17–0.62), WB+RT (0.30, 0.12–0.48) and DRT (0.21, 0.04–0.38). A tangentially negative effect was observed for the Jumping subgroup (2 studies, −0.12, −0.62 to 0.37).**

Total Hip-BMD: Of 29 groups, five training groups were considered as WB-AE (Prince et al., 1995; Hans et al., 2002; Wu et al., 2006; Sakai et al., 2010; Marques et al., 2011c), **10 groups as DRT** (Prince et al., 1995; Bemben et al., 2000; Chilibeck et al., 2002; Maddalozzo et al., 2007; Woo et al., 2007; Nicholson et al., 2015; Duff et al., 2016; de Oliveira et al., 2019), **three groups as Jumping+RT+WB** (Kemmler et al., 2004, 2013; Bolton et al., 2012), **and 9 groups as WB+RT** (Kerr et al., 2001; Bergstrom et al., 2008; de Matos et al., 2009; Bemben et al., 2010; Choquette et al., 2011; Marques et al., 2011c; Chilibeck et al., 2013; Bello et al., 2014). **The Jumping** (Sugiyama et al., 2002) **and Tai Chi** (Woo et al., 2007) **groups comprised only one intervention group, thus they were excluded from the analysis. Based on the mixed-effects analysis, no significant differences were seen between the subgroups (*P* = 0.08). According to the subgroup analysis, Jumping+RT+WB showed the largest effect (exercise vs. control, SMD = 0.65, 95%-CI: 0.30–1.00) followed by the DRT (0.51, 0.28–0.74), the WB-AE (0.36, 0.16–0.56), and the WB+RT group (0.24, 0.08–0.41).**

Ground-Reaction Forces (GRF) and Joint-Reaction Forces (JRF)

Finally, study interventions were categorized in GRF, JRF or mixed (GRF and JRF) mechanical forces.

LS-BMD: Of 79 groups, 19 training groups applied JRF exercise (Sinaki et al., 1989; Pruitt et al., 1992, 1995; Bloomfield et al., 1993; Nelson et al., 1994; Hartard et al., 1996; Kohrt et al., 1997; Bemben et al., 2000; Rhodes et al., 2000; Chilibeck et al., 2002; Maddalozzo et al., 2007; Woo et al., 2007; Orsatti et al., 2013; Moreira et al., 2014; Nicholson et al., 2015; Duff et al., 2016; de Oliveira et al., 2019), **20 applied GRF exercise** (Nelson et al., 1991; Lau et al., 1992; Hatori et al., 1993; Martin and Notelovitz, 1993; Bassey and Ramsdale, 1995; Kohrt et al., 1995, 1997; Prince et al., 1995; Brooke-Wavell et al., 1997, 2001; Ebrahim et al., 1997; Bassey et al., 1998; Sugiyama et al., 2002; Yamazaki et al., 2004; Wu et al., 2006; Silverman et al., 2009; Tartibian et al., 2011; Basat et al., 2013), **and 35 studies prescribed mixed mechanical forces protocols** (Grove and Londeree, 1992; Caplan et al., 1993; Nichols et al., 1995; Lord et al., 1996; Ryan et al., 1998; Adami et al., 1999; Kemmler, 1999; Iwamoto et al., 2001; Kerr et al., 2001; Going et al., 2003; Jessup et al., 2003; Milliken et al., 2003; Kemmler et al., 2004, 2010, 2013; Verschueren et al., 2004; Englund et al., 2005; Evans et al., 2007; Bergstrom et al., 2008; Kwon et al., 2008; Park et al., 2008; Bocalini et al., 2009; Chuin et al., 2009; de Matos et al., 2009; Deng, 2009; Bemben et al., 2010; Choquette et al., 2011; Marques et al., 2011b; Bolton et al., 2012; Karakiriou et al., 2012; Basat et al., 2013; Chilibeck et al., 2013). **A further of 5 training groups** (Chan et al., 2004; Woo et al., 2007; Liu et al., 2015; Wang et al., 2015), **could not be reliably classified within one of the categories therefore we excluded them from the subgroup analysis. A mixed-effects analysis found no significant differences between the categories (*P* = 0.46). According to the subgroup analysis, JRF exercise triggered the highest effect on LS-BMD (exercise vs. control, SMD = 0.46, 95%-CI: 0.21–0.70), followed by the mixed JRF and GRF (0.41, 0.22–0.59). GRF exercise however, did not significantly (*P* = 0.09) differ from corresponding control (0.24, −0.04 to 0.53).**

FN-BMD: Of 78 groups, 19 training groups were classified as JRF type exercise (Pruitt et al., 1992; Bloomfield et al., 1993; Nelson et al., 1994; Prince et al., 1995; Hartard et al., 1996; Kerr et al., 1996; Kohrt et al., 1997; Bemben et al., 2000; Rhodes et al., 2000; Chilibeck et al., 2002; Maddalozzo et al., 2007; Orsatti et al., 2013; Moreira et al., 2014; Nicholson et al., 2015; Duff et al., 2016;

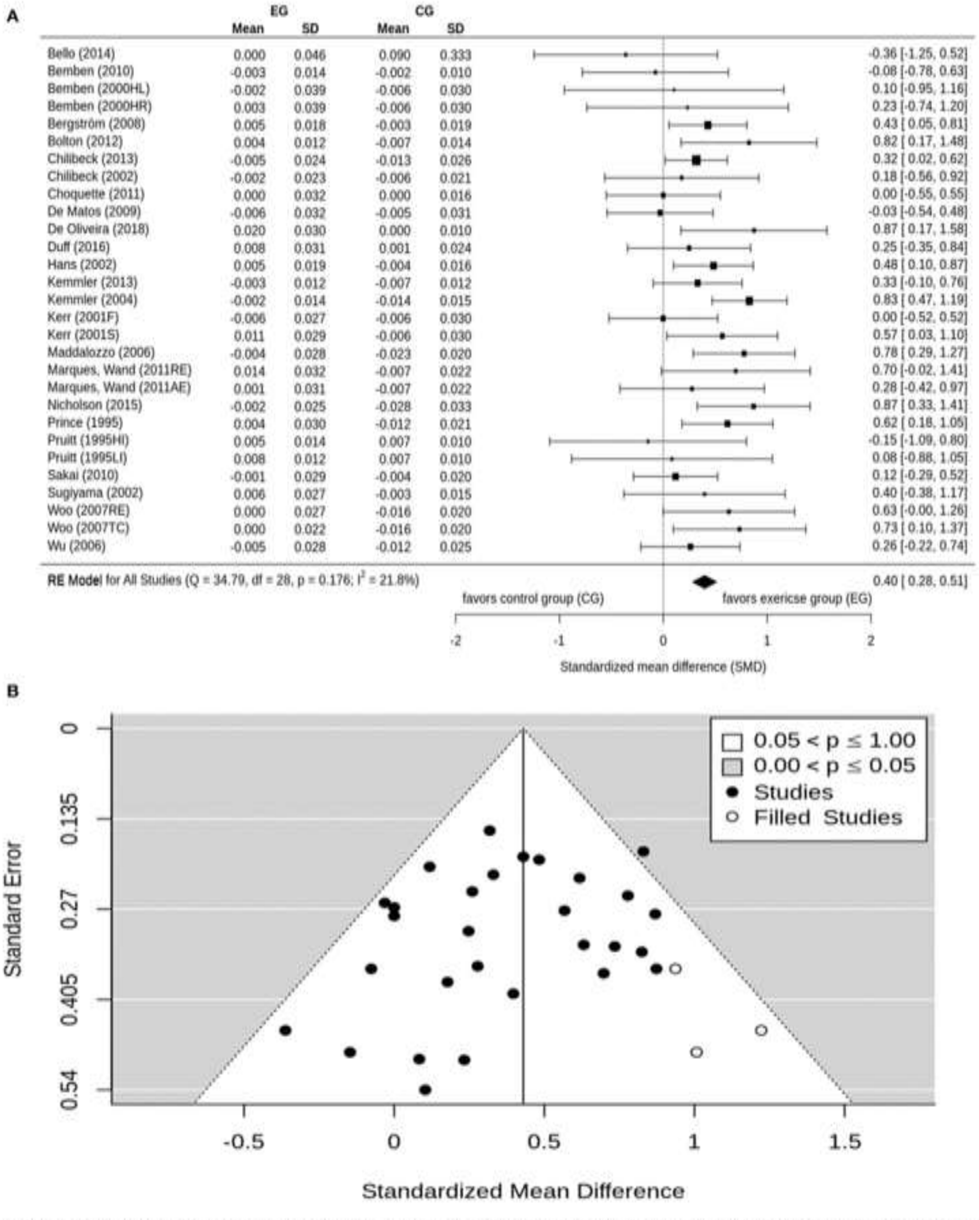

FIGURE 4 | (A) Forest plot of meta-analysis results at the total hip. The data are shown as pooled standard mean difference (SMD) with 95% CI for changes in exercise and control groups. **(B)** Funnel plot of total hip BMD with Trim and Fill. SE, standard error of standardized mean difference; SMD, standardized mean difference.

de Oliveira et al., 2019), 18 as GRF (Nelson et al., 1991; Lau et al., 1992; Bassey and Ramsdale, 1995; Kohrt et al., 1995, 1997; Prince et al., 1995; Brooke-Wavell et al., 1997, 2001; Ebrahim et al., 1997; Bassey et al., 1998; Hans et al., 2002; Sugiyama et al., 2002; Korpelainen et al., 2006; Wu et al., 2006; Silverman et al., 2009; Marques et al., 2011c; Tartibian et al., 2011; Basat et al., 2013) and 26 groups as mixed JRF and GRF protocols (Caplan et al., 1993; Nichols et al., 1995; Lord et al., 1996; Ryan et al., 1998; Adami et al., 1999; Kemmler, 1999; Going et al., 2003; Jessup et al., 2003; Milliken et al., 2003; Kemmler et al., 2004, 2010; Englund et al., 2005; Kwon et al., 2008; Park et al., 2008; Bocalini et al., 2009; Chuin et al., 2009; Deng, 2009; Tolomio et al., 2009; Bemben et al., 2010; Choquette et al., 2011; Marques et al., 2011b,c; Basat et al., 2013; Chilibeck et al., 2013; Bello et al., 2014). Five training groups cannot be reliably classified (Chan et al., 2004; Sakai et al., 2010; Liu et al., 2015; Wang et al., 2015), therefore they were excluded from the sub-group analysis. A mixed-effects analysis demonstrated no significant differences between the subgroups ($P = 0.89$). All the groups demonstrated comparable significant effects on FN-BMD (JRF: SMD = 0.29, 95%-CI: 0.14–0.44 vs. GRF: 0.35, 0.03–0.66 vs. JRF and GRF: 0.34, 0.19–0.49).

Total Hip-BMD: Of 29 groups, 10 training groups were included in the JRF group (Pruitt et al., 1995; Bemben et al., 2000; Chilibeck et al., 2002; Maddalozzo et al., 2007; Woo et al., 2007; Nicholson et al., 2015; Duff et al., 2016; de Oliveira et al., 2019). Five intervention groups were classified as GRF (Prince et al., 1995; Hans et al., 2002; Sugiyama et al., 2002; Wu et al., 2006; Marques et al., 2011c) and 12 groups as mixed intervention (Kerr et al., 2001; Kemmler et al., 2004, 2013; Bergstrom et al., 2008; de Matos et al., 2009; Bemben et al., 2010; Choquette et al., 2011; Marques et al., 2011c; Bolton et al., 2012; Chilibeck et al., 2013; Bello et al., 2014). Two training groups (Woo et al., 2007; Sakai et al., 2010) that could not be reliably classified were excluded. A mixed-effects analysis found no significant differences between the subgroups ($P = 0.57$). According to the subgroup analysis, effect size in the JRF-group was largest (SMD = 0.51, 95%-CI: 0.28–0.74), followed by the GRF (0.44, 0.22–0.66) and the mixed JRF and GRF subgroup (0.34, 0.14–0.53) obtained a positive significant difference in comparison with control groups.

DISCUSSION

A considerable number of systematic reviews and meta-analyses focus on the effect of exercise on BMD at the LS and/or proximal femur. With few exceptions (for LS; Howe et al., 2011) most studies reported low effect sizes (SMD = 0.2–0.5) on average (e.g., Kelley, 1998a,b; Martyn-St. James and Caroll, 2006; Howe et al., 2011; Marques et al., 2011a; Zhao et al., 2017). Due to continued research in the area, we have been able to include more exercise studies in our analysis than previous works (e.g., Howe et al., 2011; Marques et al., 2011a; Zhao et al., 2017). Nevertheless, our finding (SMD-LS = 0.37, SMD-FN = 0.33, SMD-tHip = 0.40) confirmed the results of a significant, but rather small effect of exercise on BMD, at the LS or a relevant proximal femur-ROIs. We largely attribute this finding of limited increase in BMD to the widely diverging effect sizes (e.g., **Figures 2A, 3B**) across the exercise trials included. Apart from participants' characteristics, considerable differences in exercise characteristics might explain these striking variations among the included trials. We sought to identify parameters that affect the impact of exercise on BMD. Therefore, studies were classified according to (1) menopausal status (Kemmler, 1999; Beck and Snow, 2003), (2) type of exercise (Giangregorio et al., 2014; Beck et al., 2017; Daly et al., 2019), (3) type of mechanical forces (JRF, GRF, JRF and GRF) (Martyn-St James and Carroll, 2011; Daly et al., 2019), and (4) duration of the intervention. Menopausal status might be an important predictor of exercise effects on BMD (Kemmler, 1999), due to the high bone-turnover during the early-menopausal years (Tella and Gallagher, 2014). However, the corresponding subgroup analysis did not determine significant differences or a consistent trend for all BMD-regions (LS, FN, tHip). Type of exercise and mechanical forces were included since mechanistically, they might be the most crucial predictors for the effect of exercise on bone (Giangregorio et al., 2014; Beck et al., 2017; Daly et al., 2019), while longer exposure to exercise (i.e., intervention duration) should result in higher effects on bone, at least when strain was regularly adjusted ("progression") (Kemmler et al., 2015). Accepting the viewpoint that exercise-induced BMD changes were predominately generated by remodeling (Eriksen, 2010), and considering the length of a remodeling cycle in (older) adults (Eriksen, 2010; Bonucci and Ballanti, 2014), interventions ≤8 months might be too short to determine the full extent of bones mineralization[1]. In contrast, although non-significant, the subgroup analysis demonstrated considerably higher effects on LS-BMD among studies with short compared with moderate or long durations (SMD = 0.59 vs. 0.30 vs. 0.28). Based on bone physiology (Eriksen, 2010), it is rather unlikely that exercise interventions ≤8 months resulted in higher increases in BMD-LS compared with interventions 18 months and longer. We attribute this dubious finding to the complex interaction of exercise parameters that might have confounded the interaction between training frequency and BMD-LS.

Significant differences in BMD changes within the corresponding subgroups was not detected. Tendentially negative effects of jumping exercise on LS- and FN-BMD[2] or the trend ($p = 0.06$) to higher effects of short exercise duration on LS and FN-BMD was observed.

We did not address exercise intensity (Rubin and Lanyon, 1985; Frost, 2003) or -frequency (Kemmler and von Stengel, 2013; Kemmler et al., 2016), which is a key modulator of effective exercise protocols (Weineck, 2019). It was planned to include "exercise intensity" in the subgroups analysis; however, it was not possible to present a meaningful and comprehensive rating of all the studies[3]. Since 15 studies did not report attendance rate and

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[1] Taking into account that DXA only determines the mineralized bone matrix (i.e., BMD).

[2] Most recommendations (e.g., Beck et al., 2017; Daly et al., 2019; Kemmler and von Stengel, 2019), however, consider Jumping as a favorable of type of exercise for PMW.

[3] The classification of exercise intensity in the area of bone research is not trivial. WK and SV failed to generate a reliable classification of exercise intensity/strain magnitude across the (endurance and resistance type) studies of the present review.

therefore the factual training frequency remained vague, exercise frequency was not evaluated.

Due to the results of the (exercise) group comparisons and subgroup analysis, we are unable to give validated exercise recommendations for optimized bone-strengthening protocols for PMW. In this context, Gentil et al. (2017) questioned whether "there is any practical application of meta-analytic results in strength training." This might be overstating the issue; however trying to derive exercise recommendations and, to a lesser degree, the proper effect size estimation will fail when addressing varying exercise interventions "en bloc." Several aspects support this view. First, exercise is a very complex intervention. The type of exercise alone ranges from HIT-RT or depth jumps, for example, to brisk walking, chair exercises and balance training. Additionally, exercise parameters (intensity, duration, cycle number, frequency etc.; Toigo and Boutellier, 2006; Weineck, 2019) and training principles (e.g., progression, periodization etc.; Weineck, 2019), fundamentally modify the effect of the exercise type on a given study endpoint. Even minor variations in single exercise parameters can result in considerable differences in BMD changes (e.g., Kemmler et al., 2016). In parallel, the present analysis indicates that a lack of consistent progression might prevent further BMD changes after initial adaptations[4], according to non-compliance with the overload principle (Weineck, 2019). At this point, a frequent limitation of exercise research arises: Unlike in pharmaceutical trials, the general effectiveness of the exercise protocol was rarely evaluated before the initiation of the clinical trial (phase III) (Umscheid et al., 2011). Further, in some cases, there is an impression that some older studies (Bloomfield et al., 1993; Brooke-Wavell et al., 1997, 2001) evaluate the least significant effect of exercise on bone. This further contributes to the considerable "apple-oranges problem" (Esteves et al., 2017; Milojevic et al., 2018) of meta-analysis in the area of "exercise." In summary thus, we conclude that uncritical acceptance of the acquired meta-analytic data (particularly) of exercise studies is certainly unwarranted.

Some study limitations may decrease the validity of our study. The lack of information related to participant and exercise characteristics and in the case of missing responses after contacting the authors meant that we estimated some variables. For example, in studies that did not provide the menopausal status of their participants, we consider the age of 51 years as the menopausal transition age to estimate the post-menopausal age (Palacios et al., 2010). Further, we excluded studies that included participants with pharmaceutic agents or diseases, known to relevantly affect BMD, in order to prevent a confounding, synergistic/additive/permissive effect on our study endpoints. However, due to the lack of information in most individual studies, we were unable to adjust for changes of medication, diet or emerging diseases.

Another predominately biometrical issue was that SDs of the absolute change in BMD were not consistently available and have thus to be imputed, which may have reduced the accuracy of the data. Further, there is considerable evidence for a publication bias with respect to exercise-induced BMD changes at the LS and tHip. Considering the aspect that most authors tend to reported positive effects the true effect size of exercise on BMD might be slightly lower compared to the results presented here (Sterne et al., 2011).

The main limitation was the extensive approach of including all types of exercise in the main analysis, which resulted in large variations in effects sizes. Moreover, our inability to categorize adequately relevant exercise characteristics hinders the proper comparison of homogeneous and widely independent subgroups and thus prevents validated exercise recommendations. Hence, upcoming meta-analysis in the area of exercise on bone should focus on dedicated areas of exercise. However, we conclude that well-designed randomized controlled trials which allow adjusting for one single parameter while keeping all others constant might be the better option for evaluating the contribution of participants and exercise parameters on exercise effect on bone and deriving sophisticated recommendations for exercise.

CONCLUSION

In summary, our approach of (1) including heterogeneous exercise studies, (2) categorizing them according to relevant modulators and exercise parameters, and (3) comparing the corresponding subgroups to identify modulators of exercise effects on bone and (more important) the most favorable exercise protocol on bone by means of enhanced statistics ultimately failed. This result can be largely attributed to fundamental and complex differences among the exercise protocols of the large amount of exercise studies included, which in effect prevent a meaningful categorization of exercise parameters.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the first author (mahdieh.shojaa@imp.uni-erlangen.de) at the Institute of Medical Physics of Friedrich-Alexander University Erlangen-Nürnberg upon reasonable request.

AUTHOR CONTRIBUTIONS

MS and WK initiated the Meta-analysis. The literature search was done by MS. MS, SV, MK, DS, and WK performed data analysis, interpretation, and drafted the manuscript. MS, WK, SV, MK, DS, GB, LB, LD, SM, MHM, AS, MM, MJ, and TR contributed to quality assessment and revised the manuscript. WK accepted responsibility for the integrity of the data sampling, analysis and interpretation. All authors contributed to the article and approved the submitted version.

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[4] We speculate that lack of progression contribute to the result of the subgroup analysis that address intervention-duration.

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REFERENCES

(1991). Consensus development conference: prophylaxis and treatment of osteoporosis. *Am. J. Med.* 90, 107–110. doi: 10.1016/0002-9343(91)90512-V

Adami, S., Gatti, D., Braga, V., Bianchini, D., and Rossini, M. (1999). Site-specific effects of strength training on bone structure and geometry of ultradistal radius in postmenopausal women. *J. Bone Miner. Res.* 14, 120–124. doi: 10.1359/jbmr.1999.14.1.120

Basat, H., Esmaeilzadeh, S., and Eskiyurt, N. (2013). The effects of strengthening and high-impact exercises on bone metabolism and quality of life in postmenopausal women: a randomized controlled trial. *J. Back Musculoskelet. Rehabil.* 26, 427–435. doi: 10.3233/BMR-130402

Bassey, E. J., and Ramsdale, S. J. (1995). Weight-bearing exercise and ground reaction forces: a 12-month randomized controlled trial of effects on bone mineral density in healthy postmenopausal women. *Bone* 16, 469–476. doi: 10.1016/8756-3282(95)90193-0

Bassey, E. J., Rothwell, M. C., Littlewood, J. J., and Pye, D. W. (1998). Pre- and postmenopausal women have different bone mineral density responses to the same high-impact exercise. *J. Bone Miner. Res.* 13, 1805–1813. doi: 10.1359/jbmr.1998.13.12.1805

Beck, B. R., Daly, R. M., Singh, M. A., and Taaffe, D. R. (2017). Exercise and sports science Australia (ESSA) position statement on exercise prescription for the prevention and management of osteoporosis. *J. Sci. Med. Sport* 20, 438–445. doi: 10.1016/j.jsams.2016.10.001

Beck, B. R., and Snow, C. M. (2003). Bone health across the lifespan–exercising our options. *Exerc. Sport Sci. Rev.* 31, 117–122. doi: 10.1097/00003677-200307000-00003

Bello, M., Sousa, M. C., Neto, G., Oliveira, L., Guerras, I., Mendes, R., et al. (2014). The effect of a long-term, community-based exercise program on bone mineral density in postmenopausal women with pre-diabetes and type 2 diabetes. *J. Hum. Kinet.* 43, 43–48. doi: 10.2478/hukin-2014-0088

Bemben, D. A., Fetters, N. L., Bemben, M. G., Nabavi, N., and Koh, E. T. (2000). Musculoskeletal responses to high- and low-intensity resistance training in early postmenopausal women. *Med. Sci. Sports Exerc.* 32, 1949–1957. doi: 10.1097/00005768-200011000-00020

Bemben, D. A., Palmer, I. J., Bemben, M. G., and Knehans, A. W. (2010). Effects of combined whole-body vibration and resistance training on muscular strength and bone metabolism in postmenopausal women. *Bone* 47, 650–656. doi: 10.1016/j.bone.2010.06.019

Bergstrom, I., Landgren, B., Brinck, J., and Freyschuss, B. (2008). Physical training preserves bone mineral density in postmenopausal women with forearm fractures and low bone mineral density. *Osteoporos Int.* 19, 177–183. doi: 10.1007/s00198-007-0445-6

Bloomfield, S. A., Williams, N. I., Lamb, D. R., and Jackson, R. D. (1993). Non-weightbearing exercise may increase lumbar spine bone mineral density in healthy postmenopausal women. *Am. J. Phys. Med. Rehabil.* 72, 204–209. doi: 10.1097/00002060-199308000-00006

Bocalini, D. S., Serra, A. J., dos Santos, L., Murad, N., and Levy, R. F. (2009). Strength training preserves the bone mineral density of postmenopausal women without hormone replacement therapy. *J. Aging Health* 21, 519–527. doi: 10.1177/0898264309332839

Bolton, K. L., Egerton, T., Wark, J., Wee, E., Matthews, B., Kelly, A., et al. (2012). Effects of exercise on bone density and falls risk factors in post-menopausal women with osteopenia: a randomised controlled trial. *J. Sci. Med. Sport* 15, 102–109. doi: 10.1016/j.jsams.2011.08.007

Bonaiuti, D., Shea, B., Iovine, R., Negrini, S., Robinson, V., Kemper, H. C., et al. (2002). Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database Syst. Rev.* 3:CD000333. doi: 10.1002/14651858.CD000333

Bonucci, E., and Ballanti, P. (2014). Osteoporosis-bone remodeling and animal models. *Toxicol. Pathol.* 42, 957–969. doi: 10.1177/0192623313512428

Brooke-Wavell, K., Jones, P. R., and Hardman, A. E. (1997). Brisk walking reduces calcaneal bone loss in post-menopausal women. *Clin. Sci.* 92, 75–80. doi: 10.1042/cs0920075

Brooke-Wavell, K., Jones, P. R., Hardman, A. E., Tsuritan and Yamada, Y. (2001). Commencing, continuing and stopping brisk walking: effects on bone mineral density, quantitative ultrasound of bone and markers of bone metabolism in postmenopausal women. *Osteoporos. Int.* 12, 581–587. doi: 10.1007/s001980170081

Caplan, G. A., Ward, J. A., and Lord, S. R. (1993). The benefits of exercise in postmenopausal women. *Aust. J. Public Health* 17, 23–26. doi: 10.1111/j.1753-6405.1993.tb00099.x

Chan, K., Qin, L., Lau, M., Woo, J., Au, S., Choy, W., et al. (2004). A randomized, prospective study of the effects of Tai Chi Chun exercise on bone mineral density in postmenopausal women. *Arch. Phys. Med. Rehabil.* 85, 717–722. doi: 10.1016/j.apmr.2003.08.091

Chilibeck, P. D., Davison, K. S., Whiting, S. J., Suzuki, Y., Janzen, C. L., and Peloso, P. (2002). The effect of strength training combined with bisphosphonate (etidronate) therapy on bone mineral, lean tissue, and fat mass in postmenopausal women. *Can. J. Physiol. Pharmacol.* 80, 941–950. doi: 10.1139/y02-126

Chilibeck, P. D., Vatanparast, H., Pierson, R., Case, A., Olatunbosun, O., Whiting, S. J., et al. (2013). Effect of exercise training combined with isoflavone supplementation on bone and lipids in postmenopausal women: a randomized clinical trial. *J. Bone Miner. Res.* 28, 780–793. doi: 10.1002/jbmr.1815

Choquette, S., Riesco, E., Cormier, E., Dion, T., Aubertin-Leheudre, M., and Dionne, I. J. (2011). Effects of soya isoflavones and exercise on body composition and clinical risk factors of cardiovascular diseases in overweight postmenopausal women: a 6-month double-blind controlled trial. *Br. J. Nutr.* 105, 1199–1209. doi: 10.1017/S0007114510004897

Christenson, E. S., Jiang, X., Kagan, R., and Schnatz, P. (2012). Osteoporosis management in post-menopausal women. *Minerva. Ginecol.* 64, 181–194.

