OPTIMAL MOBILITY AND FUNCTION ACROSS THE LIFESPAN

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PUBLISHED IN: Frontiers in Physiology and Frontiers in Sports and Active Living

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88966-593-8
DOI 10.3389/978-2-88966-593-8

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OPTIMAL MOBILITY AND FUNCTION ACROSS THE LIFESPAN

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Citation: Zernicke, R. F., Hart, D. A., eds. (2021). Optimal Mobility and Function across the Lifespan. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-88966-593-8

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frontiers in Physiology

EDITORIAL
published: 09 February 2021
doi: 10.3389/fphys.2021.652640

Editorial: Optimal Mobility and Function Across the Lifespan

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Keywords: mobility, cardiovascular, exercise physiology, musculoskeletal, aging

Editorial on the Research Topic

Optimal Mobility and Function Across the Lifespan

Mobility and the ability to functionally navigate the environment are intrinsically ingrained in the evolution leading to *Homo sapiens*. Likewise, mobility and a threshold level of exercise are essential across the lifespan from birth to old age to optimize growth and maturation early, and then to avoid deconditioning with advancing age. Connective tissues including bones, muscles, tendons, ligaments, cartilage, and menisci require mobility to maintain optimal integrity (i.e., "use it or lose it" paradigm) and need to work within the boundary conditions of Earth. In addition, it is not only the human musculoskeletal (MSK) system that depends on mobility and exercise to maintain its integrity, but also the cardiovascular system (CVS), and brain and other highly vascularized systems (e.g., kidneys and lungs). The articles in this Research Topic focus on understanding the role and effects of mobility and exercise in maintaining multiple physiological systems and avoiding the deconditioning that can accompany advancing age. The articles can be grouped into Three Themes: (1) Overview of how exercise is ingrained in human physiology, (2) Examination of how exercise can be assessed and used as an approach for disease prevention and risk mitigation in younger individuals, and (3) Examples of the effectiveness of exercise for enhancing successful aging. Given the "graying" of many global populations, the development of chronic diseases in the elderly, and the need to both prevent loss of mobility (i.e., Exercise is Health), as well as using mobility and exercise to mitigate the impact of early chronic diseases (i.e., Exercise is Medicine), many of the Research Topic articles focus on the elderly.

THEME ONE

Hart and Zernicke provide an overview of how mobility and exercise (patterned mobility) were ingrained into multiple physiologic systems during the evolutionary process leading to *Homo sapiens*. Mobility and exercise are critical for growth and maturation through to skeletal maturity as humans develop the ability to function in Earth's environment with its attendant gravitational forces. How biomechanics and biology are integrated to yield long-term functioning is also addressed.

OPEN ACCESS

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Specialty section:
This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology

Received: *12 January 2021*
Accepted: *19 January 2021*
Published: *09 February 2021*

Citation:
Hart DA and Zernicke RF (2021) Editorial: Optimal Mobility and Function Across the Lifespan. Front. Physiol. 12:652640. doi: 10.3389/fphys.2021.652640

THEME TWO

The systematic review by Patel et al. focuses on non-elite sport involvement and bone density in younger individuals (11–35 years). Peak bone density is acquired early in life, and enhanced bone density can reduce risk of osteoporotic fractures later in life, particularly for post-menopausal females, who comprise∼75% of the elderly with osteoporosis (OP). The analysis by Patel and colleagues showed that weight-bearing sport involvement has a beneficial effect on calcaneal bone density, which may also portend beneficial effects on other skeletal tissues.

Tuttor et al. compared two different exercise protocols designed to impact cardiometabolic risk factors in overweight "middle aged" males. Both protocols were effective, but a high-intensity resistance exercise was more effective. Two key findings emerged: (1) different exercise protocols can effectively have a positive influence on the CVS, and (2) variations exist between individuals regarding which type of exercise will yield the optimal response. As Hart and Zernicke note, it is known that some people respond better to resistance than aerobic exercise and vice versa.

Assessing how individuals walk in different environments (i.e., controlled vs. uncontrolled) can provide insights into how mobility is influenced by navigation cues, and how this may be also influenced by age. Renggli et al. indicate that controlled laboratory assessments yield different results when compared to uncontrolled mobility (i.e., gait) in real-world environments assessed using wearable measurement devices. For assessing both young and elderly individuals, it is important to understand the type and intensity of mobility activity, as well as the environment in which the activity occurs. An uncontrolled environment likely requires incorporation of navigation cues more so than a laboratory setting.

The final article in Theme Two bridges Themes Two and Three. Mancinelli et al. examine the ability of neuromuscular electrical stimulation (NMES) to modify the muscles of the healthy elderly, using the *vastus lateralis* muscle of active, healthy older individuals. As older individuals may develop sarcopenia, which can impede mobility, using NMES to enhance muscle integrity could lead to more effective mobility and, thus, exert greater impact on physiological systems at risk due to a lack of mobility. Given the effectiveness of the intervention, one could also postulate that application of NMES to younger individuals may prevent or inhibit the development of some forms of sarcopenia.

THEME THREE

Theme Three articles focus on the elderly and address issues in the context of mobility and successful, healthy aging.

The first contribution focuses on the MSK system in the elderly and how to optimize its integrity. Endo et al. proposed to optimize skeletal muscle fitness using resistance training in the elderly. As noted earlier, during the aging process many individuals develop sarcopenia leading to impaired mobility, and Endo et al. used exercise—alone or in combination with other modalities—in an effort to blunt the potential for developing sarcopenia. Tavoian et al. also focus on resistance exercise in the elderly to diminish the risk for development of chronic diseases, and their results support the premise that resistance exercise is more beneficial than aerobic exercise. Hill et al. compare the advantages of downhill walking vs. level walking for the retention of muscular and physical function in the elderly. In aggregate, these three studies indicate that it is not just exercise that is important, but the type of exercise can also be important. The next article focuses on using SPARC metrics to assess variations in the "timed up-and-go" test in individuals over 80 years, who were at risk for falls vs. those who were not (Figueiredo et al.). As falls are a leading cause of low impact hip fractures, being able to predict who may be at risk with a relatively simple test could lead to preventative measures to mitigate such risk. Finally, building on the theme of mitigating risk for adverse events in the elderly, including falls, Freiberger et al. provide a narrative review focused on community-dwelling elderly and the risks presented by age-related loss of cognition, physical deconditioning, and other mobility limitations.

A cluster of articles in Theme Three focuses on the role of mobility and exercise in the elderly related to bone and CVS health. Shojaa et al. provide a systematic review and meta-analysis of exercise on bone health in post-menopausal females. They evaluate and summarize existing research on optimal exercise protocols to use and their outcomes in this population. As osteoporosis (OP) is a prevalent disease in this cohort of women (∼75% of all OP), and OP can predispose individuals to hip fractures and other fractures that can lead to morbidity and mortality, optimizing preventative measures is significant. With respect to the interactions among CVS health, exercise, and successful aging, a subset of three review articles is included in Theme Three. Santos and Umpierre address the links between exercise and risk for atherosclerosis and as such emphasize not only the elderly, but also those in younger age groups. The advantages and impact of exercise, as well as current gaps in information that need additional study, indicate that while some concrete evidence exists in this area, much research remains to be done. de Oliverira Sant'Ana et al. generated a review focused on the role of exercise as a preventative measure in the healthy elderly. As such, the exercise protocols were designed to maintain the integrity of the CVS and minimize the risk for deconditioning and emergence of disease (i.e., Exercise is Health). Finally, Xing et al. provide a mini-review that focuses on the role of exercise and mobility on recovery from a CVS event (i.e., myocardial infarction) (i.e., Exercise is Medicine). Collectively, extant data suggest that exercise protocols can have a positive impact on both prevention, as well as recovery from a loss of health as it pertains to the CVS.

Integrating Ideas

The collection of articles in this Research Topic support the concept that humans require mobility to maintain the integrity of the musculoskeletal system (MSK), as well as the CVS. Because CVS integrity is central to many physiological systems (e.g., brain, kidneys, and lungs), there is a "cascade effect" for optimal health that can be traced back to the need to optimally maintain the MSK system and retain its functionality across the lifespan (Hart and Zernicke). In sum, Prevention is better than Treatment for minimizing risk for loss of function for many human physiological systems.

AUTHOR CONTRIBUTIONS

DH wrote the initial draft of this Editorial. DH and RZ edited and polished the article. Both authors agree with the final version and its submission to Frontiers.

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.

frontiers in Physiology

ORIGINAL RESEARCH
published: 27 November 2019
doi: 10.3389/fphys.2019.01459

Neuromuscular Electrical Stimulation Induces Skeletal Muscle Fiber Remodeling and Specific Gene Expression Profile in Healthy Elderly

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Specialty section:
This article was submitted to Striated Muscle Physiology, a section of the journal Frontiers in Physiology

Received: 09 July 2019
Accepted: 12 November 2019
Published: 27 November 2019

Citation:
Mancinelli R, Toniolo L, Di Filippo ES, Doria C, Marrone M, Maroni CR, Verratti V, Bondi D, Maccatrozzo L, Pietrangelo T and Fulle S (2019) Neuromuscular Electrical Stimulation Induces Skeletal Muscle Fiber Remodeling and Specific Gene Expression Profile in Healthy Elderly. Front. Physiol. 10:1459. doi: 10.3389/fphys.2019.01459

Skeletal muscle aging is a multifactorial process strictly related to progressive weakness. One of the results that were focused on was the fiber phenotype modification and their loss. The physiological muscle recruitment to contraction, basically prosecuted under volitional control, can also be engaged by means of Neuromuscular Electrical Stimulation (NMES). Knowing that the NMES is effective in improving muscle strength in active healthy elderly, the aim was to investigate which physiological modifications were able to produce in the *Vastus lateralis* muscle and the pathways involved. It was found that NMES increased the cross sectional area and the isometric strength of type II myofibers together with the activated myogenic pathway in order to shift glycolytic toward the oxidative phenotype II myofibers, at a molecular level and with an increase of maximal voluntary contraction (MVC) at a functional level. Using the TaqMan low density array on 48 different genes, we found that NMES specific gene regulation highlighted: (i) increased protein synthesis with respect to protein degradation; (ii) the activation of an apoptotic pathway involved in the differentiation process; (iii) increased regeneration signals; (iv) oxidative enzyme regulation. These pathways were validated via confirmatory RT-PCR for genes involved in the regeneration process as well as Myosin isoforms. We also investigated the oxidative stress status analyzing superoxide anion levels, the protein expression of two different superoxide dismutase and the activity of both catalase and superoxide anion dismutase, being two main antioxidant enzymes. In conclusion, data demonstrates that NMES is effective in producing physiological adaptation on *Vastus Lateralis* of active healthy elderly as well as providing new insights for further research on elderly who experienced muscle detriment for periodic or permanent immobility.

Keywords: oxidative stress, maximal voluntary contraction, neuromuscular electrical stimulation, single fiber mechanic, gene expression

INTRODUCTION

Skeletal muscle is a tissue of our organism that undergoes adaptations. However, during aging it is related to the progressive loss of the neuromuscular function that takes the name of Sarcopenia. This term describes a condition characterized by the loss of skeletal muscle strength and mass that occurs during aging (Barber et al., 2015). Sarcopenia increases in those above 60 years of age with atrophy being an important symptom (Pietrangelo et al., 2009) linked to, a reduction of hormonal levels (testosterone, GH, IGF-1), sedentary lifestyle, genetic and reduced regenerative capability-stem cells dependent on skeletal muscle (Cruz-Jentoft et al., 2019).

Skeletal muscle atrophy in the elderly is worsened by inactivity that occurs when diseases obligate them to be bed-ridden. The best countermeasure is moderate and regular exercise, despite the fact that it could be useful, there is a lack of precise indications with regards to specific training and/or the treatment of Sarcopenia (Stec et al., 2017; Steffl et al., 2017).

To date, muscle strengthening against resistance is the most widely used training protocol applied in order to avoid loss of muscle strength and mass, that occurs with aging. It has been demonstrated that in the elderly, this kind of training protocol leads to increased protein synthesis associated with muscle strength (Kosek et al., 2006). Nevertheless, one of the main problems related to aging is that some people are not able to move because of pathological conditions such as pain, osteoarthritis, scarce motivation and limited motor skills that reduce the execution of classic training protocols. Neuromuscular Electrical Stimulation (NMES) can be considered as an alternative approach in place of physical exercise mimicking the same effect. Indeed, NMES is a fine tool to counteract the onset or aggravation of the sarcopenia process activating the plasticity of muscular tissue (Dehail et al., 2008). The NMES can be utilized to counteract the progression of muscle weakness due to injury or knee surgery in medicine (Rebai et al., 2002; Stevens et al., 2003; Talbot et al., 2003) as well as increase muscle strength and hypertrophy in healthy subjects (Yanagi et al., 2003; Minetto et al., 2013; Di Filippo et al., 2017). Few studies have analyzed the effects of NMES on the functionality of muscle in elderly subjects *in vivo*; furthermore, few data are available regarding changes induced by NMES in single myofibers dissociated from aged muscle (Di Filippo et al., 2017). Studying the effects and the mechanisms activated by NMES will give indications in how to use this type of training in sarcopenic subjects, especially in the elderly who are not capable of doing voluntary exercise. The analysis of NMES training could offer significant advantages in understanding if these protocols *per se* or in association with voluntary training could defer sarcopenia in elderly people (D'Antona et al., 2003; Maffiuletti et al., 2006). Moreover, very little evidence exists with regards to oxidative management in elderly muscles stimulated with NMES. Few studies have addressed this topic on young males. Gondin et al. (2011) showed that in young males NMES improved the antioxidant defense system. Some evidence at cellular level, suggests that electrical stimulation increases the ROS production (Dong et al., 2018). Our group recently stated that NMES can influence the regeneration process as well as the oxidative stress of satellite cells in human skeletal muscle (Di Filippo et al., 2017). However, oxidative management in NMES-stimulated muscle tissue of elderly still remains to be further investigated.

The goal of the present study was to determine the adaptation of skeletal muscle tissue/myofibers especially at a molecular level as well as oxidative modulation, by using a passive muscle training program such as NMES which is applied to the quadriceps muscles related to increase muscle strength and mass in elderly subjects without any voluntary muscle contraction.

The impact of NMES on local muscle in elderly volunteers was assessed both by isometric strength developed in MVCs by thigh extensor muscles and thigh circumference. Structural modifications were evaluated using thigh circumference parameters. In particular, *Vastus Lateralis* (VL) muscle needle-biopsies obtained pre and post-NMES were used to analyze specific fiber features (cross-sectional area, types, tension development of single fiber) and the expression of specific groups of genes.

MATERIALS AND METHODS

Subjects

The study was carried out on 18 healthy elderly male subjects (67.63 ± 4.94 years old, mean ± SD). The study was approved by the local Ethics Committee (protocol nos. 1233/06, 1884/09 and 07/2016 COET), and was in accordance to the 1964 Declaration of Helsinki. All subjects provided written informed consent before participating in the research project. The following inclusion criteria have been taken into account: normal blood pressure and ECG; the absence of cardiovascular, metabolic and bone/joint diseases. Exclusion criteria were considered the presence of cardiovascular and/or metabolic diseases, evidence of acquired or hereditary muscle disease, diagnosis of respiratory or psychiatric disorders. No individual was under treatment with testosterone or other pharmacological therapies nor training protocols known to influence skeletal muscle.

NMES Protocol and Experimental Design

Neuromuscular Electrical Stimulation sessions consisted of 24 sessions of bilateral stimulation lasting 18-min each with three sessions per week according to the modified methods of Maffiuletti (2010) and Di Filippo et al. (2017). During stimulation, subjects were seated with the knee joint fixed at a 75° angle (where 0° corresponds to a full knee extension). To minimize hip and thigh motion during contractions, straps were firmly fastened across the pelvis. Three self-adhesive electrodes of 2-mmwide were placed over each thigh. Two positive electrodes (25 cm^2) were placed as close as possible to the motor point of both the *Vastus Lateralis* and *Vastus Medialis* muscles. The negative electrode (50 cm^2), was placed 5–7 cm below the inguinal crease. The NMES device was a portable battery-powered stimulator (Genesy 1200 Pro, Globus® Srl, Codognè, TV, Italy). Rectangular wave pulsed currents (75 Hz) lasting 400 μs were delivered with a rise time of 1.5 s, a steady tetanic stimulation time of 4 s, and a fall time of 0.75 s, for a total contraction duration of 6.25 s followed by a pause, lasting 20 s. The duty cycle was 24% (6.25/26.25 s of work divided by seconds of the total work). Intensity was monitored online and was gradually increased throughout the training session to a level of maximized tolerance intensity. Each session was preceded by a standardized warmup consisting of 5 Hz pulses lasting 200 μs. Furthermore, the intensity of the stimulation was monitored and recorded up to the individual's pain threshold.

Anthropometric Data

The pre-NMES session (1 week before the stimulation) and the post-NMES session (one-three days after the completion of the stimulation), the subjects were characterized for Body Mass Index (BMI) and the circumference of the dominant lower limbs measured at superior, intermediate and inferior levels as well as at the linea glutea (Pietrangelo et al., 2011, 2012).

Maximal Isometric Strength

The maximal isometric strength of the lower limbs was determined by measuring the MVC according to Pietrangelo et al. (2012). The tests were carried out (with) a leg-extension device (Nessfit Srl, San Giovanni Teatino, Italy) equipped with a strain gauge (Globus, Codognè, Italy), repeated three times, with a 2 min recovery time between each). The knees and body/limb joints were positioned at 90°. The valid MVC was the highest value recorded.

Molecular Analysis of Muscle Biopsies

Using a semi-automatic needle (Precisa 13 Gauge; Hospital Service, Rome, Italy) at pre- and post-NMES, Vastus lateralis muscle biopsies were obtained at one-third of the distance from the upper margin of the rotula to the anterior superior iliac spine as described in Pietrangelo (Pietrangelo et al., 2011). In each subject, several samples were collected from the same insertion point of the needle and were divided into three groups: (i) samples of approximately 10 mg collected in RNA Later (#AM7020, Ambion, Milan, Italy), and stored at −80°C until used to perform the RT-PCR Analysis, (ii) samples collected in ice cold skinning solution with 50% (v/v) glycerol and stored at –20°C for myofibers preservation and Electrophoretic Analysis, (iii) samples immediately frozen and stored at −80°C for enzymatic and Western Blotting Analysis.

Real-Time PCR

Total purified RNA (by TRIZOL Reagent from Invitrogen, Thermo Fisher Scientific) was quantified using NanoDrop Spectrophotometers (Thermo Fisher Scientific) and RNA quality was evaluated by gel electrophoresis according to Boscolo Papo et al. (2014). The cDNA was synthesized from 1 μg of the total RNA using the High Capacity cDNA Reverse Transcription Kit with RNase Inhibitor (Applied Biosystems, Thermo Fisher Scientific), in accordance to the manufacturer's protocol. Each sample was used to perform both the classic RT-PCR and TaqMan low density array.

The expression analysis using the classic RT-PCR was performed using the ABI 7500 Real-Time PCR System (Applied Biosystems, Thermo Fisher Scientific). The data were acquired by ABI's 7500 System SDS Software. The SYBR Green I dye chemistry detection was used to amplify myogenic regulatory factors (IGF1, MURF1, Pax7, and MSTN) and the TaqMan Assay were used to amplify myosin isoforms (MyHC 1, MyHC 2A, and MyHC 2X). Quantitative real time PCR was performed in 20 μl reaction volume containing 1X Power SybrGreen or TaqMan Gene Expression PCR Master Mix (Applied Biosystem, Thermo Fisher Scientific), 300 nM each forward and reverse primers and 100 ng of cDNA. Dissociation curves confirmed the specific amplification of the cDNA target and the absence of non-specific products.

The expression analysis using TaqMan low density array (Applied Biosystems-MDS Sciex, Toronto, ON, Canada) was performed on 100 ng (2 μl) cDNA for each sample according to Fulle et al. (2013). Subsequently, 48 μl nuclease-free water and 50 μl 2× TaqMan Universal PCR Master Mix (Applied Biosystems) were added for the RT-PCR measurements. This mixture was divided over sample-loading ports of the TaqMan low density arrays. The arrays were centrifuged twice (2 min, 331 × *g* at room temperature) and then, the card sealed. The amplification of Real-time PCR was performed using an Applied Biosystems Prism 7900HT Sequence Detection System, connected to the Sequence Detector Software (SDS version 2.0; Applied Biosystems) for data collection and subsequent analysis.

For this purpose, we chose arrays preloaded with 48 selected genes related to the following pathways: myogenesis, apoptosis, protein anabolism/catabolism and antioxidant enzymes; each array was useful to assess eight different samples.

For both classic RT-PCR and TaqMan low density array, the relative quantification of target gene expression was evaluated with data derived from the SDS software, utilizing the arithmetical formula $2^{-\Delta\Delta Ct}$, according to the comparative Ct method as reported in Di Filippo et al. (2016). The data have been deposited in NCBI's Gene Expression Omnibus and are accessible through GEO Series accession number GSE133720[1].

Mechanical Characterization of Vastus Lateralis Myofibers

The mechanical characterization of single myofibers was performed according to Di Filippo et al. (2017). Briefly, muscle biopsy fragments were stored in skinning solution until analyzed. Then, the solution was replaced with ATP, single fibers were dissected, bathed in an appropriate solution and transferred to the experimental apparatus where all parameters were measured. We tested 216 fibers.

After the mechanical measurements, the myofibers were classified according to their MyHC isoform composition which was determined by gel electrophoresis (Venturelli et al., 2015). Shortly after, appropriate amounts of protein were diluted in an appropriate solution, boiled and loaded onto a gel. Separation was performed and the following staining identified the bands corresponding to the MHC isoforms.

[1] https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE133720

NBT Assay

The NBT (Nitro Blue Tetrazolium chloride, SIGMA-Aldrich, Milan, Italy) assay is conventionally used to evaluate the production of $O_2^{\bullet-}$. It is a spectrophotometric assay, based on the reduction of NBT in Nitro blue-formazan in the presence of $O_2^{\bullet-}$, and was performed on skeletal muscle tissue biopsies.

Protein Isolation and Quantization

Antioxidant enzyme assays and Western Blotting were performed, according to Marrone (Marrone et al., 2018) using muscles homogenized in 100 mM Na-phosphate buffer pH 7.0 with 1:100 protease inhibitors cocktail (#P8340, Sigma-Aldrich) and centrifuged at 10,000 × *g* for 15 min at 4°C. Protein concentrations were measured on the deriving supernatant according to the Bradford method (Bradford Reagent, #B6916, Sigma-Aldrich).

Superoxide Enzyme Activities

The activity of Superoxide Dismutase 1 (SOD1) was determined by using the modified method of L'Abbe' and Fischer (Marrone et al., 2018). The final assay volume of 1 ml contained 20 mM Na_2CO_3, pH 10, 10 mM cytochrome c, 1 mM xantine and xantine oxidase. As the xanthine oxidase activity varies, the amount used for the assay was sufficient to stimulate a cytochrome c reduction at 550 nm at a rate of 0.025 per minute without SOD addition. SOD units were calculated on the basis of the definition that one unit represents the activity that inhibits the cytochrome c reduction by 50%.

Catalase Activity

Catalase activity was determined, as previously described in Shakirzyanova (Shakirzyanova et al., 2016) by evaluating the decrease in absorbance due to H_2O_2 consumption ($\epsilon = 0.04\ mM^{-1}\ cm^{-1}$) measured at a wavelength of 240 nm. 1 ml of the final reaction mixture contained 100 mM Na-phosphate buffer pH 7.0, 12 mM H_2O_2 and 70 μg sample.

Western Blotting Analysis

Western Blotting Analysis was performed according to Marrone (Marrone et al., 2018) on 30 μg lysates from fragments of old *Vastus Lateralis* skeletal muscle pre- and post-NMES, using SOD1 (71G8) mouse mAb (#4266, Cell Signaling Technology, Danvers, MA, United States) at 1:1000, SOD2 (D9V9C) rabbit mAb (#13194, Cell signaling Technology) at 1:1000, GAPDH (6C5) sc-32233 mouse (Santa Cruz Biotechnology, INC) at 1:600, as a primary antibody. Secondary HRP-conjugated antibodies (Cell Signaling Technology) at 1:5000. Bands were detected and pictured at Uvitec (Cambridge, United Kingdom) by Amersham ECL Prime Western Blotting Detection Reagent (#RPN2236, GE Healthcare); densitometry analyses were performed with ImageJ software (Marrone et al., 2018).

Statistical Analysis

The statistical analysis of muscle myofibers was carried out using GraphPad Prism Software, version 7 (GraphPad Software, La Jolla, United States) and R-based open source software Jamovi[2]. The normality of distribution was assessed by D'Agostino–Pearson Omnibus Test and Shapiro–Wilk Test.

The Repeated Measures ANOVA (between factor: NMES *vs.* Control) was conducted to analyze the anthropometric and strength parameters.

The CSA values then underwent logarithmic transformation, while F_0 and P_0 underwent a square root transformation. Identification of outliers was performed with the ROUT Method (Q = 0.5%). General Linear Mixed Model (GLMM) with Restricted Maximum Likelihood (REML) estimation method was used to analyze differences, setting pre-post and fiber typology as fixed effects and subjects as random effect.

The statistical analysis of NBT, enzymatic activity assays and densitometric analysis of Western Blotting were performed with GraphPad Prism Software and an unpaired *t*-test.

RESULTS

Effects of NMES on Anthropometric Data

The anthropometric characteristics of healthy male subjects did not change when comparing pre- and post-NMES conditions (**Table 1**).

Effects of NMES on the Strength of the Elderly

The isometric strength measured on lower limbs revealed that the post-NMES MVC was significantly increased (**Table 1**) with respect to pre-NMES (bilateral, $p < 0.05$).

Muscle Fiber Cross-Sectional Area, Strength and Specific Tension on Different Fiber Phenotypes

The results on all fiber type analysis showed that the CSA increased at post-NMES in respect to pre-NMES (3,720 ± 222 μm^2 *vs.* 3,700 ± 184 μm^2, $p = 0.075$). Specifically, the myofibers IIa significantly increased their CSA ($p < 0.05$,

[2]https://www.jamovi.org

TABLE 1 | Anthropometric and functional characteristics of healthy elderly subjects.

Characteristics	pre-NMES	post-NMES	Pre-control	Post-control
Weight (kg)	75.1 ± 8.1	75.2 ± 7.9	76.0 ± 6.0	76.5 ± 5.8
BMI (kg m^{-2})	27.7 ± 3.0	27.7 ± 3.1	28.8 ± 3.0	28.9 ± 2.9
Body fat (%)	26.6 ± 5.3	25.4 ± 4.9	27.0 ± 4.8	26.8 ± 4.3
Circ. Sup. (cm)	53.8 ± 3.0	54.1 ± 3.1	53.2 ± 2.5	53.5 ± 2.5
Circ. Inter. (cm)	47.0 ± 2.7	47.7 ± 2.8	45.8 ± 2.1	46.5 ± 1.8
Circ. Inf. (cm)	40.5 ± 2.9	41.2 ± 3.1	38.9 ± 1.9	39.1 ± 2.3
MVC_{bil} (N)	537 ± 104	585 ± 111*	488 ± 133	492 ± 116

*Control subject (n = 10; 70.8 ± 3.08 years old); BMI, body mass index; Cir, circumference; sup, superior; inter, inter-medium; inf, inferior; MVC_{bil}, maximal bilateral voluntary contraction, *p < 0.05. The data are expressed as mean ± standard deviation.*

Table 2). The interaction fiber x NMES ex-post showed a strong tendency, reflecting a different trend of different myofibers ($p = 0.053$).

The results on single muscle myofibers divided into typologies are displayed in **Figure 1**.

The average force (F_0) significantly increased approximately 10%, from 0.932 ± 0.281 mN to 1.02 ± 0.281 in post-NMES ($p < 0.001$). Specifically, the myofibers II (type a, ax, and x) significantly incased their F_0 as shown in **Figure 1** ($p < 0.05$ **Table 2**).

The value of specific tension (P_0), the isometric strength per unit of fiber area (F_o/CSA), was 10.9 ± 2.38 mN mm^{-2} and 11.6 ± 2.38 mN mm^{-2} in pre- and post-NMES, respectively. Though P_o tended to increase and this increment was not statistically significant, it is worth mentioning that among the myofiber types, myofibers I showed this tendency ($p = 0.058$, **Table 2**).

As can be seen in **Table 1**, weight, BMI and % of body fat did not vary significantly, while the strength increased significantly at the end of the session ($^*p < 0.05$).

Muscle Fiber CSA and Specific Tension

Figure 1 showed three parameters measured by single fiber mechanic experiments. The myofibers were grouped in type I, IIa, IIax, IIx. The empty bars indicate the pre-NMES samples, while the dotted bars indicate the post-NMES samples of the same volunteers.

The CSA (panel A), resulted to have increased at post-NMES specifically on myofibers IIa ($p < 0.05$, and also reported in the second line of Simple effect PRE-POST paragraph in **Table 2**). Panel B reported the F_0 values, that significantly increased in myofibers IIa, IIax, IIx ($p < 0.05$, and also reported in the second, third and fourth line of Simple effect PRE-POST paragraph in **Table 2**). Panel C, reported the P_0 value, that showed a tendency to increase only on fiber I ($p = 0.058$ reported in second, third and fourth line of Simple effect PRE-POST paragraph in **Table 2**).

TABLE 2 | Statistical parameters of general linear mixed model relative to skeletal muscle myofiber results showed in **Figure 1**.

Samples	CSA	F_0	P_0
NMES pre-post	$p = 0.075$	$p < 0.001$	$p = 0.072$
Myofibers	$p = 0.087$	$p = 0.256$	$p = 0.001$
Protocol x myofibers	$p = 0.053$	$p = 0.338$	$p = 0.939$
R^2	0.07	0.04	0.100
R^2 conditional	0.19	0.64	0.110
Random effect			
Intraclass coefficient	0.134	0.629	0.011
Likelihood ratio test	$p = 0.001$	$p < 0.001$	$p = 0.560$
Simple effect PRE-POST			
Myofibers I	$p = 0.219$	$p = 0.158$	$p = 0.058$
Myofibers IIa	$p = 0.046$	$p = 0.012$	$p = 0.290$
Myofibers IIax	$p = 0.670$	$p = 0.019$	$p = 0.234$
Myofibers IIx	$p = 0.088$	$p = 0.044$	$p = 0.769$

CSA, cross sectional area; F_0, isometric force of single fiber; P_0, specific tension as force divided per CSA of single fibers.

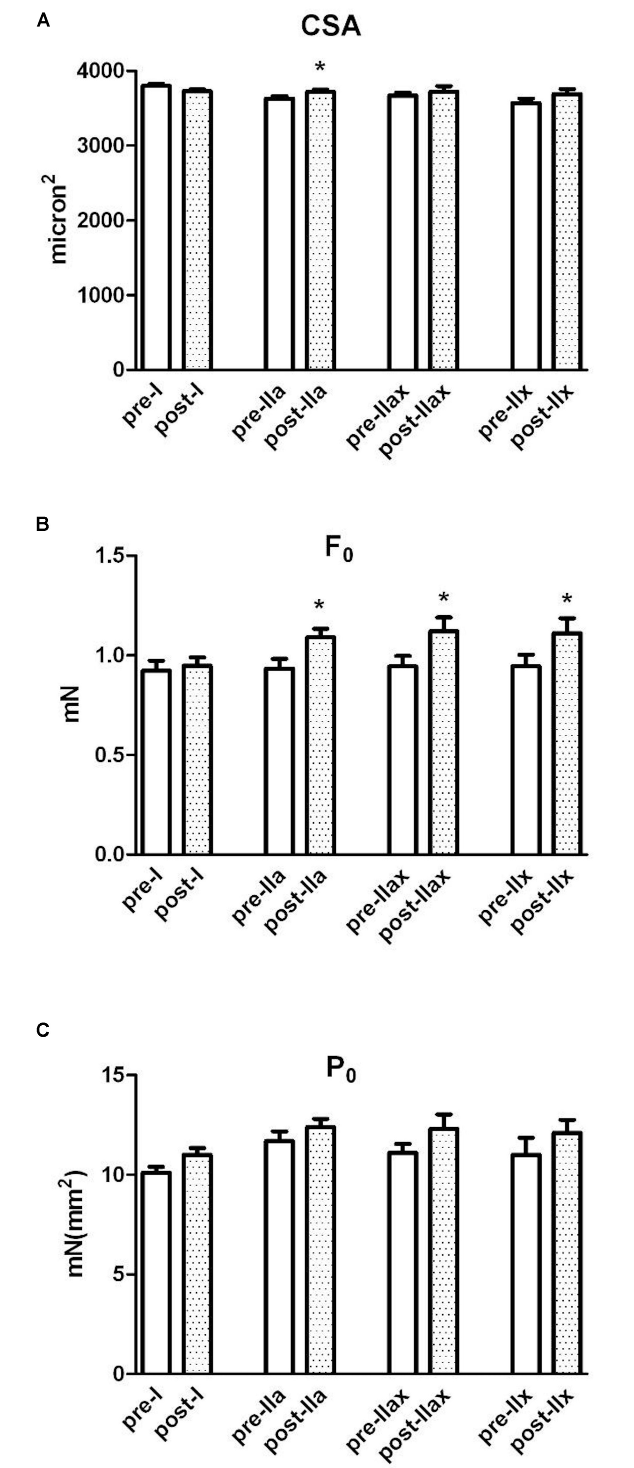

FIGURE 1 | Single-fiber analysis, cross sectional area, force and specific isometric tension. The white and dotted columns represent, respectively, pre-NMES and post-NMES samples divided in fiber types (I, IIa, IIax, IIx). **(A)** Shows the cross-sectional area (CSA) of single muscle myofibers obtained by the *Vastus Lateralis*. **(B)** Shows the force developed by single fibers. **(C)** Reports measurements of specific isometric tension (force/CSA) developed in maximal calcium activated contraction by the same myofibers. $^*p < 0.05$.

Table 2 reported the statistical GLMM parameters used for mechanical experiments that allowed us to test data as a random effect.

Gene Expression, TaqMan Low Density Array

Table 3 shows genes found significantly up and downregulated in post-NMES *versus* pre-NMES samples among 48 genes tested. Genes and their expression levels expressed as the $\log_{10}$ of Relative Quantifications (RQ) related to protein balance, oxidative management, apoptosis and myogenesis pathways, were analyzed with Real Time PCR using TaqMan low density arrays.

Protein Balance

Sarcopenic muscle presents atrophy, which partially depends on reduced anabolic processes, together with increased catabolic processes (Argilés et al., 2015). In this study, various genes related to the protein metabolism were modulated in their expression after NMES training. In particular, the up-regulation of genes involved in the anabolic pathway such as *Insulin like growth factor 1* (*IGF-1*), *Phosphatidylinositol-3-kinase* (*PI3K*), *Mechanistic target of rapamycin* (*MTOR*) and *AKT serine/threonine kinase 1* (*AKT*) in post- *vs* pre-NMES was observed. In parallel, we found that the down-regulated *Forkhead box O1A (rhabdomyosarcoma)* (*FOXO1A*) gene was involved in the catabolic pathway together with *Myostatin (MSTN), Tripartite motif containing 63* (*TRIM63* or *MURF1*), *Proteasome 26S subunit, ATPase 6* (*PSMC6*),

TABLE 3 | Significantly dysregulated genes on skeletal muscle after NMES.

Gene name	Gene symbol	Mean $\log_{10}$ RQ ± SE
Protein balance		
Insulin like growth factor 1	IGF1	0.36 ± 0.18
Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha	PI3KCA	0.12 ± 0.06
Mechanistic target of rapamycin	MTOR	0.17 ± 0.11
Forkhead box O1	FOXO1	−0.28 ± 0.15
Myostatin	MSTN	−0.15 ± 0.13
AKT serine/threonine kinase	AKT	0.05 ± 0.11
Mitochondrial E3 ubiquitin protein ligase 1	MUL1	−0.03 ± 0.05
Ubiquitin like modifier activating enzyme 1	UBA1	0.01 ± 0.11
Ubiquitin conjugating enzyme E2 A	UBE2A	−0.02 ± 0.17
Tripartite motif containing 63	TRIM63 (MURF1)	−0.06 ± 0.12
Proteasome 26S subunit, ATPase 6	PSMC6	−0.20 ± 0.23
Oxidative management		
Catalase	CAT	−0.03 ± 0.09
Superoxide dismutase 1, soluble	SOD1	0.00 ± 0.14
Superoxide dismutase 2, mitochondrial	SOD2	−0.12 ± 0.09
Glutathione peroxidase 1	GPX1	−0.39 ± 0.17
Glutathione-disulfide reductase	GSR	0.12 ± 0.10
Glutathione S-transferase kappa 1	GSTK1	−0.18 ± 0.19
Apoptosis		
BCL2 associated agonist of cell death	BAD	−0.42 ± 0.33
BCL2, apoptosis regulator	BCL2	−0.31 ± 0.09
Caspase 2	CASP2	0.43 ± 0.09
Caspase 3	CASP3	−0.03 ± 0.29
Caspase 6	CASP6	0.08 ± 0.15
Caspase 7	CASP7	0.24 ± 0.09
Caspase 8	CASP8	0.30 ± 0.30
Caspase 9	CASP9	−0.17 ± 0.71
Tumor necrosis factor	TNF	0.32 ± 0.32
Fas associated via death domain	FADD	−0.03 ± 0.31
Myogenesis		
Myogenic differentiation 1	MYOD1	0.24 ± 0.11
Paired box 7	PAX7	0.06 ± 0.14
Tumor necrosis factor	TNF	0.32 ± 0.32
Mitogen-activated protein kinase 1	MAPK1 (p38)	0.17 ± 0.07
Myogenin	MYOG	0.16 ± 0.11

Gene expression levels were analyzed with RT-PCR using TaqMan low density arrays. Data are expressed as the $\log_{10}$ of Relative Quantification (RQ) of the transcripts for the target genes versus GAPDH. Gene expressions are represented as mean ±SE comparing post-NMES versus pre-NMES. Up-regulated genes have positive values; down-regulated genes have negative values.

Ubiquitin like modifier activating enzyme 1 (*UBA1*), *Ubiquitin conjugating enzyme E2 A* (*UBE2A*) and *Mitochondrial E3 ubiquitin protein ligase 1* (*MUL1*) genes, involved in the ubiquitin-proteasome degradation system FOXO1A-dependent.

Oxidative Management

It is well-recognized that oxidation of biological substrates due to oxidants are generated in the mitochondrial respiratory chain. In particular, such oxidants could have a detrimental effect on elderly muscle myofibers (Fulle et al., 2005; Pietrangelo et al., 2009). Among the endogenous enzymatic systems capable of protecting the cell against oxidative injury, glutathione transferase and glutathione reductase, as well as selenium dependent glutathione peroxidase play a crucial role. Using glutathione (GSH) as a cofactor, glutathione peroxidase reduces H_2O_2 to water, converting GSH into its oxidized form (GSSG). Glutathione reductase, in the presence of NADPH, is able to reduce the oxidized glutathione (Mezzetti et al., 1990). NMES caused the down-regulation of the *Glutathione Peroxidase 1* (*GPX1*) gene, encoding a peroxidase protein that detoxifies hydrogen peroxide, thus representing one of the main antioxidant enzymes in humans. A gene which is up-regulated in post-NMES muscle is *Glutathione Reductase* (*GSR*), a fundamental enzyme of the cellular antioxidant defense system that reduces oxidized glutathione disulfide (GSSG) to the reduced form of GSH, being a central cellular antioxidant. Furthermore, we found the *Glutathione S-transferase kappa 1* (*GSTK1*) gene down-regulated. The encoded enzyme catalyzes the conjugation of glutathione to a wide series of hydrophobic substrates aiding the elimination of these compounds from cells.

Superoxide Dismutase 1, soluble (*SOD1*) did not vary whereas *Superoxide Dismutase 2, mitochondrial* (*SOD2*), and *Catalase* (*CAT*) genes that encode enzymes that detoxify the cell by $O_2^{\bullet-}$ and H_2O_2, respectively, were down-regulated by NMES training.

Apoptosis

To date, two main apoptotic pathways are known: a death receptor pathway or extrinsic and a mitochondrial pathway or intrinsic (Elmore, 2007). In our study, we found up-regulated genes related to the extrinsic pathway: *Tumor Necrosis Factor* (*TNF), Caspase-8 (CASP8), Caspase-6 (CASP6),* and *Caspase-7 (CASP7),* with the exception of *Caspase-3 (CASP3*) and *Fas Associated via Death Domain* (*FADD*) that were slightly down-regulated. On the other hand, it seems that the intrinsic pathway is suppressed, as we found down-regulated C*aspase-9 (CASP9), BCL2 Associated Agonist of cell Death (BAD),* and *B-cell lymphoma protein 2 (BCL2)* genes. Caspase-9 activation is required for the intrinsic pathway. The regulation and control of these apoptotic events occurs by members of the Bcl-2 protein family that include Bcl-2 and BAD. The *Caspase-2 (CASP2)* gene was also found up-regulated, but its role is not only in apoptosis, but also in cell differentiation (Fava et al., 2012).

Myogenesis

After NMES, we found several dysregulated genes involved in the myogenic process. In particular, the *Myogenic Differentiation 1* (*MYOD1*) gene was up-regulated. We also found up-regulated the *Tumor Necrosis Factor* (*TNF*) and the *Mitogen-Activated Protein Kinase 1* (*MAPK1*) an essential signal for myogenic differentiation. *Myogenin* (*MYOG*), is necessary for the fusion of the myogenic precursor cells to either previously existing or new myofibers during the differentiation in the myogenesis process, as well as in the *Paired box 7 (PAX7)*, a transcription factor involved in the regulation of muscle precursor cell proliferation (Boldrin et al., 2010).

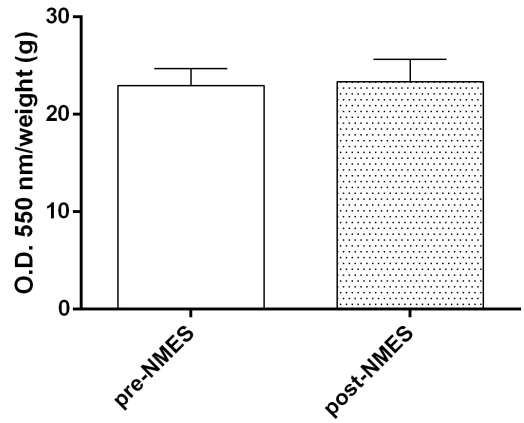

FIGURE 2 | Superoxide anion production. Quantitative analysis of pre-NMES and post-NMES muscle biopsies for $O_2^{\bullet-}$. Data (*n* = 5 subjects) are mean ± SEM of three independent experiments in quintuplicates.

Oxidative Management

NBT Assay

Intracellular $O_2^{\bullet-}$ levels, revealed by NBT Assay (**Figure 2**), did not show significant differences (pre-NMES 22.96 ± 1.7; post-NMES 23.36 ± 2.3) between the pre- and post-NMES in muscle samples.

Catalase and Superoxide Enzyme Activities

Figure 3A displays the specific activity of Catalase with a significant decrease in post-NMES in respect to pre-NMES while the SOD1 activity did not vary (data not shown).

Protein Expression of SOD1 and SOD2

We analyzed the protein expression of intracellular Super Oxide Dismutases (SOD), distinguishing between the two different forms of SOD, SOD1, and SOD2, cytosolic and mitochondrial protein, respectively. The protein expression was determined on pre- and post-NMES muscle samples using Western Blotting (**Figures 3B,C**). The SOD2 was slightly, but not statistically nor significantly decreased in POST-NMES samples in respect to the pre-NMES (**Figure 3B**), while SOD1 did not change (**Figure 3C**). Representative bands of SOD1 and SOD2 obtained by pre- and post-NMES muscle samples are shown in **Figure 3D**.

Gene Expression, Classic Real Time-PCR

The expression of myogenic transcription factors (*IGF1, Pax7, MURF1,* and *MSTN*) and skeletal muscle myosin heavy chains

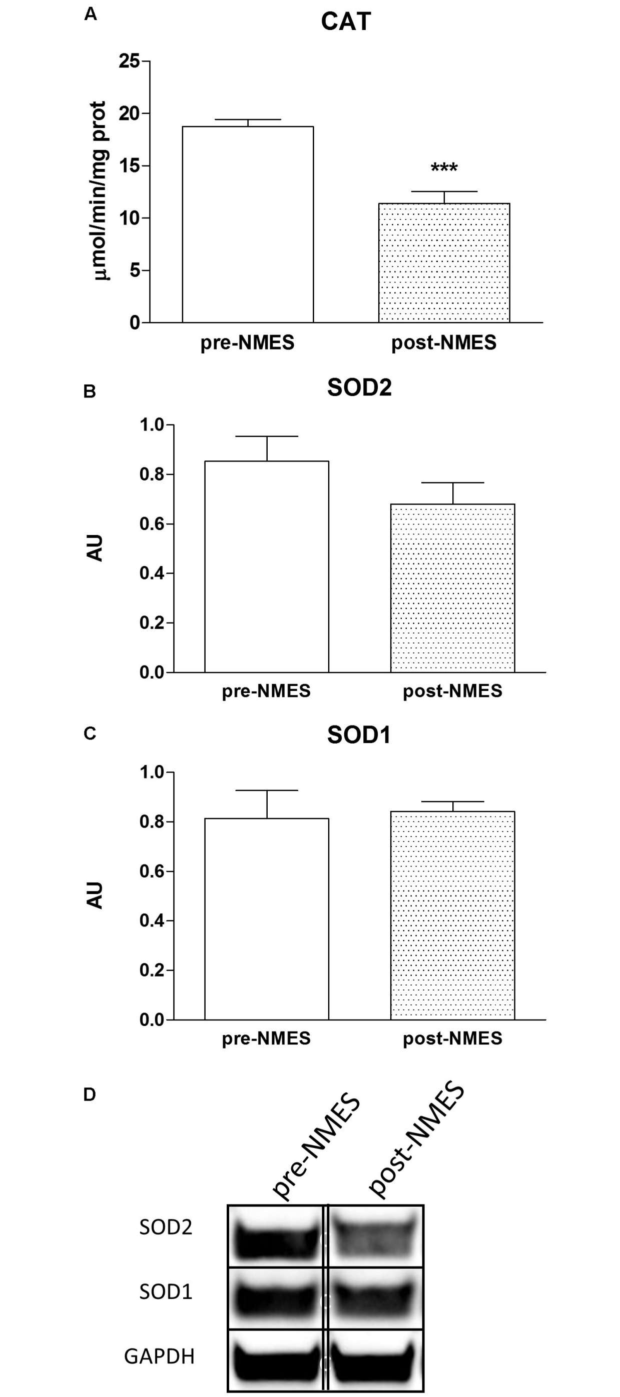

FIGURE 3 | Catalase cytosolic enzymatic activities and SOD Western blotting. In **(A)** is reported the Catalase enzymatic activity in pre- and post-NMES samples as µmol/min/ng prot (*n* = 9). ***$p = 0.0005$. Data (*n* = 5 subjects) are mean ± SEM of three independent experiments in triplicates. **(B,C)** Show SOD2 and SOD1 densitometric analysis of Western blots performed on four pre-NMES and post-NMES samples expressed as mean ± SD. AU, arbitrary units. The bands (of the same subject) were taken from two nonadjacent lanes originating from exactly the same gel and blot with the same exposure time, but spliced together indicated by double-dotted lines. No change in contrast has been performed. Western Blotting analysis of representative bands of SOD2 and SOD1 **(D)**, of skeletal muscle biopsies pre- and post-NMES.

(*MyHC 1, 2A*, and *2X*) were analyzed by the means of a RT-PCR approach and are reported in **Figure 4**. Looking at the machinery of myogenic regulatory factors that positively or negatively control the myogenic process, we observed the up-regulation of *Insulin Like Growth Factor 1* (*IGF1)* and *Paired box 7* (*PAX7)* and down-regulation of *Tripartite motif containing 63* (*MURF1)*, and *Myostatin* (*MSTN)*. The fiber type composition of the skeletal muscle is determined by the percentage of slow (MyHC1) and fast (MyHC2A and 2X) myosin heavy chain isoforms. The different isoforms of myosin act as molecular markers that allow the different types of myofibers to be identified. In particular, analyzing the expression of genes ($2^{-\Delta\Delta Ct}$) encoding myosin heavy chains, we observed the down-regulation of *MyHC* 1 (pre-NMES 1.0 ± 0.2; post-NMES 0.6 ± 0.3) and *2X* (pre-NMES 1.1 ± 0.5; post-NMES 0.4 ± 0.2) together with an up-regulation of *MyHC2A* (pre-NMES 1.0 ± 0.1; post-NMES 2.5 ± 0.9).

DISCUSSION

The skeletal muscle of the elderly is characterized by decreased strength, mass and movement velocity, all diagnostic criteria of the status defined as Sarcopenia (Doherty, 2003; Fulle et al., 2004). Physical exercise is considered one of the most effective strategy to slow down muscle aging, especially in terms of mass and function (Negaresh et al., 2019). Besides the classic training, NMES is also a valid method that enhances muscle performance and structure (Acaröz Candan et al., 2019).

Neuromuscular Electrical Stimulation is used to retrieve muscle weakness and to increase muscle strength and hypertrophy in healthy subjects (Wageck et al., 2014; Takano et al., 2016; Langeard et al., 2017; Paillard, 2018). These data are consistent with our study in which a significant increase of isometric strength after a NMES session was shown. Neural adaptations as training-induced changes in the function of the nervous system and afferent feedback to the spinal cord during contractions triggered by NMES would explain, at least in part, the increase of strength of MVC registered at the

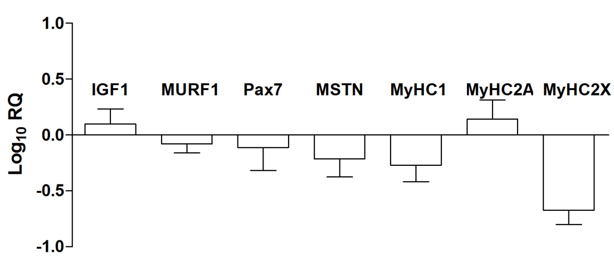

FIGURE 4 | MRFs and MyHC isoforms gene expression. *IGF1, MURF1, PAX7, MSTN, MyHC1, MyHC2A, and MyHC2X* mRNA expression levels in post-NMES muscles *versus* pre-NMES muscles. Data are expressed as the logarithm of Relative Quantification (RQ) of transcripts for these target genes, each versus GAPDH gene expression. Values are expressed as mean ±SEM of three independent experimental sets.

end of the treatment (Maffiuletti et al., 2006). To investigate the feasibility of the correlation between anthropometric and cellular changes, single myofiber mechanical properties were studied. According to our previous study, (Di Filippo et al., 2017) NMES affected cross-sectional area and force that resulted significantly increased. In particular, this study, shows that the increase in force is due to type II myofibers, and in particular the increase in CSA was due to type IIA myofibers. Thus, the increase in the force of the whole muscle group (MVC) found is based on the increase in the force-developing ability of single myofibers in accordance with previous studies showing similar results (Maffiuletti et al., 2006) therefore likely due to type II myofibers. The modulation of CSA is also in accordance with the down-regulation of MyHC1 and up-regulation of the MyHC2A gene expression.

The skeletal muscle is able to change both structure and function in response to factors that can modify its contractile activity (physical exercise, electrical stimulation, and denervation). These structural and functional adaptations that modify the skeletal muscle phenotype are the result of a rapid variation in the expression of key genes activated or silenced depending on their function.

The myogenic regulatory factor Myogenin is strongly influenced by muscular electrical activity, thus inducing changes in muscle phenotype (Hughes et al., 1999). The increase in MyHC2A and the Myogenin gene expression, with an increase in fast muscle myofiber force that was found, suggests a real metabolic NMES-dependent shift in II type myofibers in the elderly.

The metabolic shift from glycolytic to oxidative that occurs after training is usually accompanied by a modulation of the antioxidant capacity of the cells. The study demonstrates a perturbation of genes that encode the main antioxidant enzymes. Down-regulated glutathione peroxidase and catalase genes that detoxify cells by hydrogen peroxide and transferase that detoxify by metabolites was also found. The catalase enzymatic activity, also results as decreased according to the related gene expression. According to literature on aging (Doria et al., 2012), *SOD1* did not modify its gene and protein expression while *SOD2* tended to decrease both at gene and protein expression levels after NMES training. This result suggests that the SOD2 enzyme that produces mitochondrial superoxide anion, considered, the most dangerous and reactive radical, is less active despite a shift toward an oxidative metabolism. This suggests that NMES induces muscle functional amelioration given to its proper contractions with no increase in muscle oxidative stress. However, further studies could be able to characterize the effect of single bouts of NMES on the redox system inside the muscles of the elderly. This is an important finding, since senescent muscle of the elderly, *per se,* is accompanied by enhanced muscle oxidative stress after physical exercise, and at rest. Another aspect is when macromolecules as proteins are oxidized, they are likely to be degraded by the ubiquitin–proteasome pathway. However, the 24 sessions NMES did not affect the ubiquitin–proteasome pathway as a slight down-regulation of the gene expression of *UBE2A*, *TRIM63,* and *MUL1* was found. Accordingly, we observed an up-regulation of protein synthesis (Stitt et al., 2004) *versus* the protein degradation pathway (Milan et al., 2015) linked to the gene up-regulation of IGF-1, Akt, and mTOR. At the same time, *FOXO1* and *TRIM63* that mediate protein catabolism were found down-regulated.

Skeletal muscle repair, regeneration, growth and remodeling are related to the activation of satellite cells and different local responsive processes with a load-dependent modality (Fulle et al., 2005). The sequential expression of "early" Myogenic Regulatory Factors (MRFs), such as myogenic differentiation factor D (MyoD) and myogenic factor (myf)-5 and "late" MRFs, such as myogenin and myf-6 leads to skeletal muscle repair, regeneration and growth (Kosek et al., 2006). In our study, all MRF genes (*PAX7, MYOD1,* and *MYOG*) were up-regulated, suggesting an activation of the myogenic pathway and of a possible shift toward oxidative phenotype in myofibers of type II (Hughes et al., 1999), while *MSTN,* encodes a protein produced and released by myocytes acting on muscle cells in inhibiting myogenesis, is downregulated. The same results are presented in both classic RT-PCR and in TaqMan low density array (Thomas et al., 2000). The up-regulation of *TNF*, at a physiological level, which activates myogenesis, supports this data (Chen et al., 2007).

Accordingly, with gene expression results improved isometric strength and CSA of type II myofibers were observed, and as a result, an increase in MVC, in accordance to our previous study (Di Filippo et al., 2017).

It could further be argued that the NMES training could induce a hypertrophic effect on skeletal muscle due to the activation of SCs.

Another important pathway found dysregulated by NMES training is apoptosis. In particular, gene expression data revealed that in POST-NMES samples, the extrinsic pathway is activated considering the upregulation of *TNF* as well as genes that encode the initiator (*CASP2*) and executioner (*CASP6* and *CASP7)* at the expense of the intrinsic pathway that seems to be downregulated as *CASP3 and CASP9*. Commonly, apoptosis is associated with muscle degradation, contributing to skeletal muscle atrophy and sarcopenia. Conversely, it was also demonstrated that there is a new role of the apoptotic pathway which is linked to skeletal muscle repair and regeneration (Fulle et al., 2013) as well as to muscle tissue remodeling, following contractile activity (Adhihetty and Hood, 2003). Indeed, In the present study, we can explain that the activation of the apoptotic fiber be can considered in relation to the myogenic process and the progression of differentiation, as demonstrated by previous studies (Fernando et al., 2002). Caspase-8, initiator caspase canonically involved in the "extrinsic pathway", resulted up-regulated in gene expression analysis in post-NMES, without downstream activation of Caspase3, thus failing the commitment to cell apoptosis. This could indicate the possible role of an apoptotic pathway mediating the differentiation more than cell death (Fulle et al., 2013).

In conclusion, our data demonstrates that NMES is effective on producing physiological adaptation on *Vastus Lateralis* skeletal muscle of active healthy elderly, and in particular:

- increases isometric strength, CSA type II myofibers and, as a result, MVC;
- an activation of both the myogenic pathway and a shift toward oxidative phenotype in myofibers of type II;
- induces muscle functional amelioration with no increase in muscle oxidative stress.
- an apoptotic pathway involved in the differentiation process.

Overall, these results provide new insights for further researches on the elderly who experienced muscle weakening for periodic or permanent immobility.

DATA AVAILABILITY STATEMENT

Datasets for this study can be found in NCBI using the accession number GSE133720.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethic Committee of G. d'Annunzio University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SF and TP conceived and designed the research. RM, ED, MM, CD, VV, LT, LM, and CM performed the experiments. RM, ED, MM, LT, DB, LM, TP, and SF analyzed the data. RM, TP, and SF interpreted the results of experiments. RM, LT, ED, LM, MM, TP, and SF prepared the figures. RM and SF drafted the manuscript. RM, TP, and SF edited and revised the manuscript. RM, LT, ED, MM, CM, LM, DB, CD, VV, TP, and SF approved the final version of the manuscript.

FUNDING

The study was funded by the "G. d'Annunzio" University and grants to RM, TP, and SF, Projects of National Interest (PRIN) National Grants 2007AWZTHH_003 to SF, 2012N8YJC3_003 to TP, and "Departments of Excellence 2018–2022" initiative of the Italian Ministry of Education, University and Research for the Department of Neuroscience, Imaging and Clinical Sciences of "G. d'Annunzio" University Chieti–Pescara, Italy.

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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.

frontiers in Physiology

ORIGINAL RESEARCH
published: 20 February 2020
doi: 10.3389/fphys.2020.00090

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Wearable Inertial Measurement Units for Assessing Gait in Real-World Environments

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Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: 02 November 2019
Accepted: 27 January 2020
Published: 20 February 2020

Citation:
Renggli D, Graf C, Tachatos N, Singh N, Meboldt M, Taylor WR, Stieglitz L and Schmid Daners M (2020) Wearable Inertial Measurement Units for Assessing Gait in Real-World Environments. Front. Physiol. 11:90. doi: 10.3389/fphys.2020.00090

Background: Walking patterns can provide important indications of a person's health status and be beneficial in the early diagnosis of individuals with a potential walking disorder. For appropriate gait analysis, it is critical that natural functional walking characteristics are captured, rather than those experienced in artificial or observed settings. To better understand the extent to which setting influences gait patterns, and particularly whether observation plays a varying role on subjects of different ages, the current study investigates to what extent people walk differently in lab versus real-world environments and whether age dependencies exist.

Methods: The walking patterns of 20 young and 20 elderly healthy subjects were recorded with five wearable inertial measurement units (ZurichMOVE sensors) attached to both ankles, both wrists and the chest. An automated detection process based on dynamic time warping was developed to efficiently identify the relevant sequences. From the ZurichMOVE recordings, 15 spatio-temporal gait parameters were extracted, analyzed and compared between motion patterns captured in a controlled lab environment (10 m walking test) and the non-controlled ecologically valid real-world environment (72 h recording) in both groups.

Results: Several parameters (*Cluster A*) showed significant differences between the two environments for both groups, including an increased outward foot rotation, step width, number of steps per 180° turn, stance to swing ratio, and cycle time deviation in the real-world. A number of parameters (*Cluster B*) showed only significant differences between the two environments for elderly subjects, including a decreased gait velocity ($p = 0.0072$), decreased cadence ($p = 0.0051$) and increased cycle time ($p = 0.0051$) in real-world settings. Importantly, the real-world environment increased the differences in several parameters between the young and elderly groups.

Conclusion: Elderly test subjects walked differently in controlled lab settings compared to their real-world environments, which indicates the need to better understand natural walking patterns under ecologically valid conditions before clinically relevant conclusions can be drawn on a subject's functional status. Moreover, the greater inter-group differences in real-world environments seem promising regarding the sensitive identification of subjects with indications of a walking disorder.

Keywords: natural walking patterns, gait analysis, IMU sensors, ZurichMOVE, non-controlled settings, real-world environment, walking disorder, hydrocephalus

INTRODUCTION

Important indications of a person's health status can be obtained through analysis of walking patterns (König et al., 2014; Ravi et al., 2019). A variety of neurological disorders show specific gait impairments such as dementia (Allan et al., 2005; McArdle et al., 2019), normal pressure hydrocephalus (NPH) (Stolze et al., 2000, 2001) or Parkinson's disease (Stolze et al., 2001; Del Din et al., 2016). The diagnosis of these diseases is difficult, and misinterpretation is possible, especially in NPH. Here, difficulties arise in distinguishing the disease from other neurodegenerative diseases such as subcortical arteriosclerotic encephalopathy, polyneuropathy, or spinal canal stenosis (Bradley et al., 1991; Hebb and Cusimano, 2001; Relkin et al., 2005). Early indications suggest that subtle characteristics contained within a subject's gait patterns are sufficient to differentiate neurological pathologies at an early time point, and could form a fundamental basis for aiding clinical decision making (König et al., 2016a,b). With sufficient objectivity, such information could therefore support the clinical diagnosis of e.g., NPH, where it is estimated that only one in ten cases is correctly diagnosed and correctly treated (Jaraj et al., 2014). According to literature, NPH exhibits specific gait characteristics such as increased foot outward rotation, increased number of steps needed for a 180° turnaround, increased cycle time deviation, and impaired arm swing compared to asymptomatic controls (Stolze et al., 2000, 2001; Relkin et al., 2005; Gallia et al., 2006; Shrinivasan et al., 2011).

Medical examination of walking patterns is typically performed in a hospital or doctor's office environment by visual inspection. If a disease is suspected, patients are sent to specialized centers for further investigation. However, this examination process shows three main deficits: (1) Examinations in a doctor's office are rather low in complexity and cover only a small range of walking pattern characteristics. Subtle characteristics within walking patterns are often not visible to the naked eye, and can generally only be captured in specialized centers. (2) Examinations in lab environments show temporal and spatial restrictions. They cover a small time interval of the subject's performance in a predefined environment (flat floor, no obstacles) as well as under a standardized inspection range. (3) All examinations are performed in a strange environment whilst being observed by a stranger (the doctor/investigator). This is an unnatural situation for the test subject. Mental pressure, an effort by the subject to perform well in the presence of an investigator, and little or no acclimatization period to the equipment and task are potential problems. Additionally, the subject might get used to the procedure after several task repetitions and then perform better during subsequent repetitions. As a result, it is highly likely that people walk differently in a controlled lab environment compared to a non-controlled real-world setting. This circumstance would hinder the extraction of a subject's natural walking patterns and may falsify observations which would lead to the false diagnosis of particular diseases.

To address these issues, two main approaches have recently matured for capturing a subject's walking patterns objectively and accurately in non-clinical settings: (1) Non-wearable systems, such as camera-based optical motion capture, or ground reaction force plates, and (2) wearable inertial measurement unit (IMU) sensor systems (Muro-de-la-Herran et al., 2014). The former requires considerable set-up time and equipment, and is generally restricted to lab environments or specialized centers. On the other hand, IMU sensors require less effort to set up for data collection outside the lab, and studies can be run without the need for direct observation of the test subject, thus enabling various real-world investigations to be undertaken (Yu et al., 2016; Figueiredo et al., 2018; Wang and Adamczyk, 2019).

With correct application of such objective approaches, it should therefore become possible to capture real-world characteristics of natural walking patterns that are able to inform clinical decision making through measurements in a non-controlled environment. As a result, such novel technologies could potentially support the early diagnosis of particular diseases. To this aim, several researchers have reported significant differences in gait parameters between controlled lab and non-controlled real-world settings (Weiss et al., 2011; Robles-García et al., 2015; Brodie et al., 2016; Del Din et al., 2016). However, these studies are difficult to compare since they all involve different parameters, test subjects and absolute error values in the assessment methods used. Therefore, our study aims to compare a broad spectrum of parameters using a validated estimation process on both young and elderly healthy subjects. We hypothesize that elderly subjects walk differently in a controlled lab environment compared to non-controlled real-world environments. Here, the young group serves as a control cohort to assess both whether the chosen IMU approach is sufficiently sensitive to detect differences in gait patterns between lab and real-world environments, but also whether any observed effect occurs across the entire population or rather simply in elderly subjects. Differences in walking patterns between the two environments would indicate potentially unnatural walking characteristics under lab conditions and can additionally emphasize differences between the age groups.

MATERIALS AND METHODS

Subject Groups

Twenty young subjects (10 female, 10 male, 24.9 ± 2.7 years) and 20 elderly subjects (10 female, 10 male, 74.5 ± 8.6 years) were included in this study (**Table 1**). Subject inclusion criteria consisted of age (young: between 18 and 40 years, elderly: between 65 and 100 years) as well as no visible symptoms of any gait disorder, neurological disorder or cardiovascular disorder, which might affect normal standing or walking. Furthermore, female subjects during pregnancy or pre-menopausal state were excluded. All subjects provided their written, informed consent to participate in the study, which was approved by the Cantonal Ethics Committee Zurich (BASEC-No. 2018-00051) and Swissmedic (102597735).

Sensor Placement

Five wearable ZurichMOVE[1] IMU sensors (Schneider et al., 2018) were used for gait monitoring, with one attached to each ankle, and each wrist, as well as the chest, using kinesiology tape (**Figure 1**), to monitor axial acceleration $a(t)$ and angular velocity $\omega(t)$ for each segment. The global X-axis was defined as the vertical axis, the global Y-axis as the anteroposterior axis and the global Z-axis as the lateral axis. The chosen attachment sites and taping method allowed the subjects to wear the sensors for several days without removal and with full freedom of movement.

Tasks and Environment Under Investigation

While wearing the IMU sensors, all test subjects performed a calibration test for the step width estimation. They walked a distance of five meters on two parallel lines, with a specified spacing, repeating the procedure with a different line spacing (see section Gait Parameters). To assess gait in the controlled lab environment, subjects walked a marked distance of 10 m, four times (180° turnaround in-between) at their preferred walking speed. The test track in the lab was built on a flat floor with marked lines fixed to the floor as guidance. Subsequently, the sensors remained attached for 3 days to monitor the subjects' walking patterns in their own real-world environment.

Data Processing

The ZurichMOVE sensors use radio frequency time synchronization to prevent time-dependent drift between the individual sensors. The data were recorded at a frequency of over 1000 Hz and resampled at 50 Hz. Additionally, the axial acceleration values were low-pass filtered using a first-order Butterworth filter with a cut-off frequency of 5 Hz, while the angular velocity was filtered with a cut-off frequency of 12 Hz (settings adapted from Benoussaad et al., 2016). All data processing and calculations were performed using MATLAB (The MathWorks Inc., Natick, MA, United States).

[1] zurichmove.com

TABLE 1 | Subject characteristics (mean ± STD).

	Young	Elderly
Male	$n = 10$	$n = 10$
Female	$n = 10$	$n = 10$
Age (years)	24.9 ± 2.7	74.5 ± 8.6
Height (cm)	173.9 ± 9.5	171.4 ± 9.7
Weight (kg)	68.7 ± 13.4	70.7 ± 12.1

Automated Detection of Relevant Sequences

Out of the 3 days of recorded data, only sequences of walking, arm swinging and body turning were used for our analysis. To identify and extract these sequences efficiently, an automated detection process was developed, as described in the following sections.

Walking

The monitoring of angular velocity in the z-direction of the foot sensor $\omega_{foot,z}$ has been identified as a viable method to detect gait events (Jasiewicz et al., 2006; Li et al., 2010), and was used in this study. As a result, gait cycles were considered to consist of a specific sequence of gait events (**Figure 2A**): (1) The gait cycle started at the foot flat (FF) event, when the leg was in a vertical position; (2) The start of swing phase started at the point when the toe lost contact with the ground (Toe-off, TO); (3) The time point when $\omega_{foot,z}$ was at its greatest was used to identify the maximum angular velocity (MAX) event; (4) Heel strike (HS) was defined as the point when the heel touched the ground, which terminated the swing phase and started the stance phase; (5) A subsequent FF event terminated the gait cycle.

The algorithm initially searched for local minima and maxima in order to detect the gait events mentioned above using the following restrictions: the time between two minima or maxima had to be at least 0.7 s, a peak had to be more than 0.5 rad/s larger in magnitude than the surrounding data, and the absolute magnitude of all minima and maxima had to be greater than 0.5 rad/s. Minima and maxima were then assigned to the different potential gait cycles. Sequences with unrealistic assignments (e.g., more than 10 s time difference between the assigned minima and maxima) were removed. These boundary conditions were set empirically based on previously recorded test data of normal walking.

At this stage, not all labeled movement patterns were considered to be "true steps" (steps that were complete and correctly met all criteria). To discard falsely classified steps, a template matching approach based on dynamic time warping (DTW) was applied, adapted from Li et al. (2012). Every potential step was compared with a predefined template step. The DTW procedure allows sequences of different magnitude and length to be checked for their similarity by calculating the DTW distance (see section "1. Dynamic time warping" in **Supplementary Material** and Müller, 2007). If this distance was below a threshold of 2.5, which was empirically set in our study based on our previously recorded test data of normal walking (shown to work reliably for straight walking, curvy walking as well as walking with slight gradients; The applied algorithm is available at http://doi.org/10.5905/ethz-1007-243), the step was reported as a true

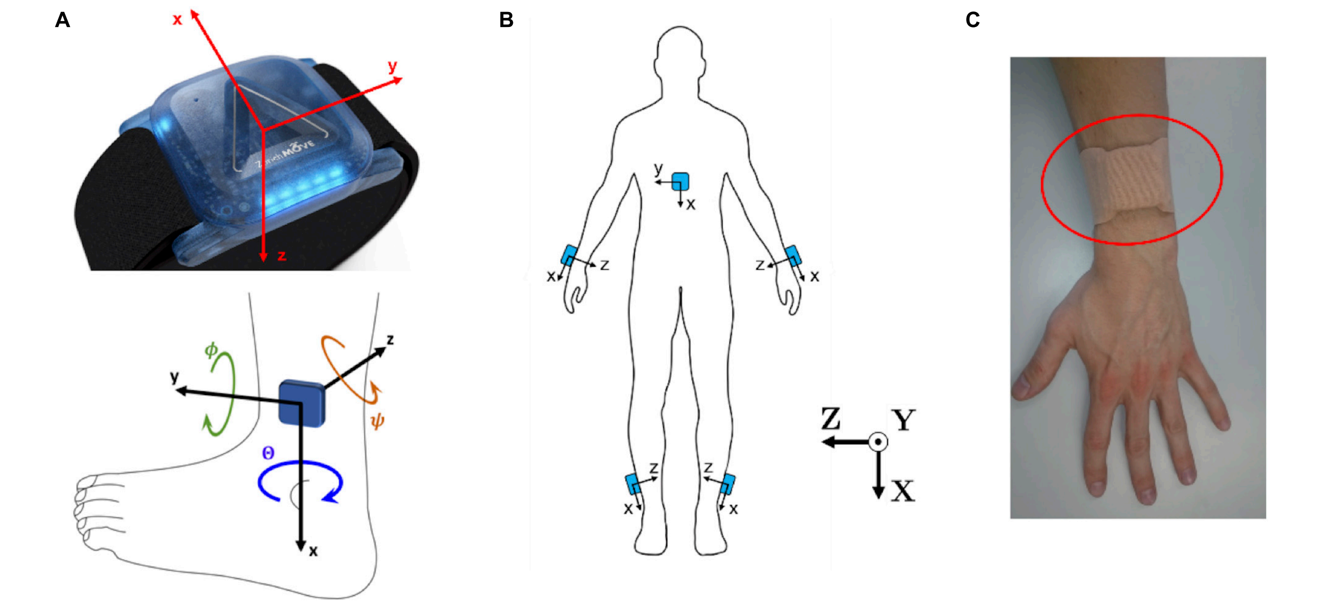

FIGURE 1 | (A) ZurichMOVE sensor axis orientation for accelerometer and gyroscope as well as the three Euler Angles, together with positive turning direction, Θ around the *x*-axis, Φ around the *y*-axis and Ψ around the *z*-axis. **(B)** ZurichMOVE sensor attachment on both ankles, both wrists and the chest including the axis orientation. **(C)** Sensor attachment to the body using kinesiology tapes.

step and was included in the analysis (**Figure 2A**). Here, stairs ascent and descent led to DTW distance values larger than 2.5 and were therefore discarded. Evaluation of other special walking conditions was not performed since they did not occur often and were therefore considered to have no major influence on the averaged gait parameters over the 72 h time span of the investigation.

