Considerations for Designing and Managing Resistance Training Intervention Studies

by

Rasha El-Kotob

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EXAMINING COMMITTEE MEMBERSHIP

The following served on the Examining Committee for this thesis. The decision of the Examining Committee is by majority vote.

External Examiner	Wayne Hing, PhD Professor and Head of Physiotherapy Program, Physiotherapy, Bond University
Supervisor	Lora Giangregorio, PhD Professor and Schlegel Research Chair in Mobility and Aging, Kinesiology and Health Sciences, University of Waterloo
Internal Member	Marina Mourtzakis, PhD Associate Professor, Kinesiology and Health Sciences, University of Waterloo
Internal-external Member	Mark Oremus, PhD Associate Professor, Public Health Sciences, University of Waterloo
Other Member(s)	Dr. Catharine (Cathy) Craven, MD Professor, Physical Medicine & Rehabilitation, University of Toronto

AUTHOR'S DECLARATION

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

Background: Osteoporosis is a bone disease characterized by low bone mineral density (BMD) which is strongly associated with an increase in fracture risk. People with a spinal cord injury (SCI) experience rapid decline in BMD during the acute phase of injury, but the prospective bone changes are yet to be determined in the chronic phase. Resistance training (RT) is a common non-pharmaceutical intervention for treating osteoporosis. However, we are unsure if the benefits of RT outweigh the harms because adverse events (AEs) are not consistently monitored or reported in RT trials involving the healthy and clinical population.

Objectives: The purpose of this thesis was to examine considerations for designing and managing RT intervention studies involving the general adult population as well as people with chronic health conditions (e.g., SCI, osteoporosis). The specific objectives were: 1) to determine if there are any prospective bone changes in people with a chronic SCI which can be used to assess the timing of exercise interventions; 2) to determine the benefits and harms of RT on health outcomes in adults aged 18 years or older, compared to not participating in RT; 3a) to explore the experiences and perspectives of individuals with chronic health conditions who had an AE as a result of RT; 3b) to understand researchers' current practices and perspectives on AE reporting in RT, and identify barriers and facilitators of AE reporting; and 3c) to adapt AE reporting guidelines to exercise which can be used to increase the quality of published research with respect to safety of RT interventions. Overall, the objective of this thesis was to inform RT interventions with respect to timing, benefits and the proper reporting of harms.

Methods: To address the above objectives, this thesis consisted of three separate studies. Study 1 was a secondary data analysis of a two-year prospective, observational study that assessed bone variables at the tibia sites among a diverse population of individuals with chronic SCI (n=70). Peripheral quantitative computed tomography scans were taken at the 4% (distal tibia) and 38% (diaphyseal tibia)

tibia site by measuring from the distal to proximal tibia starting at the inferior border of the medial malleolus. Study 2 was a review of systematic reviews exploring the effect of RT on health outcomes among community dwelling healthy adults (total of 11 systematic reviews, representing 364 primary studies and 382,627 unique participants). Study 3 was a qualitative study involving a multimethod approach. Interviews were conducted with people who have chronic health conditions and had an AE as a result of RT (n=12), and researchers who published RT studies (n=14). Interview data were analyzed using the thematic framework method. AE-reporting recommendations were generated based on interview data and were turned into an electronic survey to perform a modified Delphi consensus process involving 19 international researchers who published RT studies.

Results: Study 1 demonstrated no changes in trabecular bone (trabecular volumetric BMD at the 4% tibia site), but reported a decline in cortical bone (cortical volumetric BMD, cortical thickness and cross-sectional area at the 38% tibia site) in people with a chronic SCI. Study 2 showed that RT was associated with a reduction in all-cause mortality and cardiovascular disease incidence, and an improvement in physical functioning. However, AEs were not being consistently monitored or reported in RT studies. For study 3, we learned that despite participant awareness of the value and benefits of RT, there is concern about experiencing exercise-related AEs. Furthermore, the perceived risks of RT influenced the participants' decision to engage or return to RT. Within the exercise community, there is suboptimal implementation of existing AE reporting standards, or the perception that the available guidelines do not apply to exercise trials. The barriers identified were that researchers lack guidance, resources, or motivation for rigorous AE reporting. To facilitate AE reporting, researchers educate and value participants, use trained personnel, and implement standardized guidelines. An exercise-specific AE-reporting toolkit (i.e., checklist, template form, and decision tree) was developed based on the consensus results (3 rounds; minimum 74% agreement on each recommendation).

Conclusion: Based on the results of study 1, people with a chronic SCI could continue to benefit from exercise interventions to prevent loss in bone mass. The findings of study 2 demonstrated that although RT has health benefits, there needs to be consistency in AE reporting across studies to determine the harms of RT. For study 3, the purpose of the exercise-specific AE-reporting toolkit along with dissemination and implementation strategies is to improve AE reporting in RT studies. Accurate AE reporting will allow people with common health conditions, researchers, and health care providers to make evidence-based decisions as to whether the benefits of RT truly outweigh the harms.

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Dedication

I would like to dedicate this thesis to my son, Zeyad, and my soon-to-be-born daughter. As you grow up, I hope you will make sure to do things that will positively impact the world, even if in a very small way. I will try my best to serve as a good role model. Thank you for adding purpose to my life.

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List of Abbreviations

AE	Adverse Event
AFF	Atypical femur fractures
AIS	American Spinal Injury Association Impairment Scale
ALM	Appendicular lean mass
ALMI	Appendicular lean mass index
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
ASA24	Automated self-administered 24-hour
BCW	Behavior change wheel
BMD	Bone mineral density
BRRIE	Bone Response to Resistance and Impact Exercise
BTM	Bone turnover markers
CAROC	Canadian Association of Radiologists and Osteoporosis
CCA	Corrected covered area
CCCARE	Centre for Community, Clinical, and Applied Research Excellence
CI	Confidence interval
COI	Conflict of interest
CONSORT	Consolidated Standards of Reporting Trials
CSA	Cross-sectional area
CSEP	Canadian Society for Exercise Physiology
CTX	C-terminal cross-linked of type I collagen
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DXA	Dual X-ray absorptiometry
DSMB	Data safety monitoring board
ELISA	Enzyme-Linked Immunosorbent Assay
ES	Effect size
FBFM	Fat-and bone-free lean mass
FRAX	Fracture Risk Assessment Tool
GCP	Good Clinical Practice
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard ratio
ICC	Intraclass correlation

KT	Knowledge translation
KTA	Knowledge-to-action
LSC	Least significant change
MAP	Mean arterial pressure
MD	Mean difference
NIA	National Institute on Aging
P1NP	N-terminal procollagen of type I collagen
PI	Principal investigator
PMI	Polar moment of inertia
pQCT	Peripheral quantitative computed tomography
PRISMA	Preferred Reporting Items for Systematic Review and Meta-analyses
ProFANE	Prevention of Fall Network Europe
PROSPERO	International Prospective Register of Systematic Reviews
PTH	Parathyroid hormone
RANKL	Receptor activator of nuclear factor-$\kappa\beta$ ligand
RCT	Randomized controlled trial
REDCap	Research Electronic Data Capture
RPE	Rate of perceived exertion
RM	Repetition maximum
RT	Resistance training
SBP	Systolic blood pressure
SCI	Spinal cord injury
SD	Standard deviation
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trial
TrabvBMD	Trabecular volumetric bone mineral density
vBMD	Volumetric bone mineral density
WHO	World Health Organization
Wnt	Wingless-type

Chapter 1: General Introduction

1.1 Osteoporosis

Individuals with osteoporosis, a skeletal disorder, are at an increased risk of fracture due to compromised bone strength (1). Osteoporotic fractures most commonly occur in women over the age of 50 (> 60%); at least 1 in 3 women will experience a bone fracture due to osteoporosis in their lifetime (2). Bone strength depends on both bone mineral density (BMD) as well as bone quality (e.g., architecture and mineralization) (1). The World Health Organization (WHO) defines osteoporosis as a BMD of 2.5 standard deviations below the mean value for premenopausal women (T-score < -2.5) (1). A strong risk factor for fracture is low BMD, especially at the femoral neck; the risk of fracture increases by a factor of two to three for every one standard deviation decline in BMD (3,4). In Canada, there are two tools that can be used to estimate the 10-year risk of a major osteoporotic fracture: The Canadian Association of Radiologists and Osteoporosis (CAROC) tool and the Fracture Risk Assessment tool (FRAX) (5,6). Both tools consider BMD or T-score for the femoral neck along with clinical risk factors such as age, sex and previous fractures (5,6).