Chuin, A., Labonte, M., Tessier, D., Khalil, A., Bobeuf, F., Doyon, C. Y., et al. (2009). Effect of antioxidants combined to resistance training on BMD in elderly women: a pilot study. *Osteoporos. Int.* 20, 1253–1258. doi: 10.1007/s00198-008-0798-5

Compston, J. E., McClung, M. R., and Leslie, W. D. (2019). Osteoporosis. *Lancet* 393, 364–376. doi: 10.1016/S0140-6736(18)32112-3

Daly, R. M., Dalla Via, J., Duckham, R. L., Fraser, S. F., and Helge, E. W. (2019). Exercise for the prevention of osteoporosis in postmenopausal women: an evidence-based guide to the optimal prescription. *Braz. J. Phys. Ther.* 23, 170–180. doi: 10.1016/j.bjpt.2018.11.011

de Matos, O. D. J., Lopes da Silva, J., de Oliveira, M., and Castelo-Branco, C. (2009). Effect of specific exercise training on bone mineral density in women with postmenopausal osteopenia or osteoporosis. *Gynecol. Endocrinol.* 25, 616–620. doi: 10.1080/09513590903015593

de Morton, N. A. (2009). The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *Aust. J. Physiother.* 55, 129–133. doi: 10.1016/S0004-9514(09)70043-1

de Oliveira, L. C., de Oliveira, R. G., and de Almeida Pires-Oliveira D. A. (2019). Effects of whole-body vibration versus pilates exercise on bone mineral density in postmenopausal women: a randomized and controlled clinical trial. *J. Geriatr. Phys. Ther.* 42, E23–E31. doi: 10.1519/JPT.0000000000000184

Deng, S. (2009). Effects of exercise therapy on bone mineral density in early postmenopausal women: a controlled trial. *Front. Med. China* 3, 323–329. doi: 10.1007/s11684-009-0061-2

Duff, W. R., Kontulainen, S. A., Candow, D. G., Gordon, J. J., Mason, R. S., Taylor-Gjevre, R., et al. (2016). Effects of low-dose ibuprofen supplementation and resistance training on bone and muscle in postmenopausal women: a randomized controlled trial. *Bone Rep.* 5, 96–103. doi: 10.1016/j.bonr.2016.04.004

Ebrahim, S., Thompson, P. W., Baskaran, V., and Evans, K. (1997). Randomized placebo-controlled trial of brisk walking in the prevention of postmenopausal osteoporosis. *Age Ageing* 26, 253–260. doi: 10.1093/ageing/26.4.253

Englund, U., Littbrand, H., Sondell, A., Pettersson, U., and Bucht, G. (2005). A 1-year combined weight-bearing training program is beneficial for bone mineral density and neuromuscular function in older women. *Osteoporos. Int.* 16, 1117–1123. doi: 10.1007/s00198-004-1821-0

Eriksen, E. F. (2010). Cellular mechanisms of bone remodeling. *Rev. Endocr. Metab. Disord.* 11, 219–227. doi: 10.1007/s11154-010-9153-1

Esteves, S. C., Majzoub, A., and Agarwal, A. (2017). The problem of mixing 'apples and oranges' in meta-analytic studies. *Transl. Androl. Urol.* 6(Suppl. 4), S412–S413. doi: 10.21037/tau.2017.03.23

Evans, E. M., Racette, S. B., Van Pelt, R. E., Peterson, L. R., and Villareal, D. T. (2007). Effects of soy protein isolate and moderate exercise on bone turnover and bone mineral density in postmenopausal women. *Menopause* 14(3 Pt 1), 481–488. doi: 10.1097/01.gme.0000243570.78570.f7

Frost, H. M. (2003). Bone's mechanostat. A 2003 update. *Anat Rec.* 275A, 1081–1101. doi: 10.1002/ar.a.10119

Garber, C. E., Blissmer, B., Deschenes, M. R., Franklin, B. A., Lamonte, M. J., Lee, I. M., et al. (2011). American College of Sports Medicine Position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med. Sci. Sports Exerc.* 43, 1334–1359. doi: 10.1249/MSS.0b013e318213fefb

Gentil, P., Arruda, A., Souza, D., Giessing, J., Paoli, A., Fisher, J., et al. (2017). Is there any practical application of meta-analytical results in strength training? *Front. Physiol.* 8:1. doi: 10.3389/fphys.2017.00001

Giangregorio, L. M., Papaioannou, A., Macintyre, N. J., Ashe, M. C., Heinonen, A., Shipp, K., et al. (2014). Too fit to fracture: exercise recommendations for individuals with osteoporosis or osteoporotic vertebral fracture. *Osteoporos. Int.* 25, 821–835. doi: 10.1007/s00198-013-2523-2

Going, S., Lohman, T., Houtkooper, L., Metcalfe, L., Flint-Wagner, H., Blew, R., et al. (2003). Effects of exercise on bone mineral density in calcium-replete postmenopausal women with and without hormone replacement therapy. *Osteoporos. Int.* 14, 637–643. doi: 10.1007/s00198-003-1436-x

Grove, K. A., and Londeree, B. R. (1992). Bone density in postmenopausal women: high impact vs low impact exercise. *Med. Sci. Sports Exerc.* 24, 1190–1194. doi: 10.1249/00005768-199211000-00002

Hans, D., Genton, L., Drezner, M. K., Schott, A. M., Pacifici, R., Avioli, L., et al. (2002). Monitored impact loading of the hip: initial testing of a home-use device. *Calcif. Tissue Int.* 71, 112–120. doi: 10.1007/s00223-001-2063-1

Harlow, S. D., Gass, M., Hall, J. E., Lobo, R., Maki, P., Rebar, R. W., et al. (2012). Executive summary of the Stages of reproductive aging workshop + 10: addressing the unfinished agenda of staging reproductive aging. *J. Clin. Endocrinol. Metab.* 97, 1159–1168. doi: 10.1210/jc.2011-3362

Hartard, M., Haber, P., Ilieva, D., Preisinger, E., Seidl, G., and Huber, J. (1996). Systematic strength training as a model of therapeutic intervention. A controlled trial in postmenopausal women with osteopenia. *Am. J. Phys. Med. Rehabil.* 75, 21–28. doi: 10.1097/00002060-199601000-00006

Hatori, M., Hasegawa, A., Adachi, H., Shinozaki, A., Hayashi, R., Okano, H., et al. (1993). The effects of walking at the anaerobic threshold level on vertebral bone loss in postmenopausal women. *Calcif. Tissue Int.* 52, 411–414. doi: 10.1007/BF00571327

Higgins, J. P. T., and Green, S. (2008). *Cochrane Handbook for Systematic Reviews of Interventions.* Chichester; West Sussex: The Cochrane Collaboration; John Wiley & Sons. doi: 10.1002/9780470712184

Howe, T. E., Shea, B., Dawson, L. J., Downie, F., Murray, A., Ross, C., et al. (2011). Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database Syst. Rev.* 6:Cd000333. doi: 10.1002/14651858.CD000333.pub2

Iwamoto, J., Takeda, T., and Ichimura, S. (2001). Effect of exercise training and detraining on bone mineral density in postmenopausal women with osteoporosis. *J. Orthop. Sci.* 6, 128–132. doi: 10.1007/s007760100059

Jessup, J. V., Horne, C., Vishen, R. K., and Wheeler, D. (2003). Effects of exercise on bone density, balance, and self-efficacy in older women. *Biol. Res. Nurs.* 4, 171–180. doi: 10.1177/1099800402239628

Karakiriou, S., Douda, H., Smilios, I., Volaklis, K. A., and Tokmakidis, S. P. (2012). Effects of vibration and exercise training on bone mineral density and muscle strength in post-menopausal women. *Eur. J. Sport Sci.* 12, 81–88. doi: 10.1080/17461391.2010.536581

Kelley, G. A. (1998a). Aerobic exercise and bone density at the hip in postmenopausal women: a meta-analysis. *Prev. Med.* 27, 798–807. doi: 10.1006/pmed.1998.0360

Kelley, G. A. (1998b). Exercise and regional bone mineral density in postmenopausal women: a meta-analytic review of randomized trials. *Am. J. Phys. Med. Rehabil.* 77, 76–87. doi: 10.1097/00002060-199801000-00015

Kemmler, W. (1999). Einfluß unterschiedlicher lebensabschnitte auf die belastungsabhängige reaktion ossärer risikofaktoren einer osteoporose. *Dtsch. Z Sportmed.* 50, 114–119.

Kemmler, W., Bebenek, M., Kohl, M., and Von Stengel, S. (2015). Exercise and fractures in postmenopausal women. Final results of the controlled erlangen fitness and osteoporosis prevention study (EFOPS). *Osteoporos. Int.* 26, 2491–2499. doi: 10.1007/s00198-015-3165-3

Kemmler, W., Bebenek, M., von Stengel, S., Engelke, K., and Kalender, W. A. (2013). Effect of block-periodized exercise training on bone and coronary heart disease risk factors in early post-menopausal women: a randomized controlled study. *Scand. J. Med. Sci. Sports* 23, 121–129. doi: 10.1111/j.1600-0838.2011.01335.x

Kemmler, W., Lauber, D., Weineck, J., Hensen, J., Kalender, W., and Engelke, K. (2004). Benefits of 2 years of intense exercise on bone density, physical fitness, and blood lipids in early postmenopausal osteopenic women: results of the erlangen fitness osteoporosis prevention study (EFOPS). *Arch. Intern. Med.* 164, 1084–1091. doi: 10.1001/archinte.164.10.1084

Kemmler, W., and von Stengel, S. (2013). Exercise frequency, health risk factors, and diseases of the elderly. *Arch. Phys. Med. Rehabil.* 94, 2046–2053. doi: 10.1016/j.apmr.2013.05.013

Kemmler, W., and von Stengel, S. (2019). "Chapter 20 - the role of exercise on fracture reduction and bone strengthening," in *Muscle and Exercise Physiology*, ed J. A. Zoladz (Academic Press), 433–455. doi: 10.1016/B978-0-12-814593-7.00020-7

Kemmler, W., von Stengel, S., Engelke, K., Haberle, L., and Kalender, W. A. (2010). Exercise effects on bone mineral density, falls, coronary risk factors, and health care costs in older women: the randomized controlled senior fitness and prevention (SEFIP) study. *Arch. Intern. Med.* 170, 179–185. doi: 10.1001/archinternmed.2009.499

Kemmler, W., von Stengel, S., and Kohl, M. (2016). Exercise frequency and bone mineral density development in exercising postmenopausal osteopenic women. Is there a critical dose of exercise for affecting bone? Results of the erlangen fitness and osteoporosis prevention study. *Bone* 89, 1–6. doi: 10.1016/j.bone.2016.04.019

Kerr, D., Ackland, T., Maslen, B., Morton, A., and Prince, R. (2001). Resistance training over 2 years increases bone mass in calcium-replete postmenopausal women. *J. Bone Miner. Res.* 16, 175–181. doi: 10.1359/jbmr.2001.16.1.175

Kerr, D., Morton, A., Dick, I., and Prince, R. (1996). Exercise effects on bone mass in postmenopausal women are site-specific and load-dependent. *J. Bone. Miner. Res.* 11, 218–225. doi: 10.1002/jbmr.5650110211

Kohrt, W. M., Ehsani, A. A., and Birge, S. J. Jr. (1997). Effects of exercise involving predominantly either joint-reaction or ground-reaction forces on bone mineral density in older women. *J. Bone Miner. Res.* 12, 1253–1261. doi: 10.1359/jbmr.1997.12.8.1253

Kohrt, W. M., Snead, D. B., Slatopolsky, E., and Birge, S. J. Jr. (1995). Additive effects of weight-bearing exercise and estrogen on bone mineral density in older women. *J. Bone Miner. Res.* 10, 1303–1311. doi: 10.1002/jbmr.5650100906

Korpelainen, R., Keinanen-Kiukaanniemi, S., Heikkinen, J., Vaananen, K., and Korpelainen, J. (2006). Effect of impact exercise on bone mineral density in elderly women with low BMD: a population-based randomized controlled 30-month intervention. *Osteoporos. Int.* 17, 109–118. doi: 10.1007/s00198-005-1924-2

Kwon, Y., Park, S., Kim, E., and Park, J. (2008). The effects of multi-component exercise training on VO_{2max}, muscle mass, whole bone mineral density and fall risk in community-dwelling elderly women Jpn. *J. Phys. Fitness Sport Med.* 57, 339–348. doi: 10.7600/jspfsm.57.339

Lau, E. M., Woo, J., Leung, P. C., Swaminathan, R., and Leung, D. (1992). The effects of calcium supplementation and exercise on bone density in elderly Chinese women. *Osteoporos. Int.* 2, 168–173. doi: 10.1007/BF01623922

Liu, B. X., Chen, S. P., Li, Y. D., Wang, J., Zhang, B., Lin, Y., et al. (2015). The effect of the modified eighth section of eight-section brocade on osteoporosis in postmenopausal women: a prospective randomized trial. *Medicine* 94:e991. doi: 10.1097/MD.0000000000000991

Lord, S. R., Ward, J. A., Williams, P., and Zivanovic, E. (1996). The effects of a community exercise program on fracture risk factors in older women. *Osteoporos. Int.* 6, 361–367. doi: 10.1007/BF01623009

Maddalozzo, G. F., Widrick, J. J., Cardinal, B. J., Winters-Stone, K. M., Hoffman, M. A., and Snow, C. M. (2007). The effects of hormone replacement therapy and resistance training on spine bone mineral density in early postmenopausal women. *Bone* 40, 1244–1251. doi: 10.1016/j.bone.2006.12.059

Marques, E. A., Mota, J., and Carvalho, J. (2011a). Exercise effects on bone mineral density in older adults: a meta-analysis of randomized controlled trials. *Age* 34, 1493–1515. doi: 10.1007/s11357-011-9311-8

Marques, E. A., Mota, J., Machado, L., Sousa, F., Coelho, M., Moreira, P., et al. (2011b). Multicomponent training program with weight-bearing exercises elicits favorable bone density, muscle strength, and balance adaptations in older women. *Calcif. Tissue Int.* 88, 117–129. doi: 10.1007/s00223-010-9437-1

Marques, E. A., Wanderley, F., Machado, L., Sousa, F., Viana, J. L., Moreira-Goncalves, D., et al. (2011c). Effects of resistance and aerobic exercise on physical function, bone mineral density, OPG and RANKL in older women. *Exp. Gerontol.* 46, 524–532. doi: 10.1016/j.exger.2011.02.005

Martin, D., and Notelovitz, M. (1993). Effects of aerobic training on bone mineral density of postmenopausal women. *J. Bone Miner. Res.* 8, 931–936. doi: 10.1002/jbmr.5650080805

Martyn-St James, M., and Carroll, S. (2011). Effects of different impact exercise modalities on bone mineral density in premenopausal women: a meta-analysis. *J. Bone Miner. Metab.* 28, 251–267. doi: 10.1007/s00774-009-0139-6

Martyn-St. James, M., and Caroll, S. (2006). High intensity exercise training and postmenopausal bone loss: a meta-analysis. *Osteoporos. Int.* 17, 1225–1240. doi: 10.1007/s00198-006-0083-4

Milliken, L. A., Going, S. B., Houtkooper, L. B., Flint-Wagner, H. G., Figueroa, A., Metcalfe, L. L., et al. (2003). Effects of exercise training on bone remodeling, insulin-like growth factors, and bone mineral density in postmenopausal women with and without hormone replacement therapy. *Calcif. Tissue Int.* 72, 478–484. doi: 10.1007/s00223-001-1128-5

Milojevic, M., Sousa-Uva, M., Durko, A. P., and Head, S. J. (2018). Mixing 'apples and oranges' in meta-analytic studies: dangerous or delicious? *Eur. J. Cardiothorac. Surg.* 53, 1294–1298. doi: 10.1093/ejcts/ezx471

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., et al. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst. Rev.* 4:1. doi: 10.1186/2046-4053-4-1

Moreira, L. D., Fronza, F. C., Dos Santos, R. N., Zach, P. L., Kunii, I. S., Hayashi, L. F., et al. (2014). The benefits of a high-intensity aquatic exercise program (HydrOS) for bone metabolism and bone mass of postmenopausal women. *J. Bone Miner. Metab.* 32, 411–419. doi: 10.1007/s00774-013-0509-y

Nelson, M. E., Fiatarone, M. A., Morganti, C. M., Trice, I., Greenberg, R. A., and Evans, W. J. (1994). Effects of high-intensity strength training on multiple risk factors for osteoporotic fractures. A randomized controlled trial. *JAMA* 272, 1909–1914. doi: 10.1001/jama.272.24.1909

Nelson, M. E., Fisher, E. C., Dilmanian, F. A., Dallal, G. E., and Evans, W. J. (1991). A 1-y walking program and increased dietary calcium in postmenopausal women: effects on bone. *Am. J. Clin. Nutr.* 53, 1304–1311. doi: 10.1093/ajcn/53.5.1304

Nichols, J., Nelson, K., Peterson, K., and Sartoris, D. (1995). Bone mineral density responses to high-intensity strength training in active older *women. J. Aging Phys. Act.* 3, 26–38. doi: 10.1123/japa.3.1.26

Nicholson, V. P., McKean, M. R., Slater, G. J., Kerr, A., and Burkett, B. J. (2015). Low-load very high-repetition resistance training attenuates bone loss at the lumbar spine in active post-menopausal women. *Calcif. Tissue Int.* 96, 490–499. doi: 10.1007/s00223-015-9976-6

Orsatti, F. N., Nahas-Neto, J., Orsatti, C. L., and Teixeira, A. S. (2013). Effects of isoflavone and counter-resistance training on bone mineral density in postmenopausal women. *Rev. Bras. Cineantropom. Desempenho. Hum.* 15, 726–736. doi: 10.5007/1980-0037.2013v15n6p726

Palacios, S., Henderson, V. W., Siseles, N., Tan, D., and Villaseca, P. (2010). Age of menopause and impact of climacteric symptoms by geographical region. *Climacteric* 13, 419–428. doi: 10.3109/13697137.2010.507886

Park, H., Kim, K. J., Komatsu, T., Park, S. K., and Mutoh, Y. (2008). Effect of combined exercise training on bone, body balance, and gait ability: a randomized controlled study in community-dwelling elderly women. *J. Bone Miner. Metab.* 26, 254–259. doi: 10.1007/s00774-007-0819-z

Prince, R., Devine, A., Dick, I., Criddle, A., Kerr, D., Kent, N., et al. (1995). The effects of calcium supplementation (milk powder or tablets) and exercise on bone density in postmenopausal women. *J. Bone Miner. Res.* 10, 1068–1075. doi: 10.1002/jbmr.5650100711

Pruitt, L. A., Jackson, R. D., Bartels, R. L., and Lehnhard, H. J. (1992). Weight-training effects on bone mineral density in early postmenopausal women. *J. Bone Miner. Res.* 7, 179–185. doi: 10.1002/jbmr.5650070209

Pruitt, L. A., Taaffe, D. R., and Marcus, R. (1995). Effects of a one-year high-intensity versus low-intensity resistance training program on bone mineral density in older women. *J. Bone Miner. Res.* 10, 1788–1795. doi: 10.1002/jbmr.5650101123

R Development Core Team (2019). *A Language and Environment for Statistical Computing.* Vienna: A Foundation for Statistical Computing.

Rhodes, E. C., Martin, A. D., Taunton, J. E., Donnelly, M., Warren, J., and Elliot, J. (2000). Effects of one year of resistance training on the relation between muscular strength and bone density in elderly women. *Br. J. Sports Med.* 34, 18–22. doi: 10.1136/bjsm.34.1.18

Ribeiro de Avila, V., Bento, T., Gomes, W., Leitao, J., and de Sousa, N. F. (2018). Functional outcomes and quality of life after ankle fracture surgically treated: a systematic review. *J. Sport Rehabil.* 27, 274–283. doi: 10.1123/jsr.2016-0199

Rubin, C. T., and Lanyon, L. E. (1985). Regulation of bone mass by mechanical strain magnitude. *Calcif. Tissue Int.* 37, 411–417. doi: 10.1007/BF02553711

Ryan, A. S., Nicklas, B. J., and Dennis, K. E. (1998). Aerobic exercise maintains regional bone mineral density during weight loss in postmenopausal women. *J. Appl. Physiol. (1985)* 84, 1305–1310. doi: 10.1152/jappl.1998.84.4.1305

Sakai, A., Oshige, T., Zenke, Y., Yamanaka, Y., Nagaishi, H., and Nakamura, T. (2010). Unipedal standing exercise and hip bone mineral density in postmenopausal women: a randomized controlled trial. *J. Bone Miner. Metab.* 28, 42–48. doi: 10.1007/s00774-009-0100-8

Sherrington, C., Herbert, R. D., Maher, C. G., and Moseley, A. M. (2000). PEDro. A database of randomized trials and systematic reviews in physiotherapy. *Man. Ther.* 5, 223–226. doi: 10.1054/math.2000.0372

Silverman, N. E., Nicklas, B. J., and Ryan, A. S. (2009). Addition of aerobic exercise to a weight loss program increases BMD, with an associated reduction in inflammation in overweight postmenopausal women. *Calcif. Tissue Int.* 84, 257–265. doi: 10.1007/s00223-009-9232-z

Sinaki, M., Wahner, H. W., Offord, K. P., and Hodgson, S. F. (1989). Efficacy of nonloading exercises in prevention of vertebral bone loss in postmenopausal women: a controlled trial. *Mayo Clin. Proc.* 64, 762–769. doi: 10.1016/S0025-6196(12)61748-0

Sterne, J. A., Sutton, A. J., Ioannidis, J. P., Terrin, N., Jones, D. R., Lau, J., et al. (2011). Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 343:d4002. doi: 10.1136/bmj.d4002

Sugiyama, T., Yamaguchi, A., and Kawai, S. (2002). Effects of skeletal loading on bone mass and compensation mechanism in bone: a new insight into the mechanostat theory. *J. Bone Miner. Metab.* 20, 196–200. doi: 10.1007/s007740200028

Tartibian, B., Hajizadeh Maleki, B., Kanaley, J., and Sadeghi, K. (2011). Long-term aerobic exercise and omega-3 supplementation modulate osteoporosis through inflammatory mechanisms in post-menopausal women: a randomized, repeated measures study. *Nutr. Metab.* 8:71. doi: 10.1186/1743-7075-8-71

Tella, S. H., and Gallagher, J. C. (2014). Prevention and treatment of postmenopausal osteoporosis. *J. Steroid. Biochem. Mol. Biol.* 142, 155–170. doi: 10.1016/j.jsbmb.2013.09.008

Toigo, M., and Boutellier, U. (2006). New fundamental resistance exercise determinants of molecular and cellular muscle adaptations. *Eur. J. Appl. Physiol.* 97, 643–663. doi: 10.1007/s00421-006-0238-1

Tolomio, S., Lalli, A., Travain, G., and Zaccaria, M. (2009). Effects of a combined weight-bearing and non-weight-bearing (warm water) exercise program on bone mass and quality in postmenopausal women with low bone-mineral density. *Clin. Ter.* 160, 105–109.