Arm Swinging

The presence of arm swinging was checked for every true step reported by the step detection algorithm. Similar to the step detection algorithm, a DTW based matching approach (against a predefined template arm swing) was applied to the angular velocity signal in the z-direction of the wrist sensor $\omega_{arm,z}$. If the DTW threshold was greater than 2.5, arm swinging was positively identified and entered into the analysis (**Figure 2B**).

Turning

Sequences of turning were identified by local integration of the angular velocity signal around the *x*-axis of the chest sensor $\omega_{chest,x}$. A turning sequence $\Delta\theta(j)$ was summed as long as no sign change of $\omega_{chest,x}$ was detected (the subject was turning in the same direction). If a sign change was observed (the subject was turning in the opposite direction), $\Delta\theta(j)$ was saved, and the integration process was reset such that a new turning sequence $\Delta(j+1)$ was initiated. However, not every $\Delta\theta(j)$ directly represented one complete turning event. Due to interruptions while turning caused by e.g., step impacts, all turning sequences, $\Delta\theta$, belonging to the same turning event had to be merged to obtain the full turning angle (**Figure 2C**), further details are shown in the section "2. Merging process of several turning sequences to full turning events" in **Supplementary Material**. One of our estimated gait parameters was the number of steps per 180° turn. To also compensate for errors during integration and merging processes, all $\Delta\theta$ larger than 160° were kept, and the number of steps during these turning events normalized to the number of steps taken to 180°.

Gait Parameters

Our set of relevant gait parameters mainly consisted of standard spatial and temporal parameters commonly used in gait analysis such as stride length, gait velocity or cadence (Roberts et al., 2017). Since our gait analysis approach was motivated by the aim to identify people with signs of a walking disorder, we have included additional gait parameters that are indicative of a specific neurodegenerative disease such as NPH. For NPH patients, the following observations have been previously reported: increased foot outward rotation, increased number of steps needed for a 180° turnaround, increased cycle time deviation, and impaired arm swing compared to asymptomatic controls (Stolze et al., 2000, 2001; Relkin et al., 2005; Gallia et al., 2006; Shrinivasan et al., 2011). As a result, 15 parameters were used to capture the walking patterns of the subjects in this investigation (**Table 2**). To avoid the accumulation of errors due to the integration process, all parameters were calculated independently for every gait cycle, *i*, and the start position of integration was repetitively initialized to zero (Hamacher et al., 2014).

Temporal parameters were directly calculated in the sensor frame using the estimated gait events from the step detection. All spatial parameters were assessed using accelerations in the global (world) coordinate system as applied in similar

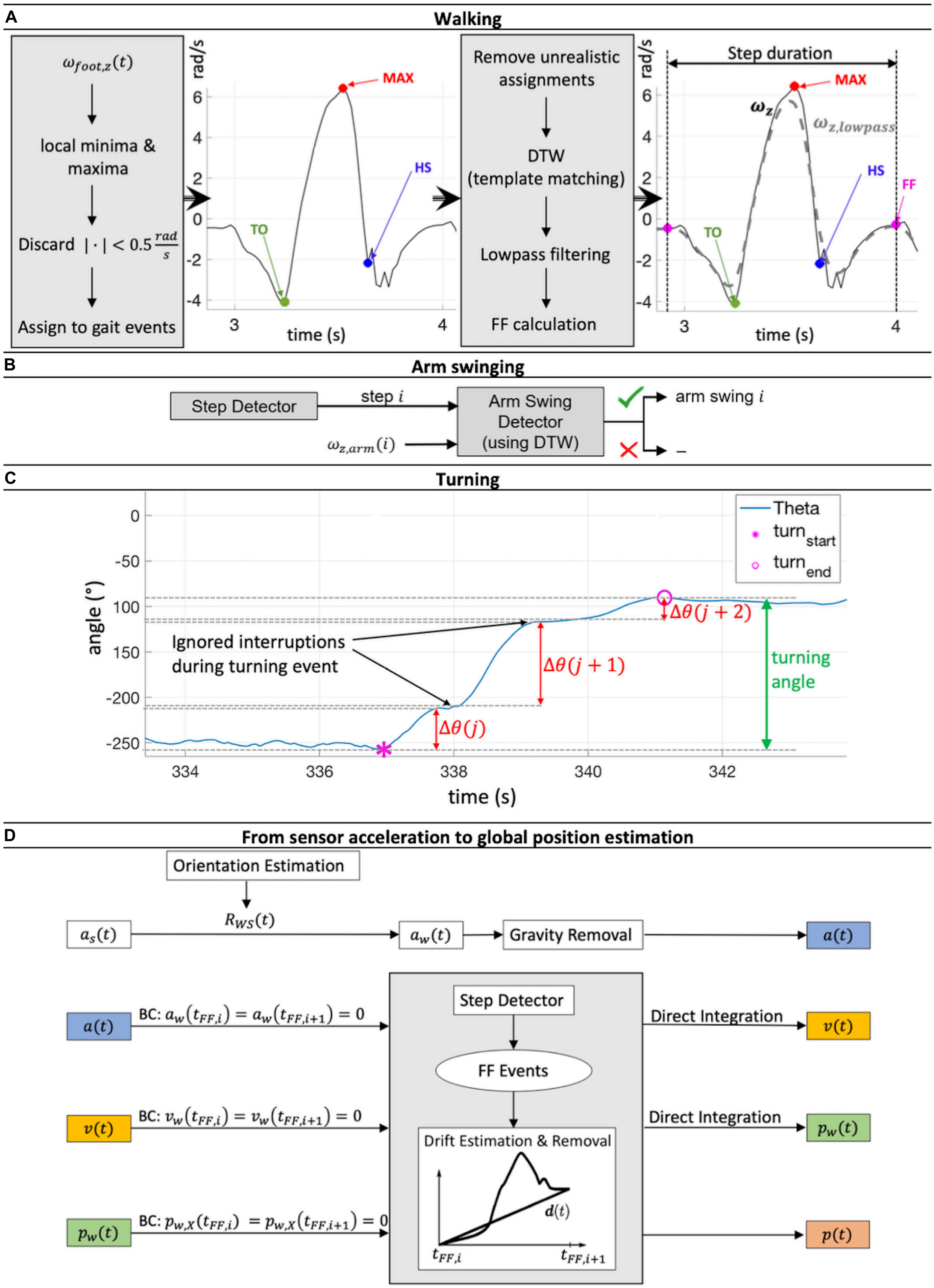

FIGURE 2 | (A) Workflow of step detection based on a minima and maxima angular velocity search in the z-direction of the foot sensor followed by a dynamic time warping (DTW) based template matching procedure. **(B)** For every reported step, the presence or not of arm swinging was checked using DTW template matching. **(C)** The process of merging turning sequences Θ(j), Θ(j + 1) and Θ(j + 2) belonging to the same turning event to get the full turning angle is illustrated. **(D)** Estimation workflow of global acceleration α(t), velocity v(t), and position p(t) during one gait cycle [between two foot flat (FF) events] via double integration of IMU acceleration data α_s(t). Rotation matrix R_{WS} (t) then rotated the sensor position into global coordinates. Drift was linearly estimated and removed, including compensation for the effect of gravity. Zero acceleration and velocity at FF events and ground-level walking were assumed. This Integration process was performed for each gait cycle individually. BC, boundary conditions.

TABLE 2 | Fifteen gait parameters were captured using the wearable ZurichMOVE IMU sensors.

Symbol	Gait Parameter	Unit	Estimation Method
SL	Stride length	m	Orientation estimation feet and double integration of $a_{foot}(t)$ during one gait cycle
FC_{max}	Max foot clearance	cm	Orientation estimation feet and double integration of $a_{foot}(t)$ during one gait cycle
V_{Gait}	Gait velocity	m/s	Orientation estimation feet and integration of $a_{foot}(t)$ during one gait cycle
Θ	Foot outward rotation	°	Use the ratio of the traveled foot displacement $d_{lateral}$ and $d_{anteroposterior}$
SW	Step width	cm	Check vertical tilting angle $\Phi_{foot}(t)$ at FF events and extra calibration
$n_{StepsTurning}$	Steps per 180° turn	–	Get turning sequences by local integration of $\omega_{chest,z}(t)$ and detect steps in-between
P_{stance}	Stance phase	% of gait cycle	Step detection algorithm based on $\omega_{foot,z}(t)$
P_{swing}	Swing phase	% of gait cycle	Step detection algorithm based on $\omega_{foot,z}(t)$
P_{DL}	Double limb support phase	% of gait cycle	Step detection algorithm based on $\omega_{foot,z}(t)$
$R_{StanceToSwing}$	Stance to swing ratio	–	Step detection algorithm based on $\omega_{foot,z}(t)$
n_{cycle}	Cadence	spm	Step detection algorithm based on $\omega_{foot,z}(t)$
T_{cycle}	Cycle time	s	Step detection algorithm based on $\omega_{foot,z}(t)$
$dev\{T_{cycle}\}$	Cycle time deviation	%	Step detection algorithm based on $\omega_{foot,z}(t)$
$A_{swing,arm}$	Arm swing amplitude	rad/s	$\sqrt{\omega^2_{arm,z}(t) + \omega^2_{arm,y}(t)}$
$dist_{arm}$	Traveled arm distance	m	Orientation estimation arm and double integration of $a_{arm}(t)$ during one gait cycle

The estimation method of all parameters is briefly described in the last column.

successful approaches (Hamacher et al., 2014; Rampp et al., 2015; Benoussaad et al., 2016; Hannink et al., 2017). As a result, the sensor acceleration data $a_s(t)$ had to be expressed in global coordinates. This was achieved using a rotation matrix $R_{WS}(t)$ that identified how the sensor frame was oriented with respect to the global frame at every time instance, t. Orientation estimation was applied individually for each gait cycle and combined the acceleration and angular velocity measurements to obtain the rotation matrices, $R_{WS}(t)$ [similar to gyroscope integration (Hannink et al., 2017), described in section "3. Orientation estimation" in **Supplementary Material**]. Additionally, the effect of gravity was removed to obtain the global movement component of acceleration $a(t)$:

$$a(t) = (R_{WS}(t) \cdot a_s(t)) + [1, 0, 0]^T \tag{1}$$

To estimate the global position trajectory during the gait cycle i, $a(t)$ was integrated twice (trapezoidal integration) between two FF events. In addition, the offset between foot and ankle was neglected during application of the following boundary conditions: the global acceleration $a(t_{FF})$, velocity $v(t_{FF})$ and vertical position $p_X(t_{FF})$ at ground contact during the FF event must be zero.

$$a(t_{FF,i}) = a(t_{FF,i+1}) = v(t_{FF,i}) = v(t_{FF,i+1}) = 0 \quad \& \quad p_X(t_{FF,i}) = p_X(t_{FF,i+1}) = 0 \tag{2}$$

In order to ensure the constraint $a(t_{FF,i}) = a(t_{FF,i+1}) = 0$, a drift estimation and removal (termed dedrifting) with a piecewise linear function as explained by Rampp et al. (2015) was applied to $a(t)$ before the integration process. Due to inaccurate orientation estimation, sensor drift, and integration errors, the integrated signal $v(t)$ does not necessarily satisfy the constraint $v(t_{FF,i}) = v(t_{FF,i+1}) = 0$. Therefore, $v(t)$ was dedrifted using the approach of Benoussaad et al. (2016):

$$v_{dedrifted}(t) = v(t) - \frac{v(t_{FF,i+1})}{t_{FF,i+1} - t_{FF,i}} \cdot t \tag{3}$$

where t is the time, $t_{FF,i+1} - t_{FF,i}$ is the entire duration of the current gait cycle, and $v(t_{FF,i+1})$ is the calculated velocity at the end of the current gait cycle. After the second integration, $p_X(t)$ was dedrifted to fulfill the constraint $p_X(t_{FF,i}) = p_X(t_{FF,i+1}) = 0$. The complete global position, $p(t)$, estimation process is summarized in **Figure 2D**. All spatial feet parameters were estimated using $p(t)$, except for step width, which required an additional calibration procedure due to the missing relative spatial relation between the IMU sensors. As an approximation, a linear reference line was defined to match sensor tilting angles at FF events $\Phi(t_{FF})$ to the width d between the heels:

$$d = w \cdot \Phi(t_{FF}) + c \tag{4}$$

To define such a line, a calibration measurement was set up where the test subject walked on two lines with a known line spacing d, and the tilting angle $\Phi(t_{FF})$ of the sensors was evaluated for this walking sequence (**Figure 3**). The procedure was performed twice with different line spacings, d_{tight} (individual to subject), and d_{broad} (predefined upper limit of 35 cm). The two resulting calibration pairs d_{tight}, Φ_{tight} and d_{broad}, Φ_{broad} determined the parameters w and c of the reference line. To avoid unnatural gait patterns during these calibration trials, d_{tight} was not predefined but was rather found by visual inspection of the subject's gait during a test walk of 5 m length. Furthermore, d_{broad} was visually corrected if the subject did not hold the default line spacing of 35 cm. The calibration was performed for every subject due to differences in anatomy and sensor alignment. After the calibration process, the step width (SW) was evaluated using the reference line:

$$SW = w \cdot \Phi(t_{FF}) + c \tag{5}$$

Finally, the global coordinates $p(t)$ of the wrist sensors were calculated by applying a workflow similar to that applied using the foot sensors (see **Figure 2D**), but without boundary conditions. The relative traveled arm distance was calculated in both the lateral (z) and anteroposterior (y) directions using the approach presented by Lewek et al. (2010). Details about the estimation of each parameter can be found in the section "4. Estimation of the 15 gait parameters" in **Supplementary Material**.

Validation Experiment

We compared and verified our developed gait parameter estimation method against measurements using an opto-electronic motion capture system (Vicon motion analysis system, Oxford Metrics Group, United Kingdom) using 10 cameras to capture the movement trajectories of 61 markers attached to the body (see section "5. Validation measurement with Vicon" in **Supplementary Material**). For validation, three subjects with a total of 60 gait cycles were assessed. Here, each subject walked around a predefined test track in the shape of an eight around two cones (König et al., 2014) at their own preferred walking speed (normal walking conditions) while wearing the 61 markers as well as the five ZurichMOVE sensors. The two systems were time-synchronized and gait parameters were estimated independently for both systems.

The validation experiment revealed an accuracy of between 1% and 6% for most parameters, which was only slightly worse than attaching ZurichMOVE sensors directly to the foot (Mohammadi et al., 2017). Measured parameters with larger error values were checked using additional walking conditions (short, long, and broad walking). On completion of these verification activities, it became clear that all parameters and the corresponding error behavior could be described using a constant offset throughout the different conditions [SW: 39.3±5.7 cm (IMU), 31.6±4.7 cm (Vicon), 7.2±4.0 cm (abs diff) during broad walking; T_{DL}: {0.29±0.08 s, 0.25±0.06 s} (IMU), {0.18±0.05 s, 0.14±0.03 s} (Vicon), {0.11±0.05 s, 0.10±0.03 s} (abs diff) during {short, long} step walking]. The reason for the constant offset of 1–2 steps in $n_{StepsTurning}$ between IMU estimation and visual inspection was differences in start and stop time definition of turning events: IMU estimation considered trunk rotation while visual inspection was focused on the feet only. As a result, all parameters developed were considered suitably verified to be used for relative comparisons between different test subjects and/or environments (**Table 3**).

FIGURE 3 | Principle of step width (SW) calibration procedure. The subject walked on two parallel lines, spaced by d_{tight} or d_{broad}, for which the tilting angles Φ_{tight} and Φ_{broad} were evaluated. These four values were used to define a linear reference line for the SW estimation where the Φ values were matched to d values between the feet.

Statistical Analyses

Each gait parameter was determined as the average of the left and right foot median values. For the evaluated gait parameters in the real-world environment, the following outlier removal was applied before the median calculation: (1) Walking phases were only considered if seven or more steps were performed in a row. (2) Times of special activities (e.g., sports) were reported by the test subjects in a protocol and removed from the analysis. (3) Values that deviated more than three times from the median value were discarded. Differences between the two environments and groups were evaluated as absolute difference (abs diff), calculated as $\text{Parameter}_{\text{Real-world}} - \text{Parameter}_{\text{Lab}}$, while mean relative difference (mean rel diff) was calculated as the mean of the relative differences $(\text{Parameter}_{\text{Real-world}} - \text{Parameter}_{\text{Lab}})/(\text{Parameter}_{\text{Real-world}})$. All analyses were performed using MATLAB (The MathWorks Inc., Natick, MA, United States). The resulting median values of each subject were then compared between the different environments, and tested for significance using the Wilcoxon signed-rank test, while differences between the two test groups (young and elderly) were examined using the Mann–Whitney U-Test. To ensure symmetrical data distribution (assumption of Wilcoxon signed-rank test), parameters with a skewed distribution were log transformed before p-value calculation. Since our hypotheses include several parameters, resulting p-values were corrected for false discovery by applying the Benjamini-Hochberg correction. All statistical tests were performed in R (R Core Team, 2017, Vienna, Austria), with p-values smaller than 0.05 considered to be statistically significant.

RESULTS

Non-controlled Real-World Versus Controlled Lab Environment

Based on the results (**Table 4** and **Figure 4**), the parameters were divided into three clusters: (A) Significant differences between the two environments for both groups; (B) Significant differences

TABLE 3 | Results of the validation experiment during normal walking.

Parameter*	Values		Absolute Error	Relative Error
	IMU	Vicon	Mean ± STD	Mean ± STD
SL (m)	1.37 ± 0.14	1.33 ± 0.14	0.02 ± 0.03	1.6 ± 2.1%
FC_{max} (cm)	11.7 ± 1.2	12.4 ± 1.7	−0.7 ± 1.4	−5.6 ± 11.2%
V_{Gait} (m/s)	1.17 ± 0.22	1.19 ± 0.24	−0.01 ± 0.02	−0.8 ± 1.6%
Θ (°)	9.3 ± 2.6	9.5 ± 2.8	−0.2 ± 3.3	−1.9 ± 34.9%
SW (cm)	16.5 ± 4.7	7.6 ± 2.7	9.1 ± 4.4	118.4 ± 57.8%
$n_{StepsTurning}$** (–)	7.2 ± 2.6	5.5 ± 3.0	1.7 ± 0.6	30.9 ± 10.9%
T_{stance}*** (s)	0.69 ± 0.10	0.72 ± 0.09	−0.02 ± 0.03	−2.9 ± 4.5%
T_{swing}*** (s)	0.46 ± 0.04	0.44 ± 0.03	0.02 ± 0.04	4.4 ± 8.5%
T_{DL}*** (s)	0.24 ± 0.10	0.16 ± 0.04	0.09 ± 0.07	56.5 ± 43.3%
n_{cycle} (spm)	105.3 ± 9.9	105.5 ± 8.6	−0.9 ± 4.5	−0.9 ± 4.3%
T_{cycle} (s)	1.15 ± 0.12	1.16 ± 0.11	0.00 ± 0.03	−0.1 ± 2.9%
$dist_{arm}$ (m)	0.66 ± 0.19	0.67 ± 0.22	−0.01 ± 0.11	−0.8 ± 16.8%

*The IMU sensors and Vicon markers were all attached to the body and the gait parameters were calculated independently with both systems. The absolute error ± standard deviation (STD) is presented as the difference between IMU and Vicon. Abbreviations are listed in **Table 2**. *$R_{StanceToSwing}$, dev{T_{cycle}} and $A_{swing,arm}$ need no validation, directly calculated from validated parameters/sensor readings. **Visual inspection as reference. ***Period T is validated instead of P =T/T_{cycle} (% of gait cycle).*

between the two environments for the elderly subjects only; (C) Remaining differences.

Cluster A: Significant Differences Between the Two Environments for Both Groups

In the real-world settings, both groups showed a significantly increased foot outward rotation [young: 19% ($p = 0.0122$); elderly: 16% ($p = 0.0025$)], a step width increase [young: 32% ($p = 0.0001$); elderly: 24% ($p = 0.0049$)], an increased number of steps per 180° turn [young: 14% ($p = 0.0145$); elderly: 15% ($p = 0.0019$)] for elderly subjects, an increased cycle time deviation [young: 51% ($p = 0.0007$); elderly: 58% ($p < 0.0001$)] and an increased stance to swing ratio [young: 3% ($p = 0.0237$); elderly: 2% ($p = 0.0429$)].

Cluster B: Significant Differences Between the Two Environments for Elderly Group Only

Several parameters showed a larger difference between the two environments for elderly subjects than for the young. For the elderly, we observed a 12% decrease in gait velocity ($p = 0.0072$), a 5% increase in cycle time ($p = 0.0051$) and a 6% decrease in cadence ($p = 0.0051$) in the real-world compared with the lab environment. For the young subjects, these differences were minor and non-significant with values of −2, −1, and ±0%, respectively.

Cluster C: Remaining Differences

The double limb support phase showed significant differences between the two environments for young subjects [7% ($p = 0.0237$)] in real-world settings while the increase for elderly subjects was not statistically significant (5%). Although not significant in both groups, similarity to the parameters of Cluster A is present. Furthermore, non-significant differences between the two environments were an increased traveled arm distance (young: 6%; elderly: 4%) as well as a decreased stride length (young: −1%; elderly: −6%) in real-world settings. The *p*-values of the stride length are much smaller in elderly subjects compared with the young which indicates a potential link to Cluster B. The arm swing amplitude was the only parameter that was considerably increased in young subjects (7%) in the real-world environment compared to a decrease in elderly subjects (−1%). Foot clearance, stance phase, and swing phase did not show relevant differences between the two environments for either group (smaller than 1.5%).

Young Versus Elderly Test Subjects

Overall, the non-controlled real-world environment *enlarged* the inter-group differences. In both environments, young test subjects took significantly longer strides ($p = 0.0047$ real-world, $p = 0.0063$ lab) and walked faster ($p = 0.0001$ in real-world, $p = 0.0063$ in lab environment) than elderly subjects. In real-world settings, young subjects also took significantly less steps per 180° turn ($p = 0.0024$), walked with higher cadence ($p = 0.0120$), and showed an increased cycle time ($p = 0.0110$) compared with elderly subjects. The remaining parameters did not show significant differences between the two test groups in either environment.

DISCUSSION

The current study compared the walking patterns of young and elderly subjects in a controlled lab environment against those captured in a non-controlled real-world environment over 72 h. Significant differences were present between the two environments for both groups, including increased foot outward rotation, step width, number of steps per 180° turn, stance to swing ratio, and cycle time deviation in real-world settings. Although only significant in young subjects, both groups also exhibited an increased double limb support phase in real-world environments. Furthermore, we observed significant differences between the two environments only in the elderly subjects, including decreased gait velocity, decreased cadence,

TABLE 4 | Estimated gait parameters of young and elderly test subjects (n = 20 each) in real-world and lab environment (mean ± standard deviation) clustered in A, B and C.

		Young					Elderly				
Parameters	**Cluster****	**Real-world**	**Lab**	**Abs diff**	**Mean rel diff**	***p*-value**	**Real-world**	**Lab**	**Abs diff**	**Mean rel diff**	***p*-value**
Θ (°)	A	12.6 ± 6.5	10.5 ± 6.2	2.2 ± 3.0	+19.4%	0.0122	15.1 ± 7.5	13.0 ± 6.9	2.1 ± 1.7	+15.8%	0.0025
SW* (cm)	A	15.8 ± 3.5	10.7 ± 3.9	5.1 ± 3.8	+31.5%	0.0001	16.2 ± 4.3	12.2 ± 4.4	4.0 ± 4.0	+23.6%	0.0049
$n_{StepsTurning}$ (–)	A	5.5 ± 0.5	4.7 ± 0.8	0.8 ± 0.7	+14.1%	0.0145	6.4 ± 0.7	5.3 ± 0.8	1.0 ± 1.0	+15.4%	0.0019
$R_{StanceToSwing}$* (–)	A	1.48 ± 0.06	1.43 ± 0.08	0.05 ± 0.08	+3.0%	0.0237	1.52 ± 0.13	1.49 ± 0.12	0.04 ± 0.08	+2.2%	0.0429
$dev\{T_{cycle}\}$* (%)	A	5.4 ± 2.1	2.4 ± 0.7	3.0 ± 2.1	+51.3%	0.0007	6.9 ± 2.4	2.6 ± 0.8	4.3 ± 2.2	+57.6%	<0.0001
V_{Gait} (m/s)	B	1.33 ± 0.11	1.35 ± 0.12	−0.02 ± 0.15	−2.1%	0.7094	1.08 ± 0.20	1.18 ± 0.15	−0.11 ± 0.14	−12.2%	0.0072
n_{cycle} (spm)	B	111.5 ± 5.8	111.5 ± 6.1	0.0 ± 5.2	−0.1%	0.9652	104.2 ± 8.2	110.2 ± 7.1	−5.9 ± 7.1	−6.0%	0.0051
T_{cycle}* (s)	B	1.07 ± 0.05	1.08 ± 0.06	−0.01 ± 0.04	−0.6%	0.9521	1.15 ± 0.09	1.09 ± 0.07	0.06 ± 0.07	+4.8%	0.0051
P_{DL} (% of gait cycle)	C	19.3 ± 2.1	17.9 ± 2.8	1.4 ± 2.8	+6.8%	0.0237	20.9 ± 3.7	19.8 ± 3.8	1.2 ± 2.5	+5.1%	0.0949
SL (m)	C	1.46 ± 0.12	1.47 ± 0.11	−0.01 ± 0.10	−1.0%	0.7094	1.27 ± 0.22	1.32 ± 0.16	−0.05 ± 0.11	−5.7%	0.0920
$A_{swing,arm}$ (rad/s)	C	3.28 ± 0.65	2.97 ± 0.63	0.31 ± 0.62	+7.3%	0.0819	2.75 ± 0.67	2.75 ± 0.81	0.00 ± 0.71	−1.3%	0.8408
$dist_{arm}$ (m)	C	0.66 ± 0.06	0.62 ± 0.10	0.04 ± 0.10	+5.7%	0.1805	0.64 ± 0.11	0.62 ± 0.16	0.02 ± 0.11	+3.6%	0.5118
P_{stance} (% of gait cycle)	C	59.5 ± 1.1	59.0 ± 1.3	0.5 ± 1.5	+0.9%	0.1805	60.4 ± 1.9	60.0 ± 1.8	0.4 ± 1.2	+0.6%	0.4450
P_{swing} (% of gait cycle)	C	40.6 ± 0.8	41.2 ± 1.7	−0.6 ± 1.7	−1.5%	0.2071	40.1 ± 2.0	40.4 ± 2.0	−0.3 ± 1.4	−0.8%	0.4661
FC_{max} (cm)	C	13.7 ± 1.8	13.6 ± 1.9	0.03 ± 0.56	+0.3%	0.3416	12.7 ± 1.9	12.7 ± 1.8	0.04 ± 0.86	±0.0%	0.4450

Absolute (abs diff) and mean relative differences (mean rel diff) between the non-controlled real-world and controlled lab environments are presented. P-values are calculated based on the abs diff data, resulting values smaller than 0.05 are considered statistically significant (marked in green). Respective abbreviations are listed in ***Table 2****. *Skew distributed data, transformed logarithmically for p-value calculation (Wilcoxon signed-rank test requires symmetric data distribution). *****(A)*** *Significant differences between the two environments for both groups;* ***(B)*** *Significant differences between the two environments for elderly group only;* ***(C)*** *Remaining differences.*

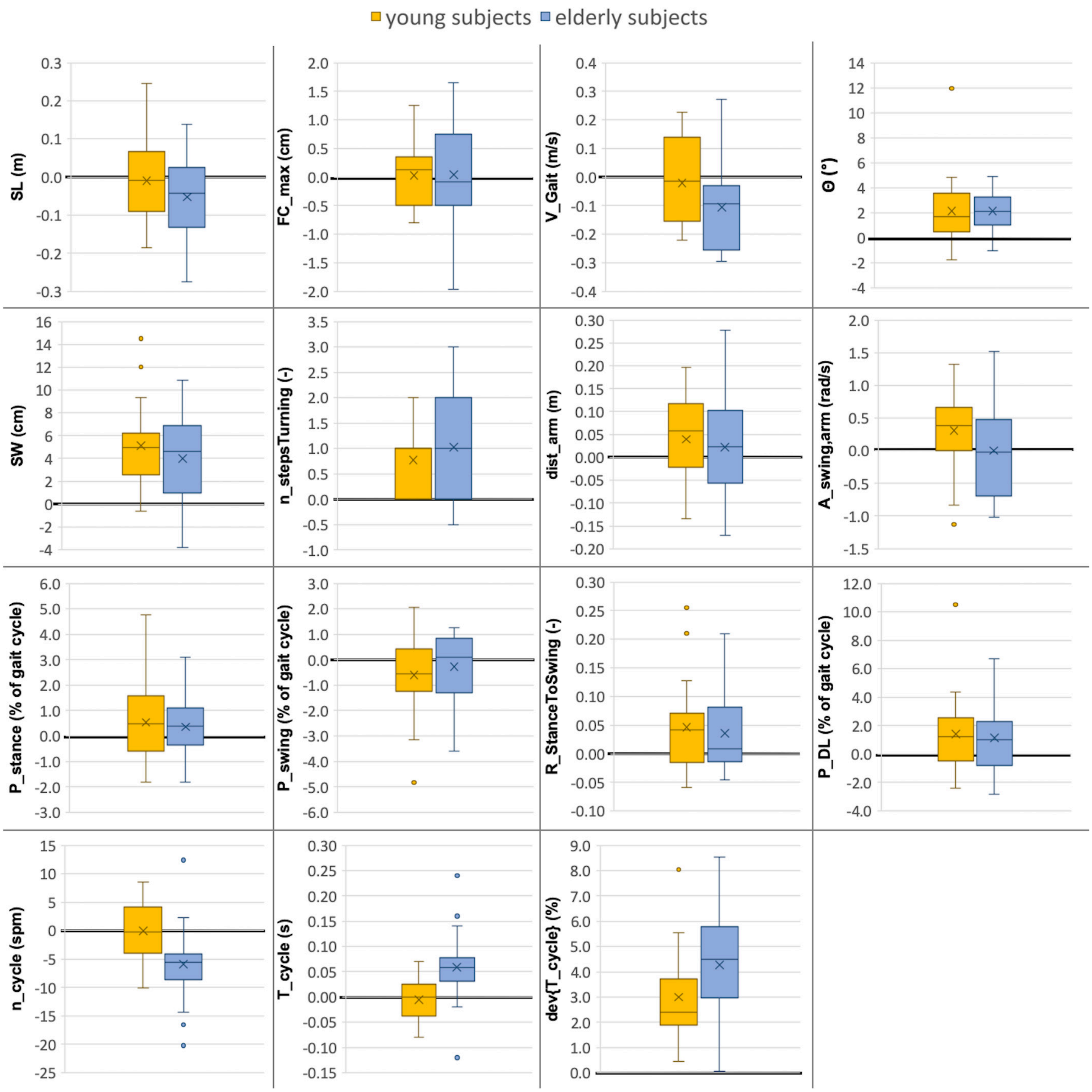

FIGURE 4 | Comparison between gait parameters collected in lab (10-m walking test) versus real-world (72 h investigation) environments for young and elderly subjects (*n* = 20 each). The boxplots indicate the absolute differences between the two environments ($Parameter_{Real-world}$ - $Parameter_{Lab}$) for both groups. The median value is illustrated as a line, the mean value as a cross and outliers as dots. The line indicating zero difference between the two settings is depicted in bold. Abbreviations are listed in **Table 2**.

and increased cycle time in real-world settings. In general, the young subjects showed only minor differences in their walking patterns between the two environments. Additionally, the gait parameters were compared between the two test groups for both environments, where the non-controlled real-world environment enlarged the inter-group differences.

The significant differences in several gait parameters between the two environments confirm our hypothesis that people walk differently in a controlled lab environment. The differences in walking patterns between the two environments were minor for young test subjects compared to the elderly, suggesting that elderly subjects tend to be more influenced in their walking patterns by their environment (Del Din et al., 2016) as well as the possible surveillance of an independent audience (Robles-García et al., 2015; Brodie et al., 2016). This observation may indicate that elderly subjects in particular tend to perform better in a controlled lab environment because they try not to stand out negatively during a test or survey (Del Din et al., 2016).

The observed differences in Cluster B match several results of other studies. Brodie et al. (2016) observed a trend toward lower cadence in real-world environments for elderly people, while Del Din et al. (2016) reported a decreased stride length, decreased gait velocity, and increased cycle time for elderly subjects and subjects suffering from Parkinson's disease in real-world settings. Furthermore, an increased cycle time deviation in real-world environments has been reported for elderly people (Brodie et al., 2016; Del Din et al., 2016) as well as an increased variability in cadence (Weiss et al., 2011). For Cluster A, no reports about similar behavior between the two environments were found in the literature, possibly reflective the bias toward reporting only positive results.

We see two main reasons for the observed differences: a mental and a physical influence of the environment. The mental status of the subject is known to influence walking behavior (Prohaska et al., 2009), while the physical influence is given by the various path characteristics, such as surface type, length and type of walking distance (e.g., straight/curved). For Cluster A, it is plausible that the physical influence of the environment plays a dominant role, since similar differences in gait parameters were present in both test groups. Perfect straight walking is possible within a controlled lab environment, but such conditions can rarely be assumed in ecologically valid real-world settings. It is likely that the differences observed in Cluster B were driven by the mental influence of the environment, as differences between the two environments were observed only in the elderly population. It is clear that the differences observed in Cluster B necessitate an improved understanding of natural walking patterns under ecologically valid conditions, including the role they play in clinical decision making.

Several parameters showed larger differences between young and elderly subjects for the non-controlled real-world environment. If this effect is also present in people with indications of a walking disorder, the enlarged separation between groups would be beneficial for diagnostic processes. Del Din et al. (2016) have already reported enlarged inter-group differences between elderly healthy controls and subjects suffering from Parkinson's disease in real-world settings. However, further studies including people with various indications of walking disorder are needed to investigate this topic.

To ensure exact sensor positioning throughout the entire recordings, the subjects did not remove the sensors at any time. To allow wearing the sensors without removal and guarantee full freedom of movement, the sensors were attached to the ankles instead of the feet. Although the accuracy of gait parameter estimation of ankle mounted sensors is lower than of foot mounted sensors (mainly due to the lack of a stationary instant during the gait cycle) several researchers have investigated ankle mounted gait analysis and confirmed its validity for gait parameter estimation. Jasiewicz et al. (2006) estimated HS and TO events similar to our approach and reported high levels of accuracy for normal gait, but showed inaccuracies for abnormal gait e.g., using walking aids. Li et al. (2010) used an ankle mounted IMU sensor to estimate the gait velocity, Benoussaad et al. (2016) estimated the foot clearance and Sijobert et al. (2015) estimated stride length, all of them with comparable accuracy to our approach. Our findings regarding the comparison of walking patterns of young and elderly subjects agree with several reports from literature. For young subjects, an increased stride length and gait velocity (Whittle, 1991; Öberg et al., 1993; Prince et al., 1997; Menz et al., 2004; Janeh et al., 2018), an increased heel clearance in young subjects (Mariani et al., 2010), less time for double limb support phase (Aminian et al., 2002; Janeh et al., 2018), and more steps taken for turning in elderly subjects (Thigpen et al., 2000; Akram et al., 2010) have all been reported and are in agreement with the results of our study. Consequently, we are confident not only that our metrics determined in ecologically valid settings are reliable, but also that the comparison against lab-based settings has revealed valid differences between the settings. As a result, clinicians should be aware of the reported changes in movement patterns, especially in cases where gait metrics play a role in the diagnosis of a patient's functional status e.g., fall risk, or when therapies require tuning to optimize muscle function and coordination e.g., deep brain stimulation.

One limitation during the assessment of the subjects' walking patterns was the range of considered gait parameters. The current study mainly focused on gait parameters that capture the gait rhythm and pace of a subject. To extend the captured walking pattern range, asymmetry or variability could be included or investigated in parameters other than only cycle time (König et al., 2014; Del Din et al., 2016; McArdle et al., 2019). Additionally, variability in real-world environments could be captured in more detail by individual evaluation and averaging of every walking sequence, as proposed by Del Din et al. (2016). On the estimation side, the following deficiencies were present in our study: (1) The parameters with relative error values larger than 6% (SW, T_{DL} and $n_{StepsTurning}$) have to be used with caution. (2) Our approach needs a calibration procedure for the step width estimation for every subject, which may be a potential source of error. (3) Although our predefined line spacing during step width measurement calibration only acted as guidance, some subjects still focused too much on them, which may have falsified their natural walking pattern. This might be a potential reason for the large error in the step width estimation. (4) The foot outward rotation estimation was prone to sensor misalignment. Therefore, the sensors need to be attached to the body precisely, with their position maintained throughout the measurement period. (5) To avoid bias of the findings, we did not observe subjects in the real-world environment as we hypothesized that such observations may influence the gait patterns. However, potential differences in daily activities between the subjects remain unknown and the ability to extrapolate results beyond the examined metrics is therefore limited. In order to minimize this influence, we recorded activity over an extended 3 days period, but also ensured that the subjects filled in an activity protocol so that we were able to ignore all non-continuous walking sequences (less than seven steps in a row). (6) Our step detection approach did not differentiate between normal walking and slope ascent/descent walking. While such gait patterns could influence the event recognition, we expected most steps to be performed under conditions with negligible slope effects, with any exclusion of such steps serving to present conservative results. Finally, besides the considered influence of the environment on the walking pattern, further factors may exist, such as the influence of the attached sensors on the movement or a potential feeling of being surveyed by the sensors. Despite these limitations, we could show that people walk differently in a controlled lab environment, which should be considered during future examinations on gait characteristics regarding natural walking pattern extraction.

CONCLUSION

We conclude that especially elderly subjects walked differently in controlled lab settings compared to their real-world environments. Elderly subjects tend to walk faster and take less time per step (increased cadence and decreased cycle time) in the controlled lab environment, whereas for young people, these differences were minor. The findings indicate the need to better understand natural walking patterns under ecologically valid conditions before clinically relevant conclusions can be drawn on a subject's functional status. Moreover, the greater inter-group differences in real-world environments seem promising regarding the identification of subjects with indications of a walking disorder.

DATA AVAILABILITY STATEMENT

The developed step detection algorithm is available at http://doi.org/10.5905/ethz-1007-243 including a test walking sequence of ankle mounted angular velocity in the lateral direction. The datasets of the study are not publicly available because test subjects was guaranteed that their data will be anonymously used for this study only and not passed to extern instances. Requests to access the datasets should be directed to MS, marischm@ethz.ch.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Cantonal Ethics Committee Zurich (BASEC-No. 2018-00051) and Swissmedic (102597735). The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DR and NT contributed to the concept and design of the parameter estimation methods. DR, CG, and NS contributed to the concept and design of the Vicon validation. DR, CG, MS, and LS contributed to the concept and study design. DR and CG contributed to the data analysis and interpretation. DR and MS contributed to the drafting of the manuscript. DR, CG, NT, NS, MM, WT, LS, and MS contributed to the critical revision of the article. DR, CG, NT, NS, MM, WT, LS, and MS contributed to the approval of the manuscript.

FUNDING

This work was financially supported by the Swiss National Science Foundation through the grant 315230_184913.

ACKNOWLEDGMENTS

We would like to thank Roger Gassert of the Rehabilitation Engineering Lab at ETH Zurich for providing the ZurichMOVE sensors and Franziska Ryser for introducing us to the sensors and her continuous technical support. We further like to thank Ravi Deepak Kumar and Yong Kuk Kim for their support during the Vicon validation experiments as well as the Seminar for Statistics at ETH Zurich for their statistical inputs and advice.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2020.00090/full#supplementary-material

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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.

frontiers in Physiology

REVIEW
published: 27 February 2020
doi: 10.3389/fphys.2020.00156

Optimal Human Functioning Requires Exercise Across the Lifespan: Mobility in a 1g Environment Is Intrinsic to the Integrity of Multiple Biological Systems

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OPEN ACCESS

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Specialty section:
This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology

Received: 02 November 2019
Accepted: 12 February 2020
Published: 27 February 2020

Citation:
Hart DA and Zernicke RF (2020) Optimal Human Functioning Requires Exercise Across the Lifespan: Mobility in a 1g Environment Is Intrinsic to the Integrity of Multiple Biological Systems. Front. Physiol. 11:156. doi: 10.3389/fphys.2020.00156

It is widely acknowledged that achieving and maintaining a healthier lifestyle can be enhanced through regular participation in sport and physical activity. Coevally, a growing number of health professionals regard exercise as a legitimate intervention strategy for those who have lost their health. Exercise has been shown to be effective for overweight or obese individuals, who are at risk to lose their health due to development of type II diabetes, cardiovascular disease, as well as, infiltration of muscles, bone and other organs with fat, so it can be considered medicine. However, exercise and associated mobility likely also have a strong prevention component that can effectively contribute to the maintenance of the integrity of multiple biological systems for those who do not have overt risk factors or ongoing disease. While prevention is preferred over intervention in the context of disease, it is clear that exercise and associated mobility, generally, can be an effective influence, although overtraining and excessive loading can be deleterious to health. The basis for the generally positive influence of exercise likely lies in the fact that many of our physiological systems are designed to function in the mechanically dynamic and active 1g environment of Earth (e.g., muscles, cartilage, ligaments, tendons, bones, and cardiovascular system, and neuro-cognitive function), and nearly all these systems subscribe to the "use it or lose it" paradigm. This conclusion is supported by the changes observed over the more than 50 years of space flight and exposure to microgravity conditions. Therefore, the premise advanced is: "exercise is preventative for loss of health due to age-related decline in the integrity of several physiological systems via constant reinforcement of those systems, and thus, optimal levels of exercise and physical activity are endemic to, essential for, and intrinsic to optimal health and wellbeing."

Keywords: exercise and health, mobility and optimal function, obesity, chronic disease, overuse injuries, musculoskeletal system, cognitive function, microgravity

INTRODUCTION

Arguably, exercise and its associated mobility are integral to optimal health and wellbeing of humans. This statement generates questions related to how does it work, which biological and physiological systems benefit the most from its effects, and why? Is it important to know these answers? The concept that "Exercise is Health" existed for centuries (Hills et al., 2015), and events of the past 50 years related to multi-national space programs now provide unique potential clues to as to why exercise is so effective from the perspectives of both prevention and intervention.

Undoubtedly, exercise (aerobic and/or resistance) can be medicinal for those with diagnosed disease conditions. For example, for some individuals, exercise may alter symptoms or progression of diabetes (Way et al., 2016), dementia or loss of cognition (Liu-Ambrose and Donaldson, 2009; Ma et al., 2016), loss of cardiovascular integrity (Ribeiro et al., 2016), impaired bone formation and rate of loss in post-menopausal females (Moreira et al., 2014), osteopenia in general (Scott et al., 2008), and muscle atrophy (Carter et al., 2015), to name several of the most prevalent. However, once a disease has been established, the effectiveness of any intervention (e.g., exercise) may be diminished as the disease process implies dysfunction of normal homeostatic control; exercise is not a cure for the condition but part of the total intervention strategy (e.g., drugs, surgery, and exercise). In this context, exercise is likely medicinal but is not the whole picture. Prevention is a preferred approach versus intervention after the fact.

The reasons why exercise in the context of disease may be less effective than in the absence of disease are varied, in part due to the chronicity of diseases where it is reported to be effective, and in part due to the pharmacological interventions used. Firstly, disease implies pathology, and pathology implies dysfunction in the target integrity. Secondly, many diseases are treated with pharmacological agents, which in themselves may impact the pathology and contain, but not cure the conditions. Thus, an exercise protocol, added to drug interventions, will have its impact influenced by both the disease and the drugs. Thirdly, in many chronic diseases, such as those in which exercise reportedly has influence, target tissues can undergo epigenetic modifications (Brunet and Berger, 2014; Raman et al., 2018; Sqalla et al., 2018), which alter their responsiveness to normal stimuli, drugs, and other interventions (Piletic and Kunei, 2016). These conditions include Alzheimer's disease (Qazi et al., 2018), osteoporosis (Ghayor and Weber, 2016), osteoarthritis (Van Meurs, 2017), rheumatoid arthritis (Cribbs et al., 2015), cardiovascular disease (Ahuja et al., 2017; Ghosh et al., 2017), diabetes (Muka et al., 2016; Raghuraman et al., 2016), and sarcopenia (Sharples et al., 2016). Exercise itself may result in epigenetic alterations both before and after development of chronic disease development (Grazioli et al., 2017), but whether exercise alone is preventative for disease development will require more investigation. Thus, the distinction between "Exercise is Medicine" and "Exercise is Health" has validity, and may explain why exercise in a prevention mode is preferred over that in a medicinal role, but that distinction does not imply that "exercise is medicine" is not a valuable intervention (Sallis, 2009).

Exercise can also contribute to the health of individuals at risk for losing it, such as in obese individuals, via re-establishing metabolic control, caloric balance, and other related energy utilization parameters. As a consequence, exercise can impact multiple biological and physiological systems via metabolic control. Exercise can influence conditions such as type II diabetes onset and progression at the level of muscle-mediated insulin-resistance (Way et al., 2016), as well as aspects of the metabolic syndrome and chronic inflammation associated with obesity, and many other aspects of the condition (Pedersen and Saltin, 2015). Nevertheless, even with obesity, epigenetic modifications can occur and progress over time (Desiderio et al., 2016; Pigeyre et al., 2016; Xu et al., 2016), and such changes may have transgenerational influences in both humans (Bays and Scinta, 2015) and preclinical models (Paul et al., 2019), so treating early obesity rather than long-term chronic obesity with exercise may yield substantially different outcomes for many individuals.

As more is learned about epigenetic modifications of both somatic and germ-line cells, there may be opportunities to reverse their potential negative impact on gene regulation, as well as enhance the positive influences. However, such epigenetic changes may be associated with alterations to DNA methylation, histone modifications, and some RNA-mediated processes (reviewed in Ling and Ronn, 2019), and as such will require a detailed analysis of negative and positive alterations, and whether transgenerational influences are associated with the changes. Interestingly, exercise is known to lead to epigenetic alterations of both skeletal muscle (reviewed in Widmann et al., 2019) and in germ cells leading to transgenerational effects, particularly as related to metabolic pathways (Denham, 2018; Axsom and Libonati, 2019). In the review by Axsom and Libonati (2019), the focus was on DNA methylation changes in offspring and included studies of both preclinical models and humans. However, it should be noted that the number of epigenetic-related studies performed to date has not been large, the number of studies done on humans versus preclinical models is small for obvious reasons associated with invasiveness, the exact mechanisms via which the epigenetic changes occur are still lacking in detail, and it remains to be determined which types of exercise (e.g., aerobic versus resistive) are most effective for generating adaptations. While there are limitations to the current findings, they are encouraging regarding exercise and disease risks (i.e., heart disease and cancer) and the transgenerational influences of such modifications—the latter may be contributed by both parents (Ashe and Khan, 2004; Ahuja et al., 2017; Denham, 2018; Axsom and Libonati, 2019). Furthermore, some epigenetic changes occur during aging (Pal and Tyler, 2016; Pagiatakis et al., 2019), so the effectiveness of exercise at the epigenetic level may be influenced by the age that it is implemented and sustained—potentially a life-long chronic exercise routine will be best.

Several of the above conditions are associated with aging, and indeed, dementia, cardiovascular diseases, sarcopenia, and osteoporosis are more common in mature or elderly populations.

Obesity, with unique fat deposition patterns in males and post-menopausal females, was in the past more common in older individuals, particularly those with mobility issues, but also those who became more sedentary after a life of hard physical labor. However, more recently, younger individuals with sedentary occupations or lifestyles, compounded by poor diets (e.g., high in saturated fats and sucrose), are becoming obese. Regrettably, children with obesity constitute one of the fastest growing populations (Karnik and Kanekar, 2012), which generates concern for multiple reasons that include early onset of type II diabetes and cardiovascular disease, as well as musculoskeletal concerns related to growth and maturation. With obesity comes infiltration of muscle and bone with fat, which can have biomechanical consequences during post-puberty maturation of the skeleton articular system. Childhood or adolescent obesity effects on bone-muscle integrative functioning may remain altered even if weight is lost as an adult. Concomitantly, these effects may be related to epigenetic modifications, which can interfere with the effectiveness of exercise. Thus, exercise, tailored to the individual, has the potential to mitigate the risk for development of several conditions prior to their onset in individuals with obesity. In rats, exercise has been shown to be preventative for the consequences of diet-induced obesity (see Collins et al., 2016 for diet details) when implemented at the same time as the animals were started on such a high-fat and sugar diet (Rios et al., 2019).

The above-discussed progression leads to a third important function of exercise: the preventative aspects throughout the lifespan to maintain the integrity of multiple physiological systems including muscle, bone, cardiovascular, and respiratory systems, as well as brain function. It is generally recommended that adults and children engage in about 150 min of moderate exercise per week. Engaging in such exercise, at a minimum, throughout the lifespan has many benefits based on the literature. In addition, different types of exercise (e.g., aerobic vs. resistance) can have differential effects on tissue adaptation and quality. For example, Armamento-Villareal et al. (2019) reported how some forms of exercise can be more effective at protecting against bone-loss during weight-loss therapy in older adults with obesity. With similar amounts of weight loss, elderly individuals (≥65 years) who combined aerobic and resistance exercises or only resistance exercises during their weight-loss program had significantly less weight loss-induced decreases in bone mineral density versus those who only participated in aerobic exercises.

Although exercise and enhanced mobility are cost-effective prevention strategies in which nearly all individuals can engage, undoubtedly genetics also plays a role in risk for cardiovascular disease, osteoporosis, and other conditions, so exercise is only one component of a series of modifiable activities for an individual (**Figure 1**). Often exercise has to be optimally matched with good dietary habits, sufficient sleep, and socialization to reap optimal benefits (**Figure 1**).

In terms of the positive effects of exercise on cognitive function, a growing body of evidence suggests that cognitive function can be enhanced via short-term and long-term exercise and physical activity. Won et al. (2019) studied brain activation

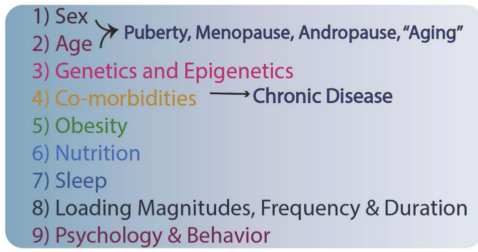

FIGURE 1 | Potential Modifiers of Exercise Effectiveness.

during a semantic memory task after a single bout of exercise in healthy older adults (55–85 years) using functional magnetic resonance imaging (fMRI)—semantic memory includes things that are "common knowledge" (e.g., names of colors, sounds of letters, capitals of countries, and other basic facts acquired over a lifetime). On separate days, subjects engaged in either 30 min of rest or 30 min of stationary cycling exercise immediately before performing a memory task during fMIR scanning. Acute exercise resulted in significantly greater semantic memory activation in the middle frontal, inferior temporal, middle temporal, and fusiform gyrus, as well as greater activation in the bilateral hippocampus. Complementing those positive responses, there are numerous studies that highlight the positive effects of longer-term exercise on cognitive and neural plasticity in older adults. In a comprehensive and critical review of related research, Kramer et al. (1999) and Erickson and Kramer (2009) concluded that even 6 months of moderate levels of aerobic activity are sufficient to produce significant improvements in cognitive function, particularly on measures of executive function. Colcombe and Kramer (2003) also reported that exercise broadly improved cognitive function across a number of domains including spatial functioning and executive control. The positive effects of exercise on cognitive function appear to extend to older adults with dementia; Heyn et al. (2004) reported that aerobic exercise interventions could reliably reverse cognitive impairments in demented individuals. In like manner, patients in the early stages of Alzheimer's disease who were more aerobically fit had less whole-brain atrophy and white matter atrophy than those patients who were less aerobically fit (Burns et al., 2008). In summarizing the state-of-knowledge about the effects of exercise on brain function, Erickson and Kramer (2009) posited that "...an active lifestyle with moderate amounts of aerobic activity will likely improve cognitive and brain function and reverse neural decay frequently observed in older adults." (p. 24). That conclusion by Erickson and Kramer (2009) was strongly corroborated by a Norwegian population-based prospective study (>30,000 men and women participants) that assessed the temporal changes in cardiorespiratory fitness and risk of dementia incidence and mortality (Tari et al., 2019). Tari et al. (2019) found that individuals who sustained high estimated cardiorespiratory fitness had a reduced risk of incident dementia and reduced risk of dementia mortality. Participants who increased their estimated cardiorespiratory fitness over time, gained 2.2 dementia-free years and 2.7 years of life when compared to those who remained unfit. Complementing the positive effects of aerobic exercise on cognitive function, Liu-Ambrose and Donaldson (2009) reported that incorporating resistance training, in conjunction with aerobic exercise, among senior individuals can also produce cognitive benefits.

While the positive effects of exercise permeate across a host of biological systems, over-exercising and excessive tissue loading can lead to deleterious effects and injury. The same parameters of exercise (i.e., duration, frequency, and intensity) that influence positive responses can also influence the risk of injury (Jones et al., 1994). Catastrophic failures of tissues (e.g., tendons, ligaments, and bone) occur when the ultimate loads of a tissue are exceeded. Such catastrophic injuries (e.g., patellar tendon rupture) have been reported for activities such as Olympic weightlifting (Zernicke et al., 1977), and extensive epidemiological data document the pervasive rates of knee anterior cruciate ligament (ACL) injuries in athletes (Joseph et al., 2013). ACL injuries account for over half of all knee injuries in sport (Risberg et al., 2004). In an extensive analysis of United States high school students participating in athletics—with nearly 10 million athlete-exposures during 2007–2012, Joseph et al. (2013) found that participants were seven times more likely to sustain an ACL injury in competition than in practice, and the highest ACL injury rates occurred in girls' soccer (12%) and boys' American football (11%), with the lowest rate in baseball (<1%).

Excess training and overuse can also produce significant injuries in bone (i.e., stress reactions and stress fractures). In particular, long-distance runners and military personnel are susceptible to bone stress injuries. Significant epidemiological data have been collected in both the Israel and United States armies on bone stress fractures of male and female soldiers (Friedl et al., 2008), with the data revealing 50% of women have one or more injuries by the end of basic training, including stress fractures. The high rates of exercise-related stress fractures in women—and also in men—can be linked to components of the Female Athlete Triad: (1) low energy availability with or without disordered eating, (2) menstrual dysfunction (females), and (3) low bone mineral density. Individuals can present with one or more of these Triad components (DeSouza et al., 2014). For male distance runners, Kraus et al. (2019) recently published a 7-year retrospective and prospective study of the bone stress injury rates of 156 male United States collegiate distance runners. They used applicable risk assessment categories from a "modified" Female Athlete Triad and discovered that male runners presented with risk factors for bone stress injuries that paralleled those found in female runners as described by the Female Athlete Triad, including "...low energy availability, low body mass index, prior bone stress injury, and low bone mineral density values." (p. 237). Their results highlighted the importance of optimizing nutrition and energy availability and achieving optimal body mass index to sustain and enhance skeletal health.

Recent data (Tenforde et al., 2016) revealed new insights about the relation between Female Athlete Triad Risk Assessment Stratification and the development of bone stress injuries. Tenforde et al. (2018) classified female collegiate athletes in 16 sports into low-, moderate-, and high-risk categories using the Female Athlete Triad Risk Assessment score and used those scores to compare incidence of bone stress injuries. Sports with the highest proportion of moderate- and high-risk scores included gymnastics, lacrosse, and cross-country runners, with the cross-country runners sustaining the majority of the bone stress injuries. To complement those results, Tenforde and researchers at Stanford University, Harvard University, and the University of North Carolina collectively investigated the interrelations among Triad Risk factors, sport-specific loading factors, and bone mineral density in female collegiate athletes. They analyzed data of 239 athletes across 16 different sports with a range of loading characteristics (e.g., high-impact and multidirectional vs. non-impact sports). They discovered that both sport type and Triad risk factors affected bone mineral density. Synchronized swimmers and swimmers/divers had the lowest bone mineral densities, while the highest bone mineral densities were found in gymnastics, volleyball, and basketball athletes. Athletes in non- or low-impact sports, with low body mass index, and oligomenorrhea/amenorrhea were at highest risk for reduced bone mineral density.

One of the lingering questions regarding the systems affected is whether some of these responses are interrelated (e.g., improved blood flow and cardiovascular system function associated with enhanced brain function), or the responses could reflect independent target systems that are uniquely sensitive to the mechanical stimulation associated with specific exercise regimens. Another lingering question relates to "precision health"—analyzing and integrating complex, individual-specific genetic, physiological, and environmental data to sustain health and well-being and to predict and prevent disease or optimize individual treatment and interventions. There is no doubt that different people respond to different exercise strategies. Healthy individuals vs. individuals with cardiovascular, pulmonary, and/or diabetes diseases may have varying responses to training modalities (moderate-intensity continuous exercise training vs. high-intensity interval training) (Ross et al., 2016). How specific exercise interventions and training can be personalized to each specific individual remains as a challenge to address with future research.

To achieve the above-mentioned goal will require more information and understanding regarding the mechanisms involved in responsiveness to exercise and better information regarding factors that modulate such responsiveness. There is clear evidence that sex can play a role in responsiveness to exercise at the level of the brain, with females responding more than males (reviewed in Barha et al., 2017, 2019; Dao et al., 2019). This is an interesting response pattern since most Alzheimer patients are female. Furthermore, it has been reported that some people are responders and others non-responders to both aerobic exercise and resistance training (reviewed in Sparks, 2017). In addition, the type of exercise may be critical.

Most studies have focused on aerobic exercise, but the type of exercise may be important in how a target system is affected, such as the cardiovascular system (Barha et al., 2017). This latter point implies that some of the mechanisms involved can vary, and there may not be a single molecular explanation for the effectiveness of exercise.

The molecular basis for the effectiveness of exercise in the brain is believed to relate to the brain levels of mature BDNF (brain-derived neurotrophic factor), but the results in humans are equivocal (discussed in Barha et al., 2017). Another possibility is the stimulation of myokine release from skeletal muscle following exercise (Nielsen and Pedersen, 2008, Nielsen and Pedersen, 2011, 2017; Pedersen and Febbraio, 2012; Giudice and Taylor, 2017; Eckel, 2019). Such myokines can then travel to target tissues via the circulation and affect their metabolism (**Figures 2**, **3**). Whether they affect the target tissues directly or indirectly via the microvasculature in different tissues remains to be determined. Finally, exercise may directly influence the metabolism of tissues responsive to biomechanical signals via the loading associated with the exercise (i.e., muscle, tendons, bone, ligaments, and endothelial cells of the microvasculature). Some of these tissues respond to tensile and compressive loading, while endothelial cells of the microvasculture can respond to stress-related changes associated with changes in blood flow with exercise (Ando and Kamiya, 1996; Boisseau, 2005). Some of these potential interrelations are outlined in **Figures 2**, **3**.

From the above discussion, some clues regarding the mechanisms involved in how exercise is effective have been surmised, but many questions still remain unanswered. The answers to these and related questions are difficult to untangle in populations who are restricted to living on Earth.

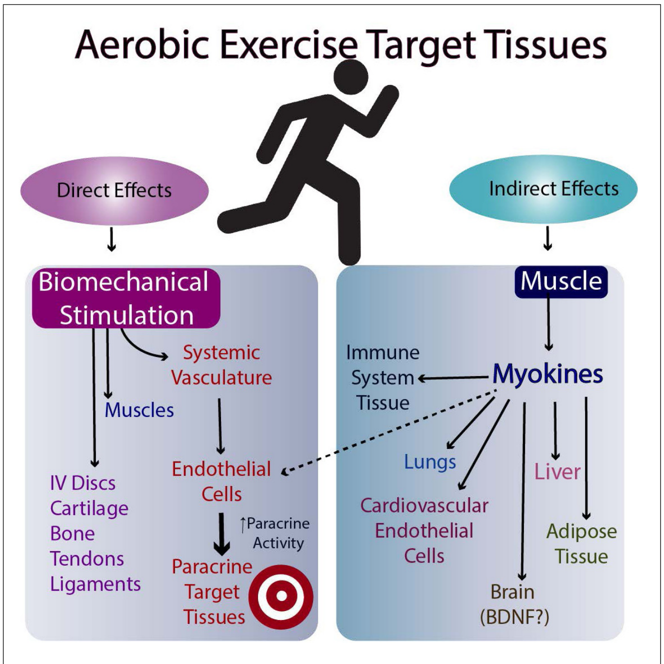

FIGURE 2 | Possible Mechanisms by which Aerobic Exercise Impacts Multiple Target Tissues.

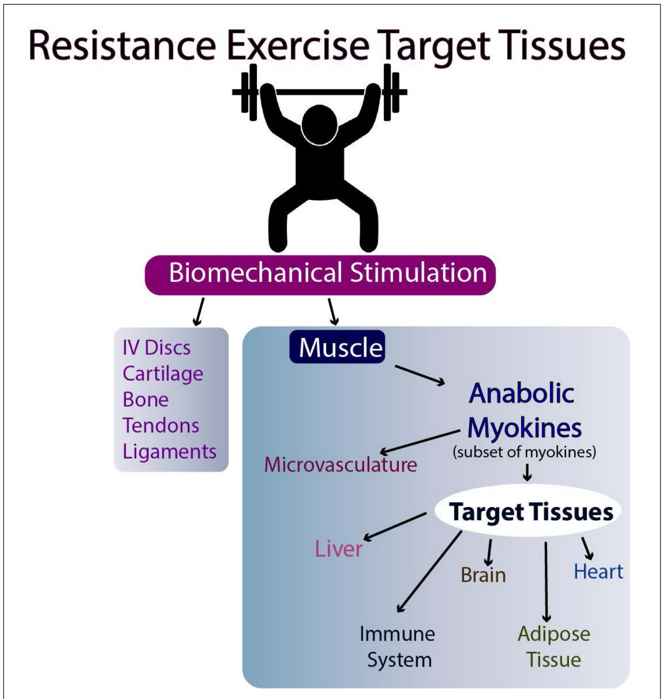

FIGURE 3 | Resistance Exercise and Effectiveness on Target Tissues.

MOBILITY AND NAVIGATION THROUGH THE ENVIRONMENT

From the preceding discussion, it is clear that mobility and mechanical loading of multiple tissues are likely intrinsic aspects of human evolution and progression to current *Homo sapiens*. However, mobility is only one aspect of functioning, with mobility and navigation (patterned mobility) integrated to contribute to survival (e.g., evading predators and hunting) and performing a multitude of tasks. Thus, navigation requires integration of mobility, vision, and neural control (brain) involvement (reviewed in Hart et al., 2019). Visual compromise with aging (e.g., cataracts, macular degeneration, or diabetic retinopathy) can inhibit function even if mobility is maintained and sustained. In addition, navigation involves other senses (e.g., hearing, smell, and touch). Recently, it was reported that diet-induced obesity in a preclinical model led to eye changes (Collins et al., 2018), and those changes could be affected, in part, by exercise. In addition, there also appears to be a link between compromise in knee integrity and the eye in other circumstances such as uveitis in juvenile idiopathic arthritis and additional links between the eye and the knee as evidenced by changes in the eye following a knee injury in preclinical models (Kydd et al., 2007); discussed in Hart, 2018b). Thus, there are multiple ways to interfere with optimal functioning related to mobility and navigation compromises due to loss of integration, which is essential for effective navigation of the organism or person.

BUILDING ON INFORMATION FROM SPACEFLIGHT-ASSOCIATED LOSS OF SYSTEM INTEGRITY

Building on the premise that optimal physiological functioning on Earth requires exercise and mobility, we posit that important and creative insights can be gleaned from space programs where exposure to microgravity or microgravity analogs generates situations diametrically opposed to exercise (i.e., loss of system integrity). Humans were not designed for microgravity environments, but the adaptive responses of humans to space flight and microgravity have the potential to reveal unique insights about the integrated responses of physiological systems to physical activity versus inactivity and explanations for why exercise is both necessary and effective to maintain health.

An often ignored reality of life is that on Earth we live in a 1g environment. During evolution, at some point, the migration from an ocean or aquatic-based environment required developing the ability to function in a 1g environment with its associated ground reaction forces (Morey-Holton, 2003). For humans, this required developing systems that allowed for upright walking and running, requirements that required an enhanced cardiovascular system, modifications to the spinal column, enhanced muscle function, and adaptations for coordinated and interactive neuro-control mechanisms from the brain to the periphery. As *Homo sapiens* represent human adaptations to this point, such adaptations allow us to function effectively in this 1g environment (Morey-Holton, 2003). Further, the implication of our Earth-related 1g adaptation is that from fetal development onward, we have been prepared for and continuously adapt to this environment during childhood and adolescence. The 1g environment is inextricably linked to regulation during maturation and in maturity, and advancing age likely impacts patterns of senescence due to subtle or overt failures of system regulation.

With the onset of human space exploration nearly six decades ago, we are now afforded the opportunity to investigate the influence of prolonged microgravity on humans. Interestingly, several of the same systems positively influenced by exercise on Earth are negatively influenced by exposure to microgravity (e.g., muscle atrophy with fatty infiltration, loss of bone quality and structure, loss of cardiovascular tone, and altered features of cognition) (Zernicke et al., 1990; Grabherr and Mast, 2010; Ploutz-Snyder et al., 2014; Ohira et al., 2015; Grimm et al., 2016; Hughson et al., 2016; Hart, 2018a). These systems, which appear to be uniquely and ubiquitously sensitive to microgravity effects, may be sentinel systems of the human body that have most effectively adapted to functioning in a 1g environment; they adhere to the use it or lose it paradigm (Scott et al., 2008; Hart and Scott, 2012; Hart, 2018a). Based on current efficacy of space-based, countermeasure attempts to overcome the negative influences of microgravity, some of the systems (e.g., skeletal muscle atrophy) are more readily responsive than others (e.g., osteopenia). Similarly, maintenance of integrated system integrity on Earth in the 1g environment is likely not based on multiple completely independent systems, but operate as highly integrated and interactive elements, with—as yet—unidentified central regulatory components. Even with chronic exposure to the 1g environment on Earth, the function and responsiveness of many of these same systems decline with age—often independently from each other. Thus, if there is a "central regulator" of these systems, some downstream components may decline with age independently—possibly due to otherwise silent mutations or epigenetic alterations. Furthermore, the regulation of these systems on Earth or in space may be sex-dependent, as several are influenced by hormones, and it is clear that regulation in females can vary across the lifespan due to events such as pregnancy and menopause. Thus, as astronauts are usually fit and free of overt chronic diseases of the systems affected by space flight, the findings of the changes associated with exposure to microgravity strongly support the notion that "Exercise is Health" and essential to maintain the integrity of the human system which evolved in the 1g environment of Earth.

THE "USE IT OR LOSE IT" PARADIGM

Even on Earth, the use it or lose it paradigm is evident. If a leg is immobilized in a cast, the muscles of that lower extremity will atrophy. Once the cast is removed and the limb is re-mobilized, the affected muscles re-adapt to a new set point. With prolonged bed rest, muscles atrophy and can become infiltrated with fat (Trudel et al., 2009). Similarly, bones can lose their integrity with prolonged bedrest, and that skeletal loss can be rapidly initiated (Kos et al., 2014). Relatedly, with bedrest, cardiovascular tone is altered, possibly involving neural control elements in ways resembling what happens in space (Hughson and Shoemaker, 2015). Thus, disuse atrophy occurs on Earth in some of the same systems as are observed to be altered in space and following exposure to microgravity.

The questions then arise as to why and how such changes occur in space and on Earth. Related to induction of atrophy, the menisci of the rabbit knee have been used as a model to better understand the involved mechanisms (Natsu-ume et al., 2005). Removing the menisci from the knee led to the rapid de-repression of a cascade of catabolic genes that could be detected within 4 h of removing the tissue from the animal. Applying intermittent cyclic compressive loading, analogous to what the tissue experiences *in vivo*, prevented the de-repression of this catabolic set of genes. Thus, a set of catabolic genes that can degrade a specific tissue were held in check by exogenous loading, such as that conveyed by ground reaction forces. Potentially, similar mechanisms apply to other tissues as well, but the genes involved may differ somewhat with different tissues; those specific differences, however, remain to be elucidated.

Conversely, loading of a tissue can also lead to up-regulation of genes that contribute to tissue integrity or healing processes. Different types of loading may be applied to a tissue (e.g., compression, shear, or tension), and cell responses can be loading-type specific (Majima et al., 2000). Vascular endothelial cells experience shear loading due to blood flow and the pulsatile nature of shear promoted by arterial forces (Koida and Hambrecht, 2005; Johnson et al., 2011). Endothelial cells experiencing loading respond to the stimuli by enhancing or suppressing production of specific molecules, and such responses influence endothelial cell functioning. Therefore, strong evidence exists at the target cell level for the how exercise and biomechanical loading may impact cells.

As noted, in space both bone and muscle can undergo atrophy and current mechanical countermeasures have proven to be reasonably effective in preventing muscle atrophy, but not as effective for bone loss. Interestingly, loss of bone while in space is more evident for bones of the lower extremities than the upper extremities (Hart, 2018a)—which are used extensively for generating contact forces by the astronauts and cosmonauts to navigate and propel themselves throughout the space station. Bones become biomechanically compromised when exposed to reduced forces and weightlessness (Zernicke et al., 1990). Therefore, the metabolic set point for bone homeostasis in an adult may depend on a bone's location in the body, and its regular and systematic exposure to exercise-related ground reaction or contact forces. Osteocytes appear to play a role in skeletal regulation and may serve mechanosensory functions in bone (Plotkin and Bellido, 2016). In space or microgravity, the integrity of osteoblasts is compromised, while osteoclasts appear to continue to function (Nabavi et al., 2011). This binary system of our skeleton may be uniquely regulated compared to other systems, and therefore, the 1g environment of Earth has led to specific evolutionary characteristics that transcend the simple use it or lose it paradigm, and thus, the need for and the impact of exercise and loading on this tissue may be essential for bone health (Grimm et al., 2016).