1.1.1 Bone imaging modalities

Dual energy X-ray absorptiometry (DXA) is widely used to measure BMD and is considered the gold standard technique for diagnosing osteoporosis (7–9). To obtain DXA scans, the participant lies on the scanner bed and two X-ray beams with different energies project through the part of the body that is being assessed (Figure 1.1) (10–12). Based on the attenuation of the beam, the mass of bone mineral can be measured (12). The total projected area of the bone (aBMD) is calculated as the ratio of bone mineral content per unit projected area (g/cm^2) (12).

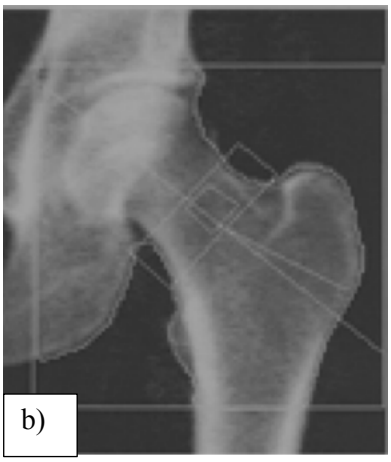

Figure 1.1 a) DXA scanner (Image retrieved from: http://www.hologic.ca/products/imaging/skeletal-health/horizon-dxa-system); b) sample DXA image of femoral neck (12)

DXA is a non-invasive, reliable and accurate measure that is quick and easy to apply, and involves minimal effort from the participants (9,13). The radiation exposure from a whole body DXA scan is low (i.e., 0.04 to 0.86 mrem which is equivalent to between 1 and 10% of a chest radiograph; the range depends on the instrument and participant size) and thus is a safe technique (7,9,12). There are however a few limitations that should be considered when using DXA. Depending on the manufacturer and model of the DXA, the maximum size of the scanning table is restricted to about 193-197 cm in length, 58-65 cm in width, and 114-159 kg for weight (14). Therefore, although DXA can be used for all ages, the scanning bed cannot accommodate individuals who are too tall or wide (9,15). Another limitation is that changes in an individual's weight can result in considerable anomalies when

measuring changes in BMD (14). Furthermore, calibration differences between DXA devices may lead to inaccurate comparisons across studies (15). A final limitation is the lack of portability, thereby the device may not always be practical in a clinical setting (15).

Another bone imaging modality is peripheral quantitative computed tomography (pQCT). PQCT is designed to assess peripheral skeleton sites (e.g., radius, tibia, femur) by having the participant place their leg or forearm through the scanner (Figure 1.2) (16,17). Common measures extracted from pQCT scans include volumetric BMD (g/cm^3), as opposed to areal BMD (g/cm^2) obtained by DXA, as well as several bone geometrical parameters (e.g., cortical thickness, polar moment of inertia) (9,12,17).

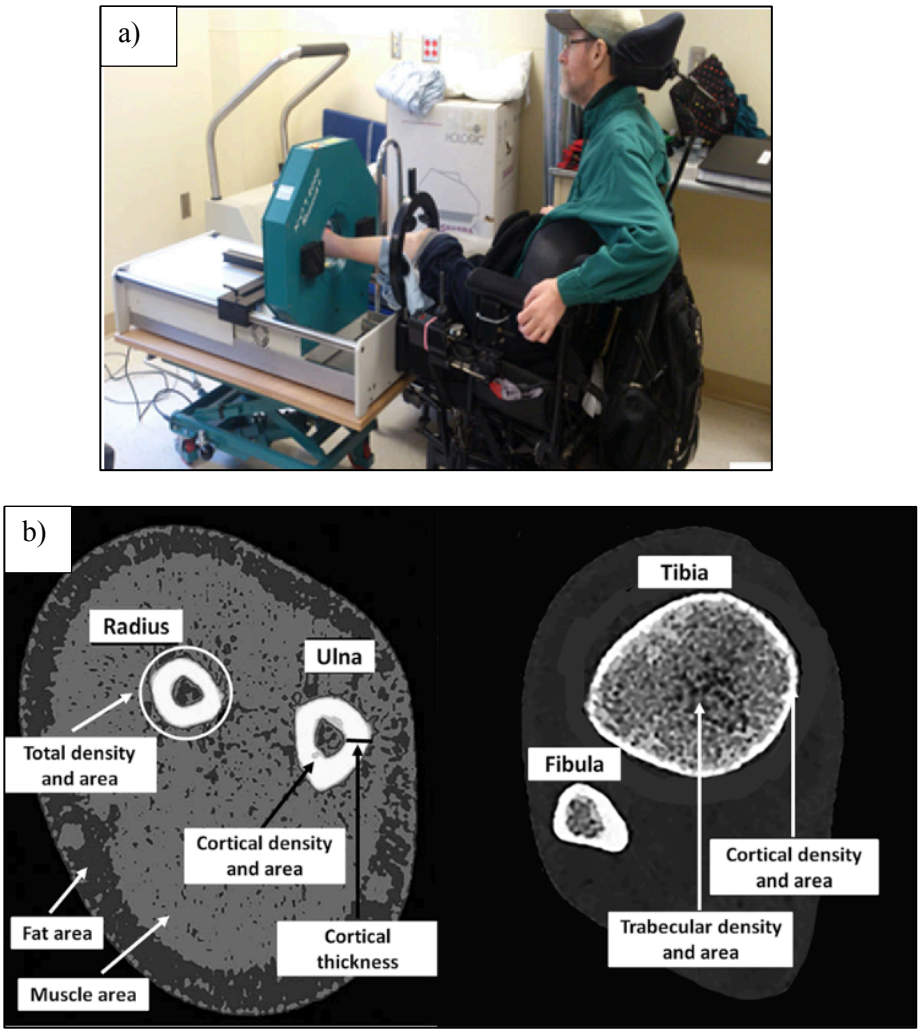

Figure 1.2 a) pQCT scanner (16)**; b) sample pQCT image of radius and tibia** (17)

Unlike DXA, pQCT is able to distinguish between cortical and trabecular bone and is the only available modality that can determine the effect of mechanical loading on the peripheral skeleton (e.g., the effect of exercise) (12,17). Given that pQCT provides a refined characterization of bone, it allows a more detailed understanding of skeletal deficits associated with fracture risk (17). Furthermore, the distinction between cortical and trabecular bone can provide earlier detection of bone mass changes due to disease or therapy (18). Despite the advantages of pQCT there are some limitations that should be considered. For instance, pQCT is not a widely applicable tool since it is expensive, uses a very specialized software, and requires an extensive amount of time to conduct the analysis (19). Another limitation is that pQCT is sensitive to movement and thus requires the participant to be still which is challenging when assessing young children or people who experience muscle spasms (e.g., people with a spinal cord injury) (16,17). Also, the physical dimensions of the device may be restrictive for some participants (e.g., limited gantry size) (12,16).

Overall, DXA should be used when diagnosing osteoporosis or assessing fracture risk while pQCT measures can be used to monitor osteoporosis treatment (e.g., pharmacological or exercise treatment).

1.1.2 Bone remodeling and mechanotransduction

According to Wolff's law and Frost's mechanostat theory, bone remodeling is influenced by mechanical forces applied to bone such as muscle forces (20). Bone remodeling occurs continuously via the coordinated action of osteoclasts (bone resorption cells) and osteoblasts (bone formation cells) and the balance between the two determines net gain or loss of bone mass (21). The number and activity of osteoclasts and osteoblasts are influenced by multiple factors including mechanical stimuli (22,23). Bone cells, called osteocytes, that are mechanically activated produce signaling molecules which in turn modulate recruitment and differentiation of osteoblasts and osteoclasts (23,24). Bone adjusts its structure and becomes stronger to adapt to the mechanical loads that are exerted on it (25).