Umscheid, C. A., Margolis, D. J., and Grossman, C. E. (2011). Key concepts of clinical trials: a narrative review. *Postgrad. Med.* 123, 194–204. doi: 10.3810/pgm.2011.09.2475

Verschueren, S. M., Roelants, M., Delecluse, C., Swinnen, S., Vanderschueren, D., and Boonen, S. (2004). Effect of 6-month whole body vibration training on hip density, muscle strength, and postural control in postmenopausal women: a randomized controlled pilot study. *J. Bone Miner. Res.* 19, 352–359. doi: 10.1359/JBMR.0301245

Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. *J. Stat. Softw.* 36, 1–48. doi: 10.18637/jss.v036.i03

Wang, H., Yu, B., Chen, W., Lu, Y., and Yu, D. (2015). Simplified tai chi resistance training versus traditional tai chi in slowing bone loss in postmenopausal women. *Evid. Based Complement Alternat. Med.* 2015:379451. doi: 10.1155/2015/379451

Weineck, J. (2019). *Optimales Training*. Erlangen: Spitta-Verlag.

Woo, J., Hong, A., Lau, E., and Lynn, H. (2007). A randomised controlled trial of tai chi and resistance exercise on bone health, muscle strength and balance in community-living elderly people. *Age Ageing* 36, 262–268. doi: 10.1093/ageing/afm005

Wu, J., Oka, J., Tabata, I., Higuchi, M., Toda, T., Fuku, N., et al. (2006). Effects of isoflavone and exercise on BMD and fat mass in postmenopausal Japanese women: a 1-year randomized placebo-controlled trial. *J. Bone Miner. Res.* 21, 780–789. doi: 10.1359/jbmr.060208

Yamazaki, S., Ichimura, S., Iwamoto, J., Takeda, T., and Toyama, Y. (2004). Effect of walking exercise on bone metabolism in postmenopausal women with osteopenia/osteoporosis. *J. Bone Miner. Metab.* 22, 500–508. doi: 10.1007/s00774-004-0514-2

Zhao, R., Zhang, M., and Zhang, Q. (2017). The effectiveness of combined exercise interventions for preventing postmenopausal bone loss: a systematic review and meta-analysis. *J. Orthop. Sports Phys. Ther.* 47, 241–251. doi: 10.2519/jospt.2017.6969

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Projekt 2

Effects of dynamic resistance exercise on bone mineral density in postmenopausal women: a systematic review and meta-analysis with special emphasis on exercise parameters

M. Shojaa, S. von Stengel, M. Kohl, D. Schoene, W. Kemmler. Effects of dynamic resistance exercise on bone mineral density in postmenopausal women: a systematic review and meta-analysis with special emphasis on exercise parameters. Osteoporosis International.2020; 31:1427–1444. https://doi.org/10.1007/s00198-020-05441-w

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ZUSAMMENFASSUNG

Hintergrund und Ziele

DRT ist definiert als jede Art vom Krafttraining, die eine Gelenkbewegung beinhaltet und sich auf die Entwicklung der Muskel-Skelett-Kraft konzentriert. DRT wird die als wichtiger Bestandteil der Osteoporose-Prävention und -Therapie angesehen. Diese vorliegende Studie wurde durchgeführt, um den Effekt des DRT auf die BMD bei PMW zu bestimmen und evidenzbasierte Empfehlungen für optimierte Trainingsprotokolle abzuleiten.

Methoden und Material

Dieser Review folgte den Vorgaben, die in der PRISMA-Erklärung (Preferred Reporting Items for Systematic Reviews and MetaAnalyses) empfohlen werden, und wurde vorab im Internationalen prospektiven Register systematischer Übersichtsarbeiten (PROSPERO) (ID: CRD42018095097) registriert. Literaturrecherchen ohne Sprachbeschränkung wurden bis März 2019 in acht elektronischen Datenbanken durchgeführt. Kontrollierte Studien mit ≥ 6 Monate Interventionsdauer bei PMW, die eine DRT-Intervention mit mindestens einer Trainings- und einer Kontrollgruppe umfassten, wurden in diese Studie eingeschlossen. Metaanalysen wurden mit Zufallseffektmodellen und Effektgrößen durchgeführt, die anhand der SMD für BMD-Veränderungen an LS, FN und tHip berechnet wurden. Moderatoren der Trainingseffekte, d.h. "Interventionsdauer", "Art der DRT", "Trainingshäufigkeit", "Reizintensität" und "Übungsvolumen", wurden durch Subgruppenanalysen angesprochen. P < 0,05 wurden als statistisch signifikant betrachtet.

Ergebnisse

Siebzehn Artikel mit 20 Trainings- und 18 Kontrollgruppen erfüllten unsere Auswahlkriterien. Die Ergebnisse der Metaanalysen zeigten einen signifikanten Effekt für die LS (SMD = 0,54, 95%-CI: 0,22-0,87), FN (SMD = 0,22, 95%-CI: 0,07-0,38) und die tHip (SMD = 0,48, 95%-CI: 0,22-0,75) (alle P ≤ 0,015). Die Analyse der Subgruppen ergab jedoch keine Unterschiede innerhalb der Kategorien der Moderatoren für FN. Eine niedrigere Trainingshäufigkeit (< 2 Sitzungen/Woche) führte zu signifikant höheren BMD-Veränderungen bei LS und tHip im Vergleich zu einer höheren

Trainingshäufigkeit (≥ 2 Sitzungen/Woche). Darüber hinaus zeigte unser Ergebnis, dass Freikrafttraining eine größere Wirkung als DRT-Geräte zur Verbesserung von tHip-BMD hatte. Leider konnten aus den Ergebnissen der Subanalyse keine aussagekräftigen Trainingsempfehlungen abgeleitet werden.

Schlussfolgerung

Diese systematische Übersichtsarbeit und Meta-Analyse ergab eine signifikante niedrig-moderate Wirkung des dynamischen Krafttrainings auf die Knochengehalt bei postmenopausalen Frauen. Die Trainingscharakteristika erlaubten es uns jedoch nicht, aussagekräftige Trainingsempfehlungen im Bereich der Bewegung und Osteoporose-Prävention oder -Therapie abzuleiten.

SUMMARY

Background and Aims

DRT defined as any kind of resistance exercise that involves joint movement and focuses on the development of musculoskeletal strength, which is considered an important component of osteoporosis prevention and therapy. This current study conducted to determine the effect of DRT on BMD in PMW and derive evidence-based recommendations for optimized training protocols.

Material and Methods

This review followed the guidelines recommended by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement and was registered in advance in the International prospective register of systematic reviews (PROSPERO) (ID: CRD42018095097). Literature searches with no language restriction were conducted through eight electronic databases up to March 2019. Controlled trials with ≥ 6 months intervention duration among PMW that comprised DRT intervention with at least one exercise and one control group were included in this study. Meta-analyses were performed using random-effects models and effect sizes calculated using the SMD for BMD changes at LS, FN, and tHip. Moderators of the exercise effects, i.e., “intervention length,” “type of DRT,” “training frequency,” “exercise intensity,” and “exercise volume,” were addressed by sub-group analyses. P-values < 0.05 were considered statistically significant.

Results

Seventeen articles with 20 exercise and 18 control groups met our eligibility criteria. Results of the meta-analyses showed a significant effect for LS (SMD = 0.54, 95%-CI: 0.22–0.87), FN (SMD = 0.22, 95%-CI: 0.07–0.38), and tHip (SMD = 0.48, 95%-CI: 0.22–0.75) (all P ≤ 0.015). However, sub-group analysis revealed no differences within categories of moderators for FN. Lower training frequency (< 2 sessions/week) resulted in significantly higher BMD changes at LS and tHip compared to higher training frequency (≥ 2 sessions/week). Furthermore, our result demonstrated that free weight training had a greater effect than DRT devices for improving tHip-

BMD. Unfortunately, sub-analysis results did not allow meaningful exercise recommendations to be derived.

Conclusions

This systematic review and meta-analysis revealed a significant low-moderate effect of dynamic resistance exercise on BMD in PMW. However, exercise characteristics did not allow us to derive meaningful exercise recommendations in the area of exercise and osteoporosis prevention or therapy.

EINLEITUNG Projekt 2

Die Wirksamkeit von körperlichem Training auf die BMD per se und der Einfluss unterschiedlichen Trainings- und Teilnehmer-Charakteristika auf dieses Ergebnis wurde im ersten Teil des Projekts evaluiert. Die Analysen der Subgruppen ergaben jedoch keine signifikanten Unterschiede zwischen den verschiedenen Trainingstypen. Entsprechend den erzielten Ergebnissen könnte sich die Frage stellen, warum der zweite Teil des Projekts durchgeführt wurde. Bei der Beantwortung dieser Frage ist zu berücksichtigen, dass wir uns im ersten Teil des Projekts aufgrund der hohen Anzahl der Artikel auf unsere Hauptergebnisse konzentriert haben. Daher wurde der Effekt von Teilnehmercharakteristika (z.B. Menopausenstatus) und Interventionscharakteristika (z.B. Interventionsdauer) nur auf der Basis der verschiedenen Knochenregionen (LS, FN, T-Hüfte) evaluiert, ohne bestimmte Trainingstypen zu berücksichtigen. Eine beträchtliche Anzahl von Studien in diesem Bereich und der hohe Effekt der Interventionsparameter auf die Wirksamkeit dieser Art von Intervention führten uns zur Durchführung dieser Analyse.

Außerdem beschränkten sich die wenigen anderen früheren Meta-Analysen auf Studien, die vor mehr als 14 Jahren veröffentlicht wurden (Martyn-St James und Carroll, 2006; Kelley et al., 2001). Aufgrund der fortgesetzten Forschung in diesem Bereich wurden weitere randomisierte kontrollierte Studien veröffentlicht (Bemben et al., 2010; Maddalozzo et al., 2007; Woo et al., 2007; de Oliveira et al., 2019; Duff et al., 2016; Nicholson et al., 2015; Orsatti et al., 2013).

Zusätzlich ist der vorliegende Artikel nach unserem besten Wissen die einzige Studie, die sich speziell mit Trainingsparametern bei PMW befasst. Daher besteht, abgesehen von einer Meta-Analyse, die sich auf isolierte DRT-Protokolle konzentriert, Forschungsbedarf mit dem Ziel, effektive Trainingsparameter zu identifizieren, um Empfehlungen für Trainingsprotokolle im Bereich der Osteoporose zu erarbeiten.

Aus diesem Grund zielten wir in der vorliegenden systematischen Review und Meta-Analyse darauf ab, den Effekt (Größe) der isolierten DRT auf die BMD bei PMW im Vergleich zu

Kontrollgruppen zu bestimmen (primäres Studienziel) und weiter relevante Trainingscharakteristika durch Subanalyse zu identifizieren, um daraus Empfehlungen für optimierte Trainingsprotokolle in der klinischen Praxis abzuleiten (sekundäres Studienziel).

Insgesamt wurden 17 eligible Studien mit 20 Trainings- und 18 Kontrollgruppen in die aktuelle systematische Review und Meta-Analyse aufgenommen (siehe Abb. 2).

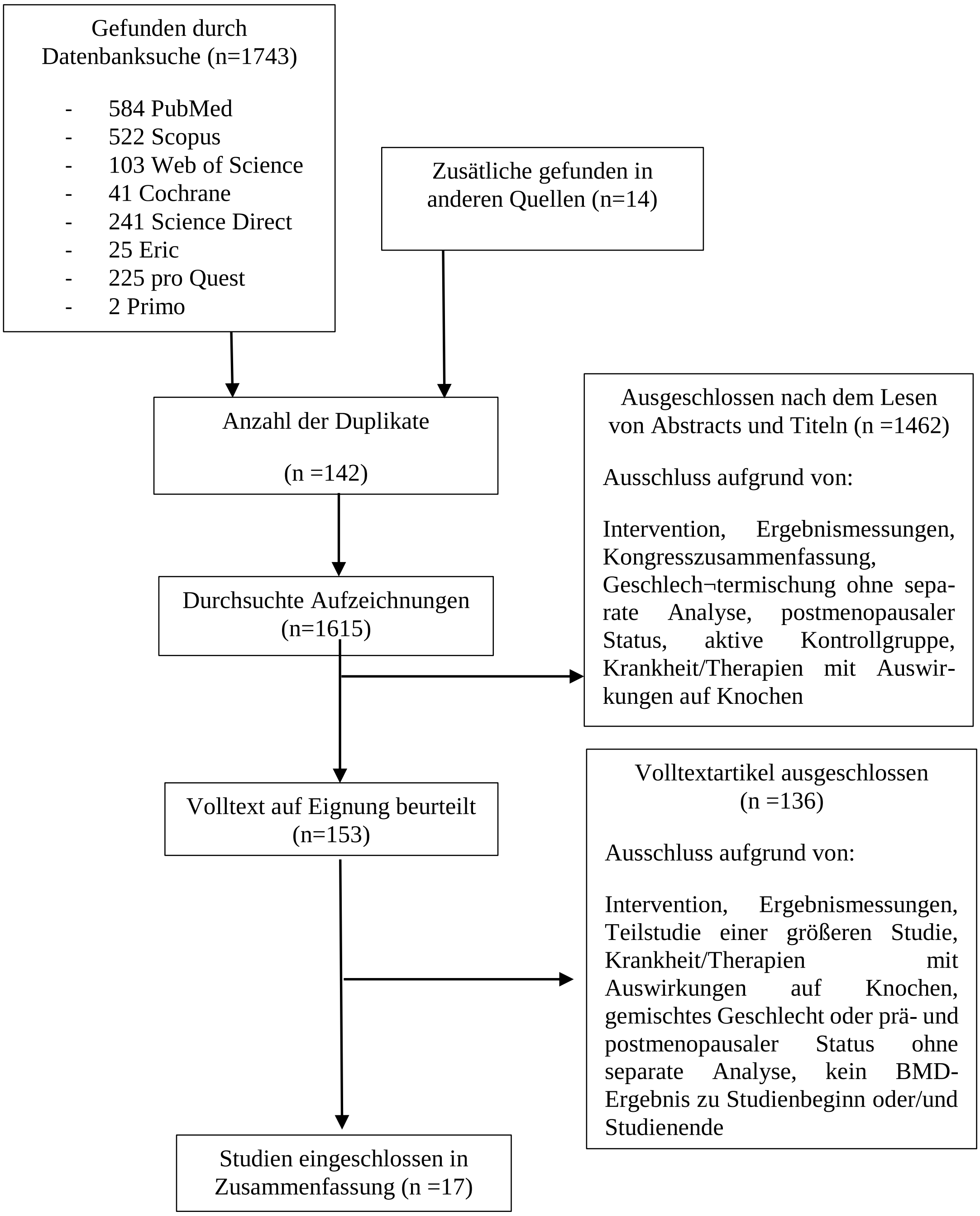

Abb.2: Flussdiagramm zum Verlauf der Studienauswahl

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REVIEW

Effects of dynamic resistance exercise on bone mineral density in postmenopausal women: a systematic review and meta-analysis with special emphasis on exercise parameters

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Abstract
This systematic review and meta-analysis set out to determine the effect of dynamic resistance exercise (DRT) on areal bone mineral density (aBMD) in postmenopausal women and derive evidence-based recommendations for optimized training protocols. A systematic review of the literature according to the PRISMA statement included (a) controlled trials, (b) of isolated DRT with at least one exercise and one control group, (c) with intervention durations ≥ 6 months, (d) aBMD assessments at lumbar spine or proximal femur, (e) in cohorts of postmenopausal women. We searched eight electronic databases up to March 2019 without language restrictions. The meta-analysis was performed using a random-effects model. Standardized mean differences (SMD) for BMD changes at lumbar spine (LS), femoral neck (FN), and total hip (TH) were defined as outcome measures. Moderators of the exercise effects, i.e., "intervention length," "type of DRT," "training frequency," "exercise intensity," and "exercise volume," were addressed by sub-group analyses. The study was registered in the international prospective register of systematic reviews (PROSPERO) under ID: CRD42018095097. Seventeen articles with 20 exercise and 18 control groups were eligible. SMD average is 0.54 (95% CI 0.22–0.87) for LS-BMD, 0.22 (0.07–0.38) for FN-BMD, and 0.48 (0.22–0.75) for TH-BMD changes (all $p \leq 0.015$). While sub-group analysis for FN-BMD revealed no differences within categories of moderators, lower training frequency (< 2 sessions/week) resulted in significantly higher BMD changes at LS and TH compared to higher training frequency (≥ 2 sessions/week). Additionally, free weight training was significantly superior to DRT devices for improving TH-BMD. This work provided further evidence for significant, albeit only low–moderate, effects of DRT on LS-, FN-, and TH-BMD. Unfortunately, sub-analysis results did not allow meaningful exercise recommendations to be derived. This systematic review and meta-analysis observed a significant low–moderate effect of dynamic resistance exercise on bone mineral density changes in postmenopausal women. However, sub-group analyses focusing on exercise characteristics found no results that enable the derivation of meaningful exercise recommendations in the area of exercise and osteoporosis prevention or therapy.

Keywords Bone mineral density · Dynamic resistance exercise · Exercise characteristics · Postmenopausal women

Introduction

Physical exercise is the most powerful non-pharmaceutical fracture prevention strategy in postmenopausal women [1, 2]. Dynamic resistance training (DRT) as defined as any kind of resistance exercise that involves joint movement and focuses on the development of musculoskeletal strength is considered an important component of osteoporosis prevention and therapy [3–5]. Nevertheless, with respect to areal bone mineral density (aBMD), recent meta-analysis on DRT reported on average low exercise-induced effect sizes at best (review in [6–9]). Reviewing the underlying studies, however, there is some evidence that not only isolated DRT protocols were included in the meta-analysis. Further, large variations between the individual study findings can be observed. The main reason for this outcome can be attributed to the complexity of exercise interventions with respect to exercise variables (e.g., exercise intensity, duration, frequency), training principles (e.g., progression, periodization), and training conditions (e.g., supervision, devices) [10]. Previous meta-analysis on

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DRT did not account for training parameters. At best, there was separate analysis for "exercise intensity" [6]. Thus, apart from meta-analysis that properly focuses on isolated DRT protocols, there is a need for research aimed at identifying effective training parameters to generate recommendations for exercise protocols in the area of osteoporosis.

Therefore, in the present systematic review and meta-analysis, our primary study aim was to determine the effect (size) of isolated DRT on BMD at lumbar spine and proximal femur regions of interest (ROI) in postmenopausal women in comparison with control groups and further (secondary study aim) to identify relevant exercise characteristics by sub-analysis to derive recommendations for optimized exercise protocols in clinical practice.

Material and methods

Data sources and search strategy

The present study on DRT was based on a comprehensive systematic review of the effect of exercise on (areal) BMD in postmenopausal women. This systematic review and meta-analysis followed strictly the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [11]. The study was registered in the international prospective register of systematic reviews (PROSPERO) (ID: CRD42018095097). Briefly, eight electronic databases (PubMed, Scopus, Web of Science, Cochrane, Science Direct, Eric, ProQuest, and Primo) were searched for relevant articles published up to March 1, 2019 without language restrictions. The search strategy related to the population, intervention, and outcomes and was constructed around search terms for "Bone Mineral Density", "Exercise," and "Postmenopausal." Key words and their synonyms were used to sensitize the search by applying the following query: ("Bone" or "Bone mass" or "Bone status" or "Bone structure" or "Bone turnover" or "Bone metabolism" or "Bone mineral content" or "Skeleton" or "Bone Mineral Density" or "BMD" or "Bone Density" or "Osteoporoses" or "Osteoporosis" or "Osteopenia") AND ("Postmenopause" or "Post-Menopause" or "Postmenopausal") AND ("Exercise" or "Training" or "Athletic" or "Sport" or" "physical activity") AND ("Clinical trial" or "Randomized clinical trial"). Unpublished reports or congress abstracts were not considered. One reviewer (MS) conducted the search and, following the omission of duplicate publication, screened studies by title and abstracts according to the eligibility criteria. In the secondary search, reference lists of articles included were reviewed to further identify relevant and eligible studies.

In summary, 42 authors were contacted by e-mail due to the following issues: (a) participants/group allocation, (b) missing drop out data, (c) separation of the pre- or postmenopausal group, (d) result given in a graph only, (e) no mean change of BMD given, (f) missing standard deviation (SD).

Inclusion and exclusion criteria

We included studies (or study arms) if they met the following criteria: (a) randomized and non-randomized controlled trials with at least one exercise group as an intervention versus one control group with sedentary/habitual active lifestyle without exercise or with sham exercise; (b) women with postmenopausal status at study onset; (c) intervention of at least 6 months; (d) areal BMD of the LS or/and the proximal femur regions "TH" and/or "FN" were listed as outcome measures at baseline and follow-up assessment; (f) BMD determined by dual-energy X-ray absorptiometry (DXA) or dual-photon absorptiometry (DPA); (g) $\leq 10\%$ of participants on hormone (replacement) therapy (HT or HRT), osteoanabolic/antiresorptive (e.g., bisphosphonate, denosumab, strontium ranelate), or osteocatabolic (glucocorticoids) and pharmaceutic agents, albeit only when the number of users was comparable between exercise and control. For the present analysis on isolated DRT effects, we further included only studies (f) that applied isolated DRT without any adjuvant exercise component and without bone specific warm-ups with validated effect on bone (e.g., running, hopping, aerobic dance).

We excluded studies that included (a) mixed gender or mixed pre- and postmenopausal cohorts without separate BMD analysis for postmenopausal women[1], (b) women undergoing chemo- and/or radiotherapy, and (c) women with diseases that relevantly affect bone metabolism. Further, (d) double/multiple publications from one study and preliminary data from subsequently published trials and (e) review articles, case reports, editorials, conference abstracts, and letters were not considered. For the present analysis on isolated DRT effects, we likewise excluded studies (f) that reported a pre-study history of RT type exercise ≥ 60 min/week 1 year prior to the study intervention.

Data extraction

Two reviewers (SvS and MS) independently evaluated full-text articles and extracted data from the included studies. If they could not reach a consensus, a third reviewer was consulted (KW). We designed a pre-piloted extraction form to extract relevant data. This covered the publication characteristics (e.g., (first) author's name, title, country, and publication year), methodology (i.e., design, objectives, sample size for each group), participant characteristics (i.e., age, weight, BMI, years since menopause), exercise characteristics (e.g.,

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[1] We do not exclude studies with participants that were not community dwelling

intervention duration, training frequency, exercise intensity, movement/velocity, progression), compliance/withdrawals, risk assessment, BMD, and outcome characteristics.

Outcome measures

The primary outcomes in the present study was the change in (areal) BMD at lumbar spine, total hip (TH), and femoral neck (FN) regions of interest (ROI) as assessed by DXA or DPA between baseline and follow-up.

Quality assessment

All the articles that satisfied the predefined inclusion criteria were independently assessed for risk of bias by two independent raters (WK and MV) using the PEDro (Physiotherapy Evidence Database) scale [12, 13]. Disagreements were solved by discussion including a third assessor (SvS) until a consensus was reached. We classified the methodological quality of the included studies as follows: ≥ 7 = high, 5–6 = moderate, and < 5 = low [14].