During a period of rapid bone growth, however, there may be loading-independent aspects to bone. That is, during growth and maturation, if a knee is immobilized by pinning in flexion, the tibia continues to grow while muscles atrophy and ligaments of the knee cease to grow and mature (Hart et al., 2002). In a rabbit model, under rigid immobilization of the knee, the tibia continued to grow at a rapid pace. When the pin was subsequently removed, the knee joint could not be extended or opened due to bone overgrowth. The extent of this dysfunction gradually diminished when the immobilization was initiated as the age of the rabbits was increased from 3 to 6 to 8 weeks (Hart et al., 2002). In this period of rapid growth by the tibia, growth continued in the absence of mechanical loading, and thus, some biological factors may override the mechanical aspects during rapid growth. It also implies that bone growth in this situation was likely the driver of growth even in the absence of the ground reaction force stimuli, and the muscles, ligaments, and likely the tendons and muscles were responding to the growth of the bone rather than progressing in a co-stimulant manner. Whether support for this concept may be associated with the second phase of accelerated growth following onset of puberty remains unclear, as this phase is complicated by the presence of sex hormones, which can exert their own impact on muscles, bone, cardiovascular system, and cognitive functioning. However, once skeletal maturity has been achieved and an integrated set point for these systems is established, homeostasis and adaptations within a physiological window are likely regulated by use and mechanical loading (e.g., exercise, ground reaction and musculoskeletal forces, and daily physical activities on Earth).

With regard to the cardiovascular system changes in space or following exposure to microgravity, it is not clear whether the changes are due to a primary effect on the cells of the system or a secondary consequence of other alterations, such as changes to fluid regulation. It is clear, however, that the system continues to function well in spite of the changes associated with space flight as the incidence of cardiovascular events in space is very low. Therefore, many aspects of how and why the changes to the cardiovascular system occur remain to be elucidated. Nonetheless, it is well-documented that exercising in space (e.g., International Space Station) can be performed effectively and with many benefits (Macias et al., 2005).

Obviously, bone, muscles, most joint tissues, and the cardiovascular system all are innervated, and some of the above regulation may be associated with neural activity. Neuromuscular control and neuroRegulation of the cardiovascular system are well recognized, and the neural input into bone regulation is also supported (Elefteriou, 2005; Masi, 2012; Dimitri and Rosen, 2017). As bone and muscle are vascularized, there are likely essential interfaces among the systems affected by exposure to microgravity. In many tissues, the neural elements parallel the microvascularity, and the microvascular elements are likely linked to other cells in a tissue in a paracrine fashion, but the relative roles of elements and their responses to microgravity outside of the 1g environment in which they develop remain to be clarified (Grabherr and Mast, 2010). As these elements appear to work as integrated units to maintain functionality, the units likely require repeated and systematic loading to maintain their integrated function.

RESPONSES TO SPACEFLIGHT AND MICROGRAVITY REPRESENT AN ACCELERATED FORM OF AGING

Many of the physiological systems most affected by space flight and exposure to microgravity are those that are frequently and adversely affected by aging processes and associated increased incidence of diseases (e.g., osteoporosis, sarcopenia, cardiovascular diseases, and cognition decline). This similarity between responses to space/microgravity and aging was noted by Ray (1991), but many details regarding potential interrelations remain to be elucidated (Vernikos and Schneider, 2010). As we noted, these same systems, or disease entities, can be impacted by exercise, and as such, exercise is often viewed as "medicine" in that context. By extension, exercise via reinforcement of these systems designed to allow humans to operate in a 1g environment—before overt disease onset—would likely be beneficial to prevent the age-associated loss of system integrity leading to overt disease. As most astronauts have been younger than 50 years of age, they have been very healthy, but mature adults. The responses to space and microgravity are specific to the individual in the extent of the changes that occur, and it is not known whether there are family history linkages to specific relevant diseases in each astronaut. Furthermore, most astronauts to date have been males, and whether the responses of females are the same remains to be confirmed (Ploutz-Snyder et al., 2014). Essentially, it is unknown why the individual astronaut's variations in response pattern exist. The changes observed and their extent may or may not be superimposed on specific genetic or epigenetic backgrounds, but this is a highly likely consideration (Hart, 2018a). Thus, under a 1g environment, silent genetic alterations may not become evident until the loading environment of living on Earth is removed by space flight or becomes evident during aging via more sedentary lifestyles. Thus, exercise and constant reinforcement of these 1g operational systems may overcome, at least in part, several genetic risk factors for disease development. As such, exercise and reinforcement of the relevant physiological systems may be particularly important during the last third of life for most individuals.

Based on the existing knowledge, much is known about **how** these systems may be regulated under Earth conditions, but we do not know a lot about **why** they are regulated in that manner, nor do we fully understand the impact of genetic and epigenetic variables on the integrity of these systems in the context of our 1g environment. Therefore, detailed analyses of individual-specific responses to microgravity and 1g during maturation and aging could provide new insights into the **why** the systems are regulated as they appear to be and identify new targets to focus on for new interventions. If these systems require constant reinforcement via exercise across the lifespan to thwart risk and maintain their integrity in *Homo sapiens*, then that could be a cost-effective approach to enhance healthy aging and mitigate health risks. Ideally that would entail having the types and doses of exercise optimized for specific physiological systems across the lifespan (Hart and Scott, 2012; Sjogaard et al., 2016) and personalized for each individual. In addition, optimal conditions will change during the different phases of life and cannot be considered constant. Similarly, what is required to maintain system integrity (e.g., threshold maintenance) versus optimizing system integrity (i.e., maximal impact) may also be different during growth, maturation, and senescence.

THE DISTINCTIONS BETWEEN EXERCISE IS HEALTH VS. EXERCISE IS MEDICINE

The preceding discussion aligns with other authors (Cheng and Mao, 2016; Sjogaard et al., 2016; Smith, 2016), who have highlighted that distinctions exist between "Exercise is Health" vs. "Exercise is Medicine." Those distinctions are not static, but are dynamically influenced by multiple factors. Firstly, for those with chronic diseases or conditions, one distinction may depend on the status of the patient's disease process when an exercise regimen is initiated. Those with early disease and modest tissue-altering pathology may respond better via interfering with the disease progression than patients that have more progressed pathology. In contrast, those with advanced disease, with associated pathological disruption of tissue integrity and more extensive epigenetic alterations, would potentially be less likely to exhibit a positive response to exercise than patients in early disease. Furthermore, the use of exercise in conjunction with suitable drugs or compounds, could provide additive or synergistic effects for the exercise component (Hart, 2018c). Secondly, if epigenetic alterations, and not just tissue disruptive pathology, are playing a critical role in the distinction between whether exercise is health vs. medicine, then it may be possible to reverse the epigenetic alterations using drugs or other interventions. While not being driven by a traditional disease process, it was noted that some of the epigenetic changes detected after a 1-year space flight were reversible after return to Earth[1] (Garrett-Bakelman et al., 2019). Thus, some epigenetic alterations to the human genome are reversible once a return to the 1g environment is established. Therefore, the distinctions between "Exercise is Health vs. Medicine" may be malleable, and there may be opportunities to shift the effectiveness of exercise for those with chronic diseases back to that of the healthy individual via interventions, which impact epigenetic alterations associated with disease.

CONCLUSION

If the proposed inverse relations are valid between the benefits of exercise and the effects of microgravity exposure on similar systems, then detailed mechanistic clues as to why exercise is health may be gleaned and could be effectively studied to elaborate new and critical insights. The most obvious conclusion is that our 1g-dependent systems require constant reinforcement to be optimized and maintained throughout life. Similar to mastering a sport or a musical instrument, practice makes perfect; these 1g-dependent systems may require regular and focused attention to maintain their integrity and effectiveness, at the levels of individual tissues and via central neural control mechanisms. Thus, the premise that "Exercise is Health" may be the preferred designation and have much of its basis in the maintenance of these 1g-dependent systems to prevent or inhibit their dysfunction or senescence (i.e., loss of system integrity with advancing age). As such, the "Exercise is Health" designation for impact on those who have not lost their health is a valid distinction from "Exercise is Medicine," which applies to those who have lost their health in an impacted system that is altered by associated pathology (e.g., epigenetics, altered cell types, and/or different cell types) and its treatment. Thus, exercise is essential to life for humans on Earth and is intrinsic to optimized and sustained system integrity across a person's lifespan.

Sedentary behavior and a lack of a minimal or reinforcing loading may allow for exercise/loading-inhibited otherwise "silent" mutations in our genomes to overcome such inhibition and contribute to senescence, and what we now label "aging related" declines in integrity.

[1] https://www.whatisepigenetics.com/epigenetic-research-space-exploration/

As such, a more apt designation for **exercise** is that it **is intrinsic to who we are,** and optimal exercise is essential to maintain and sustain integrated optimal functioning. The unique blend of independent and integrated systems influenced by exercise defines how humans evolved to thrive in Earth's 1g environment. This perspective is supported by Pontzer (2019), who discussed the role of exercise in human physiology as *Homo sapiens* evolved from great-ape lineages. Detailed investigation of how these 1g-related systems work, where they are controlled, and how they are regulated (and inter-regulated) by exercise and mobility may provide unique and significant new clues for maintaining optimal health and mitigating risks for loss of health.

AUTHOR CONTRIBUTIONS

DH wrote the initial draft of the review, and then both authors contributed equally to its further development and finalization.

FUNDING

Financial support from the Canadian Space Agency and the Alberta Health Services Strategic Clinical Network Program support to DH, and the Canadian Institutes of Health Research, National Institutes of Health, National Aeronautical and Space Administration, and University of Michigan support to RZ are gratefully acknowledged.

ACKNOWLEDGMENTS

The authors thank Dr. Nicole Buckley (Canadian Space Agency), Dr. Richard Hughson (University of Waterloo), Drs. Cyril Frank, Nigel Shrive, Walter Herzog, and Raylene Reimer (University of Calgary), Drs. Alex Scott and Karim Khan (University of British Columbia), Dr. Robert Thirsk (former Canadian astronaut), and several other colleagues and students for many interesting discussions regarding some of the topics discussed.

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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.

frontiers in Physiology

SYSTEMATIC REVIEW
published: 06 March 2020
doi: 10.3389/fphys.2020.00167

The Relationship Between Non-elite Sporting Activity and Calcaneal Bone Density in Adolescents and Young Adults: A Narrative Systematic Review

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Introduction: Osteoporotic fractures represent a major public health burden. The risk of fragility fractures in late adulthood is strongly impacted by peak bone mass acquisition by the third decade. Weight-bearing sporting activity may be beneficial to peak bone mass accrual, but previous studies have focused on elite sporting activity and have used dual energy X-ray absorptiometry as a measure of bone density. The authors performed a narrative systematic review of individual sports (performed non-competitively or at local level) and calcaneal quantitative ultrasound (cQUS) bone measures in young people.

Methods: Multiple databases were systematically searched up until the 31st of March 2019. The authors included studies of participants' mean age (11–35 years), reporting any level of recreational sporting activity and cQUS measures as well as excluding elite/professional sporting physical activity. Studies (title and abstract) were screened independently by two reviewers, and a third reviewer resolved any discrepancies. STROBE guidelines were used to check the reporting of observational studies. The Newcastle–Ottawa Scale was used to assess the risk of bias of the studies included in the review. The systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO).

Results: A search yielded 29,512 articles that considered relationships between bone density assessed by any technique and sporting activity. Duplicate and out of scope abstracts were removed. This left 424 papers that were screened by two reviewers; of these, six met the inclusion criteria, including assessment by cQUS. The authors identified papers where sports were considered, included soccer (football), swimming, cycling, gymnastics, dancing, badminton, basketball, fencing, wrestling, and judokas. Although study heterogeneity prohibited meta-analysis, all six included studies reported significant benefits of weight-bearing non-elite sports on cQUS outcomes.

Conclusion: Our study found beneficial effects of non-elite sports participation on cQUS in adolescence and young adulthood, although further work is now indicated.

Keywords: calcaneal quantitative ultrasound (cQUS), adolescent, sport, bone, systematic review

OPEN ACCESS

Edited by:
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University of Calgary, Canada

Reviewed by:
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University of Calgary, Canada
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São Paulo State University-UNESP, Brazil

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Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *18 October 2019*
Accepted: *13 February 2020*
Published: *06 March 2020*

Citation:
Patel H, Sammut L, Denison H, Teesdale-Spittle P and Dennison E (2020) The Relationship Between Non-elite Sporting Activity and Calcaneal Bone Density in Adolescents and Young Adults: A Narrative Systematic Review. Front. Physiol. 11:167. doi: 10.3389/fphys.2020.00167

INTRODUCTION

Osteoporosis is a major international public health problem through its association with fragility fractures (Cole et al., 2008). Osteoporosis is often described as a disease that occurs when one becomes older, more often in females, and preventative methods thus often focus on older people (Tan et al., 2014). However, childhood and adolescence are critical periods of bone development; modifiable lifestyle behaviors have a major impact on the development of bones throughout life, and peak bone mass (PBM) is a major determinant of later fracture risk (Hernandez et al., 2003). Previous studies have suggested that physical activity (PA) and dietary calcium intake during childhood and adolescence play a critical, synergistic role (Weaver et al., 2016). There are, however, a limited number of studies that have looked at the impact of participation in individual non-elite sports on bone health at the calcaneum in young people, with most studies focusing on the effect of elite sporting activity or organized sports on bone health as assessed using ionizing methods, such as dual energy X-ray absorptiometry (DXA) (Tan et al., 2014).

A number of previous systematic reviews have considered the relationship between sporting activity and bone health in this age group, but they have studied associations between dual energy X-ray absorptiometry (DXA) and sporting activity. The effect of sporting activity varied according to sex; the skeletal sites and bone outcomes were measured as assessed by DXA and peripheral quantitative computed tomography (pQCT), which gives an estimate of volumetric bone density and other assessments of bone strength at relevant sites, including the calcaneus (Zulfarina et al., 2016). Tan et al.'s (2014) systematic review assessed PA and bone strength: the findings indicated that bone strength modifications due to PA were related to maturity level, sex, and study quality. A review by Hind and Burrows (2007) reported that weight-bearing exercise enhanced bone mineral accrual during early puberty, but it was unclear which form of exercise was the most beneficial. Meanwhile, Nikander's et al. (2010) systematic review of targeted exercise for optimizing bone strength throughout life supported the use of exercise to develop bone strength in children at weight-bearing sites.

Overall, previous studies that aimed to understand the relationship between sport in young people and bone health used ionizing imaging tools, such as DXA (Morris et al., 2000; Matthews et al., 2006; Deere et al., 2012; Ito et al., 2017; Júnior et al., 2017; McVeigh et al., 2019). There has been an increasing interest in the use of heel ultrasound as an alternative assessment of bone density, which also provides structural information of bones. Ultrasound technology is a non-invasive, widely available, low-cost, and portable tool that provides an assessment of bone density and quality at a readily accessible weight-bearing site with high trabecular bone content (GE Medical Systems Lunar, 2010). Ultrasound technology has been shown to be associated with fragility fractures in older adults (Krieg et al., 2008). In addition, Hans et al.'s study's suggests there is potential to use QUS when DXA is unavailable to assess bone health (Hans and Baim, 2017). The aim of this review was therefore to assess the relationship between non-elite sporting activity and bone density, as assessed by heel ultrasound in adolescents and young adults, through a systematic search and a narrative synthesis.

METHODS

The systematic review study protocol is registered with the International Prospective Register of Systematic Reviews under the Registration number CRD42018080101 (Centre for Reviews and Dissemination, 2009). The initial protocol described reviewing the association between non-elite sporting activity and bone density, with the latter being assessed using any bone measurement method. While the search and screening process adhered to this, the authors of the current paper only included studies that had assessed bone density through cQUS. This was a pragmatic decision based on the number of studies identified. The additional data retrieved will be used in a separate report on relationships between DXA and elite sporting activities.

An electronic search of PubMed/Medline, Proquest, AUSPORT, Ausport Med, and Medline (Ovid) proceeded until the 31st of March 2019 to source the relevant articles under review (see **Table 1** for a summary of search strings used).

Observational studies were the main type of study for inclusion; however, if baseline data could be extracted from trial/interventional studies, these were also included. Only full-text, peer-reviewed journal articles published in English, unless they could be translated fully using Google Translate, were included (Google, 2019). There were no limitations on sample size or country of origin.

Participants, Interventions, and Comparators

The following search strategy was applied:

(1) Exposure: Non-elite participation in sporting activity performed at school or leisure time as an organized or regular activity—either self-reported or measured objectively. Participation in any type of sporting physical activity (quantitative studies).

TABLE 1 | Summary of search strings used.

(sport OR sport* OR exercise OR exercis* OR physical OR soccer OR football OR rugby OR athlet* OR swimming OR tennis OR gym* OR basketball OR "martial art" OR boxing OR cycling OR recreation OR cricket OR hockey OR Ball or golf OR badminton OR cycling OR wrestling)
AND
(bone AND health) OR (bone AND mass AND density) OR DXA OR DEXA OR BMD OR BMC OR SOS OR BUA OR SI OR (hip OR spine OR heel) AND ultrasound
AND
(adolescent OR child OR girl OR boy OR juvenile OR teen* OR young OR people OR student OR youth OR minor OR college OR school OR paed* OR pedia*)
Include: Synonyms, related terms, opposites, international terms, alternative spellings, plurals, truncations and wildcards (* or $ or # to substitute for one character within a word), and proximity operators NEAR, NEXT, ADJ.

(2) Outcome: Any bone heel ultrasound measures, such as speed of sound (SOS)/velocity of sound (VOS), broadband ultrasonic attenuation (BUA), stiffness index (SI)/quantitative ultrasound index (QUI).
(3) Population

- Inclusions: The age of study participants was mean age 11–35 inclusive. Both sexes were included. Participation in named sporting activity at a local or regional level.
- Exclusions: Those with long-term disease or health issues, such as physical/mental disability, that directly affect bone health through treatment, supplementation, or medication were excluded. Animal studies were excluded. Any participation in competition(s) at an elite or national level was also considered an exclusion, although typically elite sport is considered sport participation at a higher levels, such as at division I and professional levels (Lorenz et al., 2013; Bellver et al., 2019).

Two independent reviewers (HP and LS) screened the abstracts and titles of relevant reports and articles in duplicate to determine whether these met the given criteria for inclusion in the systematic review. Any discrepancies were resolved through discussion or with a third reviewer (ED). Then, the reviewers independently screened the articles identified from the title and abstract screening to determine whether they met the inclusion criteria for the review, and a third reviewer's (ED) agreement was sought where appropriate. Where feasible, study authors were contacted by email for completeness and clarity. For those articles and reports meeting the inclusion criteria, their reference lists and bibliographies were screened for any additional relevant studies to be included in the systematic review.

Methodological Assessment: Data Extraction and Presentation of Study Results

The review is reported using the guidelines Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher et al., 2009).

Risk of Bias in the Included Studies

The STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines were used to check the reporting of observational studies (Vandenbroucke et al., 2007). The descriptive information of each study was extracted and summarized in **Table 2**. To assess the quality of the methods used in the selected studies, the Newcastle-Ottawa Scale (NOS) risk of bias assessment tool was used (Wells et al., 2019).

RESULTS

Study Selection

Figure 1 shows a flowchart of the literature search and the study selection process. The search yielded a reference list of a total of 37,042 articles. Duplicates were removed, leaving 29,512 articles to be screened by two independent reviewers. Based on the titles and abstracts, 29,090 articles were excluded, primarily because they did not use cQUS as a measure of assessment of bone outcomes. This left 424 papers to be assessed in full where available; the reviewers were unable to obtain the full manuscript for the study performed by Coaccioli et al. (2013) despite attempts that included a direct approach to the authors. In addition, the reviewers were unable to obtain a full translation from Chinese of a study by Qian (2017). As such, those two studies were excluded. Following full text screening, a total of six studies remained as meeting the inclusion criteria for this systematic review. The sports identified from this process were soccer, swimming, cycling, gymnastics, dancing, badminton, basketball, fencing, wrestling, and judokas (see **Table 2**).

Risk of Bias Assessment

Using the NOS risk of bias assessment tool (Wells et al., 2019), the risk of bias of the six articles included in this systematic review was generally assessed as low to moderate, with one of the studies assessed as having a high risk of bias (see **Table 3**). The main area of bias identified was in the recruitment process of the studies; most studies failed to clearly indicate how the sample size calculation of the study was approached and how and why participants were invited to participate in the study. Some articles failed to report how many participants were approached to participate in the studies and why they were selected or not screened for the studies.

The bias assessment tool indicated that three of the included studies (Gomez-Bruton et al., Vlachopoulos et al., and Nurmi-Lawton et al.) had low bias with clear study designs. Additionally, confounding factors, such as diet and PA, were acknowledged, and a detailed dietary assessment was available, and face to face interviews for PA were also carried out (Nurmi-Lawton et al., 2004; Gomez-Bruton et al., 2015; Vlachopoulos et al., 2018). Of the studies with moderate bias, Yung et al.'s study had small sample numbers in each of the four groups ($n = 15$) as well as limited details of recruitment (Yung et al., 2005). Yung et al.'s study performed a questionnaire that assessed the PA and diet of participants, and Madic et al.'s study was also assessed as moderate bias due the limitations of recruitment details and lack of dietary and PA assessment. Meanwhile, Mentzel et al.'s study was assessed as high bias due to reduced clarity of the level and intensity participants' different sports activities (Mentzel et al., 2005; Yung et al., 2005; Madic et al., 2010).

Study Designs and Participant Characteristics

The studies extracted were too heterogeneous to allow for meta-analysis. A graphical display of the results and a summary of the key characteristics of the studies included in the review, along with a synthesis of the studies in a narrative form, is presented in **Table 2**. The sporting activity referred to in these studies included soccer, swimming, cycling, gymnastics, dancing and, to a limited degree, badminton, basketball, fencing, wrestling, and judokas.

Of note, the level of activity in the control groups was very different across the included studies. Vlachopoulos et al.'s study compared 116 young Caucasian male adolescents undertaking regular swimming, soccer, or cycling sports with active controls (including identifying participants that participated in other sports or swimming, soccer, or cycling for fewer than 3 h weekly) (Vlachopoulos et al., 2018). Gomez-Bruton et al.'s Spanish mixed gender cross-sectional study of 129 Caucasian

TABLE 2 | Key study characteristics.

Author/Country Setting	Type of study	Study size Population sport	Sports activity	Comparator/Controls	Bone measure & site	cQUS imaging tool	Key findings
Vlachopoulos et al. (2018) England Sport Clubs and schools	Longitudinal (PRO-BONE study)	Total $n = 116$ Caucasian males	Sport (swimming, soccer, cycling) duration >3 years	Controls: no sport like soccer, swimming or cycling for more 3 h/week nor 3 years prior	QUS heel mean of both feet, measured twice	Lunar Achilles Insight (TM Insight GE Healthcare), Milwaukee, WI, USA).	12 months football participation associated better SI than for cycling or swimming
		Aged 13.1 ± 0.1	Actual average years of training ranged from 3.9 to 5.9 years		SI only		
		$n = 37$ footballers	Actual average hours of training per week ranged from 5.2 to 9.4 h				
		$n = 37$ swimmers	Actual average MVPA(min/day) ranged from 85.0 to 119.8	Actual average MVPA(min/day) ∼83.2			
		$n = 28$ cyclists					
		$n = 14$ active controls					
Gomez-Bruton Spain Clubs and high schools	Cross-sectional study within a larger randomized controlled trial	Total $n = 129$ Caucasian males & females	Sport (swimming) duration >3 years, minimum of 6 h/week	Controls: normo-active with no participation in sports like swimming or aquatics regularly and no sporting activities more 3 h/week	QUS heel (non-dominant)	Lunar Achilles Insight (Achilles Insight, GE Health-care), Diegem, Belgium	cQUS results showed no significant differences between swimmers and controls;
		Aged 11–18	Competing in regional tournaments		SI, SOS, BUA		
		$n = 77$ swimmers (34 females/43 males)					
		$n = 52$ normoactive controls (23 females/29 males)					
Madic et al. Serbia Schools	Observational	Total $n = 62$ male soccer players	Sport duration >1 year	Control 90 min of PA/week at school	Both heels QUS	Sahara (Hologic, Inc., MA, USA) sonometer	Higher BUA and SOS Soccer players than controls
		Aged 10–12			SOS Left and right		
		$n = 32$ soccer	Actual average hours of training per week ranged from 10 to 15 h		BUA Left and right		
		$n = 30$ control regular school PA					
Yung et al. China Local university students	Cross sectional study	Total $n = 55$ Chinese male university students	Sport (swimming, dancing, soccer) duration >2 years; at least twice week for at least 2 h	Control no exercise (sedentary control)	QUS heel dominant and non-dominant heel measured, analysis on dominant heel	Paris, Norland Medical System, Fort Atkinson, WI, USA	All QUS parameters showed a significant linear increasing with the weight bearing and high impact exercise
		Aged 18–22			VOS, BUA, SI		BUA, VOS, SI Soccer players > dancers > swimmers > sedentary control group

(Continued)

TABLE 2 | Continued

Author/Country Setting	Type of study	Study size Population Sport	Sports Activity	Comparator/Controls	Bone Measure & Site	cQUS Imaging Tool	Key findings
		$n = 15$ soccer					
		$n = 10$ dancing					
		$n = 15$ swimming					
		n = 15 no exercise/sedentary control group					
Mentzel et al. Germany Regional sports schools	Cross-sectional study	Total $n = 177$ sportspeople, of which three participants excluded because of lower limb fracture	Sport duration undetermined; two training sessions/week of at least 90 min	Reference population used (age, size, and gender related)	Both heel (mean) QUS	Sahara (Hologic, Inc., Waltham, MA, USA) sonar	
		Aged 11–18 ($n = 121$ boys; $n = 56$ girls)			SOS (SDS) and BUA (SDS)		
		$n = 43$ athletes					For the level of activity: significant correlation to BUA only judokas and wrestlers
		$n = 38$ soccer players					For training sessions: SOS low negative correlation and BUA-positive correlation
		$n = 12$ badminton players					
		$n = 7$ basketball players					
		$n = 8$ gymnastics					
		$n = 18$ fencers					
		$n = 16$ wrestlers					
		$n = 29$ Judokas players					
		$n = 1$ tennis, $n = 1$ triathlon, $n = 1$ weight training					
Nurmi-Lawton England Clubs	Mixed longitudinal 3 years/cross-sectional for mothers	Total $n = 97$ females	Sport duration average for 6 years, two or more 90-min training sessions weekly; trained >10 h/week; competed at club or regional level	Normo-active sedentary controls including walking to school and attended school PE classes	QUS heel	Contact Ultra-Sound Bone Analyser (CUBA; McCue Ultrasonic Ltd., Winchester, UK)	Gymnasts had up to 24–51% higher BMC and 13–28% higher BMD, depending on skeletal site than controls.
		Age Baseline 8–17 years of age			Mean of both feet, measured twice		
		$n = 45$ gymnasts		No sports training requiring year-round training; included two competitive swimmers as they were engaged in an activity the authors considered non-weight-bearing			
		$n = 52$ controls					

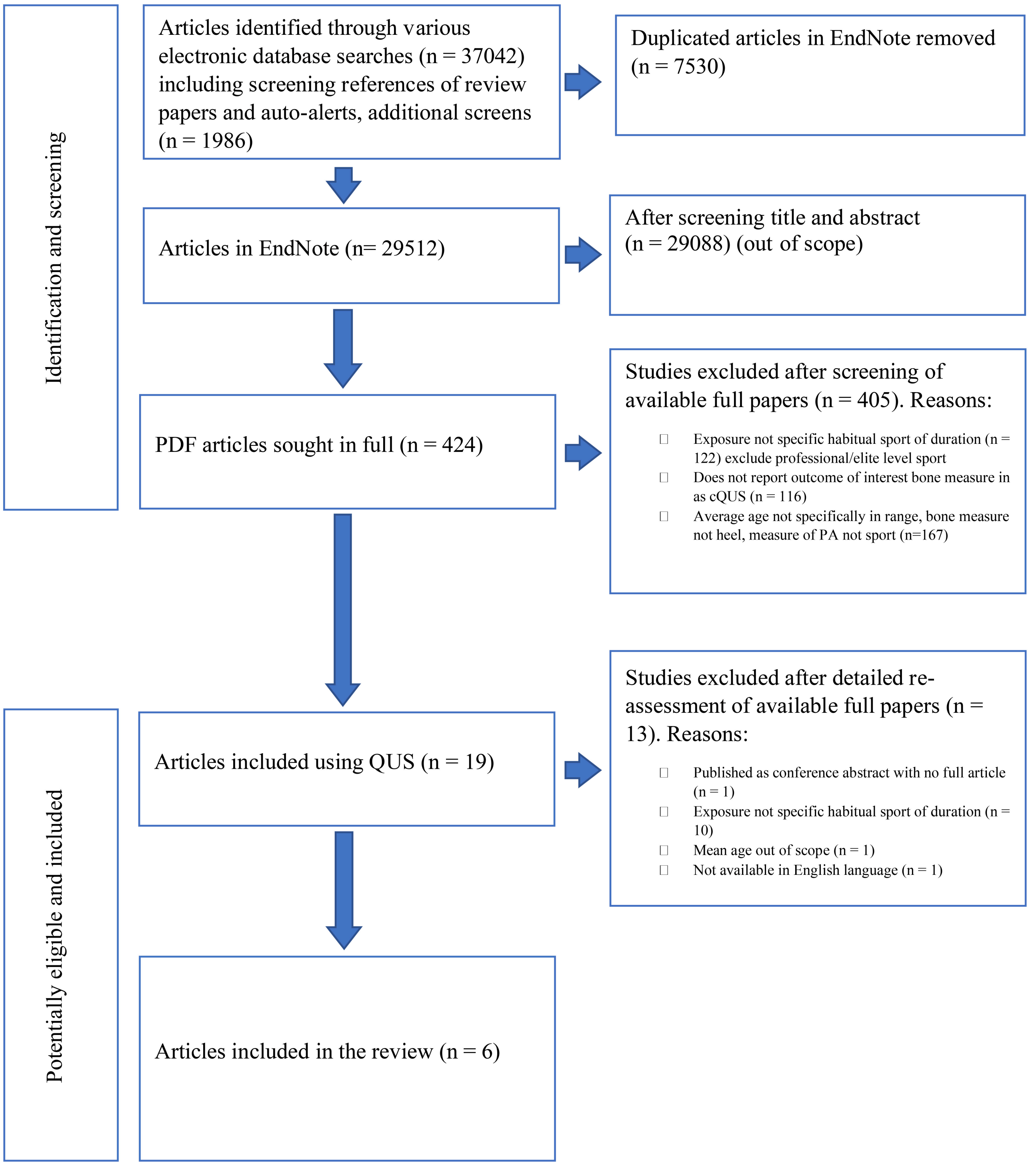

FIGURE 1 | Flowchart of the literature search and the study selection process.

children was part of a much larger controlled trial. The study compared the bone health of swimmers who competed at regional swimming tournaments at the start of the study with normally active control children who did other sports for fewer than 3 h a week and did not participate in other aquatic sports (Gomez-Bruton et al., 2015). In Madic et al.'s Serbian study of 62 participants, male soccer players were compared to controls who participated in regular school based sporting activity only (Madic et al., 2010). Yung et al.'s study of 55 Chinese male university students compared the bone effects of weight-bearing sports of

TABLE 3 | Risk of bias (NOS).

NOS tool	Yung et al.	Nurmi-Lawton et al.	Gomez-Bruton et al.	Mentzel et al.	Madic et al.	Vlachopulos et al.
How well-described is recruitment of the exposed group?	Chinese University students—numbers approached not stated	Gymnasts recruited from five clubs—numbers approached not stated	Source of recruits was local swimming clubs and numbers approached/recruited provided	Recruited from College of Physical education—numbers approached not stated	Unclear—numbers approached not stated	Provided in separate referenced article; sports recruited were swimming/ football/cycling. Recruits came from sports club and schools
How were the exposed group selected?	At least 4 h sport each week for at least 2 years; different sports described	At least 10 h per week and competing in competitions.	Swimmers training for at least 3 years, training for a minimum of 6 h per week. Group subdivided according to whether participants were also training in another sport	At least 90 min per week	Soccer training for 10–15 h weekly for at least 1 year	Training for over 3 h per week for 3 or more years. Level of training provided for cases
How well-described is recruitment of the control group?	Chinese University students	Local schools; taking part in PE lessons only though 2 were competitive swimmers	Source of recruits was local schools and numbers approached/ recruited provided. Could not be doing any sport for more than 3 h per week	Used local reference data—exposure to sport in this group was unclear	"Not engaged in active sport." Other details not provided	Provided in separate referenced article
Length of exposure to sporting activity	Variable between duration and time/week in different sports. Typically 2–3 years, range 7–15 h per week	Training for range of 2–12 years; average 6.5 years	At least 3 years	Unclear	At least 1 year	Range 4–6 years
Information on important confounders	Provided	Provided	Provided	Unclear	Unclear	Provided
Overall risk of bias	Moderate	Low	Low	High	Moderate	Low

swimmers, dancers, and soccer players by contrasting players with a sedentary control group of students who did not exercise (Yung et al., 2005). Mentzel et al.'s German study was a mixed study of 177 boys and girls from regional sports schools with various sports backgrounds whose bone health was compared against a reference population. The study presented limited details on how the levels of activity were assessed (Mentzel et al., 2005). Finally, Nurmi-Lawton et al.'s English study compared 97 female gymnasts and normally active controls (the controls did not participate in high impact sports for the past year at a competitive level, although two of the controls were competitive swimmers) (Nurmi-Lawton et al., 2004).

The six studies included in this review had a sample size that ranged from 55 to 177 participants. Five of the six studies included in this review studied school-aged children, with the study participants recruited from schools or sports clubs (Nurmi-Lawton et al., 2004; Mentzel et al., 2005; Madic et al., 2010; Gomez-Bruton et al., 2015; Vlachopoulos et al., 2018). The remaining study recruited students from their local university (Yung et al., 2005). The inclusion criteria varied amongst the six studies, with the main criteria being healthy children or adolescents with a reported sport history. General exclusion criteria in the studies included a history of chronic or musculoskeletal disease and taking medication that affected bone metabolism. Gomez-Bruton et al., Mentzel et al., and Vlachopoulos et al. specifically stated that participants with a known fracture history were excluded (Mentzel et al., 2005; Gomez-Bruton et al., 2015; Vlachopoulos et al., 2018). Mentzel et al.'s study also excluded children with a small shoe size participants that missed appointments (drop-outs), or participants that could not be located (Mentzel et al., 2005).

The mean age of participants in the studies included in this systematic review were between 11 and 22 years. Pubertal status was considered in the studies by Madic et al. (2010), Gomez-Bruton et al. (2015), and Vlachopoulos et al. (2018). None of the reviewed articles included the upper age range from 23 to 35. Collectively, 210 females and 426 males were included in this systematic review. One study included females only (Nurmi-Lawton et al., 2004), three studies included males only (Yung et al., 2005; Madic et al., 2010; Vlachopoulos et al., 2018), and two studies included both male and female participants (Mentzel et al., 2005; Gomez-Bruton et al., 2015). The ethnicity of the study participants was clearly stated in four of the six studies. Two studies recruited those who were of white healthy Caucasian ethnicity only (Gomez-Bruton et al., 2015; Vlachopoulos et al., 2018). The third study declared all the participants were white except for one participant in their study (Nurmi-Lawton et al., 2004), while the fourth study exclusively recruited Chinese university students (Yung et al., 2005). The Serbian and German studies did not state the study participants' ethnicity but, for the purposes of this review, the authors assumed their ethnicity based on each study's locality (Mentzel et al., 2005; Madic et al., 2010).

Nutrition was acknowledged as a factor of bone health in all six studies: four of the six studies completed some form of dietary analysis (Nurmi-Lawton et al., 2004; Yung et al., 2005; Gomez-Bruton et al., 2015; Vlachopoulos et al., 2018). A trained researcher helped participants complete a calcium frequency questionnaire in Gomez-Bruton et al.'s study (Gomez-Bruton et al., 2015). Yung's university students completed a 7-day recall for the participant's usual calcium intake (Yung et al., 2005). Similarly, Nurmi-Lawton et al.'s longitudinal study used regular estimated food diaries for the duration of this study (Nurmi-Lawton et al., 2004). Vlachoppoulos et al.'s study stated that one of its limitations was the lack of nutrition-related covariates in the analysis despite the fact that data was collected for the study (Vlachopoulos et al., 2018).

Assessment Tool

The cQUS tools used included Lunar Achilles Insight (used in two studies), Sahara Hologic (used in two studies), Heel ultrasound densitometer Paris (Norland), Contact Ultrasound Bone Analyser, and Lunar Achilles Insight (TM Insight GE Healthcare, Milwaukee, WI, USA with OsteoReport PC (software version 5 GE Healthcare) (see **Table 2**). There was considerable variability in the bone measurements taken and the level of detail in the description of methods used to perform the measurements. All the papers employed statistical analysis using SPSS. The six study results were all presented *a priori* with $p < 0.05$ being considered statistically significant, but, due to the heterogeneity of the tools and methods employed, output values were not directly comparable.

Sports Participation—Duration and Intensity

The sports measured in this review included soccer, swimming, cycling, dancing, badminton, basketball, gymnastics, fencing, wrestling, and judokas. Lack of comparability of intensity of sports training and duration of involvement in regular sport made it hard to draw comparisons between studies. For example, in Vlachopoulos et al.'s study, athletic sports male participants at baseline had been engaged (≥3 h/week) in osteogenic (soccer) and/or non-osteogenic (swimming and cycling) sports for the previous 3 years or more (Vlachopoulos et al., 2018). Average years of training ranged from 3.9 to 5.9 years (Vlachopoulos et al., 2018). By contrast, Gomez-Bruton et al.'s study assessed swimming training in both girls and boys who had a previous history of swimming and competing in regional tournaments for more than 3 years and training for a minimum of 6 h per week (Gomez-Bruton et al., 2015). The inclusion criteria for this study was that participants had to have been training on a regular basis in a sport (cycling was not included) for more than 3 h per week for at least 3 years prior to the study. The swimmers were divided into those who were considered as pure swimmers, who had only participated in other sports for 1 or 2 years, and other swimmers, who were classified as participants in other sports for more than 2 h per week and/or other sports for a period of more than 2 years prior to the study (Gomez-Bruton et al., 2015). Madic et al.'s study on boys' soccer activity required that participants had a sport history of a minimum 1 year of active sports occupation in soccer with weekly training sessions of typically lasting up to 10–15 h (Madic et al., 2010). Yung et al.'s male university students were categorized by main sporting activity from high to low impact weight bearing and non-weight bearing exercises (soccer, dancing, swimming, and no exercise) (Yung et al., 2005). This exercise group of participants had to be engaged in supervised training in either soccer or dancing or swimming for at least 2 years twice a week for at least 2-h sessions (Yung et al., 2005). Mentzel et al.'s study with both boys and girls included eight sporting activities: soccer, badminton, basketball, gymnastics, fencing, wrestling, and judokas (as only one child each represented tennis, triathlon, and weight-training and, therefore, those sporting activities were not included in the analysis) (Mentzel et al., 2005). Sport participants had two or more 90-min training sessions weekly at the start of the study; past and current sporting activity details of participants were not stated (Mentzel et al., 2005). Finally, Nurmi-Lawton et al. studied female artistic gymnasts who had trained 2 or more years with more than 10 h of weekly training and had competed at club or regional level (Nurmi-Lawton et al., 2004).

The studies were not comparable for many reasons, including the duration and intensity of sporting activity of participants. For example, the athletes in Mentzel et al.'s study potential activity levels of the sporting participants could potentially be equated to Vlachopoulos et al.'s and Gomez-Bruton et al.'s control group (Mentzel et al., 2005; Gomez-Bruton et al., 2015; Vlachopoulos et al., 2018).

Comparator (Control) Groups Activity Level

The details provided in the six studies for the comparator (controls) measurement for potential past sporting history and other physical activities (which may have impacted the bone measurements) was often lacking and was too heterogeneous to compare across the studies.

Vlachopoulos et al.'s study of athletic sports compared osteogenic soccer against non-osteogenic sports (swimming and cycling) with a small control group of 14 active boys who did not participate in any sports (soccer, swimming, or cycling) for more than 3 h per week or in the 3 years prior to the start of the study (Vlachopoulos et al., 2018). Gomez-Bruton et al.'s study of swimmers were compared with a control group who had neither performed in any aquatic sports on a regular basis nor participated in any other sport activity for more than 3 h a week (Gomez-Bruton et al., 2015). Madic et al.'s study on boys' soccer activity was compared to that of young boys not actively engaged in sport, aside from 90 min per week of PA at school (Madic et al., 2010). Yung et al.'s university male athletes were compared to a sedentary group who did not participate in exercise (Yung et al., 2005). In the study by Mentzel et al. (2005), athletes were compared to local reference data of 3,299 healthy Caucasian children and adolescents obtained from an earlier study by the same author. The two studies used the same conditions and same device, although details of the reference population's past sports history or PA level was not reported (Wunsche et al., 2000). Nurmi-Lawton et al.'s gymnasts were compared to controls who were involved in normal activities (including walking to school and physical education classes at school) for an average of

2.6 h weekly and not engaged in sports that required all year training at competition level (Nurmi-Lawton et al., 2004). The potential sporting activity levels of the control participants from Vlachopoulos et al.'s and Gomez-Bruton et al.'s studies, which reached a maximum of 3 h per week, may potentially equate to the sporting activity of Mentzel et al.'s participants, as this study included participants from a sports college that trained less than participants in other studies (Mentzel et al., 2005; Gomez-Bruton et al., 2015; Vlachopoulos et al., 2018).

Bone Measurement Results

Overall, high-impact weight-bearing sports, such as soccer playing and gymnastics or dancing, were associated with the greatest benefits for bone health (**Table 2**). Swimmers and cyclists were not at any apparent bone advantage compared to controls. Hence Madic et al.'s study of male soccer players reported significant differences in cQUS between soccer players and controls (Madic et al., 2010). Yung et al.'s study found weight-bearing and high-impact exercise to be associated with higher QUS parameters. In particular, soccer players and dancers had significantly greater BUA, VOS, and SI than swimmers and the sedentary control group (Yung et al., 2005). In Vlachopoulos et al.'s study, soccer players had statistically greater cQUS ultrasound parameter SI compared to swimmers, cyclists, and controls at baseline (Vlachopoulos et al., 2018).

Similarly, Gomez-Bruton et al.'s gender study compared swimmers with controls and found no significant differences in any cQUS parameters when measuring the non-dominant calcaneus between any of the groups (Gomez-Bruton et al., 2015). In the only study to compare a very wide range of sporting activities, and with attendant power considerations for that reason, Mentzel et al.'s study showed significant differences between cQUS SOS and BUA between the sports students (a mixed gender study of 177 children aged 11–18) and the reference group. Although direct sporting comparisons were more challenging, the authors reported higher SOS values in athletes than wrestlers, in basketball players than fencers, in basketball players than wrestlers, and in gymnasts compared with judokas sports players (Mentzel et al., 2005).

Some studies investigated the level (or impact) of weight-bearing activity and bone health. While Mentzel et al.'s study did not observe strong correlations between increased weight-bearing activity in basketball ($n = 7$) and bone health, this may be reflective of the very small sample size and lower study power (Mentzel et al., 2005). As such, the authors consider that the results of Mentzel et al.'s study should be interpreted with caution (Mentzel et al., 2005). In Mentzel et al.'s study, judokas players and wrestlers showed a significant positive correlation between heel BUA vs. level of activity (Mentzel et al., 2005). Further, when considering age related SOS as an outcome, significant differences were shown between badminton players and gymnasts, between basketball players and fencers, as well as between judokas players and gymnasts (Mentzel et al., 2005). Finally, one study considered body build in more athletic young people; Numri-Lawton et al.'s study of gymnasts revealed that the gymnasts were smaller and lighter than controls, but they still had significantly higher QUSs (Nurmi-Lawton et al., 2004).

DISCUSSION

In contrast to many other reviews, this review focused only on specific non-elite sporting activity performed at a non-competitive level in young people as assessed by calcaneal ultrasound. The quality of the six articles was generally assessed as moderate quality, though variability was present, and methodological differences prevented a meta-analysis.

The overall aim of the six studies was to investigate the effects of different non-elite sporting activities, some of which were classified as weight-bearing and non-weight-bearing non-elite sporting activities of different intensities on bone mineral accrual in adolescence and early adulthood. The studies were heterogenous, but a consistent pattern emerged. Vlachopoulos et al. showed that boys playing soccer produced had better bone heel ultrasound outcomes than those who participated in cycling or swimming (Vlachopoulos et al., 2018). Similarly, Nurmi-Lawton et al. showed that female gymnasts had significantly higher bone density than controls (Nurmi-Lawton et al., 2004). Gomez-Bruton et al.'s study indicated there were no differences found in QUS parameters between swimmers and controls (both male and female) (Gomez-Bruton et al., 2015). Madic et al.'s study of male soccer players reported significant higher QUS values compared to controls (Madic et al., 2010). Mentzel et al.'s comparison of those children involved in sports found the QUS (SOS and BUA) parameters were significantly higher in sport participants engaged in weight-bearing activities compared to the reference data (Mentzel et al., 2005). Yung et al.'s study indicated a linear increase in all QUS measures as weight-bearing activity increased (Yung et al., 2005). In general, the six studies suggested that weight-bearing non-elite sporting activity was associated with higher QUS, and that some dose effect was reported with greater levels of sporting activity (frequency and duration).

Weight-bearing physical activity is thought to stimulate bone formation and thus improve bone mineral density (BMD) by exposing the skeleton to mechanical strain, provided that it is performed at a high enough frequency and high impact intensity (as evident in the studies that included swimmers or cyclists who had similar cQUS results to their comparative controls) (Yung et al., 2005; Gomez-Bruton et al., 2015; Vlachopoulos et al., 2018). Importantly, there is little epidemiological evidence that walking improves BMD (Martyn-St James and Carroll, 2008). Rather, mixed loading programs that included jogging, walking, and stair climbing consistently improve hip BMD in older people, although far fewer data exist in young adults (Martyn-St James and Carroll, 2009). The optimum type and level of PA for improving BMD remains unknown, and it is unclear whether a specific threshold strain needs to be exceeded. It is also unclear whether or not different loading movements in different sports may have varying effects on BMD and whether the effects are identifiable at different sites. Lower limb impact during weight bearing reflects their ground reaction force. In a study of adolescents from the Avon Longitudinal Study of Parents and Children, using pQCT and DXA found that vigorous PA (equivalent to jogging) was positively related to cortical bone mass, but no independent relationship was seen for moderate PA after adjusting for vigorous PA; this highlighted the importance of vigorous activity in this age group (Sayers et al., 2011). This also highlighted the importance of quantifying the intensity, frequency, and duration of PA in comparators controls when assessing the changes in cQUS measures associated with non-elite sporting activity.

There are several limitations to this systematic review. The QUS tools used varied, with distinct model versions used in the measurements undertaken. As such, the output values were not directly comparable. There was considerable variability in the bone measurements taken and the level of detail provided of methods used to perform the measurements. These methods varied from measuring both feet separately to find the mean of the two, performing measurements in duplicate or triplicate, performing measurements either on the dominant foot or the non-dominant foot, and measuring both left and right feet but presenting the results of the left foot only. Overall, the reproducibility of the QUS measurements within the individual studies themselves were within an acceptable range and researchers followed manufacturer's instructions validating the use of the QUS measurement. Unfortunately, two articles were not obtainable despite numerous attempts to search for the English translations of the full article or to contact the authors (Coaccioli et al., 2013; Qian, 2017). Funding precluded the use of an official translation service, and we were therefore reliant on Google Translate. This is a limited service; although the study by Mentzel et al. was subject to translation bias, its inclusion was justified as it was within the scope of this review. Mentzel et al.'s study was therefore translated from German to English using Google Translate, a freely available online tool. This translation may include inaccuracies since sentences could be translated out of context, especially when translating colloquial words or words with multiple meanings. Another limitation of this review is that the age of the study participants under review leaned toward the younger end of the 11–35 age group. The lack of detail regarding the power of the studies made it difficult to assess whether and how the sample size recruited affected the results. The ethnicity of the study participants was not always clearly stated in the study. Furthermore, although nutrition was acknowledged as a factor in bone health in all six studies, only four of the six studies completed any dietary analysis. Details for sports measurement for sporting history, duration, and other physical activities included were heterogeneous, and sometimes the methods of recording and confirming the details were ambiguous. For example, the duration of participation in regular sporting activity prior to enrolment in each study was often not provided. The mean weekly sport training regimes ranged from a minimum of 3 h to up to 27 h, and the level of participation in non-elite sporting activity between studies were not directly comparable. Inter-study comparisons of results may not be made as in the six selected studies the selection criteria for participants, and the controls were inconsistent between the studies. For example, some study participants selected for controls in one study would be sufficiently active to be participants in another study in this group of six studies. Finally, resource limitations meant we were unable to include SPORTDiscus and Web of Science in our search.

In comparison, a number of other systematic reviews have assessed bone health at other bone sites using various imaging tools, and this review complements those data. Our results are complementary and support the findings of those studies. Specifically, weight-bearing sporting activity, and particularly high-impact weight-bearing activity, appeared to be beneficial, while swimming did not enhance bone mineral accrual. Previous studies compared differing age ranges or assessed bone outcomes in relation to pubertal status, while some reviews have been undertaken in groups of young people participating in exercise regimes or individual sports such as swimming, soccer, gymnastics, and ballet, which may be at a combination of recreation or elite or competitive level. For example, in a systematic review undertaken by Nikander's et al. (2010), the authors found, using various imaging techniques, such as DXA, pQCT, MRI (Magnetic Resonance Imaging), and HSA (Hip Structural Analysis), that, in children, an exercise regime lasting more than 6 months enhanced bone strength at loaded sites, but this effect was not seen in adults. Gomez-Bruton et al. suggested that swimmers may not be reaching their PBM potential: Gomez-Bruton et al.'s systematic review in 2016 found higher DXA-derived BMD values in young Caucasian children and adolescents engaged in osteogenic sports relative to swimmers and controls (Gomez-Bruton et al., 2016). Gomez-Bruton et al.'s recent systematic review in 2018 focused on young adult swimmers aged 18 to 30 and found that, in these young adults, limited osteogenic effects of swimming during adolescence persisted through early adulthood (Gomez-Bruton et al., 2018). The systematic review by Lozano-Berges et al. (2018) also used various imaging tools and found children aged 6 to 18 playing soccer had positive bone mass outcomes compared to the controls (Lozano-Berges et al., 2018). Burt et al. (2013) systematically reviewed participation in gymnastics during the pre-pubertal growth period and found there was skeletal health benefits mostly for the upper body regions (Burt et al., 2013). Similarly, a systematic review by Wewege and Ward (2018) in pre-professional female ballet dancers found site-specific osteogenic effects compared to the controls. A systematic review by Krahenbühl et al. (2018) addressed the effects of weight-bearing sports, such as soccer and gymnastics, on bone geometry in children and adolescents, and found that the benefit was dependent on the frequency and intensity of the PA measured. The systematic review by Koedijk et al. (2017) assessed bone health in children up to the age of 24 and measured PA subjectively through questionnaires or objectively using an accelerometer, with a focus on sedentary behavior rather than a specific non-elite sport. Three of the studies identified by Koedijk et al.'s review that were of higher quality indicated that there was no association between sedentary behavior and total body bone outcomes as measured by DXA; although 12 of the studies included in the same review assessed the lower peripheral bone outcomes with DXA or QUS found a negative association with sedentary behaviors (Koedijk et al., 2017).

The authors chose to undertake this systematic review of non-elite sporting activity with bone health using cQUS as the outcome measure in order to capture studies that may not have been included in previous systematic reviews. The authors used a heel ultrasound as the outcome measure in this study to assess the effects of non-elite sports. Many studies indicated that a heel ultrasound is used to assess bone structure and strength and is used worldwide for osteoporotic fracture risk assessment when DXA the gold standard tool in diagnosis is not available, although it is not to be used as a diagnostic tool (ISCD, 2013; Quiros Roldan et al., 2017). The positive attributes of the heel ultrasound test are that it involves no risks or harm and is a cost-effective, comfortable, pain-free, and radiation-free test that is easy to use and only takes a few minutes to perform (Shewale et al., 2017; Komar et al., 2019). Studies have shown the quantitative ultrasound densitometry technique to be useful in assessing skeletal health status changes due to exercise in all age groups and as a research tool (GE Medical Systems Lunar, 2010; Babatunde and Forsyth, 2013; Yesil et al., 2013). Jaworski et al.'s study in 1995, Baroncelli's study in 2008, and Daly et al.'s study in 1997 found the use of ultrasound in normal healthy children to be a safe and non-invasive method when comparing the skeletal status of exercising children (Jaworski et al., 1995; Daly et al., 1997; Baroncelli, 2008). Different studies have used either the dominant heel, the non-dominant heel, or a mean of the two to measure the reported outcome. While it is possible that this might impact findings, the consistency of our results suggested this was not a major consideration here, particularly given the sports studied. Perhaps this plays a lesser role compared to the effect on the dominant limb in racquet sports such as tennis (Kontulainen et al., 2003).

CONCLUSION

Although study heterogeneity prohibited meta-analysis, all six studies reviewed reported significant benefits of weight-bearing non-elite sporting activity in children and young adults. While both sexes were studied in several of these individual reports, small sample sizes made it difficult to dissect differences in outcomes between the two sexes. The studies revealed habitual levels of high-impact sports such as soccer produced better bone outcomes (particularly in males) compared to non-weight bearing sports such as swimming and cycling. Sporting behaviors commencing in the early years is an opportunity to improve PBM potential and set in place other healthy long-term lifestyle behaviors. More studies, especially in young adults in their 20s and 30s, are now urgently required to examine this issue in greater detail with more clearly defined control groups.

AUTHOR CONTRIBUTIONS

HP performed the searches. HP, LS, and ED reviewed the search results and extracted the data. HD provided advice and guidance regarding the systematic review methods. HP, ED, HD, PT-S, and LS edited the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

HP was in receipt of a Ph.D. scholarship from Victoria University of Wellington, New Zealand.

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Conflict of Interest: ED has received consulting fees from Pfizer and UCB.

The remaining 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.

frontiers in Physiology

MINI REVIEW
published: 24 April 2020
doi: 10.3389/fphys.2020.00270

The Beneficial Role of Exercise Training for Myocardial Infarction Treatment in Elderly

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Worldwide, elderly people have a higher prevalence of myocardial infarction (MI), which is associated with body function aging and a sedentary lifestyle. In addition to medication, exercise training is a well-established supplementary method to prevent and treat cardiovascular diseases (CVDs). Substantial evidence has shown the value of different intensity exercise programs in the prevention and treatment of MI, and exercise rehabilitation programs are also applicable to elderly patients with MI. Although exercise rehabilitation programs could significantly improve function, quality of life (QoL), and lower mortality and morbidity for people with MI, such programs are underused because their mechanisms are not accurately elucidated. To promote the application of exercise therapy for MI, this review summarizes the benefits and mechanisms of exercise rehabilitation for post-MI patients and provides rationalized proposals for outpatient cardiac rehabilitation.

Keywords: aging, cardio protection, cardiopulmonary rehabilitation, exercise, myocardial infarction

OPEN ACCESS

Edited by:
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University of Calgary, Canada

Reviewed by:
Irene Cantarero-Villanueva,
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Daniele Jardim Feriani,
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Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *07 December 2019*
Accepted: *09 March 2020*
Published: *24 April 2020*

Citation:
Xing Y, Yang S-D, Wang M-M, Feng Y-S, Dong F and Zhang F (2020) The Beneficial Role of Exercise Training for Myocardial Infarction Treatment in Elderly. Front. Physiol. 11:270. doi: 10.3389/fphys.2020.00270

HIGHLIGHTS:

- Exercise therapy contributes to improve behavioral risk factors that may result in MI, promotes exercise capacity, and elevates QoL for MI patients.
- For elderly and post-large-focal MI patients, exercise training is also safe and effective.
- Early exercise training, even short-term exercise, is a safe and feasible way to exert protective effects in post-MI patients.
- In the early stages of MI, moderate-intensity exercise is the best choice to improve the outcomes for MI patients.
- Cardiovascular rehabilitation and interval exercise had unique advantages, which should be recommended for MI patients.

INTRODUCTION

Myocardial infarction (MI) is related to formation of plaques in the inner wall of the artery, which blocks or reduces blood flow to the heart and damages heart muscles because of the lack of oxygen supply (Lu L. et al., 2015). In China, the mortality of acute MI increased 5.6-fold from 1987 to 2014 (Chang et al., 2017). Individuals aged 8,084 years have 190.70 and 220.15 times higher mortality risk of acute MI compared to those aged 1,519 years in Chinese rural and urban populations, respectively (Chang et al., 2017). A total of 2,812 elderly patients followed on 9 years showed that disability in basic strength and mobility increased the year following being diagnosed with MI (Mendes de Leon et al., 2005).

Currently, multiple therapy options, including thrombolytic drugs, percutaneous transluminal coronary angioplasty (PTCA), and coronary artery bypass grafting, are available to treat acute MI in clinic (Kahn et al., 1993; Sorensen and Maeng, 2015; Lhermusier et al., 2019; Song et al., 2019). In addition to medications and surgeries, epidemiological evidence has shown that exercise, such as stair climbing, walking, and sports, is inversely correlated to the mortality of cardiovascular causes (PaffenbargerJr., Hyde et al., 1986). Thus, exercise is an effective supplementary therapy and usually plays a key role in the process of treatment for patients with acute MI. Exercise training in patients with acute MI can improve work load, functional capacity, test duration, and heart rate response (Andjic et al., 2016), as well as promote the improvement of cardiac pump function – a 34.7 and 32.0% mean rise in ejection fraction and stroke index, respectively (Chursina and Molchanov, 2006).

In this review, we summarize the evidence for the beneficial effect of exercise rehabilitation programs for MI from randomized controlled trails (RCTs), epidemiological reports, meta-analysis and clinical studies, and laboratory experiments so as to extend the application of exercise in the prevention and treatment for MI.

EXERCISE AND AGE-RELATED MI

According to epidemiological results, aging will become a main risk factors for CVD after the age of 65 (North and Sinclair, 2012). Aging is independently associated with peak oxygen uptake (VO_2 peak) and total work capacity (TWC), accounting for nearly 70% of the age-related decay (Marchionni et al., 2000). Controlling life risk factors including physical inactivity and sedentary behaviors might be an effective method to reduce global mortality and morbidity in patients with CVD (Fletcher et al., 2018; Blaum et al., 2019; Lavie et al., 2019). Lifelong (>25 years) exercise may alleviate a sedentary- and aging-induced decrease in systolic longitudinal strain (LS) through improving left ventricular (LV) diastolic filling (Howden et al., 2018). Regular exercise plays an important role in healthy aging and contributes to lower risk of chronic disease and all-cause mortality (Mora and Valencia, 2018; Adams and Linke, 2019). The lowered risk of cardiovascular events in elderly individuals (age, 66.6 $\pm$ 2.1 years) was associated with improving exercise capacity (+ 2.0 ml kg^{-1} min^{-1}) and reducing body fat mass (–2.3%) (Niederseer et al., 2011). Regular moderate-intensity training (MIT) for 8 weeks enhanced exercise tolerance and promoted microcirculatory vascular function in postmenopausal women (Alkhatib and Klonizakis, 2014). In summary, exercise training could improve the physical function and parameters of MI related to aging, indicating that the elderly should adhere to appropriate physical exercise, which is conducive to heart health (as shown in **Figure 1**).

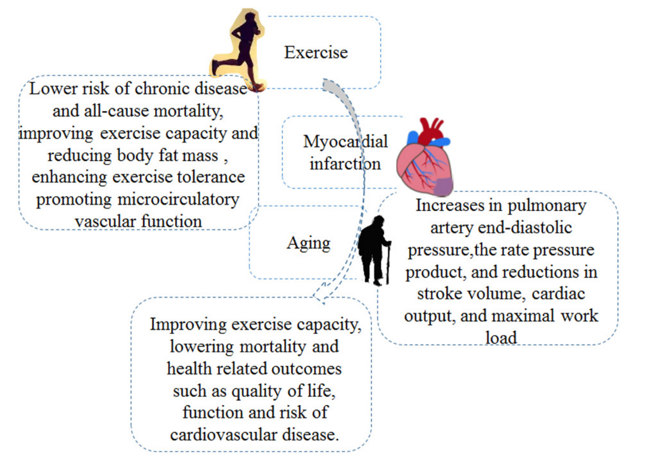

FIGURE 1 | The involved mechanisms for exercise intervention in myocardial infarction (MI) treatment in elderly.

THE BENEFITS OF EXERCISE FOR MI

Exercise training concerns planned and organized body movement to improve physical capacities; examples include swimming, yoga, aerobic and resistance/strength exercise, and so on (Tulpule and Tulpule, 1980; Ferrera et al., 2014; Moraes-Silva et al., 2017; Ostman et al., 2017). After MI, Exercise training may induce positive effects; improve QoL, metabolic equivalents (METs), circulation function, and heart rate; and lower the risk of chronic disease and all-cause mortality (Greif et al., 1995; Adams et al., 2017; Elshazly et al., 2018; Mora and Valencia, 2018) (as shown in **Figure 1**).

Exercise training exerted beneficial effects in the process of cardiopulmonary rehabilitation and LV remodeling in the LV dysfunction patients after MI, and the greatest effects were achieved when exercise began at the post-MI acute phase (Zhang et al., 2016). A cross-sectional study of 65 men (60 $\pm$ 6 years) found that lifelong exercise training maintained LV systolic function and probably alleviated or minimized the detrimental effects of LV remodeling after MI in veteran athletes (Maessen et al., 2017). LV end diastolic and systolic volumes had significantly decreased in MI patients after 10 weeks of exercise training (Mc et al., 2016). Following acute MI, patients who participated in interval training or MIT for 12 weeks significantly increased their VO_2 peak (Santi et al., 2018). In summary, exercise training effectively promoted cardiac circulation by improving cardiac performance in MI patients.

Dynamic resistance training may alleviate sympathetic tonus to the heart vessels in rats after MI (Barboza et al., 2016). Resistance exercise training for 3 months reduced the vascular and cardiac sympathetic regulation and increased the parasympathetic regulation so as to improve cardiac autonomic balance in post-MI rats (Grans et al., 2014). The improvement of activated sympathetic drive was associated with elevated NO bioavailability in paraventricular nucleus (PVN) of chronic heart failure rats induced by MI during 3-week progressive treadmill exercise (Sharma et al., 2019). In summary, exercise regulated the autonomic balance of nerves in MI patients, resulting in an improvement of cardiac performance and a reduction in cardiac mortality.

DIFFERENT TYPES OF EXERCISE PROGRAMS AND MI

Cardiac Rehabilitation and MI

Exercise-based cardiac rehabilitation (CR) is a multidisciplinary program for individuals after MI to reduce cardiorespiratory fitness (CRF), morbidity and mortality as well as improve QoL and exercise capacity (Franklin et al., 2013; Korzeniowska-Kubacka et al., 2015; Tessitore et al., 2017). It covers 10 domains of cardiac risk factor regulation, including weight management, exercise training, patient assessment, and so on (Costantino et al., 2016; Richardson et al., 2019). The main benefits associated with CR are produced by exercise training (Oldridge, 2012; Lewinter et al., 2015; Anderson et al., 2016).

In a cohort study, 37 patients (mean age, 66 years) with MI underwent a 5-week CR program, and the results indicated that cardiac rehabilitation improved QoL, exercise capacity, and autonomic modulation (Fallavollita et al., 2016). Kim et al. suggested that a 6-week CR exercise program with an intensity of 60–85% heart rate reserve improved cardiopulmonary function in patients with ischemic cardiomyopathy (Kim et al., 2016). Patients with a home-based walking program showed an obvious improvement of functional capacity, increasing their inspiratory muscle endurance (PTHmax) and maximal inspiratory pressure (MIP) in 15 and 60 days following MI (Matos-Garcia et al., 2017). A study of 359 patients with acute MI who underwent a CR program (6-week hospital- or home-based aerobic exercise) suggested that those patients had significant improvements in their resting heart rate, VO_2 peak, total exercise duration (TED), and METs after cardiac rehabilitation, regardless of obesity (Lim et al., 2016).

After percutaneous intervention, patients with a 4-week outpatient CR program had obvious improvements in their maximum VO_2 peak and METs (Choe et al., 2018). CR for 3 years showed reduced major adverse cardiovascular events (e.g., MI) compared to those without CR (9.9 vs. 18.3%) (Lee et al., 2019). Moreover, CR contributed to a decrease in all-cause mortality, cardiac mortality, and reinfarction risk (Lawler et al., 2011) and helped to regulate cardiovascular-risk-related factors, such as blood pressure, body weight, smoking, and lipid profile (Lawler et al., 2011).

In summary, as shown in **Table 1**, not only did CR lower cardiac mortality and improve QoL and exercise capacity, but it also ameliorated cardiovascular risk factors in the basis of multidisciplinary program, which was mainly due to benefits induced by exercise training.

Physical Activity and MI

Physical activity (PA) is a crucial preventive measure against CVD (Jefferis et al., 2019), which is recognized as part of occupation, active transportation, leisure, and daily living, such as walking for several minutes in the park and chatting with a friend, and the leg muscles voluntarily contract and the energy expenditure ascends exponentially from baseline levels (Moraes-Silva et al., 2017).

Physical activity in patients with acute MI, even at a low intensity, can play an important role in improving health-related QoL (Lovlien et al., 2017). Renninger et al. (2018) suggested that leisure-time physical activity was an independent factor in association with risk of MI, and it might reduce the risk of MI-related excess bodyweight. In a prospective study on postmenopausal MI survivors, patients with increased physical activity following a first MI showed a reduced risk of all-cause mortality than patients with low physical activity (Gorczyca et al., 2017). Elderly patients (age > 65 years) who underwent the highest level activity had a lower mortality from CVD than those who underwent the lowest level activity (Park et al., 2012). After MI, elderly patients with pre-infarction angina who participated in a high level of physical activity had a lower in-hospital mortality compared to those without pre-infarction angina (Abete et al., 2001). High level of physical activity could restore the protective effect of pre-infarction angina on lower in-hospital mortality in elderly patients after MI (Abete et al., 2001).

In summary, physical activity can play a crucial role in reducing mortality of CVD in post-MI patients. Therefore, daily physical activity is important to MI patients, especially for elderly patients with low levels of physical activity. Well-planned and high-level physical activity can also help elderly people reduce the mortality risks associated with CVD.

Moderate-Intensity Exercise and MI

Moderate-intensity continuous training (MICT) is one of the best choices for exercise rehabilitation during the early stages following MI (Cai et al., 2018). Such physical training showed sufficient efficacy in the physical capacity of 197 patients during the early stage of ischemic heart disease, including an increase in the efficiency of cardiac work and work performed volume (+74.3%, $p < 0.001$) as well as the prolongation of exercise time (+ 31.7%, $p < 0.001$) (Aronov et al., 2009). Microcirculatory perfusion cardiorespiratory capacity also improved in sedentary postmenopausal participants after MIT for 8 weeks as evidenced by this ventilator threshold: 11.5 ± 2.1 vs. 14.0 ± 3.0 ml kg^{-1} min^{-1}, $p < 0.05$ (Alkhatib and Klonizakis, 2014).

MIT was helped reduce atrioventricular (AV) block cycle length, AV intervals, sinus cycle length, and ventricular effective refractory period (Kannankeril and Goldberger, 2002); it also led to a significant structural functional improvement of the heart via increasing ejection fraction (7.2%) and LV stroke volume (4.5%) while reducing LV volume (2.5%) and systolic LV volume (8.1%) in individuals with ischemic heart disease (Aronov et al., 2009).

High-Intensity Exercise

The benefits of high-intensity training (HIT) was twice as good as MIT through analyzing VO_2 peak in healthy subjects and patients with heart disease (Kemi and Wisloff, 2010). Participation in exercise once a week could lower the risk of cardiovascular death

TABLE 1 | Exercise and MI.

References	Time	Disease	Participation	Outcome
Cardiac rehabilitation				
Fallavollita et al. (2016)	5 weeks	MI	37 patients	Improvements in QoL exercise capacity (from 423 ± 94 to 496 ± 13 m) and autonomic modulation
Kim et al. (2016)	6 weeks	Ischemic cardiomyopathy	48 patients	Improving cardiopulmonary function and increasing LVEF.
Matos-Garcia et al. (2017)	2 months	MI	31 patients	Improvement of functional capacity by increasing PTHmax and MIP
Lim et al. (2016)	6 weeks	MI	359 patients	Improvements in HRrest, VO_2 peak, TED and METs
Choe et al. (2018)	4 weeks	MI	66 patients	Improvements in VO_2 peak and METs.
Lee et al. (2019)	3 years	MI	265 patients	Reduced major adverse cardiovascular events (e.g., MI) than those without CR (9.9% vs. 18.3%).
Moderate-intensity exercise				
Cai et al. (2018)	Moderated-intensity exercise	MI	10 rats	Suppress skeletal muscle atrophy
Aronov et al. (2009)	Moderate-intensity exercise	Ischemic heart disease.	197 patients	Increases of efficiency of cardiac work and work performed volume (+ 74.3%), prolongation of exercise time (+ 31.7%), structural functional improvement of heart
Alkhatib and Klonizakis (2014)	Moderated-intensity exercise	Sedentary postmenopausal participants	15 patients	Improvement of microcirculatory perfusion cardiorespiratory capacity
Aronov et al. (2009)	Moderated-intensity exercise	Acute coronary events	188 patients	Lowering atherogenic index, total cholesterol and body mass index
Xu et al. (2018)	Moderate exercise	MI	10 rats	Promoting α-myosin heavy chain (α-MHC) expression and myocardial contractile function, and improve prognosis.
High- and low-intensity exercise				
Wisloff et al. (2006)	High-intensity exercise	Cardiovascular disease	27,143 men and 28,929 women	Lower the cardiovascular death risk
Ades et al. (1996)	High-intensity exercise	Elderly patients with coronary bypass surgery or myocardial infarction	60 patients	16 and 20% increase in peak aerobic capacity and increased the difference of arteriovenous oxygen at peak exercise
Kemmler et al. (2013)	Intense multipurpose exercise	Osteopenic Caucasian females	137 patients	Improve metabolic and lower cardiac risk
Al'khimovich et al. (1985)	Intensive exercise	large-focal myocardial infarction	21 patients	Improved myocardial functional potentials, better physical stress tolerance, better psychological outlook and smaller pulmonary venous congestion
Hua et al. (2009)	Low-intensity exercise	Mildly hypertensive men and women	20 patients	Improved VO_2 peak
Worcester et al. (1993)	Low-intensity exercise	MI	224 patients	Improvement of QoL

both in women and men. The risk reduction induced by exercise promoted with age for men (Wisløff et al., 2006). A 12-year-long clinical study reported that subjects with an intense multipurpose exercise program effectively improved metabolic parameters and lowered cardiac risk in postmenopausal women as compared to those with habitual physical activity (Kemmler et al., 2013).