Mechanotransduction is a process in which a bone's adaptive response is regulated by the ability to translate mechanical energy into a cascade of structural and biochemical changes within the bone cells (26). Bone cells detect high stresses (e.g., mechanical loading) and act as mechanotransducers to send local signals and cause an anabolic response (25). Osteocytes, embedded in the bone matrix and comprising 90% of bone cells, are responsible for sensing the mechanical forces exerted on bones (21). Within one minute of mechanical loading, there is an increase in intracellular calcium ions concentrations and the release of adenosine triphosphate from the cell (26). A few minutes later, prostaglandins and nitric oxide are released from bone cells (27,28). Nitric oxide decreases recruitment of osteoclasts by decreasing expression of receptor activator of nuclear factor-$\kappa\beta$ ligand (RANKL) which is an osteoclast differentiation factor, and increases expression of osteoprotegerin which is an inhibitor of osteoclast differentiation (29). Prostaglandins, on the other hand, increase recruitment of osteoblasts via the prostaglandin receptors E_2 or E_4 and in turn enhance bone formation (25,30,31). Further downstream, the wingless-type (Wnt) signaling pathway is activated, through the low-density lipoprotein receptor-related protein 5 (LRP5), which is considered a necessary step to couple mechanotransduction with synthesis of matrix proteins (25). Sclerostin is a protein that is a potent inhibitor of bone formation via the Wnt signaling pathway (26). In the absence of mechanical loading, osteocytes produce and secrete sclerostin that inhibits Wnt signaling by antagonizing the LRP5 receptor (26). In the presence of mechanical stimulation, sclerostin levels drop and the LRP5 receptor becomes available for Wnt binding (26). Ultimately, we need to understand and target bone signaling pathways to develop osteoporosis pharmacological therapies that can effectively strengthen bones (25).

1.1.3 Pharmacological treatment: Antiresorptive medications

Pharmacological approaches are considered the first line of therapy for osteoporosis and most commonly include antiresorptive medications such as bisphosphonates and denosumab (32). In general, antiresorptive medications have been shown to be an effective treatment for reducing the risk of hip, non-vertebral and vertebral fractures (33–39).

Bisphosphonates and denosumab inhibit bone resorption via different cellular pathways. Bisphosphonates are characterized by a Phosphonate-Carbon-Phosphonate (P-C-P) bond structure which is essential for binding to bone mineral surfaces (32,40) (Figure 1.3). The R^1 side chain is usually a hydroxyl group which enhances the binding ability of bisphosphonates to bone mineral surfaces (32,40). The molecular structure of the of the R^2 side chains determines the potency of the drug and corresponds to the different available types of bisphosphonates (e.g., a R^2 side chain of $-CH_3$ is Etidronate) (32,40). Bisphosphonates are selectively taken up and internalized by osteoclasts and they inhibit bone resorption by causing a disruption in osteoclast function (e.g., osteoclast recruitment and differentiation) or by promoting osteoclast apoptosis (32,40). Denosumab, on the other hand, is a human monoclonal antibody that inhibits bone resorption by binding to RANKL and preventing it from activating its receptor RANK located on the surface of osteoclasts (41). As a result, the differentiation of osteoclasts is inhibited by influencing formation, function and survival of osteoclasts (41).

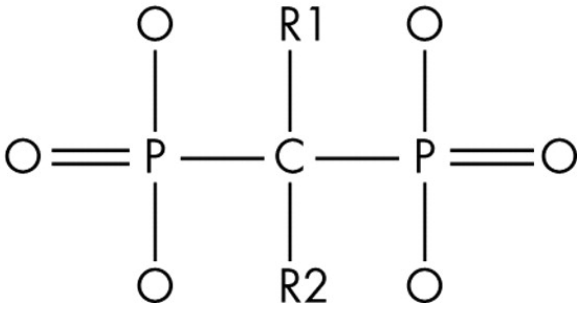

Figure 1.3 Chemical structure of a bisphosphonate (40)

BMD is frequently used as a surrogate measure to determine whether bone tissue responds to a therapeutic intervention such as pharmaceutical drugs (1,42). Bisphosphonates have been shown to increase lumbar spine, total hip, femoral neck and total body BMD (37,39,43). Increase in BMD tends to be greater in women who have low BMD at baseline (43). In addition to changes in BMD, changes in bone turnover markers (BTMs) are used to determine whether individuals with osteoporosis respond to antiresorptive medications (44). BTMs are biomarkers of bone formation (e.g., N-terminal

procollagen of type I collagen (P1NP)] and bone resorption (e.g., C-terminal cross-linked of type I collagen (CTX)] (45). Antiresorptive medications, specifically bisphosphonates, have been shown to decrease BTM by decreasing bone resorption markers earlier and to a greater extent than bone formation markers (46–48). There is a greater decrease in BTMs if baseline levels were higher and if there was at least 80% drug compliance (44). Individuals are considered to be responsive to pharmaceutical treatment if there is a decrease in BTMs that is beyond the least significant change value or if it is within a reference interval (e.g., the mean value in premenopausal women) (44). A recent meta-analysis showed that a reduction in BTM is strongly associated with a reduction in vertebral fracture risk in men and women taking antiresorptive medications (49).

1.2 Bone turnover response to loading and disuse

Bone turnover (bone remodeling) decreases with loading and increases with disuse or lack of loading (26). An example of loading is exercise, while disuse could occur as result of a chronic injury (e.g., spinal cord injury). The effect of exercise shifts from building bone during skeletal growth to preventing bone loss in the adult skeleton (26). Exercise preserves bone mass by decreasing bone resorption, whereas disuse leads to loss of bone mass by increasing bone resorption to an extent that it overwhelms bone formation (26,50).

The ideal range of loading is within a specific "physiological window" in which bone turnover is minimal (51). Overuse of bone can result in damage and thus bone turnover increases as a reparative process (26). However, if the damage exceeds the repairing process it will result in a fracture (26). Therefore, the effect of loading on bone turnover is U-shaped with "disuse" and "overload" at each peak (Figure 1.4) (26). The mechanisms controlling growth and reshaping of bone differ from bone remodeling; periosteal bone formation continues to increase as load increases (Figure 1.4) (26). In general, to design exercise interventions that can effectively strengthen bones without overloading, the extent of mechanical loading should be within the "physiological window".

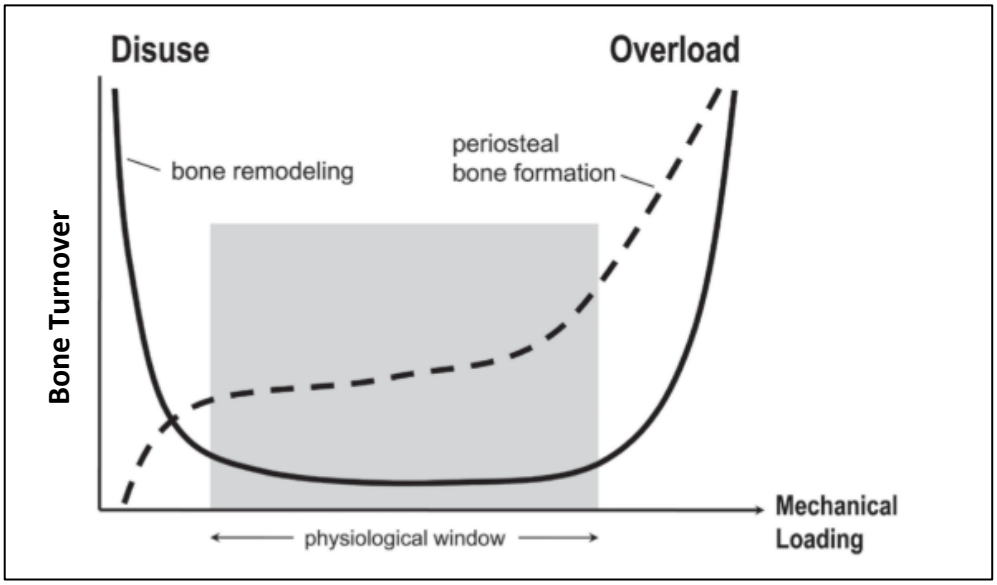

Figure 1.4 Bone turnover follows a U-shaped pattern as it increases in states of disuse or overuse (26)

1.2.1 Effects of loading: Exercise

Following exercise guidelines (specifically engaging in high impact aerobic exercises, and physical activities that challenge balance) is associated with an improvement in bone health and a lower risk of falls and fall-related injuries (52–54). There are evidence-based exercise guidelines for the generally healthy adult and older adult population as well as in people with osteoporosis. In October of 2020, *The Canadian 24-Hour Movement Guidelines for Adults aged 18-64 years and 65 years and older: An Integration of Physical Activity, Sedentary Behaviour, and Sleep* were released (52). With respect to physical activity, adults 18 years of age and older should engage in moderate to vigorous aerobic physical activities at least 150 minutes per week, muscle strengthening activities using major muscle groups at least twice a week, and several hours of light physical activities including standing (52). For adults 65 years of age and older, they should also engage in physical activities that challenge balance (52). However, the guidelines were developed based on data from a generally healthy population and thus may not be appropriate for people with disabilities or chronic health conditions (52). *Osteoporosis Canada* recommends that all people with osteoporosis engage in exercise, including those who have had a spine or hip fracture (55–57). The recommendations are comprised of four types

of exercise: strength or resistance training (RT) at least twice a week, posture awareness every day, balance exercises every day, and moderate to vigorous aerobic physical activity at least 150 minutes per week (55–57). The recommendations warn that individuals who have a spine fracture should consult a health care provider before using weights and should choose moderate aerobic physical activity as opposed to vigorous (55–57).