Data synthesis

According to the "Cochrane Handbook for Systematic Reviews of Interventions" [15], standard deviation (SD) can be obtained from the standard error (SE) or confidence interval (CI) by using the following formulas[2]:

$$\mathrm{SD} = \mathrm{SE} \times \sqrt{}_N$$

$$\mathrm{SD} = \sqrt{}_N \times (\text{upper limit}-\text{lower limit})/3.92$$

Further, authors ($n = 11$) were contacted to provide missing SDs. In cases of no reply or unavailable data ($n = 11$), the exact p value of the absolute change in BMD was obtained to compute the SD of the mean change. In cases of unreported p values ($n = 11$), we calculated the SDs using pre- and post-SDs and correlation coefficients according to the Cochrane Handbook of Systemic Reviews [15]. Lastly, when the absolute mean difference was not available, it was imputed by calculation of the difference between post- and pre-intervention ($n = 7$). In cases of multiple BMD assessments, we considered only changes between the baseline and final BMD assessments.

To identify potential predictors of successful DRT protocols, we applied several sub-group analyses for the following: (a) intervention period (≤ 8 months vs. 9–18 months vs. > 18 months); (b) type of RT (machines vs. free weight vs. both types); (c) net training frequency[3] (< 2 vs. ≥ 2 sessions/week); (d) exercise intensity (low (< 65% 1RM) vs. moderate (65–< 80% 1RM) vs. high (≥ 80% 1RM)); and (e) exercise volume per session (exercises × sets × repetitions) as structured in low (< 160 reps/session), moderate (160 to < 300 reps session), and high (≥ 300 reps/session) volume.

Statistical analysis

The statistical analysis was performed using the statistical software R (R Development Core Team) [16]. Effect size (ES) value was considered as the standardized mean differences (SMDs) combined with the 95% confidence interval (CI).

Random-effects meta-analysis was performed by applying the metafor package [17]. Heterogeneity for between-study variability was determined using the Cochran Q test; comparable to other statistical analysis, a p value < 0.05 was considered significant. The level of heterogeneity was analyzed with the I^2 statistic. An I^2 of between 0 and 40% is considered as low, 30 to 60% as moderate, and 50 to 90% as substantial heterogeneity, respectively [15]. For those studies with two different intervention groups, the control group was proportionally split into two groups for comparison against each intervention group [15]. Sensitivity analysis was conducted to check whether the overall result of the analysis is robust regarding the use of the imputed correlation coefficient. Funnel plots with regression test and the rank correlation between effect estimates and their standard errors (SEs), using the t test and Kendall's τ statistic respectively, were applied to explore potential publication bias. To adjust the results for possible publication bias, we also conducted a trim and fill analysis using the L0 estimator proposed by Duval et al. [18]. A p value of < 0.05 was considered as significant for all tests.

In order to identify potential moderators of exercise, subgroup analyses were performed with the exercise parameters and their corresponding categories as listed above.

Results

Study characteristics and quality assessments

In total, our search identified 17 eligible studies ([19–35]; Fig. 1), with 20 exercise and 18 control groups. Table 1 displays participant baseline characteristics of the included studies.

The pooled number of participants in the intervention and control groups was 423 and 373 women, respectively. Sample sizes in the exercise arms ranged from 10 [31] to 35 participants [27] per group. Only one study [24] included women with osteopenia/osteoporosis[4]; none of the other studies considered bone status (Table 2). Age of the postmenopausal women in the studies ranged between 41 and 60 years [19] and 65–82 years [32]. Menopausal age varied from 0.5 [34] to

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[2] One study reported CI and 8 studies utilized SE.

[3] …considering participants attendance rate.

[4] > 30% of bone tissue loss as determined by X-ray assessment at LS or hip.

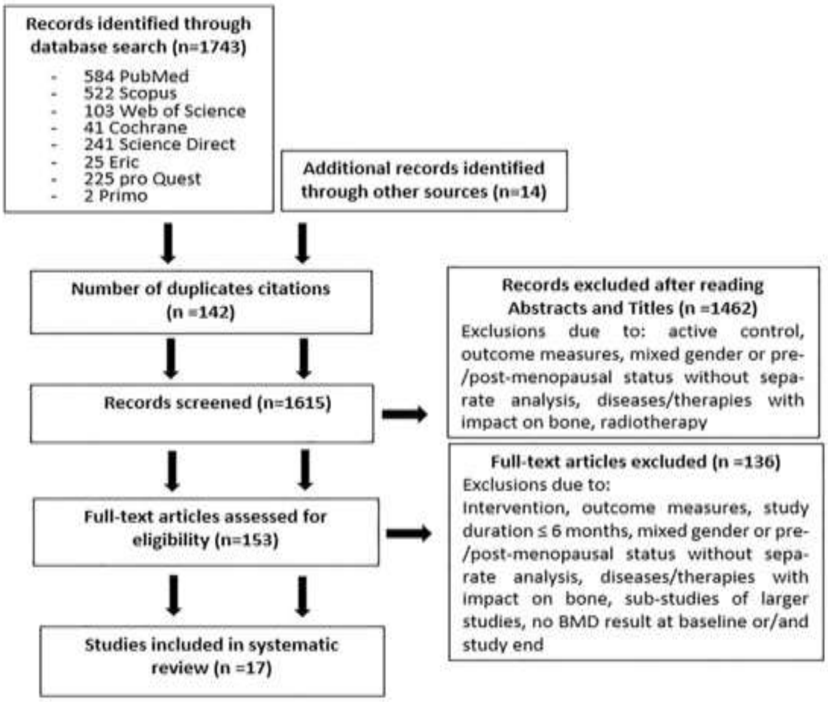

Fig. 1 Flow diagram of search process according to PRISMA [11]

> 21 years post [26]. Three studies [19, 27, 31] focused particularly on cohorts of "early postmenopausal women" (1–≤ 7 years post). Average body mass index among the groups averaged from 23.1 [28] to 28.7 kg/m^2 [19]. Six studies included participants with sedentary/habitually active lifestyles or at least no prior RT exposure [20, 22, 26, 28, 30, 33, 35], 8 trials involved participants with exercise activities presumably with minor effects on bone [19, 21, 23–25, 29, 31, 32], and two studies did not provide corresponding information [27, 34]. The studies were conducted in Australia [29], Brazil [22, 30], Canada [21, 23, 36], Germany [24], Hong Kong [35], and the USA [19, 20, 25–28, 31, 32, 34].

Intervention characteristics

Vitamin-D and calcium supplementation

Six studies provided Vit-D and/or calcium supplementation [19, 21, 23, 26, 32] in their exercise and control groups.

Exercise

Table 2 specifies the exercise protocols of included studies. Apart from three studies [19, 25, 32], all trials compared a single exercise group (EG) with a single non-exercise control group (CG). From the criteria, all the studies applied DRT; the majority of studies used conventional RT machines or free weights, one study [22] applied "Pilates exercises" with specific devices (e.g., reformer, cadillac), and another study [35] used an resistance band of low–moderate strength.

Length of the intervention (or study) ranged from six [19, 22, 24, 29] to 24 months [34]; no study reported a delay between the end of the intervention and the control assessment. Most studies focused on all or most main muscle groups.[5] Kerr et al. [25] applied a unilateral DRT that stresses the "ipsilateral forearm and hip region," Sinaki et al. [34] focused on back strengthening in a prone position, Woo et al. [35] predominately conducted hip and lower limb exercises, and Maddalozzo et al. [27] specified back squats and deadlifts. Apart from two studies that did not provide sufficient information for the LS-site [25, 35], all the studies addressed their specified BMD ROI (i.e., LS and hip) with specific exercises.

Most studies prescribed a training frequency of three sessions per week (Table 2); however, when considering participant attendance, the net training frequency of five studies [24, 26–29] was on average below two sessions per week. Length

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[5] In addition to the DRT, Kohrt et al. [26] applied 2–3 × 10 min bouts of intense rowing exercise.

Table 1 Baseline characteristics of participants in included studies ($n = 17$)

First author, year	Initial sample size (n)	Age (years)	Menopausal age (years)	Body mass (kg)	Height (cm)	BMI (kg/m^2)
Bemben[a], 2000	HI: 13 HR: 11 C: 11	HI: 50 ± 2 HR: 52 ± 2 C: 52 ± 1	HI: 4 ± 1 HR: 2 ± 1 C: 3 ± 1	HI: 74.7 ± 5.6 HR: 62.7 ± 3.4 C: 66.5 ± 4.2	HI: 162 ± 2 HR: 165 ± 2 C: 166 ± 2	HI: 28.7 ± 2.4 HR: 23.2 ± 1.2 C: 24.2 ± 1.7
Bemben 2010	E: 22 C: 12	E: 64 ± 1 C: 63 ± 1	> 5	E: 76.6 ± 3.2 C: 77.9 ± 4.5	E: 161 ± 2 C: 163 ± 1	E: 30 ± 1 C: 29 ± 1
Chilibeck, 2002 *	E: 14 C: 14	E: 57 ± 2 C: 59 ± 2	E: 9 ± 2 C: 8 ± 2	E: 72 ± 4.3 C: 73.2 ± 4.8	E: 164 ± 2 C: 165 ± 1	E: 27.0 ± 1.7 C: 26.6 ± 1.2
de Oliveira, 2018	E: 17 C: 17	E: 56 ± 7 C: 54 ± 5	E: 8 ± 7 C: 9 ± 7	E: 67.4 ± 8.6 C: 64.6 ± 6.6	E: 157 ± 6 C: 154 ± 4	E: 27.2 ± 2.7 C: 27.3 ± 2.5
Duff, 2016	E: 22 C: 22	E: 65 ± 5 C: 65 ± 5	n.g. n.g.	n.g. n.g.	E: 162 ± 6 C: 160 ± 7	n.g. n.g.
Hartard 1996	E: 18 C: 16	E: 64 ± 6 C: 67 ± 10	E > 2 C > 2	E: 67 ± 7.7 C: 63.8 ± 11.2	E: 162 ± 7 C: 158 ± 6	n.g. n.g.
Kerr[b], 1996	HI: 28 HR: 28	HI: 58 ± 4 HR: 56 ± 5	HI: 8 ± 3 HR: 6 ± 4	HI: 69.4 ± 11.4 HR: 70.8 ± 10	HI: 165 ± 7 HR: 165 ± 6	n.g. n.g.
Kohrt, 1997 *	E: 15 C: 15	E: 65 ± 1 C: 68 ± 1	n.g. n.g.	E: 72.6 ± 2.3 C: 71.6 ± 1.8	E: 164 ± 2 C: 163 ± 2	n.g. n.g.
Madda-lozzo, 2007	E: 35 C: 34	E: 52 ± 3 C: 52 ± 3	E: 2 ± 1 C: 2 ± 1	E: 70 ± 8.7 C: 67.1 ± 12.6	n.g. n.g.	n.g. n.g.
Nelson, 1994	E: 21 C: 19	E: 61 ± 4 C: 57 ± 6	E: 12 ± 5 C: 10 ± 5	E: 64.7 ± 7.7 C: 62.2 ± 8.9	E: 163 ± 6 C: 164 ± 8	E: 24.4 ± 2.5 C: 23.1 ± 2.2
Nicholson, 2015	E: 28 C: 29	E: 66 ± 4 C: 66 ± 5	E: > 5 C: > 5	E: 70.6 ± 9.1 C: 66.8 ± 10.7	E: 164 ± 4 C: 163 ± 5	E: 26 ± 3.2 C: 24.5 ± 2.9
Orsatti, 2013	E + Pl: 20 Pl: 20	E + Pl: 56 ± 9 Pl: 55 ± 8	E + Pl: 9 ± 6 Pl: 8 ± 6	n.g. n.g.	n.g. n.g.	E + Pl: 26 ± 3.0 Pl: 30.4 ± 5.3
Pruitt, 1992 *	E: 17 C: 10	E: 54 ± 1 C: 56 ± 1	E: 3 ± 1 C: 4 ± 1	E: 64.2 ± 1.9 C: 65.5 ± 2.9	E: 162 ± 1 C: 163 ± 2	n.g. n.g.
Pruitt, 1995	HI: 15 HR: 13 C: 12	HI: 67 ± 1 HR: 68 ± 1 C: 70 ± 4	n.g. n.g. n.g.	HI: 64.5 ± 9.2 HR: 61.5 ± 4.6 C: 63.8 ± 9.1	HI: 162 ± 7 HR: 160 ± 5 C: 160 ± 9	HI: 24.5 ± 3.4 HR: 23.9 ± 1.6 C: 25.1 ± 3.1
Rhodes, 2000	E: 22 C: 22	E: 69 ± 3 C: 68 ± 3	n.g. n.g.	E: 68.4 ± 12 C: 61.7 ± 12.9	E: 161 ± 5 C: 159 ± 4	n.g. n.g.
Sinaki, 1989	E: 34 C: 34	E: 56 ± 4 C: 56 ± 4	n.g. n.g.	E: 66.2 ± 9.3 C: 66.1 ± 10.6	E: 163 ± 6 C: 161 ± 5	n.g. n.g.
Woo, 2007	E: 30 C: 30	E: 70 ± 3 C: 69 ± 3	n.g. n.g.	n.g. n.g.	n.g. n.g.	E: 24.6 ±4.0 C: 24.9 ± 3.0

All values are presented as mean ± SD, otherwise stated

HI high intensity, *HR* high repetition, *C* control (group), *E* exercise (group), *Pl* placebo, *n.g.* not given

*Values are presented as mean ± SE

[a] Baseline data of the study completers ($n = 25$)

[b] Unilateral loading (hip, forearm) with the contralateral side as control

of the exercise sessions varied from about 1–2 min (i.e., 10× back extension [34]) to about 120 min (i.e., 36 sets × 20 reps, 2–3 min of rest between the sets). Most studies applied a multiple set approach ([19–21, 23–28, 30, 32, 33]. The protocol of Nicholson et al. [29] scheduled 10 × 4–6 min blocks of one (e.g., squats) or several exercises for the same muscle groups (e.g., chest, back, triceps). As a result, repetitions per set for a single exercise were up to 108 reps (132 reps/block) [29] for the latter study, but most studies applied sets with 7–12 repetitions [19–28, 30–34].[6] Three studies [19, 25, 32], comparing high versus low intensity RT protocols, further scheduled sets of 14–20 reps in their low intensity study arms. Correspondingly, relative exercise intensity ranged between 80% 1RM [19, 20, 25, 26, 28, 30, 32] and ≤ 30% 1RM [29, 34]. Absolute exercise intensity (i.e., "effort")

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[6] This relates to the high intensity exercise groups of three studies [19, 25, 32]. Further, one study [30] prescribed sets of 20–30 reps for two exercises.

Table 2 Exercise characteristics of included studies ($n = 16$)

Author, year	Health and exercise status	Length (months)	PR-INT	Type of exercise, amount of exercises, methods	Site specificity	Volume in min/w.; setting; (attendance rate)	Exercise/strain composition
Bemben, 2000 Low intensity	Healthy, no RT	6	Yes	DRT (most main muscle groups) on machines	LS: Yes TH: Yes	3 × 60; S-JE; (93%)	8 exercises, 3 sets, 16 reps, 40% 1RM
Bemben, 2000 High intensity	Healthy, no RT	6	Yes	DRT (most main muscle groups) on machines	LS: Yes TH: Yes	3 × 60; S-JE; (87%)	8 exercises, 3 sets, 8 reps, 80% 1RM
Bemben, 2010	Healthy, no RT	8	No	DRT (most main muscle groups) on machines	LS: Yes TH: Yes	3 × 60; S-JE; (92%)	8 exercises, 3 sets, 10 reps, 80% 1RM
Chilibeck, 2002	Healthy, no BSE	12	Yes	DRT (all main muscle groups) on machines	LS: Yes TH: Yes	3× RT; S-JE; (78%)	12 exercises, 2 sets, 8–10 reps, ≈ 70–80% 1RM ("a weight that could be lifted comfortably for 10 reps")
Campos de Oliveira, 2018	Healthy, Sed/HA	6	Yes	Pilates (strengthening and flexibility; all mains muscle groups) on Pilates "devices."	LS: Yes TH: Yes	3 × 60; S-JE; (93%)	21 exercises (strengthening and flexibility), 1 set, 10 reps, RPE 5–6 at Borg CR10
Duff, 2016	Healthy, no RT	9	Yes	DRT (all main muscle groups) on machines and with free weights	LS: Yes TH: Yes	3× RT; S-JE; (n.g.)	12 exercises, 2 sets of 8–12 reps to muscular fatigue
Hartard, 1996	Osteopenia, < 1 h week	6	Yes	DRT (all main muscle groups) on machines, stretching	LS: Yes TH: Yes	2× ≈ 60; S-JE; n.g.	14 exercises, 2 sets, 8–12 reps to "marked fatigue" (≈ 70% 1RM), 3–4 s per reps
Kerr, 1996 Low intensity	Healthy, no RT	12	Yes	Unilateral DRT (randomized allocation of the upper or hip/lower limb to exercise or control) on machines or free weights.	LS:? TH: yes	3× ≈ 120; S-JE; (82%)	12 exercises; 3 sets, 20 RM (≈ 60–65% 1RM), 2–3 min rest between sets
Kerr, 1996 High intensity	Healthy, no RT	12	Yes	Unilateral DRT (see above) on machines or free weights.	LS:? TH: yes	3× ≈ 100 S-JE; (82%)	12 exercises; 3 sets, 8 RM (≈ 75–80% 1RM), 2–3 min rest between sets
Kohrt, 1997	Healthy, Sed/HA	11	Yes	DRT (most main muscle groups) on machines and with free weights, rowing	LS: Yes TH: Yes	5 × 45–50; n.g. (presumably S-JE); (≈ 70%)	DRT: 2× week, 8 exercises, 2–3 sets, 8–12 reps "to fatigue" (≈ 70–80% 1RM) and rowing: 3× week, 2–3 sets × 10 min at 80–85% HRmax
Maddalozzo, 2007	Healthy, n.g.	12	Yes	DRT (back squat, deadlifts) with free weights; subordinate: exercises that focus on alignment, flexibility, posture, abdominal strength	LS: Yes TH: Yes	2 × 50; S-JE; (85%)	2 exercises, 2 warm-ups sets, 10–12 reps, 50% 1RM; 3 sets, 8–12 reps, 60–75% 1RM; TUT: 1–2 s concentric – 0 s isometric −2-3 s eccentric
Nelson, 1994	Healthy, Sed/HA	12	Yes	DRT ("most" main muscle groups) on machines.	LS: Yes TH: Yes	2 × 45; S-JE; (88%)	5 exercises, 3 sets, 8 reps, 80% 1RM; TUT-6-9 s/rep; 3 s rest between reps, 90–120 s rest between sets
Nicholson, 2015	Healthy, no RT	6	Yes	DRT (all main muscle groups): "Body Pump Release 83" (i.e., barbell exercises with (very) low intensity)	LS: Yes TH: Yes	2 × 50, S-JE; (89%)	10× ≈ 4–6 min blocks of exercises for all main muscle groups (21 exercises in total); up to 108 reps (squats), ≤ 30% 1RM
Orsatti, 2013	Healthy, Sed/HA	9	Yes	DRT (all main muscle groups) on machines and with free weights	LS: Yes TH: Yes	3 × 50–60, S-JE; (n.g.)	8 exercises 3 sets at 8–12 RM; 3 sets, 20–30 reps for trunk flexion and calf raises; 1–2 min rest

Table 2 (continued)

Author, year	Health and exercise status	Length (months)	PR-INT	Type of exercise, amount of exercises, methods	Site specificity	Volume in min/w.; setting; (attendance rate)	Exercise/strain composition
Pruitt, 1992	Healthy, no BSE	9	Yes	DRT (all main muscle groups) on machines and with free weights	LS: Yes TH: Yes	3 × 60; S-JE; (83%)	11 exercises, 1 set at 10 RM (no more details given)
Pruitt, 1995 High intensity	Healthy no RT	12	Yes	DRT (all main muscle groups) on machines	LS: Yes TH: Yes	3 × 60; S-JE; (79%)	10 exercises, 1 warm up set, 14 reps, 40% and 2 sets, 7 reps, 80% 1RM
Pruitt, 1995 Low intensity	Healthy No RT	12	Yes	DRT (all main muscle groups) on machines	LS: Yes TH: Yes	3 × 60; S-JE; (79%)	10 exercises, 3 sets, 14 reps, 40% 1RM
Rhodes, 2000	Healthy, "no organi-zed sports"	12	Yes	DRT (all main muscle groups) on machines	LS: Yes TH: Yes	3 × 60; PS-IE; (86%)	≥6 exercises (n.g. in detail), 3 sets, 8 reps, ≈75% 1RM, TUT: 2–3 s concentric – 3-4 s eccentric movement/rep applied in a circuit mode.
Sinaki, 1989	Healthy, n.g.	24	No	DRT (back strengthening exercise in a prone position using a back pack; ≈hyperextensions) with a free weight	LS: Yes ---------	5× ≈ 1–2 min; HE; n.g.	One back strengthening exercise, 1 set, 10 reps, with a weight „equivalent to 30% of the maximum isometric back muscle strength in pounds (maximum 23 kg)
Woo, 2007	Healthy, no RT	12	No	DRT (arm-lifting, hip-abduction, heel raise, hip-flexion,-extension, squat) using resistance bands	LS:? TH: Yes	3× ≈ 15 min; (n.g.); (76%)	6 exercises, 1 set, 30 reps with a resistance band "of medium strength" (no more information given).

Health status: We focused on reported osteoporosis/osteopenia and fractures only. Otherwise, women were listed as "healthy." Exercise status: we mainly used the characterization of the authors. In some cases, we summarize the information given as "no bone-specific exercise." Progression: We only considered the progression of exercise intensity during the intervention. Site specificity: Estimated site specificity of the exercise to address LS- or hip-BMD. Exercise volume/week, setting, attendance: Number of sessions per week × minutes per session (e.g., 3 × 60). Setting of the exercise session, i.e., either supervised group (S-JE), partially supervised individual (PS-IE) or home exercise/exercise individually performed without supervision (HE). Attendance defined as rate of sessions performed in relation to total exercise sessions (%). Composition of strain/exercise variables per session: number of exercises, number of sets, number of repetitions; exercise intensity, set endpoint (e.g., …"to failure"), time under tension per rep/movement velocity, rest pauses between sets

BSE bone specific exercise, *Sed/HA* sedentary/habitually active, *PrInt* progression of exercise intensity, *BSE* bone-specific exercise, *DRT* dynamic resistance exercise, *S* supervised, *PS* partially supervised, *JE* joint exercise program, *HE* home exercise program, *RPE* rate of perceived exertion, *TUT* time under tension was rarely prescribed, however. Five studies prescribed either work to repetition maximum [30, 31, 37] or work to muscular fatigue [23, 26] as a set endpoint [38]; another study [22] referred to 5–6 (i.e., strong–strong+) on the Borg CR10 scale. Reviewing the repetition number and relative exercise intensity (% 1RM), some studies [34] or study arms [19, 32] clearly exercised with low or very low effort.[7] Time under load or velocity during the different sections of the movement (concentric–isometric–eccentric) [39] was also rarely mentioned [24, 27, 33]. Time under load varied from 3 to 4 s [40] to 5–6 s [36] per repetition. None of the studies reported an explosive movement in the concentric or eccentric phase. Apart from the 24 month study by Sinaki et al. [34], progression or at least regular adjustments of exercise intensity was realized by all the studies. The application of periodization models [41] was not reported by any of the studies.

Most studies focused on a supervised group exercise protocol ([19–25, 27–32, 35], while two other studies relied on partially supervised individual gym-based RT [33] or non-supervised exercise training at home [34].

The Pedro Score of the reviewed studies ranged from 4 to 8 of 10 total score points (Table 3). Level of agreement between the raters for methodological quality of the studies was 100%. The methodological quality of five studies can be considered as high [35],[8] 10 were considered to be of moderate, and 2 of low quality. According to the mixed-effects analysis, no significant differences between the Pedro Score categories (high vs. moderate vs. low) were detected at LS- ($p = 0.639$), FN- ($p = 0.968$), or TH-BMD ($p = 0.416$).

Results for primary outcomes

Apart from two studies [31, 34] that applied DPA, all the others used DXA. Furthermore, all the other studies except two ([25]: hip only; [34]: LS only) determined both BMD at LS and proximal femur regions of interest.