In addition, high-intensity interval training (HIIT) was considered as a beneficial and feasible supplementary therapy in international clinical-based exercise guidelines to MICT (Kim et al., 2015; Taylor et al., 2019). Patients with MI who participated in HIIT had greater decreases in fat mass, body fat percentage, waist circumference, abdominal fat percentage, low-density lipoprotein cholesterol, total cholesterol, triglycerides, and greater improvements in body composition and metabolic syndrome as compared to MICT (Dun et al., 2019a,b). HIIT was also superior to MICT in decreasing oxidative stress, improving glucolipid metabolism, and enhancing exercise capability and cardiac function in post-MI rats (Lu K. et al., 2015).

Low-Intensity Exercise and MI

Long-term (4 months) low-intensity training (LIT) mitigated the enhancement of myocardial type I and III collagen and lysyl oxidase gene expression in LV (Pagan et al., 2015). In a randomized controlled trial lasting 12 weeks, patients with CVD received LIT or HIT, and the significant improvement in VO_2 peak had no significant difference (Hua et al., 2009). The improvement of QoL provided by LIT for 11 weeks was similar to HIT during the early stages of acute MI (Worcester et al., 1993).

In summary, as shown in **Table 1**, well-planned HIT may have better effects than MIT and LIT, while LIT may be safer compared to MIT and HIT. Moreover, MIT was both safe and effective for MI patients; it lowers possible risks as compared to HIT and had better effects as compared to LIT. Therefore, MIT was most commonly used in clinics.

Interval Exercise and MI

In a randomized control study on patients with MI, both aerobic interval training and usual care rehabilitation increased serum adiponectin, improved endothelial function and QoL, and decreased resting heart rate and serum ferritin; only aerobic interval training, however, increased the level of high-density lipoprotein cholesterol, which could exert benefits for patients (Moholdt et al., 2012). Interval training also had a more beneficial effect in improving VO_2 peak from 31.6 ± 5.8 to 36.2 ± 8.6ml kg^{-1} min^{-1} as compared to the usual care rehabilitation, which was from 32.2 ± 6.7 to 34.7 ± 7.9ml kg^{-1} min^{-1} (Moholdt et al., 2012). After 12 weeks of interval training, the VO_2 peak had increase from 19.2 ± 5.1 to 21.9 ± 5.6 ml kg^{-1} min^{-1} in 31 patients (55.1 ± 8.9 years) with MI in the anterior wall (Santi et al., 2018). Thus, participation in interval exercise had unique advantages as compared to other types of exercise training for MI patients, which needs further research in the future.

Resistance and Aerobic Exercise and MI

Resistance exercise (RT) with weight training machines, even one time or < 1 h/week, is related to lower risks of CVD and global mortality (Liu et al., 2019). In animal experiment, LM et al. indicated that aerobic exercise and dynamic RT might decrease pro-inflammatory cytokine level and alleviate sympathetic tonus to the vessels and heart in rats after MI (Barboza et al., 2016). A meta-analysis on 35 randomized controlled trials showed that isolated progressive resistance training exerted beneficial effects in lower (standardized MD, 0.57; 95% CI, –0.17 to –0.96) and upper [1.43 (0.73–2.13)] body strength. In addition, progressive resistance training plus aerobic training was more effective in both strength and fitness than aerobic training alone (Ostman et al., 2017). Twelve-month resistance in combination with aerobic exercise at a 2 days/week frequency may improve muscle strength and cardiorespiratory fitness in all age groups (Ciolac et al., 2014).

Swimming and MI

Swimming is a popular recreational activity and unique exercise form, regarded as an effective exercise to maintain and improve CRF (Lazar et al., 2013). In animal experiment, 3-week swimming training may alleviate acute-MI-caused acute cardiac damage by elevating the early adaptive altering of mitochondrial biogenesis and improving myocardial energy metabolism (Tao et al., 2015).

Yoga and MI

Yoga-based lifestyle intervention may significantly decrease estimated 10-year cardiovascular disease (CVD) risk and Framingham Risk Score (FRS), so as to obviously lower CVD risk (Yadav et al., 2017). There was also an obvious shift from sympathovagal balance toward parasympathetic predominance and increase in overall heart radio variability in MI patients with optimally medication treatment (Christa et al., 2019).

DIFFERENT EXERCISE TIME AND MI

The Benefits of Exercise Intervention Before MI

In one study with animals, exercise pretreatment preserved cardiomyocyte contractile and morphological properties, which played a crucial role in cardioprotection against cardiac structural deterioration and dysfunction caused by MI (Bozi et al., 2013). Exercise pretreatment could also reduce collagen accumulation, thicken infarcted wall, alleviate MI volume, improve muscle strength, enhance responsiveness to calcium, and preserve cardiac myocyte shortening; it could also improve the maximum relengthening and shortening velocities in infarcted hearts of rats (Bozi et al., 2013; Ciolac et al., 2014). There was a close relationship between cardio protection against myocardial injury induced by exercise pretreatment and cardiac natriuretic peptide receptor B (NPR-B) and C-type natriuretic peptide (CNP) (Lu and Pan, 2017). In summary, exercise before MI could benefit the recovery process following MI.

Exercise in the Early Stages of MI

Early exercise programs were beneficial to patients with MI through improving psychological responses to exertion and promoting functional capacity, even short-term exercise training (Williams et al., 1985; Greif et al., 1995). Early exercise training also helped improve exercise tolerance, ventricular remodeling, and autonomic nerve balance in post-MI patients (Batista et al., 2013). However, Batista et al. (2013) demonstrated that delayed exercise may exert better effects than early exercise. Therefore, the reasonable exercise time requires further exploration so as to provide rational advice for MI patients.

CONCLUSION

CVD such as MI are associated with poor health behaviors, such as a sedentary lifestyle. Exercise therapy is an effective intervention method to improve behavioral risk factors that may result in MI, promote exercise capacity, and elevate QoL for MI patients. Even low-level physical activity reduced the risk of MI. Therefore, daily physical activity should be recommended to people with or without MI instead of a sedentary lifestyle. For elderly and post-large-focal MI patients, exercise training is also safe and effective, but it should be further confirmed in future research. Early exercise training, even short-term exercise, is also a safe and feasible way to improve functional capacity, exercise tolerance, ventricular remodeling, and autonomic nerve balance in post-MI patients. In the early stages of MI, MIT is the best choice to improve the outcomes for MI patients. In addition, CR programs and interval exercise had unique advantages, which should also be recommended for MI patients. The combination of RT and aerobic exercise is an effective therapy to lower the risk of CVD. The intervention of swimming and yoga can effectively improve sedentary lifestyle, so as to lower the risk of CVD. In conclusion, exercise training is an effective and reliable alternative treatment for MI patients in the basis of medication and surgery therapy, as it has fewer side effects and more long-lasting benefits. This type of treatment should be standardized and widely applied in clinics to help MI patients all over the world.

AUTHOR CONTRIBUTIONS

YX, S-DY, and FZ had the idea for the article and drafted and critically revised the work. M-MW, Y-SF, and FD performed the literature search and data analysis.

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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.

frontiers in Physiology

ORIGINAL RESEARCH
published: 10 June 2020
doi: 10.3389/fphys.2020.00540

OPEN ACCESS

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Specialty section:
This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology

Received: 30 December 2019
Accepted: 30 April 2020
Published: 10 June 2020

Citation:
Figueiredo AI, Balbinot G, Brauner FO, Schiavo A, Baptista RR, Pagnussat AS, Hollands K and Mestriner RG (2020) SPARC Metrics Provide Mobility Smoothness Assessment in Oldest-Old With and Without a History of Falls: A Case Control Study. Front. Physiol. 11:540. doi: 10.3389/fphys.2020.00540

SPARC Metrics Provide Mobility Smoothness Assessment in Oldest-Old With and Without a History of Falls: A Case Control Study

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Aging-related neuromuscular and neurocognitive decline induces unsmooth movements in daily functional mobility. Here, we used a robust analysis of linear and angular spectral arc length (SPARC) in the single and dual task instrumented timed up-and-go (iTUG) test to compare functional mobility smoothness in fallers and non-fallers aged 85 and older. 64 participants aged 85 and older took part in this case control study. The case group (fallers, $n = 32$) had experienced falls to the ground in the 6 months prior to the assessment. SPARC analyses were conducted in all phases of the single and dual task iTUGs. We also performed correlation mapping to test the relation of socio-demographic and clinical features on SPARC metrics. The magnitude of between-group differences was calculated using D-Cohen effect size (ES). SPARC was able to distinguish fallers during the single iTUG (ES $\approx$ 4.18). Turning while walking in the iTUG induced pronounced unsmooth movements in the fallers (SPARC ≈ -13; ES = 3.52) and was associated with the ability to maintain balance in the functional reach task. This information is of importance in the study of functional mobility in the oldest-old and to assess the efficacy of fall-prevention programs.

Keywords: movement smoothness, functional mobility, falls, aging, oldest-old

INTRODUCTION

Aging is a natural process associated with musculoskeletal and cognitive decline (Harada et al., 2013). This process ultimately leads to reduced movement smoothness and cognitive reserve, impairing the mobility in daily life, such as walking, turning, and sitting (Sunderaraman et al., 2019). The fact that daily living activities (ADLs) require multi-tasking increases the cognitive demand and may lead to a higher risk of falls in the oldest-old (Bock, 2008; Montero-Odasso et al., 2012; Fernandez et al., 2019). Complex tasks demand higher processing speeds and greater attention, memory, and executive function, which are all affected by the natural aging process (Harada et al., 2013). The occurrence of falls may reduce life expectancy due to several secondary conditions of particular importance to the fragile elderly (Deandrea et al., 2010). Therefore, fall prevention programs are of utmost importance to the elderly, especially the fragile and the oldest-old.

To identify the above-mentioned neuromuscular and neurocognitive deficits and subsequent risk of falls, more sensitive and robust measurements of mobility smoothness during such complex tasks are warranted. Regarding complexity, the timed up-and-go (TUG) task is considered a reliable and valid test for quantifying functional mobility in the elderly—the test involves complex mobility tasks such as turning while walking or transitions from walking to sitting on a chair, which are of importance to daily living functional mobility (Podsiadlo and Richardson, 1991). While time taken in the test is the most commonly used in the test, the typical TUG lacks more specific information on movement quality, such as movement smoothness. Moreover, measures of time and transitioning angles obtained by instrumented TUG (iTUG) do not provide better fall risk classification when compared with the measures provided by typical TUG test (Jackson et al., 2018). On the other hand, unsmooth movements have been associated with poor balance and risk of falls in many populations, such as stroke survivors (Isho and Usuda, 2016; Kerr et al., 2017; Pickford et al., 2019) and people living with Parkinson's disease (Buckley et al., 2019). Thus, movement smoothness might be of importance when performing iTUG-based mobility assessment (Weiss et al., 2011). Several approaches are used to quantify movement smoothness during walking, such as the autocorrelation coefficient (Moe-Nilssen and Helbostad, 2004) or harmonic ratios (Menz et al., 2003). Recently, the spectral arc length (SPARC), a new approach to quantifying movement smoothness, has shown great sensitivity, robustness, and reduced dependence on speed or task duration (Balasubramanian et al., 2012; Balasubramanian, 2015; Beck et al., 2018). Traditional smoothness metrics, such as the number of peaks, dimensionless, and log dimensionless jerk, are more susceptible to movement amplitude and duration (Balasubramanian, 2015). Although some of these metrics also show reduced effects of movement amplitude and duration, SPARC is less susceptible to signal noise artifacts—common in accelerometry-based measurements.

Assessing mobility smoothness using robust smoothness measures, such as SPARC, may reveal unique characteristics among populations prone to falling. In this study, we aimed to explore whether the mobility smoothness assessed by the SPARC metrics in the iTUG is different in non-institutionalized elderly aged 85 and older, with and without a history of falls in the last 6 months. In addition, we used the dual-task iTUG (a cognitive-motor task) to better understand how increasing the cognitive load might affect mobility smoothness and its relationship with the history of falls. We hypothesized that mobility smoothness, as measured by SPARC metrics, would clearly show a difference between oldest-old with and without history of falls.

MATERIALS AND METHODS

Participants and Procedures

Participants with (case, n = 32) and without (control, n = 32) self-reported history of falls were recruited by convenience. A fall was defined as an unexpected and unexplained event in which the participant comes to rest on the ground/floor (Deandrea et al., 2010). In this study, to minimize bias in the self-reported assessment, we did not consider other types of falls. The participant who has fallen at least once in the 6 months prior to the study was considered a faller. Based on the inclusion criteria, we selected participants of any gender, aged ≥85 years, who walked independently (walking-assistant devices allowed) and understood the verbal commands necessary to adequately perform the proposed evaluation. The exclusion criteria were: uncertainty regarding the history of falls; hospitalization for more than 7 days in the previous 3 months; major unresolved orthopedic injuries; and diagnosis of neurological and/or severe respiratory, cardiovascular, visual, or auditory diseases. Data collection was as follows: (1) we explained the study aims to the participants; (2) informed consent was signed; (3) we applied the General Screening Questionnaire, Mini Mental State Examination (MMSE) (Folstein et al., 1975), Geriatric Depression Scale (GDS) (Yesavage et al., 1982)—short version, Activities Specific Balance Confidence (ABC) Scale (Powell and Myers, 1995), Falls Efficacy Scale—International (FES-I) (Yardley et al., 2005), and the International Physical Activity Questionnaire (IPAQ) adapted for the elderly (Rubio Castañeda et al., 2017). Functional reach, blood pressure, body mass, and height were also assessed. Finally, two types of TUG tests (three single task TUG and three dual task TUG trials) were performed in the following order: single task TUG—dual task TUG—dual task TUG—single task TUG—single task TUG—dual task TUG. We used three trials of each type of the TUG test to assess both possible learning and fatigue effects in the oldest-old. A similar approach was used in a previous study in multiple sclerosis (Witchel et al., 2018). The participants were seated on a standard chair (43 cm in height, without armrest) and asked to get up and walk as fast as possible. The verbal command "get up and go" was given and the participants moved from sit to stand, walked 3 m (walk 1), performed a 180° turn (turn), walked 3 m (walk 2) turned, and sat on the same chair from which they had started (turn-to-sit on the chair). The spot at which the subjects were expected to perform the 180° turn was marked by a cross on the ground using adhesive tape (30 × 30 cm). During the dual task TUG, participants followed the same above-mentioned protocol while speaking the days of the week in reverse order (e.g., Wednesday, Tuesday, Monday, Sunday, Saturday, Friday, Thursday, and so on until the test finished). The rationale for choosing this dual task was based on previous research (Barbosa et al., 2008; Fatori et al., 2015; Silva et al., 2017). They were instructed to start speaking, as quickly as-possible, while still sitting. While no penalty was applied when they had a mistake in speaking, each participant was advised the right/wrong replies would be recorded and scored. At each dual task TUG trial, the initial day of the week was changed (e.g., Wednesday, then Tuesday, and finally Monday).

Inertial Measurement Unit (IMU)

Linear acceleration and angular velocity were measured during the TUG test using a Bluetooth-compatible inertial measurement unit (IMU; G-Walk®, BTS Bioengineering, MA, United States), with a sampling rate of 100 Hz. The IMU was positioned between the L5 and S1 vertebrae using an elastic belt provided by the manufacturer (Kleiner et al., 2018; Pau et al., 2018). The device has a built-in triaxial accelerometer and gyroscope. Linear acceleration (Acc L) and angular velocity (Vel A) were acquired in the vertical (V), mediolateral (ML), and anteroposterior (AP) axes. Raw acceleration and angular velocity data were extracted using the G-sensor® software and exported in ASCII format.

Mobility Smoothness Measurement and Data Analyses

Offline signal processing and analyses were performed using LabVIEW® (version 8.5; National Instruments, Austin, TX, United States) custom software routines. Acc L and Vel A data were considered when the mean of a 10-frame moving window was greater than three times the SD of the initial noise (100 frames window). We developed a mathematical routine to segment the TUG test into phases. A visual inspection of the yaw and pitch angles was implemented, followed by manual cropping of each curve. The pitch angle was used to crop "sit to stand." A combination of the yaw and pitch angles was used to detect the turn-to-sit phase, i.e., the yaw angle was used to detect the turn before sitting (≈180°), and the pitch angle to detect the trunk flexion when starting the sitting movement. The midway point of the 180° turn was detected using the yaw angle (turn phase). During the pilot data analysis, we suspected the automatic algorithm provided by BTS failed to correctly determine the duration of the TUG phases. For example, we identified the turn and turn-to-sit on the chair phases took much longer than expected considering previous trials. We understand there are two separate or combined explanations for this situation. While important papers have proposed the use of automatic algorithms in lumbar-mounted IMU (also used by BTS), they have not been specifically validated for use in people aged between 85 and 101 years old (Weiss et al., 2013; Vervoort et al., 2016; Kleiner et al., 2018; O'Brien et al., 2019). Moreover, the automatic algorithms usually consider a TUG test in which a cone is used to mark the turning point (180°). In the present study, the cone was replaced by a cross on the ground made using adhesive tape (30 × 30 cm) to minimize the influence of the visual cue in the turning performance (provided by the shape of the cone). As expected, this change increased the variability of the movement strategies adopted by the oldest-old during the turning phase, which sometimes exceeded the ability of the automatic algorithm to precisely determine the duration of the TUG phases. Thus, we developed a manual signal analysis routine in order to minimize measurement errors in the detection of TUG phases (previously published by Pinto et al., 2019). Two trained, independent assessors tested the reliability of this routine and found reliable results (**Supplementary Figure S1** and **Supplementary Table S1**). Mean subtractions were used to remove the direct current (DC) components from raw acceleration data and whenever signal manipulations caused the drifting of the signal (Beck et al., 2018). Removing DC and drifting is important when processing acceleration measured by accelerometers, especially to remove the large DC component in the spectrum (accelerometers also pick up gravity). Subsequently, high frequencies not involved in the TUG test were removed when applying the limits of integration (0–10 Hz bandwidth). The upper and lower limits of integration were set at 0 and 10 Hz to encompass higher frequencies present during the TUG test (Pinto et al., 2019), when compared to steady-state walking (which assumed 0–5 Hz in previous studies) (Beck et al., 2018). We divided a distance of 3 m by the duration of the walk to obtain the average speed during the walking bouts (in $m.s^{-1}$). The TUG test involves sharp turns, sit-to-stand, and turn-to-sit movements, which may induce more abrupt acceleration. We also hypothesized the oldest-old may have gait impairments, such as intermittency, i.e., as occurs in Parkinson's disease (8 Hz freezing band). The SPARC calculation was adapted for the iTUG test, as previously described (Balasubramanian, 2015). We calculated the SPARC metrics from each trial and the average SPARC from three TUG trials using the following formula:

$$SPARC = -\int_{0}^{10} \sqrt{\left(\frac{1}{10}\right)^2 + \left(\frac{normPSD(w)}{dw}\right)^2}\, dw \quad (1)$$

where 0 and 10 Hz are the limits of integration, normPSD is the normalized power spectrum density (PSD), and dw is an infinitesimal amount of PSD frequency.

For total Acc L (Acc L total) and total Vel A (Vel A total), we used previously proposed signal processing and equations (Beck et al., 2018). Importantly, SPARC metrics assume less smooth movements are more complex in terms of their frequency composition; hence, lower SPARC values indicate less movement smoothness. The SPARC was calculated for the full iTUG as well as for the distinct phases of the test such as (i) sit-to-stand, (ii) walk 1, (iii) turn, (iv) walk 2, and (v) turn and turn-to-sit.

Measurement of Sample Characteristics

To estimate the sample size, we used a previous study (Weiss et al., 2016). Sample size was set as 64 individuals when adopting a power of 80% and an alpha of 0.05. Thus, we decided to enroll 32 fallers and 32 non-fallers. To calculate sample size, we used an online resource from the University of British Columbia (Brant, 2017). **Table 1** shows the sample characteristics.

Statistical Analyses

Statistical analyses were performed in GraphPad Prism® version 6.01 (GraphPad Software, San Diego, CA, United States),

TABLE 1 | Sample characteristics.

	Fallers (n = 32)		Non-fallers (n = 32)	
	Mean/n (category)	SD	Mean/n (category)	SD
Age	89.9	4.4	88.6	4.1
Gender (male = 0/female = 1)	7 (0)/25 (1)	n.a	5 (0)/27 (1)	n.a
Blood pressure/systolic	127.3	11.1	127.5	11.6
Blood pressure/diastolic	77.7	12.5	74.7	8.0
Mean arterial pressure	94.2	10.4	92.3	8.1
Level of schooling/years	7.9	5.7	7.9	4.2
Marital Status (widow or not = 0/married = 1)	22 (0)/10 (1)	n.a.	24 (0)/8 (1)	n.a.
Number of medications in use	5.3	2.8	4.4	2.3
MMSE	25.8	3.6	26.8	2.5
FES-I	24.3	7.6	22.0	2.7
ABC	**73.4**	**21.1**	**82.0**	**11.6**
Ethnicity (0 = white; 1 = brown or black)	26 (0)/6 (1)	n.a.	31 (0)/1 (1)	n.a.
IPAQ (0 = sedentary; 1 = active)	**12 (0)/20 (1)**	**n.a.**	**2 (0)/30 (1)**	**n.a.**
Functional reach test (cm)	26.3	10.2	30.1	7.8
GDS depression symptoms (0 = no; 1 = yes)	20 (0)/12 (1)	n.a.	27 (0)/5 (1)	n.a.
Smoker (0 = no; 1 = yes)	31 (0)/1 (1)	n.a.	31 (0)/1 (1)	n.a.
Alcoholic drink (0 = no; 1 = yes)	26 (0)/6 (1)	n.a.	27 (0)/5 (1)	n.a.

Independent t-test for quantitative variables and Chi-square with Yates' correction for qualitative variables. Bold values denote statistical significance ($p < 0.05$).

LabVIEW® and the Statistical Package for the Social Sciences (SPSS) version 17.0. We used the Shapiro–Wilk test to assess normality and applied square root and logarithmic transformations for asymmetrical variables. Nevertheless, these procedures did not work properly for many variables in this study. Thus, we performed both parametric and non-parametric analyses. Given the main findings were the same in both analyses, we decided to show them using parametric tests (the statistical plan is summarized in **Supplementary Figure S2**). Ordinary ANOVA using the factors falls (yes/no), trial (1, 2, 3), and task (single/dual-task TUG) was used to explore the potential between-factor interactions. We collapsed non-significant factors (i.e., trial for SPARC outcomes) and performed two-way repeated-measures ANOVA to test the factors falls (yes/no) and task (simple or dual-task TUG). Spearman's correlation was used to test the relationship between clinical scores, demographics, and SPARC outcomes (the averages of the single and dual task TUG trials were used in the correlations). D-Cohen effect size (ES) was calculated to compare fallers and non-fallers. Qualitative data were compared using the Chi-square test with Yates' correction and proportions. The intraclass correlation coefficient (ICC) was used to test the reliability of manual detection of the TUG phases. Data were expressed as mean and SEM and significance was set at $\alpha < 0.05$.

Ethics

This cross-sectional study was approved by the Research Ethics Committee of the Pontifical Catholic University of Rio Grande do Sul (number 099196/2017). All the participants agreed to take part and signed informed consent. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.

RESULTS

Table 1 describes the sample characteristics. Fallers displayed a reduced level of confidence in performing activities without losing balance (ABC score; $t = 2.00$, $p = 0.049$) and reduced level of physical activity (IPAQ; $\chi^2 = 7.40$, $p = 0.006$). **Supplementary Table S2** summarizes the main effects of the exploratory ANOVA.

Greater TUG Duration for Fallers, but the Dual Task Affected Walking and Turning in Both Groups

The iTUG was performed in different complexities, i.e., single or dual tasks. Angles extracted from the gyroscope were used to determine the duration of each TUG phase (**Figure 1**). The reliability of TUG phase detection using the above-mentioned procedure is shown in **Supplementary Table S1**. The analysis suggested an excellent between-assessor reliability in detecting most of the TUG phases (Cronbach's $\alpha > 0.9$). The turn and turn-to-sit phases obtained lower, but still acceptable, ICC (Cronbach's $\alpha > 0.5$). Fallers took longer to move from sit to the stand and turn to sit. Both groups took longer when performing the dual task and turning (see the statistics in **Table 2**). Although walking speed increased from the first to the third trial, movement smoothness (SPARC), overall, displayed the absence of trial effects.

Mobility Smoothness Between Fallers and Non-fallers: Walking Bouts

Given the absence of trial effects, we averaged the SPARC data from all trials to express the participant's performance (**Table 3**). SPARC was lower for fallers, displayed task effects, and absence of trial effects (except for turn Acc L—dual task; explored

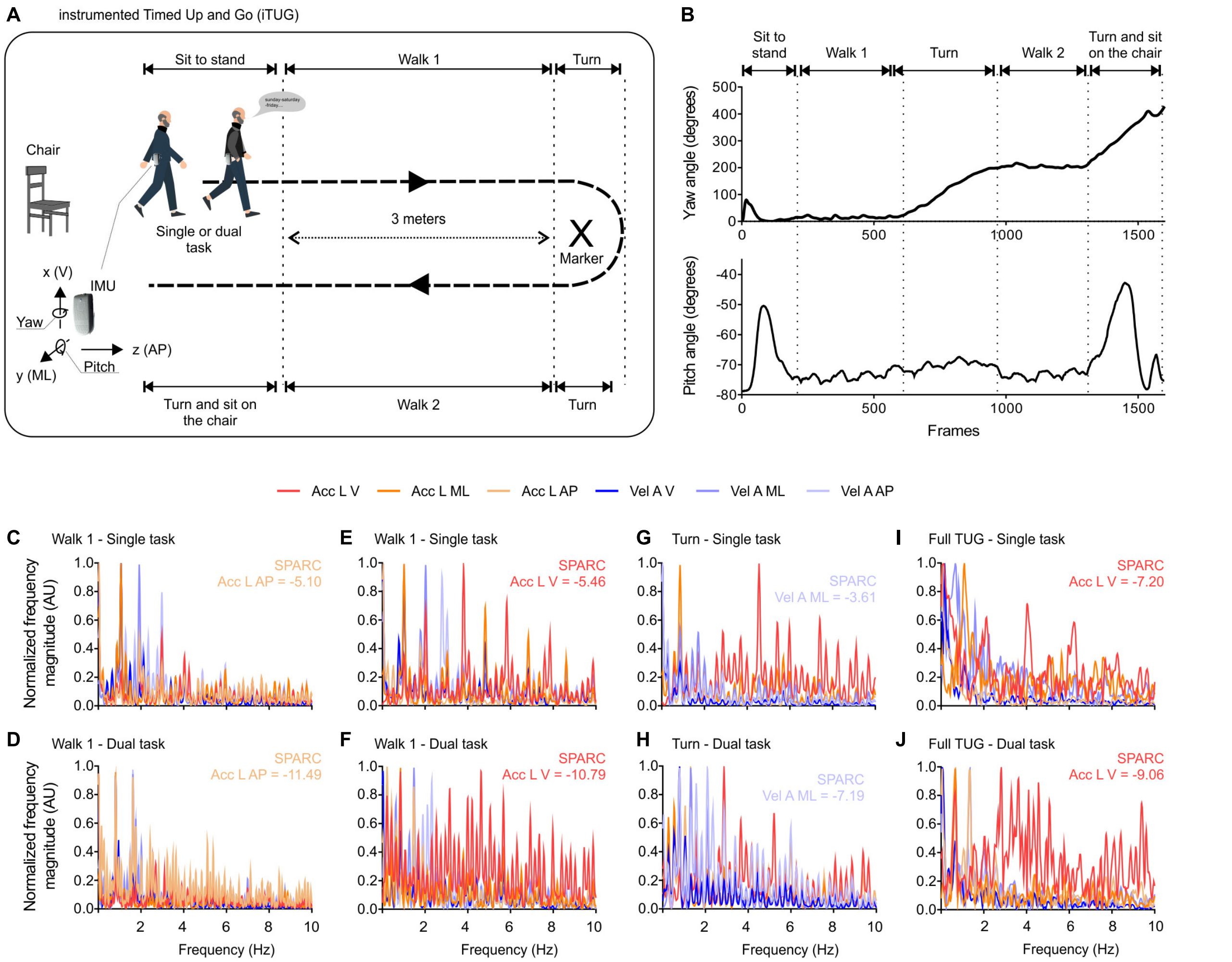

FIGURE 1 | Instrumented timed up-and-go (iTUG) test and mobility smoothness (SPARC). **(A)** The TUG test was performed in single or dual task conditions, participants wore an inertial measurement unit (IMU) attached to the waist. The IMU measured linear accelerations (Acc L), angular velocities (Vel A), and angles in the three axes of movement. **(B)** TUG phases were identified using yaw and pitch angles. The full TUG and the following phases of the TUG were analyzed: sit-to-stand, walk 1, turn, walk 2, turn, and turn-to-sit (also depicted by arrows in **A**). **(C–J)** Representative spectral profiles used for the calculation of SPARC, note how some participants showed abundant frequency spectra above 5 Hz (expected to contain most of the frequencies components during steady-state walking). V: ventral; ML: mediolateral; AP: anteroposterior; SPARC: spectral arc length; Acc L: linear acceleration; Vel A: angular velocity; AU: adimensional unit; TUG: timed up-and-go; IMU: inertial measurement unit.

below). SPARC metrics also showed several correlations with the functional reach and ABC score for fallers. Additionally, mobility smoothness was also correlated with other variables, such as MMSE, level of schooling, and age for non-fallers (**Figure 2** and **Supplementary Table S3**).

Mobility Smoothness Between Fallers and Non-fallers: Turn and Full TUG

In addition to steady-state walking, we analyzed other aspects of functional mobility such as turning while walking. Indeed, fallers exhibited a notable reduction in movement smoothness during the turn phase of the TUG. While there was no between-trial learning effect for the time taken to turn (i.e., time to turn was stable between trials), SPARC showed a change from trial 1 to 3 during the turn phase of the TUG (**Figure 3**). Together, these findings suggest the participants experienced difficulty maintaining good levels of mobility smoothness when performing faster movements in less stable conditions, as typically occur during the turning phase of the TUG. In agreement with walk 1 and 2 phases of the TUG, SPARC metrics during the turning phase were consistently correlated with the functional reach and ABC score for fallers; but also correlated with MMSE, level of schooling, and age for non-fallers (particularly during the dual task; **Figure 3**). Altogether, these findings indicate the oldest-old have a pronounced difficulty turning smoothly and, subsequently, an adaptive motor control change is required to complete the task, which is not possible to assess using the traditional TUG with a stopwatch.

TABLE 2 | Duration and speed in the single and dual-task TUG tests.

TUG phase	Single task—duration (s)				Dual task—duration (s)					Main effects	
	Fallers		Non-fallers		Fallers		Non-fallers				
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM		*F*	*P*
Sit to stand—Trial 1	3.148	0.405	1.798	0.080	3.542	0.572	1.888	0.082	Group	**38.164**	**0.000**
Sit to stand—Trial 2	3.677	0.895	1.799	0.095	3.245	0.431	1.872	0.078	Trial	0.135	0.874
Sit to stand—Trial 3	3.220	0.600	1.753	0.088	3.154	0.500	1.855	0.096	Task	0.012	0.913
Walk 1—Trial 1	5.572	0.722	3.921	0.308	8.975	1.788	5.799	0.868	Group	**19.201**	**0.000**
Walk 1—Trial 2	5.500	0.919	3.736	0.365	8.387	1.595	5.343	0.470	Trial	0.851	0.428
Walk 1—Trial 3	5.430	0.809	3.468	0.300	7.552	1.531	4.237	0.433	Task	**13.851**	**0.000**
Turn—Trial 1	4.569	0.898	2.891	0.221	5.798	1.088	4.000	0.346	Group	**15.641**	**0.000**
Turn—Trial 2	4.327	0.654	2.973	0.299	5.240	0.925	3.806	0.267	Trial	1.049	0.351
Turn—Trial 3	3.723	0.417	2.940	0.325	4.736	0.763	3.373	0.239	Task	**6.767**	**0.010**
Walk 2—Trial 1	5.414	0.788	3.648	0.302	8.725	1.462	5.841	0.574	Group	**16.415**	**0.000**
Walk 2—Trial 2	5.140	0.736	3.604	0.419	7.452	1.098	5.400	0.587	Trial	2.070	0.128
Walk 2—Trial 3	4.758	0.649	3.412	0.373	6.276	1.192	4.559	0.595	Task	**19.369**	**0.000**
Turn to sit—Trial 1	4.323	0.496	2.976	0.178	4.895	0.820	3.623	0.269	Group	**24.548**	**0.000**
Turn to sit—Trial 2	4.412	0.730	2.820	0.266	4.529	0.561	3.317	0.219	Trial	0.766	0.466
Turn to sit—Trial 3	4.169	0.671	2.594	0.196	4.381	0.601	2.963	0.220	Task	2.019	0.156
Full TUG—Trial 1	23.026	3.099	15.233	0.971	31.935	5.391	21.151	1.886	Group	**24.193**	**0.000**
Full TUG—Trial 2	23.056	3.797	14.931	1.332	28.853	4.357	19.737	1.404	Trial	1.119	0.328
Full TUG—Trial 3	21.300	3.046	14.167	1.181	26.099	4.367	16.986	1.408	Task	**9.748**	**0.002**
TUG phase	**Single task—speed (m.s^{-1})**				**Dual task—speed (m.s^{-1})**					**Main effects**	
	Fallers		**Non-fallers**		**Fallers**		**Non-fallers**				
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**		***F***	***P***
Walk 1—Trial 1	0.717	0.058	0.888	0.057	0.553	0.057	0.669	0.047	Group	**24.120**	**0.000**
Walk 1—Trial 2	0.789	0.069	0.976	0.067	0.584	0.063	0.666	0.043	Trial	**4.135**	**0.017**
Walk 1—Trial 3	0.766	0.064	1.021	0.067	0.653	0.067	0.878	0.066	Task	**29.933**	**0.000**
Walk 2—Trial 1	0.773	0.060	0.951	0.061	0.547	0.060	0.639	0.047	Group	**19.157**	**0.000**
Walk 2—Trial 2	0.809	0.069	1.058	0.077	0.586	0.058	0.700	0.053	Trial	**6.583**	**0.002**
Walk 2—Trial 3	0.855	0.069	1.102	0.079	0.753	0.075	0.858	0.063	Task	**42.358**	**0.000**

Three-way ordinary ANOVA (df = 372) with factors group (fallers X non-fallers; df = 1). trial (1 × 2 × 3; df = 2) and task (single X dual; df = 1). All interactions were not significant (not shown). Bold values denote statistical significance (p < 0.05).

TABLE 3 | Main effects of time and group for SPARC Acc L total and SPARC Vel A total.

TUG phase	SPARC Acc L total		SPARC Vel A total	
	Time	Group	Time	Group
Sit to stand	**$F(1,62) = 27.19$; $p < 0.0001$**	**$F(1,62) = 4.65$; $p = 0.0350$**	**$F(1,62) = 24.24$; $p < 0.0001$**	**$F(1,62) = 4.20$; $p = 0.0447$**
Walk 1	**$F(1,62) = 14.68$; $p = 0.0003$**	$F(1,62) = 2.90$; $p = 0.0939$	**$F(1,62) = 18.76$; $p < 0.0001$**	**$F(1,62) = 4.01$; $p = 0.0497$**
Turn	**$F(1,62) = 66.49$; $p < 0.0001$**	$F(1,62) = 3.30$; $p = 0.0739$	**$F(1,62) = 47.77$; $p < 0.0001$**	**$F(1,62) = 4.55$; $p = 0.0369$**
Walk 2	**$F(1,62) = 58.99$; $p < 0.0001$**	**$F(1,62) = 4.47$; $p = 0.0385$**	**$F(1,62) = 12.69$; $p = 0.0007$**	**$F(1,62) = 4.79$; $p = 0.0323$**
Turn to sit	$F(1,62) = 3.06$; $p = 0.0852$	**$F(1,62) = 8.33$; $p = 0.0054$**	$F(1,62) = 0.09$; $p = 0.7633$	**$F(1,62) = 7.98$; $p = 0.0064$**
Full TUG	$F(1, 62) = 0.76$; $p = 0.3867$	**$F(1,62) = 7.31$; $p = 0.0088$**	**$F(1,62) = 7.58$; $p = 0.0077$**	**$F(1,62) = 6.18$; $p = 0.0156$**

Two-way repeated-measures ANOVA with factors time (single X dual task) and group (fallers X non-fallers). All interactions were not significant (not shown). Bold values denote statistical significance (p < 0.05).

SPARC metrics displayed stronger group differences (ES ≈ 4.18) compared to the time taken to complete the full TUG test (ES = 2.96) (**Figures 2**, **3**). Again, consistent correlations between SPARC in the full TUG, the functional reach and ABC score for fallers were found. Movement smoothness of the participants without a history of falls was

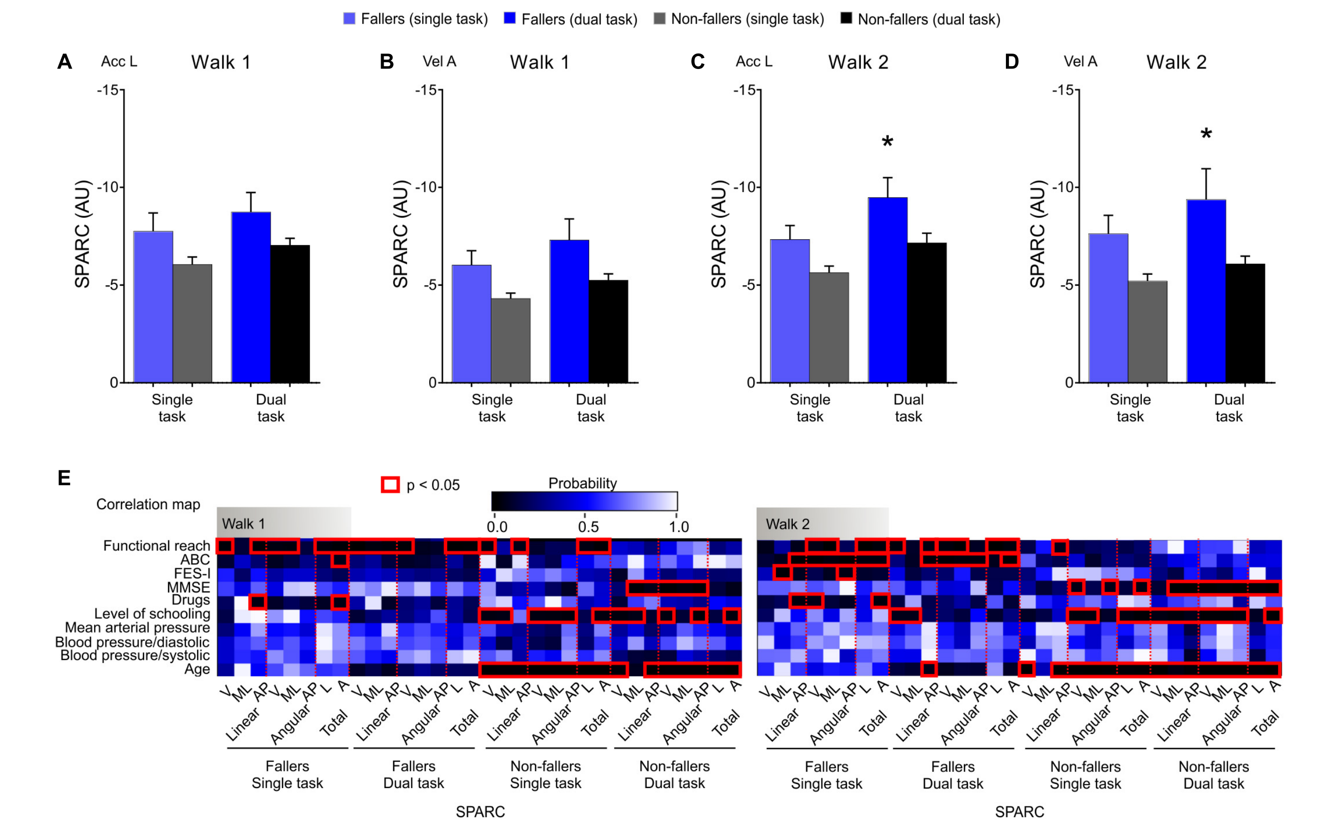

FIGURE 2 | Walking smoothness (SPARC) outcomes were stable across trials and reduced for fallers. **(A–D)** SPARC outcomes during walk 1 and 2 showed group and task, but not trial, main effects, thus we collapsed the three trials. Group and time effects were evident (**Table 3**), alongside with *post hoc* effect for the dual task walk 2 phase. **(E)** The correlation map analysis showed a consistent correlation between functional reach, ABC scale, and movement smoothness in both the fallers and non-fallers. Correlations were also found with MMSE, level of schooling, and age for non-fallers. Two-way repeated-measures ANOVA with factors time (single X dual task) and group (fallers X non-fallers) followed by Sidak-correction (*post hoc*). Data are shown as mean ± SEM; $n_{\text{Fallers}} = 32$; $n_{\text{Non-fallers}} = 32$; $^*p < 0.05$ (*post hoc*); red rectangles in **E** are $^*p < 0.05$ (Spearman correlation). V: ventral; ML: mediolateral; AP: anteroposterior; SPARC: spectral arc length; Acc L: linear acceleration; Vel A: angular velocity; AU: adimensional unit; TUG: timed up-and-go.

only correlated with age when considering the full TUG test (**Figure 3**).

Fallers showed reduced smoothness (SPARC) while transitioning from "sit to stand" during the dual task. The final phase "turn to sit" was not affected by the task. This is expected since most participants stopped or reduced the vocalization of the weekdays in this phase of the dual task TUG (**Supplementary Figure S3**).

DISCUSSION

Here we described mobility smoothness during the TUG, a widely used test (Barry et al., 2014), applying robust and sensitive movement smoothness metrics (SPARC). This study supports the iTUG test in providing a smoothness mobility index, which may contribute to understanding functional mobility and falls in community-dwelling oldest-old. Fallers took longer to complete the test and exhibited reduced smoothness when performing the single and dual task TUG. In comparison to the traditional TUG test outcome (duration), mobility smoothness may reveal larger between-group effect sizes between oldest-old with and without a history of falls. Moreover, this is the first study to highlight how the iTUG can provide valuable insights into the relation between mobility smoothness and time taken to move when performing different phases of a walking-based task. For instance, the time taken to complete the sit-to-stand phase of the TUG is different between fallers and non-fallers, whereas mobility smoothness showed no *post hoc* effect. Interestingly, during the turning and standing to sit phases, fallers and non-fallers did not differ regarding the time spent to complete these phases of the test, but mobility smoothness was drastically affected for participants with a history of falls. The movement smoothness also showed remarkable positive correlations with the ability to maintain stability during the functional reach test in the group of fallers. Additionally, there was a consistent correlation between SPARC metrics and age and less consistent relation with MMSE and the level of schooling in the non-fallers.

Dual task situations involve attention and other cognitive processes of importance to posture and locomotion (Bayot et al., 2018). However, the complexity of the TUG test was previously shown to add little value when assessing falls in

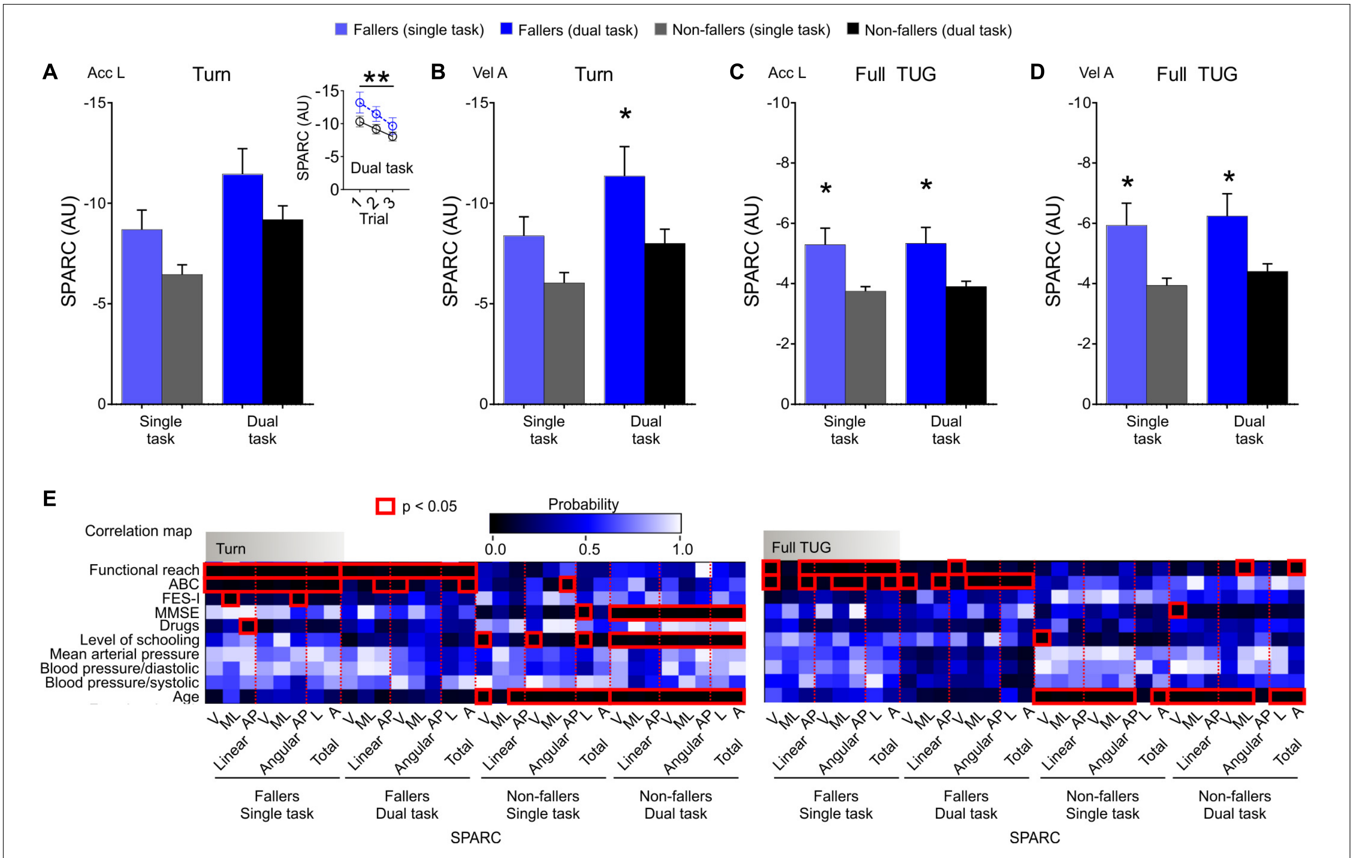

FIGURE 3 | Turning displayed drastically reduced smoothness (SPARC) values for oldest-old fallers and non-fallers. **(A)** The turning phase of the TUG test showed reduced smoothness (SPARC Acc L) mostly in the first trial, but increased movement smoothness was evident between trials (inset). The between-trial collapsed data showed the absence of group effects. **(B)** The SPARC angular component (SPARC Vel A) during turning, on the other hand, displayed group effects and a *post hoc* effect for the dual task. **(C,D)** During the full TUG, the SPARC was reduced for fallers performing single or dual tasks. **(E)** Similar to the walking bouts, SPARC metrics during turning consistently correlated with the functional reach test and ABC scale for fallers. Non-fallers also showed correlations with MMSE, level of schooling, and age. Note that when the full TUG is considered, non-fallers showed fewer correlations with the MMSE and level of schooling. Two-way repeated-measures ANOVA with factors time (single X dual task) and group (fallers X non-fallers) followed by Sidak correction (*post hoc*). Data are mean ± SEM; $n_{\text{Fallers}} = 32$; $n_{\text{Non-fallers}} = 32$; *$p < 0.05$ (*post hoc*); **$p < 0.05$ trial effect in the ordinary ANOVA (group Fallers X Non-fallers; trial 1 × 2 × 3; task Single X Dual); red rectangles in **E** are *$p < 0.05$ (Spearman correlation). V: ventral; ML: mediolateral; AP: anteroposterior; SPARC: spectral arc length; Acc L: linear acceleration; Vel A: angular velocity; AU: adimensional unit; TUG: timed up-and-go.

older adults (age ≈ 76 years) (Asai et al., 2018). Here, we reported similar findings for mobility smoothness as both fallers and non-fallers displayed reduced movement smoothness while performing the dual task TUG. Movement smoothness was noticeably low during turning in the dual task TUG, ranging up to -13 for fallers, a higher value when compared with previous reports of -5.5 for walking (Beck et al., 2018) or -6 for turning (Parkinson's disease; Pinto et al., 2019). Difficulties of turning while walking in the oldest-old are also evident in the adaptation pattern of mobility smoothness from the first to the third trial of the dual task. This may indicate the oldest-old adapt motor learning and behavior to overcome the difficulties experienced when turning while walking, for example, by using different movement strategies (Weiss et al., 2016). Interestingly, this adaptation was not noticeable in the traditional TUG duration outcomes, which were stable between trials. Turning involves approximately 40% of all the steps taken during the activities of daily living, depending on how often certain activities are performed (Glaister et al., 2007), and sharp turns, such as the 180° turns during the TUG test, are energetically demanding (Justine et al., 2014). Altogether, these findings suggest the turning phase is a challenging situation for the oldest-old at risk of falls. This is in line with research showing older adults and stroke survivors have similar deficits when turning 90° under dual task conditions (Hollands et al., 2014). Together, the current findings contribute to consolidating the importance of turning assessment as a marker to explain falls in the oldest-old.

Similarly, standing up from a chair is a dynamic equilibrium task susceptible to age-related modifications (Mourey et al., 2000). When evaluating movement smoothness and time taken to transit from sit to stand together, we found an interesting behavior in fallers (**Supplementary Figure S1**). The cautious transition of fallers during the sit to stand phase may represent an attempt to control horizontal motion and increase movement smoothness to avoid falls (Mourey et al., 2000). By contrast, while turning and transitioning from turn to sit, there was little difference between fallers and non-fallers in terms of time taken, but mobility smoothness was markedly different (ES ≈ 4.59). These findings highlight the importance of evaluating mobility smoothness in addition to movement duration in the TUG test, with important implications for fall assessment.

Day-to-day gait speed and variability involve several factors and may be linked to different brain networks in vulnerable older adults (Lo et al., 2017). Falls risk may be missed if walking speed exceeds a threshold on a given day or a given trial after learning/performance effects on the TUG are seen. Our results support the concept of SPARC as a stable, robust, and sensitive measurement of movement smoothness regardless of movement speed and duration (Balasubramanian et al., 2012; Balasubramanian, 2015) likely able to identify falls risk regardless of speed ability on the day.

Indeed, increased speed of walking bouts between trials is not reflected in the SPARC outcomes. In addition, SPARC is ≈10 times less susceptible to signal-to-noise ratio artifacts (Balasubramanian et al., 2012; Balasubramanian, 2015), a particularly important point when analyzing accelerometric data, which are more prone to noise than kinematic data, for example. Furthermore, the mobility smoothness data from SPARC metrics in the TUG provide new insights into mobility, especially when considered concerning duration and speed, with a noteworthy power to distinguish between fallers and non-fallers. Altogether, the findings described here support the use of SPARC during the TUG test to evaluate age-related motor control decline and its association with a history of falls.

In addition, correlation maps suggest that further studies should address the association between mobility smoothness, a history of falls, and unhealthy habits such as physical inactivity and subsequent depressive symptoms (Jorgensen et al., 2002; Hollands et al., 2010; Schuch et al., 2016).

Finally, current data support using SPARC metrics in the iTUG is feasible and allow the test conduction outside of the lab, which might provide realistic data, since laboratory kinematic measurements (e.g., axial segment coordination) have failed in distinguishing a history of falls in stroke survivors (Hollands et al., 2010).

This study has some limitations. The convenience sample may have influenced the effect sizes of the SPARC metrics. While the process of determining the duration of each TUG test phase has been reliably conducted by the assessors in this research group, visual inspection of the signal may prove challenging for untrained assessors. Moreover, the ICC results suggest the SPARC outcomes are reliable, with the exception of the final TUG phase (turn and sit on the chair). This is probably due to the wide range of motor strategies adopted by the oldest-old during this TUG phase. For example, some participants stopped during the final part of the turn and, after a pause, sat. Others performed a combined turning and sitting movement or turned completely before sitting without a between-subphase pause. Overall, in the oldest-old, the signals from this TUG phase are challenging, even for trained experts, and are a matter for further research. Thus, the SPARC results in the "turn to sit on the chair" phase of the TUG should be interpreted with caution. Further studies should compare data from the G-Walk software, manual detection (as performed here), and kinematics as the gold standard. In addition, while the retrospective analysis revealed SPARC is associated with history of falls, we do not know the extent to which it can be used to independently predict future falls. Thus, more research is necessary to assess the value of movement smoothness as a predictor of the likelihood of future falls.

CONCLUSION

This study characterized mobility smoothness in elderly subjects aged 85 and older during a functional mobility task involving different degrees of complexity. Using robust SPARC smoothness metrics, we identified important factors associated with a history of falls, namely, age, unsmooth movements, and performance in a functional reach task. We suggest including mobility smoothness measures in the iTUG to ensure movement quality is more fully assessed in the test. These findings provide a better understanding of functional mobility in the oldest-old and may be of importance when assessing the efficacy of fall prevention programs.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study protocol was reviewed and approved by the Research Ethics Committee of the Pontifical Catholic University of Rio Grande do Sul. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AF carried out the data collection, conceived and planned the experiments, analyzed the data, and contributed to the writing of the manuscript. GB designed the model framework, performed signal analyses, analyzed the data, and contributed to the writing of the manuscript. FB and AS carried out the data collection and reviewed the manuscript. RB contributed to implementation of the research and reviewed the manuscript. AP and KH conceived of the study design and reviewed the manuscript. RM conceived of the presented idea, supervised the findings, and wrote and reviewed the manuscript. All authors discussed the results and contributed to the final manuscript.

FUNDING

The Coordenação de Aperfeiçoamento de Pessoal de Nivel Superior—Brasil (CAPES)—Finance Code 001 and the National Council for Scientific and Technological Development (CNPq)—Brazil—provide scholarships to support this investigation.

ACKNOWLEDGMENTS

We thank Clarissa Pedrini Schuch (Ph.D.) for acting as the second assessor in the detection of the TUG phases (ICC analysis).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2020.00540/full#supplementary-material

FIGURE S1 | Data analysis to extract the TUG task phases. The pitch **(a)** and yaw **(b)** angles were extracted from the IMU. **(a)** The pitch angle was used to detect the trunk flexion and extension, characteristic of the sit and the stand movements. These movements are depicted between the vertical lines 1a and 2a (sit to stand), and 3a and 4a (turn to sit), the trunk flexion is a decrease in the pitch angle and the trunk extension is an increase in the pitch angle. **(b)** Next, the yaw angle was used to detect the walk and the turn phases. Importantly, the yaw angle is also used to fine-tune the detection of the turn and sit on the chair phase (vertical line 3a in **a**) and to assist in the detection of the walk 1 phase. The walk 1 start frame (vertical line 1b) is set at the same index of the vertical line 2a (≈200 frames in this example). The end of the walk 1 phase and the start of the turn phase is detected when the yaw angle starts to change (2b), the turn is considered from this point until a 180° change in the yaw angle occurred. This 180° turn is followed by another period of oscillatory yaw angle variation (from 3b to 4b; walk 2 phase). At this point in the visual inspection procedure, the evaluator searched for the final turn, which occurs before sitting and used this value (4b) to fine-tune the detection of the turn and sit on the chair phase (≈1100 frames in this example; 3a in **a**).

FIGURE S2 | Statistical plan. This step-by-step plan illustrates the statistical choices and decisions.

FIGURE S3 | Fallers displayed reduced smoothness while standing from a chair or turning and sitting on the chair, but the latter displayed absence of task effect. **(a,b)** Fallers showed reduced smoothness (SPARC) while transitioning from the sitting to the standing position during the dual task. **(c,d)** The final TUG transition "turn-to-sit" was not affected by the task. **(e)** The representative spectral profile of a participant performing the "turn-to-sit" phase of the TUG task under single and dual task conditions. Note the mild SPARC values and the lack of noticeable difference between single and dual task. V: ventral; ML: mediolateral; AP: anteroposterior; SPARC: spectral arc length; Acc L: linear acceleration; Vel A: angular velocity; AU: adimensional unit; TUG: time up-and-go.

TABLE S1 | Reliability statistics: Two independent assessors determined the TUG phases detection in a random sub-sample (24 participants).

TABLE S2 | Three-way ordinary ANOVA summary. This was used as a first step to explore the dataset.

TABLE S3 | Significant correlations between SPARC, demographics, and functional variables.

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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.

frontiers
in Sports and Active Living

ORIGINAL RESEARCH
published: 16 June 2020
doi: 10.3389/fspor.2020.00068

High Intensity Resistance Exercise Training vs. High Intensity (Endurance) Interval Training to Fight Cardiometabolic Risk Factors in Overweight Men 30–50 Years Old

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Sports and Active Living

Received: *11 June 2019*
Accepted: *14 May 2020*
Published: *16 June 2020*

Citation:
Tuttor M, von Stengel S, Kohl M, Lell M, Scharf M, Uder M, Wittke A and Kemmler W (2020) High Intensity Resistance Exercise Training vs. High Intensity (Endurance) Interval Training to Fight Cardiometabolic Risk Factors in Overweight Men 30–50 Years Old. Front. Sports Act. Living 2:68. doi: 10.3389/fspor.2020.00068

Cardiovascular and cardiometabolic diseases are leading causes of death worldwide. Exercise favorably affects this problem, however only few invest (enough) time to favorably influence cardiometabolic risk-factors and cardiac morphology/performance. Time-effective, high-intensity, low-volume exercise protocols might increase people's commitment to exercise. To date, most research has focused on high-intensity interval training (HIIT), the endurance type of HIT, while corresponding HIT-resistance training protocols (HIT-RT) are rarely evaluated. In this study we compared the effect of HIIT vs. HIT-RT, predominately on cardiometabolic and cardiac parameters in untrained, overweight-obese, middle-aged men. Eligible, untrained men aged 30–50 years old in full-time employment were extracted from two joint exercise studies that randomly assigned participants to a HIIT, HIT-RT or corresponding control group. HIIT predominately consisted of interval training 90 s−12 min, (2–4 sessions/week), HIT-RT (2–3 sessions/week) was applied as a single set resistance training to muscular failure. Core intervention length of both protocols was 16 weeks. Main inclusion criteria were overweight-obese status (BMI 25–35 kg/m^2) and full employment (occupational working time: ≥38.5 h/week). Primary study-endpoint was the Metabolic Syndrome (MetS) Z-Score, secondary study-endpoints were ventricular stroke volume index (SVI) and myocardial mass index (MMI) as determined by Magnetic Resonance Imaging. The Intention to treat (ITT) principle was applied to analyze the summarized data set. Twenty-seven eligible men of the HIT-RT and 30 men of the HIIT group were included in the ITT. Both interventions significantly ($p < 0.001$) improve the MetS Z-Score, however the effect of HIIT was superior ($p = 0.049$). In parallel, HIT-RT and HIIT significantly affect SVI and MMI, with the effect of HIIT being much more pronounced ($p < 0.001$). Although HIIT endurance exercise was superior in favorably affecting cardiometabolic risk and particularly cardiac performance, both exercise methods positively affect cardiometabolic risk factors in this overweight to obese, middle-aged cohort of males with low time resources. Thus, the main practical application of our finding might be that in general overweight-obese people can freely choose their preferred exercise type (HIIT-END or HIT-RT) to improve their cardiometabolic health, while investing an amount of time that should be feasible for everybody.

Trial Registrations: NCT01406730, NCT01766791.

Keywords: high intensity interval training, high intensity resistance exercise training, single set resistance exercise training, cardiometabolic risk, cardiac parameters, metabolic syndrome

INTRODUCTION

Cardiovascular and cardiometabolic diseases are leading causes of death worldwide (Rao, 2018). Physical activity and in particular exercise favorably affect the incidence and development of this problem (Börjesson et al., 2010; Lin et al., 2015), however only the minority of people (Clark, 1999; Rütten et al., 2005) exercise frequently enough to favorably affect cardiorespiratory and musculoskeletal fitness (Garber et al., 2011). Since most people gave time constraints as the main obstacle to exercising frequently (Rütten et al., 2009), time-effective exercise protocols might be appropriate methods for increasing people's compliance with exercise or training interventions. High intensity exercise training (HIT)—applied as either endurance (HIIT) or resistance exercise (HIT-RT) training—i.e., methods that feature low exercise volumes, are such candidates. While the effect of high intensity interval training (HIIT) on cardiovascular and cardiometabolic risk factors has been frequently addressed (e.g., Gibala, 2007; Kessler et al., 2012; Haykowsky et al., 2013; Weston et al., 2013, HIT-RT defined as single set exercise protocol with work to failure; Gießing, 2008; Steele et al., 2017a) has been rarely validated to the same extent. A recent study that applied HIT-RT reported significant effects on cardiometabolic risk factors including abdominal fat mass in 30–50 year-old men (Kemmler et al., 2016a). Few studies set out to address the effect of resistance exercise vs. endurance exercise programs on cardiometabolic risk factors in overweight-obese people (e.g., Bateman et al., 2011; Sigal et al., 2014; Ramirez-Velez et al., 2016). Data of the studies were inconsistent with comparable favorable effects on cardiometabolic markers (e.g., Sigal et al., 2014) or significantly higher effects of endurance vs. resistance exercise (e.g., Bateman et al., 2011). However, all the studies focus on time-consuming high volume/low intensity protocols, and only one non-realized study protocol (Ramirez-Velez et al., 2016) addressed middle-aged men, i.e., a cohort with particularly low time resources. This aspect is of importance since drop-out rates observed for the 4–6 month interventions of Bateman et al. (2011) and Sigal et al. (2014) were high (27 and 21%) and most participants reported time constraints and loss of interest as a reason for their withdrawal.

The aim of the present study was thus to compare the effects of two closely related exercise trials, one focusing on HIIT exercise, the other on HIT-RT, in an untrained cohort of overweight to obese men 30–50 years old with low time resources.

Our primary hypothesis was that (1) HIIT is significantly more effective for favorably affecting the Metabolic Syndrome Z-score (MetS Z-Score) compared with HIT-RT, while (2) both exercise protocols generated significant changes in the MetS Z-Score.

Our core secondary hypothesis was that HIIT is significantly more effective for favorably affecting (1) ventricular stroke volume index and (2) myocardial mass index compared with HIT-RT.

Another secondary hypothesis was that (1) HIIT is significantly more effective for favorably affecting body fat rate compared with HIT-RT while (2) HIT-RT is significantly more effective for favorably affecting Lean Body Mass (LBM) compared with HIIT.

MATERIALS AND METHODS

Experimental Design

We compared two randomized controlled trials (Kemmler et al., 2015, 2016c) of comparable length with two independent cohorts of men 30–50 years old living in the area of Erlangen-Nürnberg. Both studies, i.e., the Running Strengthen the Heart (RUSH) study and the Physical Adaptions in Untrained on Strength and Heart (PUSH), were studies that focus on time-efficient exercise strategies applied with high intensity (HIT). In this paper we concentrate on the effect of high intensity interval training (HIIT) vs. high intensity resistance training (HIT-RT) on cardiometabolic risk factors and markers in a subgroup of overweight to obese men. The studies were initiated by the Institute of Medical Physics (IMP) and conducted in close cooperation with the Department of Radiology, Friedrich-Alexander University of Erlangen-Nürnberg (FAU). The studies were approved by the ethics committee of the FAU (RUSH: No. 4463, PUSH: No. 53_12 B) and complied with the Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects." After detailed study information all participants gave written informed consent. The studies are fully registered under ClinicalTrials.gov (RUSH: NCT01406730, PUSH: NCT01766791).

Participants

Briefly, we used the citizens' register of the municipality to contact 2,000 randomly selected men aged 30–50 years in the area of Erlangen-Nürnberg, Germany. Personalized letters gave detailed study information including the most relevant eligibility criteria [e.g., training status, study period, contraindications, Body Mass Index (BMI)]. Men who responded were checked for eligibility by phone and physical assessments before being invited to joint information sessions. Eligibility criteria applied for both studies were (1) untrained (i.e., ≤ one endurance (RUSH) or resistance (PUSH) exercise session/week; (2) pathological changes in the heart; (3) acute inflammatory diseases; (4) medication/diseases affecting cardiovascular system or muscles; (5) severe obesity (BMI >35 kg/m^2); (6) contraindication for Magnetic Resonance Imaging (MRI) assessment; and (7) foreseeable absence of more than 2 weeks during the intervention period. For details of the number of subjects excluded due to the eligibility criteria, the reader is kindly referred to the corresponding publications (Kemmler W. et al., 2014; Wittke et al., 2017). Finally, 120 (PUSH) and 81 men (RUSH) respectively, eligible and willing to participate, were randomly assigned to three (PUSH) or two (RUSH) subgroups with different intervention protocols vs. a non-training control group. However, in this retrospective comparative analysis we focus on overweight-obese (BMI 25–35 kg/m^2), fully employed (occupational working time: ≥38.5 h/week) men who conducted the HIIT or HIT-RT protocol. Thus, finally 27 participants of the PUSH HIT-RT and 30 participants of the RUSH HIIT intervention groups were included in the present analysis. In order to give the reader an overview of the study-arm effects, we have also listed the results of the 42 eligible (see criteria above) participants of the pooled control group who were not included in the statistical analysis.

Study Procedure, Intervention

Subjects were thoroughly informed about the does and don'ts by the principal study investigators. This included avoiding intense physical activity and exercise 48 h pre-assessment.

Intervention

Apart from introduction, briefing and early conditioning, HIIT/HIT-RT core interventions of both RUSH and PUSH were 16 weeks. For details of study invention the reader is kindly referred to the corresponding publication (Kemmler W. et al., 2014; Wittke et al., 2017; Tuttor et al., 2018).

Rush protocol

Briefly, the RUSH study provided a non-linearly periodized 16-week high intensity running protocol that started with 2 sessions per week and progressively increased to 3–4 sessions per week after week 8. At least two of the sessions were performed on a Finnenbahn wood-chip trail. The participants were provided with training logs that set out the intensity, volume and frequency of running exercise for 4 weeks each. Individual prescription of running intensity based on stepwise treadmill tests to a voluntary maximum. Using the "Schwelle" software (Wassermann, 2005), the individual aerobic threshold (IAT) concept of Dickhuth et al. (1991) and Tuttor et al. (2018) (IAT: minimum lactate + 2 mmol/l) was applied to determine the IAT and the heart rate at IAT (IAT-HR), respectively. Of importance, validity of the calculated IAT-HR was tested at baseline and after 8 weeks by a 30 min run at the IAT-HR. The IAT-HR was then adjusted as necessary based on the subjects' perceived exertion and lactate tests. Heart rate watches (Polar RS 400, Kempele, Finland) enabled participants to properly monitor their prescribed heart rate. Depending on the length of the intervals (90 s−12 min), exercise intensity during the HIIT-sessions ranged between 95 and >110% IAT-HR. Rest periods between the high intensity cycles averaged 1–3 min at ≈70–75 IAT-HR and consisted of slow jogging and/or fast walking. Apart from HIT intervals, high intensity continuous running was applied for 25–45 min at the IAT (i.e., 100% IAT-HR) every 4–5th session. Total volume per session including warm up and cool down averaged 40–50 min/session. Two of the three to four sessions/week were consistently supervised by the principal investigator (MT).

Push protocol

The PUSH study provided a periodized 16-week high intensity resistance exercise training protocol with 2 to (every 3rd−4th week) 3 sessions/week. All the main muscle groups were addressed by 10–12 exercises/session (from an exercise pool of 17 exercises) using resistance training machines (MedX, Ocala, Fl., USA). Following recent definitions (Gießing, 2008; Giessing et al., 2016), HIT-RT was set as a single set RT to muscular failure+ (Steele et al., 2017a) using intensifying strategies. As with RUSH, participants were provided with 4 week training logs (linearly periodized with each 4th week a recreational exercise week) that prescribed the order of exercises, number of repetitions, intensity (Steele et al., 2017a) and movement velocity (time under tension (TUT in s) during the concentric, isometric, eccentric phase). The number of repetitions was steadily decreased from 8–10 to 3–5 reps over all four 4 weeks phases. After the 4 weeks of this exercise protocol, phase 2 also focused on work to muscular failure (MMF) with rest periods that progressively decreased from 2–3 min to 1 min of rest between the exercises using a TUT of 2 s-1 s-2 s. Phase 3 introduced a superset/compound/giant set strategy with one session per week prescribing a synergistic approach (consecutively blocks of 2–4 exercises for the same muscle group) and one session applying an antagonistic approach (blocks with one exercise each for the agonist and one exercise each for the antagonist consecutively). Rest periods were 1 min within the blocks and 2 min between the blocks. TUT varied between "explosive" -1 s -2 s (range 8–10 reps) and 3 s-1 s-3 s (range <8 reps). During phase 4, we enhanced the muscle effort (MMF+) by prescribing further reps with reduced loads immediately after the initial work to MMF ("drop sets") using one (week 13–14) or two (week 15–16) drop sets while reducing the load by about 10% each.

Apart from exercise training parameters, training logs completed by the participants asked for rate of perceived exertion/session and net time for conducting the exercise protocol. Attendance and compliance (i.e., proper completion of prescribed length and intensity (IAT-HR) of the exercise bout) of the exercise were monitored by the instructors during the two joint sessions. Of note, HR was not monitored during the HIT-RT sessions of PUSH. Attendance and compliance of the 1–2 non-supervised RUSH sessions were protocoled in the training logs and randomly checked using the memory function of the heart rate watches. Attendance by the PUSH participants was monitored using the chip card system of the gym (Kieser, Erlangen, Germany); compliance with the exercise protocol was checked by instructors who supervised each of the HIT-RT sessions.

Study Outcome

Primary Study Endpoint

Changes in the metabolic syndrome (MetS) Z-Score according to the International Diabetes Federation (IDF; Alberti et al., 2006) from baseline to follow-up (FU).

Secondary Study Endpoints

- Changes in left ventricular (LV) stroke volume index as determined by cardiovascular MRI from baseline to FU.
- Changes in LV myocardial mass index at end-diastole as determined by CMRI from baseline to FU.
- Changes in body fat rate from baseline to FU.
- Changes in soft lean body mass from baseline to FU.

Explanatory Study Endpoints

- Changes in parameters constituting the MetS according to International Diabetes Federation (IDF; Alberti et al., 2006) from baseline to FU.
    - Resting glucose.
    - Triglycerides.
    - HDL-cholesterol.
    - Mean arterial pressure.
    - Waist circumference.

Measurements

Each participant was tested by the same experienced researcher at baseline and follow-up at about the same time of the day (±1 h). FU tests were conducted in the week (i.e., 5–7 days) after the last exercise session.