RT is a potential treatment for osteoporosis as it has been shown to stimulate bone formation (58–67). RT involves muscle contractions against a resistance in order to "overload" the muscular system and result in a training effect (68). Resistance can be introduced using an external source (e.g., resistance bands, free weights) or by simply using one's own body weight while performing gravity challenging positions (e.g., push-ups, squats) (68). An RT program should: 1. involve an initial assessment of the individual's physical abilities, 2. be tailored to the participants involved, and 3. progress as physical ability of the participants improves (68). Moderate-high intensity RT and impact exercise programs have been shown to increase BMD (58–67). It is also not surprising that with greater exercise compliance there tends to be a greater effect on bone mass (69). Furthermore, although it is not often assessed, changes in BTM may also have the potential to determine whether individuals with osteoporosis are considered to be responsive to exercise interventions. Strategies for maximizing the osteogenic (bone forming) effects of exercise should be incorporated when designing interventions aimed to improve bone health.

Osteogenic exercise involves dynamic loading, high impact exercise, high loading frequency, and sufficient periods of rest. Bone tissue responds to dynamic rather than static loading because only dynamic loading can create fluid shear stresses that can initiate bone mechanotransduction (70,71). The effect of impact exercise on bone mass is commonly observed in tennis players; the forearm that holds the tennis racket is exposed to high impact forces leading to an increase in bone mass of 5-10% in comparison to the contra-lateral forearm (72). High impact exercise produce large rates of deformation in the bone matrix (70). Deformations that occur in the bone matrix due to physical forces are expressed as strains (21). When examined in animal studies, increase in bone formation was only observed if the

strain was above a certain threshold (73). The peak strain required to initiate osteogenesis decreases as the loading frequency increases (74). For instance, an animal study showed that the peak bone strain required to initiate osteogenesis decreased from 1820 microstrain at 1Hz to 650 microstrain at 10Hz (74). Furthermore, prolonged exercise sessions (i.e., extended mechanical loading) can desensitize bone cells and therefore the anabolic effect of loading becomes saturated (70). In other words, the osteogenesis response to mechanical loading does not increase when the loading session is lengthened (70,75). For example, rats trained to jump 100 times/day did not demonstrate a significantly greater bone mass than those trained to jump 40 times/day (76). However, bone mechanosensitivity is eventually restored after a sufficient period of rest (e.g., 24-hour period) (77). Consequently, recovery periods should be incorporated when designing osteogenic exercise intervention programs.

Despite the benefits, RT and impact training programs at a moderate-high intensity are not often prescribed for individuals who are considered at a high risk of fracture (e.g., people with osteoporosis) due to safety concerns.

1.2.1.1 Exercise safety

There is insufficient evidence that exercise interventions can increase or prevent fractures in people with osteoporosis. Exercise interventions or increased physical activity have been associated with an increased risk of fractures among individuals who are at risk (e.g., older adults, people with osteoporosis) (78–80). However, the relationship between exercise and the risk of fractures is considered ambiguous and may depend on other factors such as exercise type, fracture type, or season (e.g., fractures occurred more often in winter countries due to icy/slippery conditions) (78,79,81). Therefore, individuals who are at risk of fractures should consider safety precautions during exercise transitions (e.g., rolling from supine to prone) and must tailor exercise programs based on ability and risk (81). On the other hand, exercise interventions have been associated with a reduction in fracture risk among older adults, but there is no direct evidence that exercise can prevent fractures in individuals with osteoporosis (67,81–83). Clear reporting of adverse events (AEs) in exercise trials involving

people with osteoporosis is required to assess safety of exercise intervention programs. A recent systematic review and meta-analysis examined AE reporting in patients (including people with osteoporosis) being treated with exercise therapy versus a non-exercise control group (84). The authors concluded that exercise therapy may be a relatively safe intervention, however the results should be interpreted with caution as the included primary studies did not systematically monitor or report AEs (84). Although AE reporting guidelines already exist, exercise researchers may not apply the available guidelines because the recommendations are either inconsistent with respect to exercise or are drug trial-focused (85–87). Consequently, there should be consensus on what type of AEs to look for, when to report an AE, and how to classify AEs in exercise intervention trials (84). To improve AE reporting in exercise trials, knowledge translation strategies should be considered.

1.2.1.2 Knowledge Translation

Knowledge translation (KT) is "the concept of moving beyond simple dissemination of knowledge to actual use" (88). The major goal of KT is to communicate knowledge and change behavior (89). A common model of KT is the knowledge-to-action (KTA) framework which involves an iterative, dynamic and multifaceted process to identify and address knowledge gaps (Figure 1.5) (90). In the KTA framework, the funnel represents "knowledge creation" while the cycle represents "knowledge action" (i.e., activities or processes to apply knowledge) (90). As knowledge passes through the funnel it becomes more refined and useful to the target population (90). Knowledge can be tailored at each phase of knowledge creation based on the intended users (e.g., what should be disseminated and to whom?) (90). The knowledge-to-action process is the implementation of knowledge and represents activities required for knowledge application (90). The action process is dynamic and can be influenced by the knowledge action and knowledge creation phases (90).

The KTA framework can be considered in the context of AE reporting practice in exercise trials. Based on the "synthesis" stage in knowledge creation, initially a systematic review to examine AE reporting practice in RT studies should be conducted. Once the problem is clearly identified, the

participant and researcher perspective on AE reporting should be investigated to understand the gap between guidelines and practice, assess barriers, and appropriately select, tailor and implement interventions. A potential solution to bridge the gap between guideline and practice is by adapting available AE reporting recommendations specifically to exercise trials. However, access to guideline recommendations is not enough to change practice or behavior without effective dissemination and implementation strategies.

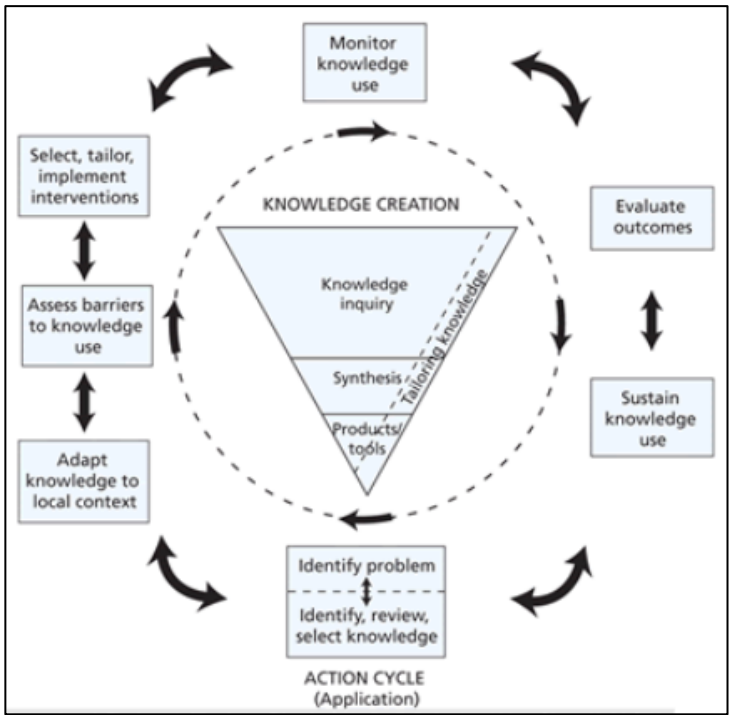

Figure 1.5 Knowledge-to-action framework (90)

1.2.1.2.1 Classifying dissemination and implementation strategies

To select appropriate dissemination and implementation strategies for the exercise-specific AE reporting guidelines, the adapted Leeman et al. framework can be considered (91). Leeman and colleagues proposed a framework comprised of five classification strategies to disseminate and implement evidence-based interventions (92). The list includes: dissemination, implementation process, integration, capacity-building, and scale-up (92). Evidence-based guidelines are a common tool to facilitate KT, but cannot change behavior or improve care if not optimally disseminated and

implemented (90,93). Tomasone et al. adapted Leeman and colleagues' framework when identifying strategies for dissemination and implementation of national physical activity, sedentary behavior, and/or sleep guidelines (91). The strategies were categorized into seven classifications, instead of five, and were divided into two groups (91). The classification strategies for dissemination included: dissemination process strategies, dissemination strategies, and dissemination scale-up strategies (91). While the classification strategies for implementation included: implementation process strategies, integration strategies, capacity building strategies, and scale-up strategies (91). Each classification was also further categorized into sub-classifications (Table 1.1) (91). Consistent with the KTA framework, barriers should be assessed and strategies should be selected accordingly in order to successfully promote guideline uptake into practice (94,95). For the adapted exercise-specific AE reporting guidelines, effective dissemination and implementation strategies can include distribution of guideline materials, mass-media/communication (e.g., advertise the adapted guidelines on relevant websites), education (e.g., educate exercise researchers on the available AE reporting recommendations), engage stakeholders (e.g., involve organizations that support accurate AE reporting in exercise studies), technology (e.g., create electronic AE reporting forms), and implementation toolkits (e.g., create AE reporting checklist and template form).