Effect of exercise on LS-BMD

Sixteen studies with 18 exercise groups evaluated the effect of exercise on LS-BMD. In summary, the exercise interventions resulted in significant positive effects ($p = 0.001$). The pooled estimate of random effect analysis was SMD 0.54, 95% CI 0.22–0.87, however with a substantial level of heterogeneity between trials ($I^2 = 74.8\%$, $Q = 70.1$) (Fig. 2). A sensitivity analysis imputing minimum SD (best case; SMD 0.70, 95% CI 0.27–1.13) or maximum SD (worst cases: SMD 0.42, 95% CI 0.17–0.67) resulted in significant result in all cases. We expect that the mean value imputation comes closest to the true effect (Fig. 2).

The funnel plot suggested positive evidence of publication bias (Fig. 3). The regression ($p = 0.920$) and rank ($p = 0.881$) correlation test for funnel plot asymmetry did not indicate any significant asymmetry. Adjusting for possible publication bias using a trim and fill analysis [18] did not result in varying results.

Sub-group analyses for LS-BMD

Intervention duration

Of 18 groups, 6 training groups conducted short-term interventions (≤ 8 months), 11 groups applied a moderate duration (9–18 months) intervention, and one training group scheduled a 24-month intervention (Table 2). According to a mixed-effects analysis, no significant difference was observed between the sub-groups ($p = 0.421$).

Type of exercise

Of 18 training groups, 10 groups worked with resistance training devices, four with free weights or resistance bands, and four conducted a mix of both types (Table 2). According to a mixed-effects analysis, no significant difference was observed between the sub-groups ($p = 0.700$).

Training frequency

Of 18 training groups, 5 groups exercised fewer than 2 sessions per week and 13 groups exercised ≥ 2 sessions per week (Table 2). According to a mixed-effects analysis, a significant difference was observed between the two groups ($p = 0.002$). The sub-group analysis demonstrated the highest effects sizes for the lower training frequency (SMD 1.26, 95% CI 0.88–1.64) compared to an SMD of 0.24 (95% CI −.05–0.54) in the sub-group that exercised ≥ 2 sessions per week.

Exercise intensity

Of 18 training groups, 5 groups exercised with low (< 65% 1RM), 7 with moderate (65–< 80% 1RM), and 6 with high relative intensity (≥ 80% 1RM) (Table 2). According to a mixed-effects analysis, no significant difference was observed between the sub-groups ($p = 0.404$).

Exercise volume/session (exercises × sets × reps)

Of 18 training groups, 7 groups applied a low (< 160 reps/session), 8 a moderate (160 to < 300 reps/session), and

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[7] E.g. 10 reps at 30% maximum isometric back muscle strength [34] or 14–16 reps at 40% 1RM [19, 32]. The same might be true for some exercises of the protocol of Woo et al. [35].

[8] Comparing Pedro Score categories (low < 5 vs. moderate 5–6 vs. high ≥ 7 score points; [14]) did not indicate significant BMD differences ($p > 0.416$) at LS-, FN-, and TH-ROI.

Table 3 Assessment of risk of bias for included studies

First author, year	Eligibility criteria	Random allocation	Allocation concealment	Inter group homogeneity	Blinding subjects	Blinding personnel	Blinding assessors	Participation ≥ 85% allocation	Intention to treat analysis [a]	Between group comparison	Measure of variability	Total score
Bemben, 2000	Y	1	0	1	0	0	0	0	0	1	1	4
Bemben 2010	Y	0	0	1	0	0	0	1	1	1	1	5
Chilibeck, 2002	Y	1	1	1	0	0	0	0	1	1	1	6
de Oliveira, 2018	Y	1	1	1	0	0	1	1	1	1	1	8
Duff, 2016	Y	1	1	1	1	0	1	0	1	1	1	8
Hartard, 1996	Y	0	0	1	0	0	0	1	1	1	1	5
Kerr, 1996	Y	1	0	1	0	0	0	0	1	1	1	5
Kohrt, 1997	Y	0	0	1	0	0	0	0	1	1	1	4
Maddalozzo, 2007	Y	1	0	1	0	0	0	1	1	1	1	6
Nelson, 1994	Y	1	0	1	0	0	0	1	1	1	1	6
Nicholson, 2015	Y	1	1	1	0	0	0	1	1	1	1	7
Orsatti, 2013	Y	1	1	1	0	0	0	1	1	1	1	7
Pruitt, 1995	Y	1	0	1	0	0	0	0	1	1	1	5
Pruitt, 1992	Y	0	0	1	0	0	0	1	1	1	1	5
Rhodes, 2000	Y	1	0	1	0	0	0	1	1	1	1	6
Sinaki, 1989	Y	1	0	1	0	0	0	1	1	1	1	6
Woo, 2007	Y	1	1	1	0	0	1	1	1	1	1	8

[a] The point is awarded not only for intention to treat analysis but also when all subjects for whom outcome measures were available received the treatment or control condition as allocated

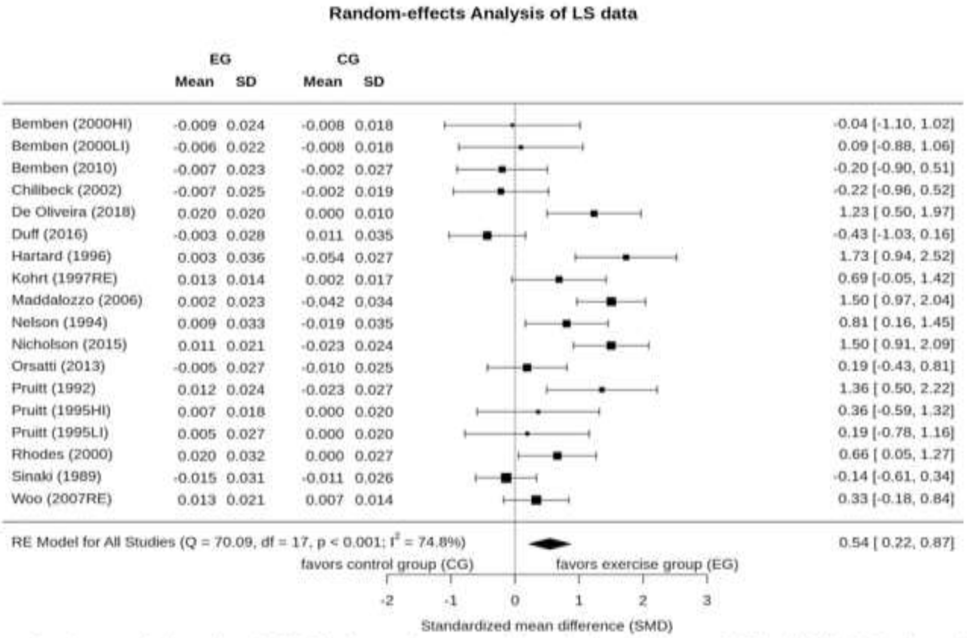

Fig. 2 Forest plot of meta-analysis results at the LS. The data are shown as pooled standard mean difference (SMD) with 95% CI for changes in exercise and control groups

3 a high (≥ 300 reps/session) exercise volume/session (Table 2). The mixed-effects analysis did not demonstrate any significant difference between the sub-groups ($p = 0.697$).

Effect of exercise on FN-BMD

Fifteen studies with 18 exercise groups evaluated the effect of exercise on FN-BMD. In summary, the exercise interventions resulted in significant ($p = 0.005$), but low effects sizes (SMD 0.22, 95% CI 0.07–0.38) (Fig. 4). There was a negligible level of heterogeneity in estimates of the exercise effect ($I^2 = 0.0\%$, $Q = 13.0$). Sensitivity analysis of imputation determined that even in the worst case (i.e., imputing maximum SD), there is a significant effect (SMD 0.17, 95% CI 0.02–0.33, $p = 0.027$). Results listed in Fig. 4 are based on mean value imputation.

The funnel plot indicates evidence for a publication bias (Fig. 5). The regression ($p = 0.604$) and rank correlation test ($p = 0.601$) for funnel plot asymmetry indicate relevant asymmetry. The analysis indicates missing studies on the lower right-hand side. A trim and fill analysis resulted in slightly higher effects sizes (SMD 0.26, 95% CI 0.11–0.41), after adjusting for publication bias.

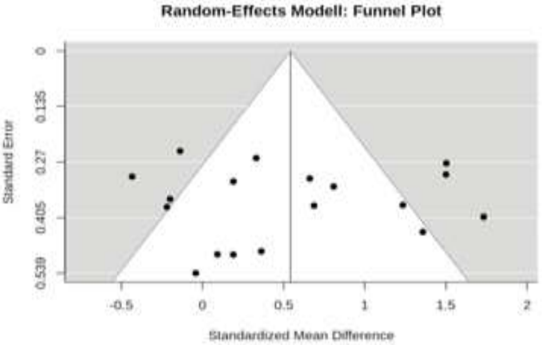

Fig. 3 Funnel plot of the DRT studies that address LS BMD

Sub-group analyses for FN-BMD

Intervention duration

Of 18 groups, 6 studies applied a short, 12 groups a moderate, and no group a long duration of the exercise intervention (Table 2). A mixed-effects analysis did not observe significant differences between the sub-groups ($p = 0.694$).

Type of exercise

Ten groups worked with resistance training devices, two with free weights or resistance bands group, and six groups conducted a mix of both types (Table 2). A mixed-effects analysis

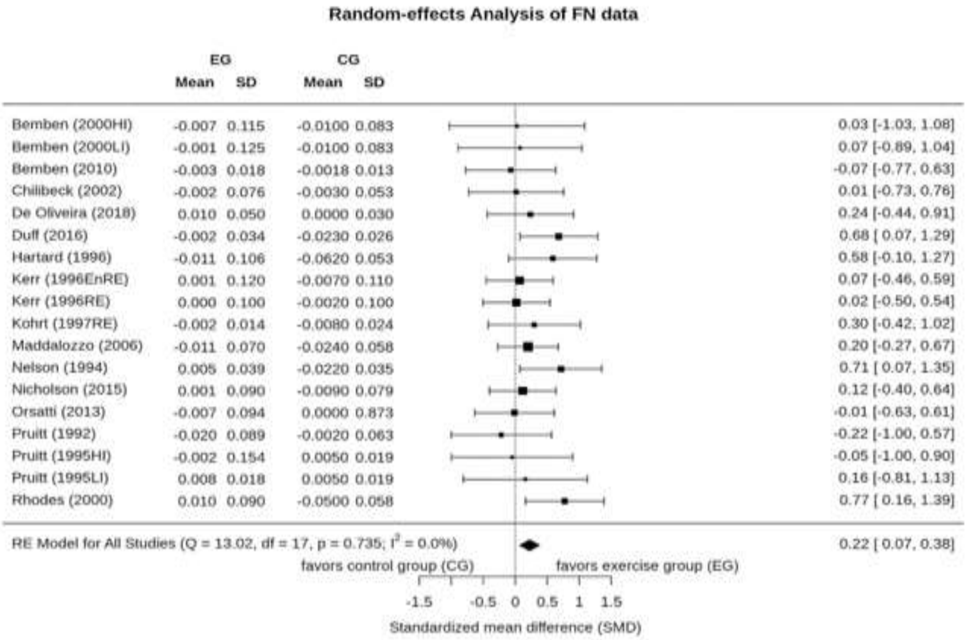

Fig. 4 Forest plot of meta-analysis results at the femoral neck. The data are shown as pooled standard mean difference (SMD) with 95% CI for changes in exercise and control groups

demonstrated no significant differences between the sub-groups ($p = 0.490$).

Training frequency

Five groups exercised fewer than 2 sessions per week and 13 groups exercised ≥ 2 sessions per week (Table 2). In contrast to LS-ROI, no significant difference was observed between the two groups ($p = 0.260$) from mixed-effects analysis.

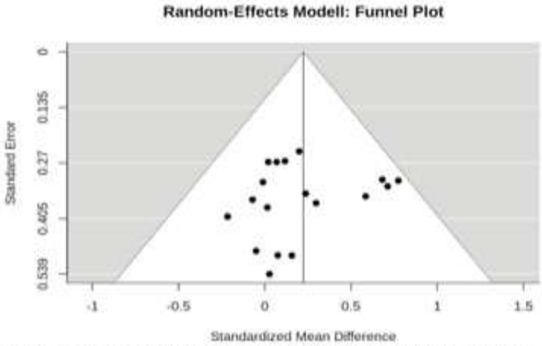

Fig. 5 Funnel plot of the DRT studies that address femoral neck BMD

Exercise intensity

Four groups exercised with low (< 65% 1RM), 7 with moderate (65–< 80% 1RM), and 7 with high relative intensity (≥ 80% 1RM) (Table 2). The mixed-effects analysis determined no significant differences between the sub-groups ($p = 0.279$).

Exercise volume/session (exercises × sets × reps)

Six groups applied a low (< 160 reps/session), 7 a moderate (160 to < 300 reps/session), and 5 a high (≥ 300 reps/session) exercise volume/session (Table 2). No significant differences between the sub-groups ($p = 0.373$) were demonstrated by the mixed-effects analysis.

Effect of exercise on TH-BMD

Nine studies with 11 exercise groups evaluated the effect of exercise on TH-BMD (Fig. 6). In summary, the pooled estimate of random effect analysis was 0.48, 95% CI 0.22–0.75. Level of heterogeneity between trials was low ($I^2 = 35.8\%$, $Q = 14.7$). Sensitivity analysis demonstrated that even in the worst case (i.e., maximum SD), there is a significant effect (SMD 0.44, 95% CI 0.22–0.65, $p = 0.001$). Results listed in Fig. 6 are based on mean value imputation.

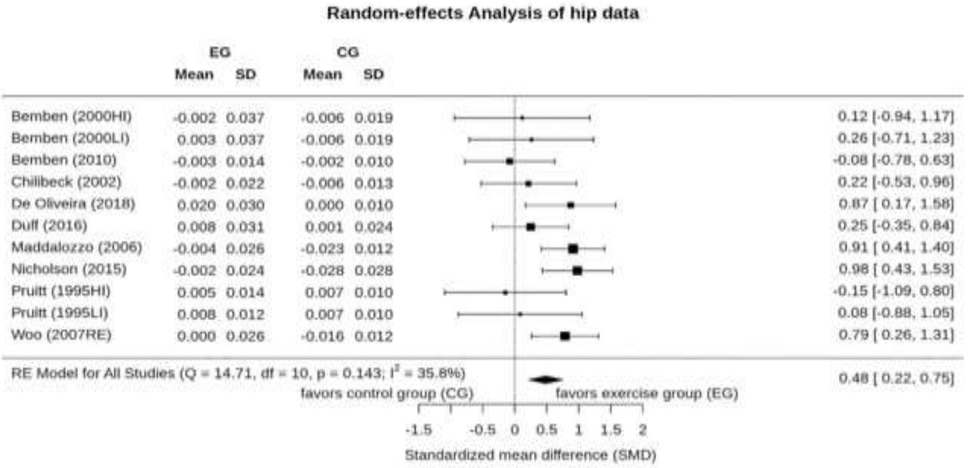

Fig. 6 Forest plot of meta-analysis results at the total hip. The data are shown as pooled standard mean difference (SMD) with 95% CI for changes in exercise and control groups

The funnel plot suggested positive evidence of publication bias (Fig. 7). The regression ($p = 0.013$), but not the rank correlation test ($p = 0.218$) for funnel plot asymmetry, demonstrated significant asymmetry. Comparable to FN-BMD, there is a lack of studies on the (lower) right-hand side. A trim and fill analysis resulted in considerably higher effects sizes after adjusting for publication bias (SMD 0.67, 95% CI 0.40–0.93).

Sub-group analyses for the TH-BMD

Intervention duration

Of 11 groups, 5 training groups were classified as short-term, 6 groups as moderate, and no training groups was categorized as long-term interventions (Table 2). A mixed-effects analysis indicated no significant difference between the sub-groups ($p = 0.835$).

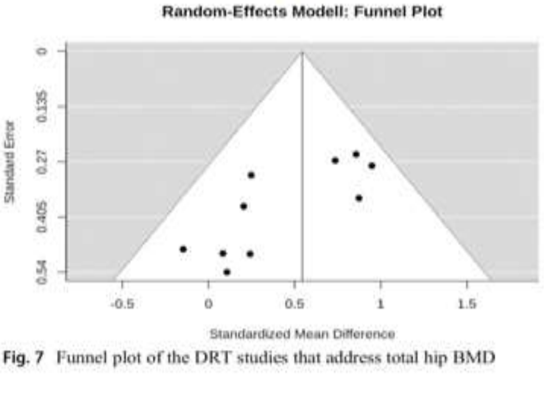

Fig. 7 Funnel plot of the DRT studies that address total hip BMD

Type of exercise

Of 11 groups, 7 groups worked with resistance training devices, three with free weights or resistance bands group, and one group conducted a mix of both types (Table 2). A mixed-effects analysis indicated a significant difference between the sub-groups ($p = 0.013$). The sub-group analysis demonstrated the highest effects sizes (SMD 0.89, 95% CI 0.59–1.19) for the "free weight" training group (vs. RT devices 0.23, − 0.09–0.55; vs. mix 0.25, − 0.35–0.84).

Training frequency

Only two training groups applied low training frequency (< 2 sessions/week); nine training groups prescribed a high training frequency (≥ 2 sessions/week). Differences between the groups were significant ($p = 0.023$); sub-groups analysis provided higher effect sizes for the sub-group with lower training frequency (SMD 0.94, 95% CI 0.57–1.31 vs. high frequency 0.34, 0.07–0.61).

Exercise intensity

Four groups worked with low relative intensity (< 65% 1RM), four with moderate relative intensity (65–< 80% 1RM), and three with high relative intensity (≥ 80% 1RM) (Table 2). The mixed-effects analysis did not determine any significant differences between the sub-groups ($p = 0.090$).

Exercise volume/session (exercises × sets × reps)

Two groups exercised with low, six with moderate, and three with high exercise volume/session protocols (Table 2). No significant differences between the sub-groups ($p = 0.84$) were observed.

Discussion

In this systematic review and meta-analysis, we clearly confirmed the significant positive effects of DRT type exercise on BMD in postmenopausal women. However, effect sizes differed considerably between the regions of interest. While SMD for the LS-BMD (0.59) and total hip BMD (0.48) can be considered as moderate, the corresponding effect for the FN was quite low (SMD 0.22). We hypothesize that different loading configuration during DRT might predominately explain the different results at not only LS and FN but also FN and TH-ROI.[9] One explanation for the significantly lower effect on the femoral neck region during resistance exercise might be the high stress level from everyday activities at this site. Due to leverage ratios, weight-bearing loads in one-legged stand situations such as walking result in high tensions of the abductor muscles and high stresses especially at the femoral neck region. Force measurements revealed corresponding loads of approximately three times the body mass (e.g., [42]). Also, RT-induced joint reaction forces might not have exceeded the threshold for bone adaptation, and hence, no exercise effect occurred.

Summarizing the few other meta-analyses [6, 8, 43, 44] that focus on the effect of RT on BMD at LS, or proximal femur ROIs, effect sizes vary considerably. Most of them reported negligible to low effects of RT on BMD, be it at the LS (SMD ≤ 0.24 [43]) or femoral neck (SMD ≤ 0.21 [9]). We observed higher effects sizes particularly for LS (SMD $= 0.54$) and TH-BMD (SMD 0.48). Due to the longer search period, we included more studies than most other systematic reviews but the main difference between the present study and previous analyses might be the more careful screening of eligibility [43] related to isolated DRT protocols. Of importance for the generation of exercise protocols, one analysis [6], which divided studies according to their exercise intensity, reported a missing effect for low "force" RT protocols (LS $n = 5$, MD -0.17%; FN $n = 3$, MD -0.03%; TH, $n = 3$: MD 0.21%). "High force" RT protocols ($\approx 60\%$ 1RM), however, demonstrated significant but low–moderate BMD effects at the LS ($n = 8$, MD 0.86%) and FN ($n = 8$, MD 1.03%) but not for BMD at TH ($n = 5$, MD 0.11%, 95% CI -0.06–0.29%). On the other hand, the study of Martyn-St-James et al. [8] that included only high intensity DRT studies and our sub-group analyses did not confirm the result that RT with moderate (65–< 80% 1RM) or high intensity ($\geq 80\%$ 1RM) is superior to RT protocols with low "force" [6].[10] If anything, reviewing the data of the sub-analyses revealed some unexpected findings.

Intervention duration

Considering that the mechanical stress during RT induces changes of BMD in adults might be triggered predominately by remodeling, we hypothesized that studies below 9 months of length would not determine the full amount of new mineralized bone [45].[11] Nevertheless, addressing this issue by mixed-effects analysis, no significant BMD difference was observed between studies of longer and shorter durations, be it at the LS-, FN-, or TH-ROI. One may thus speculate that despite (Table 2) progressive increase of exercise intensity,[12] no relevant further exercise-induced effects occur after initial bone adaptation, be it by modeling or (fast) remodeling [24, 46]. We are unable to reject this conjuncture for pure RT protocols; however, previously published studies applying mixed exercise long-term protocols [47, 48] observed an ongoing effect of exercise on BMD at LS and FN up to 16 years.

Type of exercise

From a pragmatic point of view, it is important to determine whether specific RT devices are needed to generate successful exercise programs. In summary, in consistent favor for "free weight training" (vs. "device" and "mixed type" of training), we observed BMD differences at the LS-, FN-, and total hip-ROI, but albeit significant for the TH-ROI. This result is very welcome, not only due to the much lower material effort of free weight training. Of relevance for older people, free weights might be more favorable to increase function [49] and in particular leg extensor strength [50] with its crucial relevance on mobility limitations, disability, morbidity, and mortality [51–53].

TrFr

This parameter might be the most important aspect for designing an exercise protocol. Apart from its direct impact on the

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[9] Of importance, femoral neck ROI is a usually 15 mm slide across the middle-distal end of the femoral neck, while total hip ROI started slightly below the trochanter minor and include intertrochanter, trochanter, ward, and femoral neck ROI.

[10] …nor the results of higher effects on femoral neck ROI compared to total hip ROI.

[11] At least when bearing in mind that initial conditioning phases conducted by most studies might further shorten the period of over-threshold strain application…

[12] Apart from two studies, all the RT studies included progressively increased exercise intensity during the intervention (Table 2).

outcome addressed, training frequency (TrFr) immediately affects the feasibility of the program and thus participant compliance [54]. In summary, our result clearly indicates that lower net training frequency (< 2 sessions/week, s/w) demonstrated significantly higher effect sizes for BMD changes at the LS-ROI and TH-ROI[13] versus higher training frequency (≥ 2 s/w). At the latest at this point, we have to subject our meta-analytical results to a critical review. Although some exercise studies did not detect significant BMD differences after exercising with varying TrFr[14] [55–57], other studies [58–61] clearly demonstrated significantly higher effect sizes for BMD changes at LS and hip-ROI when applying TrFr of at least 2 s/w, compared with 1–< 2 s/w. In these studies, lower TrFr was not only less favorable but showed no effects on BMD at LS or hip-ROIs at all. Nevertheless, there might be some explanations for at least similar BMD results after exercising with different TrFr. Firstly, one may speculate that higher intensity might compensate the effect of lower frequency or (vice versa) high frequency combined with high intensity might result in incomplete adaptation to exercise [10]. However, a sub-analysis combining training frequency with exercise intensity did not support this hypothesis. From the literature results mentioned above,[15] it would also be conceivable that particularly during the early phase of an intervention, each bone-specific exercise protocol might trigger positive effects on BMD largely independent of TrFr. However, combining training frequency and intervention duration in another sub-analysis did not support this hypothesis, either. Finally, the rather low variance within net TrFr (≈ 1.5–3.5 s/w) might confound a proper result on this issue. However, summarizing the result on TrFr of the present study, from a sport-scientific point of view, it is hardly possible that in this reasonable range of TrFr, a lower TrFr triggers significantly higher effects on BMD changes compared with higher TrFr.

Exercise intensity

Another key parameter of exercise effects on a given outcome is "exercise intensity." We categorized relative exercise intensity according to % 1RM (low < 65% vs. moderate 65–< 80% vs. high intensity ≥ 80% 1RM) as listed by the exercise trials. In summary, however, the sub-group analysis did not reveal significant differences between the groups. Although not consistently determined (e.g., [19, 57]), there is a high level of evidence [25, 62–64] that high exercise intensity is superior to moderate or low exercise intensity for addressing BMD. The superiority of high intensity RT is strongly supported by basic research [65, 66], which indicates that the higher strain magnitude generated by higher deformation of the bone increases bone formation linearly to its deformation magnitude. Contrary to a fixed "bone adaptation threshold" at 1000 μΣ, as suggested by the Mechanostat theory [67], other authors revealed that loading thresholds for modeling/remodeling vary between different skeletal sites, according to their habitual loading history [68–70]. However, as reported, we did not find any evidence for the superiority of high intensity RT at any ROI[16] addressed by this study.