Anthropometry

Height was measured with a stadiometer (Holtain, Crymych Dyfed., Great Britain), body mass and -composition were determined via direct-segmental, multi-frequency Bio-Impedance Analysis (DSM-BIA; Inbody 770, Seoul, Korea). The latter device measures impedance of the trunk, arms and legs separately using a tetrapolar eight-point tactile electrode system that applies six frequencies (1, 5, 50, 250, 500 and 1000 kHz). In order to standardize the test procedure, participants were requested to refrain from intense physical activity 12 h and from nutritional intake 3 h prior to the DSM-BIA assessment. Waist circumference was determined as the minimum circumference between the distal end of the rib cage and the top of the iliac crest along the midaxillary line. Body mass index was calculated body mass (kg)/body height (m^2).

Metabolic Syndrome

The MetS Z-Score was calculated according to the calculation proposed by Johnson et al. (2007), albeit based on the more recent MetS definition presented by the IDF (Alberti et al., 2006) instead of the NCEP-ATP-III definition (Expert-Panel, 2001). Using this approach, MetS is prevalent if waist circumference is increased (≥94 cm for Caucasian males) and two of the following four factors are also present: (1) reduced HDL-C (<40 mg/dl for males; or specific treatment for reduced HDL-C); (2) raised triglyceride (TriGly) levels ≥ 150 mg/dl (or specific treatment); (3) raised blood pressure (≥85 or ≥135 mmHG, or specific treatment); (4) raised fasting plasma glucose (≥100 mg/dl, or previously diagnosed type 2 diabetes). Based on these cut-off points, the individual participant data and the corresponding baseline standard deviation (SD) of the entire cohort the Z-Score were calculated as follows: [(40 –HDL-cholesterol)/SD HDL-C] + [(triglycerides – 150)/SD TriGly] + [(Glucose – 100)/SD Glucose] + [(waist circumference – 94)/SD WC] + [(Mean arterial (blood) pressure (MAP) – 107.5)/SD MAP].

Blood pressure was determined in a sitting position after 5 min rest with an automatic oscillometric device (Bosco, Bosch, Jungingen, Germany). Subjects were requested to avoid intense physical activity 12 h prior to the assessment and to refrain from coffee or tea for at least 3 h prior to testing.

After an overnight fast, blood was sampled in the morning (7:00 a.m. to 9:00 a.m.) in a sitting position from an antecubital vein. Serum samples were centrifuged at 3000 RPM for 20 min and immediately analyzed by the Medical Department of the FAU. Glucose, total cholesterol, HDL-and LDL-cholesterol and triglycerides (Olympus Diagnostica GmbH, Hamburg, Germany) were determined.

For details of the CMRI procedure and image analysis the reader is kindly referred to other publications (Scharf et al., 2015, 2017). Briefly, the CMRI of both studies were consistently conducted on a 1.5 Tesla device (Magnetom Avanto, Siemens Erlangen, Germany) using a six-channel phased array surface and spine matric receiver coil. Four-, three- and two-chamber long- and short-axis cine images were compiled while using breath-hold balanced steady-state free-precession sequences with retrospective electrocardiographic gating. The following scan parameters were applied: field of view: 215 to 265 × 300 to 340 mm^2; slice thickness: 6 mm; intersection gap: 1.5 mm; repetition/echo time: 41.25 to 50.7/1.12 to 1.38 ms; flip angle: 61° to 75°; pixel size: 1.5 to 2.8 × 1.2 to 2.0 mm^2; matrix: 105 to 156 × 192 to 256; number of reconstructed phases: 25; integrated parallel acquisition techniques (PAT) acceleration factor: 2.

CMR Image Analysis

Quantitative image analysis of both studies were consistently performed using Argus 4.01 software (Siemens, Erlangen, Germany). Left (LV) and right ventricular (RV) functional analysis was independently performed by two experienced researchers. Tracing of the endo- and epicardial borders from base to apex was conducted manually at end-diastole and -systole. Papillary muscles and epicardial adipose tissue were excluded from the analysis. Stroke volume was calculated as end-diastolic volume—end-systolic volume. The myocardial mass of the left ventricle was measured at end diastole by multiplying the myocardial volume by the specific gravity of myocardium (1.05 g/ml). All results were divided by body surface area (BSA) to adjust data for weight and height.

Baseline characteristics and confounding factors (i.e., lifestyle, diseases, medication, physical activity, exercise) were assessed at baseline and FU by standardized questionnaires and personal interviews. The participants' dietary intake was assessed pre- and post-trial by a 4-day dietary protocol conducted by all participants. The consumed food was analyzed using the Freiburger Ernährungs-Protokoll [Freiburger Nutrition Protocol] (nutri-science, Hausach, Germany).

Changes in Trial Outcomes After Trial Commencement

No changes of trial outcomes were made after trial commencement.

Sample Size Analysis

Focusing on differences between HIIT and HIT-RT for the primary study endpoint "MetS Z-Score," we expected higher reductions of MetS Z-Score in the HIIT compared with the HIT-RT protocol. Based on a MetS Z-Score reduction of -2.06 ± 1.31 in the HIIT (Kemmler W. et al., 2014) and -1.03 ± 1.56 in the HIT-RT (Kemmler et al., 2016c) for the entire corresponding study arm, 31 participants per groups were needed to verify a $\alpha = 0.05$ with 80% power. However, since we expected more pronounced differences for overweight to obese people with a corresponding higher risks or prevalence of the MetS, we decided to conduct this analysis with a slightly lower sample size.

Randomization Procedures and Enrollment

Stratified for age (5-year strata), 81 (RUSH) and 120 (PUSH) participants were randomly assigned to two (RUSH) or three (PUSH) study arms: (a) HIIT or HIT-RT; (b) waiting-control group (CG) and for PUSH only (c) HIT and protein supplementation using a uniform allocation rate (1:1 or 1:1:1). However, the randomization methods differ between the studies. While RUSH used a computer-generated random list provided by an independent statistician to allocate participants to the study groups (i.e., allocation sequence generation), in the PUSH study lots were drawn by the participants themselves. Lots were put in opaque plastic shells ("kinder egg," Ferrero, Italy), and drawn from 4 bowls with three lots each (HIT-RT, CG; HIT-RT&Protein) in order to generate strata of 5 years and a uniform allocation rate. Independently of the randomization strategy, neither participants nor researchers knew the allocation beforehand. Subsequently, status of the participants was listed by the primary investigator (MT) who enrolled participants and instructed them in detail about their status including corresponding dos and don'ts.

Blinding

While participants and instructors were aware of the group status, research assistants were kept blind to the allocation of the participants and were not allowed to ask, either.

Statistical Analysis

An intention to treat analysis was applied that included all the participants who were randomly assigned independently of lost to follow-up or compliance. R statistics software was used in combination with multiple imputation by Amelia II. The full data set was used for multiple imputation, with imputation being repeated 100 times. Over-imputation diagnostic plots provided by Amelia II confirmed that the multiple imputation worked well in all cases. Based on a statistically and graphically checked normal distribution of the primary and secondary outcomes presented here, dependent *t*-tests were used to analyze within-group changes. Due to our hypothesis, we consistently focused on the two group comparison of HIIT and HIT-RT in our statistical analysis. Corresponding group differences between the exercise groups vs. control group were not addressed. Thus, Welch *t*-Tests were used to analyze differences between HIIT and HIT-RT for all primary and secondary study endpoints. However, only in order to allow the reader to assess the net changes in the exercise groups, changes in the control groups were additionally listed in **Tables 2–5**. All tests were 2-tailed, significance was accepted at $p < 0.05$ or adjusted $p < 0.05$, respectively. Effect sizes (i.e., standardized mean differences) between HIIT and HIT-RT for primary and secondary study outcomes were calculated using Cohen‘s d (Cohen, 1988). Effect sizes below d‘< 0.20 were considered negligible, 0.2− <0.5 as low, 0.5− <0.8 as moderate, 0.8− <1.3 as large and d‘≥1.3 as very large. Apart from R-statistic software and Amelia II, all the other statistical procedures were performed with SPSS 25 (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline Characteristics, Participant Flow, Lost to Follow-Up, Attendance

Table 1 shows baseline characteristics of the HIT-RT and HIIT groups. In summary, no significant differences between the HIIT and HIT-RT study-arms were observed. Further, data of the CG did not differ relevantly from results of the intervention groups. At baseline, 63% of the participants of the HIIT and 53% men of the HIT-RT were diagnosed as having the MetS according to IDF (Alberti et al., 2006).

While no participant of the HIT-RT withdrew, four subjects of the present HIIT group were lost to follow-up. Two of these men reported running-related complaints as a reason for their withdrawal. The attendance rate was significantly higher ($p < 0.001$) in the HIT-RT (93 ± 5%) compared with the HIIT group (83 ± 8%); however, due to the higher training frequency, net exercise attendance (HIIT: 41 ± 5 sessions vs. HIT-RT: 36 ± 3 sessions) was higher ($p < 0.001$) in the HIIT. Average exercise time/session was 37 ± 3 min (including 3–5 min warm up) in the HIT-RT vs. 50 ± 4 min/session (including 10 warm-up and 5 cool-down) in the HIIT ($p = 0.001$). Apart from periods of muscle pain and delayed onset of muscular soreness (DOMS), no further exercise-induced complaints were reported in the HIT-RT. In contrast, about one third of the HIIT group reported frequent periods of hip, knee or (rarely) ankle problems related to the running exercise; as mentioned, two participants quit the study due to joint problems.

Primary and Secondary Outcomes

Table 2 shows data for primary and secondary study endpoints. In order to allow the reader to adequately estimate changes in the exercise groups we additionally provide changes in the CG. Based on comparable baseline values, in summary we confirmed our primary hypothesis that (1) HIIT is significantly

TABLE 1 | Baseline data for the HIT-RT and HIIT study with between group differences.

Variable		HIT-RT (*n* = 27) MV ± SD	HIIT-END (*n* = 30) MV ± SD	*P*-value
Age [years]		43.1 ± 5.6	43.6 ± 5.0	0.748
Body height [cm]		180.0 ± 6.9	180.3 ±7.5	0.807
Body mass [kg]		92.3 ± 12.0	93.8 ±12.8	0.663
BMI [kg/m^2]		28.5 ± 2.6	28.9 ± 2.4	0.692
Occupational working time [h][a]		43.9 ± 3.7	44.7 ± 3.1	0.410
Physical activity [Index][b]		2.93 ± 1.43	2.90 ± 1.38	0.592
Training volume [min/week][a]		28 ± 31	29 ± 32	0.918
Energy Intake [kcal/d][c]		2614 ± 763	2697 ± 762	0.894
Protein Intake [g/kg/d][c]		1.07 ± 0.50	1.18 ± 0.54	0.416
CHO/Fat/Alcohol [g/d][c]		285/108/13	307/98/15	>0.403
Hypertonia [n][a]		4	4	0.872
Diabetes [n][a]		2	1	0.492
Antihypertensive drugs [n][a]		3	4	0.799
Smoker [n][a]		2	3	0.730
Ventricular ejection fraction [%]	LV	62.1 ± 7.1	61.1 ± 6.8	0.709
	RV	61.1 ± 7.0	60.9 ± 7.3	0.581

Data of the control group are shown (right column), but not included in the inference-statistical analysis listed in the table. MV, mean value; SD, standard deviation.
[a]As assessed by baseline questionnaires. [b]Based on a scale from 1 (very low) to 7 (very high) according to a subjective assessment of professional, household, and recreational activities. [c]Based on a 4-day dietary intake protocol.

TABLE 2 | Baseline data and changes in the Metabolic Syndrome Z-Sore (Met-S-Z-Score) in HIT-RT and HIIT with corresponding between group differences.

	HIT-RT (*n* = 27) MV ± SD	HIIT-END (*n* = 30) MV ± SD	*P*- value	CG (*n* = 42) MV ± SD
Metabolic Syndrome Z-score				
Baseline	0.68 ± 2.26	0.77 ± 2.54	0.896	−0.40 ± 2.55
Changes	−1.28 ± 1.32***	−2.01 ± 1.37***	0.049	0.09 ± 1.34

*Data of the control group (CG) are shown (right column), but not included in the analysis. MV, mean value; SD, standard deviation. ***$p < 0.001$.*

(p = 0.049, d' = 0.54) more effective for favorably affecting the Metabolic Syndrome Z-score (MetS-Z-Score) compared with HIT-RT. Additionally, we confirmed our hypothesis that both exercise protocols favorably affect ($p < 0.001$) the MetS Z-Score.

Table 3 gives results of our secondary study outcomes. LV stroke volume index and LV myocardial mass index increased significantly (HIT-RT: $p = 0.001$ and $p \leq 0.024$; HIIT: both $p < 0.001$) in both groups, however in line with our expectation, changes were significantly higher in the HIIT compared with the HIT-RT group ($p \leq 0.002$); effect sizes for corresponding differences were large – very large (d' = 85 and d' = 1.56). Thus, we confirmed our core secondary hypothesis that HIIT is significantly more effective for favorably affecting (1) ventricular stroke volume index and (2) myocardial mass index compared with HIT-RT.

TABLE 3 | Baseline data and changes on core secondary endpoints in the HIT-RT and HIIT with corresponding between group differences.

	HIT-RT (*n* = 27) MV ± SD	HIIT-END (*n* = 30) MV ± SD	*P*- value	CG (*n* = 42) MV ± SD
Left ventricular (LV) stroke volume index [ml/m^2]				
Baseline	48.1 ± 7.6	45.4 ± 5.8	0.137	48.3 ± 6.2
Changes	2.18 ± 3.10***	5.03 ± 3.60***	0.002	0.24 ± 2.07
LV myocardial mass index at end diastole [g/m^2]				
Baseline	56.6 ± 5.7	58.3 ± 5.9	0.273	55.7 ± 6.3
Changes	1.24 ± 2.76*	5.78 ± 3.04***	<0.001	−0.37 ± 0.68

*MV, mean value; SD, standard deviation. Data of the CG are shown (right column), but not included in the analysis. *$p < 0.05$; ***$p < 0.001$.*

TABLE 4 | Baseline data and changes on secondary endpoints in the HIT-RT and HIIT with corresponding between group differences.

	HIT-RT (*n* = 27) MV ± SD	HIIT-END (*n* = 30) MV ± SD	*P*- value	CG (*n* = 42) MV ± SD
Body fat rate [%]				
Baseline	25.2 ± 3.2	26.6 ± 3.9	0.117	26.6 ± 3.0
Changes	−1.23 ± 1.82***	−0.88 ± 2.11*	0.498	0.48 ± 1.50
Soft lean body mass [kg]				
Baseline	68.8 ± 7.2	68.4 ± 8.0	0.835	68.9 ± 6.8
Changes	0.36 ± 1.66 $^{n.s.}$	0.15 ± 2.14 $^{n.s.}$	0.673	−0.32 ± 1.42

*Data of the CG are shown, but not included in the analysis. MV, mean value; SD, standard deviation. $^{n.s.}$ $p \geq 0.05$; *$p < 0.05$; ***$p < 0.001$.*

The body fat rate (**Table 4**) decreased significantly in both exercise groups (<0.026). In contrast to our expectation, no significant differences were observed between the groups (p = 0.498; d' = 0.18). In parallel, changes of LBM (**Table 4**) did not differ significantly between the groups (p = 0.673, d' = 0.11). Of interest, no significant changes ($p \geq 0.22$) of LBM were observed in the exercise groups. Thus, we have to reject our secondary hypothesis that (1) HIIT is significantly more effective for favorably affecting body fat rate compared with HIT-RT while (2) HIT-RT is significantly more effective for favorably affecting Lean Body Mass (LBM) compared with HIIT.

Table 5 shows selected parameters constituting the MetS according to IDF (Alberti et al., 2006). Although non-significant for resting glucose (−3.3 ± 11.2 mg/dl, p = 0.160), HIIT favorably affects ($p < 0.001$) all MetS components, while HIT-RT significantly improves two out of five components (glucose: −3.1 ± 10.9 mg/dl, p = 0.146) (**Table 5**). However, significant differences between the groups were determined for HDL-C only.

Confounding Variables

Although strong emphasis was placed on the maintenance of lifestyle, diet and exercise, energy intake decreased significantly (−69 ± 176 kcal, p = 0.016) in the HIT-RT and increased slightly in the HIIT (29 ± 245 kcal, p = 0.701; p = 0.123 to HIT-RT). However, protein intake did not change relevantly in the groups

TABLE 5 | Baseline data and changes of explorative study outcomes in the HIT-RT and HIIT with corresponding between group differences.

	HIT-RT ($n = 27$) MV ± SD	HIIT-END ($n = 30$) MV ± SD	P-value	CG ($n = 42$) MV ± SD
Waist circumference [cm]				
Baseline	103.7 ± 8.3	102.7 ± 7.5	0.615	103.5 ± 7.0
Changes	−2.21 ± 2.63***	−2.78 ± 3.06***	0.449	0.61 ± 2.29
MAP				
Baseline	102.9 ± 9.3	103.4 ± 8.2	0.837	98.3 ± 9.3
Changes	−5.30 ± 5.01***	−4.10 ± 5.44***	0.376	0.12 ± 3.96
HDL-C [mg/dl]				
Baseline	46.9 ± 8.5	42.7 ± 10.7	0.104	47.9 ± 10.9
Changes	1.52 ± 5.06 $^{n.s.}$	8.33 ± 5.79***	<0.001	0.74 ± 5.43
Triglycerides [mg/dl]				
Baseline	185 ± 77	179 ± 89	0.104	155 ± 73
Changes	−12.0 ± 35.0 $^{n.s.}$	−23.1 ± 23.4***	0.191	−5.0 ± 36.3

Data of the CG are shown, but not included in the analysis. MV, mean value; SD, standard deviation. $^{n.s.}p \geq 0.05$; $^{***}p < 0.001$.

(HIT-RT: −2.5 ± 14.6 vs. HIIT 1.1 ± 12.7 g/d, $p = 0.508$). Physical activity and exercise did not change ($p \geq 0.601$) according to the FU questionnaires, however after one-on-one interviews with participants with conspicuous results for body composition changes, two participants each of the HIT-RT and CG group admitted to starting endurance exercise training (1.5–2.5 sessions of 30–60 min/w.) and/or (HIT: $n = 3$, CG: $n = 1$) reduced energy consumption (≈10–20%). No participant of the HIIT group reported corresponding changes of confounding parameters. Apart from these changes in lifestyle, no changes of medication or incidence of new diseases were reported by the participants of the groups.

DISCUSSION

The aim of this study was to determine the comparative effect of resistance vs. endurance exercise on cardiometabolic parameters in overweight-obese men using the time-effective high intensity training method. HIT-RT is defined as single set resistance exercise training to muscular failure using intensifying strategies (Gießing, 2008; Steele et al., 2017a) and HIIT is defined as repeated very short (<45 s) or short (2–4 min) bouts of high to near maximum intensity exercise (Buchheit and Laursen, 2013). Due to their low exercise volume and corresponding time effectiveness, HIT protocols might be a particularly suitable exercise strategy for middle-aged, fully employed men (Rommel et al., 2008), a group with low time resources.

Several studies that focus on HIIT and the few studies that evaluate HIT-RT protocols showed that they are effective for favorably affecting cardiometabolic risk factors and functional cardiac parameters (Gibala, 2007; Haykowsky et al., 2013; Kemmler W. et al., 2014; Scharf et al., 2015, 2017; Kemmler et al., 2016a,c; Batacan et al., 2017; Wilson et al., 2019) in different male cohorts. In general, our study confirmed these results for a cohort of overweight-obese middle-aged men, however the aim of the present study was not “proof of principle” but to compare HIT endurance and resistance protocols with respect to their dedicated effect on cardiometabolic and cardiac parameters.

In summary, our results indicate that a HIIT (endurance) protocol was superior to HIT–RT program for improving the Metabolic Syndrome Z-Sore ($p = 0.049$) and developing parameters of cardiac morphology and performance ($p < 0.001$). Surprisingly, no significant difference was determined for LBM and body fat rate. Further, reviewing the components of the Metabolic Syndrome, apart from HDL-C with more favorable changes in the HIIT ($p < 0.001$), changes of waist circumference, MAP, resting glucose and triglycerides improved favorably in both groups to a similar high extent.

Only few exercise trials (Banz et al., 2003; Stensvold et al., 2010; Bateman et al., 2011; Earnest et al., 2014; Sigal et al., 2014) focus on the direct comparison of resistance (RT) vs. aerobic (endurance) training (AET) with respect to cardiometabolic and cardiac markers. To our best knowledge, however, apart from the protocol (Ramirez-Velez et al., 2016) of an otherwise unpublished study, none of them focus on HIT-strategies for AET and RT. Revisiting the MetS, results of studies comparing AET and RT were quite heterogeneous. Bateman et al. (2011) and Earnest et al. (2014) reported significant differences for the MetS-Score in favor of AET with no or minor effects of RT on the MetS. In contrast, Sigal et al. (2014) and Stensvold et al. (2010) observed comparable favorable effects of endurance and resistance exercise on MetS components. In line with the present study, the two latter studies (Stensvold et al., 2010; Sigal et al., 2014) reported favorable changes of LBM and body fat rate in their endurance and resistance study arms without significant differences between the groups. Banz et al. (2003), who focus on CAD risk factors in a small cohort of middle aged-older overweight men, listed significantly higher reductions of body fat rate in their RT compared with their AET group. The latter study (Banz et al., 2003) further supports our result of high HDL-C increases after aerobic exercise while the effect of RT was also negligible. Thus, although both AET and RT protocols are generally effective for positively impacting the metabolic syndrome, some components of the METS differ considerably in their adaptive response. As a consequence, summarizing RT and AET is not appropriate for evaluating the effect of “exercise” on cardiometabolic health (Lin et al., 2015). Apart from differences in exercise type, the intensity and volume of the particular exercise protocol are relevant predictors of cardiometabolic effects. While there is an ongoing discussion whether HIIT or MICE (moderate intensity continuous exercise) endurance protocols are more effective for impacting the MetS (e.g., Johnson et al., 2007; Tjonna et al., 2008; Earnest et al., 2013; Kemmler W. et al., 2014; Ramirez-Velez et al., 2017) and related anthropometric or cardiometabolic parameters (review in e.g., Hansen et al., 2010; Hwang et al., 2011; Weston et al., 2013; Wewege et al., 2017; Costa et al., 2018; Andreato et al., 2019), the effect on cardiac parameters[1] is much more pronounced after HIIT protocols (e.g., Scharf et al., 2015; Huang et al., 2019). Unfortunately, corresponding data on HIT-RT (vs. high volume, low intensity RT) are not

[1]E.g., left and right ventricle end-diastolic and systolic volume index, stroke volume index, Mass index at end-diastole, myocardial mass (Scharf et al., 2015), left ventricular (LV) contractile and diastolic functions (Huang et al., 2019).

available. Spence et al. (2011) who applied CMRI to monitor ventricular adaptation from 24 weeks of endurance ($n = 10$) or resistance exercise ($n = 13$) reported significant favorable changes of morphometric and functional CMRI parameters in the endurance group only, while there were positive, albeit non-significant, effects in the RT. Apart from the (too) low statistical power, another difference between the present study and the study of Spence et al. (2011) is the more intense HIIT or HIT-RT intervention. More recently, Christensen et al. (2019) reported a comparable effect on left ventricular mass from endurance and resistance training. Of note, the authors also observed a significant reduction of epicardial adipose tissue mass after endurance and resistance exercise (32 and 24% respectively). However, while the effect on pericardial adipose tissue mass after endurance training failed to reach statistical significance, resistance training significantly reduced pericardial adipose tissue mass by 31% ($p < 0.001$). Thus, the nimbus of superiority of endurance exercise protocols in the area of cardiac health is not justified.

However, in a recent study we observed similar results of HIT-RT (as defined as single set RT to muscular failure) and high intensity multiple set RT (also to muscular failure) on the cardiometabolic syndrome Z-Score (Kemmler et al., 2016c). Thus, in parallel to AET (Swain and Franklin, 2006) there is some evidence that intensity rather than volume (per session) of RT might be the critical exercise parameter for triggering cardiometabolic effects.

Revisiting the practical application of our finding, an argument frequently cited for the implementation of HIIT and HIT-RT protocols in public health settings are their time efficiency. We confirmed this aspect fully for HIT-RT whole body exercise protocols with their net exercise time of below 35 min/session (Kemmler et al., 2016b; Wittke et al., 2017). Less clearly, HIIT protocols applied in health care settings vary considerably in interval (30 s to 4 min) and rest period (60 s to 3 min) length (Weston et al., 2013; Wewege et al., 2017; Costa et al., 2018). Further and in contrast to MICE, the high musculoskeletal strain entailed by HIIT may well make complex, and ultimately time consuming, warm-up protocols inevitable in order to prevent muscle damage and injuries. Nevertheless, in a recent systematic review and meta-analysis of HIIT vs. MICE effects in overweight to obese adults, Wewege et al. (2017) reported a significantly lower training time (i.e., ≈29 min[2] vs. ≈42 min/session) when applying HIIT.

At this point, we would like to draw the reader's attention to some limitations and features of this study. (1) The main study feature—which can be also considered as a study limitation however—was that we addressed the comparison between HIIT and HIT-RT, not in a parallel group design but consecutively in two trials. In actual fact, the project should be regarded as a combination of two randomized controlled trials with identical eligibility criteria, sample size/group, assessments, statistical procedures, and comparable length of the intervention. Nevertheless, from a methodological point of view this approach is problematic and might confound important aspects of our study. A less prominent problem might be the time effect. HIIT ran from September to December, HIT-RT was conducted between January to May. Thus, season changes of physical activity or diet may have impacted our results, although no corresponding changes were detected from the FU questionnaires. More importantly, participants were randomly assigned to an exercise or control group, but randomization did not address group allocation to HIT-RT or HIIT, which is the main issue of this contribution. Due to this inadequate randomization and stratification approach, it might have been possible that resultant differences affected our results. However, as listed in **Tables 1–5**, we did not observe corresponding group differences for baseline characteristics. (2) In the present contribution we exclusively focus on differences between HIT-RT and HIIT; the CG was not included in the analysis in order to prevent problems related to multiple testing. Corresponding data was released in previous publications (Kemmler W. et al., 2014; Kemmler W. M. T. et al., 2014; Scharf et al., 2015, 2017; Kemmler et al., 2016c; Wittke et al., 2017). However, in order to allow the reader to estimate the dimensions of changes in the HIIT and HIT-RT, we added the results of the CG in **Tables 2–5**. (3) With intervals of 90 s to 12 min but (rarely applied) also continuous bouts (25–40 min) at the IAT, our HIIT approach differs from purebred "HII̲T" protocols defined as repeated very short (<45 s) or short (2–4 min) bouts of high to near maximum intensity exercise (Buchheit and Laursen, 2013). (4) One may also criticize the less rigorous control of the exercise protocol at least in the HIIT-group. Indeed, only 2 out of 3–4 sessions were supervised; in addition, we did not consistently monitor heart rate watches in order to check whether participants actually conducted their individual sessions. Further, with respect to compliance with exercise intensity we did not analyze all the heart rate watches after the session, but randomly selected 15–20 participants (i.e., 50%) for this procedure. On the other hand, after monitoring the training logs of the HIT-RT and comparing the rate of repetitions to load we are not always convinced whether participants really worked to MMF. However, considering the close and sincere communication between researchers and participants we conclude that participants closely adhered to the exercise protocol. (4) Contrary to the commitment given, 5 HIT-RT participants started relevant endurance exercise and/or energy reduction programs. Excluding these subjects from the analysis resulted in slightly higher LBM changes (0.45 vs. 0.36 kg, **Table 4**) but lower body fat reductions (1.18 vs. 1.32 kg, **Table 4**), and did not relevantly confound our results of non-significant group differences. (5) We opted to use the MetS-Z-Score, a single continuous score based on individual participant data and cut off values for MetS criteria (Johnson et al., 2007). However, more recognized cardiometabolic parameters might have increased the evidence and generalization of the study. (6) We put together a homogeneous cohort of untrained middle-aged men for whom the relevance of time-efficient exercise protocols might be of particularly interest. With respect to generalizability, one may argue that exhausting HIT approaches might be limited to motivated or predominately healthy younger cohorts. However, considering that (a) HIIT was reported to be perceived more

[2]However, warm-up might not be consequently considered when calculating the length of the session.

"enjoyable" compared with the monotone MICE (Bartlett et al., 2011) and (b) HIIT and HIT-RT protocols were applied in cardiac rehabilitation (e.g., Haykowsky et al., 2013) or with older cohorts (e.g., Steele et al., 2017b), we do not support the latter limitation. (7) In summary, there is a considerable amount of evidence that in parallel to combined resistance and endurance exercise (e.g., Bakker et al., 2017), the effect of combined HIIT and HIT-RT protocols might result in more pronounced effects. This still has to be proven, however, considering the premise of time efficiency.

CONCLUSION

In this contribution we determined positive effects of HIIT or HIT-RT on cardiometabolic, cardiac and morphometric parameters closely related to cardiometabolic health. However, at least for the outcomes addressed here, HIIT effects were on average more pronounced. Nevertheless, we conclude that overweight to obese people can freely choose their preferred exercise type (AET or RT) to positively affect their cardiometabolic risk, while investing an amount of time that should be feasible for everybody.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of the Friedrich Alexander University Erlangen-Nürnberg; Krankenhausstrasse 12, 91052 Erlangen. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MT, SS, MK, ML, MS, MU, AW, and WK designed the study, completed data analysis and/or interpretation and drafted the manuscript. MT, AW, SS, MS, AW, and WK contributed to study conception and design and revised the manuscript. MT and WK accepts responsibility for the integrity of the data sampling, analysis, and interpretation. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by the Institute of Medical Physics, University of Erlangen-Nürnberg and the non-profit organization Städtler-Stiftung Nürnberg.

ACKNOWLEDGMENTS

The authors acknowledge support of the Institute of Radiology, the Institute of Sport Sciences, FAU-Erlangen-Nürnberg and Nürnberg Hospital. We are further very grateful for the support of the Staedtler-Stiftung (Nürnberg, Germany), Kieser Training (Erlangen, Germany) and Post SV Nürnberg (Nürnberg, Germany). The present work was performed in (partial) fulfillment of the requirements for obtaining the degree Dr. rer. biol. hum. of the FAU.

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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.

frontiers in Physiology

SYSTEMATIC REVIEW
published: 23 June 2020
doi: 10.3389/fphys.2020.00652

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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OPEN ACCESS

Edited by:
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Brad Schoenfeld,
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Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: 17 March 2020
Accepted: 22 May 2020
Published: 23 June 2020

Citation:
Shojaa M, Von Stengel S, Schoene D, Kohl M, Barone G, Bragonzoni L, Dallolio L, Marini S, Murphy MH, Stephenson A, Mänty M, Julin M, Risto T and Kemmler W (2020) Effect of Exercise Training on Bone Mineral Density in Post-menopausal Women: A Systematic Review and Meta-Analysis of Intervention Studies. Front. Physiol. 11:652. doi: 10.3389/fphys.2020.00652

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:

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

where "*corr*" is the correlation coefficient which was imputed using the mean of the correlations available for some included studies. SD_{pre} and SD_{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.

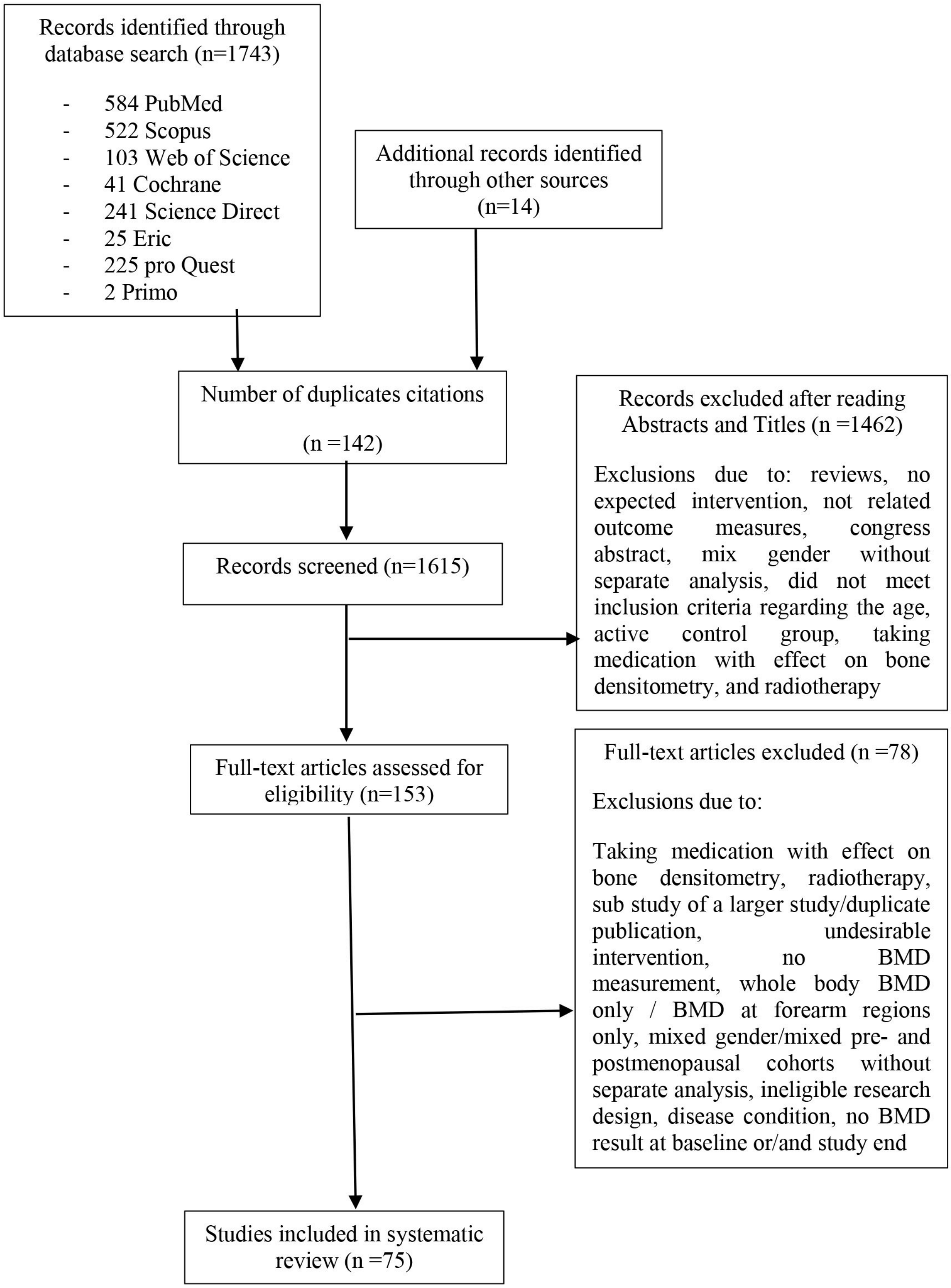

FIGURE 1 | Flow diagram of search process.

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+Pl: 86 Pl: 88	E+Pl: 55 ± 6 Pl: 56 ± 7	>1	E+Pl: 73.4 ± 14.1 Pl: 73.6 ± 15.9	E+Pl: 163 ± 5 Pl: 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+Pl: 25 Pl: 26	E+Pl: 58 ± 6 Pl: 59 ± 6	E+Pl: 8 ± 8 Pl: 10 ± 8	E+Pl: 75.4 ± 12.1 Pl: 79.5 ± 9.2	E+Pl: 161 ± 6 Pl: 160 ± 6	E+Pl: 29.1 ± 3.9 Pl: 31 ± 2.9
Chuin et al. (2009)	E+Pl: 11 Pl: 7	E+Pl: 65 ± 3 Pl: 67 ± 4	n.g. n.g.	E+Pl: 66.6 ± 8.5 Pl: 64.2 ± 7.6	n.g. n.g.	E+Pl: 26.5 ± 2.7 Pl: 26 ± 2.8
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/m²)
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+Pl: 15 Pl: 15	E+Pl: 79 Pl: 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/m²)
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, ? 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, ?1RM (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 (85%)	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 9 ± 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;

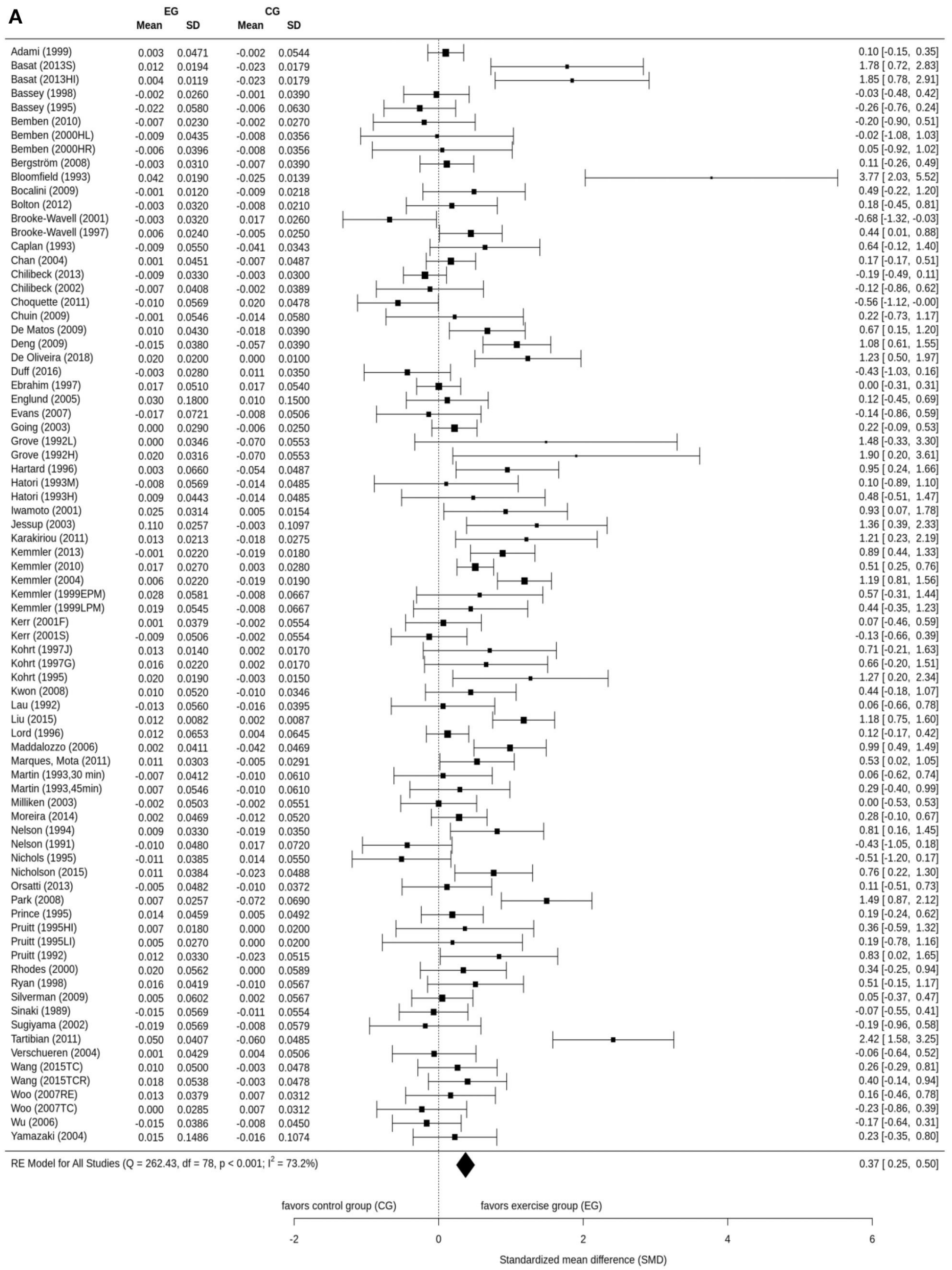

FIGURE 2 | Continued

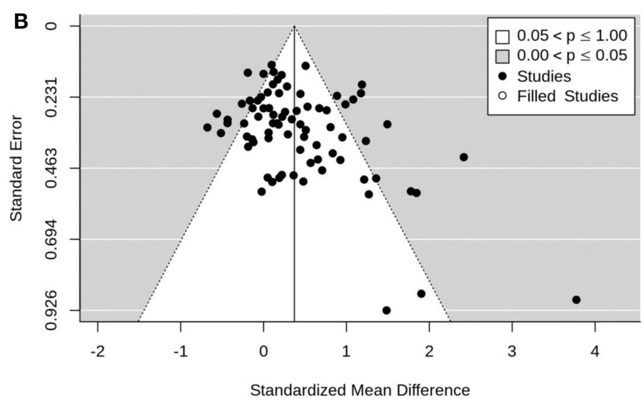

FIGURE 2 | (A) Forest plot of meta-analysis results at the LS. The data are shown as pooled standard mean difference (SMD) with 95% CI for changes in exercise and control groups. **(B)** Funnel plot of LS BMD with Trim and Fill. SE, standard error of standardized mean difference; SMD, standardized mean 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 ($\geq$18 months) (Sinaki et al., 1989; Caplan et al., 1993; Prince et al., 1995; Ebrahim et al., 1997; Iwamoto et al., 2001; Kerr et al., 2001; Kemmler et al., 2004, 2010; Chilibeck et al., 2013). According to a mixed-effects analysis, no significant difference was observed between the sub-groups ($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

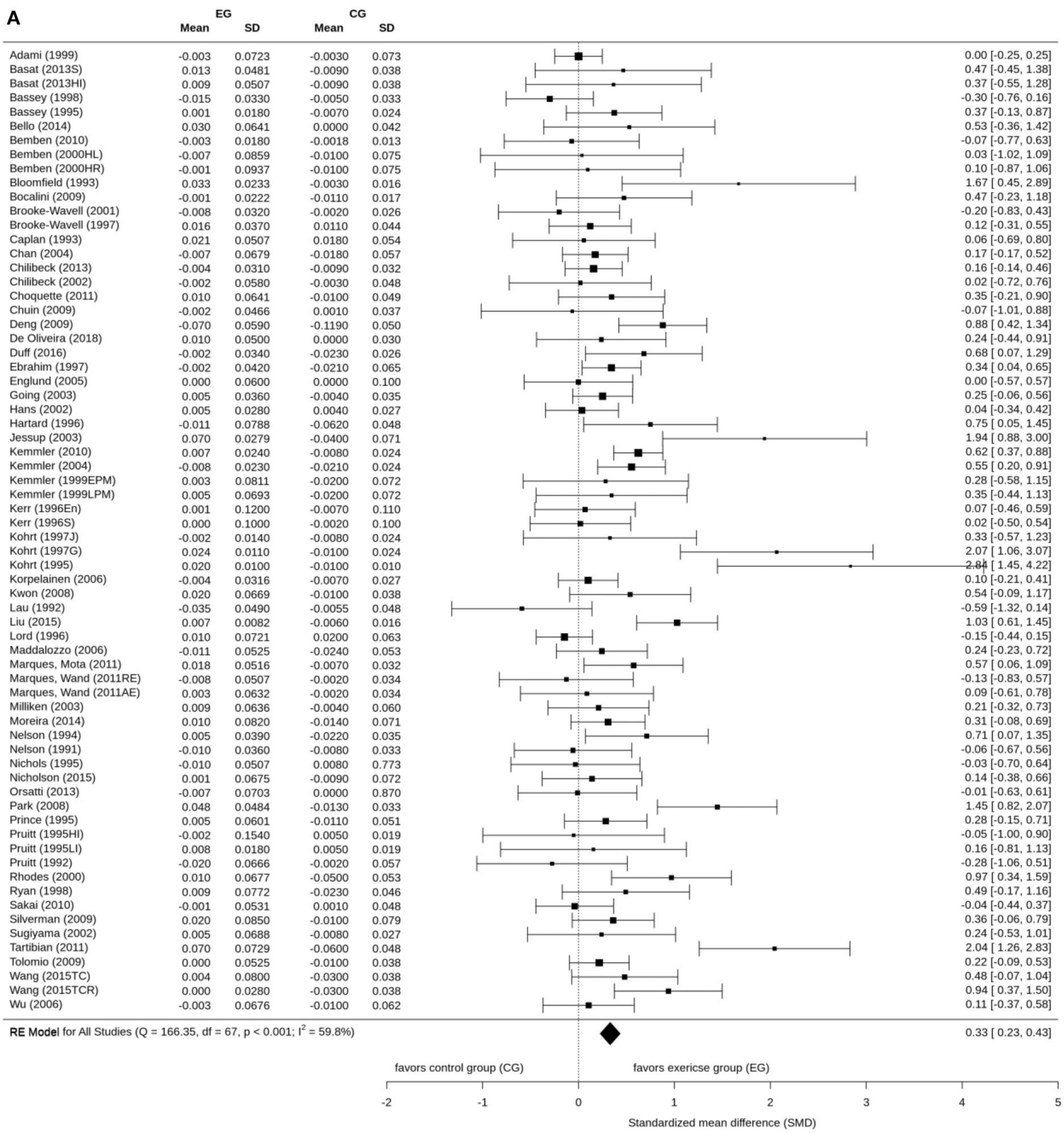

FIGURE 3 | Continued

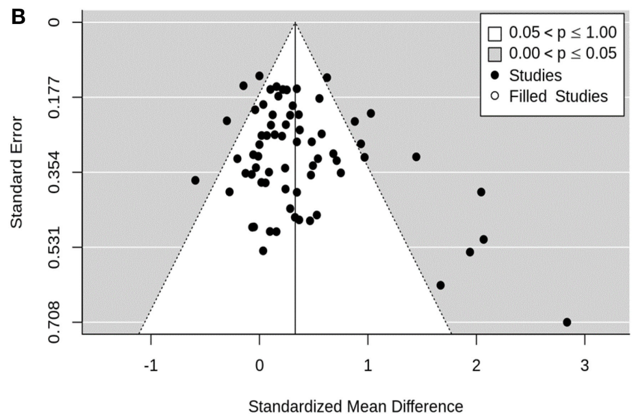

FIGURE 3 | (A) Forest plot of meta-analysis results at the FN. The data are shown as pooled standard mean difference (SMD) with 95% CI for changes in exercise and control groups. **(B)** Funnel plot of FN BMD with Trim and Fill. SE, standard error of standardized mean diffterence; SMD, standardized mean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

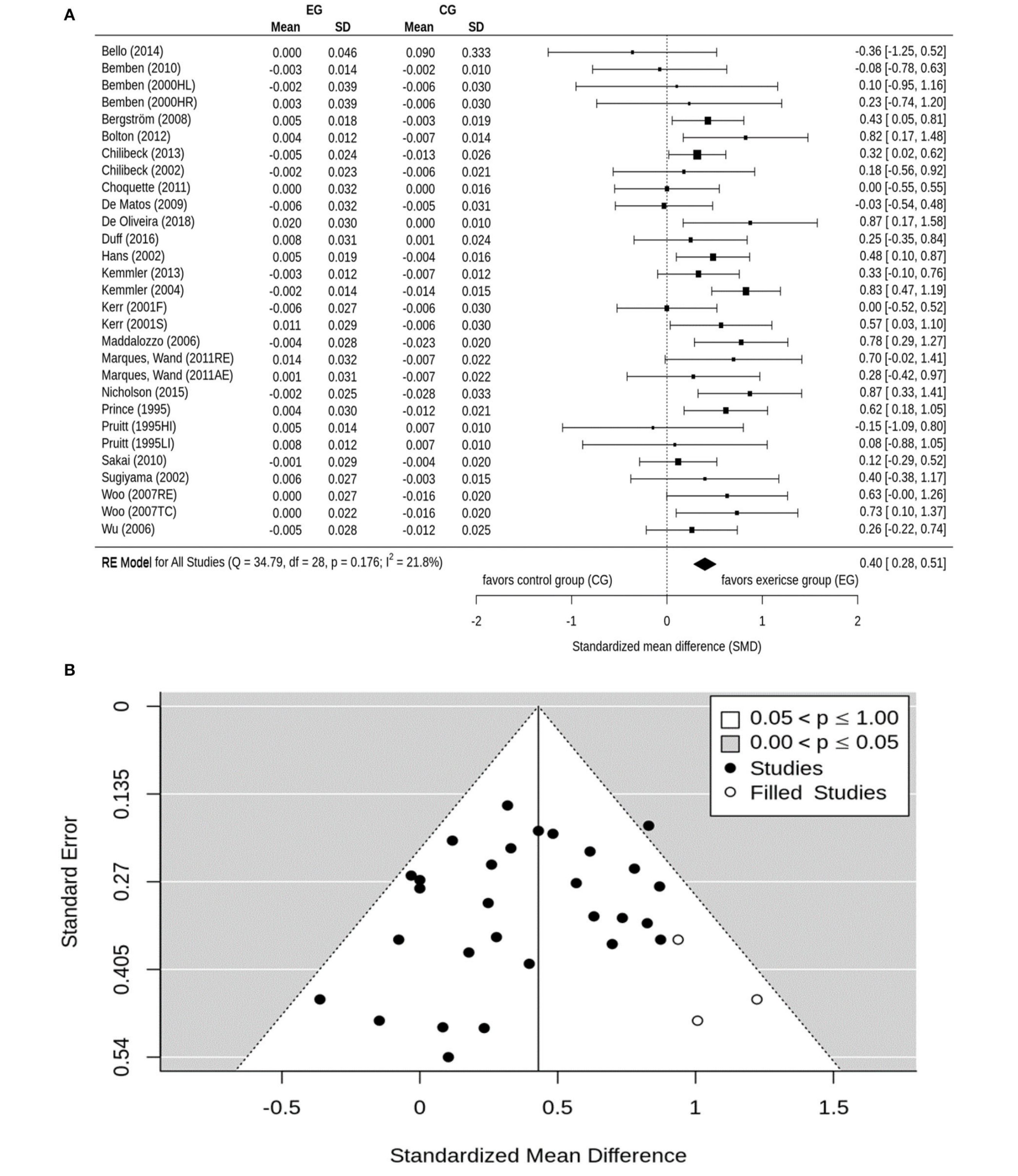

FIGURE 4 | (A) Forest plot of meta-analysis results at the total hip. The data are shown as pooled standard mean difference (SMD) with 95% CI for changes in exercise and control groups. **(B)** Funnel plot of total hip BMD with Trim and Fill. SE, standard error of standardized mean difference; SMD, standardized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

[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.

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

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.

FUNDING

This study is one of the intellectual outputs of the project ACTLIFE-Physical activity the tool to improve the quality of life in osteoporosis people and had grant support from the European

Union's Erasmus Plus Sport program under grant agreement No. 2017-2128/001-001.

With the support of the Erasmus+ Programme of the European Union

ACKNOWLEDGMENTS

The present work was performed in (partial) fulfillment of the requirements for obtaining the degree Dr. rer. biol. hum for the MS.

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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.

frontiers in Physiology

PERSPECTIVE
published: 03 July 2020
doi: 10.3389/fphys.2020.00799

Perspective: Pragmatic Exercise Recommendations for Older Adults: The Case for Emphasizing Resistance Training

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Optimal health benefits from exercise are achieved by meeting both aerobic and muscle strengthening guidelines, however, most older adults (OAs) do not exercise and the majority of those who do only perform one type of exercise. A pragmatic solution to this problem may be emphasizing a single exercise strategy that maximizes health benefits. The loss of muscle mass and strength at an accelerated rate are hallmarks of aging that, without intervention, eventually lead to physical disability and loss of independence. Additionally, OAs are at risk of developing several chronic diseases. As such, participating in activities that can maintain or increase muscle mass and strength, as well as decrease chronic disease risk, is essential for healthy aging. Unfortunately, there is a widely held belief that adaptations to aerobic and resistance exercise are independent of each other, requiring the participation of both types of exercise to achieve optimal health. However, we argue that this assertion is incorrect, and we discuss crossover adaptations of both aerobic and resistance exercise. Aerobic exercise can increase muscle mass and strength, though not consistently and may be limited to exercise that overloads a particular muscle group, such as stationary bicycling. In contrast, resistance exercise is effective at maintaining muscle health with increasing age, and also has significant effects on cardiovascular disease (CVD) risk factors, type 2 diabetes (T2D), cancer, and mortality. We posit that resistance exercise is the most effective standalone exercise strategy for improving overall health in OAs and should be emphasized in future guidelines.

Keywords: aerobic, resistance, exercise, muscle, older adults, strength, cardiovascular, diabetes

OPEN ACCESS

Edited by:
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Reviewed by:
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Anouska M. Carter, Sheffield Hallam University, United Kingdom

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Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *30 April 2020*
Accepted: *15 June 2020*
Published: *03 July 2020*

Citation:
Tavoian D, Russ DW, Consitt LA and Clark BC (2020) Perspective: Pragmatic Exercise Recommendations for Older Adults: The Case for Emphasizing Resistance Training. Front. Physiol. 11:799. doi: 10.3389/fphys.2020.00799

INTRODUCTION

Over the next 40 years the number of adults over 65 years of age will more than double in the United States from 46 million to 98 million (Mather et al., 2015). In this context, the importance of habitual exercise as it relates to healthy aging cannot be overstated. For instance, there is overwhelming evidence that lifelong exercise can delay the onset of at least 40 chronic

Abbreviations: 1RM, one repetition maximum; AET, aerobic exercise training; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; OAs, older adults; RET, resistance exercise training; T2D, type 2 diabetes.

conditions/diseases (Ruegsegger and Booth, 2018). OAs are more likely to suffer from multiple chronic conditions and poor health status than young (18–44 years) or middle-aged (45–64 years) adults (National Center for Health Statistics, 2017) accompanied by an increasing rate of health care expenditures (Alemayehu and Warner, 2004). However, from a health economics perspective, OAs who participate in community exercise programs at least once per week have annual healthcare costs 21% lower than those who do not participate (Ackermann et al., 2003) due, at least in part, to the prevention or delay of chronic diseases (Ruegsegger and Booth, 2018).

Nationally endorsed physical activity guidelines recommend a minimum of 150 min per week of Aerobic Exercise Training (AET), accompanied by muscle strengthening activities at least 2 days per week in order to maximize health benefits (US Department of Health Human Services, 2018). Unfortunately, only 13% of OAs achieve optimal health benefits by meeting both guidelines concurrently, whereas a third of OAs meet only AET or only muscle strengthening guidelines (National Center for Health Statistics, 2018; **Figure 1**). However, OAs may be overestimating their time spent in moderate-vigorous AET and/or misclassifying light-intensity activity as moderate-vigorous. For example, using accelerometer data it was reported that only 2.4% of OAs met the AET guidelines (Troiano et al., 2008), while another study reported that only 35% of OAs who self-reported meeting AET guidelines actually met them (Visser et al., 2014). Misclassification of intensity during muscle strengthening exercise is also a risk, however, this can be circumvented if exercises are performed to failure, even at low intensities (e.g., 30% of 1RM) (Mitchell et al., 2012; Van Roie et al., 2013). With the vast majority of OAs not exercising regularly or only performing one type of exercise, a more pragmatic approach of emphasizing a single exercise type may be warranted. Resistance Exercise Training (RET), arguably the most common muscle strengthening exercise, may be the most effective standalone exercise strategy for OAs as it can counteract the age-related loss of muscle mass, strength, and power that lead to poor physical function and loss of independence (Miszko et al., 2003; Liu and Latham, 2009). Additionally, there is evidence that RET can reduce the prevalence of T2D, cancer, CVD, and all-cause mortality (Stamatakis et al., 2018; Mcleod et al., 2019), historically believed to be achieved with AET. Emphasizing the importance of RET for OAs to physicians and policymakers is the first step to widespread acceptance of RET as an essential tool to combat age-related declines in health and physical function. In this Perspective article we will discuss recent evidence indicating that there are some potential crossover benefits for both types of exercise. Additionally, we will make the case that RET is the most effective standalone exercise strategy at improving overall health and reducing physical disability in OAs, and as such should be emphasized in future exercise guidelines.

PHYSICAL ACTIVITY AND CHRONIC CONDITIONS IN OLDER ADULTS

In 2008 the first nationally endorsed guidelines for physical activity were published based primarily on the Physical Activity Guidelines Advisory Committee's Scientific Report, with the intention to be updated every 10 years (US Department of Health Human Services, 2008; US Department of Health Human Services, 2018; Physical Activity Guidelines Advisory Committee, 2018). Physical activity guidelines are essentially the same for OAs and adults under the age of 65, with the additional recommendation that OAs complete some sort of balance training as part of their weekly physical activity (US Department of Health Human Services, 2018). The 2018 national guidelines are intended as a resource for policy makers and health professionals, as well as the general public, for understanding the health benefits of different types, amounts, and intensities of physical activities for individual, community, and/or national implementation strategies (US Department of Health Human Services, 2018). The overarching goal is to increase the amount of physical activity for all age groups, in turn reducing the burden of lifestyle-induced diseases and conditions that are largely preventable. Current recommendations are based on the assumption that not all health benefits can be achieved through a single type of exercise, though greater emphasis is placed on the potential benefits of AET over muscle strengthening exercise (Physical Activity Guidelines Advisory Committee, 2018). Given the evidence presented herein, these traditional beliefs should be revisited.

As previously mentioned, OAs are at higher risk of accumulating chronic health conditions (National Center for Health Statistics, 2017). Additionally, OAs are at risk of developing sarcopenia, a progressive muscular condition characterized by low muscle mass and strength (Cruz-Jentoft et al., 2019) which contributes to the loss of functional independence (Trombetti et al., 2016). It is estimated that muscle mass decreases by 10% by age 50, and that nearly half of muscle mass is lost by age 80 (Lexell et al., 1988) whereas knee extensor strength and power decline by 10–15% per decade after the age of 50 (Lindle et al., 1997; Liu and Fielding, 2011). Additionally, it has been reported that 10–15% of OAs suffer from chronic and disabling conditions that result in irreversible frailty (Vellas and Sourdet, 2017). Importantly, an individual can gain the health benefits of physical activity, regardless of age, as long as the threshold for irreversible frailty has not been reached (Serra-Rexach et al., 2011; Cadore et al., 2014). Beginning regular exercise later in life results in lower incidence of physical and/or cognitive limitations, major chronic diseases, and poor mental health compared to those who remain inactive (Hamer et al., 2014) and improvements have even been seen in previously sedentary nonagenarians (Serra-Rexach et al., 2011; Cadore et al., 2014).

AEROBIC EXERCISE TRAINING

There are several types of activity that are classified as AET, including, but not restricted to, running, hiking or brisk walking, dancing, swimming, aerobic classes or water aerobics, bicycle riding, and yard work, such as raking or pushing a lawn mower (US Department of Health Human Services, 2018). AET is known to reduce all-cause and CVD-mortality in a curvilinear dose-response manner, wherein the slope of the

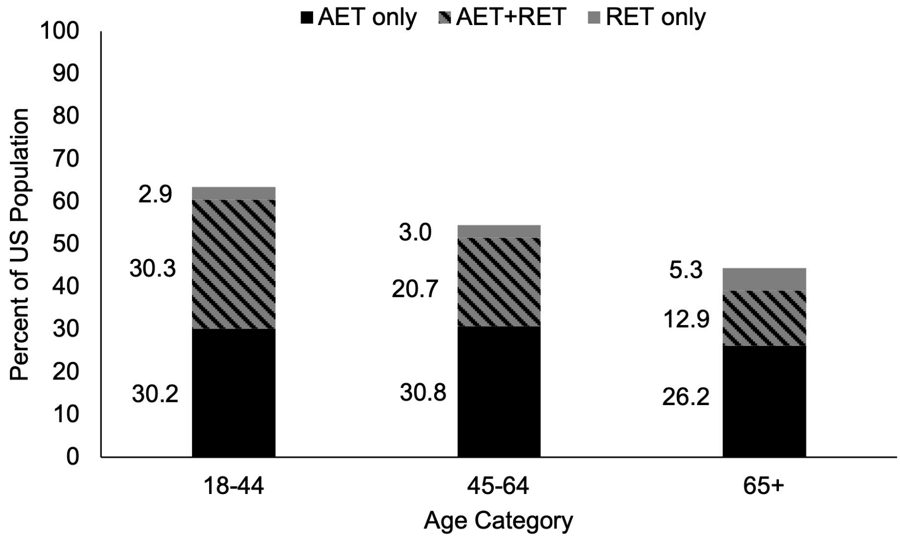

FIGURE 1 | Proportion of Adults in the United States Meeting the 2008 Physical Activity Guidelines for Americans. The proportion of young, middle-aged, and older adults who self-report meeting only the aerobic exercise guidelines of 150 min per week of moderate-intensity or 75 min per week of vigorous-intensity aerobic exercise, only the muscle strengthening guidelines of activities that strengthen the major muscle groups at least two times per week, or both aerobic and muscle strengthening guidelines concurrently. As age increases, self-reported adherence to exercise guidelines declines. A greater proportion of adults meet aerobic exercise guidelines than muscle strengthening guidelines in all age categories. AET, aerobic exercise training; RET, resistance exercise training. Adapted from public-use data provided by National Center for Health Statistics (2018).

curve is steepest early in the relationship, but levels off with increased volume (Hamer and Chida, 2008; Kelly et al., 2014). For example, Sadarangani et al. (2014) reported decreased risk of all-cause and CVD mortality of 35% and 40%, respectively, in adults with diabetes who were meeting or exceeding the aerobic guidelines, compared to those who did not exercise. However, they also reported that those who performed some AET, but did not meet the AET guidelines, still had 26% and 32% lower all-cause and CVD mortality risk, respectively (Sadarangani et al., 2014), implying that some AET is better than none, and nearly as good as meeting the guidelines. Other well-known benefits include lower incidence of CVD (Wahid et al., 2016), reduced blood pressure (Cornelissen and Smart, 2013), improved Cardiorespiratory Fitness (CRF) (Lin et al., 2015), and lower incidence of T2D and risk of cancer (Kyu et al., 2016; Wahid et al., 2016). Attenuation of long-term weight gain has also been reported (Moholdt et al., 2014), though short-term weight loss is minimal without the addition of caloric restriction (Franz et al., 2007). There is also moderate evidence that AET can reduce fall risk (Gillespie et al., 2012), increase bone mineral density (Benedetti et al., 2018), and delay onset and progression of physical disability in OAs (Tak et al., 2013). While it is clear that AET can affect several aspects of human health, the inclusion of muscle strengthening activities in the guidelines implies that AET does not increase muscular strength. However, several investigations in OAs have reported increased strength in response to AET (Izquierdo et al., 2004; Harber et al., 2009; Lovell et al., 2010; Hollings et al., 2017; Timmons et al., 2018), though careful review of the methodology suggests these adaptations may depend on the mode of exercise employed.

The rhythmic and continuous nature of AET requires that muscular contractions are of low enough intensity that they can be repeated for multiple cycles in order to reach adequate exercise duration (i.e., 30 min per day) (Chodzko-Zajko et al., 2009), and low-intensity muscle contractions (i.e., <60% of maximal) are typically less effective at increasing muscle mass if not performed to failure (Wernbom et al., 2007). Because AET has traditionally been conceived as exercise for the heart, measures of muscle mass, strength, power, and quality have largely been neglected. The few studies that have addressed muscular adaptations to AET report mixed results (Grgic et al., 2019). A recent meta-analysis comparing the hypertrophic response to either AET or RET found that while some AET protocols can result in knee extensor hypertrophy, RET is more effective at both the whole-muscle and myofiber level (Grgic et al., 2019). Of the included studies, none that utilized walking or running exercise resulted in hypertrophy, wherein half of those that utilized stationary bicycling resulted in hypertrophy, though not to the same extent as RET (Grgic et al., 2019). A number of other studies without a RET comparison group have reported hypertrophic effects using stationary bicycling in both young and OAs (Harber et al., 2009, 2012; Konopka et al., 2010, 2014; Konopka and Harber, 2014). However, muscle size is, at best, a modest contributor to strength changes with exercise in OAs (Lee et al., 2019), and few studies have measured changes in strength in response to AET.

Increases in knee extensor isometric force and/or 1RM squat have been reported in the range of 11–35% after 12–16 weeks of stationary bicycling in OAs (Izquierdo et al., 2004; Harber et al., 2009; Lovell et al., 2010), occasionally increasing to a greater extent than time-matched RET (Timmons et al., 2018).

However, walking exercise does not appear to increase knee extensor strength (Rooks et al., 1997; Kubo et al., 2007; Ozaki et al., 2011). Pooling different modes of AET results in large heterogeneity, exemplified by a meta-analysis in adults with coronary heart disease reporting changes in lower body strength ranging from −15.8% to +22.0% (median +6.3%) (Hollings et al., 2017). However, while the effects of AET on strength gains are inconsistent, long-term AET may at least protect muscular strength from age-related declines, as OAs who regularly participate in AET (10+ years) have higher knee extensor strength than sedentary OAs (Crane et al., 2013). Measurement of muscle power and quality is rare in AET studies, but some improvements have been reported (Harber et al., 2009; Konopka et al., 2010; Brightwell et al., 2019). From the data summarized herein it appears that both muscle mass and strength can be improved with AET, particularly in OAs, but this has only consistently been demonstrated in response to stationary bicycling. It should also be noted that AET is unlikely to have a global effect on muscle strength and mass, as improvements are specific to the muscles being used (i.e., lower extremities) (Physical Activity Guidelines Advisory Committee, 2018).

RESISTANCE EXERCISE TRAINING

It is widely accepted that RET promotes hypertrophy and strength gains at all ages (Peterson et al., 2010, 2011; Steib et al., 2010; Churchward-Venne et al., 2015; Law et al., 2016), and that muscular power can be increased when a high-velocity component is included in the RET protocol (Bean et al., 2009). Similar to AET, there appears to be a dose-response relationship regarding RET and health benefits, wherein higher intensities and higher volumes of RET result in greater improvements in strength and mass in OAs (Peterson et al., 2010, 2011; Steib et al., 2010; Churchward-Venne et al., 2015; Law et al., 2016). Whether the adaptive response to RET is equivalent in both young and old adults is still debatable, as several investigations have reported no difference between age groups (Häkkinen et al., 1998; Roth et al., 2001; Newton et al., 2002; Walker and Häkkinen, 2014), while others have reported a blunted response in OAs (Raue et al., 1985; Lemmer et al., 2000; Macaluso et al., 2000; Martel et al., 2006). Regardless, RET is clearly beneficial for musculoskeletal health, and is likely the most effective strategy for maintaining and/or increasing muscle mass and strength with age (Law et al., 2016) in turn preventing and potentially reversing sarcopenia and delaying loss of independence (Evans, 1996). Muscle quality, fatigue resistance, and physical function are also improved with RET (Hunter et al., 2004). Additionally, bone mineral density increases (Going and Laudermilk, 2009) and blood pressure is reduced to an equal or greater extent with RET compared to AET (MacDonald et al., 2016).

The benefits of RET, as summarized in the 2018 Scientific Report, include (1) reductions in blood pressure equivalent to AET, (2) improved physical function, (3) reduced risk of falls and injury due to falls, and (4) maintenance of lean body mass during a program of weight (Physical Activity Guidelines Advisory Committee, 2018). The effects of muscle strengthening exercise on all-cause mortality, CVD mortality, CVD risk, T2D risk, and cancer risk were not addressed in the report (Physical Activity Guidelines Advisory Committee, 2018) but not due to lack of available data. A recent analysis of nearly 400,000 Americans (age range 18–80) reported that individuals meeting muscle strengthening guidelines alone had lower prevalence of hypertension, hypercholesterolemia, diabetes, myocardial infarction, and heart disease than those only meeting AET guidelines (Bennie et al., 2019). Additionally, regular RET is associated with reduced all-cause mortality (Stamatakis et al., 2018; Liu et al., 2019), cancer incidence (Keum et al., 2016) and mortality (Stamatakis et al., 2018), CVD morbidity and number of CVD events (Liu et al., 2019), and T2D risk and markers of metabolic dysregulation (i.e., glucose disequilibrium and insulin resistance) (Grøntved et al., 2012), independent of AET participation. A prospective cohort study from the Health Professionals Follow-up Study reported a comparable dose-response relationship between increased time spent on RET or AET and lower risk of T2D in men (Grøntved et al., 2012). Causation can only be inferred from these reports, though there have been numerous randomized control trials and epidemiological studies that have attempted to better define these associations, which are discussed in the next paragraph (Smutok et al., 1993; Tanasescu et al., 2002; Gelecek et al., 2012; Grøntved et al., 2012; Yang et al., 2014; MacDonald et al., 2016; Hollings et al., 2017; Shiroma et al., 2017; Villareal et al., 2017; Ihalainen et al., 2019).