Table 1.1 Adapted Leeman et al (92) **dissemination and implementation classification strategies framework** (91)

Dissemination	Implementation
Dissemination process strategies • Formative research (e.g., surveys, focus groups, interviews)	Implementation process strategies • Engaging stakeholders (e.g., creation of partnerships with community leader) • Human resources (e.g., increasing the number of staff or changing qualifications of staff to facilitate guideline implementation) • Technology (e.g., electronic referral form)
Dissemination strategies • Distribution of guideline materials (e.g., scientist report for practitioners)	Integration strategies • Feedback (e.g., compliance feedback, social comparison feedback)

• Mass-media/communication campaign (e.g., website, TV, radio, print, social media, videos) • Education (e.g., information from a trained exercise professional, education from research team)	• Financial incentives (e.g., individuals receiving direct or indirect financial rewards/benefits if they comply with a guideline's behavioural benchmarks) • Planning tools (e.g., online interactive planning tools) • Counselling (e.g., a multi- strategy approach including the assessment of an individual's current behaviour, education, goal-setting, resources, and monitoring to support the improvement of that behaviour)
Dissemination scale-up strategies • Dissemination toolkit (e.g., Tools and resources to help organizations promote materials to their networks like sample social media messages, graphics, newsletter)	Capacity-building strategies • Stakeholder training [e.g., actions to enhance stakeholders' capacity (motivation, self-efficacy) to execute implementation process strategies]
	Scale-up strategies • Implementation toolkits (e.g., checklists, template form) • Infrastructure development (e.g., creation of physical activity programs)

1.2.2 Effects of disuse: Spinal cord injury

In contrast to exercise, the absence of mechanical stimuli results in loss of bone mass (21). After a spinal cord injury (SCI), bone resorption increases with only small changes in bone formation (96,97). Consequently, individuals with a SCI are likely to develop osteoporosis as a secondary complication. SCI-induced osteoporosis has specific risk factors that distinguish it from age-related or postmenopausal osteoporosis (98). The risk factors for developing osteoporosis in individuals with a SCI include older age, low body mass index, alcohol use, past history of fracture, female sex, older age at time of injury, longer duration since injury, and having a motor complete injury (98–100). Shortly after a SCI, there is extensive and rapid decline in BMD below the level of injury, but whether BMD continues to decline in the chronic phase (≥2 years post injury) is not yet clear (101–105); two cross-sectional studies and one prospective study reported a BMD steady state (101,102,106), while two

cross-sectional studies did not (105,107). It is worthwhile to determine what happens to BMD in the chronic stage of SCI due to its association with fracture risk. A cross-sectional study examining people with a SCI found that each 0.1g/cm^2 decrease in BMD and each unit reduction in T-value of BMD at the femoral neck was associated with an increased risk of fracture by a factor of 2.2 and 2.8, respectively (100). Fractures commonly occur below the level of injury and in skeletal sites that are mainly comprised of trabecular bone (e.g., distal femur, distal and proximal tibia) (102). People with SCI-induced osteoporosis can experience fractures due to low-impact forces that would not normally cause a fracture (e.g., transferring from bed to chair, turning in bed) (108). Treatment of fractures (e.g., prolonged immobilization and hospitalization) can further contribute to periods of disuse thus increasing bone turnover as well as impacting the individual's personal life (e.g., inability to work and generate income, lower quality of life) (26). To reduce the risk and impact of fractures, pharmacological and non-pharmacological interventions were investigated in people with SCI-induced osteoporosis.

1.2.2.1 Treatment of secondary osteoporosis

A recent systematic review demonstrated that although the efficacy of pharmacological and non-pharmacological interventions in reducing bone loss after SCI were examined in many studies, there is insufficient evidence in favor of any treatment (109). With respect to pharmacological therapy, there is very low-moderate quality evidence for prevention of BMD loss in the first year after SCI and low-quality evidence in people one year or more after SCI (109–118). For non-pharmacological interventions (e.g., standing with or without treadmill walking, cycling, electrical stimulation, tilt-table standing), there was very low-low quality evidence for preventing or treating BMD loss in the first year after SCI and very low-quality evidence in people one year or more after SCI (109,119–123). There were no randomized controlled trials that examined a combination intervention, but there was a pre-post study involving teriparatide and body weight-support treadmill training that showed no significant changes in lumber spine or total hip BMD in people a chronic SCI (124). Overall, it was challenging to infer strong recommendations due to low sample size, high risk of bias (e.g., insufficient details of

random sequence generation, allocation concealment, and lack of blinding), and heterogeneity in the included primary studies (e.g., heterogeneity in type of interventions, primary outcome measures, and follow-up durations) (109). Therefore, there are no evidence-based recommendations for effectively treating SCI-related osteoporosis.

1.3 Thesis rationale and objectives

1.3.1 Original thesis plan

BMD is considered the gold standard for diagnosing osteoporosis and provides insight regarding overall bone health. Given that individuals with a SCI are likely to develop osteoporosis as a secondary complication it is imperative to determine the time course of BMD changes in people with a chronic injury. Antiresorptive medications as well as RT are considered effective treatments for osteoporosis. However, the combined effect of RT and antiresorptive medication on BTM is yet to be examined. The original thesis plan was to explore bone adaptations to neurologic injury or RT and consisted of three complimentary studies: 1) a secondary data analysis to determine if there are any prospective bone changes in people with a chronic SCI; 2) a systematic review of reviews to determine the benefits and harms of RT on health outcomes in adults aged 18 years or older, compared to not participating in RT; and 3) a randomized clinical trial to compare the bone response to moderate-high intensity progressive resistance and impact training intervention versus a low-intensity posture and balance exercise program among women taking antiresorptive medications.

1.3.2 Modified thesis plan

The thesis plan had to be modified due to COVID-19. The exercise clinical trial involved in-person research activities such as blood collection and supervised exercises. The target population was women who are taking osteoporosis medications (i.e., mostly older adults). Given that blood collection was a primary outcome measure, the target population included older adults, and there were still many uncertainties regarding the end of COVID-19, we decided that it was best to suspend the exercise clinical trial (Appendix A) and develop an alternative project that can be completed remotely.

The first two studies were already completed and remained unchanged. The results of the overview of systematic reviews demonstrated that AEs were not being consistently monitored or reported in RT trials and thus we are unsure if the benefits of RT outweigh the harms. AE reporting guidelines already exist, but are not commonly used by exercise researchers. Therefore, consistent with the KTA framework, we conducted a qualitative study (no in-person data collection) with a multimethod approach to understand the gap between guidelines and practice, assess barriers to AE reporting in RT studies, and inform development of a tool (i.e., exercise-specific AE reporting guidelines/toolkit) to change behavior. Overall, the thesis plan was modified to examine considerations for designing and managing RT intervention studies involving the general adult population as well as people with chronic health conditions (e.g., SCI, osteoporosis). The overarching objective of this thesis was to inform RT interventions with respect to timing, benefits and the proper reporting of harms (Table 1.2).