Exercise volume/session

Basically, there is a close interaction between exercise volume, in particular cycle number (i.e., number of reps) and strain magnitude (i.e., exercise intensity) [10]. With respect to bone physiology, the number of loading cycles is negligible when applying a high strain magnitude [71]; however, there is some evidence [5, 72] that higher cycle numbers might compensate for low to borderline strain magnitudes. In this context, Cullen et al. [73] demonstrated that 40 repetitions with a strain magnitude of 1000 μΣ did not relevantly affect bone formation rate, while 120 or 400 reps resulted in a significant increase in this parameter. However, addressing the relevance of exercise volume/session for BMD changes by our sub-analysis, we do not observe any relevant ($p \geq 0.373$) effect of this parameter.

Limitations

In summary, our evaluation of exercise characteristics with particular relevance on BMD to identify moderators of exercise effects on bone strength largely failed. Accordingly, we are unable to recommend any promising DRT protocols for bone strengthening. In his critical review, Gentil et al. [74] questioned the relevance and practical application of meta-analytic results in strength training. While this might be going too far, it is nevertheless obvious, however, that the complex interaction of exercise variables, training principles, and training conditions[17] prevent, or at least aggravate, a proper analysis of single exercise parameters even when focusing on relative homogeneous types of exercise (i.e., DRT). This is even more the case when applying exercise regimens in the real world and not in laboratory-based, artificially supported study settings. In addition, the brief reporting on relevant

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[13] LS-BMD: 5 (low ExFr) vs. 13 (high ExFr) study groups TH: 2 vs. 9 study groups (see "Results").

[14] Ashe et al. [55]: 0–2 sessions/w.(s/w); Bailey et al. [56]: 0–7 s/w; Bemben et al. [57]: 2 vs. 3 s/w. However, studies did not adjust for subjects' attendance; therefore, results should be interpreted with caution.

[15] While exercise protocols of studies that did not detect difference for TrFr were 6, 8, and 12 months, the lengths of studies that detected significant higher BMD changes in favor of the higher TrFr were 1.5, 4, 12, and 16 years.

[16] In detail, the subgroup analysis on this issue was inconsistent, with higher effects of low intensity for TH-BMD and moderate intensity for FN- and LS-BMD.

[17] This might be the main difference to meta-analysis in the area of pharmaceutic agents or supplements (e.g. [75, 76], with their limited number of inherent modulators.

characteristics in research papers often does not provide sufficient information. Thus, meta-analyses might be an appropriate tool for determining the general effects of dedicated exercise on a given outcome, but their ability to distinguish between exercise parameters is more limited.

Some limitations and features of this work should be addressed to allow the reader to adequately interpret our findings and to follow our conclusions.

(1) We set out to determine the effect of preferably isolated DRT. DRT was defined as any kind of resistance exercise that involves joint movement and focuses on the development of musculoskeletal strength,[18] correspondingly excluded studies with other types of exercise, be it as training components or (bone) specific warm-ups. However, in reality, our approach might not always be considered consistent. Indeed, we included a study that also applied short bouts of rowing [26]. While accepting that 10 min of intense rowing can no longer count as RT,[19] we did not think that the joint reaction force character of rowing [26] would confound our results. In parallel, studies that applied cycling or stretching, i.e., exercises with no relevant mechanical impact on bone [79, 80], were included. (2) Although, with 17 studies, including 20 exercise and 18 control groups, our sample size of isolated DRT studies was higher than the sample size of recent meta-analyses, the statistical power might have been too low to address some dedicated issues by sub-group analyses. This limitation refers particularly to TH-ROI with considerably lower sample sizes. (3) There is a consistent lack of reporting of relevant DRT exercise parameters in the present literature; correspondingly, we are unable to evaluate all the promising exercise variables. Apart from absolute intensity ("effort"),[20] movement velocity[21] was rarely reported [27]. However, strain rate (corresponding to movement velocity in DRT), as defined as alteration in strain magnitude per second during the acceleration or deceleration of loading (μΣ/s) is an important mechanical parameter. Turner et al. [81], for example, observed a linear increase in bone formation rate with higher strain rates when using a protocol with constant strain magnitude but varying strain rates. Von Stengel et al. [82] confirmed this finding for DRT, by comparing fast-explosive vs. slow movement velocity during high intensity DRT. The authors reported that BMD changes in the power training group (i.e., explosive concentric velocity) significantly exceeded the results of the resistance training group (i.e., TUT 4 s–0 s–4 s). Considering the importance of this parameter for bone strengthening and the easy and safe applicability of high strain rates/fast movement velocity generated by joint reaction forces during DRT even in older, more vulnerable cohorts [83], more exercise studies should focus on this exercise variable. (4) Although we did our best to adequately classify our exercise characteristics according to exercise terminology or bone physiology, we admit that some of the categorizations (e.g., exercise volume/session) were made somewhat arbitrarily in order to ensure an appropriate distribution for comparisons. (5) Even after adjusting primary study outcomes (LS-, FN-, TH-BMD) for multiple testing, the significance of the results remained. However, following recent recommendations [84], we do not adjust on secondary outcomes (i.e., sub-analyses). (6) There is some evidence for a publication bias for LS-, FN-, and TH-BMD data. Due to the preference to report positive effects [85], the true effect size of exercise on BMD was in general considered lower for unadjusted data. However, the lack of studies in the (lower) right-hand corner of the funnel plot indicates that small-moderate size studies with positive effects are missing. Indeed, using trim and fill analysis [18], we determined no changes for the LS-BMD but higher effects sizes for FN and particular TH-BMD.

In conclusion, it is difficult to generate exercise recommendations on bone strengthening based on the meta-analytic results of the present exercise trials. Uncritical acceptance of the acquired meta-analytic data is certainly unwarranted in this context. Based on this experience, we conclude that dedicated, accurately designed randomized controlled exercise trials might be the more appropriate tool for addressing single exercise characteristics and thus generating exercise recommendations in the area of osteoporosis prevention and therapy.

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Data availability The data that support the findings of this study are available from the corresponding author (WK), upon reasonable request.

Compliance with ethical standards

Conflicts of interest None.

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[18] In contrast to other researchers (e.g. [77]), we do solely include studies that apply progression (i.e. progressive resistance training as defined as "exercise in which a load is increased in predetermined steps" [78]).

[19] By definition "strength" started at 30% 1RM [10]; relative intensity of 10 min of rowing (at least ≥ 250 reps) is below this cutoff.

[20] E.g., as defined according to the set endpoint approach of Steele et al. [38].

[21] as reported in time under tension in different sections of the movement (e.g., concentric–isometric–eccentric).

References

1. Kemmler W, Bebenek M, Kohl M, Von Stengel S (2015) Exercise and fractures in postmenopausal women. Final results of the controlled Erlangen Fitness and Osteoporosis Prevention Study (EFOPS). Osteoporos Int 26:2491–2499
2. Kemmler W, Haberle L, von Stengel S (2013) Effects of exercise on fracture reduction in older adults: a systematic review and meta-analysis. Osteoporos Int 24:1937–1950
3. Beck BR, Daly RM, Singh MA, Taaffe DR (2016) Exercise and Sports Science Australia (ESSA) position statement on exercise prescription for the prevention and management of osteoporosis. J Sci Med Sport 20:438–445
4. Daly RM, Dalla Via J, Duckham RL, Fraser SF, Helge EW (2019) Exercise for the prevention of osteoporosis in postmenopausal women: an evidence-based guide to the optimal prescription. Braz J Phys Ther 23:170–180
5. Kemmler W, Stengel V (eds) (2019) The role of exercise on fracture reduction and bone strengthening. Avademic Press, London
6. Howe TE, Shea B, Dawson LJ et al (2011) Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database Syst Rev:CD000333
7. Kelley GA, Kelley KS, Kohrt WM (2012) Effects of ground and joint reaction force exercise on lumbar spine and femoral neck bone mineral density in postmenopausal women: a meta-analysis of randomized controlled trials. BMC Musculoskelet Disord 13:177
8. Martyn-St. James M, Caroll S (2006) High intensity resistance training and postmenopausal bone loss: a meta-analysis. Osteoporos Int 17:1225–1240
9. Zhao R, Zhao M, Xu Z (2015) The effects of differing resistance training modes on the preservation of bone mineral density in postmenopausal women: a meta-analysis. Osteoporos Int 26:1605–1618
10. Weineck J (2019) Optimales training. Spitta-Verlag, Erlangen
11. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151(264–269):W264
12. de Morton NA (2009) The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. Aust J Physiother 55:129–133
13. Sherrington C, Herbert RD, Maher CG, Moseley AM (2000) PEDro. A database of randomized trials and systematic reviews in physiotherapy. Man Ther 5:223–226
14. Ribeiro de Avila V, Bento T, Gomes W, Leitao J, Fortuna de Sousa N (2018) Functional outcomes and quality of life after ankle fracture surgically treated: a systematic review. J Sport Rehabil 27:274–283
15. Cochrane (2016) Cochrane handbook for systematic reviews of interventions. In: Higgins J, Green S (eds) The Cochrane Collaboration
16. R_Development_Core_Team (2019) R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing
17. Viechtbauer W (2010) Conducting meta-analyses in R with the metafor package. J Stat Softw 36:1–48
18. Duval SJ, Tweedie RL (2000) A nonparametric "trim and fill" method of accounting for publication bias in meta-analysis. JASA 95:89–98
19. Bemben DA, Fetters NL, Bemben MG, Nabavi N, Koh ET (2000) Musculoskeletal responses to high- and low-intensity resistance training in early postmenopausal women. Med Sci Sports Exerc 32:1949–1957
20. Bemben DA, Palmer IJ, Bemben MG, Knehans AW (2010) Effects of combined whole-body vibration and resistance training on muscular strength and bone metabolism in postmenopausal women. Bone 47:650–656
21. Chilibeck PD, Davison KS, Whiting SJ, Suzuki Y, Janzen CL, Peloso P (2002) The effect of strength training combined with bisphosphonate (etidronate) therapy on bone mineral, lean tissue, and fat mass in postmenopausal women. Can J Physiol Pharmacol 80:941–950
22. de Oliveira LC, de Oliveira RG, de Almeida Pires-Oliveira DA (2019) Effects of whole-body vibration versus pilates exercise on bone mineral density in postmenopausal women: a randomized and controlled clinical trial. J Geriatr Phys Ther 42:E23–E31
23. Duff WR, Kontulainen SA, Candow DG et al (2016) Effects of low-dose ibuprofen supplementation and resistance training on bone and muscle in postmenopausal women: a randomized controlled trial. Bone Rep 5:96–103
24. Hartard M, Haber P, Ilieva D, Preisinger E, Huber JC (1996) Systematic strength training as a model of therapeutic intervention. Arch Phys Med Rehabil 75:21–28
25. Kerr D, Morton A, Dick I, Prince R (1996) Exercise effects on bone mass in postmenopausal women are site-specific and load-dependent. J Bone Miner Res 11:218–225
26. Kohrt WM, Ehsani AA, Brige SJ Jr (1997) Effects of exercise involving predominantly either joint-reaction of ground-reaction forces on bone mineral density in older women. J Bone Miner Res 12:1253–1261
27. Maddalozzo GF, Widrick JJ, Cardinal BJ, Winters-Stone KM, Hoffman MA, Snow CM (2007) The effects of hormone replacement therapy and resistance training on spine bone mineral density in early postmenopausal women. Bone 40:1244–1251
28. Nelson ME, Fiatarone MA, Morganti CM, Trice I, Greenberg RA, Evans WJ (1994) Effects of high-intensity strength training on multiple risk factors for osteoporotic fractures. A randomized controlled trial. Jama 272:1909–1914
29. Nicholson VP, McKean MR, Slater GJ, Kerr A, Burkett BJ (2015) Low-load very high-repetition resistance training attenuates bone loss at the lumbar spine in active post-menopausal women. Calcif Tissue Int 96:490–499
30. Orsatti F, Petri-Nahas E, Nahas-Neto J, Orsatti C, Teixeira A (2013) Effects of isoflavone and counter-resistance training on bone mineral density in postmenopausal women. Rev Bras Cineantropom Desempenho Hum 15:726–736
31. Pruitt LA, Jackson RD, Bartels RL, Lehnhard HJ (1992) Weight-training effects on bone mineral density in early postmenopausal women. J Bone Miner Res 7:179–185
32. Pruitt LA, Taaffe DR, Marcus R (1995) Effects of a one-year high-intensity versus low-intensity resistance training program on bone mineral density in older women. J Bone Miner Res 10:1788–1795
33. Rhodes EC, Martin AD, Taunton JE, Donnelly M, Warren J, Elliot J (2000) Effects of one year of resistance training on the relation between muscular strength and bone density in elderly women. Br J Sports Med 34:18–22
34. Sinaki M, Wahner HW, Offord KP, Hodgson SF (1989) Efficacy of nonloading exercises in prevention of vertebral bone loss in postmenopausal women: a controlled trial. Mayo Clin Proc 64:762–769
35. Woo J, Hong A, Lau E, Lynn H (2007) A randomised controlled trial of Tai Chi and resistance exercise on bone health, muscle

strength and balance in community-living elderly people. Age Ageing 36:262–268

36. Rhodes EC (1995) Effect of one year of resistance training on strength and bone density in elderly women. Med Sci Sports Exerc 27:S21
37. Kerr D, Ackland T, Maslen B, Morton A, Prince R (2001) Resistance training over 2 years increases bone mass in calcium-replete postmenopausal women. J Bone Miner Res 16:175–181
38. Steele J, Fisher J, Giessing J, Gentil P (2017) Clarity in reporting terminology and definitions of set end points in resistance training. Muscle Nerve 368-374:368–374
39. Toigo M, Boutellier U (2006) New fundamental resistance exercise determinants of molecular and cellular muscle adaptations. Eur J Appl Physiol 97:643–663
40. Hartard M, Haber P, Ilieva D, et al. (1994) Einfluß eines systematischen Krafttrainings auf die Knochendichte und auf das Niveau von Schmerzen und Befindlichkeit in einer Gruppe von Frauen mit Osteopenie. In Ließen H, Weiß M, Baum M (eds) Regulations- und Repairmechanismen. Köln
41. Hoover DL, VanWye WR, Judge LW (2016) Periodization and physical therapy: bridging the gap between training and rehabilitation. Phys Ther Sport 18:1–20
42. Bergmann G, Deuretzbacher G, Heller M, Graichen F, Rohlmann A, Strauss J, Duda GN (2001) Hip contact forces and gait patterns from routine activities. J Biomech 34:859–871
43. Kelley GA, Kelley KS, Tran ZV (2001) Resistance training and bone mineral density in women: a meta-analysis of controlled trials. Am J Phys Med Rehabil 80:65–77
44. Zhao R, Zhang M, Zhang Q (2017) The effectiveness of combined exercise interventions for preventing postmenopausal bone loss: a systematic review and meta-analysis. J Orthop Sports Phys Ther 47: 241–251
45. Eriksen EF (2010) Cellular mechanisms of bone remodeling. Rev Endocr Metab Disord 11:219–227
46. Frost HM (1988) Vital biomechanics: proposed general concepts for skeletal adaptations to mechanical usage. Calcif Tissue Int 42: 145–156
47. Kemmler W, Engelke K, von Stengel S, Weineck J, Lauber D, Kalender WA (2007) Long-term four-year exercise has a positive effect on menopausal risk factors: the Erlangen Fitness Osteoporosis Prevention Study. J Strength Cond Res 21:232–239
48. Kemmler W, Engelke K, von Stengel S (2016) Long-term exercise and bone mineral density changes in postmenopausal women-are there periods of reduced effectiveness? J Bone Miner Res 31:215–222
49. Haff GG (2000) Roundtable discussion: machines versus free weights. Strength Conditioning J 22:18–30
50. Schott N, Johnen B, Holfelder B (2019) Effects of free weights and machine training on muscular strength in high-functioning older adults. Exp Gerontol 122:15–24
51. Newman AB, Kupelian V, Visser M, Simonsick EM, Goodpaster BH, Kritchevsky SB, Tylavsky FA, Rubin SM, Harris TB, on Behalf of the Health, Aging and Body Composition Study Investigators (2006) Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. J Gerontol A Biol Sci Med Sci 61:72–77
52. Roshanravan B, Patel KV, Fried LF, Robinson-Cohen C, de Boer IH, Harris T, Murphy RA, Satterfield S, Goodpaster BH, Shlipak M, Newman AB, Kestenbaum B, for the Health ABC study (2017) Association of muscle endurance, fatigability, and strength with functional limitation and mortality in the health aging and body composition study. J Gerontol A Biol Sci Med Sci 72:284–291
53. Visser M, Goodpaster BH, Kritchevsky SB, Newman AB, Nevitt M, Rubin SM, Simonsick EM, Harris TB, for the Health ABC Study (2005) Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. J Gerontol A Biol Sci Med Sci 60: 324–333
54. Wagner P (2000) Aussteigen oder Dabeibleiben? Institute of Sportsciences. Technical University Darmstadt, Darmstadt, p 298
55. Ashe MC, Gorman E, Khan KM, Brasher PM, Cooper DM, McKay HA, Liu-Ambrose T (2013) Does frequency of resistance training affect tibial cortical bone density in older women? A randomized controlled trial. Osteoporos Int 24:623–632
56. Bailey CA, Brooke-Wavell K (2010) Optimum frequency of exercise for bone health: randomised controlled trial of a high-impact unilateral intervention. Bone 46:1043–1049
57. Bemben DA, Bemben MG (2011) Dose-response effect of 40 weeks of resistance training on bone mineral density in older adults. Osteoporos Int 22:179–186
58. Cussler EC, Going SB, Houtkooper LB, Stanford VA, Blew RM, Flint-Wagner HG, Metcalfe LL, Choi JE, Lohman TG (2005) Exercise frequency and calcium intake predict 4-year bone changes in postmenopausal women. Osteoporos Int 16:2129–2141
59. Kemmler W, von Stengel S (2013) Exercise frequency, health risk factors, and diseases of the elderly. Arch Phys Med Rehabil 94: 2046–2053
60. Kemmler W, von Stengel S (2014) Dose-response effect of exercise frequency on bone mineral density in post-menopausal, osteopenic women. Scand J Med Sci Sports 24:526–534
61. Kemmler W, von Stengel S, Kohl M (2016) Exercise frequency and bone mineral density development in exercising postmenopausal osteopenic women. Is there a critical dose of exercise for affecting bone? Results of the Erlangen Fitness and Osteoporosis Prevention Study. Bone 89:1–6
62. Maddalozzo GF, Snow CM (2000) High intensity resistance training: effects on bone in older men and women. Calcif Tissue Int 66: 399–404
63. Taaffe DR, Pruitt L, Pyka G, Guido D, Marcus R (1996) Comparative effects of high- and low-intensity resistance training on thigh muscle strength, fiber area, and tissue composition in elderly women. Clin Physiol 16:381–392
64. Vincent KR, Braith RW (2002) Resistance exercise and bone turnover in elderly men and women. Med Sci Sports Exerc 34:17–23
65. Hsieh YF, Turner CH (2001) Effects of loading frequency on mechanically induced bone formation. J Bone Miner Res 16:918–924
66. Rubin CT, Lanyon LE (1985) Regulation of bone mass by mechanical strain magnitude. Calcif Tissue Int 37:411–417
67. Frost HM (1987) Bone mass and the mechanostat. A proposal. Anat Rec 219:1–19
68. Hsieh YF, Robling AG, Ambrosius WT, Burr DB, Turner CH (2001) Mechanical loading of diaphyseal bone in vivo: the strain threshold for an osteogenic response varies with location. J Bone Miner Res 16:2291–2297
69. Mosley JR, Lanyon LE (1998) Strain rate as a controlling influence on adaptive modeling in response to dynamic loading of the ulna in growing male rats. Bone 23:313–318
70. Turner CH (1998) Three rules for bone adaptation to mechanical stimuli. Bone 23:399–407
71. Rubin CT, Lanyon LE (1984) Regulation of bone formation by applied dynamic loads. J Bone Joint Surg Am 66:397–402
72. Kemmler W, von Stengel S (2011) Exercise and osteoporosis-related fractures: perspectives and recommendations of the sports and exercise scientist. Phys Sportmed 39:142–157
73. Cullen DM, Smith RT, Akhter MP (2001) Bone-loading response varies with strain magnitude and cycle number. J Appl Physiol 91: 1971–1976
74. Gentil P, Arruda A, Souza D, Giessing J, Paoli A, Fisher J, Steele J (2017) Is there any practical application of meta-analytical results in strength training? Front Physiol 8:1
75. Wang YK, Zhang YM, Qin SQ, Wang X, Ma T, Guo JB, Zhu C, Luo ZJ (2018) Effects of alendronate for treatment of

glucocorticoid-induced osteoporosis: a meta-analysis of randomized controlled trials. Medicine (Baltimore) 97:e12691

76. Tai V, Leung W, Grey A, Reid IR, Bolland MJ (2015) Calcium intake and bone mineral density: systematic review and meta-analysis. BMJ 351:h4183
77. Martyn-St James M, Carroll S (2006) Progressive high-intensity resistance training and bone mineral density changes among premenopausal women: evidence of discordant site-specific skeletal effects. Sports Med 36:683–704
78. Kent M (2007) The Oxford dictionary of sports science & medicine. Oxford University Press, Oxford
79. Chubak J, Ulrich CM, Tworoger SS et al (2006) Effect of exercise on bone mineral density and lean mass in postmenopausal women. Med Sci Sports Exerc 38:1236–1244
80. Olmedillas H, Gonzalez-Aguero A, Moreno LA, Casajus JA, Vicente-Rodriguez G (2012) Cycling and bone health: a systematic review. BMC Med 10:168
81. Turner CH, Owan I, Takano Y (1995) Mechanotransduction in bone: role of strain rate. Am J Physiol Endocrinol Metab 269: E438–E442
82. von Stengel S, Kemmler W, Lauber D, Weineck J, Kalender WA, Engelke K (2005) Power training is more effective than strength training to maintain bone mineral density in postmenopausal woman. J Appl Physiol 99:181–188
83. Mangione KK, Miller AH, Naughton IV (2010) Cochrane review: improving physical function and performance with progressive resistance strength training in older adults. Phys Ther 90:1711–1715
84. Li G, Taljaard M, Van den Heuvel ER et al (2017) An introduction to multiplicity issues in clinical trials: the what, why, when and how. Int J Epidemiol 46:746–755
85. Sterne JA, Sutton AJ, Ioannidis JP et al (2011) Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 343:d4002

SCHLUSSFOLGERUNG / RESÜMEE

Auf der Grundlage der aktuellen Meta-Analysen haben wir die folgenden Schlussfolgerungen zusammengefasst:

1) Körperliche Bewegung kann die BMD an der LS, FN und t-Hip bei PMW erhöhen.

2) Die Analysen der Subgruppen zeigen einen größeren Nutzen von Multikomponenten-Interventionen, die WB- und RT-Übungen beinhalten, im Vergleich zu einem einzigen Trainingsmodus. Die Unterschiede zwischen den Gruppen waren jedoch statistisch nicht signifikant. Daher sind die Ergebnisse nicht auf bestimmte Trainingstypen verallgemeinerbar.

3) Aufgrund der grundlegenden und komplexen Unterschiede zwischen den Trainingsprotokollen der zahlreichen eingeschlossenen Trainingsstudien konnten wir mit Blick auf die meta-analytischen Ergebnisse der vorliegenden Trainingsstudien keine Trainingsempfehlungen zur Knochenstärkung erstellen.

Die untersuchten Artikel dieser Dissertation betreffen nur die erste Phase des Projekts "ACTLIFE-Physikalische Aktivität - das Werkzeug zur Verbesserung der Lebensqualität von Osteoporose-Patienten". Auf der Grundlage dieser Betrachtungen kommen wir zu dem Schluss, dass spezielle, genau konzipierte, randomisierte und kontrollierte Trainingsstudien das geeignetere Instrument sein könnten, um einzelne Trainingscharakteristika anzusprechen und so Trainingsempfehlungen im Bereich der Osteoporose-Prävention und -Therapie zu generieren. Daher besteht der nächste Teil des Projekts darin, eine RCT mit einer geeigneten kombinierten Trainingsintervention unter PMW durchzuführen.