As previously mentioned, RET significantly reduces blood pressure, particularly in hypertensive individuals (MacDonald et al., 2016). The effect of RET on additional CVD and/or T2D risk factors has been reported as similar to those observed in response to AET. AET was once thought to be the lone type of exercise to reduce body fat and insulin resistance, however, research now supports RET as an effective treatment, especially if prescribed at moderate volumes and/or frequency (Villareal et al., 2017; Ihalainen et al., 2019). For example, Ihalainen et al. (2019) reported significant reductions in fat mass when RET was performed 3 days per week for 6 months, but not when performed one or 2 days per week. Additionally, RET appears to be more effective than AET at reducing fat mass (−7.3 kg vs. −6.3 kg) and attenuating loss of thigh muscle volume (−1.9% vs. −6.2%) when combined with caloric restriction (Villareal et al., 2017). OAs with T2D can also improve skeletal muscle insulin action in response to RET, independent of changes in skeletal muscle mass (Holten et al., 2004), highlighting the multifaceted benefits of RET in the skeletal muscle of OAs. Regarding CRF, RET produces similar improvements as AET (15.6% and 20.1%, respectively) in OAs with coronary heart disease (Hollings et al., 2017). Additionally, a review by Ozaki et al. (2013) reported that CRF consistently increased in response to RET in OAs (6 of 9 included studies), while improvements were rare in young adults (3 of 17 included studies). The reason for a greater response in OAs is unclear, but may be related to the lower baseline levels of CRF associated with increasing age (Jackson et al., 2009). Additional risk factors of

CVD and/or T2D that reportedly improve in response to RET in adults include insulin sensitivity (Ibañez et al., 2005), lipids and lipoproteins (Kelley and Kelley, 2009; Yang et al., 2014), triglycerides (Kelley and Kelley, 2009; Yang et al., 2014), and glycosylated hemoglobin (Gordon et al., 2009). Taken together, these results underline the critical role that RET may

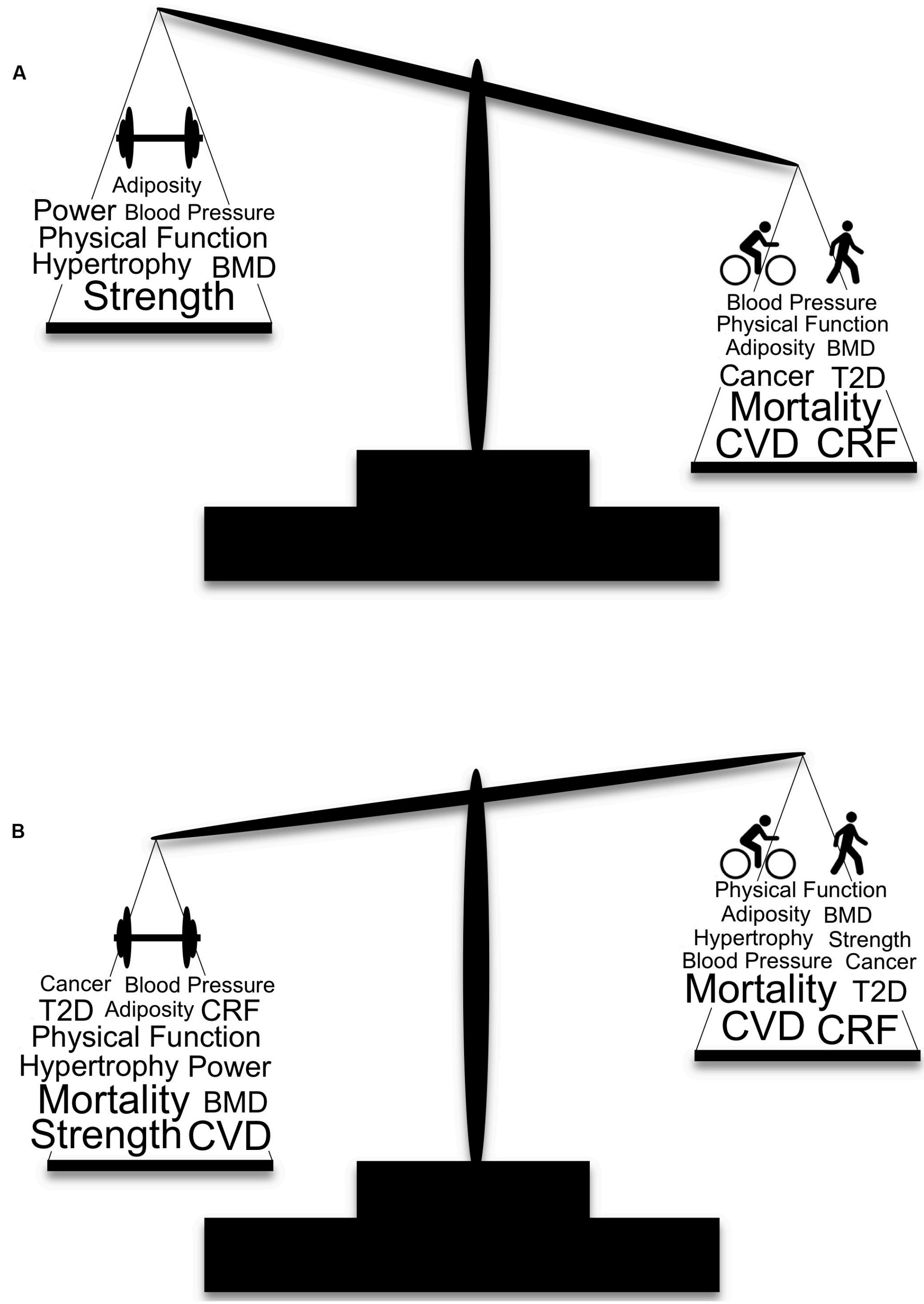

FIGURE 2 | Traditional and modern depictions of the weighted importance of aerobic and muscle strengthening exercise and selected health benefits. **(A)** The traditional view of physical activity and health is based on the tenet that adaptations from AET and RET are largely independent of one another, with recommendations for AET given more weight for their beneficial effects on cardiovascular disease and mortality. **(B)** Our modern view of physical activity and health that includes the crossover benefits of AET and RET, indicating greater weight should be given to RET over AET. Larger font indicates a greater effect of the specific health benefit. BMD, bone mineral density; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; T2D, type 2 diabetes.

have in preventing and treating detrimental health conditions that target OAs.

EMPHASIZING RET FOR OLDER ADULTS

Muscle strengthening activities result in beneficial musculoskeletal adaptations that are not consistently seen in response to AET, which is the primary reason for their inclusion in the current guidelines for the general population (US Department of Health Human Services, 2018). It is our belief that the emphasis of muscle strengthening exercise is even more critical for OAs because of the higher risk of sarcopenia and loss of independence in this population (Yazar and Yazar, 2019). There are several barriers to physical activity in OAs that can be targeted to increase participation [e.g., time, cost, disinterest, ongoing pain or illness, fear of injury, and feeling too old (Rasinaho et al., 2007; Aily et al., 2017; Burton et al., 2017a)]. Additional barriers specific to RET include perceived complexity of RET programs, lack of knowledge, and lack of age-appropriate programs (Phillips and Winett, 2010; Burton et al., 2017a,b). Addressing these barriers will be a necessary step in achieving widespread adherence to muscle strengthening guidelines. In contrast, the guidelines for AET are simplistic and can be met without specialized equipment or training (e.g., walking), though walking activity is affected by seasonal changes (Kimura et al., 2015). Presumably this is linked to why a greater proportion of OAs in the United States report meeting the AET guidelines than the muscle strengthening guidelines [39% and 18%, respectively (**Figure 1**; National Center for Health Statistics, 2018)]. Interestingly, 71% of OAs who report meeting muscle strengthening guidelines also meet the AET guidelines, whereas only 33% of OAs who report meeting AET guidelines also meet muscle strengthening guidelines (National Center for Health Statistics, 2018) suggesting that emphasizing muscle strengthening activities for OAs may indirectly result in greater AET participation. Considering the fact that 87% of OAs report either not exercising regularly or only meeting the guidelines for one type of exercise (National Center for Health Statistics, 2018) implementing a new approach to increasing exercise participation is necessary. Additionally, self-isolation due to the ongoing COVID-19 pandemic likely has detrimental effects on physical activity (Peçanha et al., 2020), making this a critical time to leverage at-home exercise programs (Hammami et al., 2020). Specifically, the creation of simple, age-appropriate, and educational RET programs that are easily accessible would address existing barriers to widespread adherence, protect OAs from exposure by not requiring gym attendance, and reduce sedentary behavior associated with self-isolation. Promoting RET as the exercise type with the greatest overall effect on health is a reasonable strategy, particularly for OAs. Of primary importance is overcoming the widespread belief that the benefits of AET and RET are independent of one another (**Figure 2**).

CONCLUSION

It is the opinion of the authors that optimal benefits from exercise are achieved by meeting both AET and muscle strengthening guidelines concurrently, and that the Physical Activity Guidelines for Americans are rational and efficacious. However, given the fact that the majority of OAs either do not exercise regularly or only perform one type of exercise, a pragmatic approach of emphasizing the exercise strategy with the greatest overall effect is now warranted. OAs have a higher prevalence of CVD, cancer, osteoporosis, and T2D compared to young or middle-aged adults, highlighting the importance of participating in activities that can reduce the risk of developing these conditions. Furthermore, OAs are at risk of losing muscle mass and strength at an accelerated rate, increasing their risk of developing the aforementioned conditions, as well as loss of independence and mortality. Therefore, participating in activities that increase, or at a minimum, maintain, muscle mass and strength should be a critical component of exercise prescription for OAs. The historical belief that the benefits of AET and RET are independent of one another, with minimal crossover, is no longer founded. However, despite the potential for some types of AET (i.e., stationary bicycling) to have an impact on muscle strength and mass in targeted muscles, RET remains the most consistent and effective method for global muscular adaptations. In addition, given the mounting evidence that RET is just as beneficial as AET at mitigating chronic diseases highly prevalent in the aging population, we posit that, as a standalone exercise strategy, RET has the greatest effect on overall health in OAs and should be emphasized in future guidelines, particularly as an entry-level program for non-exercisers.

AUTHOR CONTRIBUTIONS

DT and BC conceived of the manuscript. DT wrote the initial draft of the manuscript. BC, DR, and LC critically reviewed the manuscript. All authors contributed to the refinement of the final manuscript.

FUNDING

This work was supported, in part, by grants from the National Institutes of Health (NIA R01AG044424 to BC) and the American Heart Association (19PRE34380496 to DT).

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Yazar, T., and Yazar, H. (2019). Prevalance of sarcopenia according to decade. *Clin. Nutr. ESPEN* 29, 137–141. doi: 10.1016/j.clnesp.2018.11.005

Conflict of Interest: In the past 5-years, BC has received research funding from NMD Pharma, Regeneron Pharmaceuticals, Astellas Pharma Global Development, Inc., and RTI Health Solutions for contracted studies that involved aging and muscle related research. In the past 5-years, BC has received consulting fees from Regeneron Pharmaceuticals, Zev Industries, and the Gerson Lehrman Group for consultation specific to age-related muscle weakness. BC is a co-founder with equity of AEIOU Scientific.

The remaining 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.

frontiers in Physiology

MINI REVIEW
published: 23 July 2020
doi: 10.3389/fphys.2020.00874

Optimizing Skeletal Muscle Anabolic Response to Resistance Training in Aging

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Loss of muscle mass and strength with aging, also termed sarcopenia, results in a loss of mobility and independence. Exercise, particularly resistance training, has proven to be beneficial in counteracting the aging-associated loss of skeletal muscle mass and function. However, the anabolic response to exercise in old age is not as robust, with blunted improvements in muscle size, strength, and function in comparison to younger individuals. This review provides an overview of several physiological changes which may contribute to age-related loss of muscle mass and decreased anabolism in response to resistance training in the elderly. Additionally, the following supplemental therapies with potential to synergize with resistance training to increase muscle mass are discussed: nutrition, creatine, anti-inflammatory drugs, testosterone, and growth hormone (GH). Although these interventions hold some promise, further research is necessary to optimize the response to exercise in elderly patients.

Keywords: sarcopenia, resistance training, skeletal muscle hypertrophy, exercise, aging

OPEN ACCESS

Edited by:
Ronald F. Zernicke, University of Michigan, United States

Reviewed by:
Richard Kreider, Texas A&M University, United States
Darren Candow, University of Regina, Canada
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Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *30 April 2020*
Accepted: *29 June 2020*
Published: *23 July 2020*

Citation:
Endo Y, Nourmahnad A and Sinha I (2020) Optimizing Skeletal Muscle Anabolic Response to Resistance Training in Aging. Front. Physiol. 11:874. doi: 10.3389/fphys.2020.00874

INTRODUCTION

The loss of skeletal muscle mass with aging is a well-known phenomenon (Doherty, 2003). Lean muscle mass decreases substantially after the age of 60 (Melton et al., 2000). Severe, aging-associated loss of muscle mass and strength, also termed sarcopenia (Rosenberg, 1989) and dynapenia (Volpi et al., 2004), respectively, have profound consequences that extend beyond simple loss of mobility (Wolfson et al., 1995). Specific diagnostic criteria for sarcopenia continues to evolve (Cruz-Jentoft et al., 2010; Studenski et al., 2014), but it manifests with increased insulin resistance, loss of bone density, and an increase in falls (Dutta and Hadley, 1995; Rantanen et al., 1999). As such, these patients are at an increased risk of all-cause mortality, incident and mobility disabilities, and loss of independence (Angulo et al., 2020). From a public health perspective, the economic burden of caring for sarcopenic patients is tremendous and accounts for nearly $28.5 billion per year in expenditures, after adjusting for inflation (Janssen et al., 2004).

Many recent studies suggest that regimented physical activity, including resistance training, can be beneficial in maintaining muscle strength and function in elderly individuals (Pahor et al., 2014; Losa-Reyna et al., 2019; Martínez-Velilla et al., 2019; Rodriguez-Mañas et al., 2019; Yu et al., 2019). However, although physical training is beneficial at any age, the anabolic response to exercise decreases substantially with aging (Welle et al., 1996; Phillips et al., 2017; Lee et al., 2019). This review explores the mechanisms of cellular and molecular adaptations of skeletal muscle to exercise, with a focus on the aging-associated changes that cause hinderance of its anabolic response to exercise. We further evaluate the efficacy of supplements commonly used with physical training to optimize the exercise benefit on skeletal muscle, with the ultimate goal of preventing sarcopenia and associated adverse events.

SKELETAL MUSCLE AND AGING

Aging is associated with changes in multiple biological processes and impacts nearly every facet of tissue homeostasis (López-Otín et al., 2013). Changes specific to skeletal muscle include diminished fiber number and cross-sectional area (Lexell et al., 1988), a decline in fast-twitch muscle-fibers (Lexell, 1995), and increased fat infiltration (Marcus et al., 2010). These structural changes are responsible for the loss of strength that accompanies muscle aging (Thompson, 2002; Distefano and Goodpaster, 2018). A complex network of signaling factors are precisely regulated to maintain myogenesis and muscle mass. Protein metabolism is regulated by Akt and mammalian target of rapamycin (mTOR) signaling pathways, which are, in turn, activated by various anabolic stimuli to bring about hypertrophic response in skeletal muscle. The induction of the insulin-like growth factor (IGF) pathway, upstream of Akt/mTOR prevents muscle atrophy (Yoon, 2017), highlighting its importance in the maintenance of muscle mass. The circulating levels of IGF-1 and IGF-1 binding proteins are decreased in aging, with a corollary reduction in mTOR activation in sarcopenic individuals (Pallafacchina et al., 2002; Léger et al., 2008; Deane et al., 2013; Sharples et al., 2013).

The maintenance of muscle mass may be further limited by diminished nutritional stimuli due to poor nutritional intake (Buford et al., 2010). A lack of nutrients, including essential amino acids (EAAs), is further paired with improper post-prandial nutrient handling in the elderly (Wall et al., 2015). These changes contribute to an inability to increase muscle protein synthesis in response to exercise or nutritional availability and results in muscle atrophy with aging (Wilkinson et al., 2018). The inability to properly utilize nutrition is synonymous with anabolic resistance, in which skeletal muscle in old age cannot gain mass despite appropriate cues. Two major factors contributing to this phenomenon in elderly subjects are poor nutrition and a reduction in regimented physical activity (Steffl et al., 2017; Wilkinson et al., 2018).

Muscle hypertrophy can also be negatively regulated by catabolic signals, most prominent of which are the transforming growth factor (TGF)-β superfamily and related cytokines. Myostatin and TGF-β both limit muscle hypertrophy by regulating the expression of genes involved in differentiation and proliferation in muscle stem cells (Langley et al., 2002; Yang et al., 2007), increasing protein degradation (Sartori et al., 2009), and inhibiting mTOR activation by anabolic stimuli in mature myofibers (Trendelenburg et al., 2009). While their role in sarcopenia remains unclear, some studies have shown that an age-related increase in TGF-β signaling from myofibers occurs in parallel with a decline in Notch signaling in satellite cells (Conboy et al., 2003; Chakkalakal et al., 2012), thus resulting in a reduced regenerative capacity of aged muscle. Myostatin was found to be increased in type II muscle fibers (Shibaguchi et al., 2018), suggesting that myostatin may play a role in selective type II fiber atrophy as seen in old age.

Androgenic depravation may be a factor contributing to sarcopenia in old males (Katznelson et al., 1996; Kenny et al., 2001; Ly et al., 2001). Testosterone promotes skeletal muscle hypertrophy directly by increasing protein synthesis (Ferrando et al., 1998) and muscle stem cell division (Powers and Florini, 1975), and indirectly by increasing IGF-1 expression via ERK and mTOR signaling (Sculthorpe et al., 2012). The exact role of testosterone in sarcopenia remains to be established; however, a study reported a significant association between serum-free testosterone and muscle mass in well-nourished, elderly men (Baumgartner et al., 1999). A corollary study demonstrated that lower circulating testosterone was associated with decreased maximal performance capacity in elderly men (Häkkinen and Pakarinen, 1993).

Chronic inflammation, as occurs with aging, has been shown to have detrimental effects on muscle physiology. In particular, the NF-κB pathway may be causative in limiting skeletal muscle repair following injury and hastening atrophy (Li et al., 2008). NF-κB is highly expressed in elderly people with muscle wasting (Bruunsgaard and Pedersen, 2003) and its level correlates with decreased anabolic response (Cuthbertson et al., 2005). In multiple preclinical models, NF-κB limited myoblast differentiation and regeneration following injury (Oh et al., 2016). Taken together, the evidence suggests that pharmacological inhibition of chronically activated NF-κB may limit aging-associated muscle loss. Indeed, non-steroidal anti-inflammatory drugs (NSAID)s promote muscle regeneration following injury, although its benefit in limiting sarcopenia remains to be elucidated (Thaloor et al., 1999; Oh et al., 2016).

In addition to alterations in the systemic milieu, intrinsic changes within myofibers and muscle stem cells with aging also affects the ability of skeletal muscle to respond to anabolic stimuli. Hyperphosphorylation of mTORC1, which impairs its activation (Kang et al., 2013), is found in aged muscle of human (Markofski et al., 2015). Therefore, defective mTOR signaling likely underlies the resistance of skeletal muscle to anabolic stimuli (Guillet et al., 2004), insulin resistance (Rasmussen et al., 2006), and impaired protein/glucose homeostasis in aged skeletal muscle (Petersen et al., 2015). Mitochondrial dysfunction has also been associated with sarcopenia (Coen et al., 2013) and mitochondrial DNA damage has been shown to cause muscle wasting (Amara et al., 2007). While there are no pharmacotherapeutics that are efficacious in attenuating skeletal muscle loss in aging, resistance training may limit some of these pathologic aging associated changes in skeletal muscle by augmenting mTOR activity (Song et al., 2017).

EFFECT OF RESISTANCE EXERCISE TRAINING ON SKELETAL MUSCLE

Physical activity, especially resistance training, is unequivocally beneficial for elderly patients with regards to enhancing muscle mass and strength (Fiatarone et al., 1990; Dibble et al., 2006; Peterson et al., 2011; Drummond et al., 2012). A recent review found that when progressive resistance training (PRT) is performed 2–3 times a week at a high intensity, it results in improved physical function and strength (Liu and Latham, 2009). The frequency and duration of resistance exercise in elderly are recommended at 2–4 times per week on alternating days and lasting 30–60 min each; 1–3 sets of 8–15 reps at 80% of one-rep maximum strength, with a monthly progressive adjustment (American College of Sports Medicine Position Stand, 1998; Law et al., 2016). In skeletal muscle, functional overload induces hypertrophy resulting in increased muscle mass and fiber size in a dose-dependent manner (Frontera et al., 1988). Previous studies have demonstrated that resistance exercise or muscle contraction increases overall muscle protein turnover in favor of protein synthesis through the activation of the mTOR pathway (Biolo et al., 1995). In addition to its direct anabolic effect, exercise has been shown to increase the circulating levels of IGF-1 (Borst et al., 2001) and androgens (Hawkins et al., 2008), while decreasing myostatin levels (Hittel et al., 2010). Furthermore, physical activity promotes restoration of insulin sensitivity, mitochondrial biogenesis, and reduces inflammation (Nieman et al., 2003; Campbell and Turner, 2018).

ATTENUATED EXERCISE BENEFIT IN THE ELDERLY ON MUSCLE MASS AND STRENGTH

Despite the consensus that regimented physical training is beneficial for the maintenance of strength and function, numerous studies suggest that the effects of exercise on skeletal muscle physiology decreases with aging. Anabolic resistance describes the inability of the body to add muscle mass despite physical activity (Kumar et al., 2009; Rivas et al., 2012; Francaux et al., 2016). In older patients, the increase in lean muscle mass following resistance exercise training is substantially less than younger subjects (Pedersen et al., 2003). As such, the gain in strength following regimented exercise programs are substantially less in the elderly (Welle et al., 1996; Kosek et al., 2006; Booth and Laye, 2010). Diminished induction of muscle regeneration following exercise further dampens the overall hypertrophic response in the elderly (Ogawa et al., 1992; Behnke et al., 2012; Suetta et al., 2013). In addition, elderly patients suffer from impaired muscle activation secondary to aging-associated changes in motor unit density and morphology (Campbell et al., 1973; Raj et al., 2010; Hepple and Rice, 2016). Resistance exercise training improves innervation and thus muscle strength in elderly even without fiber hypertrophy (Messi et al., 2016). Despite exercise, however, the numbers of motor units may still decline with aging (Power et al., 2012; Piasecki et al., 2016), limiting the functional improvement attainable from exercise. Understanding the limitations of resistance training and potential mechanisms underlying this phenomenon is critical for improving exercise benefit in the elderly population.

OPTIMIZING SKELETAL MUSCLE RESPONSE TO EXERCISE IN AGING

Nutritional Supplementation

The acute anabolic responses to feeding and exercise were found to be dampened in old subjects compared to their young counterparts, thus limiting their recovery, and muscle growth (Cuthbertson et al., 2005; Durham et al., 2010). It has been hypothesized that the blunted increase in protein synthesis following acute muscle loading may influence the smaller gains in lean tissue following resistance exercise training in older adults (Durham et al., 2010). As such, supplementation of high-quality protein may improve anabolic response to a single bout of exercise (Drummond et al., 2008; Dideriksen et al., 2011; Pennings et al., 2011). Whole protein supplements such as whey and casein, both milk-derivatives, are popularly ingested with the intention to increase muscle mass. Casein, when used as a pre-sleep protein supplement, has been shown to increase myofibrillar protein synthesis rates overnight in older adults (Kouw et al., 2017). When combined with a bout of resistance exercise in the evening, rates of protein synthesis were even higher (Holwerda et al., 2016). While fiber hypertrophy was seen with pre-sleep protein ingestion during a resistance training regimen in young men (Snijders et al., 2015), outcomes in older individuals require further investigation (Holwerda et al., 2016).

Specific amino acid supplements are also available, in the forms of EAAs, branched-chain amino acids (BCAAs), and leucine. Leucine-rich EAA supplementation enhanced muscle strength following exercise, although the study included elderly women only (Kim et al., 2012). It is important to note, however, that prolonged protein supplementation with whey or casein, in the setting of a training program, does not appear to improve the exercise response in elderly patients (Godard et al., 2002; Kukuljan et al., 2009; Verdijk et al., 2009). β-hydroxy-β-methylbutyrate (HMB), a metabolite of leucine which directly activates mTOR, has also been investigated and increased lean muscle mass and strength in sarcopenic individuals (Oktaviana et al., 2019). In total, protein and amino acids are a promising exercise supplement for the elderly. Current recommendations for daily protein intake in most older individuals are 1.2–1.5 grams protein/kilogram body weight (Duetz et al., 2014). Interventional trials are required to identify the appropriate composition of proteins and/or amino acids, as well as the timing of delivery.

Separately, creatine is essential for muscle ATP production and has been commonly ingested to enhance anabolic response to exercise. Multiple studies have presented some evidence that creatine treatment, in combination with resistance training, enhances gains in muscle mass and strength following exercise beyond what is attainable with resistance exercise alone (Candow et al., 2019). The benefit of creatine therapy alone without resistance training remains unclear; some have suggested that creatine ingestion improves lean muscle mass in the elderly (Gotshalk et al., 2002), whereas others have observed no benefit in muscle mass or strength with creatine administration (Lobo et al., 2015; Baker et al., 2016; Chami and Candow, 2019). However, in elderly subjects, supplementing resistance training with creatine increased lean muscle mass and strength when compared to placebo (Candow et al., 2014; Devries and Phillips, 2014; Chilibeck et al., 2017). In addition to its known role in ATP production, numerous studies suggest that creatine's positive effect on aging muscle may work through several mechanisms, including by inducing proteins downstream of the mTOR pathway (Safdar et al., 2008), decreasing protein degradation (Parise et al., 2001), and functioning as an antioxidant (Sestili et al., 2011). Importantly, creatine therapy appears to have a low risk profile with minimal adverse effects (Kreider et al., 2017), making it an attractive supplement.

Other recently proposed nutritional supplements to counter sarcopenia and dynapenia include vitamin D and omega-3 polyunsaturated fatty acids. Vitamin D is diminished by up to 4 fold in older adults (MacLaughlin and Holick, 1985). Low vitamin D levels have been linked to muscle atrophy (Visser et al., 2003). Several studies found that vitamin D3 supplementation in the elderly results in increased muscle strength (Moreira-Pfrimer et al., 2009) as well as reduction in falls and fractures when combined with calcium (Pfeifer et al., 2009). However, others have reported no improvement in functional capacity with vitamin D supplementation (Uusi et al., 2015; Levis and Gómez-Marín, 2017; Shea et al., 2019). Omega-3, commonly found in fatty fish and seafood, may also limit sarcopenia progression and improve protein synthesis in response to anabolic stimuli (Smith et al., 2011). In addition, multiple studies show that omega-3 augments the effects of resistance training and further increases muscle mass and strength in older adults (Rodacki et al., 2012; Da Boit et al., 2017). Further interventional studies will be required to better define the efficacy and dosage for these compounds, but both are potentially efficacious supplements.

Multi-ingredient protein (MIP)-based supplements may prove to be more efficacious in improving muscle mass and strength gains with exercise as compared to single nutritional supplements alone. In a clinical trial, a MIP supplement consisting of whey protein, creatine, calcium, vitamin D, eicosapentaenoic acid, and docosahexanoic acid improved both lean muscle mass and strength in elderly patients, during exercise, as compared to placebo (Bell et al., 2017; O'Bryan et al., 2020). However, within a metanalysis, there was no benefit in muscle strength and mass, as compared to protein supplementation alone, in response to exercise (O'Bryan et al., 2020). This highlights that future research must focus on defining specific combinations and dosages.

NSAID Therapy

Chronic, age-related inflammation in skeletal muscle may play a role in aging-associated muscle loss (Barnes and Karin, 1997). As mentioned previously, NF-κB, a master transcriptional regulator of inflammation, becomes upregulated in skeletal muscle with aging (Hayden and Ghosh, 2004). This has led to investigations of whether NF-κB inhibition using commercially available NSAIDs can improve the maintenance of muscle mass (Yamamoto and Gaynor, 2001). Inhibition of NF-κB directly improves muscle regeneration after injury in aged muscle (Oh et al., 2016) and limits muscle atrophy by decreasing MuRF signaling (Cai et al., 2004). The efficacy of NF-κB inhibition, using commercially available NSAIDs, on the maintenance of muscle mass and strength in response to exercise has been explored in many clinical studies in elderly patients. A 3-month bout of resistance exercise in elderly patients with knee osteoarthritis, NSAIDs therapy resulted in a mild improvement in muscle strength, however, without hypertrophy (Petersen et al., 2011). Other studies found that NSAID treatment augmented training-induced improvement in strength with associated muscle hypertrophy and limited muscle catabolism (Trappe et al., 2011, 2013). Others have instead shown that NSAID supplementation does not improve skeletal muscle strength or function during physical training (Dideriksen et al., 2016). In addition, it should be noted that NSAID therapy is not without its risks in the elderly population. Chronic NSAID use can result in risk of renal failure, cardiovascular events, and gastrointestinal ulceration (Wongrakpanich et al., 2018). As such, the use of NSAIDs during exercise remains a controversial, but potential treatment to augment response to exercise in the aging population. Improved specificity and identifying the correct dosage are, however, requisite to further promotion of this therapy.

Testosterone Therapy

Testosterone has emerged as another potential supplement to exercise for the elderly population. Multiple studies have demonstrated that testosterone levels decrease with age (Morley et al., 1997; Wang et al., 2009). Testosterone administration to elderly patients increases both muscle mass and maximal voluntary strength in a dose-dependent fashion, possibly by the induction of myogenic gene expression (Bhasin et al., 2001). Despite this assertion, the additional benefits of physiological testosterone replacement in elderly patients remains unclear. A prospective study demonstrated increased upper body strength following testosterone treatment of elderly patients with low to normal serum testosterone, but this treatment did not offer any benefit beyond resistance exercise alone (Hildreth et al., 2013). Others have similarly reported no synergistic or additional benefits of testosterone treatment in PRT (Sullivan et al., 2005). Of note, this is in direct contrast to the benefits of supra-physiological testosterone supplementation with regards to muscle strength and mass in young men, in whom combined treatment with testosterone and exercise was more efficacious than treatment with testosterone or exercise alone (Bhasin et al., 1996). Therefore, it is necessary to consider adjustment of the duration and dosage of testosterone supplementation in exercise regimens for the elderly before conclusion about its efficacy can be drawn. Additionally, like NSAID therapy, testosterone supplementation does not come without potential adverse events, and therefore the clinical efficacy of testosterone for sarcopenia treatment should be carefully evaluated (Basaria et al., 2010).

Growth Hormone/Insulin-Like Growth Factor Supplementation

The growth hormone (GH) axis is another area that has received attention as a potential supplement for exercise therapy for the elderly. GH is made in the pituitary gland and promotes IGF-1 (insulin growth factor) expression in skeletal muscle (Jorgensen et al., 2006; Velloso, 2008). IGF-1, in turn, stimulates the Akt/mTOR pathway which, as discussed before, promotes muscle anabolism and protein synthesis in response to exercise (Bolster et al., 2003). In elderly patients, GH treatment increases lean body mass and decreases fat-to-muscle ratio from baseline, although it is unclear as to whether this was attributable to increased skeletal muscle mass (Rudman et al., 1990, 1991). However, multiple studies have shown that healthy elderly patients do not see any additional benefit in strength or muscle hypertrophy with GH supplementation as compared to exercise alone, even at 6-month follow-up (Taaffe et al., 1994, 1996; Hennessey et al., 2001; Lange et al., 2002), despite confirmation of increased levels of circulating IGF-1. Interestingly, IGF-1 administration in isolation does not increase lean muscle mass. Its effects in combination with exercise, however, have not been independently tested (Friedlander et al., 2001). Separately, losartan, an angiotensin II type I receptor blocker which potentiates IGF-1 activity, failed to improve the anabolic response to physical resistance training (Heisterberg et al., 2018). Despite the integral role of the GH/IGF axis on muscle development or hypertrophy, it does not appear to have a therapeutic benefit in physical training in healthy individuals.

CONCLUSION

Aging is a complex and heterogenous process. It is, however, uniformly associated with loss of skeletal muscle mass, strength, and function. Resistance exercise in older patients unequivocally results in substantial benefits exemplified by muscle fiber hypertrophy, increased strength, extended independent living, and reduced fall risk (Fragala et al., 2019). Many efforts have focused on improving this response further with nutritional supplements, anti-inflammatory drugs, and anabolic agents. While numerous studies have reported synergistic benefits of combining a supplement with exercise, many others suggest marginal benefits versus exercise alone, especially in elderly individuals. Future studies should utilize a standard resistance training regimen, guided by previously published position statements (American College of Sports Medicine Position Stand, 1998), with resistance exercise three times weekly at 30 min per bout at 60–80% resistance. Moreover, supplements must be individualized to patients. Elderly patients with low levels of IGF-1 or testosterone may benefit from those specific supplements, where as other elderly patients may not. New studies may focus on MIP therapies combining supplements which have demonstrated significant benefit with regards to muscle mass and strength during exercise, such as combining EAAs, Creatinine, Vitamin D, and omega-3 fatty acids. Heterogeneity in the patient population, physical training intensity, and duration of interventions make it difficult to draw generalizable conclusions, but understanding the mechanisms of anabolic resistance and augmenting response to exercise is paramount to maintaining muscle strength and function in aging.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

This work was supported by the National Institute of Aging (K76AG059996 to IS) and a Research and Education Committee Grant (IS) from the Boston Claude D. Pepper Center, which is funded by the National Institute of Aging (P30AG031679).

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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.

frontiers in Physiology

REVIEW
published: 31 July 2020
doi: 10.3389/fphys.2020.00840

Exercise, Cardiovascular Health, and Risk Factors for Atherosclerosis: A Narrative Review on These Complex Relationships and Caveats of Literature

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *13 December 2019*
Accepted: *22 June 2020*
Published: *31 July 2020*

Citation:
Santos LP and Umpierre D (2020) Exercise, Cardiovascular Health, and Risk Factors for Atherosclerosis: A Narrative Review on These Complex Relationships and Caveats of Literature. Front. Physiol. 11:840. doi: 10.3389/fphys.2020.00840

The following narrative review addresses the relationship between physical activity and exercise with cardiovascular health, focusing primarily on the following risk factors for atherosclerosis: hypertension, dyslipidemia, and vascular function. Cardiovascular diseases are intimately associated with mortality and morbidity, and current societal organization contributes to the incidence of cardiovascular events. A worldwide epidemiological transition to cardiovascular deaths was observed in the last century, with important decrements in physical activity and diet quality. An atherogenic environment started to be the new normal, with risk factors such as dyslipidemia, hypertension, and endothelial dysfunction observed in great portions of the population. Exercise is an important tool to improve overall health. For hypertension, a great amount of evidence now puts exercise as an effective therapeutic tool in the treatment of this condition. The effects of exercise in modifying blood lipid–lipoprotein are less clear. Despite the rationale remaining solid, methodological difficulties impair the interpretation of possible effects in these variables. Vascular function, as assessed by flow-mediated dilatation, is a good measure of overall vascular health and is consistently improved by exercise in many populations. However, in individuals with hypertension, the exercise literature still needs a further description of possible effects on vascular function variables. Physical activity and exercise are associated with improved cardiovascular health, especially with reduced blood pressure, and should be encouraged on the individual and population level. Evidence regarding its effects on blood lipids and flow-mediated dilatation still need solid landmark studies to guide clinical practice.

Keywords: exercise, physical activity, cardiovascular health, atherosclerosis, cardiovascular disease

INTRODUCTION

Cardiovascular diseases (CVDs) are not only the main cause of death worldwide, accounting for around 20% of deaths, but also additionally impose relevant morbidity and disability to those non-fatally affected by them (Benjamin et al., 2019). Additionally, CVDs also cause an important financial burden, loss of quality of life for the families of those who survived an event, and are one of the most expensive conditions for public health spending due to its marked prevalence (Benjamin et al., 2019).

Contemporary societies face a pandemic of hard cardiovascular outcomes, and although the mortality of such events dropped (Ribeiro et al., 2016; Mensah et al., 2017), risk factors such as lack of physical activity (PA), hypertension, and dyslipidemia still remain important. In the plethora of preventive strategies for health, exercise stands out as one intervention that can potentially address multiple classical cardiovascular risk factors (Eckel et al., 2014; Arnett et al., 2019), whereas possibly also affecting various surrogate measures of cardiovascular risk, such as cardiac structure (Kokkinos et al., 1995), baroreflex sensitivity (Laterza et al., 2007), and vascular health (Ashor et al., 2015).

In the following review, we intend to explore the context of CVDs with an emphasis in specific risk factors, such as hypertension, dyslipidemia, and endothelial dysfunction, their relationship with PA and exercise, how the current state-of-art can support these interventions, and what are the next steps to enhance the scientific knowledge in this field. We chose to explore these factors due to their importance for CVDs, together with the interesting presentation of the literature.

EPIDEMIOLOGIC TRANSITION CAUSES AND CONSEQUENCES IN POPULATION HEALTH

Modern societies have been going through many changes driven by technological advances. Some of these changes were so deep that these are now reflected not only in the way people live but also in how they die. A transition from deaths related to communicable diseases to those caused by non-communicable diseases was first observed in developed countries, amidst the last century, and is often termed as an "epidemiologic transition" (Omran, 2005; McKeown, 2009).

In low-to-middle-income countries (LMICs), between 1960 and 1980, CVDs became the leading cause of mortality (Frenk et al., 1989; Ribeiro et al., 2016). Yet, three of the five leading causes of years of life lost in 1990 were still related to poor sanitary and healthcare conditions (Frenk et al., 1989; Marinho et al., 2018). Data from Brazil in 2016 now show a shift toward non-communicable diseases. Moreover, conditions related to lifestyles such as ischemic heart disease, stroke, and diabetes have sharply gained importance, and CVDs are now responsible for more than 30% of mortality in this country (Ribeiro et al., 2016).

Urbanization and industrialization processes resulted in changes in PA and dietary intake. In developed countries, this was observed when work-related PA dropped (Church et al., 2011), whereas the consumption of high-fat and high-sugar foods had substantial growth (von Deneen and Liu, 2011). Nowadays, LMICs are no different, with rates of overweight and obesity, physical inactivity, and all health conditions attributable to these factors comparable with those in more developed nations.

PHYSICAL ACTIVITY AND EXERCISE AS THE LOST LINK BETWEEN LIFESTYLE AND HEALTH

One key aspect of humans' successful evolution was the ability to run long distances. As a societal hunter–scavenger, sustaining a high-paced pursuit for food was a strong evolutionary advantage (Lieberman et al., 2009), and therefore, our bodies were built to be physically active. As modernization advanced, these characteristics became less needed, and now, individuals spend less and less energy on a regular day.

Morris et al. were the first to show an association between PA and CVD when compared inactive and active workers, with a lower incidence of hard events shown in the latter. Since then, a great amount of evidence shows the benefits of PA. On the other hand, a decrease in occupational-related PA is noted, as demonstrated in a five-decade analysis (1960–2010), when a sharp increase in physically light [2.0–2.9 metabolic equivalents (METs)] and sedentary (<2.0 METs) work activities was coupled with plummeting levels of moderate activities (>3.0 METs) (Church et al., 2011).

Although prospective randomized studies evaluating the effects of PA on all-cause or cardiovascular mortality are non-existent, causative links between these factors are undeniable. One of the latest evidence to support such a claim is a recent meta-analysis by Ekelund et al. (2016) who found that high amounts of moderate-to-vigorous PA were associated with the elimination of the risk of death associated with high sitting time. This new evidence added importance to PA, showing that it could mitigate the associations of sedentary behavior with hard outcomes that were once thought independent. Conversely, evidence from an observational analysis of 354,277 employees between 18 and 75 years evaluated in occupational health screenings in Sweden showed a population decrease of 6.7% in absolute and 10.8% in relative cardiorespiratory capacity assessed by maximal oxygen consumption (Ekblom-Bak et al., 2019), showing that conditioning levels are dropping on a population level. Additional subgroup analyses showed that younger ages and men were the most affected strata.

Taken together, these facts reveal a "pandemic of physical inactivity." A recent report, including 1.9 million participants, showed a 27.5% prevalence of insufficient levels of PA worldwide (Guthold et al., 2018). These numbers directly impact public health, with an attributable fraction to physical inactivity of 6% of coronary heart disease burden and 9% of premature deaths (Lee et al., 2012). This way, PA is now strongly recommended as a public health measure to diminish the impact of non-communicable diseases by many scientific societies and governmental institutions (World Health Organization, 2010; Eckel et al., 2014; Physical Activity Guidelines Advisory Committee, 2018).

ATHEROSCLEROSIS – THE DISEASE OF THE CENTURY

While hard cerebro/cardiovascular outcomes such as ischemic stroke or myocardial infarction can produce devastating consequences on their own, they have one silent and long-lasting underlying factor in common: a diseased artery. In these cases, susceptible sites on the vasculature have been going through a process of subendothelial lipoprotein retention, vascular wall inflammation, and plaque formation. This process can take decades until it peaks either with vessel stenosis (and manifestations such as angina) or with plaque rupture and subsequent cellular death. The etiologic process of cerebro/CVDs relies heavily on the complex pathophysiological process of atherogenesis (Tabas et al., 2007; Gimbrone and García-Cardeña, 2016).

In a post-mortem analysis of 2,876 subjects between 15 and 34 years old, Strong et al. (1999) showed that atherosclerotic lesions were present in all aortas within the youngest age strata (15–29 years) and that the extent and prevalence of such findings increased in the oldest age group (30–34 years). These results are corroborated by other autopsy-based (McGill et al., 2000) and imaging (Tuzcu et al., 2001) studies, demonstrating that the process of subendothelial fatty-streak accumulation begins early in life and tends to happen in every human. However, lipid trapping and accumulation are not sufficient to explain why this process tends to spin out of control, leading to plaque growth and possible destabilization. Ultimately, the establishment of atherosclerotic disease is multifactorial, consisting of different components (physical, inflammatory, immunologic, metabolic, and biochemical), all of which play a role in its development.

In the following sections, we will specifically address three of these factors: dyslipidemia, hypertension, and endothelial dysfunction, later exploring their interface with PA and exercise. We also briefly mention two other factors that pertain to the pathophysiology of atherosclerosis: blood rheology and inflammation. These factors were chosen due to their close relationship with atherogenesis and the potential to be affected by exercise. **Figure 1** summarizes the effects of exercise on the explored outcomes.

DYSLIPIDEMIA AND THE ROOTS OF ATHEROSCLEROSIS ETIOLOGY

An imbalance in lipoprotein serum levels can disrupt homeostasis and lead to pathological conditions in the cardiovascular system. The term dyslipidemia was coined for any metabolic state that denotes this imbalance and is used to classify several conditions affecting lipoprotein metabolism and that implies an increased risk of disease. Subendothelial infiltration of apoB-containing lipoproteins, such as low-density lipoprotein cholesterol (LDL-c), is the basis of atherogenic processes (Ference et al., 2017). If plasma levels of these molecules are elevated, there is an increased chance of their infiltration and retention in the vascular wall, initiating plaque formation. A robust review of mendelian randomized studies has shown a logarithmic risk reduction for coronary heart disease for individuals exposed to lower LDL-c levels through life, independently by which mechanism these lower LDL-c levels are achieved (Ference, 2015).

High-density lipoprotein cholesterol (HDL-c), however, as opposed to LDL-c and other atherogenic molecules, plays a protective role in atherosclerosis pathophysiology. The main antiatherogenic property of HDL-c seems to be related to macrophage cholesterol efflux in a process that leads to the removal of cholesterol from macrophages for subsequent transport to the liver (Rothblat and Phillips, 2010). Evidence shows that each increase in 1 mg/dl of HDL-c is related to 2–3% of CVD risk reduction (Gordon et al., 1989).

Triglyceride levels, despite having a less clear association with CVDs, also compose the commonly assessed "lipid profile" and are believed to be important in the pathophysiology of atherosclerosis. In fact, hypertriglyceridemia affects LDL-c and HDL-c composition and metabolism, resulting in a dysfunctional and more atherogenic lipid profile (Miller et al., 2011). Therefore, disturbances in the balance between lipid levels, as supported by the information mentioned earlier, result in augmented CVD risk, especially in lipid profiles presenting what is called the atherogenic dyslipidemic triad (high triglycerides and LDL-c and low HDL-c) (Nordestgaard et al., 2020).

Interaction Between Lipids and Exercise: Clear as Mud

The physiological rationale for exercise interventions to positively alter the lipid–lipoprotein profile is clear. Several mechanisms could influence these changes, for example, improvements in the inflammatory profile, enhanced overall oxidative capability, and increased baseline and total daily energy expenditure. The logic behind this claim is such that exercise is indeed recommended as a tool for modifying serum lipids and to help address dyslipidemia (Riebe et al., 2018). Nonetheless, when it comes to the evidence regarding the effects of exercise training in modifying lipid–lipoprotein profile, there is still much debate. Several meta-analyses were published, with disagreeing results. We bring a non-exhaustive list of these studies to illustrate these disparate findings inside this literature.

Halbert et al. (1999), were pioneers in the synthesis of the effects of either aerobic or resistance exercise training on blood lipids profile. In their meta-analysis, 1,833 sedentary adults with no established disease were included in 31 trials (Halbert et al., 1999). The authors reported that aerobic exercise training was effective in modifying all measures of serum lipids evaluated [total cholesterol (TC): -3.9 mg/dl, LDL-c: -3.9 mg/dl, HDL-c: +1.9 mg/dl, and triglycerides: -7.1 mg/d]. However, these results should be interpreted with caution due to the limited clinical significance of the effect sizes reported and the high heterogeneity presented among the selected studies. In the same study, only four trials examining the effects of resistance training were included, with no differences in serum lipid associated with the exposure to this modality of exercise.

Hespanhol et al. (2015) examined the effects of running-based training on health markers of previously sedentary

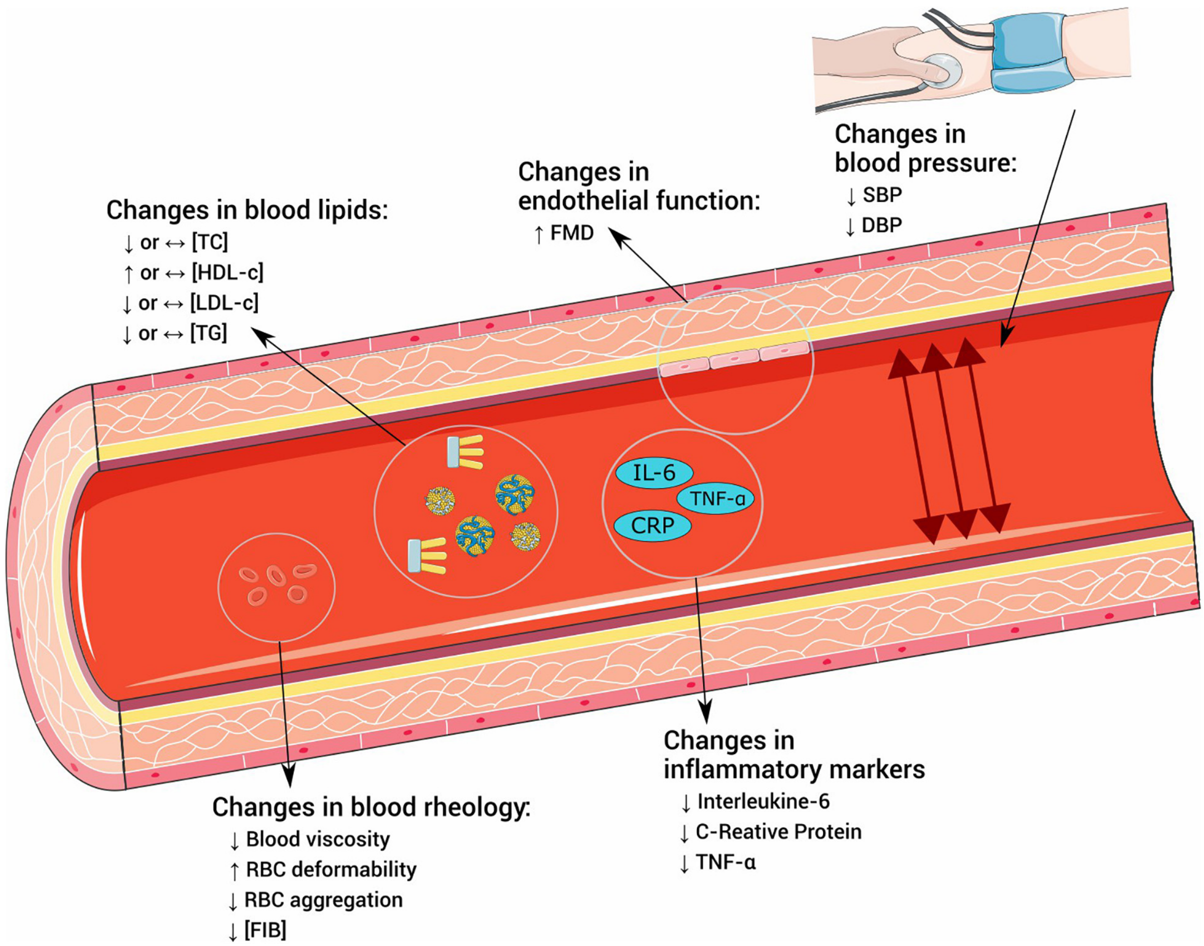

FIGURE 1 | Effects of exercise in risk factors for atherosclerosis. TC, total cholesterol; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TG, triglycerides; FMD, flow-mediated dilatation; SBP, systolic blood pressure; DBP, diastolic blood pressure; RBC, red blood cell; FIB, fibrinogen; IL-6, interleukin 6; CRP, C-reactive protein; TNF-α, tumoral necrosis factor α.

subjects. Their meta-analysis included 2,024 subjects, distributed in 35 studies. Regarding lipid–lipoproteins, the authors found a significant intervention effect only on HDL-c (+2.2 mg/dl) and triglycerides (-13.7 mg/dl), with no effects observed on TC or LDL-c. Murtagh et al. (2015) on the other hand, examined the effects of walking interventions on cardiovascular health outcomes, including lipid–lipoproteins, through a meta-analytical approach. Lipid–lipoprotein markers did not change with interventions. The results of a systematic review conducted by Tambalis et al. (2009) agree with the notion implied by the opposite effects in HDL-c in running and walking interventions observed earlier. In their review, the authors state that only 6 out of 28 trials evaluating moderate-intensity aerobic training showed a significant improvement in HDL-c, whereas 22 out of 37 trials of high-intensity aerobic training improved HDL-c. Therefore, a dose–response relationship on aerobic training intensity seems to exist in HDL-c responses to exercise, as higher intensities tend to elicit more favorable changes in this variable. However, this dose–response relationship is yet to be demonstrated experimentally.

The effects of resistance exercise training on lipid–lipoproteins were explored by Kelley & Kelley, on a reevaluation of a previous meta-analysis (Kelley and Kelley, 2009a), using an improved statistical approach (Kelley and Kelley, 2009b). The authors reported that despite observed improvements for TC, LDL-c and triglycerides, the prediction intervals calculated for a true effect in a new study in all variables pointed to a neutral effect, and therefore, caution is advised when recommending resistance exercise training to modify blood lipid profile.

Kelley & Kelley, in another meta-analytic synthesis, explored the effects of aerobic exercise training alone, diet alone, or the combination of these two approaches on serum lipid–lipoproteins. In the six included trials with direct comparisons between the interventions, exercise was not effective in modifying TC, LDL-c, and HDL-c but had a significant effect of -6.0 mg/dl in triglycerides. Diet alone was effective in reducing TC (-10.0 mg/dl), LDL-c (-5.3 mg/dl), and TG (-10.6 mg/dl), with no effect in HDL-c. On the other hand, combining diet with exercise was also not effective in modifying HDL-c values, whereas TC (-13.7 mg/dl), LDL-c (-8.8 mg/dl), and triglycerides (-13.3 mg/dl) were positively affected by this intervention (Kelley et al., 2012).

Taken together, these results demonstrate that the effectiveness of exercise training in lipid–lipoprotein balance remains debatable. Although the biological plausibility to this claim is still solid and evidence regarding impacts of aerobic exercise training intensity on HDL-c points to a possible dose–response effect, the literature on blood lipid–lipoprotein responses to exercise warrants further development. Therefore, as recommended by the current lipid management guidelines (Grundy et al., 2019), comprehensive behavior change, also encompassing dietary changes, might be the most reasonable lifestyle approach to address dyslipidemia.

HYPERTENSION – THE SILENT COMPANION OF CARDIOVASCULAR DISEASE

Arterial blood pressure (BP) is the force exerted by the blood in any given unit area of the artery walls. It is the result, in terms of fluid mechanics, of the interaction between the heart pumping blood during each cardiac cycle and the resistance exerted by the arteries to the produced blood flow. Higher and sustained BP values characterize hypertension, and its prevalence exceeds 1.3 billion people worldwide – around 30% of the world's adult population (Mills et al., 2016). Its prevalence increases with age, with pooled estimates pointing to figures around 60% among individuals older than 60 years (Mills et al., 2016). Hypertension is an important public health issue, as there is a strong association between BP levels and CVD, with data showing that each increase in 20 mm Hg in systolic BP (SBP) or 10 mm Hg in diastolic BP (DBP) doubles the risk for acute myocardial infarction or ischemic stroke (Lewington et al., 2002).

The multifactorial etiology of hypertension adds to the complexity of this health condition. Because the bodily processes involved in BP regulation derive from varied physiological systems and their interactions (i.e., nervous, humoral, cardiovascular, renal systems), maladaptation in any of these regulatory mechanisms can result in sustained elevated BP. Furthermore, chronic periods of high BP can also negatively impact these regulation processes, worsening BP levels even more. This vicious cycle sums up to the natural vascular aging process, resulting in a scenario of sympathetic hyperactivation (Grassi et al., 2015), impaired baroreflex sensitivity (Bristow et al., 1969), shear-stress-related endothelial insults (Davies, 2009), endothelial dysfunction (Mordi et al., 2016), and structural changes in the vascular system (Zanchetti et al., 1998) and the heart (Im et al., 1995). Its prevalence, imposed risk, and tendency of worsening with age and/or lack of control make hypertension the most relevant preventable cardiovascular risk factor in the contemporary ages (GBD, 2015; Risk Factors Collaborators, 2016). Yet, hypertension remains poorly treated in LMICs, with estimates of around only 10% of individuals with hypertension considered within controlled ranges of BP (Geldsetzer et al., 2019).

Recently, a robust randomized clinical trial designed to test intensive SBP treatment to a target below 130 mm Hg – against the usual target of 140 mm Hg – in hard cardiovascular outcomes was conducted. The trial had a premature ending because mortality rates were significantly different between groups, favoring intensive control (SPRINT Research Group et al., 2015). This new evidence prompted changes in hypertension guidelines in the United States, which now considers the cutoff points of 120 mm Hg for SBP and 80 mm Hg for DBP (Whelton et al., 2018). These changes result in 46% of the adult American population with at least hypertension stage I. The new European guidelines, however, did not follow the changes, and the cutoff for hypertension in Europe remains 140/90 mm Hg (Williams et al., 2018). Although the debate on cutoff points may persist in the following years, both guidelines agree when underscoring the importance of lifestyle changes, such as a healthy diet and exercise, as part of hypertension treatment. Those are accessible and effective measures that can help lower population BP levels, increase the quality of life, and lower public health expenses, especially in countries with limited resources and poor healthcare coverage.

Exercise as Therapy to Hypertension

The acute, subacute, and chronic responses to exercise – as defined by immediate (at exercise onset), short-term (minutes to several hours after an exercise session), and long-term adaptations (weeks to months after exercise training commencement), respectively – are widely studied physiological effects in BP levels. These responses were described in many aspects of cardiovascular responses to effort, ranging from how immediate changes take place in the cardiovascular system when exercising, to potential morphological adaptations induced by chronic reductions in BP related to exercise. To date, exercise is well regarded as a key lifestyle tool for hypertension, mentioned and endorsed with the maximal grade of evidence in most guidelines for hypertension management (Malachias, 2016; Whelton et al., 2018; Williams et al., 2018).

Acute Effects of Exercise in Blood Pressure

Exercise onset implies in augmented cardiovascular demand. In aerobic and resistance exercises, there are increased needs for blood flow in the exercised muscle tissues, which raises heart rate and cardiac output – determinants of SBP. Therefore, raises in this variable are expected to a certain extent. On the other hand, DBP is more influenced by peripheral vascular resistance, which behaves differently among these two modalities, leading to maintenance or decreases in this variable with aerobic exercise and increases with resistance exercise for healthy individuals.

In individuals with hypertension, however, this hemodynamic behavior might not be so clear. Exaggerated BP responses to exercise are a common finding in this population and known to be related to cardiovascular maladaptations (Ren et al., 1985) and poorer prognostic (Mundal et al., 1994). Mechanisms inherent to hypertension pathophysiology such as sympathetic hyperactivity (Manolis et al., 2014) and increased peripheral vascular resistance (Mayet and Hughes, 2003) might influence these responses. Additionally, these observations are irrespective of treatment status, suggesting limited pharmacological effectiveness of antihypertensive medication regarding BP responses to physical efforts (Chant et al., 2018). Although no consensus on a clear definition has been established, values equal or above 200 mm Hg for SBP and/or 110 mm Hg for DBP during submaximal aerobic efforts can be considered exaggerated responses (Kokkinos, 2015).

Subacute Effects of Exercise in Blood Pressure

With descriptions dating more than 120 years (Hill, 1898), subacute exercise-induced hypotension [named post-exercise hypotension (PEH)] is vastly explored, mainly because it is thought to be the driving force behind chronic BP changes with exercise (Thompson et al., 2001). These subacute effects are produced in varied exercise settings and different populations. For example, Pescatello et al. (1991) demonstrated acute BP reductions that lasted for 12.7 h in a control-matched sample of men with hypertension exposed to an aerobic exercise session. Later, the same group demonstrated an apparent intensity dose–response effect in a mixed sample of 45 men with prehypertension and hypertension, where the more pronounced effects of BP reductions were found in the day when the exercise intensity was higher, as compared with moderate and low intensities (Eicher et al., 2010). Keese et al. (2011) showed the presence of PEH after different exercise modalities (aerobic, resistance, and combined), with shorter durations observed in resistance exercise sessions when compared with aerobic or combined. Rondon et al. (2002) in an experiment with acute exercise and ambulatory BP monitoring, demonstrated that PEH is also observed in older adults with hypertension and can persist for 22 h. Moreover, we have described that individuals with resistant hypertension, despite their pharmacological unresponsiveness, also exhibit PEH for 19 h in ambulatory BP monitoring evaluations after an aerobic exercise session. In this population, however, lower intensities seemed to be more efficient in acutely reducing BP values when compared with moderate intensities (Santos et al., 2016).

These subacute BP responses to exercise are derived from changes in hemodynamic regulation, and its mechanisms are not fully elucidated to date. In fact, there is evidence showing the effects of exercise in many different aspects of BP regulation (Halliwill et al., 2013), which can ultimately lead to BP reductions. Some of the known mechanisms behind these acute responses involve a compensatory sympathetic withdrawal (Kulics et al., 1999), baroreflex resetting (Halliwill et al., 1996), and peripheral vascular resistance reduction (Cléroux et al., 1992) – as a possible consequence of sustained histamine-induced vasodilation (Barrett-O'Keefe et al., 2013) – coupled with possible changes in cardiac output after an exercise session (Rondon et al., 2002). More importantly, these reductions are closely related to chronic decreases in BP related to exercise training. A prospective interventional study evaluating 17 middle-aged individuals with prehypertension explored the relationship between exercise-induced acute and chronic BP changes, showing that the magnitude of subacute reductions may predict the extent of chronic BP lowering after training (Liu et al., 2012). This close relationship raises the hypothesis that chronic exercise-induced BP reductions are an expression of a summation of recent acute exercise effects in BP values (Thompson et al., 2001).

Chronic Effects of Exercise in Blood Pressure

Chronic exposure to exercise directly impacts BP values. The quantity and quality of evidence available to make this claim are such that many meta-analytic estimates show the positive chronic effects of various exercise modalities in BP (Cornelissen and Smart, 2013; Corso et al., 2016; MacDonald et al., 2016; Wu et al., 2019).

Cornelissen and Smart (2013) conducted one of the most robust meta-analytic explorations of chronic exercise effects on BP values. The authors explored the effects of exercise training in different modalities on BP parameters of individuals with varied categories of BP (normotension, prehypertension, and hypertension). The authors included in their analysis 93 randomized clinical trials that lasted ≥4 weeks, totaling 5,223 patients in 153 intervention groups. Exercise type was divided into endurance, resistance, combined, and isometric resistance training (IRT). Their most compelling finding was that for individuals with hypertension, aerobic exercise training could imply a reduction of 8.2 mm Hg for SBP and 5.2 mm Hg for DBP. On the other hand, no significant BP reduction was observed in the other modalities, probably due to the inclusion of fewer studies in those arms in comparison with aerobic training.

Recently, however, the current paradigm that exercise prescription for hypertension needed to be focused on aerobic exercise and only complemented by other types of exercise started to be challenged. MacDonald et al. conducted a meta-analysis evaluating 64 controlled studies (n = 2,344) to determine the efficacy of resistance training as a sole therapy to modify BP values (MacDonald et al., 2016). With the same approach, Corso et al. investigated 68 controlled studies (n = 4,110) examining the effects of concurrent training (i.e., combining resistance and aerobic training) on the same outcome (Corso et al., 2016). The authors of both meta-analyses found that, in individuals with higher baseline BP values, either resistance or combined resistance and aerobic training can be effective in chronically reducing BP values with an effect between 5 and 6 mm Hg for both SBP and DBP. With current evidence, it is safe to say that chronic exercise training in either aerobic or resistance modalities can be effective tools in modifying BP values and can be used as therapeutic tools for hypertension. These new pieces of evidence prompted a change in the current recommendations of exercise prescription for hypertension from the American College of Sports Medicine, which now considers both modalities to target BP (American College of Sports Medicine, 2019; Pescatello et al., 2019).

Other modalities of exercise might also impact BP. Wu et al. (2019) recently conducted a meta-analysis on the effects of yoga training on BP. In their pooled analysis of 49 trials, yoga was more effective than control in reducing SBP and DBP values of individuals with prehypertension (-5.2 mm Hg for SBP and -2.8 mm Hg for DBP) and hypertension (-8.7 mm Hg for SBP and -4.8 mm Hg for DBP). These results were even more pronounced in those yoga interventions with breathing and meditation components. Yet, the authors warn that the methodological quality of the included studies is low, and because of this fact, the confidence assigned to the meta-analysis results is suboptimal.

More recently, motivated by the previously observed potential effect of IRT (Cornelissen and Smart, 2013), a new meta-analysis using the "individual patient data" approach (Smart et al., 2019) examined the effects of this intervention in BP values. Using a robust methodology, the authors evaluated 12 trials, with 14 intervention groups, totaling 326 patients (191 enrolled in IRT and 135 in control), analyzed at the individual level. The authors showed reduction effects from 6.2 to 7.3 mm Hg for SBP and 2.8 to 3.3 mm Hg for DBP favoring IRT. While interesting and promising, several points should also be taken into consideration while interpreting these results. It is important to notice that this meta-analysis had mixed samples of individuals with and without hypertension, with 52% of the total samples receiving antihypertensive medication. IRT-induced adaptations might overlap with the physiological effects of antihypertensive medication (Millar et al., 2014), bearing a potential hindering-effect in the benefit for individuals treated for hypertension. Also, the total sample size of 326 patients, coupled with the information discussed earlier, demonstrates that more robust trials, evaluating individuals with hypertension solely and exploring the interactions with medications, are still warranted to improve the evidence of IRT as a treatment for hypertension.

Adding to the earlier discussed evidence on the importance of exercise in the management of hypertension, Naci et al. (2018) in a robust network meta-analysis indirectly comparing more than 39.000 subjects, demonstrated that exercise effects are comparable with those produced by common antihypertensive drugs in SBP. In their pioneer analysis, the authors have shown that for individuals with SBP >140 mm Hg, both pharmacological and exercise interventions present a similar reduction effect of approximately 9 mm Hg. In this context, it is clear that exercise training is a notably efficient tool as a non-pharmacological therapy for hypertension. Despite the known limitations of network approaches in meta-analytic studies, the presented findings are novel and exciting. At the same time, they might bear the potential to increase the importance given to exercise as an antihypertensive therapy (Pescatello, 2019).

ENDOTHELIAL DYSFUNCTION CLOSE RELATIONSHIP WITH HYPERTENSION AND CARDIOVASCULAR DISEASE

A significant aspect of cardiovascular health is closely related to endothelial function. The vascular endothelium, located in the intimal portion of the vascular wall, is responsible for secreting a myriad of vasoactive molecules, playing a key role in vasomotor balance. Likewise, these cells are also involved in a series of physiological processes such as the regulation of coagulation/anticoagulation cascades, inflammatory/anti-inflammatory activity, immunologic responses, and morphological remodeling (Konukoglu and Uzun, 2017). Because of this important role in vascular homeostasis, impairments in endothelial cell function are a critical aspect in the pathophysiology of atherogenesis (Gimbrone and García-Cardeña, 2016), and therefore, the assessment of endothelial function was used to describe several populations of interest.

Endothelial vasodilatory function, mediated mostly by nitric oxide (NO) release, is considered one of the endothelium's most relevant physiological modulations and can be assessed directly or indirectly in various forms. With the advance biomedical sciences, developments of techniques, such as the catheter-based angiography, venous occlusion plethysmography, and ultrasound imaging of flow-mediated dilatation (FMD), allowed the assessment of the endothelium-mediated vascular motricity. Together with these techniques, physiological studies allowed the role of endothelial cells to be more well elucidated with the understanding of NO metabolism and its correlates (L-arginine, nitrites, and nitrates) (Kelm, 1999) and the important role of NO modulation by NO synthase on vascular regeneration (Heiss et al., 2010).

The use of high-definition ultrasound is now preferred in vascular function evaluation due to its reduced costs and easiness to perform, when compared with catheter-based assessments, and its accuracy when compared with venous occlusion plethysmography. Nowadays, other techniques, such as finger plethysmography and peripheral artery tonometry, have also been described (Nohria et al., 2006; Matsuzawa et al., 2010).

The endothelial function assessment performed by ultrasonographic imaging of FMD, commonly performed after an occlusion maneuver in the brachial artery, is considered a proxy of general vascular health. Evidence from a comprehensive meta-analysis of prospective observational studies showed that increased FMD is correlated with reduced risk for cardiovascular outcomes in both non-CVD and CVD populations. This pooled estimate of more than 17,000 patients, followed between 6 and 115 months, demonstrated that each increase of 1% in FMD is related to a 12% risk reduction for cardiovascular outcomes (Matsuzawa et al., 2015). Interventions that positively alter endothelial function might bear the potential of protecting against future cardiovascular events, although controlled clinical studies prospectively evaluating changes in FMD and its associations with cardiovascular outcomes are lacking in the literature.

Endothelial dysfunction is widely associated with hypertension. Panza et al. (1990), on an early observation of this relationship, compared the responses to acetylcholine of forearm blood flow and vascular resistance of patients with hypertension with those of normal controls, showing impaired endothelial responsiveness in hypertension. Similarly, Treasure et al. (1993) showed impaired endothelium-dependent coronary vasodilation in subjects with hypertension when compared with normotensive controls. Additionally, vascular repair seems to be also impaired in hypertension, as shown by a cross-sectional evaluation of 160 subjects, demonstrating that aging and hypertension are associated with a lower number of circulating endothelial progenitor cells (Umemura et al., 2008). Although the understanding if endothelial dysfunction is a consequence or a cause of hypertension is not clear, both conditions indicate poor cardiovascular health, and strategies to address either one might bear the potential to affect the other.

Exercise Impacts on Endothelial Function

Even before the Nobel-winning discovery of the endothelial vasodilatory function (Furchgott and Zawadzki, 1980) and the later understanding of the role of NO and shear-stress on this endothelial-derived vasodilation, the potential of exercise to modify vascular function sparked great interest. Early experiments using indirect measures of vascular function (i.e., venous occlusion plethysmography) were pioneers to demonstrate peripheral hemodynamic behavior during and after exercise (Barendsen, 1973).

Nowadays, the notion that exercise can improve vascular function is well-established. Mechanisms of these changes are related to short-term positive adaptations in NO bioavailability and regulation by endothelial NO synthase that can ultimately lead to vascular remodeling and sheer normalization (Green et al., 2004). These mechanisms counteract the vascular maladaptation related to aging and should be considered as a first-line approach to vascular dysfunctions (Tanaka, 2019). In an example of these claims, a pooled analysis of 51 randomized controlled trials on the effects of exercise training in different modalities (aerobic, resistance, or combined) on FMD showed that all examined types of exercise could be effective in improving vascular function (Ashor et al., 2015). In this analysis, the mean effect sizes observed were among 2–3% increases in FMD for all modalities.

On the other hand, sedentary behavior is associated with impaired endothelial function. Quasi-experimental data show that 5 days of bed rest (Hamburg et al., 2007; Nosova et al., 2014) or, in the data from a crossover trial, even prolonged sitting for periods as low as 3 h (Thosar et al., 2015) can immediately affect vascular function in healthy individuals. Additionally, in the referred trial, 5-min walks as breaks in sedentary behavior prevented the decrease of vascular function associated with prolonged sitting (Thosar et al., 2015). Taken together, these results show how quickly physical inactivity can impair vascular function and how PA and exercise can contribute to mitigate these effects.

In patients with a history of CVD, such as coronary artery disease and heart failure, exercise interventions are demonstrated to restore endothelial function. Hambrecht et al. evaluated the coronary artery function of patients with coronary artery disease exposed to a 4-week high-frequency (daily) exercise training program compared with a control group receiving usual care (Hambrecht et al., 2000). Arterial function was assessed through drug-infusion angiographies. The patients in the exercise group improved coronary vascular function as expressed by a 54% smaller acetylcholine-induced vasoconstriction, whereas no changes were observed in the control group. The same author also demonstrated similar benefits in patients with heart failure exposed to an exercise intervention. When compared with non-exercising controls, these patients showed enhanced vascular function as expressed by a 203% increase in peripheral blood flow in response to acetylcholine (Hambrecht et al., 1998).

In individuals with hypertension, however, it is not clear whether exercise can be effective in improving vascular function. A recent meta-analysis, including five trials in individuals with hypertension exposed to aerobic exercise, found a +1.5% (95% confidence interval of -0.11 to +3.0%) improvement in FMD values (Pedralli et al., 2018). These results are indicative of a possible increase that still needs confirmation in future studies due to the neutral effects pointed by the confidence intervals.

Westhoff et al. (2007) evaluated a 12-week, 3 days/week program of walking-based interval training in variables of cardiovascular health, including FMD, in older adults with isolated systolic hypertension, compared with a sedentary control group. The authors reported a difference in the variation of pre–post FMD among the study arms, with the exercise group expressing an increase in FMD values of 2.3%. Interestingly, the pre–post difference in FMD values did not achieve statistical significance ($p = 0.43$). It is unknown, however, if these findings are generalizable to those with regular hypertension, who might have different impairments in their vascular control.

The current state-of-art challenges the notion that endothelial function impairments are easily reversible in samples with a dysfunctional vasculature. In individuals with hypertension, for example, the degree of vascular maladaptation can be such that exercise interventions in common research settings (i.e., short-term, small sample sizes) might not be enough to elicit verifiable improvements in these parameters. As endothelial dysfunction is associated with cardiovascular risk factors and chronic conditions, more studies with robust sample sizes and designs are needed to better understand the effects of exercise on vascular function of populations with different health conditions.

BLOOD RHEOLOGY, INFLAMMATION, AND THE ROLE OF EXERCISE

Despite this review's focus on the risk factors for atherosclerosis mentioned earlier, two other factors deserve a brief mention: blood rheology and inflammation. Both are crucial to atherogenesis and are potentially affected by exercise interventions. More comprehensive reviews on both topics can be found in the work of others (Brun et al., 1998; Toth et al., 2007; Libby, 2012; Connes et al., 2013).

Blood viscosity, determined by hematocrit, plasma viscosity, and red blood cell (RBC) profile, is associated with cardiovascular risk factors (Koenig and Ernst, 1992), incident events (Sweetnam et al., 1996), and disease severity (Kesmarky et al., 1998). Biophysical and flow-related changes in the blood are observed in arterial bifurcations and bends. By disrupting endothelial function and structure, these events facilitate lipid trapping and platelet adherence, especially in scenarios of increased blood viscosity and fibrinogen levels. Additionally, resultant decreases in flow velocity allow conformational changes in RBC, promoting further RBC aggregation (Toth et al., 2007). Evidence shows that hemorheological markers of atherogenesis can be positively affected by increased PA and exercise in healthy populations, in those at risk for CVDs and in secondary prevention (Romain et al., 2011; Sandor et al., 2014). These practices are associated with lower blood viscosity and hematocrit, as well as RBC deformability (Brun et al., 1998). Additionally, reductions in plasma viscosity and RBC aggregation, mainly through decreased fibrinogen levels, are also observed in individuals exposed to higher PA and in patients with CVD exposed to exercise interventions (Brun et al., 1998; de Meirelles et al., 2014). However, high-quality randomized clinical trials exploring these parameters in exercise interventions are still scarce.