Table 1.2 Summary of thesis structure and objectives

	Study Design	Title	Specific Objectives	Overarching Objective
Study 1	Secondary data analysis	Exploring changes in bone mass in individuals with a chronic spinal cord injury	1) To explore changes in bone [primary measure: trabecular volumetric BMD; secondary measures: cortical volumetric BMD, cortical thickness, cortical cross-sectional area and polar moment of inertia] over two years in individuals with a chronic SCI; and 2) to explore whether muscle density changes were potential correlates of the observed bone changes.	To inform exercise interventions with respect to timing (i.e., timing effective interventions aimed to reduce the risk of fracture).
Study 2	Systematic review	Resistance training and health in adults: An overview of systematic reviews	The objective of this overview of systematic reviews was to determine the benefits and harms of RT on health outcomes in adults aged 18 years or older, compared to not participating in RT.	To inform RT interventions with respect to benefits.
Study 3	Qualitative study	Stage 1: A qualitative study exploring participants' perspectives on adverse events due to resistance training Stage 2: A qualitative study of researchers' perspectives on adverse event reporting in resistance training trials Stage 3: A modified Delphi process to adapt adverse event reporting guidelines to resistance training studies	Stage 1: The objective of this study was to explore the experiences and perspectives of individuals with chronic health conditions who had an AE as a result of RT. Stage 2: The objectives of this study were to understand researchers' current practices and perspectives on AE reporting in clinical trials of RT, and identify barriers and facilitators of AE reporting. Stage 3: The objective of this study was to adapt existing AE reporting guidelines to RT studies.	To inform proper reporting of harms in RT interventions.

Abbreviations: BMD, Bone Mineral Density; SCI, Spinal Cord Injury; RT, Resistance Training; AE, Adverse Event.

Chapter 2: Study 1

Title: Exploring Changes in Bone Mass in Individuals with a Chronic Spinal Cord Injury

2.1 Overview

Purpose: 1. To explore changes in bone [primary measure: trabecular volumetric bone mineral density (vBMD); secondary measures: cortical vBMD, cortical thickness, cortical cross-sectional area (CSA) and polar moment of inertia] over two years in individuals with a chronic spinal cord injury (SCI). 2. To explore whether muscle density changes were potential correlates of the observed bone changes.

Methods: This study is a secondary data analysis of a prospective, observational study involving 70 people with a chronic SCI (≥2 years post injury). The study included 4 strata of participants with diverse impairments: 1. Paraplegia (T1-T12) motor complete American Spinal Injury Association Impairment Scale (AIS) A/B (n=23), 2. Paraplegia motor incomplete AIS C/D (n=11), 3. Tetraplegia (C2-C8) AIS A/B (n=22), and 4. Tetraplegia AIS C/D (n=14). Peripheral quantitative computed tomography scans were taken at the 4% (distal tibia), 38% (diaphyseal tibia) and 66% (muscle cross-sectional area) tibia sites by measuring from the distal to proximal tibia starting at the inferior border of the medial malleolus. The tibia sites were assessed annually over a span of two years. Comparisons were made using a paired samples t-test and simple linear regression was used to adjust for sex, time post injury and bisphosphonate use.

Results: We observed no changes in trabecular vBMD at the 4% tibia site, but there was a statistically significant decline in cortical vBMD, cortical thickness and CSA at the 38% tibia site. Changes in muscle density were not associated with the decreases observed in cortical bone.

Conclusion: Our findings suggest that individuals with chronic SCI (mean duration of injury: 15.5 ±10 years) may have reached a plateau in bone loss with respect to trabecular bone, but cortical bone loss can continue well into the chronic stages.

2.2 Introduction

Persons with a spinal cord injury (SCI) are at an increased risk of lower extremity fragility fracture due to the rapid declines in bone mass and architecture that occurs below the level of the injury within the first year of injury (125–127). The changes in bone mass and architecture below the level of injury occur early, predominantly in trabecular bone and thus skeletal sites that are mainly comprised of trabecular bone (e.g., distal femur, distal and proximal tibia) are considered the most common fracture sites (102). It is unclear whether bone mineral density (BMD) reaches a steady state in the chronic phase (≥2 years post injury); two cross-sectional studies and one prospective study reported a BMD steady state (101,102,106), while two cross-sectional studies did not (105,107). We must explore changes in bone after the first few years post injury since we are unsure if fracture risk differs among people with a chronic SCI versus individuals with an acute injury. Understanding changes in bone mass over time in people with a SCI will be useful for timing effective interventions aimed to reduce the risk of fracture.

Several studies have attempted to establish the trajectory of bone loss after SCI, but there are variable findings that limit our understanding of what happens after the first few years post-injury. The majority of studies examining bone changes after chronic SCI are cross-sectional (102–105). There are only two prospective studies examining changes in BMD over time and both studies reported no association between changes in BMD after 30 months and 21 months, respectively (106,128). However, the available prospective studies were limited either by participant characteristics or by outcome assessments. For instance, one of the studies was limited to only men (n=39) with a complete SCI and included both acute and chronic injuries, while the other study included both men and women with complete and incomplete chronic SCI (n=152) but assessed BMD using dual X-ray absorptiometry (DXA) as opposed to peripheral quantitative computed tomography (pQCT) (106,128). Bone data acquired using DXA, as opposed to pQCT cannot be used to distinguish between bone geometry and BMD (129). Furthermore, based on cross-sectional study findings, it is possible that BMD changes may depend on the skeletal site examined as well as the severity of injury. For example, a study reported

that a BMD steady state was reached after 4.1 years in the distal femur, as opposed to the distal tibia where it occurred at 6.8 years (102). As for severity of impairment, another cross-sectional study showed that individuals with an incomplete injury had higher BMD values and were less likely to fracture than those with complete injuries (127).

The reduction or absence of mechanical loading that occurs post-SCI is thought to greatly contribute to loss in bone mass (104–106,130). Wolff's law and Frost's mechanostat theory indicate that the mechanical forces applied to the bone, such as muscle forces, may influence the bone remodeling process (20). Therefore, muscle properties that can impact the ability to generate muscle forces should be examined when assessing bone changes (104–106,130). Along with bone deterioration, acutely after a SCI, there is substantial and rapid decline in the muscle size and muscle quality below the level of injury (131–133). Changes in the physiological properties of muscle that occur after a SCI have been shown to increase fatigability and alter the rate of contraction and relaxation (134). Therefore, low muscle density, a marker of muscle fat infiltration, may reduce the muscle force that is applied on the bone (135–138). A secondary data analysis using the same cohort as this study demonstrated that there was a statistically significant reduction in muscle density, even after outliers were omitted, in people with a chronic SCI (136). Given that low muscle density persists in the chronic phase of SCI, it is worth exploring whether muscle density changes influence or are associated with bone changes. At this time, however, little is known about whether prospective changes in muscle density contribute to changes in bone.

Given that the trajectory of bone loss still remains unclear among individuals with a chronic SCI, we conducted a secondary data analysis to prospectively examine bone variables measured using pQCT in both men and women with complete and incomplete injuries. The purpose of this study was to explore whether bone mass continues to decline or whether it reaches a steady state in individuals with chronic SCI. Specifically, the primary objective was to explore changes in bone [primary measure: trabecular volumetric BMD (vBMD); secondary measures: cortical vBMD, cortical thickness, cortical cross-sectional area (CSA) and polar moment of inertia (PMI)] over two years while adjusting for sex, time

post injury and bisphosphonate use. For bone variables where statistically significant changes occurred over time, we explored whether muscle density changes were potential correlates of the observed bone changes.

2.3 Methods

2.3.1 Study design

We performed secondary analyses using data from a prospective, observational study conducted at the University of Waterloo and Lyndhurst Centre, Toronto Rehabilitation Institute, University Health Network. Participant recruitment began in March 2009 using the Lyndhurst Long-term Follow-up Database and the Outpatient Services Program at Lyndhurst Centre and Hamilton Health Sciences. PQCT baseline assessments were performed between April 2009 and June 2012 and were assessed annually over a span of two years (April 2010 - June 2014). Current and past medical history, demographics and impairment data were collected by chart abstraction or by interviewing participants. The study received approval from the local research ethics boards.

2.3.2 Participants

Eligible individuals were ≥18 years of age, had diverse levels of SCI [Tetraplegia (C2-C8), Paraplegia (T1-T12), motor complete American Spinal Injury Association Impairment Scale (AIS) A/B, and motor incomplete AIS C/D] of sudden onset (<24 hours), were at least 2 years post injury, and were able to provide informed consent and understand instructions in English. The primary study involved stratified recruitment to include 4 strata: 1. Paraplegia AIS A/B, 2. Paraplegia AIS C/D, 3. Tetraplegia AIS A/B, and 4. Tetraplegia AIS C/D. Potential participants were excluded if they: (a) had current or prior conditions other than paralysis that may influence bone metabolism, including metabolic disorders, chronic alcoholism, oral glucocorticoids use ≥7.5 mg/day for 3 months or longer, malignancy, and known liver, kidney, or intestinal disease; (b) had a body weight ≥270 lbs (densitometer capacity); (c) had conditions that may reduce image quality such as bilateral metal implants in limbs to be assessed, or severe spasticity and allergy to Ativan which is used to treat muscle spasms; or (d) were pregnant or

planning to become pregnant. A detailed description of the recruitment strategies and included participants is provided in a previous publication (127). All participants provided written informed consent.