Die Ergebnisse der aktuellen Meta-Analyse zeigen, dass alle Arten von Training, insbesondere die kombinierte Trainingsintervention, den BMD-Verlust bei PMW verringern können. Trainingsprogramme können nicht nur knochenfestigkeit, sondern auch die Sturzrate, die Gehfähigkeit, das Gleichgewicht und die Kraftleistung bei älteren Menschen verbessern (Cadore et al., 2013; Sherrington et al., 2019). Sie können auch die Muskelkraft, Muskelmasse und körperliche Leistung bei Senioren positiv beeinflussen (Bao et al., 2020; Law et al., 2016).

LITERATURVERZEICHNIS

AMS: AUSTRALASIAN MENOPAUSE SOCIETY. (accessed on 20 November2020); Available online: https://www.menopause.org.au/hp/information-sheets/622-osteoporosis

Bao, W., Sun, Y., Zhang, T., Zou, L., Wu, X., Wang, D., & Chen, Z. (2020). Exercise Programs for Muscle Mass, Muscle Strength and Physical Performance in Older Adults with Sarcopenia: A Systematic Review and Meta-Analysis. Aging and disease, 11(4), 863–873. https://doi.org/10.14336/AD.2019.1012

Basat, H., Esmaeilzadeh, S., and Eskiyurt, N. (2013). The effects of strengthening and high-impact exercises on bone metabolism and quality of life in postmenopausal women: a randomized controlled trial. *J. Back Musculoskelet. Rehabil*. 26, 427–435. doi: 10.3233/BMR-130402.

Bassey, E. J., and Ramsdale, S. J. (1995). Weight-bearing exercise and ground reaction forces: a 12-month randomized controlled trial of effects on bone mineral density in healthy postmenopausal women. *Bone* 16, 469–476. doi: 10.1016/8756-3282(95)90193-0.

Bassey, E. J., Rothwell, M. C., Littlewood, J. J., & Pye, D. W. (1998). Pre- and postmenopausal women have different bone mineral density responses to the same high-impact exercise. *Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research*, 13(12), 1805–1813. https://doi.org/10.1359/jbmr.1998.13.12.1805.

Beck, B. R., Daly, R. M., Singh, M. A., and Taaffe, D. R. (2017). Exercise and sports science Australia (ESSA) position statement on exercise prescription for the prevention and management of osteoporosis. *J. Sci. Med. Sport* 20, 438–445. doi: 10.1016/j.jsams.2016.10.001.

Bello, M., Sousa, M. C., Neto, G., Oliveira, L., Guerras, I., Mendes, R., et al. (2014). The effect of a long-term, community-based exercise program on bone mineral density in postmenopausal women with pre-diabetes and type 2 diabetes. *J. Hum. Kinet*. 43, 43–48. doi: 10.2478/hukin-2014-0088.

Bemben, D. A., Palmer, I. J., Bemben, M. G., and Knehans, A. W. (2010). Effects of combined whole-body vibration and resistance training on muscular strength and bone metabolism in postmenopausal women. *Bone* 47, 650–656. doi: 10.1016/j.bone.2010.06.019.

Benedetti, M. G., Furlini, G., Zati, A., & Letizia Mauro, G. (2018). The Effectiveness of Physical Exercise on Bone Density in Osteoporotic Patients. *BioMed research international*, 2018, 4840531. https://doi.org/10.1155/2018/4840531.

Blake, H., & Hawley, H. (2012). Effects of Tai Chi exercise on physical and psychological health of older people. *Current aging science*, 5(1), 19–27. https://doi.org/10.2174/1874609811205010019.

Bliuc, D., Alarkawi, D., Nguyen, T. V., Eisman, J. A., & Center, J. R. (2015). Risk of subsequent fractures and mortality in elderly women and men with fragility fractures with and without osteoporotic bone density: the Dubbo Osteoporosis Epidemiology Study. *Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research*, 30(4), 637–646. https://doi.org/10.1002/jbmr.2393.

BMUS: The Burden of Musculoskeletal Diseases in the United States. Bone and Joint Initiative. (2015). 3rd ed. American Academy of Orthopaedic Surgeons; Rosemont, IL, USA.

Börjesson, M., Hellenius, M.L., Jansson, E., Karlson, J., Leijon, M., Staehle, A., et al. (2010). Physical Activity in the Prevention and Treatment of Disease. Stockholm: Swedish Institute of Health

Bolton, K. L., Egerton, T., Wark, J., Wee, E., Matthews, B., Kelly, A., et al. (2012). Effects of exercise on bone density and falls risk factors in post-menopausal women with osteopenia: a randomised controlled trial. *J. Sci. Med. Sport* 15, 102–109. doi: 10.1016/j.jsams.2011.08.007.

Bonaiuti, D., Shea, B., Iovine, R., Negrini, S., Robinson, V., Kemper, H. C., Wells, G., Tugwell, P., & Cranney, A. (2002). Exercise for preventing and treating osteoporosis in postmenopausal women. *The Cochrane database of systematic reviews*, (3), CD000333. https://doi.org/10.1002/14651858.CD000333.

Borer, K. T., Fogleman, K., Gross, M., La New, J. M., & Dengel, D. (2007). Walking intensity for postmenopausal bone mineral preservation and accrual. *Bone*, 41(4), 713–721. https://doi.org/10.1016/j.bone.2007.06.009.

Brown, J.P., Josse, R.G. (2002). Scientific Advisory Council of the Osteoporosis Society of Canada. Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *Can Med Assoc J*, 167(suppl 1), 1–34.

Budhia, S., Mikyas, Y., Tang, M., & Badamgarav, E. (2012). Osteoporotic fractures: a systematic review of U.S. healthcare costs and resource utilization. *PharmacoEconomics*, 30(2), 147–170. https://doi.org/10.2165/11596880-000000000-00000.

Cadore, E. L., Rodríguez-Mañas, L., Sinclair, A., & Izquierdo, M. (2013). Effects of different exercise interventions on risk of falls, gait ability, and balance in physically frail older adults: a systematic review. Rejuvenation research, 16(2), 105–114. https://doi.org/10.1089/rej.2012.1397

Caputo, E. L., & Costa, M. Z. (2014). Influência do exercício físico na qualidade de vida de mulheres pós-menopáusicas com osteoporose [Influence of physical activity on quality of life in postmenopausal women with osteoporosis]. *Revista brasileira de reumatologia*, 54(6), 467–473. https://doi.org/10.1016/j.rbr.2014.02.008.

Cauley J. A. (2013). Public health impact of osteoporosis. The journals of gerontology. Series A, *Biological sciences and medical sciences*, 68(10), 1243–1251. https://doi.org/10.1093/gerona/glt093.

Chan, W. P., Liu, J. F., & Chi, W. L. (2004). Evaluation of bone mineral density of the lumbar spine and proximal femur in population-based routine health examinations of healthy Asians. *Acta radiologica*, 45(1), 59–64. https://doi.org/10.1080/02841850310003221.

Cheung, A. M., & Giangregorio, L. (2012). Mechanical stimuli and bone health: what is the evidence?. *Current opinion in rheumatology*, 24(5), 561–566. https://doi.org/10.1097/BOR.0b013e3283570238.

Chien, M. Y., Wu, Y. T., Hsu, A. T., Yang, R. S., & Lai, J. S. (2000). Efficacy of a 24-week aerobic exercise program for osteopenic postmenopausal women. *Calcified tissue international*, 67(6), 443–448. https://doi.org/10.1007/s002230001180.

Chilibeck, P. D., Vatanparast, H., Pierson, R., Case, A., Olatunbosun, O., Whiting, S. J., et al. (2013). Effect of exercise training combined with isoflavone supplementation on bone and lipids in postmenopausal women: a randomized clinical trial. *J. Bone Miner. Res*. 28, 780–793. doi: 10.1002/jbmr.1815.

Choquette, S., Riesco, E., Cormier, E., Dion, T., Aubertin-Leheudre, M., and Dionne, I. J. (2011). Effects of soya isoflavones and exercise on body composition and clinical risk factors of cardiovascular diseases in overweight postmenopausal women: a 6-month double-blind controlled trial. *Br. J. Nutr*. 105, 1199–1209. doi: 10.1017/S0007114510004897.

Chow, T. H., Lee, B. Y., Ang, A., Cheung, V., Ho, M., & Takemura, S. (2017). The effect of Chinese martial arts Tai Chi Chuan on prevention of osteoporosis: A systematic review. *Journal of orthopaedic translation,* 12, 74–84. https://doi.org/10.1016/j.jot.2017.06.001.

Compston, J. E., McClung, M. R., and Leslie, W. D. (2019). Osteoporosis. *Lancet,* 393, 364–376. doi: 10.1016/S0140-6736(18)32112-3.

Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. (1993). *The American journal of medicine*, *94*(6), 646–650. https://doi.org/10.1016/0002-9343(93)90218-e.

Cosman, F., de Beur, S. J., LeBoff, M. S., Lewiecki, E. M., Tanner, B., Randall, S., Lindsay, R., & National Osteoporosis Foundation (2014). Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*, *25*(10), 2359–2381. https://doi.org/10.1007/s00198-014-2794-2.

Cramer, H., Krucoff, C., & Dobos, G. (2013). Adverse events associated with yoga: a systematic review of published case reports and case series. *PloS one*, 8(10), e75515. https://doi.org/10.1371/journal.pone.0075515.

Daly, R. M., Dalla Via, J., Duckham, R. L., Fraser, S. F., and Helge, E. W. (2019). Exercise for the prevention of osteoporosis in postmenopausal women: an evidence-based guide to the optimal prescription. *Braz. J. Phys. Ther*. 23, 170–180. doi: 10.1016/j.bjpt.2018.11.011.

de Oliveira, L. C., de Oliveira, R. G., and de Almeida Pires-Oliveira D. A. (2019). Effects of whole-body vibration versus pilates exercise on bone mineral density in postmenopausal women: a randomized and controlled clinical trial. *J. Geriatr. Phys. Ther*. 42, E23–E31. doi: 10.1519/JPT.0000000000000184.

Duff, W. R., Kontulainen, S. A., Candow, D. G., Gordon, J. J., Mason, R. S., Taylor-Gjevre, R., et al. (2016). Effects of low-dose ibuprofen supplementation and resistance training on bone and muscle in postmenopausal women: a randomized controlled trial. *Bone Rep*. 5, 96–103. doi: 10.1016/j.bonr.2016.04.004.

Fleg J. L. (2012). Aerobic exercise in the elderly: a key to successful aging. *Discovery medicine*, 13(70), 223–228.

Florencio-Silva, R., Sasso, G. R., Sasso-Cerri, E., Simões, M. J., & Cerri, P. S. (2015). Biology of Bone Tissue: Structure, Function, and Factors That Influence Bone Cells. *BioMed research international*, 2015, 421746. https://doi.org/10.1155/2015/421746

Gómez-Cabello, A., Ara, I., González-Agüero, A., Casajús, J. A., & Vicente-Rodríguez, G. (2012). Effects of training on bone mass in older adults: a systematic review. *Sports medicine (Auckland, N.Z.)*, 42(4), 301–325. https://doi.org/10.2165/11597670-000000000-00000.

Greendale, G. A., Sowers, M., Han, W., Huang, M. H., Finkelstein, J. S., Crandall, C. J., Lee, J. S., & Karlamangla, A. S. (2012). Bone mineral density loss in relation to the final menstrual period in a multiethnic cohort: results from the Study of Women's Health Across the Nation (SWAN). *Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research*, 27(1), 111–118. https://doi.org/10.1002/jbmr.534.

Greenway, K. G., Walkley, J. W., & Rich, P. A. (2012). Does long-term swimming participation have a deleterious effect on the adult female skeleton?. *European journal of applied physiology*, 112(9), 3217–3225. https://doi.org/10.1007/s00421-011-2305-5.

Guadalupe-Grau, A., Fuentes, T., Guerra, B., & Calbet, J. A. (2009). *Exercise and bone mass in adults. Sports medicine (Auckland, N.Z.)*, 39(6), 439–468. https://doi.org/10.2165/00007256-200939060-00002.

Heinonen, A., Oja, P., Sievänen, H., Pasanen, M., & Vuori, I. (1998). Effect of two training regimens on bone mineral density in healthy perimenopausal women: a randomized controlled trial. *Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research*, 13(3), 483–490. https://doi.org/10.1359/jbmr.1998.13.3.483.

Hernlund, E., Svedbom, A., Ivergård, M., Compston, J., Cooper, C., Stenmark, J., McCloskey, E. V., Jönsson, B., & Kanis, J. A. (2013). Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Archives of osteoporosis*, 8(1-2), 136. https://doi.org/10.1007/s11657-013-0136-1.

Hingorjo, M. R., Zehra, S., Saleem, S., & Qureshi, M. A. (2018). Serum Interleukin-15 and its relationship with adiposity Indices before and after short-term endurance exercise. *Pakistan journal of medical sciences*, 34(5), 1125–1131. https://doi.org/10.12669/pjms.345.15516.

Hong, A. R., & Kim, S. W. (2018). Effects of Resistance Exercise on Bone Health. *Endocrinology and metabolism (Seoul, Korea)*, 33(4), 435–444. https://doi.org/10.3803/EnM.2018.33.4.435.

Horlick, M., Wang, J., Pierson, R. N., Jr, & Thornton, J. C. (2004). Prediction models for evaluation of total-body bone mass with dual-energy X-ray absorptiometry among children and adolescents. *Pediatrics*, 114(3), e337–e345. https://doi.org/10.1542/peds.2004-0301.

Howe, T. E., Shea, B., Dawson, L. J., Downie, F., Murray, A., Ross, C., Harbour, R. T., Caldwell, L. M., & Creed, G. (2011). Exercise for preventing and treating osteoporosis in postmenopausal women. *The Cochrane database of systematic reviews*, (7), CD000333. https://doi.org/10.1002/14651858.CD000333.pub2.

Huang, T. H., Lin, S. C., Chang, F. L., Hsieh, S. S., Liu, S. H., & Yang, R. S. (2003). Effects of different exercise modes on mineralization, structure, and biomechanical properties of growing bone. *Journal of applied physiology (Bethesda, Md.: 1985)*, 95(1), 300–307. https://doi.org/10.1152/japplphysiol.01076.2002.

Johnell, O., & Kanis, J. A. (2006). An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*, 17(12), 1726–1733. https://doi.org/10.1007/s00198-006-0172-4.

Kamienski, M., Tate, D., & Vega, M. (2011). The silent thief: diagnosis and management of osteoporosis. *Orthopedic nursing*, 30(3), 162–173. https://doi.org/10.1097/NOR.0b013e318219ab9d.

Kanis, J. A., Melton, L. J., 3rd, Christiansen, C., Johnston, C. C., & Khaltaev, N. (1994). The diagnosis of osteoporosis. *Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research*, 9(8), 1137–1141. https://doi.org/10.1002/jbmr.5650090802.

Kanis, J. A., McCloskey, E. V., Johansson, H., Oden, A., Melton, L. J., 3rd, & Khaltaev, N. (2008). A reference standard for the description of osteoporosis. *Bone*, 42(3), 467–475. https://doi.org/10.1016/j.bone.2007.11.001.

Kanis, J. A., McCloskey, E. V., Johansson, H., Cooper, C., Rizzoli, R., Reginster, J. Y., & Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the Committee of Scientific Advisors of the International Osteoporosis Foundation (IOF) (2013). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*, *24*(1), 23–57. https://doi.org/10.1007/s00198-012-2074-y

Kanis, J.A., Cooper, C., Rizzoli, R., Reginster, J.Y. (2019). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int*, 30:3–44. doi: 10.1007/s00198-018-4704-5.

Karakiriou, S., Douda, H., Smilios, I., Volaklis, K. A., and Tokmakidis, S. P. (2012). Effects of vibration and exercise training on bone mineral density and muscle strength in post-menopausal women. *Eur. J. Sport Sci*. 12, 81–88. doi: 10.1080/17461391.2010.536581.

Kelley, G. A. (1998). Exercise and regional bone mineral density in postmenopausal women: a meta-analytic review of randomized trials. *American journal of physical medicine & rehabilitation*, 77(1), 76–87. doi: 10.1097/00002060-199801000-00015.

Kelley, G. A., Kelley, K. S., & Tran, Z. V. (2001). Resistance training and bone mineral density in women: a meta-analysis of controlled trials. *American journal of physical medicine & rehabilitation*, 80(1), 65–77. https://doi.org/10.1097/00002060-200101000-00017.

Kelley, G. A., Kelley, K. S., & Kohrt, W. M. (2012). Effects of ground and joint reaction force exercise on lumbar spine and femoral neck bone mineral density in postmenopausal women: a meta-analysis of randomized controlled trials. *BMC musculoskeletal disorders*, 13, 177. https://doi.org/10.1186/1471-2474-13-177.

Kemmler, W., Bebenek, M., von Stengel, S., Engelke, K., and Kalender, W. A. (2013). Effect of block-periodized exercise training on bone and coronary heart disease risk factors in early post-menopausal women: a randomized controlled study. *Scand. J. Med. Sci. Sports* 23, 121–129. doi: 10.1111/j.1600-0838.2011.01335.x.

Kemmler, W., Bebenek, M., Kohl, M., and Von Stengel, S. (2015). Exercise and fractures in postmenopausal women. Final results of the controlled erlangen fitness and osteoporosis prevention study (EFOPS). *Osteoporos. Int.* 26, 2491–2499. doi: 10.1007/s00198-015-3165-3.

Kemmler, W., von Stengel, S., and Kohl, M. (2016). Exercise frequency and bone mineral density development in exercising postmenopausal osteopenic women. Is there a critical dose of exercise for affecting bone? Results of the erlangen fitness and osteoporosis prevention study. *Bone* 89, 1–6. doi: 10.1016/j.bone.2016.04.019.

Kemmler, W., Stengel, V. (eds) (2019). The role of exercise on fracture reduction and bone strengthening. *Avademic Press*, London.

Korpelainen, R., Keinanen-Kiukaanniemi, S., Heikkinen, J., Vaananen, K., and Korpelainen, J. (2006). Effect of impact exercise on bone mineral density in elderly women with low BMD: a population-based randomized controlled 30-month intervention. *Osteoporos. Int*. 17, 109–118. doi: 10.1007/s00198-005-1924-2.

Kostka, J., Kostka, T., & Borowiak, E. (2017). Physical Activity in Older Adults in Relation to Place of Residence and Coexistent Chronic Diseases. *Journal of physical activity & health*, 14(1), 20–28. https://doi.org/10.1123/jpah.2016-0097.

Law, T. D., Clark, L. A., & Clark, B. C. (2016). Resistance Exercise to Prevent and Manage Sarcopenia and Dynapenia. Annual review of gerontology & geriatrics, 36(1), 205–228. https://doi.org/10.1891/0198-8794.36.205

Lee, M. S., Pittler, M. H., Shin, B. C., & Ernst, E. (2008). Tai chi for osteoporosis: a systematic review. *Osteoporosis international: a journal established as result of cooperation between the*

European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 19(2), 139–146. https://doi.org/10.1007/s00198-007-0486-x.

Lerner U. H. (2006). Bone remodeling in post-menopausal osteoporosis. *Journal of dental research*, 85(7), 584–595. https://doi.org/10.1177/154405910608500703.

Leung, D. P., Chan, C. K., Tsang, H. W., Tsang, W. W., & Jones, A. Y. (2011). Tai chi as an intervention to improve balance and reduce falls in older adults: A systematic and meta-analytical review. *Alternative therapies in health and medicine*, 17(1), 40–48.

Liu, B. X., Chen, S. P., Li, Y. D., Wang, J., Zhang, B., Lin, Y., Guan, J. H., Cai, Y. F., Liang, Z., & Zheng, F. (2015). The Effect of the Modified Eighth Section of Eight-Section Brocade on Osteoporosis in Postmenopausal Women: A Prospective Randomized Trial. *Medicine*, 94(25), e991. https://doi.org/10.1097/MD.0000000000000991.

Liu, F., & Wang, S. (2017). Effect of Tai Chi on bone mineral density in postmenopausal women: A systematic review and meta-analysis of randomized control trials. *Journal of the Chinese Medical Association: JCMA*, 80(12), 790–795. https://doi.org/10.1016/j.jcma.2016.06.010.

Logghe, I. H., Verhagen, A. P., Rademaker, A. C., Bierma-Zeinstra, S. M., van Rossum, E., Faber, M. J., & Koes, B. W. (2010). The effects of Tai Chi on fall prevention, fear of falling and balance in older people: a meta-analysis. *Preventive medicine*, 51(3-4), 222–227. https://doi.org/10.1016/j.ypmed.2010.06.003.

Lou, L., Zou, L., Fang, Q., Wang, H., Liu, Y., Tian, Z., & Han, Y. (2017). Effect of Taichi Softball on Function-Related Outcomes in Older Adults: A Randomized Control Trial. *Evidence-based complementary and alternative medicine: eCAM*, *2017*, 4585424. https://doi.org/10.1155/2017/4585424.

Maddalozzo, G. F., Widrick, J. J., Cardinal, B. J., Winters-Stone, K. M., Hoffman, M. A., and Snow, C. M. (2007). The effects of hormone replacement therapy and resistance training on spine bone mineral density in early postmenopausal women. *Bone* 40, 1244–1251. doi: 10.1016/j.bone.2006.12.059.

Marques, E. A., Mota, J., Machado, L., Sousa, F., Coelho, M., Moreira, P., et al. (2011). Multicomponent training program with weight-bearing exercises elicits favorable bone density, muscle strength, and balance adaptations in older women. *Calcif. Tissue Int*. 88, 117–129. doi: 10.1007/s00223-010- 9437-1.

Marques, E. A., Mota, J., & Carvalho, J. (2012). Exercise effects on bone mineral density in older adults: a meta-analysis of randomized controlled trials. *Age (Dordrecht, Netherlands)*, 34(6), 1493–1515. https://doi.org/10.1007/s11357-011-9311-8.

Martyn-St James, M., & Carroll, S. (2006). Progressive high-intensity resistance training and bone mineral density changes among premenopausal women: evidence of discordant site-specific skeletal effects. *Sports medicine (Auckland, N.Z.),* 36(8), 683–704. https://doi.org/10.2165/00007256-200636080-00005.

Martyn-St James, M., & Carroll, S. (2009). A meta-analysis of impact exercise on postmenopausal bone loss: the case for mixed loading exercise programmes. *British journal of sports medicine,* 43(12), 898–908. https://doi.org/10.1136/bjsm.2008.052704.

Martyn-St James, M., & Carroll, S. (2010). Effects of different impact exercise modalities on bone mineral density in premenopausal women: a meta-analysis. *Journal of bone and mineral metabolism*, 28(3), 251–267. https://doi.org/10.1007/s00774-009-0139-6.

Mishra, N., Mishra, V. N., & Devanshi (2011). Exercise beyond menopause: Dos and Don'ts. *Journal of mid-life health*, 2(2), 51–56. https://doi.org/10.4103/0976-7800.92524.

Moreira, L. D., Oliveira, M. L., Lirani-Galvão, A. P., Marin-Mio, R. V., Santos, R. N., & Lazaretti-Castro, M. (2014). Physical exercise and osteoporosis: effects of different types of exercises on bone and physical function of postmenopausal women. *Arquivos brasileiros de endocrinologia e metabologia*, 58(5), 514–522. https://doi.org/10.1590/0004-2730000003374.

Nelson, M. E., Fisher, E. C., Dilmanian, F. A., Dallal, G. E., & Evans, W. J. (1991). A 1-y walking program and increased dietary calcium in postmenopausal women: effects on bone. *The American journal of clinical nutrition*, 53(5), 1304–1311. https://doi.org/10.1093/ajcn/53.5.1304.

NIAMS: Osteoporosis Overview. (accessed on 26 September 2020); Available online: https://www.bones.nih.gov/health-info/bone/osteoporosis/osteoporosis-hoh.

Nichols, J., Nelson, K., Peterson, K., and Sartoris, D. (1995). Bone mineral density responses to high-intensity strength training in active older women. *J. Aging Phys. Act*. 3, 26–38. doi: 10.1123/japa.3.1.26.

Nicholson, V. P., McKean, M. R., Slater, G. J., Kerr, A., and Burkett, B. J. (2015). Low-load very high-repetition resistance training attenuates bone loss at the lumbar spine in active post-menopausal women. *Calcif. Tissue Int.* 96, 490–499. doi: 10.1007/s00223-015-9976-6.