Inflammation is key to all steps of atherogenesis. The endothelial impairments mentioned earlier trigger the adhesion and infiltration of monocytes and T cells. The uptake of lipid molecules by macrophages in the subendothelial space then leads to the formation of foam cells. From there, an intense cross talk, mediated by immune, endothelial, and smooth muscle cells, and pro-atherogenic cytokines [mainly interleukins (IL) 1 and 6 and tumoral necrosis factor α] (Tedgui and Mallat, 2006), beyond the scope of this review, ensures a positive feedback loop for further plaque development and destabilization (Libby, 2012). Epidemiological studies demonstrate clear associations between levels of inflammatory markers, especially C-reactive protein (CRP), and the incidence of CVD (Emerging Risk Factors Collaboration et al., 2012), strengthening the so-called "inflammatory hypothesis" for atherogenesis. Cumulative evidence from robust placebo-controlled clinical trials targeting lipid-lowering therapies (Nissen et al., 2004; Ridker et al., 2008) and, more recently, the Canakinumab Anti-inflammatory Thrombosis Outcome Study trial (Ridker et al., 2017), targeting IL-1β for reducing cardiovascular events, now serve as a proof-of-concept on the possible impact of improving inflammatory markers on future cardiovascular events and mortality. Exercise interventions have been shown as potential mediators of improved inflammatory profiles. A recent meta-analysis of randomized controlled trials, evaluating 1,138 healthy middle-aged and older patients, showed improvements in tumoral necrosis factor α, IL-6, and CRP levels in individuals exposed to aerobic exercise training, when compared with those in non-exercising controls (Zheng et al., 2019). These results are following a previous meta-analysis evaluating the effects of exercise on CRP levels that, in sensitivity analyses, also showed reduced concentrations of this inflammatory marker in patients with established CVD and type 2 diabetes (Fedewa et al., 2017).

FINAL REMARKS

PA and exercise are undeniably tied to improved cardiovascular health in varied scenarios. Interventions aiming to increase the time people spend in these activities can have positive impacts on individual and population health. Nonetheless, the exercise literature still needs further development to improve the understanding of whether exercise can be used to enhance specific markers of health. This fact is ultimately related to the methodological characteristics of the literature. A common caveat observed is that some areas (i.e., effects of exercise on lipids and FMD) still lack a body of literature comprised of robust landmark studies, with enough quantity and quality to draw more definite conclusions on the potential of such interventions. On the other hand, however, exercise is better described as an effective treatment for hypertension. Although improvements in this area of knowledge are still needed, this fact alone should be sufficient for stakeholders to stimulate the implementation of such practices in the public health context, especially in LMICs.

AUTHOR CONTRIBUTIONS

LS developed the conceptual framework and drafted the manuscript. DU suggested topics, discussions, references, and items, as well as revised the manuscript. Both authors contributed to the article and approved the submitted version.

FUNDING

This piece of work has not received any specific funding for its development. However, LS was currently being funded by the Coordenação de Aperfeiçoamento do Pessoal do Nível Superior – Finance Code 001, and DU receives research productivity grant and support from the Conselho Nacional de Desenvolvimento Científico e Tecnológico. Both authors were also funded by the Fundação de Apoio à Pesquisa do Estado do Rio Grande do Sul.

ACKNOWLEDGMENTS

We acknowledge the aid of those colleagues who took the time to revise the final version of this article. The figure presented in this article was created using templates from Servier Medical Art (http://smart.servier.com), under a Creative Commons Attribution 3.0 Unported License.

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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.

frontiers in Physiology

SYSTEMATIC REVIEW
published: 31 July 2020
doi: 10.3389/fphys.2020.00739

Effects of Cardiovascular Interval Training in Healthy Elderly Subjects: A Systematic Review

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OPEN ACCESS

Edited by:
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Reviewed by:
Henry N. Williford, Auburn University at Montgomery, United States
Karen Søgaard, University of Southern Denmark, Denmark

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Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *28 March 2020*
Accepted: *08 June 2020*
Published: *31 July 2020*

Citation:
Sant'Ana LO, Machado S, Ribeiro AAS, Reis NR, Campos YAC, Silva JGV, Scartoni FR, Brown AF, Monteiro ER, Novaes JS, Vianna JM and Budde H (2020) Effects of Cardiovascular Interval Training in Healthy Elderly Subjects: A Systematic Review. Front. Physiol. 11:739. doi: 10.3389/fphys.2020.00739

The aim of this review is to demonstrate the effects of cardiovascular interval training (IT) on healthy elderly subjects. We used the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. The following variables were observed: resting heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MBP), heart rate variability (HRV), baroreflex activity (BA), and maximal oxygen uptake (VO_{2max}). Studies were searched for in the MedLine, PubMed, and Sport Discus databases considering publications between 1990 and 2019. To find the studies, the keywords used were "Interval and Elderly Training" or "Interval Training and Baroreflex Sensing" or "Interval Training and Aging and Pressure Arterial and Blood Pressure Training" or "Interval Training and Variation in Aging and Heart Rate" or "Interval Training and Sensitivity to the Elderly and Baroreflex" or "Interval Training and Variability in the Elderly and Heart Rate." The systematic search identified 1,140 hits. The analysis of the study was performed through a critical review of the content. One thousand one hundred forty articles were identified. Of these, 1,108 articles were excluded by checking the articles and abstracts. Finally, 32 studies were selected for full reading while 26 studies were eliminated because they did not contain a methodology according to the purpose of this review. Thus, six studies were included for the final analysis. The PEDro score was used for analyzing the study quality and found 4,8 ± 1,3 points (range: 3–6). Positive results were found with the different IT protocols in the observed variables. Results show that IT protocols can be an efficient method for functional improvement of cardiovascular and cardiorespiratory variables in the healthy elderly, especially HR, SBP, DBP, MAP, HRV, BA, and VO_{2max}. However, this method can be included in the prescription of aerobic training for the elderly to obtain conditional improvements in the cardiovascular system, thus being an important clinical intervention for the public.

Keywords: aerobic training, autonomic response, hemodynamic response, blood pressure, healthy elderly

INTRODUCTION

According to the World Health Organization, the number of elderly people has been increasing over the years (World Health Organization, 2016). The American College of Sports Medicine (ACSM) and the American Heart Association (AHA) jointly directed positions on the importance of physical training in improving cardiovascular and cardiorespiratory fitness in the face of aging (Nelson et al., 2007). Physiological changes in aging are inevitable (Adamson et al., 2019) but can be partially prevented by the practice of cardiovascular (Soares-Miranda et al., 2014) and cardiorespiratory exercise (Lepretre et al., 2009). Aging promotes severe changes in the cardiovascular system (Molmen et al., 2012). Disorders related to the cardiovascular system are known to be the major cause of morbidity and mortality worldwide (Lavie et al., 2019), and it seems to have greater effects on the elderly.

Therefore, with the aging process, the cardiovascular functional decline is significant (Ogliari et al., 2015) and the maintenance and improvement of this system are extremely important for the elderly's organic integrity (Pichot et al., 2005). The cardiovascular system is driven by autonomic and hemodynamic actions, where in an integrated manner it provides the functional efficiency of this system (Benda et al., 2015). However, the cardiorespiratory system is extremely important not only in the aging process but also in cardiovascular potentiality and efficiency, which can suffer significant functional reductions (Chaves et al., 2008). Thus, the cardiovascular and cardiorespiratory systems are linked to the health of the elderly and require attention in the conditional improvement of their actions (Madssen et al., 2014).

To maintain and enhance cardiovascular and cardiorespiratory functions in elderly people, the strategy seems to promote an increased aerobic profile (e.g., maximal oxygen uptake—VO_{2max}). Previous studies have reported enhances in VO_{2max} reduce the risk of death from cardiovascular and cardiorespiratory events (± 15%) (13). Studies report that the harmful physiological effects in the elderly are not related to aging, but to lifestyle habits, such as a lack of regular physical activity (Inouye et al., 2018). Pichot et al. (2005) mentions that aging is not a limiting factor of the autonomic nervous system. Thus, the improvement in physical conditioning is related to cardiovascular and cardiorespiratory efficiency, especially in the face of aging (Fletcher et al., 2018; Lavie et al., 2019).

Therefore, to improve the aerobic profile, specific training is necessary and interval training (IT) seems to promote positive adaptations (Astorino and Schubert, 2014). It has been suggested to improve the maximal aerobic profile in the elderly (Nemoto et al., 2007; Molmen et al., 2012) and to improve autonomic and hemodynamic modulation (Pichot et al., 2005), thus consolidating an improvement of the cardiovascular system (Rakobowchuk et al., 2013). Recently, high-intensity interval training (HIIT) has shown important results with VO_{2max} and improved cardiovascular system (Taylor et al., 2019). These are important health markers (Frazão et al., 2016; Cabral-Santos et al., 2017). Other studies have used HIIT in interventions with different populations and achieved positive results on cardiorespiratory (Castro et al., 2019), cardiometabolic (Fisher et al., 2015; Kong et al., 2016), cardiovascular, and psychological effects (Shepherd et al., 2015). In addition, regarding IT intensities, studies have focused more on the application of high intensity. However, there are still few studies concerning IT with the elderly population. Some have shown that IT is a relevant intervener in cardiovascular (Bertani et al., 2018) and cardiorespiratory (Rognmo et al., 2004) variables in the elderly.

The purpose of the present review is to synthesize findings of the cardiovascular effects concerning healthy elderly subjects. For this, the following variables were analyzed: resting HR, SBP, DBP, MBP, HRV, BA, and VO_{2max}.

Abbreviations: PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; HR, Heart Rate; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; MBP, Mean Arterial Pressure; HRV, Heart Rate Variability; BA, Baroreflex activity; VO_{2max}, Maximal Oxygen Uptake; ACSM, American College of Sports Medicine; AHA, American Heart Association; IT, Interval Training; HIIT, High-Intensity Interval Training.

METHODS

Literature Search

This systematic review was designed and reported according to the recommendations of the PRISMA guidelines (Liberati et al., 2009) and with the proposed MOOSE report (Meta-analysis of Observational Studies in Epidemiology) (Stroup et al., 2008).

A systematic literature search was conducted through May 2019, using the following databases: PubMeb, Medline, and Sport Discus. Search terms were defined according to population (elderly) and intervention (interval training), based on previous systematic reviews on the field. The following search strategies, Medical Subject Headings (MeSH), and Boolean operators were considered: "Interval Training and Elderly and Interval Training and Aging and Baroreflex Sensitivity" OR "Interval Training and Aging and Blood Pressure" OR "Interval Training and Aging and Heart Rate Variability" OR "Interval Training and Elderly and Baroreflex Sensitivity and Interval Training and Elderly and Heart Rate Variability." Four researchers who reached consensus in case of disagreement performed these procedures.

We included studies that used IT as an intervention protocol (even if compared to other types of intervention), using a sample of healthy individuals aged 60 years or older, who investigated at least one variable (even indirectly, not thus the main objective of the study) that was of interest to our review. Articles that had no association with the purpose of this study, articles that had protocols that did not fit the selection, and that did not mention the description of the protocols, methodology, and sampling were excluded. Pilot and review studies were also excluded.

After merging search results and discarding duplicates, two researchers independently screened titles and abstracts in order to identify relevant studies. Full-text articles of the included reports were retrieved and independently assessed for eligibility by the two researchers according to the previously described criteria. A consensus meeting was performed in case of disagreement regarding any report and a third researcher completed the decision when required. When it was not possible to retrieve full-text articles, authors were contacted using email and Research Gate in order to provide the required report. After three failed attempts to obtain a response from the respective authors, the report was excluded from analysis. Some reports were seemingly published based on data from the same trials. Corresponding authors were contacted in order to confirm whether these reports were actually produced from different trials or not.

Eligibility Criteria and Study Selection

The eligibility criteria for study inclusion were established according to the PICOS strategy:

- Population: participants must be healthy elderly.
- Intervention: any sort of acute or regular interval training intervention aimed at increasing cardio protection in elderly individuals.
- Comparison/Control: interval training interventions must be compared to another type of cardiorespiratory training, waiting control groups, or treatment-as-usual.
- Outcomes: outcomes were measures related to cardio protection in elderly (HR, HRV, SBP, DBP, MAP, BA, and VO_{2max}).
- Study Design/Type: Original article. Randomized controlled trials, using either cross-over or parallel group designs, comparing an intervention(s) encompassing interval training with a group of another type of cardiorespiratory training, waiting control groups, or treatment-as-usual.

We included studies that used IT as an intervention protocol (even in comparison with other types of intervention), using a sample of healthy individuals aged 60 or over (free of any functional limitations or medical conditions) and that investigated at least one variable (even if indirectly, therefore not being the main objective of the study) of interest for our analysis. For organizational determination, only original studies published between 1990 and 2019 in English were included. Screening was performed by reading the title, summary, and, when necessary, reading in full for a more detailed assessment. Then, an eligibility process was carried out by reading all the articles in full. The reference lists studied were revised to identify other studies. Finally, after the entire eligibility process, articles for systematic review were included. Studies based on methodological quality and those that did not fit the research objectives were excluded.

Risk of Bias in Individual Studies

To assess the risk of bias in individual studies, the researchers carried out an analysis of the methodological quality of the studies. The assessment tool for the selected studies was carried out using the PEDro scale (Center for Evidence-Based Physiotherapy, 2019). The PEDro scale is considered an appropriate tool in systematic reviews for qualitative analysis of quantitative studies. The method consists of component classifications for the following categories: selection criteria, equation between groups, data collection methods, and outcome factors. The components were classified at 0 (not identified) and 1 (identified). Studies with PEDro scores between 6 and 10 points, 4 and 5 points, and 0 and 3 points were considered high, moderate, and low quality, respectively. All disagreements regarding rating of PEDro scores were resolved by a consensus discussion between the reviewers.

RESULTS

Study Selection

After using the keywords, 1,140 articles were identified. However, in the article screening process, 1,108 articles were excluded by checking their titles and abstracts. Finally, 32 studies were selected for full reading. After eligibility, 26 were eliminated because they did not contain a methodology according to the purpose of this review, with six studies included for the final analysis. The whole study selection process is shown in the PRISMA flow diagram in **Figure 1**.

Study Quality

The mean PEDro score for the studies included in the review was 4.8 ± 1.3 points with a range of 3–6 points (**Table 1**). According to the quality criteria set, the average quality of the studies included in this review is therefore moderate. Moreover, there was not a high degree of variation in quality between studies. All studies met the eligibility criterion (PEDro scale question 1) and outcome measures. Three studies (Nemoto et al., 2007; Lepretre et al., 2009; Adamson et al., 2019) performed a crossover randomized design (PEDro scale question 2). None of the studies concealed criteria (PEDro scale question 3). Four studies (Ahmaidi et al., 1998; Nemoto et al., 2007; Lepretre et al., 2009; Adamson et al., 2019) showed similarity between groups (PEDro scale question 4). None of the studies had blinded methodological criteria (PEDro scale questions 5, 6, and 7). All studies showed results in more than 85% of the sample (PEDro scale question 8) and all studies met criteria 9, related to the intervention condition (PEDro scale question 9). Five studies (Ahmaidi et al., 1998; Nemoto et al., 2007; Lepretre et al., 2009; Molmen et al., 2012; Adamson et al., 2019) showed statistical comparisons between groups (PEDro scale question 10) and provided point measures and measures of variability (Pichot et al., 2005; Nemoto et al., 2007; Lepretre et al., 2009; Molmen et al., 2012; Adamson et al., 2019) (PEDro scale question 11).

Study Characteristics

The summary of articles, in **Table 2**, was based on a structured questionnaire that considered the following items: Authors, year of publication, sampling (amount, gender, and age), training protocols, dependent variable, and results (Neto et al., 2017).

In these selected studies, the findings were from publications from 1998 (Ahmaidi et al., 1998) to 2019 (Adamson et al., 2019). Regarding sampling, 251 individuals were found, 107 men and 144 women. However, two studies used only men in their interventions (Ahmaidi et al., 1998; Pichot et al., 2005) and the other four studies used men and women in their analyses (Nemoto et al., 2007; Lepretre et al., 2009; Molmen et al., 2012; Adamson et al., 2019). No female-only studies were found, and two studies used active individuals (Ahmaidi et al., 1998; Pichot et al., 2005) and four studies included inactive individuals (Nemoto et al., 2007; Lepretre et al., 2009; Molmen et al., 2012; Adamson et al., 2019). The sample size in the selected studies

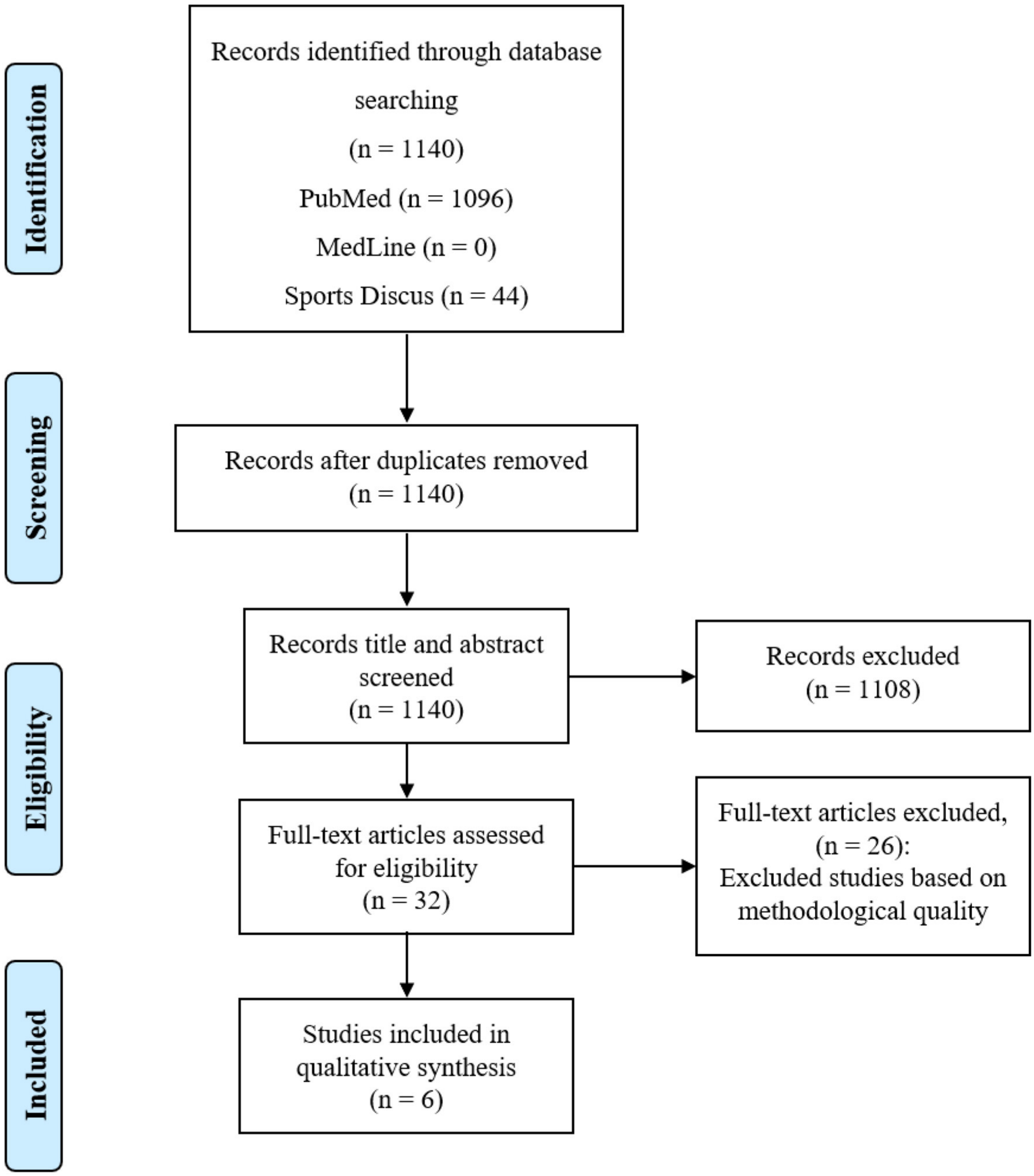

FIGURE 1 | Flow diagram of information on the different phases of the systematic review.

ranged from 11 (Pichot et al., 2005) to 139 individuals (Nemoto et al., 2007).

Regarding the body composition of the participants in the selected studies, two studies did not present these data (Ahmaidi et al., 1998; Nemoto et al., 2007). Pichot et al. (2005) presented weight 81 ± 12.0 (kg) and BMI 28.4 ± 4.0 (kg/m^2) but did not present data on height. Lepretre et al. (2009) presented weight 82.9 ± 11.2 and 65.0 ± 9.9 (kg) and height 177 ± 5.7 and 161.5 ± 5.4 (cm) for men and women, respectively, but did not present BMI. Molmen et al. (2012) used three groups, two with elderly people and one with young people (control). Regarding the elderly, one group had values of weight 76.5 ± 9.4 (kg) and BMI 25.0 ± 2.5 (kg/m^2) and another with weight of 74.5 ± 8.3 (kg) and BMI 23.0 ± 1.9 (kg/m^2). In the group with young people, the weight was 76.0 ± 16.0 (kg) and BMI 22.7 ± 3.1 (kg/m^2). They did not provide data on height. Adamson et al. (2019) presented for the experimental group weight 77 ± 1.3 (kg), height 169 ± 9 (cm), and BMI 26.9 ± 3.5 (kg/m^2) and for the control group weight of 70 ± 1.3 (kg), height 1.64 ± 10, and BMI 25.9 ± 3.3 (kg/m^2).

The findings of the present study identified different protocols for interventions: IT (Ahmaidi et al., 1998; Pichot et al., 2005; Lepretre et al., 2009; Molmen et al., 2012), Sprint Interval Training (SIT) (Adamson et al., 2019), and the High Intensity Interval Walking Training (HIIWT) (Nemoto et al., 2007). With the advances and popularization of the interval training using different intensities of effort, it was necessary to elaborate on different nomenclatures for this method. The commonly used IT is represented by physical exertion with cyclic and repetitive exercises, alternating stimulus periods based on some physiological parameters, which may be below the anaerobic threshold, lower than 85% of maximum heart rate (HRmax) or 85% of VO_{2max} (Buchheit and Laursen, 2013). Therefore, it is a method that provides significant physiological adaptations in improving fitness (Billat, 2001). The SIT is conducted by short (5 to 60") stimuli with markedly high intensities that may be a high intensity (90% VO_{2max} or above the 2nd ventilatory threshold), maximal (100% VO_{2max}), supramaximal (>100% VO_{2max}), or subjectively, commonly called "all-out" (30). HIIWT is an IT protocol that uses walking as a mechanical rhythm. However,

TABLE 1 | PEDro score of methodological quality for included studies.

Reference	1	2	3	4	5	6	7	8	9	10	11	Totality
Ahmaidi et al. (1998)	1	0	0	1	0	0	0	1	1	1	0	4
Pichot et al. (2005)	1	0	0	0	0	0	0	1	1	0	1	3
Nemoto et al. (2007)	1	1	0	1	0	0	0	1	1	1	1	6
Lepretre et al. (2009)	1	1	0	1	0	0	0	1	1	1	1	6
Molmen et al. (2012)	1	0	0	0	0	0	0	1	1	1	1	4
Adamson et al. (2019)	1	1	0	1	0	0	0	1	1	1	1	6

0: Did not meet criterion; 1: Met the criterion.

TABLE 2 | Selected studies that investigated interval training in cardioprotective variables in the elderly.

References	Sampling (groups, *N*, gender, age)	Training protocols	Duration	Results
Ahmaidi et al. (1998)	*N* = 22 Mens GE: 11 (62.7 + 1.4) GC: 11 (61.7 + 1.9)	In Natural way IT 10 ' Heating 1' St./1' Rec.; 2 ' St./1' Rec. 4' St./1' Rec.; 10' St./3' Rec. Intensity: St.: $HR\text{-}VT_H$/Rec.: 20 BPM less $HR\text{-}VT_H$ 10' Deceleration	12 weeks/2 x week	Improved relative VO_{2max}. There was no difference in absolute VO_{2max}
Pichot et al. (2005)	*N* = 11 Mens GE: M: 11 (73.5 ± 4.2) GC: NR	In Cycle ergometer IT 9 x 4' 65% HR 1' 85% HR	14 weeks/4 x week	Improved HR, HRV, BA and VO_{2max} relative. There was no difference in HRV (PNN50) SBP, DBP, and MAP
Nemoto et al. (2007)	*N* = 28 Mens/111 Womens GE 1: M: 11 (67 + 4)/W: 31 (64 + 6) GE 2: M: 8 (67 + 5)/W: 43 (62 + 5) GC: M: 9 (66 + 5)/W: 37 (62 + 6)	In Natural Way IT (HIIWT) 5 (or more) x 3' 40% VO_{2peak} 3' 70–85% VO_{2peak}	5 months/2–4 weeks	Improved HR (womens), SBP and DBP (men and women).
Lepretre et al. (2009)	*N* = 16 Mens/19 Womens GE: M: 16 (64 ± 3.7) / W: 19 (65.5 ± 5.4) GC: NR	In Cycle ergometer IT 6 x 4' 1° VT_H 1' 2° VT_H	9 weeks/2 x weeks	Improved VO_{2max} relative. There was no difference in SBP and DBP.
Molmen et al. (2012)	*N* = 21 Mens/6 Womens GE: M: 10/W: 6 (73 ± 3) GC1: M 10 (23 ± 2) GC2: M: 11 (74 + 2)	In Treadmill IT 10' Heating ~60% HR_{max} 4x 4' 90–95% HR_{max} 3' 60–70% HR_{max} 3' Deceleration	12 weeks/3 x weeks	Improved HR, SBP, DBP and VO_{2max} relative.
Adamson et al. (2019)	*N* = 9 Mens/8 Womens GE: M: 6/W: 4 (66 ± 4) GC: M: 3/W: 4 (66 ± 2)	In Cycle ergometer IT (SIT) 6 a 11 x 6" All Out 30" Passive Rec. (or HR below 120 BPM)	10 weeks/2 x weeks	Improved SBP (mens and womens) and DBP (mens). There was no difference in DBP (womens) and MAP (mens and womens).

EG, Experimental Group; CG, Control Group; NR, Not done; IT, Interval Training; HIIWT, High Intensity Interval Walking Training; SIT, Sprint Interval Training; St., Stimulus; Rec., Recovery; $HR\text{-}VT_H$, Heart Rate at Ventilatory Threshold; HR_{max}, Maximum Heart Rate; VO_2peak, Peak Oxygen Consumption; VT, Ventilatory Threshold; VO_{2max}, Maximum Oxygen Consumption; HRV, Heart Rate Variability; BA, Baroreflex Activity; HR, Resting Heart Rate; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; MAP, Mean Arterial Pressure.

even though it is not common among IT applications, HIIWT can be an important strategy for the elderly unable to perform an activity with a high level of impact and motor demands (Oliveira et al., 2012). Regardless of the methodological variation, all these protocols have characteristics for a predominance of aerobic metabolism (Gaitanos et al., 1993; Billat, 2001).

The different IT protocols were conducted in order to obtain improvements in cardio protective variables in the elderly. Ahmaidi et al. (1998) introduced a varied sequence of stimuli with HR related to ventilatory threshold (VT) and recovery in HR of 20 beats below that obtained in VT, totaling 43 min of activity. Pichot et al. (2005) applied six sets of 4 min at 65% HRmax and 1 min at 85% HRmax for 45 min. Nemoto et al. (2007) did not fix a number of interval series, performing five or more blocks of 3 min at 40% VO_{2peak} with 3 min at 70–85% VO_{2peak}, establishing a volume of at least 30 min. Lepretre et al. (2009) used VT as a parameter to control IT intensities for 30 min, with six series of 4 min in the 1st with 1 min in the 2nd. Molmen et al. (2012) performed 28-min sessions with 4-min stimuli at 90–95% HRmax and 3-min recovery at 60–70% HRmax. Adamson et al. (2019) used a protocol with 6 to 11 sets of 6 s at maximum intensity (all-out) for 30 s of passive recovery or when heart rate below 120 BPM was reached. Additionally, considering the methodological aspects of IT, the present study identified that all selected articles used high-intensity stimuli.

Regarding the location, equipment, and time of intervention, two studies performed the training in the natural way (Ahmaidi et al., 1998; Nemoto et al., 2007) and four were conducted in laboratories using cycle ergometers (Pichot et al., 2005; Lepretre et al., 2009; Adamson et al., 2019) or treadmills (Molmen et al., 2012). All selected studies applied chronic interventions ranging from 9 (Lepretre et al., 2009) to 20 weeks (Nemoto et al., 2007). To determine the statistical analysis, all selected studies had a significance level of $p < 0.05$. Regarding the hemodynamic, autonomic, and cardiorespiratory responses resulting from the different IT protocols, four studies investigated the measurement of HR (Ahmaidi et al., 1998; Pichot et al., 2005; Nemoto et al., 2007; Molmen et al., 2012), five studies verified the behavior of SBP and DBP (Pichot et al., 2005; Nemoto et al., 2007; Lepretre et al., 2009; Molmen et al., 2012; Adamson et al., 2019), and two studies measured MAP (Pichot et al., 2005; Adamson et al., 2019). Regarding autonomic control, only one study investigated this performance through BA and HRV (Pichot et al., 2005). In the cardiorespiratory condition, four studies evaluated the influence of IT on VO_{2max} (Ahmaidi et al., 1998; Pichot et al., 2005; Lepretre et al., 2009; Molmen et al., 2012). However, only one study investigated hemodynamic, autonomic, and cardiorespiratory variables (Pichot et al., 2005).

On measurement procedures for HR, a study (Pichot et al., 2005) used the Holter method and two studies (Nemoto et al., 2007; Molmen et al., 2012) used the electrocardiogram method. Regarding Blood Pressure (BP), a study (Pichot et al., 2005) used the measurement using the volume clamp method on the fingers, one study used the auscultatory method (Nemoto et al., 2007), one study used the electrocardiogram method (Molmen et al., 2012), one study (Adamson et al., 2019) used an automatic device, and only one study (Lepretre et al., 2009) did not mention which method for BP was used, possibly because it did not present BP results in an indirect way in the study, not being the main target of the study. Regarding BA, only one study analyzed this variable (Pichot et al., 2005) and used the sequence and cross-spectral analysis method using an electrocardiogram. For HRV, only Pichot et al. (2005) analyzed and was using the Holter method. Finally, for the analysis of VO_{2max}, all studies that performed this evaluation (Ahmaidi et al., 1998; Pichot et al., 2005; Lepretre et al., 2009; Molmen et al., 2012) used the method with incremental testing gases. Two studies were carried on a treadmill (Ahmaidi et al., 1998; Molmen et al., 2012) and two studies on cycle ergometers (Pichot et al., 2005; Lepretre et al., 2009). Ahead, the results for each variable on the effects of IT on different protocol formats will be displayed.

OUTCOME MEASURES

Resting Heart Rate (HR)

HR is extremely important in clinical evaluation and is related to cardiovascular disorders (Schneider et al., 2018). Several factors can modify the behavior of this variable, one of which is aging (Ogliari et al., 2015). Regarding the HR of the selected studies, some important results about this variable are presented. Pichot et al. (2005) obtained significant results in HR, being 71.9 ± 9.9 BPM at baseline and 67.2 ± 11.4 BPM post-intervention ($p < 0.001$). Nemoto et al. (2007) achieved interval HR improvements for women (81 ± 2 to 78 ± 1 BPM, $p < 0.05$). More expressively, Molmen et al. (2012) demonstrated a reduction of 10 beats ($p < 0.01$) after intervention with IT.

Systolic, Diastolic and Mean Blood Pressure (SBP, DBP, and MAP)

BP is a feature that changes significantly in the aging process and one of the main factors is the stiffness caused in the arterial structures (Figueroa et al., 2010) and the loss of functional efficiency of the elderly cardiovascular system (Deley et al., 2009). Thus, regarding SBP, some related studies showed significant results after their interventions. In the study by Nemoto et al. (2007) there was a reduction of 10 mmHg for men (146 ± 2 to 136 ± 2, $p < 0.001$) and 8 mmHg for women (140 ± 3 to 132 ± 2, $p < 0.001$). Molmen et al. (2012) were able to reduce SBP by 12% (143 ± 15.0 to 126 ± 8.5, $p < 0.05$). Adamson et al. (2019) achieved improvements of 4 mmHg for men (136 ± 13 to 122 ± 9, $p < 0.05$) and 10 mmHg for women (141 ± 13 to 131 ± 6, $p < 0.05$). Pichot et al. (2005) failed to observe significant differences in SBP (111.6 ± 13.9 to 111.1 ± 13.3, $p > 0.05$), as did Lepretre et al. (2009) for whom SBP reduced very discreetly for men and women (0.7% and 1.3%, respectively, $p > 0.05$). Regarding DBP, the results followed the same line. Nemoto et al. (2007) obtained a reduction in DBP for both men and women, with 87 ± 3 to 82 ± 2 ($p < 0.05$) and 85 ± 2 to 80 ± 2 ($p < 0.001$), respectively. Molmen et al. (2012) decreased by 9% ($p < 0.01$) from 80.0 ± 8.7 to 73 ± 5.0 after the interventions. Adamson et al. (2019) were able to decrease DBP by 8 mmHg for men (85 ± 5 to 77 ± 9, $p < 0.05$), but for women did not obtain significant differences (85 ± 5 to 84 ± 4, $p > 0.05$). Pichot et al. (2005) and Lepretre et al. (2009) did not achieve significant results in DBP behavior after the training period ($p > 0.05$). Regarding MAP, only two studies verified that Pichot et al. (2005) did not achieve significant differences (76.9 ± 14.9 to 77.9 ± 12.3, $p > 0.05$). On the other hand, Adamson et al. (2019) demonstrated significant reductions for both men (104 ± 9 to 94 ± 10, $p < 0.05$) and women (94 ± 8 to 88 ± 11, $p < 0.05$).

Heart Rate Variability (HRV)

HRV is an important measure to diagnose the cardiovascular condition (Ogliari et al., 2015). Therefore, the interpretation of the acquired data is subdivided into the time domain and frequency domain with their respective indices (Laborde et al., 2017). In the time domain, the values on beats to beats (RR), PNN50, and RMSSD that are associated with the parasympathetic activity are acquired (Young and Benton, 2018). SDNN and SDANN are related to global autonomic activity. In the frequency domain, the low frequency (LF) components are analyzed, corresponding to the sympathetic and parasympathetic joint action with sympathetic predominance. The high frequency (HF) component indicates parasympathetic performance and the LF/HF ratio is a marker of autonomic balance (Vanderlei et al., 2009). Given the studies selected for the present review, only one study investigated HRV. Pichot et al. (2005) demonstrated relevant results on HRV assessment items. In time-domain analyses, the researchers in this study found a 7.7% improvement in RR values (847 ± 100 to 912 ± 133, $p < 0.001$) and a 15.4% reduction in SDNN (149 ± 45 to 126 ± 40, $p < 0.05$). Significant results were also found in the RMSSD indices (30.3 ± 7.5 to 36.4 ± 8.8, $p < 0.01$). However, for PNN50 there were no significant differences (3.52 ± 2.53 to 4.41 ± 2.79, $p > 0.05$). For frequency domain analysis, Pichot et al. (2005) also presented interesting results. For the LF (n.u.), baseline results were 62.4 ± 9.5 and 58.4 ± 11.4 after interventions ($p < 0.05$). For HF (n.u.) the results were also positive, being 37.6 ± 9.5 pre-intervention and 41.4 ± 11.4 after training ($p < 0.05$). Regarding the LF/HF measurement, there was a 19.1% reduction (2.93 ± 1.35 to 2.37 ± 1.10, $p < 0.05$).

Baroreflex Activity (BA)

BA is a feature that demonstrates cardiovascular efficiency (Deley et al., 2009; Figueroa et al., 2010), promoting in an integrated way the modulation of hemodynamic and autonomic systems. Only one study investigated the behavior of BA (Pichot et al., 2005). In this study, we used the sequence methods that use RR behavior with SBP and cross-spectral analysis that observes the performance of low (LF) and high (HF) frequency components with BP, all expressed in ms.mmHg. The results of Pichot et al. (2005) demonstrated improvements in BA. In the sequence method, baroreflex activity increased 40% significantly from 7.0 ± 1.8 to 9.8 ± 2.1 ms.mmHg ($p < 0.01$). From these findings, 10 subjects showed improvement and only one subject reduced BA. Regarding spectral analysis, when the researchers performed the calculations through the HF, they obtained positive results increasing significantly from 6.9 ± 2.2 to 10.5 ± 3.7 ms.mm/Hg-1 (52.5%, $p < 0.05$), with eight subjects showing an increase in BA and two showing a decrease. When the evaluation was performed using the LF values as the basis of calculation, no significant differences were observed (from 5.3 ± 2.3 to 6.9 ± 3.1 ms.mmHg-1, $p = 0.22$).

Maximum Oxygen Consumption (VO_{2max})

VO_{2max} is of paramount importance for the elderly because in the aging process there is a reduction in the efficiency of cardiovascular function due to the decrease in cardiorespiratory fitness, and in the elderly VO_{2max} can reduce 10% in sedentary and 5% in assets (Oliveira et al., 2012). Studies have found relevant results on VO_{2max} after interventions. Ahmaidi et al. (1998) obtained a significant increase in absolute and relative VO_{2max}, from 1.77 to 2.11 l.min^{-1} ($p < 0.01$) and from 25.42 to 30.63 ml.kg.min^{-1} ($p < 0.01$), respectively. Pichot et al. (2005) also demonstrated significant differences. The authors found an 18.6% increase in relative VO_{2max} values (26.84 ± 4.38 to 31.82 ± 5.15 ml.kg.min^{-1}, $p < 0.01$) and observed relevant absolute VO_{2max} results ($p < 0.01$), however the exact values were not exposed. Lepretre et al. (2009) found a 14.9% increase in relative VO_{2max} for men (27.0 ± 5.1 to 29.9 ± 4.5 ml.kg.min^{-1}, $p < 0.05$) and 14.5% for women (18.6 ± 3.6 to 21.1 ± 3.7 ml. kg.min^{-1}, $p < 0.05$). However, these authors did not observe intergroup differences ($p = 0.237$). Molmen et al. (2012) conducted the investigation on VO_{2max} of men ($N = 10$) and women ($N = 6$) and found significance in their results. In the analyses for men, VO_{2max} changed from 35.0 ± 5.0 to 39.0 ± 7.2 ml.kg.min^{-1} ($p < 0.01$) and, when considering the group containing men and women, a 15% increase in VO_{2max} was found after the interventions, from 32.5 ± 5.5 to 37.0 ± 6.1 ml.kg.min^{-1} ($p < 0.01$). Therefore, it is concluded that, as presented in the investigated studies, IT is an important intervener on VO_{2max} with its different protocol variations.

DISCUSSION

This study aimed to verify the efficiency of IT on cardiovascular and cardiorespiratory variables, more specifically HRR, HRV, SBP, DBP, MAP, BA, and VO_{2max}. These directly act on the cardio protection functionality. We identified 1,140 articles, but only six studies fit our purpose (Ahmaidi et al., 1998; Pichot et al., 2005; Nemoto et al., 2007; Lepretre et al., 2009; Molmen et al., 2012; Adamson et al., 2019). From these results, it is valid to state that there is a significant limitation of studies related to the elderly population submitted to IT. Thus, the scarcity of studies related to the theme of the present review corroborates those of Ferreira et al. (2017) who aimed to select studies that intervened with aerobic training in HRV in the elderly and found only seven studies for a systematic review. Given our findings, it is necessary to state that the selected studies obtained positive results in cardiovascular and cardiorespiratory variables. Regarding the cardiovascular system, the selected studies presented important results on the IT responses on hemodynamic (Ahmaidi et al., 1998; Pichot et al., 2005; Nemoto et al., 2007; Lepretre et al., 2009; Molmen et al., 2012; Adamson et al., 2019) and autonomic variables (Pichot et al., 2005). Regarding VO_{2max}, studies have also shown improvements after distinct interventions using IT (Ahmaidi et al., 1998; Pichot et al., 2005; Lepretre et al., 2009; Molmen et al., 2012). This demonstrates the potentiality of IT in the main cardiovascular and cardiorespiratory variables, these being HR, HRV, SBP, DBP, MAP, BA, and VO_{2max} that, in an integrated manner, act directly and decisively on the efficiency and balance of the cardiovascular system.

HR is an important predictor of cardiovascular health (Ogliari et al., 2015) and our findings reinforce the hypothesis that IT is efficient in HR behavior (Pichot et al., 2005). Studies have improved from 3 beats (Nemoto et al., 2007) to 10 beats (Molmen et al., 2012) in the elderly surveyed. About HRV, only one study (Pichot et al., 2005) investigated this variable that indicates the level of cardiovascular health and possible risks of this system (Young and Benton, 2018; Geus et al., 2019). However, in the study by Pichot et al. (2005) improvements in time between one cardiac cycle and another by 7.7% (RR) were observed. In the time domain analysis, improvements were found in parasympathetic performance indices (RMSSD). Regarding the PNN50 index (%) that is related to parasympathetic reactivation, no statistical differences were found. However, they found a reduction in values on the SDNN index that is related to both autonomic actions with a sympathetic prevalence. Also, the reduction in this index is a consequence of the parasympathetic system's role in promoting balance and cardiovascular control. In the frequency domain, all indices have been improved. In the LF (sympathetic-parasympathetic) there was a significant reduction, demonstrating a positive parasympathetic performance. Regarding HF, which is related to the parasympathetic system, there was a significant increase. Consolidating IT efficiency over HRV in the elderly, Pichot et al. (2005) found a 19.1% reduction in LF/HF values, demonstrating that the intervention was efficient in autonomic modulation.

Regarding BP, one of the factors that makes this functionality worse is arterial stiffness caused by the aging process (Figueroa et al., 2010), thus reflecting the functional inefficiency and impairing the cardiovascular system (Deley et al., 2009). However, this review has shown that IT is a great intervention in hemodynamic improvement. Of the five selected studies investigating hemodynamic functionality, three obtained positive results after their interventions in SBP and DBP (Nemoto et al., 2007; Molmen et al., 2012; Adamson et al., 2019). Pichot et al. (2005) and Lepretre et al. (2009) did not observe statistical differences in these measures. Regarding MAP, Pichot et al. (2005) did not present significant differences, but Adamson et al. (2019) achieved positive results. However, we can say that IT is an efficient methodology for hemodynamic improvement. Regarding the integration of the autonomic and hemodynamic system, BA is the indicator of cardiovascular condition on this aspect. However, only Pichot et al. (2005) evaluated this measure using HRV and SBP and found positive results after interventions. The researchers used the sequence and spectral method and found significant differences in both (40% and 52%, respectively), demonstrating that IT is an excellent method for improving this measure of great importance in the control and balance of the cardiovascular system (Deley et al., 2009).

In VO_{2max} all studies that performed this measure obtained positive results (Ahmaidi et al., 1998; Pichot et al., 2005; Lepretre et al., 2009; Molmen et al., 2012). The increases were from 15 to 18.6%, which are of great value, considering that in the aging process the reduction of aerobic capacity can be 10% for sedentary individuals and 5% for those who are active (Oliveira et al., 2012). Among these studies, all directly measured VO_{2max} (gas analyzers), determining the reliability of the data obtained and that IT is efficient in improving cardiorespiratory capacity, which is an important determinant of cardiovascular health in the elderly (Kodama et al., 2009).

The mechanisms related to hemodynamic, autonomic, and cardiorespiratory improvements may be due to hormonal, neural, metabolic, and structural changes caused by different IT stimuli. In the hemodynamic condition, IT balances the renin-angiotensin system allowing for better behavior of both systolic and diastolic BP (Pichot et al., 2005). Other beneficial factors of IT are reduced arterial stiffness and improved endothelial function and plasma volume (Molmen et al., 2012; Adamson et al., 2019). In this way, the BP behavior becomes better both in the exercise condition and at rest. HR refers to the reduction caused naturally due to aging. But it is suggested that IT acts on improving cardiac conditioning by interfering with atrioventricular efficiency (Molmen et al., 2012). Regarding neural control over cardiovascular condition, it is speculated that repeated series of effort and recovery promotes stimuli capable of altering the activity of the autonomic nervous system, which chronically may improve neuro-cardial functioning being signaled by a higher HRV and better BA, and these features are considered as excellent markers of the integration of the autonomic and hemodynamic system (Pichot et al., 2005). Consequently, the higher the ratio, the better the cardiovascular conditional status. Pichot et al. (2005), through the analysis of HRV and BA, observed better parasympathetic responses after IT intervention. This suggests that advanced age is not a limiting factor for adaptations in the autonomic nervous system, more specifically in a population with a mean age of 73 years. Regarding cardiorespiratory fitness, the aging process promotes considerable decline for both sedentary and active individuals (Oliveira et al., 2012). However, IT can enable a significant increase in VO_{2max} for the elderly public. This improvement may occur due to higher capillary and mitochondrial density (Nemoto et al., 2007). Other factors related to increased VO_{2max} in the elderly is that IT promotes more efficiency in the relationship between transport and consumption of O_2 by higher amounts of circulating hemoglobin and better muscle condition (Lepretre et al., 2009). However, it seems that the hemodynamic, autonomic, and cardiorespiratory improvements in the elderly are triggered in an integrated manner.

All studies applied IT with different protocols in terms of stimulus and recovery. There is a difficulty in determining which type of interval (intensive or extensive) is most productive. In the present study, Pichot et al. (2005) demonstrated relevant results with an extensive feature protocol. However, Adamson et al. (2019), using an intensive protocol, also achieved great results. The important thing is to identify which level of conditioning is needed for correct and effective application of the different IT protocols. For the elderly, IT can be a great option for prescription variation, being an activity with greater motivation potential. In addition, the exposure to intensity is shorter, which can preserve the elderly from tissue and systemic overloads. In this review, only one study positively described adherence and that no individual was injured (Ahmaidi et al., 1998).

Concerning the elderly public, more information is needed to further materialize the data obtained by this review. Our findings demonstrate that there is a need for further investigation of cardio protective variables on IT intervention with the elderly, thus mitigating the existing gaps on this topic. However, the selected studies showed positive results in the evaluated measures. It is suggested that these findings are dependent on a multifactorial performance, such as stimulus time, recovery, intervention, elderly conditioning level, and other methodological factors. Thus, intensity is not the only factor that determines hemodynamic, autonomic, and cardiorespiratory changes.

CONCLUSION

Interval training shows an efficient and non-medicated method that can be used to improve the cardiovascular health of the elderly population. Of the six selected studies, different results were possibly found due to the methodological approach applied by each research, but even with some discrete results, IT may be included in the prescription of aerobic training for the elderly in order to obtain conditional improvements in the cardiovascular system, thus being an important clinical intervention for this audience.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

LS, SM, JN, and JV conceptualized the project. AR, NR, YC, and JS performed the literature review. LS, FS, AB, and EM wrote the first draft of the manuscript. SM, JN, JV, and HB critically reviewed the manuscript regarding their areas of expertise. All authors contributed to the article and approved the submitted version.

FUNDING

Post Graduate Program in Physical Education, Federal University of Juiz de Fora (UFJF). SM was supported by a grant from Carlos Chagas Foundation for the Research Support in the State of Rio de Janeiro (FAPERJ), Young Scientists from the State of Rio de Janeiro, E−26/203.295/2017. The native speaker proofreading was accomplished by Alexander von Gradowski.

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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.

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REVIEW
published: 15 September 2020
doi: 10.3389/fphys.2020.00881

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Mobility in Older Community-Dwelling Persons: A Narrative Review

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Integrative Physiology, a section of the journal Frontiers in Physiology

Received: *14 October 2019*
Accepted: *29 June 2020*
Published: *15 September 2020*

Citation:
Freiberger E, Sieber CC and Kob R (2020) Mobility in Older Community-Dwelling Persons: A Narrative Review. Front. Physiol. 11:881. doi: 10.3389/fphys.2020.00881

Due to the demographic changes and the increasing awareness of the role of physical function, mobility in older age is becoming an important topic. Mobility limitations have been reported as increasingly prevalent in older persons affecting about 35% of persons aged 70 and the majority of persons over 85 years. Mobility limitations have been associated with increased fall risk, hospitalization, a decreased quality of life, and even mortality. As concepts of mobility are multifactorial and complex, in this narrative review, definitions, physical factors, and their age-related changes associated with mobility will be presented. Also, areas of cognitive decline and their impact on mobility, as well as neuromuscular factors related to mobility will be addressed. Another section will relate psychological factors such as Fall-related psychological concerns and sedentary behavior to mobility. Assessment of mobility as well as effective exercise interventions are only shortly addressed. In the last part, gaps and future work on mobility in older persons are discussed.

Keywords: mobility, gait, risk factors, older person, narrative review, community-dwelling

INTRODUCTION

Due to the demographic changes in the western world, healthy aging becomes an important issue on the individual as well as on a population level. Between 2015 and 2050, the proportion of the world's population over 60 years will increase from 12 to 22% (WHO, 2015). The WHO defines healthy aging "as the process of developing and maintaining the functional ability that enables wellbeing in older age" (WHO, 2015). One important component of healthy aging is mobility. Self-reported mobility limitations are frequent among older persons but this prevalence varies due to different concepts and models. Nevertheless, mobility limitations are increasingly commonplace in older persons affecting approximately 35% of persons aged 70 and the majority of persons over 85 years (Cummings et al., 2014; Musich et al., 2018). Mobility limitations have been associated with an increased fall, disability, hospitalization, and mortality risk as well as decreased quality of life, and poor psycho-social health next to declining function (Shumway-Cook et al., 2005; Gill et al., 2006; Hardy et al., 2011; Lee et al., 2012; Rosso et al., 2013b). Hardy et al. (2011) demonstrated additional health care costs in older persons with mobility limitations. In older persons with mobility limitations, an additional \$2773 (95% CI \$1443–4102) in total health care expenditures, an additional \$274 (95% CI \$30–518) in out-of-pocket expenditures, and an additional 14 (95% CI 8–20) hospitalizations per 100 beneficiaries occurred (Hardy et al., 2011). These numbers demonstrate the need to understand the mechanism and risk factors for mobility limitations.

It is commonly understood that a low physical activity level has negative impact on health, and is responsible for many chronic diseases (Booth et al., 2012, 2017). A low activity level has been linked to sarcopenia (Freiberger et al., 2011; Marzetti et al., 2017a), and to mobility limitations (Gill et al., 2012; Brown and Flood, 2013). With regard to the fact that most people in the western world over 65 years do not meet the recommended physical activity level for healthy aging (Hallal et al., 2012), this area seems mandatory to include in preventing mobility limitations. Decreasing sedentary behavior or inactivity by maintaining mobility in older persons is, with regard to independence, mortality, and health in older persons, a priority on an individual as well as a population level. In 2009 the WHO stated that physical inactivity increased the risk for global mortality by 6% and was one of the four leading risk factors (WHO, 2018).

Ferrucci and others have even argued that mobility is a "hallmark of aging" and an important pillar for independent status (Ferrucci et al., 2016; Brabrand et al., 2018).

As mobility is such an important factor, two important issues occur: (1) early identification of mobility limitations in older persons and (2) the installation of effective interventions to modify or even reverse mobility limitations.

This narrative review will address on a broader base the mechanism and risk factors for mobility limitations, possible screening methods, and, briefly, on effective interventions.

DEFINITION OF MOBILITY

Although at present, there is no gold standard definition of mobility in older persons, in most concepts and models mobility is understood as "one's ability to move independently around their environment" (Mitchell et al., 2018). The theoretical framework by Webber et al. (2010) takes the different and complex determinants for mobility into account. Webber defines mobility "as the ability to move oneself (either independently or by using assistive devices or transportation) within environments that expand from one's home to the neighborhood and to regions beyond" (Webber et al., 2010). The theoretical framework by Webber et al. (2010) includes multiple determinants of mobility, covering transportation/ environmental aspects, cognitive, physical, financial, psychosocial, cultural, and gendered aspects. The included determinants demonstrate the need for holistic approaches in the area of mobility in older persons. As the interaction of these domains is dynamic over the aging process, it is mandatory that biology, medicine, and population science overcome boundaries and work together for a better understanding of the life course of mobility. Furthermore, the integration of older persons and their needs is vital for future mobility research.

As addressed above, mobility includes several domains ranging from physical, cognitive, and neuromuscular to psychological domains. On a physical level, gait, balance, and strength play an important role. In the neuromuscular domain, changes in the motor units are important, and in the cognitive domain, age-related changes are relevant as well as psychological factors such as fall-related psychological concern (FrPC). **Figure 1** displays a conceptual model of these domains on the concept of mobility.

AGE-RELATED PHYSICAL CHANGES ASSOCIATED WITH MOBILITY

Age-Related Balance and Gait Changes

Postural control includes two domains: (a) static (balance) and (b) dynamic (gait) components. In the static condition the center of mass remains between the base of support whereas in gait the center of mass as well as the base of support shifts (Osoba et al., 2019).

Balance Changes With Aging

With aging, postural control in the static condition, or balance, is influenced by the visual, sensory, and vestibular systems (Manchester et al., 1989; Choy et al., 2003). The decline of the sensory system occurs with increasing age and results in balance instability and gait limitations. Sensory feedback is necessary for balance control in the light of different environmental circumstances, e.g., different light situations such as sun or shadow, or traffic situations, e.g., sound recognition or localization (Cavazzana et al., 2018). Sensory feedback in static balance is necessary to reduce sway movement, e.g., in a situation where the room lights suddenly turn off, the upright position of the body needs feedback from other sensory systems.

A sensory decline occurs with aging especially for vision and hearing (Pinto et al., 2017). As declining hearing abilities as well as impaired vision have a negative impact on mobility, in addition it also has an impact on quality of life in older persons (Pinto et al., 2017; Liljas et al., 2020). The study by Pinto et al. (2017) in a US population demonstrated that no single sensory impairment had a negative effects on mobility –measured with the Timed-up and Go test (TUG) – but a global sensory index showed significant effects on mobility (Pinto et al., 2017).

Gait Changes With Aging

In general, mobility limitations are characterized by temporal or spatial gait changes in numerous studies. In addition, gait has been used as a marker for physical function, as a predictor for falls, and even mortality (Studenski et al., 2011; Herssens et al., 2018). Gait is a highly complex process that is influenced by the central/peripheral nervous system, muscular skeletal changes, and by brain changes, e.g., the basal ganglia or the motor cortical regions (Montero-Odasso et al., 2012; Herssens et al., 2018; Clark et al., 2019).

One of the most used variables in aging research is gait speed (Studenski et al., 2011; Cruz-Jimenez, 2017). Gait speed

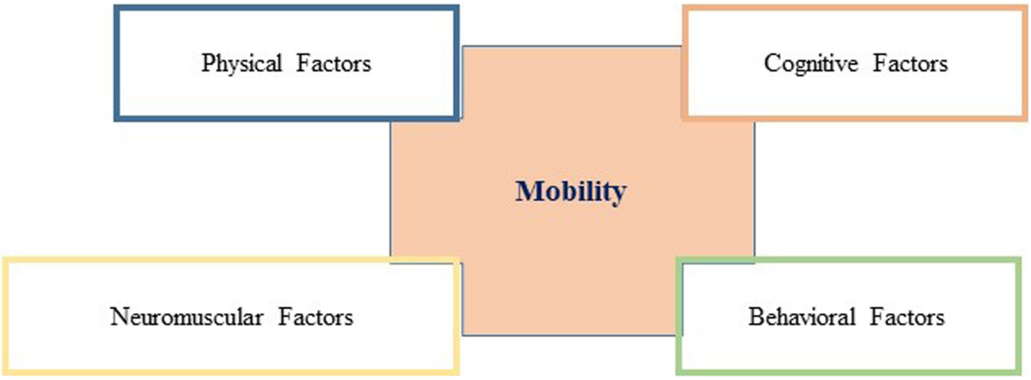

FIGURE 1 | Age-related physiological changes with regard to mobility in older community-dwelling Persons.

can be measured in self-selected (often describes as "normal" or "usual") gait and in fast gait speed to identify resources. Other gait variables are stride length or width and cadence (Herssens et al., 2018).

Early research by Winter et al. (1990) demonstrated a significant reduction in gait speed due to a shortened stride length in a study comparing self-selected gait in younger and healthy older persons. These early findings were later confirmed by Ko et al. (2010) adding the age-related changes in step width to the earlier findings. As usual, gait speed had been related to mortality by showing an 89% increased risk in mortality in older persons with the slowest gait speed (Liu et al., 2016). It has been suggested that gait is the "6th vital sign" in geriatrics (Fritz and Lusardi, 2009). A recent review by Herssens et al. (2018) confirmed the decrease in step length and step time, as well as an increase in stance with aging. In conclusion, evidence now exists that proves that spatio-temporal parameters in gait decline with age. In contrast, the question of any gender specific differences in gait changes with aging is less investigated.

Fast gait speed seems to decline at an earlier age then normal walking speed (Ko et al., 2010; Ferrucci et al., 2016; Callisaya et al., 2017). Fast gait speed is needed in daily life, e.g., in a timely pedestrian crossing. A walking speed of about >1.2 m/s is needed to cross safely during the green signal lights (Donoghue et al., 2016; Eggenberger et al., 2017). An Irish TILDA study demonstrated that one third of the population walked slower than the required 1.2 m/s (Donoghue et al., 2017) putting these older persons at stress when crossing a street. Eggenberger et al. (2017) presented similar findings in their study by showing that 30% of people in the age group 70–79 years and 73% of persons aged 80 years and older were not able to reach the 1.2 m/s threshold.

In the InCHIANTI study, Ferrucci et al. (2016) demonstrated that the above mentioned gait changes occurred at different stages over the life span. In their study cohort, the normal gait speed was stable in persons up to 65–70 years whereas the fast gait speed performance started to decline even after the age of 40–50 years.

Another important marker is the walking speed reserve, which is calculated by the difference between fast to normal gait speed (Callisaya et al., 2017). In a daily routine, catching the bus or keeping up with peers can require reserve capacity in gait speed. The walking speed reserve marker can become more important in the future. In the study by Callisaya et al. (2017) about 12.8% of the participants could not increase their gait speed to the level for a safe road crossing speed.

AGE-RELATED NEUROMUSCULAR CHANGES ASSOCIATED WITH MOBILITY

On a muscular level, a change in muscle fiber sizes occurs with aging (Tieland et al., 2018). It is commonly understood that the type II fibers (fast twitch) are especially affected – they are responsible for generating the power in chair-rise performance (Tieland et al., 2018). Next to the reduction in muscle fiber size, other age-related changes are coming into the focus, e.g., the role of motor units (MU).

Motor units are responsible for the organization of neural control in any muscle. The MUs are composed of a single alpha motor neuron and the connected muscle fibers (Malafarina et al., 2012; Drey et al., 2014; Piasecki et al., 2016; Walker et al., 2018). The number of MUs can be estimated with the motor unit number index (MUNIX; Drey et al., 2014). At present, in the neuro-centric approach the loss of MUs is responsible for one pathophysiologic pathway of sarcopenia (Drey et al., 2014). In addition, there is an increase in the size of the surviving MUs (meaning an increased number of innervated muscle fibers per alpha motor neuron) reported to compensate for the MUs loss (Drey et al., 2014; Piasecki et al., 2016; Tieland et al., 2018). The compensation and remodeling process can lead to the re-innervation by axonal sprouting from other motor neurons (Tieland et al., 2018). Next to this process, a greater variability in MU discharge is reported (Tieland et al., 2018; Walker et al., 2018). A variety of firing rates, in muscles with reduced MU (up to 30–40%) are reported during maximal isometric contractions (Tieland et al., 2018).

Clark (2019) demonstrated that neural activation of skeletal muscle is a key component for muscle weakness. Other processes of interest are impaired voluntary muscle activation and/or increased antagonist activation (Russ et al., 2012; Clark, 2019).

In conclusion, morphological and physiological changes to MU due to aging is followed by alterations in the discharge properties of the MU (Russ et al., 2012; Clark, 2019).

Age-Related Changes in Muscle Mass, Strength, and Power

Muscle performance declines with age (Doherty, 2001; Goodpaster et al., 2006; Brady et al., 2014; Ferrucci et al., 2014; Bell et al., 2016). Muscle performance is linked to muscle mass, muscle strength, and muscle power. Muscle strength is the ability to generate maximal muscle force whereas muscle power refers to the product of force and velocity of the muscle contraction (Reid and Fielding, 2012).

Muscle mass and strength have their peak on average in the third decade of life and slowly decline afterwards (Goodpaster et al., 2006; Ferrucci et al., 2016). Changes in muscle mass occur due to fat infiltration and loss of muscle fibers (Visser et al., 2005). Interestingly, evidence is accumulating that the loss of muscle mass and muscle strength deviate with advanced age (Goodpaster et al., 2006; Chen et al., 2013; Charlier et al., 2015). Muscle strength declines faster compared to the loss of muscle mass with a reduction of about 3 vs. 1% in older age (Bell et al., 2016). The loss of muscle mass can reach about 40% in persons older than 80 years but this decline can be modified by gender and lifestyle behavior. Furthermore, the national US sample by Chen et al. (2013) revealed that women have lower muscle mass and lower strength compared to their male counterparts.

Sarcopenia has formerly been recognized solely as the loss of muscle mass (Rosenberg, 1997). Due to the evidence that the loss of muscle mass is not congruent to the loss of muscle strength, the new definition of sarcopenia includes muscle mass and muscle quality with strength and gait parameters (Cruz-Jentoft et al., 2018). Based on the understanding that both muscle mass as well as strength have an impact on physical function, in the present sarcopenia definition, gait speed is included as a marker of physical performance (Cruz-Jentoft et al., 2018). Research has shown that sarcopenia is related to impairments in physical function, e.g., mobility limitations, and negative health outcomes as well as hospitalizations or falls (Cawthon et al., 2009; Brady et al., 2014; Cruz-Jentoft et al., 2018; Tieland et al., 2018; Cawthon et al., 2019).

The impact of muscle power on mobility in older age has been investigated with chair-rise or stair-climbing performance (Bell et al., 2016). With regard to strength decline, it seems that muscle power deteriorates on a faster slope. Reid et al. (2014) demonstrated in a longitudinal study that muscle power in their study population declined by about 3% per year. The rate of decline in muscle power seems to be 10% greater than the loss of muscle strength (Brady et al., 2014). Through research regarding muscle power and its impact on mobility limitation, a picture emerged that suggested muscle power (Reid and Fielding, 2012) has a higher impact on mobility than muscle strength (Bean et al., 2003, 2010; Trombetti et al., 2016). Research demonstrated that low leg power leads to a 2 to 3-fold higher risk of mobility limitation (Bean et al., 2003). Bean et al. (2003) revealed in their study that leg power was more related to reduced gait speed and chair-rise times then leg strength.

In conclusion, the role of muscle mass alone in mobility is less important than the role of muscle strength. Muscle strength only partly contributes to mobility but it especially contributes if strength is reduced in the lower extremity and when falling below a “threshold” it contributes to mobility limitations (Bean et al., 2003; Ferrucci et al., 2016). The role of muscle power is being looked at more in the present research. As it seems, muscle power has an even higher impact on mobility limitations than muscle strength (Reid and Fielding, 2012) and needs to be looked into closely when mobility in older age is investigated.

AGE-RELATED CHANGES IN COGNITION ASSOCIATED TO MOBILITY

In normal cognitive aging, the concepts of fluid and crystalized abilities describe different patterns of decline. Crystallized abilities include vocabulary and general knowledge, which the older person has gathered over their lifespan. With aging, the crystallized abilities remain stable for a long time (Harada et al., 2013).

In contrast, the fluid abilities including information processing speed, reasoning, and problem solving, declines with advancing age (Harada et al., 2013). The components of fluid abilities are especially important for mobility and will be described.

Processing speed starts to decline in the third decade of life, and continues with a linear decline over a life span (Harada et al., 2013; Salthouse, 2019). Processing speed is an important element for mobility, as the information from sensory input needs to be processed before the motor control system can adequately start.

In contrast to processing speed, attention and memory abilities show an accentuated decline with advancing age (Salthouse, 2019). The role of attention is especially important regarding mobility, as it is one important factor in gait. In combination, low attention followed by slow processing speeds might cause a hazard situation for balance or gait control.

Another important cognitive ability for balance and gait is executive function (EF). Executive functioning refers to capacities allowing an older person to successfully engage in independent, appropriate, and goal oriented behavior (Harada et al., 2013). Included in the EF concept are problem-solving abilities, and planning and organizing actions, which are cognitive elementary abilities with regard to mobility.

Age-Related Relationship Between Gait and Cognition

In the last two decades, research has demonstrated that gait is no longer an “automatically controlled” but a cognitive influenced process. The first to demonstrate the “stops walking while talking” paradigm in relationship to falls was Lundin-Ollsson in 1997. The “dual-task costs” arise from the additional cognitive task during gait performance (Lundin-Ollsson et al., 1997; Verghese et al., 2013).

Emerging evidence shows that a decline in gait speed can predict cognitive decline by more than a decade (Verghese et al., 2013; Kikkert et al., 2016; Dumurgier et al., 2017; Montero-Odasso et al., 2018). The brain areas for gait control involve regions responsible for attentional, executive, and visuospatial functions as well as the cerebellum, basal ganglia, and motor cortex (Verghese et al., 2013; Holtzer et al., 2014; Kikkert et al., 2016; Demnitz et al., 2017; Wilson et al., 2019). Evidence is accumulating that proves there is an overlap between brain areas related to cognitive and gait decline (Verghese et al., 2013; Kikkert et al., 2016; Wilson et al., 2019). One of the important questions at present, originates from the complexity of cognition. The most investigated areas of cognitive function are EF (being responsible for planning and performing the movement), memory, and processing speed. All these cognitive areas have been related to gait and mobility (Rosso et al., 2013a,b). In a recent study, De Cock et al. (2019) demonstrated the relationship of spatiotemporal gait parameters with stages of cognitive impairments. They showed that the type of the additional cognitive task is essential to determine future dementia subtypes (De Cock et al., 2019).

In conclusion, gait and different gait variables are commonly used for quantifying mobility limitations. In addition, evidence of the predictive value of gait parameters with regard to cognitive decline is established (Kikkert et al., 2016).

RISK FACTORS FOR MOBILITY LIMITATION

Mobility and Chronic Diseases

Several studies have demonstrated that chronic diseases are a risk factor for mobility limitations (Welmer et al., 2013; Kujala et al., 2019). In the Twin study by Kujala et al. (2019) about 23.2% of their participants reported mobility restriction by a disease. Most commonly were musculoskeletal (60.2%), followed by cardiovascular (18.8%), and neurological disease (7.7%). Welmer et al. (2013) demonstrated in the Swedish National Study on Aging and Care that cardiovascular disease was followed by an increased odds ratio for mobility limitations. In their study mobility limitation was defined by a walking speed of 0.8 m/s.

As explained under the cognition section, neurological diseases such as dementia or mild cognitive impairments are related to mobility limitations (Demnitz et al., 2017, 2018).

Physical and Cognitive Risk Factors for Mobility Limitation

Factors having an impact on muscle performance (muscle mass, strength, and power) are complex and multifactorial. Numerous research papers have described risk factors for sarcopenia (the loss of strength, muscle mass, and muscle performance) including a decreased anabolism pathway with sedentary lifestyle, bed rest, malnutrition, anorexia, age-related hormonal changes, and aging (Marzetti et al., 2017b). An increased catabolism pathway fostered by disease, injury, inflammation, oxidative stress, mitochondrial dysfunction, and an increase in myostatin also adds to the risk of sarcopenia (Narici and Maffulli, 2010; Morley et al., 2014; Marzetti et al., 2017b).

As described under age-related cognitive decline several cognitive capacities are also associated with mobility. The study by Pedersen et al. (2014) demonstrated higher mobility limitations in older persons with mild cognitive impairments. This was supported by Demnitz et al. (2018) who demonstrated an increasing relationship between cognition and mobility with advancing age. Furthermore, the INCHIANTI study (Ferrucci et al., 2016), showed that mobility limitations became evident even in the middle-aged group in challenging walking conditions supporting the influence of cognition on walking abilities even at an earlier age.

Psychological Risk Factors for Mobility Limitation

It is commonly understood that next to physiological risk factors, lifestyle and psychological risk factors are coming into the picture of mobility in older persons (Gill et al., 2012; Brown and Flood, 2013).

One risk factor for mobility limitations least investigated is FrPC. Fall-related psychological concern is at present being used as an umbrella term including fear of falling, self-efficacy and balance related concern, and outcome expectance (Hughes et al., 2015; Payette et al., 2016; Pauelsen et al., 2018). Self-efficacy or balance related concerns address the individual thoughts of being able to cope with a situation, e.g., "I will not fall walking down the stairs," whereas a fear of falling is a lasting concern that leads an older person to avoid activity irrespective of the capacities of the person (Delbaere et al., 2010; Hughes et al., 2015). Fall-related psychological concern has been investigated for decades with regard to falls but less in regard to mobility limitations. Fall-related psychological concern is present in about 55% of older persons, and more prevalent in women then in men (Pauelsen et al., 2018). FrPC has been strongly related to activity avoidance or declined physical activity, and social withdrawal thus contributing through an additional channel to mobility limitation (Hughes et al., 2015; Pauelsen et al., 2018). Older persons with FrPC reduce their activities to avoid falling or due to social embarrassment, e.g., asking for help to cope with environmental barriers. The association between FrPC and mobility has been only been investigated in the last few years (Auais et al., 2016, 2017; Litwin et al., 2018) demonstrating the strong association between FrPC and mobility decline. A barrier of investigating FrPC and mobility is the inconsistent use of concepts and terms. Confusion has been created by the interchangeable use of terms, e.g., fear of falling vs. self-efficacy (Hughes et al., 2015).

Another complex field of risk factors on mobility are, of course, environmental barriers (Levasseur et al., 2015; Cerin et al., 2017; Hinrichs et al., 2019). Reviews confirm the positive and negative impacts of a built environment, or the perceived environment by older persons on mobility.

In conclusion, next to physiological risk factors, life style as physical activity, environment, and psychological factors such as FrPC pose an additional risk on mobility in older persons. The complexity of risk factors and mobility in older persons is outlined in **Figure 2**.

Sedentary Behavior as a Risk Factor for Mobility Limitation

Research has demonstrated that older persons are more prone to sedentary behavior (Harvey et al., 2015; Loyen et al., 2017). Sedentary behavior is defined by the Sedentary Behavioral Research Network (SBRN) as "any waking activity characterized by an energy expenditure ≤ 1.5 metabolic equivalents while being in a sitting, reclining, or lying posture" (Tremblay et al., 2017). A recent systematic review (Scher et al., 2019) demonstrated that higher sedentary levels were related to mobility limitation. An interesting aspect in this area is that breaks or shorter periods of sedentary behavior have less negative impact on mobility limitations (Scher et al., 2019).