2.3.3 Image acquisition

A pQCT scanner (XCT- 2000; Stratec Medizintechnik, Germany) was used to acquire images of the 4%, 38% and 66% tibia sites by measuring from the distal to proximal tibia starting at the inferior border of the medial malleolus. The 4% tibia site (distal tibia) was used to determine trabecular vBMD (mg/cm^3), the 38% tibia site (diaphyseal tibia) was used to determine cortical vBMD (mg/cm^3), cortical thickness (mm), cortical CSA (mm^2), and PMI (mm^4), and the 66% tibia site (muscle cross-sectional area) was used to examine muscle density (mg/cm^3) (127,139,140). The precision, in root mean square coefficient of variation, was reported to be 2% or less for all the included bone variables when it was examined in individuals with and without SCI (139). For muscle density, the root mean square coefficient of variation was 1.42% when using this technique in people with a SCI (140). Scans were made on the right tibia except in cases of severe lower spasticity, contractures, the presence of metal or fracture, or if the calf girth exceeded the gantry opening. Single 2.5mm scan slices were obtained; the voxel size was 0.2 mm at the 4% site and 0.5 mm at the 38% and 66% site.

2.3.4 Image analysis

The pQCT manufacturer's software (Stratec XCT-2000, version 6.00) was used to analyze the bone variables. To assess trabecular vBMD at the 4% site, CALCBD mode was applied using contour mode 3, peel mode 2, outer threshold of 130 mg/cm^3, and inner threshold of 400 mg/cm^3 (141). At the 38% site, CORTBD mode using contour mode 1 and threshold of 710 mg/cm^3 was used to assess cortical vBMD (mg/cm^3), cortical thickness (mm), cortical CSA (mm^2) and PMI (mm^4) (141). Analysis of muscle density at the 66% site was performed using SliceOmatic (Tomovision, Montreal, Canada, version 4.3). Tissue segmentation was performed using a watershed algorithm and watershed spillover

was manually fixed. The analysis protocol using the watershed technique has been previously reported (142).

2.3.5 Statistical analysis

Descriptive statistics of the participants' demographic characteristics, type and duration of SCI, medical history, and physical activity level were obtained via participant interview and chart abstraction and were reported at baseline. Age, time post injury and physical activity level were presented as means [standard deviation (SD)], while sex, level of injury, severity of injury, bisphosphonate exposure, history of lower extremity fragility fracture were expressed as counts (n) and percentages (%). As part of an exploratory analyses, a paired-samples t-test was selected to compare trabecular vBMD (mg/cm^3), cortical vBMD (mg/cm^3), cortical thickness (mm), cortical CSA (mm^2), and PMI (mm^4) between baseline and year-1 and baseline and year-2 in the total sample and in subgroups of participants with complete and incomplete SCI. Both unadjusted and adjusted results were reported; using simple linear regression (Enter method) the change from baseline values were adjusted for sex, time post injury and bisphosphonate use. Participants must have a baseline scan and at least one study time point (year-1 or year-2) to be included in the analyses. In addition, as part of an exploratory analysis, bivariate regression was performed to examine muscle density changes as a potential correlate of any statistically significant bone changes observed. Statistical significance was set at p-value ≤ 0.05. The p-values need to be interpreted with caution as the analyses was exploratory and not intended for definite inferences. All analyses were performed using IBM SPSS version 26 (Armonk, NY: IBM Corp).

2.4 Results

2.4.1 Participant characteristics

A detailed description of the recruitment results have been previously published (127). A total of 70 participants with a SCI were included in the study. The participants' demographic characteristics, type and durations of SCI, medical history, and physical activity level are described in Table 2.1.

Table 2.1 Participant characteristics at baseline (n=70)

Characteristics	All Participants
Age in years, mean (±SD) [Min, Max]	48.8 (12) [24, 77]
Sex, n (%)	
Males	50 (71)
Females	20 (29)
Time post injury in years, mean (±SD) [Min, Max]	15.5 (10) [2, 41]
Impairment group, n (%)	
Paraplegia AIS A/B	23 (33)
Paraplegia AIS C/D	11 (16)
Tetraplegia AIS A/B	22 (31)
Tetraplegia AIS C/D	14 (20)
Bisphosphonate Exposure[a], n (%)	51 (73)
History of lower extremity fragility fracture n (%)	19 (27)
Physical Activity[b] in min/day, mean (±SD)	
Mild	121 (133)
Moderate	86 (114)
Vigorous	25 (35)
Total	232 (210)

Abbreviations: SD, standard deviation; Min, minimum; Max, maximum
[a]Current or previous use of bisphosphonate medications including alendronate (Fosamax/Fosavance), risedronate (Actonel/Actonel Delayed Release), zoledronate (Aclasta), etidronate (Didrocal), and pamidronate (Aredia).
[b]Assessed by the Physical Activity Recall Assessment for People with Spinal Cord Injury

2.4.2 pQCT scans

Out of the 70 participants, 63, 57, and 51 participants completed the baseline, year-1 and year-2 study visits, respectively. A total of 53 participants were included in the bone analysis for baseline to year-1 and 49 participants for baseline to year-2. Reasons for missing pQCT scans (e.g., if the participant had severe lower limb spasticity or a calf circumference that exceeded the gantry opening) is described in detail elsewhere (136). As for the muscle analysis, 50 participants were included in baseline to year-1

and 41 participants were included in baseline to year-2 (136). No cases of heterotopic ossification were observed or diagnosed at the measured sites during the span of the study.

2.4.3 Changes in trabecular vBMD

At baseline, mean trabecular vBMD (TrabvBMD) was 136.0 ± 57.0 mg/cm^3 when examined at the 4% tibia site (distal tibia). The results depicted no statistically significant change in TrabvBMD between baseline and year-1 and between baseline and year-2, even when adjusted for sex, time post injury and bisphosphonate use (Table 2.2). Similarly, when examined based on severity of injury there were still no statistically significant changes between the study time points (Table 2.2).

Table 2.2 Between-visit changes in TrabvBMD at the 4% tibia site (distal tibia)

Sample and sub-samples	Time period	n	Time Post Injury in years (mean ±SD) [Min, Max]	Mean difference in mg/cm^3 (95% CI), p-value	Adjusted[a] mean difference in mg/cm^3 (95% CI), p-value
Full cohort	Baseline – Year-1	53	14.7 ±10.2 [2, 41]	4.7 (-8.2 to 17.6), 0.468	-26.0 (-59.7 to 7.8), 0.129
	Baseline – Year-2	49	15.3± 10.2 [2, 41]	-5.0 (-13.9 to 3.9), 0.266	-5.2 (-29.4 to 19.1), 0.670
Participants with complete SCI (AIS A/B)	Baseline – Year-1	30	16.8 ± 10.8 [2, 41]	8.5 (-14.7 to 31.7), 0.459	-46.6 (-120.4 to 27.3), 0.207
	Baseline – Year-2	29	17.2 ±10.7 [2, 41]	-5.7 (-20.5 to 9.0), 0.431	7.5 (-44.5 to 59.4), 0.770
Participants with incomplete SCI (AIS C/D)	Baseline – Year-1	23	12.0 ±9.0 [2, 30]	-0.3 (-2.9 to 2.4), 0.836	1.0 (-5.4 to 7.3), 0.749
	Baseline – Year-2	20	12.7 ±9.3 [2, 30]	-3.8 (-10.5 to 2.8), 0.243	-9.3 (-24.7 to 6.2), 0.223

Abbreviations: SCI, spinal cord injury; SD, standard deviation; Min, minimum; Max, maximum; CI, confidence interval

[a]Adjusted for sex, time post injury and bisphosphonate use: Simple linear regression analysis using change from baseline values.