Nikander, R., Sievänen, H., Heinonen, A., Daly, R. M., Uusi-Rasi, K., & Kannus, P. (2010). Targeted exercise against osteoporosis: A systematic review and meta-analysis for optimising bone strength throughout life. *BMC medicine,* 8, 47. https://doi.org/10.1186/1741-7015-8-47.

NOF: National Osteoporosis Foundation. Osteoporosis Exercise for Strong Bones. (accessed on 26 September 2020); Available online:https://www.nof.org/patients/fracturesfall-prevention/exercisesafe-movement/osteoporosis-exercise-for-strong-bones/.

Nuti, R., Brandi, M. L., Checchia, G., Di Munno, O., Dominguez, L., Falaschi, P., Fiore, C. E., Iolascon, G., Maggi, S., Michieli, R., Migliaccio, S., Minisola, S., Rossini, M., Sessa, G., Tarantino, U., Toselli, A., & Isaia, G. C. (2019). Guidelines for the management of osteoporosis and fragility fractures. *Internal and emergency medicine*, 14(1), 85–102. https://doi.org/10.1007/s11739-018-1874-2.

Oh, E. G., Yoo, J. Y., Lee, J. E., Hyun, S. S., Ko, I. S., & Chu, S. H. (2014). Effects of a three-month therapeutic lifestyle modification program to improve bone health in postmenopausal Korean women in a rural community: a randomized controlled trial. *Research in nursing & health*, 37(4), 292–301. https://doi.org/10.1002/nur.21608.

Orsatti, F. N., Nahas-Neto, J., Orsatti, C. L., and Teixeira, A. S. (2013). Effects of isoflavone and counter-resistance training on bone mineral density in postmenopausal women. *Rev. Bras. Cineantropom. Desempenho. Hum.* 15, 726–736. doi: 10.5007/1980-0037.2013v15n6p726.

OSG: Office of the Surgeon General (US). (2004). Bone Health and Osteoporosis: A Report of the Surgeon General. Office of the Surgeon General (US).

Overlie, I., Moen, M. H., Morkrid, L., Skjaeraasen, J. S., & Holte, A. (1999). The endocrine transition around menopause--a five years prospective study with profiles of gonadotropines, estrogens, androgens and SHBG among healthy women. *Acta obstetricia et gynecologica Scandinavica*, *78*(7), 642–647.

Palombaro, K. M., Black, J. D., Buchbinder, R., & Jette, D. U. (2013). Effectiveness of exercise for managing osteoporosis in women postmenopause. *Physical therapy*, 93(8), 1021–1025. https://doi.org/10.2522/ptj.20110476.

Papaioannou, A., Morin, S., Cheung, A. M., Atkinson, S., Brown, J. P., Feldman, S., Hanley, D. A., Hodsman, A., Jamal, S. A., Kaiser, S. M., Kvern, B., Siminoski, K., Leslie, W. D., & Scientific Advisory Council of Osteoporosis Canada (2010). 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*, 182(17), 1864–1873. https://doi.org/10.1503/cmaj.100771.

Rahimi, G. R., Smart, N. A., Liang, M., Bijeh, N., Albanaqi, A. L., Fathi, M., Niyazi, A., & Mohammad Rahimi, N. (2020). The Impact of Different Modes of Exercise Training on Bone Mineral Density in Older Postmenopausal Women: A Systematic Review and Meta-analysis Research. *Calcified tissue international*, *106*(6), 577–590. https://doi.org/10.1007/s00223-020-00671-w.

Raisz L. G. (2005). Pathogenesis of osteoporosis: concepts, conflicts, and prospects. *The Journal of clinical investigation*, *115*(12), 3318–3325. https://doi.org/10.1172/JCI27071.

Satpathy, S., Patra, A., & Ahirwar, B. (2015). Experimental techniques for screening of antiosteoporotic activity in postmenopausal osteoporosis. *Journal of complementary & integrative medicine*, *12*(4), 251–266. https://doi.org/10.1515/jcim-2015-0034 .

Sherk, V. D., Barry, D. W., Villalon, K. L., Hansen, K. C., Wolfe, P., & Kohrt, W. M. (2014). Bone loss over 1 year of training and competition in female cyclists. *Clinical journal of sport medicine: official journal of the Canadian Academy of Sport Medicine*, *24*(4), 331–336. https://doi.org/10.1097/JSM.0000000000000050.

Sherrington, C., Fairhall, N. J., Wallbank, G. K., Tiedemann, A., Michaleff, Z. A., Howard, K., Clemson, L., Hopewell, S., & Lamb, S. E. (2019). Exercise for preventing falls in older people living in the community. The Cochrane database of systematic reviews, 1(1), CD012424. https://doi.org/10.1002/14651858.CD012424.pub2

Schmitt, N. M., Schmitt, J., & Dören, M. (2009). The role of physical activity in the prevention of osteoporosis in postmenopausal women-An update. *Maturitas*, 63(1), 34–38. https://doi.org/10.1016/j.maturitas.2009.03.002.

Simas, V., Hing, W., Pope, R., & Climstein, M. (2017). Effects of water-based exercise on bone health of middle-aged and older adults: a systematic review and meta-analysis. *Open access journal of sports medicine*, *8*, 39–60. https://doi.org/10.2147/OAJSM.S129182.

Sobolev, B., Sheehan, K. J., Kuramoto, L., & Guy, P. (2015). Risk of second hip fracture persists for years after initial trauma. *Bone*, *75*, 72–76. https://doi.org/10.1016/j.bone.2015.02.003.

Svedbom, A., Hernlund, E., Ivergård, M., Compston, J., Cooper, C., Stenmark, J., McCloskey, E. V., Jönsson, B., Kanis, J. A., & EU Review Panel of IOF (2013). Osteoporosis in the European Union: a compendium of country-specific reports. *Archives of osteoporosis*, *8*(1-2), 137. https://doi.org/10.1007/s11657-013-0137-0.

Sun, Z., Chen, H., Berger, M. R., Zhang, L., Guo, H., & Huang, Y. (2016). Effects of tai chi exercise on bone health in perimenopausal and postmenopausal women: a systematic review and meta-analysis. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*, *27*(10), 2901–2911. https://doi.org/10.1007/s00198-016-3626-3.

Taaffe, D.R., Daly, R.M., Suominen, H., Galvao, D.A., Bolam, K.A.(2013). Physical activity and exercise in the maintenance of the adult skeleton and the prevention of osteoporotic fractures. editors. 4th ed. Vol. 1. Elsevier; Amsterdam, The Netherlands, 683–719.

Treloar, A. E., Boynton, R. E., Behn, B. G., & Brown, B. W. (1967). Variation of the human menstrual cycle through reproductive life. *International journal of fertility*, *12*(1 Pt 2), 77–126.

Troy, K. L., Mancuso, M. E., Butler, T. A., & Johnson, J. E. (2018). Exercise Early and Often: Effects of Physical Activity and Exercise on Women's Bone Health. *International journal of environmental research and public health,* 15(5), 878. https://doi.org/10.3390/ijerph15050878.

Turner, C. H., & Robling, A. G. (2005). Mechanisms by which exercise improves bone strength. *Journal of bone and mineral metabolism*, 23 Suppl, 16–22. https://doi.org/10.1007/BF03026318.

Wade, S. W., Strader, C., Fitzpatrick, L. A., Anthony, M. S., & O'Malley, C. D. (2014). Estimating prevalence of osteoporosis: examples from industrialized countries. *Archives of osteoporosis*, *9*, 182. https://doi.org/10.1007/s11657-014-0182-3.

Wang, H., Yu, B., Chen, W., Lu, Y., and Yu, D. (2015). Simplified tai chi resistance training versus traditional tai chi in slowing bone loss in postmenopausal women. *Evid. Based Complement Alternat. Med.* 2015:379451. doi: 10.1155/2015/379451.

WHO Scientific Group on Research on the Menopause in the 1990s (1994: Geneva, Switzerland) & World Health Organization. (1996). Research on the menopause in the 1990s: report of a WHO scientific group. World Health Organization. https://apps.who.int/iris/handle/10665/41841.

Woo, J., Hong, A., Lau, E., and Lynn, H. (2007). A randomised controlled trial of tai chi and resistance exercise on bone health, muscle strength and balance in community-living elderly people. *Age Ageing*, 36, 262–268. doi: 10.1093/ageing/afm005.

Xu, J., Lombardi, G., Jiao, W., & Banfi, G. (2016). Effects of Exercise on Bone Status in Female Subjects, from Young Girls to Postmenopausal Women: An Overview of Systematic Reviews and Meta-Analyses. *Sports medicine (Auckland, N.Z.)*, *46*(8), 1165–1182. https://doi.org/10.1007/s40279-016-0494-0 .

Yang, Y., Du, F., Ye, W., Chen, Y., Li, J., Zhang, J., Nicely, H., & Burge, R. (2015). Inpatient cost of treating osteoporotic fractures in mainland China: a descriptive analysis. *ClinicoEconomics and outcomes research : CEOR*, *7*, 205–212. https://doi.org/10.2147/CEOR.S77175.

Zehnacker, C. H., & Bemis-Dougherty, A. (2007). Effect of weighted exercises on bone mineral density in post menopausal women. A systematic review. *Journal of geriatric physical therapy (2001)*, *30*(2), 79–88. https://doi.org/10.1519/00139143-200708000-00007.

Zhao, R., Zhang, M., & Zhang, Q. (2017). The Effectiveness of Combined Exercise Interventions for Preventing Postmenopausal Bone Loss: A Systematic Review and Meta-analysis. *The Journal of orthopaedic and sports physical therapy*, *47*(4), 241–251. https://doi.org/10.2519/jospt.2017.6969

Zou, L., Wang, C., Chen, K., Shu, Y., Chen, X., Luo, L., & Zhao, X. (2017). The Effect of Taichi Practice on Attenuating Bone Mineral Density Loss: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *International journal of environmental research and public health*, 14(9), 1000. https://doi.org/10.3390/ijerph14091000.

ABKÜRZUNGSVERZEICHNIS

	Deutsch	Englisch
WHO	Weltgesundheitsorganisation	World Health Organization
PMW	postmenopausale Frauen	Post-Menopausal Women
BMD	Knochenmineralgehalt/knochendichte	Bone Mineral Density
DEXA	Dual-Energy-Röntgenabsorptiometrie	Dual-Energy X-ray Absorptiometry
DPA	Dual-Photonen-Absorptiometrie	Dual-Photon Absorptiometry
SD	Standardabweichung	Standard Deviation
NOF	Nationale Osteoporose-Stiftung	National Osteoporosis Foundation
RCT	Randomisierte Kontrollstudie	Randomised Control Trial
PF	Proximaler Femur	Proximal Femur
LS	Lendenwirbelsäule	Lumbar Spine
FN	Schenkelhals	Femoral Neck
ROI	Regionen von Interesse	regions of interest
tHip	gesamte Hüfte	total Hip
WB-AE	Gewichttragendes aerobes Training	Weight Bearing- Aerobic Exercise
TC	Tai Chi	Tai Chi
RT	Krafttraining	Resistance Training
DRT	Dynamisches Krafttraining	Dynamic Resistance Training
ES	Effekt-Größe	Effect Size
HRT	Hormon-Ersatz-Therapie	Hormone Replacement Therapy
HT	Hormontherapie	Hormone Therapy
SMD	standardisierte Mittelwertunterschiede	Standardized Mean Differences

CI	Konfidenzintervall	Confidence Interval
PRISMA	Bevorzugte Berichtselemente für systematische Rezensionen und Meta-Analysen	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Internationalen prospektiven Register systematischer Übersichtsarbeiten	International Prospective Register of Systematic Reviews

PUBLIKATIONSLISTE

2008 - VERÖFFENTLICHUNGEN

1. **Shojaa, M.,** Jouybari, L., & Sanagoo, A. (2008). Relieve the discomfort of dysmenorrhea & herbal remedies. *Pain practice: the official journal of World Institute of Pain*, *8*(3), 222.
2. **Shojaa M.**, Jouybari, L.M, Sanagoo, A. (2008). Common myths about Sex. *Iranian Journal of Psychology*, 14(2):220-21[auf Persisch].

2009 – VERÖFFENTLICHUNGEN

3. **Shojaa, M.,** Jouybari, L., & Sanagoo, A. (2009). Common myths among a group of Iranian women concerning sexual relationships during pregnancy. *Archives of Medical Science*, 5(2), 229-232.

4. **Shojaa, M**., Jouybari, L., & Sanagoo, A. (2009). The sexual activity during pregnancy among a group of Iranian women. *Archives of gynecology and obstetrics*, *279*(3), 353–356.

2010 – VERÖFFENTLICHUNGEN

5. **Shojaa,** M., Jouybari, L., Qorbani, M., Sanagoo, A., Shojaee, H., Kia Kajoori, Z. (2010). Prevalence and Cause of Smoking among the Dormitories Students in Gorgan University of Medical Sciences. *Pajoohandeh Journal,* 15 (3):123-128. [auf Persisch].

2011 – VERÖFFENTLICHUNGEN

6. **Shojaa, M.,** Jouybari, L., Sanagoo, A. (2011). The changes in sexual and behavioral relationships among the couples during pregnancy. *Qom University of Medical Sciences Journal*, 3 (5).18-22 [auf Persisch].
7. Motie, M. R., Besharat, S., Torkjazi, R., **Shojaa, M**., Besharat, M., Keshtkar, A., Roshandel, G., Besharat, S., & Fateme, A. A. (2011). Modifiable Risk of Breast Cancer in Northeast Iran: Hope for the Future. A Case-Control Study. *Breast care (Basel, Switzerland),* 6(6), 453–456.

8. Aghaei, M., Gharibdost, F., Zayeni, H., Akhlaghi, M., Sedighi, S., Rostamian, A., Aghdami, N., **Shojaa, M**. (2011). The Correlation between endothelin-1 antibody plasma concentrations in patients with scleroderma and different manifestations of the disease. *Tehran University Medical Journal*, 68(12): 699-704 [auf Persisch].

9. Aghaei, M., Gharibdost, F., Zayeni, H., Akhlaghi, M., Sedighi, S., Rostamian, A., Aghdami, N., **Shojaa, M**. (2011). Endothelin-1 level in scleroderma patients with and without fingertip pitting ulcer. *Journal of Jahrom University of Medical Sciences,* 9(1):23-26[auf Persisch].

10. Aghaei, M., Sedighi, S., Shirashiani, M., Gharibdost, F., Zayeni, H., Akhlaghi, M., Hezar Khani, S.H., Rostamian, A., Aghdami, N., **Shojaa, M.**, Gholam Mohebi, E. (2011). Various Clinical Features and Changes In Plasma Et-1 Level Of Scleroderma Patients. *Journal of Medical Science & Research*, 2(2):60-63.

2012– VERÖFFENTLICHUNGEN

11. Aghaei, M., Sedighi, S., Behnam Pour, N., Hezar Khani, S., Jamshir, M., Agh, A., **Shojaa, M**. (2012) Prevalence and risk factors of osteoporosis in postmenopausal women with rheumatoid arthritis: a brief report. *Tehran University Medical Journal*, 2012; 70(7): 447-451 [auf Persisch].

12. Aghaei, M., Gharibdost, F., Zayeni, H., Akhlaghi, M., Sedighi, S., Rostamian, A., Aghdami, N., **Shojaa, M**. (2012). Endothelin-1 in systemic sclerosis. *Indian Dermatology Online Journal*, 3(1): 14-16

2013 – VERÖFFENTLICHUNGEN

13. **Shojaa, M**., Javid, N., Amoli, M., Shakeri, F., Samaei, N. M., Aghaie, M., Khashayar, P., & Livani, S. (2013). No evidence of association between CTLA-4 polymorphisms and systemic lupus erythematosus in Iranian patients. *International journal of rheumatic diseases*, 16(6), 681–684.

14. Aghaei, M., Sedighi, S., Behnam Pour, N., Hezar Khani, S., Shirashiani, M., Gholam Mohebi, E., Zayeni, H., **Shojaa, M.**, Jamshir, M., Agh, A. (2013). Change in Bone Mineral Density in Post-

Menopausal Women with Rheumatoid Arthritis. *Bangladesh Journal of Medical Science*, 12(2), 158-163

15. Aghaei, M., Sedighi, S., Behnam pour, N., Hezar Khani, S., Hashemizadeh, P., Shirashiani, M., Agh, A., **Shojaa, M**. (2013). The study of bone mineral density in postmenopausal women with rheumatoid arthritis. *J Shahrekord Univ Med Sci*, 15(2): 53-60 [auf Persisch].

2014 – VERÖFFENTLICHUNGEN

16. **Shojaa, M.**, Qorbani, M., Jouybari, L.M., Sanagoo, A., Mohebi, R., Bamyar, R., Aghaie, M. (2014). Prevalence of Smoking among the Students resided at Dormitories in Golestan University of Medical Sciences, Iran. *Bangladesh Journal of Medical Science*, 13(4):460-65.

17. **Shojaa, M.**, Aghaie, M., Jouybari, L., Qorbani, M., Sanagoo, A. (2014). Family and friends influence on cigarette smoking tendency among the dormitory's students of Golestan University of Medical Sciences in North of Iran. *Al Ameen J Med Sci*, 7(3):235-239.

18. **Shojaa, M.**, Khashayar, P., Amoli, M., Aghaie, M., Qorbani, M., Akbarian, M., Ranjbarpour, N. (2014). Association of CTLA-4 polymorphism with systemic lupus erythematosus. *Journal of Kermanshah University of medical science*, 17(10):617-21 [auf Persisch]

19. **Shojaa, M.**, Aghaie, M., Qorbani, M., Khashayar, P., Amoli, M., Keshtkar, A., Mohebi, R., Akbarian, M., Rokn Sharifi, S. (2014). Evaluation of CTLA-4 exon-1 +49A/G polymorphism in systemic lupus erythematosus patients: A Meta-analysis. *Knowledge & Health Journal,* 9(3): 11-20 [auf Persisch]

20. **Shojaa, M**., Amoli, M., Aghaie, M., Khashayar, P., Javid, N., Shakeri, F., Keshtkar, A., Qorbani, M., & Mohebi, R. (2014). CTLA-4 polymorphism in Iranian patients with systemic lupus erythematosus. *American Journal of Experimental and Clinical Research, 1*, 68-71.

21. **Shojaa, M.**, Amoli, M., Javid, N., Shakeri, F., Aghaie, M., Qorbani, M., Rokn Sharifi, S., Mohammadi, Z., Haghighi, H. (2014). The 1661AG polymorphism of the CTLA-4 gene is not

associated with systemic lupus erythematosus. *Feyz Journal, Kashan university of Medical Sciences*, 18(3): 247-52[auf Persisch].

22. **Shojaa, M.**, Aghaie, M., Qorbani, M., Khashayar, P., Amoli, M., Keshtkar, A., Mohebbi, R., Akbarian, M., Roknsharifi, S. (2014). Association of the CTLA-4 1722TC polymorphism and systemic lupus erythematosus: a systematic review and Meta-analysis. *Medical Journal of the Islamic Republic of Iran*, 19; 28:132.

2015– VERÖFFENTLICHUNGEN

23. **Shojaa, M.**, Aghaie, M., Amoli, M., Khashayar, P., Javid, N., Shakeri, F., Qorbani, M., Mohebbi, R. (2015). Association between CTLA-4 gene polymorphism and the risk of systemic lupus erythematosus: brief report. *Tehran Univ Med J,* 73(2): 127-131. [auf Persisch]
24. Mohammadi, Z., Ebrahimi, M., Keshtkar, A., Aghaei Meybodi, H., Khashayar, P., Jouyande, Z., Bayegi, F., **Shojaa, M.**, Ghodsi, M., Djalalinia, S. (2015). Protocol for Systematic Review: Peak Bone Mass Pattern in Different Parts of the World. *J Clinic Res Bioeth*, 6:2.

2017 – VERÖFFENTLICHUNGEN

25. **Shojaa, M.**, Aghaie, M., Amoli, M., Javid, N., Shakeri, F., Khashayar, P., Tabarraei, A., Keshtkar, A. A., Joshaghani, H. R., Kouroshnia, A., Qorbani, M., Mahmoudi, F., Mohebbi, R., & Ranjbarpour, N. (2017). Association between 318C/T polymorphism of the CTLA-4 gene and systemic lupus erythematosus in Iranian patients. *International journal of rheumatic diseases*, *20*(12), 2040–2044.

26. Kemmler, W., Weissenfels, A., Teschler, M., Willert, S., Bebenek, M., **Shojaa, M.**, Kohl, M., Freiberger, E., Sieber, C., & von Stengel, S. (2017). Whole-body electromyostimulation and

protein supplementation favorably affect sarcopenic obesity in community-dwelling older men at risk: the randomized controlled FranSO study. *Clinical interventions in aging*, *12*, 1503–1513..

2018 – VERÖFFENTLICHUNGEN

27. Kemmler, W., Weissenfels, A., Willert, S., **Shojaa, M**., von Stengel, S., Filipovic, A., Kleinöder, H., Berger, J., & Fröhlich, M. (2018). Efficacy and Safety of Low Frequency Whole-Body Electromyostimulation (WB-EMS) to Improve Health-Related Outcomes in Non-athletic Adults. A Systematic Review. *Frontiers in physiology*, *9*, 573.

28. Kemmler, W., **Shojaa, M**., Kohl, M., & von Stengel, S. (2018). Exercise effects on bone mineral density in older men: a systematic review with special emphasis on study interventions. *Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*, *29*(7), 1493–1504.

29. Kemmler, W., **Shojaa, M.**, von Stengel, S.(2018). Effekt eines körperlichen Trainings auf die Knochendichte bei Männern: Eine systematische Übersicht. *Osteologie*, 27(01):38-47.

2020 – VERÖFFENTLICHUNGEN

30. **Shojaa, M**., Von Stengel, S., Schoene, D., Kohl, M., Barone, G., Bragonzoni, L., Dallolio, L., Marini, S., Murphy, M. H., Stephenson, A., Mänty, M., Julin, M., Risto, T., & Kemmler, W. (2020). Effect of Exercise Training on Bone Mineral Density in Post-menopausal Women: A Systematic Review and Meta-Analysis of Intervention Studies. *Frontiers in physiology*, *11*, 652.

31. **Shojaa, M**., von Stengel, S., Kohl, M., Schoene, D., & Kemmler, W. (2020). Effects of dynamic resistance exercise on bone mineral density in postmenopausal women: a systematic review and meta-analysis with special emphasis on exercise parameters. *Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*, *31*(8), 1427–1444.

32. **Shojaa, M.**, von Stengel, S., Schoene, D., Kohl, M., Kemmler, W. (2020). Effekte verschiedener Trainingsformen auf den Knochenmineralgehalt postmenopausaler Frauen: Eine systematische Übersicht und Meta-Analyse. *Osteologie*, 29(03), 179-193.

33. Kemmler, W., **Shojaa, M.**, Kohl, M., von Stengel, S. (2020) Effects of Different Types of Exercise on Bone Mineral Density in Postmenopausal Women: A Systematic Review and Meta-analysis. *Calcif Tissue Int*. doi: 10.1007/s00223-020-00744-w.

34. Kemmler, W., **Shojaa, M.**, Kohl, M., Schoene, D., von Stengel, S. (2020). Dynamisches Krafttraining und Knochendichte an der Lendenwirbelsäule postmenopausaler Frauen Eine Meta-Analyse unter besonderer Berücksichtigung trainingswissenschaftlicher Kriterien. *Osteologie*, 29(03), 194-206

35. Kemmler, W., Hettchen, M., Kohl, M., Murphy, M., **Shojaa, M**., Ghasemikaram, M., et al. (2020). Effects of High Intensity Exercise during Early Postmenopause-the Randomized Controlled ACTLIFE-Study. *J Osteopor Phys Act 8:228. doi: 10.35248/2329-9509.20.8.228.*

36. Kemmler, W., Hettchen, M., Kohl, M., Murphy, M., **Shojaa, M**., Ghasemikaram, M., et al. (2020). Effects of high-intensity aerobic exercise and resistance training on cardiometabolic risk in early-postmenopausal women 16-week results of the randomized controlled ACTLIFE-ER study. Deutsche Zeitschrift für Sportmedizin. (in press).

2021 – VERÖFFENTLICHUNGEN

37. Hettchen, M., von Stengel, S., Kohl, M., Murphy, M., **Shojaa, M**., Ghasemikaram, M., et al. (2021). Changes in Menopausal Risk Factors in Early Postmenopausal Osteopenic Women After 13 Months of High-Intensity Exercise: The Randomized Controlled ACTLIFE-RCT. *Clin Interv Aging, 16, 83-96.*