ASSESSMENT OF MOBILITY

Mobility is an important aspect of healthy aging and researchers as well as clinicians in a daily routine need effective and reliable assessment tools. The complex construct of mobility as well as the different courses to assess mobility in older persons makes different approaches in the assessment mandatory. Mobility measures are used for different reasons: (a) to screen for early mobility limitations at one time point or (b) to obtain changes in an individual's mobility, e.g., after an intervention. Next to the purpose of assessment, available time and location also play an important role in the decision of assessment. The assessment of mobility in community-dwelling older persons range from self-reported mobility questionnaires (Brown and Flood, 2013; Taylor et al., 2019) or performance based measures to GPS obtained data (Fillekes et al., 2019). A new review of possible assessments for mobility has recently been performed by Soubra et al. (2019) including performance measures such as the well-known TUG, the Short Physical performance Test (SPPB), or the different walk tests (6-min, 2-min, or 400 m tests). Self-reported mobility ranges

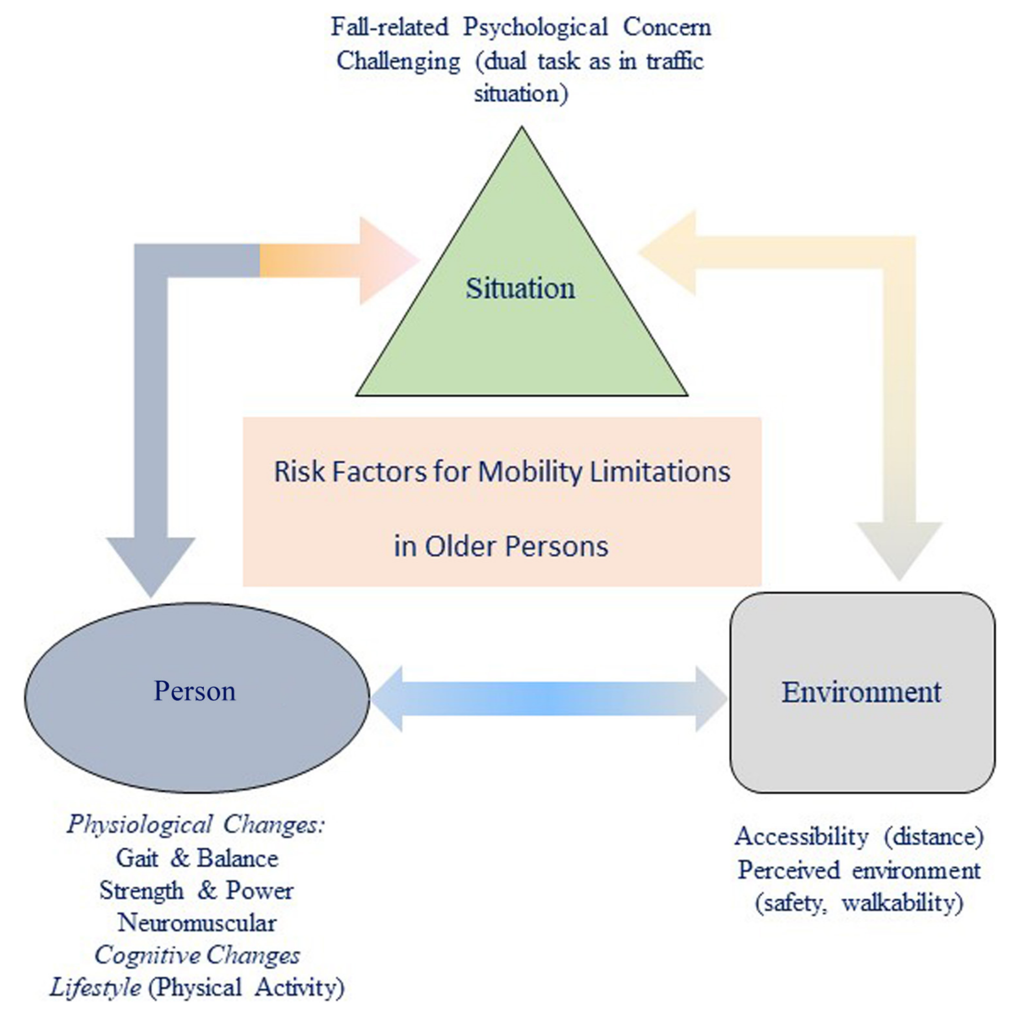

FIGURE 2 | Interaction of risk factors for mobility limitation in older community-dwelling persons.

from simple questionnaires to life-space mobility (Brown and Flood, 2013; Taylor et al., 2019). Brown and Flood (2013) suggest stepwise questions by asking for difficulties in climbing up 10 stairs and walking - mile. If no difficulties are reported, a further question about modifications on climbing up 10 stairs (e.g., using the handrails) or in walking - mile (e.g., using an assistant device) should be provided.

As strength, balance, and gait are important components for mobility the SPPB is an excellent tool with good psychometric properties (Freiberger et al., 2012), and is often used in research as well as in the clinic to identify mobility limitations or functional decline (Gill et al., 2012; Pahor et al., 2014; Zunzunegui et al., 2015; Cruz-Jentoft et al., 2018).

Gait can be measured by a stopwatch and different lengths (ranging from 4 to 10 m to the 400 m walk) or with extensive technology. To show subclinical gait decline, the dual task paradigm is recommended (Beauchet et al., 2017). Evidence is accumulating that additional cognitive tasks, or tasks of increasing complexity, e.g., naming animals or reciting every second letter while walking/crossing over obstacles, is slowing down gait speed (Verghese et al., 2012; Kikkert et al., 2016; Muir et al., 2019). In many studies gait is obtained with modern technology based on sensors for spatial and temporal parameters (Oh-Park et al., 2010; Beauchet et al., 2017).

Fall-related psychological concerns are self-reported or obtained by questionnaires. One of the most used tools is the FES-I which was translated into many different languages (Yardley et al., 2005). Other questionnaires in this area are the SAFFEE and the ABC scale (Bladh et al., 2013).

EXERCISE INTERVENTION ON MOBILITY

One of the most effective interventions in counteracting mobility limitation is exercise. Taking into account the physiological risk factors, it seems evident that an exercise intervention is based on strength, gait, and balance. The most effective interventions have addressed the muscle pathway by strength training exercises or in combination with balance and gait exercises (Martone et al., 2015; Marzetti et al., 2017a). One multidisciplinary, randomized, and controlled study contributing to the existing evidence of effective multicomponent exercise intervention on mobility prevention is the Lifestyle Interventions and Independence for Elders (LIFE) study by Pahor et al. (2014). The study addressed vulnerable and physically limited persons aged 70 years and older. The multicomponent exercises included walking, and strength and balance training. In the LIFE study, incidents of mobility disability – defined by the 400 m walk – were investigated demonstrating a significant positive effect in the prevention of mobility disability in the exercise group compared to the health education group. The intervention group experienced mobility disability at 30.1% in contrast to 35.9% in the health education group. Persistent mobility disability occurred in only 14.7% of the intervention versus 19.8% in the health education group (Pahor et al., 2014).

The LIFE study has been copiedby the European SPRINTT Study (*S*arcopenia & *P*hysical F*R*ailty *IN* older people: multi-componen*T* *T*reatment strategies) which is currently ongoing. SPRINTT uses the same methods and intervention program, so that data on mobility will be easily comparable at a later date (Landi et al., 2017; Marzetti et al., 2018).

In both studies, exercise intervention was individualized and tailored with regard to intensity including supervised and unsupervised sessions. The intervention was provided for between 24 and 36 months (Pahor et al., 2014; Marzetti et al., 2018).

One of the most disseminated and effective exercise programs is the OTAGO program developed by Campbell & Robertson in New Zealand. The first intervention was a home-based strength and balance exercise accompanied by a walking activity in women aged 80 years and older. Several other interventions with the same components (balance and strength exercises) replicated the positive effects on physical function, reduced fall rate, and other health outcomes (Campbell et al., 1999; Day, 2011). Later research demonstrated the effectiveness of the OTAGO program delivered as a group exercise (Kyrdalen et al., 2013). Although fall prevention was the first outcome of the OTAGO program, on a secondary level it also had positive effects on other health outcomes (Shubert et al., 2017). Overall the OTAGO program reduced falls by 32% and even reduced mortality over 12 months with a risk ratio of 0.48 (95% confidence interval 0.25–0.80) (Thomas et al., 2010).

A common component of the above-mentioned exercise programs are the structured format with increasing intensity and standardized repetitive exercises and the supervision and social feedback by experienced trainers. However, long-term adherence without this tight monitoring is questionable. Therefore, new concepts are developed to integrate exercise into daily routine. One approach would use a daily walking routine, e.g., walking to the store (Weber et al., 2018) whereas another approach would integrate functional exercises to help improve balance and strength in the daily routine (Clemson et al., 2012; Boulton et al., 2019). Integrating training exercises into a daily routine seems to have several advantages: requires no additional time to perform the exercise, includes a relationship to the daily routine (balance exercises, e.g., semi-tandem during cooking or washing), and improvements are linked to the daily routine thus enhancing motivation and compliance (Weber et al., 2018).

Newer concepts investigated the integration of video gaming to improve physical function but do not address mobility as a primary outcome.

DISCUSSION

Functional limitation increases with age and, due to demographic changes, early identification of older persons at risk is becoming mandatory (Tieland et al., 2018). Mobility is a major pillar of function, and mobility limitations in older community-dwelling persons are highly prevalent and followed by negative health events such as hospitalization or falls or even a higher mortality risk (Gill et al., 2006; Studenski et al., 2011; Brown and Flood, 2013; Musich et al., 2018). Research on mobility over the lifespan is rare and probably not feasible given the heterogeneity of mobility decline on an individual level and the complexity of factors involved (Ferrucci et al., 2016). Nevertheless, screening for early onset of mobility decline in older persons with regard to healthy aging and quality of life is without any alternative. Several important components of mobility in older persons were addressed in this narrative review. Several gaps remain which should be addressed in the future to move the research on mobility in older persons forward.

Gaps to Be Addressed: Definitions and Concepts

To push the mobility research in older persons further, firstly an agreement of a concept as well as definition, and standardized assessment tools are needed (Rosso et al., 2013a; Varma et al., 2016; Beauchet et al., 2017; Cornman et al., 2019; Donoghue et al., 2019). With regard to definitions, these should not only be provided by researchers and clinicians but also by the older persons themselves. Intervention studies found that integrated adapted mobility strategies, e.g., taking longer to walk to the shop, might not be recognized by an older person. This activity is not –in an older person's perception- related to mobility but to shopping, and therefore does not provide any understanding or motivation for improving mobility. Raising awareness of the components of mobility limitations to older persons by installing definitions and concepts needs to be addressed in the future.

Mobility in older age should not only be directed by disease-specific approaches but take into account the intrinsic capacity approach by the WHO (2015) including function and functional reserve (Cesari et al., 2018). Especially, the evidence that under challenging conditions mobility limitations occur even in apparently healthy older persons underlines the importance of the assessment of the functional reserve capacity.

From a scientific perspective, additional barriers arise from the use of different terms and mobility outcomes (mobility vs. walking or life-space mobility vs. functional mobility), posing a challenge when comparing different results and data.

Gaps to Be Addressed: Physical Function and Mobility

Slow gait speed, and decline in muscle strength and power have all negative effects on mobility. Numerous studies have shown that having a higher level of physical function prevents mobility limitations (Guralnik et al., 2000). Exercise intervention, e.g., strength training, has demonstrated positive effects on functional mobility (Papa et al., 2017).

Nevertheless, a recent statement showed that the focus on musculoskeletal mechanisms and processes might not be the equivalent approach to counteract mobility limitations (Clark et al., 2019). The role of muscle mass related to mobility is much less than earlier anticipated. There is accumulating evidence that neuronal changes are more important in the process of mobility decline than biomechanical age-related changes.

In contrast to the existing literature on physical function and mobility, little evidence exists as to whether mobility decline occurs in a linear, dynamic, or even a mixed trajectory (Gill et al., 2006; Ahmed et al., 2019). Gill et al. (2006) have demonstrated that transitions between different mobility levels are very dynamic and it can be dangerous to estimate mobility limitations at only one point in time. The individual might revert back to their previous level of mobility limitation for different reasons (e.g., normal recovery after an injurious fall, or hip replacement, shortly after hospitalization) or develop an even more severe mobility limitation level.

Gaps to Be Addressed: Cognition Brain and Mobility

One important topic that needs further investigation is the interaction between structural and functional brain changes and mobility in older persons. An initiative utilizing three workshops (Rosso et al., 2013a; Sorond et al., 2015; Varma et al., 2016) addressed this topic. New technological equipment such as magnetic resonance imaging (MRI) or functional MRI (fMRI) are being used. Functional near-infrared spectroscopy (fNIR) helped investigate which brain areas are involved in mobility and found evidence that the basal ganglia, cerebellum, and the frontal and parietal cortex are involved (Holtzer et al., 2014). Nevertheless, the specific brain regions, and neuronal networks involved in mobility need further clarification. The variability on the functional level in the older population – ranging from healthy/fit to disability/immobile – adds another important aspect to this topic. Up to now, no investigation on the impact of different functional levels in the research area of brain structures and mobility has been conducted. Further questions remain on the specific relationship between single gait parameters and cognitive variables. At present, research is investigating the involved brain regions related to mobility (Rosso et al., 2013a; Holtzer et al., 2014; Demnitz et al., 2017; Van Ooteghem et al., 2019).

Gaps to Be Addressed: Neuromuscular Factors Related to Mobility

As Clark et al. (2019) concluded their editorial (2019) with the question "are we barking up the wrong tree?" future research has to take into account the area of neuromuscular changes. This will be an upcoming field for new evidence in the near future, as it seems to explain functional changes more than muscle mass. Furthermore, the question of past exercise experience over a lifetime – e.g., playing tennis – on intramuscular coordination with aging has yet to be integrated.

Gaps to Be Addressed: Psychological and Behavioral Aspects

Another less investigated topic is the psychological aspects of mobility. In older persons, perceived mobility is related to personal experience and to psychological components such as FrPC (Goins et al., 2015). In addition, FrPC should be included in mobility research as it does not only moderate the physical activity level or risk of falling, but it also might act on a pathophysiology level by increasing inflammation and thus acting on the muscular pathway.

Furthermore, the motivation to change behavior in mobility is linked to intrapersonal, interpersonal, and environmental factors

(Yardley et al., 2007; Goins et al., 2015). Changes in mobility strategies can be perceived as a support, e.g., using a wheeled walker to be able to still go out for shopping, or as a barrier, e.g., using a wheeled walker is perceived as an embarrassment, demonstrating the two-fold nature of the assistant device. Other elements to be recognized are self-efficacy, attitudes, and fear of falling (Hughes et al., 2015) as low self-efficacy – having low confidence in one's abilities – will pose a barrier for the uptake of an appropriate intervention.

Another important aspect with regard to health and physical activity behavior is a positive self-perception on aging by older persons (Wurm et al., 2010; Wolff et al., 2014). Integrating such a "positive self-perception" component, e.g., in exercise intervention programs, might be an additional asset to motivate older persons into being more mobile (Beyer et al., 2019).

Gaps to Be Addressed: Exercise Intervention and Mobility

Although there are exercise interventions being carried out on mobility, or are just finishing as with the EU SPRINTT project, several questions remain. In the LIFE study (Pahor et al., 2014), intervention was most effective in participants having an SPPB score of between 3 and 7 but was less effective in participants with an SPPB score of 8–9. This opens the question: which older person will profit most from an exercise intervention to maintain mobility? This question might depend on the time period of a follow up. In longitudinal observational studies such as one by Ferrucci et al. (2016) it becomes obvious that, depending on the demanding level of mobility, decline occurs at an earlier age but can be compensated. Furthermore, as there seems to be a gender aspect, future research should be conducted to investigate effects in both genders separately.

Another aspect regarding exercise intervention is the question of "how and if" exercise intervention has an impact on the intramuscular coordination by addressing neuromuscular age-related changes.

Gaps to Be Addressed: Assessments

Most physical assessments, e.g., gait or walking performance, are obtained in the lab or under clinical conditions. Research suggests that this might not reflect the real physical capacity. Hillel et al. (2019) demonstrated that in comparison gait parameters under "real-world" conditions were much worse than in the lab-measured gait parameters. The development of new technology to obtain mobility data under "real-world" conditions such as the newly started EU Project "Mobilise-D" (connecting digital mobility assessment to clinical outcomes for regulatory and clinical endorsement) will in the future close this gap. The underlying thesis of Mobilise-D is that loss of mobility (slower walking, fewer steps per day, or more time sitting) predicts adverse medical outcomes regardless of underlying disease such as chronic obstructive pulmonary disease, Parkinson's disease, multiple sclerosis, hip fracture recovery, and heart failure. The frame of Mobilise-D is that loss of mobility is itself a medical problem regardless of the underlying chronic disease.

CONCLUSION

Mobility limitations are highly prevalent with increasing age and are related to negative health outcomes such as hospitalization and falls.

As mobility is a multi-factorial and complex construct, interdisciplinary approaches are mandatory. The lack of a sole definition as well as concepts across disciplines and persons involved are posing barriers for effective mobility prevention. A central aspect in age-related mobility research is the understanding of the interaction of the involved mechanisms, processes, and contributing systems which is complex. Old approaches, e.g., the role of muscle mass, are being questioned and new approaches such as neuromuscular and cognitive processes are coming into focus. Psychological aspects are less investigated, e.g., FrPCs and aging images, as well as behavioral domains, e.g., sedentary behavior with relationships to mobility.

Medical, social, and psychological research is needed for mobility research under the approach of healthy aging.

AUTHOR CONTRIBUTIONS

EF designed and wrote the manuscript. RK and CS wrote and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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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.

frontiers in Physiology

ORIGINAL RESEARCH
published: 21 October 2020
doi: 10.3389/fphys.2020.544559

Delayed Impairment of Postural, Physical, and Muscular Functions Following Downhill Compared to Level Walking in Older People

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OPEN ACCESS

Edited by:
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Reviewed by:
Xin Ye, University of Mississippi, United States
Ronald F. Zernicke, University of Michigan, United States

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Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *21 March 2020*
Accepted: *18 September 2020*
Published: *21 October 2020*

Citation:
Hill MW, Hosseini E-A, McLellan A, Price MJ, Lord SR and Kay AD (2020) Delayed Impairment of Postural, Physical, and Muscular Functions Following Downhill Compared to Level Walking in Older People. Front. Physiol. 11:544559. doi: 10.3389/fphys.2020.544559

Transient symptoms of muscle damage emanating from unaccustomed eccentric exercise can adversely affect muscle function and potentially increase the risk of falling for several days. Therefore, the aims of the present study were to investigate the shorter- and longer-lasting temporal characteristics of muscle fatigue and damage induced by level (i.e., concentrically biased contractions) or downhill (i.e., eccentrically biased contractions) walking on postural, physical, and muscular functions in older people. Nineteen participants were matched in pairs for sex, age and self-selected walking speed and allocated to a level (n = 10, age = 72.3 ± 2.9 years) or downhill (n = 9, age = 72.1 ± 2.2 years) walking group. Postural sway, muscle torque and power, physical function (5× and 60 s sit-to-stand; STS), and mobility (Timed-Up-and-Go; TUG) were evaluated at baseline (pre-exercise), 1 min, 15 min, 30 min, 24 h, and 48 h after 30 min of level (0% gradient) or downhill (−10% gradient) walking on a treadmill. Following downhill walking, postural sway (+66 to 256%), TUG (+29%), 60 s STS (+29%), five times STS (−25%) and concentric power (−33%) did not change at 1–30 min post exercise, but were significantly different ($p < 0.05$) at 24 and48 h post-exercise when compared to baseline ($p < 0.05$). Muscle torque decreased immediately after downhill walking and remained impaired at 48 h post-exercise (−27 to −38%). Immediately following level walking there was an increase in postural sway (+52 to +98%), slower TUG performance (+29%), fewer STS cycles in 60 s (−23%), slower time to reach five STS cycles (+20%) and impaired muscle torque (−23%) and power (−19%) which returned to baseline 30-min after exercise cessation ($p > 0.05$). These findings have established for the first time distinct impairment profiles between concentric and eccentric exercise. Muscle damage emanating from eccentrically biased exercise can lead to muscle weakness, postural instability and impaired physical function persisting for several days, possibly endangering older adult's safety during activities of daily living by increasing the risk of falls.

Keywords: fatigue, muscle damage, falls, balance, aging, functional performance, walking

INTRODUCTION

Falls among older people represents a substantial health and social priority. Falling often leads to progressive functional decline, the development of comorbidities and the start of dependency (Okubo et al., 2017). It is well established that ∼35% of adults aged 65 years and over fall annually (Stalenhoef et al., 2002). Although the etiology of falling is complex (Rubenstein, 2006), several modifiable risk factors have been documented including diminished balance and mobility (Delbaere et al., 2010), a progressive reduction in muscle strength and/or power (Orr et al., 2006) and poor cognitive function (Mirelman et al., 2012). Exercise can protect against a loss of physical (Cadore et al., 2013; Chou et al., 2012; Giné-Garriga et al., 2014) and cognitive function (Colcombe and Kramer, 2003) in older age. However, an inevitable consequence of being physically active is short-term muscle fatigue (Vuillerme et al., 2002). Exercise may acutely increase the risk of falling by negatively influencing postural, muscular, and physical functions (Helbostad et al., 2010). However, the importance of such transient muscle fatigue as a fall-risk factor in older people is not well understood.

Fatigue (or tiredness) is a common complaint among older adults with more than 50% of people over 70 years reporting fatigue during daily activities (Avlund, 2010). One area that has garnered attention recently is the effects of daily activities (such as walking) on intrinsic fall risk factors (i.e., balance, strength, mobility, and cognitive function) (Sturnieks et al., 2018). Although walking is an essential prerequisite to quality of life and independent living (Lee and Buchner, 2008) most falls occur during ambulation (Berg et al., 1997; Robinovitch et al., 2013; Talbot et al., 2005).Consequently, careful consideration of activities that may influence gait are important. During uphill or level walking the lower extremity muscles predominantly perform concentric contractions, resulting in a high metabolic cost (Malm et al., 2004). Consequently, walking can affect several factors associated with falls including an increase in postural sway (Hill et al., 2015; Donath et al., 2013, 2015; Walsh et al., 2018), altered gait characteristics (Nagano et al., 2014), slower reaction time (Morrison et al., 2016) and the decreased muscle strength (Morrison et al., 2016), and power (Foulis et al., 2017). Concentric-dominant exercise, such as level walking, provokes a high energetic metabolism and an intracellular accumulation of metabolic by-products (Green, 1997). These metabolites can adversely influence sensorimotor coupling mechanisms responsible for postural control (Paillard, 2012). However, fatigue-related functional impairments are often transient with performance measures returning to baseline within 20 min (Hill et al., 2015; Donath et al., 2013, 2015). Therefore the relative impact of short-term fatigue induced by level or uphill walking may be limited.

Daily activities are not isolated to concentric contractions but can also incorporate eccentric contractions (such as walking downhill or descending flights of stairs). Conversely to concentric exercise, these activities can result in non-metabolic fatigue. For example, downhill walking elicits a considerably lower oxygen uptake than level or uphill walking when matched at the same speed (Laursen et al., 2000). However, this exercise imposes greater loading on the muscle-tendon complex (Howatson et al., 2011) during braking to control the rate of knee flexion (Maeo et al., 2017). One of the hallmarks of eccentric muscle contractions is the short-term manifestation of myocellular damage and disruption to extrafusal and intramuscular fibers (Raastad et al., 2010). Muscle damage often results in a concomitant reduction in muscle force (Proske and Allen, 2005) and proprioception (Paschalis et al., 2008). These changes typically present ∼6 h after exercise and peak at one to three days thereafter (Paschalis et al., 2008). The amalgamation of muscle damaging effects lasting for several days is likely to be problematic for postural and physical functions and may substantially increase the risk of sustaining a fall for a prolonged period. Consequently, it is likely the magnitude of change and recovery of muscular, physical function and postural profiles associated with prolonged downhill walking may differ from those observed following level walking.

To date, no study has compared the effects of concentric-versus eccentric-dominant exercise-induced fatigue on fall risk factors among older adults; information likely valuable for elucidating some of the fundamental aspects of task-dependent muscle fatigue on fall risk factors. Therefore, the aims of the present study were to investigate the shorter- (up to 30 min) and longer-lasting (up to 48 h) temporal characteristics of muscle fatigue induced by level (i.e., concentric contractions) and downhill (i.e., eccentric contractions) walking on physical, muscular and postural functions associated with fall risk in older people. We hypothesized that level walking, characterized by metabolic fatigue, would provoke an immediate increase in postural sway, a reduction in physical functional performance and reduced isometric strength and concentric power, recovering to baseline levels within 30 min of exercise cessation. Secondly, we hypothesized that downhill walking, characterized by non-metabolic fatigue (i.e., muscle damage), would elicit a delayed (24–48 h) recovery of postural sway, a reduction physical functional performance and impaired muscle function.

MATERIALS AND METHODS

Participants

Effect sizes (Cohen's *d*) were calculated from similar studies from mean changes in the anteroposterior centre of pressure (COP) displacement ($d = 2.08$), mediolateral COP displacement ($d = 1.79$) (Hill et al., 2015) and knee extensor concentric power ($d = 1.47$) (Foulis et al., 2017). Sample size was estimated using an *a priori* power analysis (G* Power software [Version 3.1.9.4]) for knee extensor concentric power (i.e., variable with the smallest effect size to avoid bias) (statistical power = 0.80, alpha = 0.05, effect size = 1.47) and revealed that a total of nine participants in each group would be sufficient to detect significant effects of level and downhill walking on measures of postural, muscular, and physical functions (Faul et al., 2009). A total of 19 community-dwelling older adults (**Table 1**) were recruited with no prior experience of eccentric training and able to walk without the use of an assistive device. All participants had some previous experience of walking on a motorized treadmill but none had any experience of walking downhill on a treadmill. Participants were excluded if they were unable to stand unassisted or had a history of neurological (e.g., stroke, Parkinson's disease), musculoskeletal (e.g., tendinitis), cognitive impairment (e.g., dementia) and/or cardiovascular or pulmonary diseases (e.g., coronary heart disease, chronic obstructive pulmonary disease). A screening medical questionnaire revealed that no participants had any conditions that would preclude them from participating. Following ethical approval by Coventry University's Ethical Review Board (Ref; P90521) and prior to any data collection, all participants gave written and informed consent. All risks associated with the experimental procedures were explained before testing began with the study undertaken in accordance with the Declaration of Helsinki (1964).

Questionnaires

During the consenting visit, all participants completed questionnaires for self-reported physical activity, concern about falls, fatigue and cognitive function. Participants were moderately active (**Table 1**), as confirmed by the screening medical and physical activity questionnaire. The 16 item Falls Efficacy Scale (FES-I) measures concern about falling during physical and social activities with each item scored on a 4-point Likert scale [1 = not at all concerned to 4 = very concerned; Yardley et al. (2005)] with cumulative scores of 16–19, 20–27, and 28–64 indicating low, moderate and high concern about falling, respectively (Delbaere et al., 2010). Participants also completed the Mini Mental State Examination (MMSE), consisting of 11 questions to determine cognitive function (Crum et al., 1993). An MMSE score of <24 separates individuals with mild dementia from participants with normal cognitive function (Folstein et al., 1983). Self-reported fatigue was measured using the nine item Brief Fatigue Inventory (BFI) to assess the impact of fatigue on daily functioning (Mendoza et al., 1999). This inventory has been validated in healthy people over 65 years of age (Shuman-Paretsky et al., 2014). Participants rated their fatigue on an 11-point scale (0 = no fatigue, 10 = "as bad as you can imagine") with higher scores on the BFI corresponding to greater self-reported levels of fatigue.

TABLE 1 | Mean ± SD sample characteristics.

Sample characteristics	Level walking (n = 10)	Downhill walking (n = 9)
Sex (male/female)	(5/5)	(4/5)
Age (years)	72.3 ± 2.9	72.1 ± 2.2
Body mass (kg)	72.8 ± 13.7	72.2 ± 9.0
Height (m)	1.65 ± 0.09	1.64 ± 0.09
BMI (kg·m^2)	26.9 ± 5.0	26.9 ± 4.5
Cognitive status (MMSE)	28.7 ± 1.2	28.4 ± 1.0
Physical activity (hr·w^{-1})	5.9 ± 3.5	5.9 ± 3.3
Self-reported fatigue (BFI)	8.5 ± 4.5	8.4 ± 2.5
Falls efficacy (FES-I)	17.4 ± 2.1	17.7 ± 1.0
Self-selected walking speed (km·h^{-1})	3.9 ± 1.0	4.0 ± 0.5

BMI, body mass index; MSSE, Mini Mental State Examination; BFI, Brief Fatigue Inventory; FES-I, Falls Efficacy Scale International.

Experimental Design

The study was conducted as a repeated-measures between group design with criterion measurements evaluated at baseline (pre-exercise), immediately post-exercise (1-min), and again at 15-min, 30-min, 24 h, and 48 h following exercise interventions. We opted against a within-subject crossover design as the protective effect against muscle damage from a single bout of eccentric exercise (McHugh, 2003) may influence level walking characteristics. Following the consenting visit, all participants completed a familiarization session prior to the experimental trials at least 72 h, but not more than 7 days before the first experimental trial. Anthropometric characteristics, postural sway, muscle function (torque and power), physical function (60 s sit-to-stand; STS) and mobility (timed up and go) were collected during this time (described later). To habituate participants to walking on the treadmill and to ascertain self-selected walking speed for subsequent experimental trials, each participant walked for 5–10 min on the treadmill at a 0% gradient (Roberts et al., 2018). Participants were specifically instructed to walk at a preferred comfortable pace that they felt they could maintain for ~30 min. The starting speed was 2.5 km·h^{-1} with an increase of 0.2 km·h^{-1} every 30 s until the participant indicated that the next increment in speed would be too fast. Familiarizing the participants during downhill walking was deliberately avoided as a small volume of non-damaging downhill walking (5 min at −28%) can prevent muscle damage during subsequent prolonged (40 min at −28%) downhill walking (Maeo et al., 2017). All participants were blind to their self-selected walking speed, and the principal investigator adjusted speed in 0.2 km·h^{-1} increments in response to instructions from the participant to go "slower" or "faster" with the principal investigator standing next to the treadmill to assist the participants to complete the tests safely (Roberts et al., 2018). Following baseline assessments, participants were allocated to a level (0%) or downhill (−10%) walking intervention. Participants were matched in pairs for sex, age, physical activity levels, and self-selected walking speed to minimize potential confounding factors between groups. Independent-sample t-tests revealed no significant difference between groups for any participant characteristic at baseline ($p > 0.05$; **Table 1**). During the experimental period, participants were instructed not to perform any unfamiliar activities and to avoid any interventions that might influence recovery, such as massage, application of ice packs, or nutritional supplements.

Posturography

Postural sway was measured during quiet standing as a measure of static balance performance. Each participant performed quiet stance trials while standing on a force platform (AMTI, AccuGait, Watertown, MA, United States) for 30 s. Data were sampled at 100 Hz (AMTI, Netforce) and the total displacement of COP in the anteroposterior and mediolateral directions (both cm) and mean COP velocity (cm·s^{-1}) were subsequently calculated (AMTI, BioAnalysis, Version 2.2). The validity and reliability of these parameters have previously been established for this sampling duration (Pinsault and Vuillerme, 2009). To ensure continuity during trials, unshod foot position was standardized by instructing participants to stand with the feet together (i.e., Romberg stance). To avoid unnatural postural sway, internal focus of attention and restriction of exploratory behavior, participants were not specifically asked to stand as still as possible. Participants' arms were left to hang freely by their sides and were instructed to look straight ahead at a target 1.5 m away; adjusted to the eye level of each individual. Throughout all tests, the investigator stayed close to the participants to prevent falling but without interfering with balance performance. Before the walking exercise intervention, participants performed three 30 s trials for each condition of eyes open (EO) and eyes closed (EC), in a counterbalanced order, with the mean of the three trials for each condition used in the subsequent analysis. To capture the immediate effects of fatigue on postural sway, a single EO and EC trial was collected at 1, 15-, and 30-min post-exercise, with longer-term effects measured 24 and 48 h after the exercise bouts with all tests undertaken at the same time of the day (±1 h).

Mobility and Physical Function

The Timed Up and Go Test (TUG) was used as described by Podsiadlo and Richardson (1991). Participants were instructed to stand up from a chair without using their hands, walk 3 m at a normal pace to a line on the floor, walk back to the chair and sit down. Before performing the TUG, an experienced researcher provided verbal and visual instructions regarding the test procedures. Participants were asked to perform the TUG at their self-selected walking speed. The time taken to complete the test was recorded using a stopwatch (nearest 0.01 s) with a total of three trials recorded with 30 s rest between trials; the fastest trial was included in the subsequent analyses. Two minutes later, the participants completed the 60 s STS test (Strassmann et al., 2013). In addition to the total number of repetitions performed in the 60 s STS, the time taken for the first five repetitions were also recorded. Participants were instructed to sit down on a chair (seat height 45 cm) with arms folded across the chest and feet shoulder width apart. Participants were instructed to stand up fully with complete knee and hip extension and sit down as many times as possible within 60 s, with participants verbally encouraged throughout the duration of the test. Given the onerous nature of the test, only a single trial was recorded before exercise, and at 1, 15-, and 30-min, 24 and 48 h post-exercise. Among community dwelling older people, test-retest reliability [intraclass correlation coefficient (ICC)] of the TUG (ICC = 0.99; Podsiadlo and Richardson, 1991), 60 s STS (ICC = 0.80; Ritchie et al., 2005) and five times STS (ICC = 0.89; Lord et al., 2002) are excellent.

Muscle Torque and Power

The pre-intervention functional balance and mobility tests were also used as the warm-up for subsequent maximal muscle function tests. All maximal voluntary contractions (MVCs) of the knee extensors were performed on the dominant leg (self-selected by participants) using the Cybex Norm isokinetic dynamometer (Computerized Sports Medicine Inc., United States). Participants were seated comfortably in an upright position with the backrest angle at 100° and the knee flexed to 90°. The lateral femoral epicondyle (i.e., axis of rotation) of the dominant knee was aligned with the axis of rotation of the dynamometer with extraneous movements during MVC's prevented with restraining straps placed over the trunk, pelvis, thigh and ankle. The knee angle was placed at 90° for all isometric MVC's (torque; Nm) and initial position for concentric contractions (power; W) with gravity correction performed for all tests. The range of motion for dynamic contractions was 70° (range 90°–160° extension). For familiarization of isokinetic and isometric contractions, participants performed three submaximal (∼70% MVC) isometric and concentric contractions, with 3 min of rest between each contraction type. For all time points, each participant first completed three knee extensor isometric MVCs with each isometric contraction lasting ∼4 s. Following the isometric MVCs, participants completed three concentric MVC's at 180° s^{-1}, with the angular velocity based on their tolerance and ability documented during prior pilot testing. High velocity contractions were chosen because they are functionally relevant to physical performance tasks, such as rising from a chair (Hortobagyi et al., 2003) and changes in high velocity muscle power (270° s^{-1}) are associated with increases in chair rise time following level walking in older adults (Foulis et al., 2017).

Participants were instructed to contract maximally over the complete range of motion and rested for 1 min between each set. During each testing session, participants were given verbal encouragement to help to ensure a maximal effort with visual feedback of the torque trace provided. During the three repetitions for both contraction modes, the trial with the highest torque was used in subsequent analysis for each mode.

Exercise Interventions

Immediately following baseline assessments, participants completed 30 min of level (0% gradient) or downhill (-10% gradient) walking on an instrumented treadmill (h/p/Cosmos Mercury 4.0; h/p/cosmos Sports & Medical gmbh, Nussdorf-Traunstein, Germany). The −10% gradient was adopted because this is the point at which minimum total body energy costs occurs for downhill walking (Wanta et al., 1993). Participants wore a safety harness attached to an automated overhead suspension arm during the interventions to prevent possible falls from the treadmill (**Figure 1**). Starting with a treadmill speed of 1.5 km·h^{-1}, the velocity was progressively increased until participants reached their pre-determined (during familiarization) self-selected walking speed after ∼30–60 s. As with the baseline assessment, all participants were blind to their self-selected walking speed, with the principal investigator adjusting speed in 0.2 km·h^{-1} increments and standing next to the treadmill to assist the participants to complete the tests safely. Participants wore their own comfortable sports shoes and clothes, however compression garments were not permitted. During both level and downhill walking, participants were instructed to walk at their most comfortable stride length and stride rate and not to change it throughout the trial (Maeo et al., 2017). The 30 min walking time was selected as previous studies have reported that this is sufficient to elicit muscle fatigue-related effects on postural control (Hill et al., 2015; Foulis et al., 2017; Walsh et al., 2018). Additionally, this exercise duration aligns with the American College of Sports Medicine recommendations for health benefits in older people (Nelson et al., 2007).

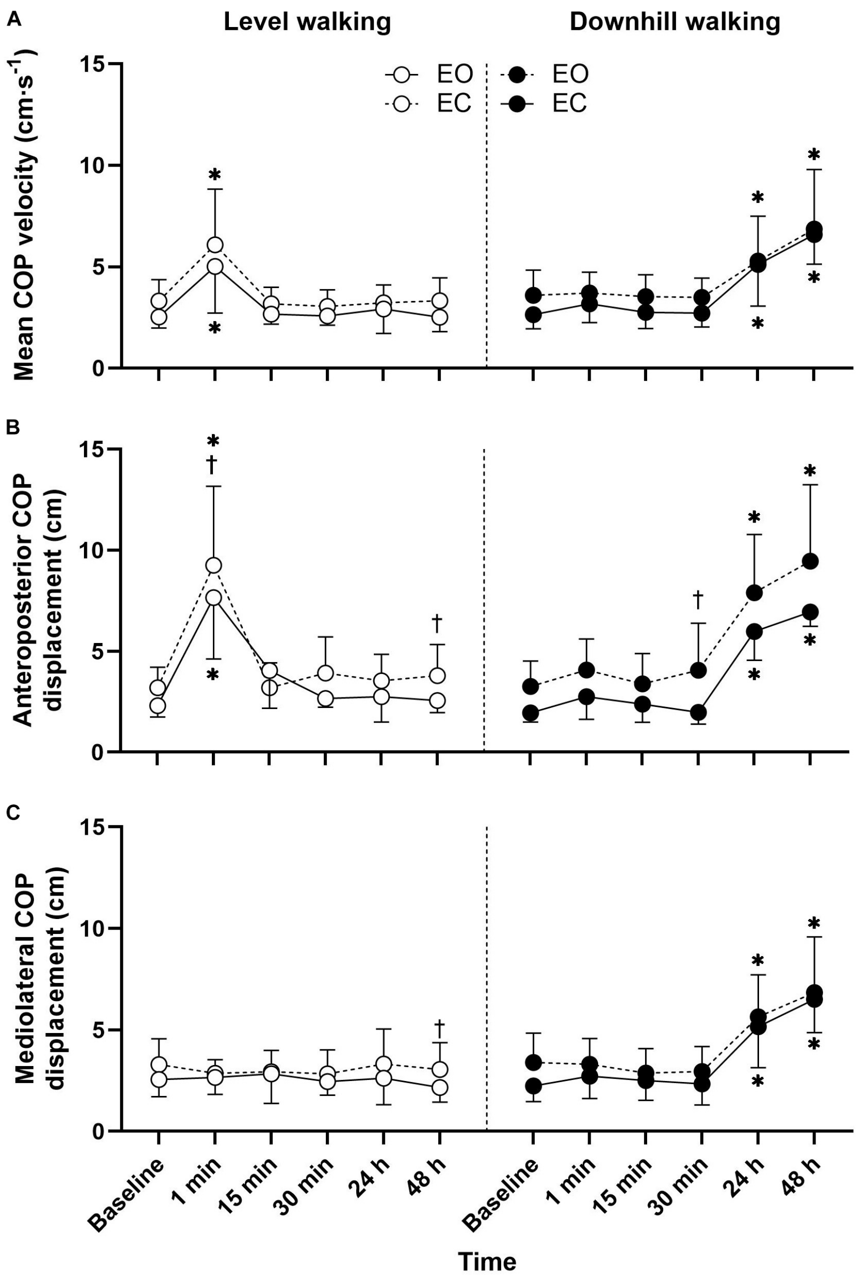

FIGURE 1 | Mean ± SD mean COP velocity **(A)**, anteroposterior COP displacement **(B)**, and mediolateral COP displacement **(C)** responses to 30 min level and downhill walking. *Significantly different to baseline. †Significant vision effect.

Physiological and Perceptual Responses

During the walking test, expired gases were analyzed using a breath-by-breath online analysis system (MetaMax, Cortex Biophsik, Borsdorf, Germany) for oxygen uptake ($\dot{V}O_2$), pulmonary ventilation ($\dot{V}_E$) and respiratory exchange ratio (RER). Expired gas data were subsequently calculated and averaged over the final 20 s of each 5 min interval. Oxygen and carbon dioxide sensors and the gas turbine were calibrated prior to each test according to the manufacturer's guidelines. Heart rate (HR) was continually monitored (Polar Electro, Oy, Finland) and recorded in the final 10 s of each 5 min interval. The 15-point (6–20) Borg scale was used to determine cardiorespiratory (heart and lungs; RPE_C) and local (working muscles; RPE_L) ratings of perceived exertion (Borg, 1982). RPE_L and RPE_C were obtained at the same time as HR.

Statistical Analysis

Data were analyzed using SPSS version 25.0 (IBM Inc., Chicago, IL, United States). All measures are reported as mean ± SD. Separate two-way mixed-model ANOVAs examined the effects of time (×6; pre-exercise, 1, 15, 30-min, 24, and 48 h post-exercise) and group (×2; level vs. downhill walking) on TUG, STS, muscle torque, and power. Three-way ANOVA were used for postural sway metrics (group × time × vision). Separate two-way mixed-model ANOVAs were also used to examine the effects of time (×7; pre-exercise, 5, 10, 15, 20, 25, 30-min post-exercise) and group (×2; level vs. downhill walking) on cardiorespiratory and perceptual variables. For all measures, normality (Shapiro–Wilk test) and homogeneity of variance (Levene's test) and sphericity (Macuhley's test) were confirmed prior to undertaking parametric tests. Where significant differences were detected, *post hoc* analyses with Bonferroni-adjusted α for multiple comparisons were conducted to determine the location of any significant differences. Effect sizes are reported as partial eta-squared value (η_p^2) for ANOVA and as Cohen's d (*d*) for pairwise comparisons, with 0.2, 0.6, 1.2, and 2.0 indicating small, medium, large and very large effects, respectively (Hopkins et al., 2009). Pearson's product moment correlation coefficients (*r*) were computed to quantify the relationship between the absolute change score data in all variables. Statistical significance for all tests was accepted at $p < 0.05$.

Reliability

Within-session reliability was examined using ICC and coefficients of variation (CV) during baseline conditions between the second and third trials. No significant differences ($p > 0.05$) were detected between any measure of postural sway, TUG, isometric strength or concentric power. Moderate-to-high ICC and low-to-moderate CV were calculated for anteroposterior COP displacement (EO; ICC = 0.82, CV = 11.1%, EC; ICC = 0.92, CV = 10.9%), mediolateral COP displacement (EO; ICC = 0.95, CV = 8.1%, EC; ICC = 0.94, CV = 9.5%), mean COP velocity (EO; ICC = 0.99, CV = 3.1%, EC; ICC = 0.97, CV = 5.0%), TUG (ICC = 0.99, CV = 1.5%), isometric strength (ICC = 0.97, CV = 4.3) and concentric power (ICC = 0.99, CV = 5.8%). Given that participants completed only one STS test before exercise, ICC's and CV's are not reported for the five times STS or 60 s STS tests.

RESULTS

Postural Sway

Postural sway responses are illustrated in **Figure 1**. The three-way ANOVA revealed significant group × time interactions for all postural sway outcomes (**Table 2**). Follow up *post hoc* analysis indicated that the anteroposterior COP displacement ($p < 0.001$, $d = 2.45$) and mean COP velocity ($p < 0.001$, $d = 1.49$) with eyes open were significantly greater 1-min after level walking compared to pre-exercise, returning to pre-exercise levels within 15 min ($p > 0.05$). During the eyes closed condition the anteroposterior COP displacement ($p < 0.001$, $d = 2.12$) and mean COP velocity ($p = 0.002$, $d = 1.33$) were significantly greater 1-min following level walking compared to pre-exercise, returning to pre-exercise levels within 15 min ($p > 0.05$).

Following downhill walking, *post hoc* analysis indicated that with the eyes open the mediolateral COP displacement ($p < 0.001$, $d = 1.90$), anteroposterior COP displacement ($p < 0.001$, $d = 3.83$), and mean COP velocity ($p < 0.001$, $d = 1.61$) increased at 24 h post-exercise when compared to baseline and did not recover to baseline levels after 48-h recovery (all $p < 0.001$). For the eyes closed condition, the mediolateral COP displacement ($p = 0.031$, $d = 1.26$), anteroposterior COP displacement ($p < 0.001$, $d = 2.08$) increased at 24 h post-exercise when compared to baseline values, did not recover to baseline levels after 48 h recovery (all $p < 0.001$).

Physical Function

There were statistically significant interactions for 60 s STS ($F_{(5,102)} = 6.209$, $p < 0.001$, $\eta_p^2 = 0.233$), five times STS ($F_{(5,102)} = 5.992$, $p < 0.001$, $\eta_p^2 = 0.227$) and TUG ($F_{(5,102)} = 3.318$, $p = 0.008$, $\eta_p^2 = 0.140$) (**Figure 2**). Immediately following level walking there was a reduction in the number of STS in 60 s ($p = 0.017$, $d = 2.50$) and TUG increased ($p = 0.003$, $d = 1.56$), with the TUG remaining significantly slower 15 min post-exercise ($p = 0.019$, $d = 1.31$). Following downhill walking, there was a reduction in the number of STS in 60 s ($p = 0.016$, $d = 1.45$), whilst the time to reach 5 STS cycles ($p = 0.042$, $d = 1.45$) and TUG ($p = 0.050$, $d = 0.92$) both increased at 24 h post-exercise. The 60 s STS ($p = 0.004$, $d = 1.54$), five times STS ($p = 0.019$, $d = 1.50$) and TUG ($p = 0.004$, $d = 1.83$) remained significantly different to baseline values at 48 h post-exercise.

Muscle Function

The analysis revealed a statistically significant group × time interaction for isometric MVC ($F_{(5,102)} = 7.227$, $p < 0.001$, $\eta_p^2 = 0.262$). **Figure 3** follow up *post hoc* analysis revealed that compared to baseline, there was a reduction in isometric MVIC 1 min after level walking ($p < 0.001$, $d = 1.44$), returning to baseline after 15 min recovery ($p > 0.05$). Following downhill walking, there was an immediate reduction in MVIC, which remained significantly different to baseline throughout the recovery period ($p < 0.001$, $d = 1.50$–2.15). A significant time × group interaction was also revealed for concentric power ($F_{(5,102)} = 6.608$, $p < 0.001$, $\eta_p^2 = 0.245$). *Post hoc* analyses revealed that compared to baseline, there was a reduction in concentric power at 1 min ($p = 0.042$, $d = 0.73$) and 15 min ($p = 0.041$, $d = 0.70$) following level walking. Following downhill walking, the analysis revealed that compared to baseline, there was a reduction in isometric concentric power at 24 h ($p = 0.004$, $d = 1.02$) and 48 h ($p < 0.001$, $d = 1.32$) post-downhill walking. As part of our initial exploratory analyses we performed correlational analysis to determine the relationships among changes in muscle, physical and postural functions. There were no significant associations between changes in muscle and physical function with any postural sway outcomes ($p > 0.05$, $r = 0.11$–0.30).

Physiological Responses

Although the analyses revealed no statistically significant group × time interactions for any physiological outcomes ($p > 0.05$), main group effects were observed for all variables (**Table 3**). Follow up *post hoc* analyses revealed that with the

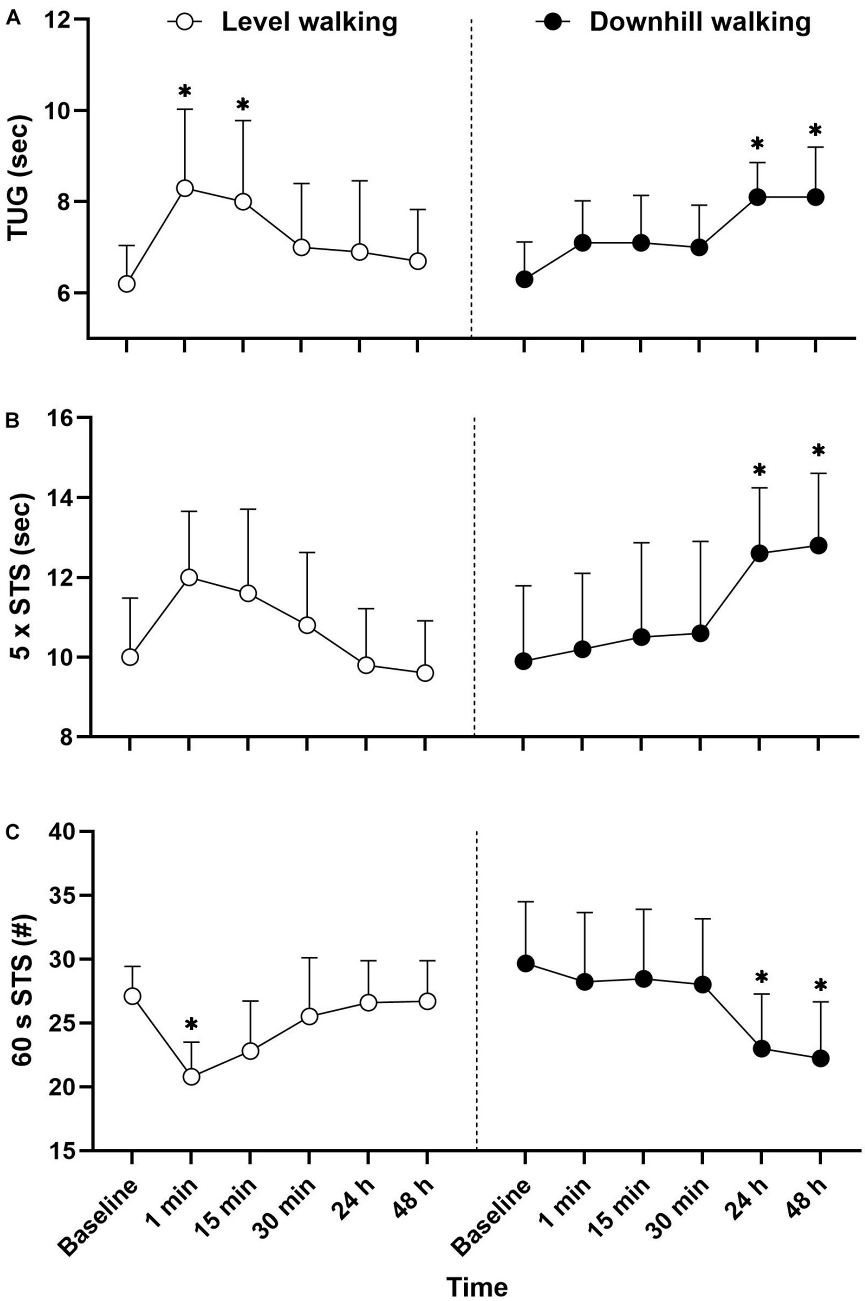

FIGURE 2 | Mean ± SD TUG **(A)**, 5 times STS **(B)**, and 60 s STS **(C)** responses to 30 min level and downhill walking. *Significantly different to baseline.

exception of $\dot{V}_E$, HR, RER, and RPE_C at minute 5, all responses were greater throughout the exercise trials in the level compared to downhill walking group (**Figure 4**). The analysis also revealed main effects of time for RPE_L ($F_{(5,102)} = 13.035$, $p < 0.001$ $\eta_p^2 = 0.291$) and RPE_C ($F_{(5,102)} = 4.202$, $p = 0.002$, $\eta_p^2 = 0.171$). Follow up *post hoc* analyses revealed that compared to 5 min, RPE_L was greater at 20 min ($p = 0.008$), 25 min ($p < 0.001$), and 30 min ($p < 0.001$) exercise. Similarly, RPE_C was greater at 20 min ($p = 0.050$), 25 min ($p = 0.022$), and 30 min ($p = 0.006$) compared to 5 min.

DISCUSSION

This experiment shows that the recovery profiles of postural, physical and muscular functions associated with eccentrically biased exercise differ from those observed following concentrically biased exercise. In accordance with our first hypothesis, the relative impact of short-term fatigue induced by concentrically biased exercise (i.e., metabolic fatigue during level walking) is limited, with a full recovery of postural, physical and muscle functions occurring within 30 min of exercise

TABLE 2 | Group × time × vision repeated measures ANOVA of postural sway responses to level and downhill walking.

	Anteroposterior COP displacement			Mediolateral COP displacement			Mean COP velocity		
	F	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2
Group	0.831	0.363	0.004	21.832	0.001	0.097	13.882	0.001	0.064
Time	21.718	0.001	0.349	12.969	0.001	0.242	13.663	0.001	0.252
Vision	21.709	0.001	0.097	6.551	0.011	0.031	10.044	0.002	0.047
Group × Time	29.517	0.001	0.421	11.224	0.001	0.217	16.866	0.001	0.293
Group × Vision	0.842	0.360	0.004	0.875	0.351	0.004	0.211	0.647	0.001
Time × Vision	0.938	0.457	0.023	0.155	0.978	0.004	0.225	0.951	0.006
Group × Time × Vision	0.491	0.783	0.012	0.959	0.444	0.023	0.159	0.977	0.004

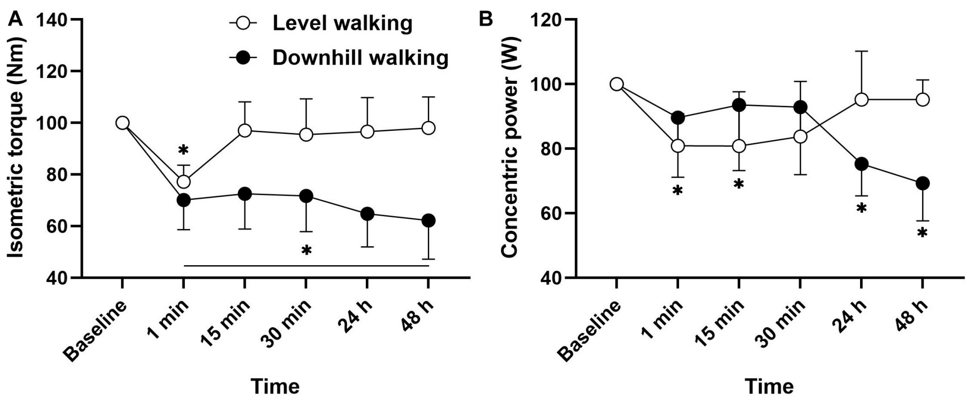

FIGURE 3 | Mean ± SD changes in isometric muscle force **(A)** and concentric power **(B)** from pre-exercise value (100%) before (baseline), during a short term recovery (1–30 min) and up to 48 h after 30 min of level and downhill walking.

cessation. In support of our second hypothesis, following eccentrically biased exercise (i.e., muscle damage following downhill walking), not only was the impairment of postural, physical and muscular functions delayed until 24 h post-exercise, these functions remained impaired for at least 48 h post-exercise.

TABLE 3 | Repeated measures ANOVA of physiological responses to level and downhill walking.

Analysis	Group × Time ANOVA		
Group × time	*F*	*p*	η_p^2
$\dot{V}O_2$	0.127	0.986	0.006
$\dot{V}_E$	0.336	0.890	0.016
HR	0.324	0.898	0.016
RER	0.467	0.800	0.022
RPE_L	0.678	0.641	0.032
RPE_C	0.649	0.663	0.031
Group			
$\dot{V}O_2$	44.364	<0.001	0.303
$\dot{V}_E$	46.768	<0.001	0.314
HR	7537.469	<0.001	0.250
RER	26.302	<0.001	0.205
RPE_L	75.619	<0.001	0.426
RPE_C	55.440	<0.001	0.352

The delayed impairment and recovery of postural, physical and muscular functions following low-intensity downhill walking suggest that eccentrically biased contractions could affect daily activities and increase the risk of falling for several days. Collectively, these findings identify distinct temporal profiles which have important practical applications for physical therapists, exercise professionals and geriatricians to provide guidance on behavior following exercise modes likely to differentially elevate fall risk.

Physiological and Perceptual Responses

It has previously been shown that $\dot{V}O_2$ is ∼25% lower during 15 min downhill (–10%) compared to level (0%) walking among older people (Navalta et al., 2004; Gault et al., 2013). In the present study, $\dot{V}O_2$ was approximately 34% lower in the downhill compared to the level walking group, accompanied by a lower HR (–32%), $\dot{V}_E$ (–15%), and RER (–6%). Additionally, both local and central RPE were consistently two to three points lower during downhill walking (i.e., "very light" to "light") compared to level walking (i.e., "somewhat hard"). Therefore, we can confirm that the level walking group experienced significantly greater demands on metabolic, cardiovascular and pulmonary systems and elicited a greater perceived exertion compared to the downhill walking group. The underlying physiological process rendering downhill walking less metabolically demanding than level walking involves differences in the energetics of the

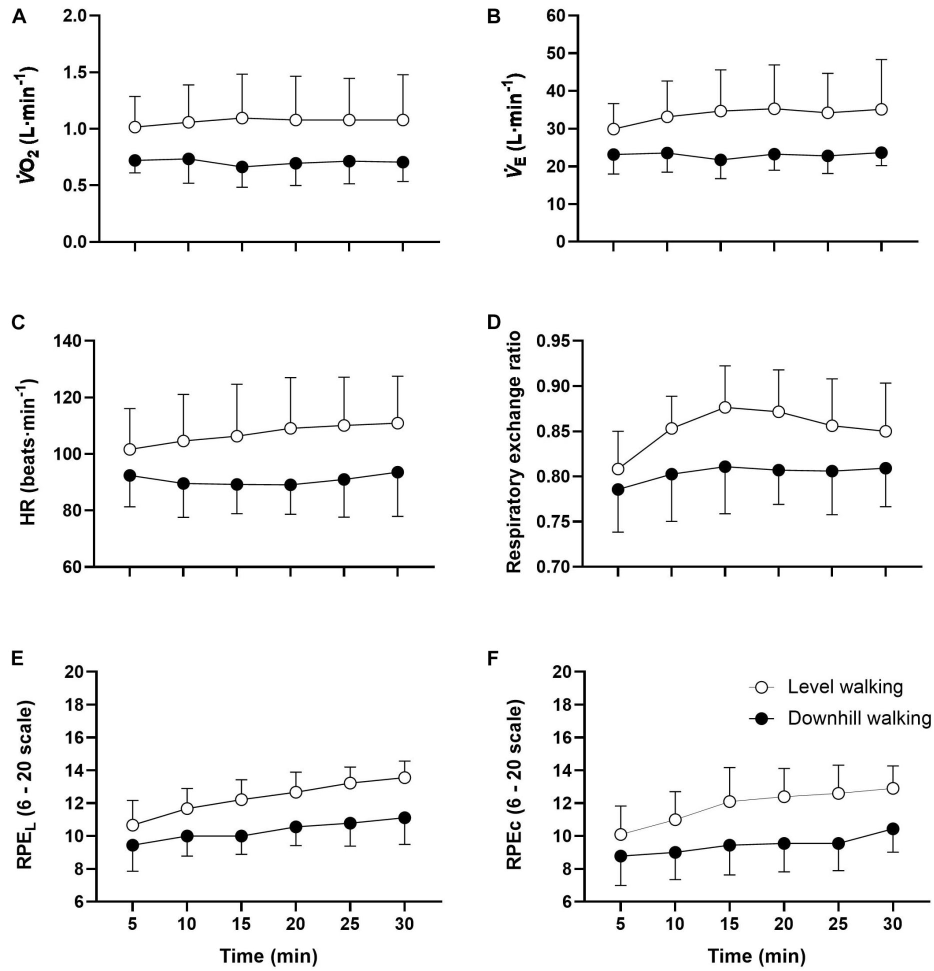

FIGURE 4 | Mean ± SD $\dot{V}O_2$ **(A)**, $\dot{V}E$ **(B)**, HR **(C)**, RER **(D)**, RPE_L **(E)**, and RPE_C **(F)** responses to 30 min level and downhill walking. All responses were greater during level than downhill walking ($p < 0.001$).

cross-bridge cycles and the elastically stored energy is released from the muscle-tendon complex (Nishikawa, 2016).

Fatigue and Recovery Profiles Following Eccentric Exercise

To our knowledge, this is the first study to attempt to identify differences in the effects of concentric- versus eccentrically biased exercise on postural, physical and muscular functions in older adults. Contrary to the level walking group (discussed later), the downhill walking group presented with symptoms of muscle damage. Specifically, maximal isometric muscle force decreased by 35% at 24 h after downhill walking and remained lower (−38%) than the baseline at 48 h post-exercise. Similarly, compared to baseline, concentric power decreased by 25 and 31% at 24 and 48 h, respectively. Although these changes are typical following downhill walking (> 40 min) in healthy young adults (Ahmadi et al., 2008; Maeo et al., 2015; Maeo et al., 2017; Nakayama et al., 2019), limited data exist describing changes in muscle force following downhill walking in older people. Gault et al. (2011) observed a 15% decline in maximal isometric voluntary contraction of the knee extensor muscles 48 h following a 30 min downhill (−10%) treadmill walk at a self-selected walking speed (4.6 km·hr^{-1}). These changes in isometric muscle torque were considerably less than the changes observed in the present study. These observations may suggest that muscle damage was present following the downhill walking protocol performed in the present study.

Changes in postural sway did not present until 24 h after downhill walking and remained altered at 48 h post-exercise; findings that broadly align with studies undertaken in young adults (Twist et al., 2008). Multiple mechanisms may account for the delayed impairment and recovery of postural control following eccentric exercise-induced muscle damage. First, an increase in postural sway following downhill walking may have resulted from reduced isometric muscle force generation capacity. Weaker muscles require the activation of larger motor units to achieve the same force. Crucially, large motor neurons have less fine control (Saxton et al., 1995), requiring a greater recruitment following eccentric exercise to compensate for the reduction in muscle force (Davies and White, 1981). Consequently, eccentric exercise can lead to an increase in physiological tremor for 24 h after eccentric exercise (Saxton et al., 1995), which may explain the delayed increase in postural sway at 24 h in the present study (Kouzaki and Masani, 2012). This problem might also be exacerbated by the fact that eccentrically biased exercise preferentially recruits and damages fast twitch motor units (Brockett et al., 2002), which could affect the ability to react quickly to large amounts of body sway. Secondly, the temporal changes in postural sway observed in the present study are consistent with recovery profiles of neuromuscular impairments (i.e., force and joint position sense) following eccentric exercise reported in previous studies. For example, several authors have reported that muscle spindles and golgi tendinous receptors become desensitized after 24 h following eccentric exercise-induced muscle damage (Brockett et al., 1997; Paschalis et al., 2007; Saxton et al., 1995), with impairments persisting for several days. These findings suggest that metabolite accumulation associated with concentrically biased exercise cannot be attributed to the delayed and long lasting impairments in postural sway reported here. Whilst the deficits in muscle and joint mechanoreceptors following eccentric exercise-induced muscle damage remains unclear (Torres et al., 2010), it is clear that muscle spindles and golgi tendinous receptors contribute to joint position and movement (Brockett et al., 1997). Finally, it is possible the high ground reaction impact forces during downhill ambulation (Gottschall and Kram, 2005) provoke substantial damage to the plantar cutaneous receptors. It is well established that there is a functional relationship between plantar cutaneous afferents and maintenance of upright stance (Meyer et al., 2004). Regardless of the underlying mechanisms, given that increased postural sway has been shown to be predictive of falls (Piirtola and Era, 2006; Johansson et al., 2017), these findings suggest that exercise-induced muscle damage might impair balance control and lead to a long term "window" of increased fall risk.

Downhill walking involves a substantial eccentric component that causes considerable muscle damage (Nottle and Nosaka, 2005) and a subsequent reduction in muscle strength (Ahmadi et al., 2008; Girard et al., 2018) that typically presents ∼6 h after exercise and peaks at one to three days thereafter. On this basis, we hypothesized that downhill walking would elicit a marked reduction in the performance of the TUG and STS, given their relationship with muscle strength (Bohannon et al., 2010; Coelho-Junior et al., 2018). In addition to the concentric contractions required to stand up, the TUG and STS tasks also involve eccentric contractions of the knee extensors to control lowering of the body to the seated position. Importantly, the delayed impairments in TUG and STS performance followed the same profile as the changes in concentric power. This is not surprising given that Hortobagyi et al. (2003) observed a peak knee extension velocity of $138^\circ\ s^{-1}$ in older adults performing a chair rise, emphasizing that fast velocity concentric actions are functionally relevant to physical performance tasks. The delayed impairment and recovery of power reported here is most likely explained by damage induced excitation-contraction uncoupling as a result of reduced release of calcium (Power et al., 2010) and damage to contractile fibers resulting in a reduced shortening velocity. These structural disruptions to excitation-contraction coupling are likely responsible for the delayed impairment and recovery of functional performance following eccentric exercise. The reduced ability to perform the STS and TUG for several days after eccentric exercise may lead to functional impairments during daily activities. As already discussed, there is evidence that older people perform many daily activities close to their maximum capability (Bieryla et al., 2009; Hortobagyi et al., 2003). From a practical perspective, many precarious, high risk tasks (e.g., descending stairs or walking downhill), rely on eccentric muscle contractions (LaStayo et al., 2014).Therefore, exercise professionals, therapists and practitioners should be aware of the negative effects of eccentric exercise-induced muscle damage Further studies are required to develop interventions to minimize exercise-induced muscle damage, especially in older people.

Fatigue and Recovery Profiles Following Concentric Exercise

Our findings are consistent with previous studies that have reported a transient increase in postural sway (anteroposterior COP displacement and mean COP velocity) immediately following level treadmill walking (Hill et al., 2015; Donath et al., 2013, 2015; Foulis et al., 2017; Walsh et al., 2018). The worsening of postural control immediately following treadmill walking, followed by the rapid recovery of performance has been linked to the accumulation of metabolic by-products (i.e., hydrogen ions, inorganic phosphate or adenosine diphosphate; Paillard, 2012). Metabolic-fatigue can provoke a number of disturbances at the peripheral level [e.g., decreased muscular excitability, increased force fluctuation and deceleration of the afferent conduction velocity (Enoka and Duchateau, 2008; Hunter et al., 2004)], which can deteriorate the accuracy of the sensory proprioceptive information and/or decreases muscular system efficiency (Nardone et al., 1997).

The present findings complement previous work by demonstrating a reduction in isometric force and concentric power following 30 min of level waking (Foulis et al., 2017). Here, we found deficits in isometric torque (–23%) and concentric power (–20%) immediately following level walking, returning to baseline after 15 min and 30 min recovery, respectively. Our observed power and strength deficits were greater than those reported by Foulis et al. (2017) (isometric strength; –8% and concentric power [$270^\circ\cdot s^{-1}$]; –13%). Whilst we found a similar reduction in muscle strength and power, contrary to the findings of Foulis et al. (2017), we additionally observed a reduction in the number of STS cycles in 60 s and slower TUG performance following level walking, returning to baseline after 15 and 30 min, respectively. During baseline, participants in the present study completed the TUG in 6.2 ± 0.8 s, times at the faster end of the normative spectrum (7.1–9.0 s) for community-dwelling older adults aged 60–69 years (Bohannon, 2006). Therefore, although unlikely to be of clinical relevance to increase the risk of a fall, the 2.1 s increase in the TUG test indicates a that fatigue negatively contributed to one or more of the tasks of standing up, sitting down, walking or turning, indicating a general decline in mobility. Considering that older adults may use up to 80% of their maximal leg strength to rise of a chair (Hortobagyi et al., 2003), it is not surprising that we observed a reduction in performance of the 60 s STS test following level walking. However, we observed no change in the performance of the five times STS test following fatigue, which aligns with previous research (Foulis et al., 2017). Taken together, the relatively short lasting effects (<30 min) of level walking on muscular, postural and physical functions support the notion that there is an acute post-exercise period in which older people are at an increased risk of falls.

Practical Implications

There has been considerable attention directed toward the potential applications of eccentric exercise in the last decade, mainly due to the substantial improvements in muscle mass and strength than can be achieved (Hody et al., 2019). Crucially, because of the high force- low cost attributes, eccentric exercise may be ideally suited to exercise-intolerant individuals, such as older people (LaStayo et al., 2003). Indeed, it has been demonstrated that eccentric exercise training elicits superior adaptations in muscle strength/power, muscle mass and physical performance (i.e., mobility) when compared with concentric training in this population (LaStayo et al., 2003; Mueller et al., 2009; Gault and Willems, 2013; Kay et al., 2020). However, given the high muscle forces that can be achieved, it is not surprising that this exercise can cause muscle damage. Our findings show that muscle damage resulting from eccentric exercise can lead to muscle weakness, postural instability and impaired physical function which can persist for several days, endangering older adult's safety during daily activities and potentially increase the risk of falls. Nevertheless, there is now emerging evidence that muscle damage is not an inevitable consequence of eccentric contractions. For example, low intensity eccentric exercise can elicit protective effects on muscle damage markers induced by high intensity eccentric exercise (Maeo et al., 2017).

Limitations and Future Directions

We acknowledge a number of study limitations. First, whilst we chose our outcomes (i.e., mobility, balance and muscle weakness) for their associations with fall risk, muscle fatigue and/or damage may also affect fall risk by factors that were not ascertained in this study, such as gait disturbances, impaired cognitive function, and poorer recovery from an unexpected trip or slip. Secondly, we failed to observe a full recovery of postural, muscular and physical functions 48 h after eccentric exercise-induced muscle damage. Therefore, the full timescale of the development of, and recovery from, muscle damage on fall risk remains unclear. Third, our sample was relatively healthy and homogenous, which may restrict the generalizability of the study, although the samples homogeneity may have limited the influence of potential confounding factors. Frail or less active older people would likely be more susceptible to eccentric exercise-induced muscle damage, leading to a greater increase in fall risk in these groups. Fourth, we did not objectively quantify muscle soreness [delayed onset of muscle soreness (DOMS)] or knee pain. However, we asked all participants if they experienced soreness in any muscles of the lower body; eight out of nine participants in the downhill walking group reported modest soreness in the plantar flexors and quadriceps. Only 1 of out 10 participants reported muscle soreness following level walking. Finally, we did not measure eccentric muscle power. Prior pilot testing revealed that older participants (not included in the study) experienced significant difficulty with learning the technique of attempting to "slow down" the dynamometer arm as it moved toward them. Although we acknowledge familiarization may have allowed for adequate learning, we were reluctant to familiarize participants to eccentric exercise due to the risk of conferring protective adaptations against potential further damage (McHugh, 2003). In light of this final point, future research should aim to develop interventions (i.e., non-damaging pre-conditioning exercises) that can minimize the effects of eccentric exercise-induced muscle damage on fall risk factors, especially in older people. There is a reasonable theoretical basis for expectation that performing eccentric pre-conditioning exercise will reduce the eccentric induced consequences (i.e., the repeat bout effect) on balance performance and risk of fall related accidents.

CONCLUSION

This is the first investigation to examine the short-term and long-lasting effects of level and downhill walking on fall risk factors among older people. We have demonstrated that exercise-induced muscle damage elicits impairments in postural, muscular and physical functions. Notably, these impairments did not present until 24 h post-exercise, and remained for at least 48 h post-exercise. The delayed impairment and incomplete recovery of these fall risk factors following eccentrically biased exercise suggest that this type of exercise may increase fall risk for several days. Collectively, these findings have important practical implications for exercise prescription.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Coventry University Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MH conceived and designed research, performed the analyses, and wrote the manuscript. MH, E-AH, and AM conducted the experiments. MH, MP, AK, and SL revised the manuscript. All authors read and approved the final manuscript.

FUNDING

MH received grant # 216948/Z/19/Z from the Wellcome Trust. The URL of the funder website: https://wellcome.ac.uk/. This work was funded by the Wellcome Trust. The opinions expressed herein are those of the authors and not of the Wellcome Trust (216948/Z/19/Z). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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