TrabvBMD changes ranged from -183.6 to 207.6 mg/cm^3 at year-1, and -188.2 to 76.4 mg/cm^3 at year-2. At 2 years from the baseline assessment, TrabvBMD increased in 5 participants (time post injury: 3-28 years), decreased in 7 participants (time post injury: 2-14 years), and the remaining 37 participants had a change less than or equal to the least significant change (LSC) value of ±10.45 mg/cm^3 (139) (Figure 2.1). Out of the 5 participants who experienced an increase in TrabvBMD, 2 had complete

injuries, and out of the 7 individuals who displayed a decrease in TrabvBMD, 4 had complete injuries (Figure 2.1). Also, there were no sex differences observed as there were no statistically significant changes in TrabvBMD between the study time points [Females: Baseline – Year-1, mean difference of -2.0 (95% CI: -7.9 to 4.0) mg/cm^3, p=0.493; Baseline – Year-2, mean difference of -1.3 (95% CI: -5.2 to 2.7) mg/cm^3, p=0.509; Males: Baseline – Year-1, mean difference of 7.8 (95% CI: -11.2 to 26.9) mg/cm^3, p=0.408; Baseline – Year-2, mean difference of -6.8 (95% CI: -20.0 to 6.5) mg/cm^3, p=0.306].

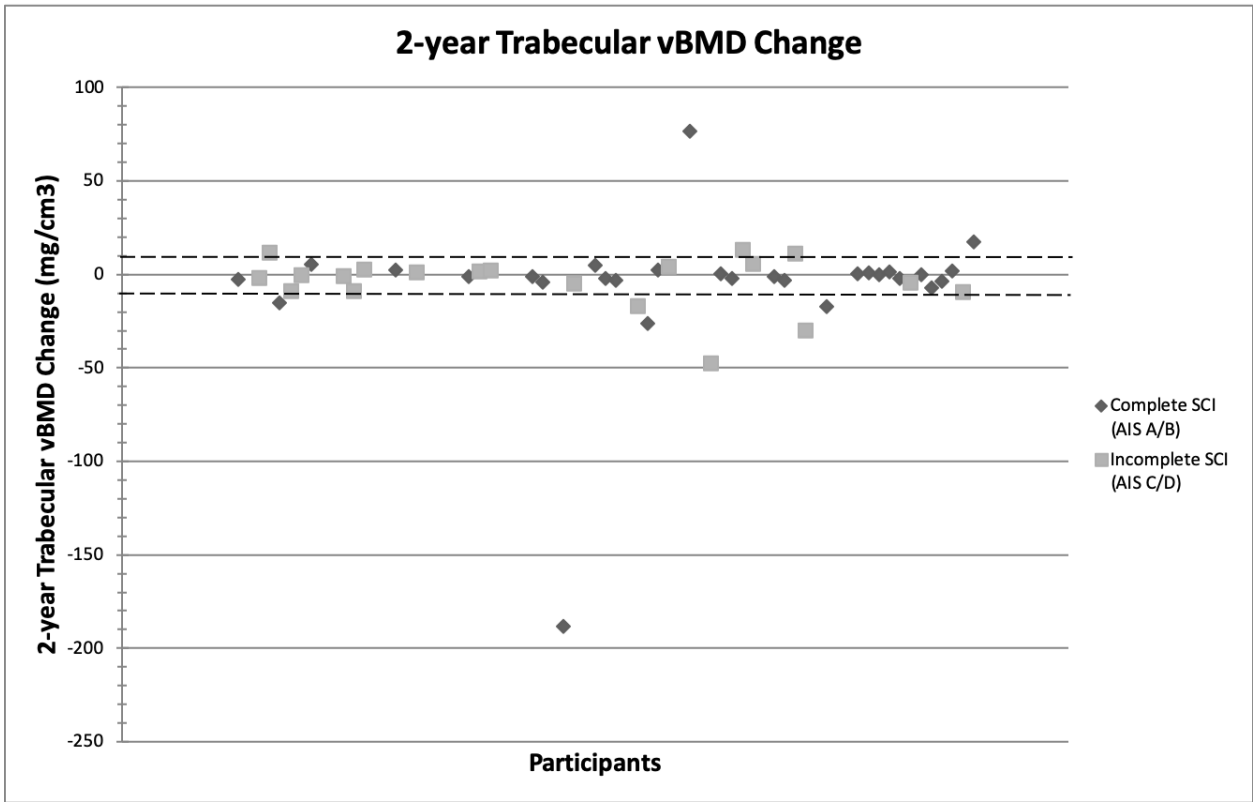

Figure 2.1 Participants' two-year changes in trabecular vBMD changes based on severity of injury. The dashed lines represent the least significant change value of ±10.45 mg/cm^3

2.4.4 Changes in other bone variables

At baseline, mean cortical vBMD was 1166.2 ± 47.7 mg/cm^3, cortical thickness was 4.4 ± 1.2 mm, cortical CSA was 263.1 ± 68.0 mm^2 and PMI was 25798.2 ± 9035.2 mm^4 when examined at the 38% tibia site (diaphyseal tibia). The results demonstrated that there was a statistically significant reduction observed in cortical vBMD between baseline and year-1 (unadjusted) in the total sample and in the

complete injury subgroup, however the reduction was no longer statistically significant when it was adjusted for sex, time post injury and bisphosphonate use (Tables 2.3 and 2.4). There was a statistically significant reduction observed in cortical thickness between baseline and year-1 (both adjusted and unadjusted), and baseline and year-2 (only when adjusted) in the total sample and in the complete injury subgroup (Tables 2.3 and 2.4). There was a statistically significant reduction observed in cortical thickness between baseline and year-2 (both adjusted and unadjusted) in the incomplete injury subgroup (Tables 2.3 and 2.4). The cortical CSA was statistically significantly lower after two years from baseline in the full sample (only when adjusted) and in individuals with an incomplete SCI (both adjusted and unadjusted) (Tables 2.3 and 2.4). There were no statistically significant changes observed in PMI when examined in the total sample or in the subgroups (Tables 2.3 and 2.4).

Table 2.3 Between-visit changes in secondary bone variables at the 38% tibia site (diaphyseal tibia) when examined in the total sample

Bone variable	Time period	Mean difference (95% CI), p-value	Adjusted[a] mean difference (95% CI), p-value
Cortical vBMD (mg/cm^3)	Baseline – Year-1	-16.1 (-29.3 to -2.9), 0.018*	-6.9 (-42.6 to 28.8), 0.700
	Baseline – Year-2	-2.1 (-8.6 to 4.5), 0.532	-10.8 (-29.0 to 7.3), 0.234
Cortical thickness (mm)	Baseline – Year-1	-0.3 (-0.4 to -0.1), 0.003*	-1.7 (-2.7 to -0.6), 0.003**
	Baseline – Year-2	-0.04 (-0.1 to 0.03), 0.260	-0.3 (-0.4 to -0.2), 0.000**
Cortical CSA (mm^2)	Baseline – Year-1	-5.5 (-13.8 to 2.9), 0.194	-1.2 (-24.2 to 21.7), 0.915
	Baseline – Year-2	-1.9 (-4.5 to 0.6), 0.140	-11.5 (-17.9 to -5.0), 0.001**
PMI (mm^4)	Baseline – Year-1	1142.4 (-452.4 to 2737.2), 0.157	707.9 (-3666.2 to 5081.9), 0.746
	Baseline – Year-2	-138.9 (-442.2 to 164.4), 0.362	-777.1 (-1586.0 to 31.7), 0.059

*$p \leq 0.05$

**$p \leq 0.05$ for adjusted values

n=53 Baseline – Year-1; Time post injury in years [mean ±SD (Min, Max)] = 14.7 ± 10.2 (2, 41)

n=49 Baseline – Year-2; Time post injury in years [mean ±SD (Min, Max)] = 15.3 ±10.2 (2, 41)

Abbreviations: vBMD, volumetric bone mineral density; CSA, cross-sectional area; PMI, polar moment of inertia; CI, confidence interval

[a]Adjusted for sex, time post injury and bisphosphonate use: Simple linear regression analysis using change from baseline values.

Table 2.4 Between-visit changes in secondary bone variables at the 38% tibia site (diaphyseal tibia) when examined based on severity of injury

Bone variable	Time period	Mean difference (95% CI), p-value	Adjusted[a] mean difference (95% CI), p-value
Participants with complete SCI (AIS A/B)			
Cortical vBMD (mg/cm^3)	Baseline – Year-1	-23.1 (-45.5 to -0.67), 0.044*	-15.0 (-90.0 to 60.9), 0.689
	Baseline – Year-2	1.7 (-7.2 to 10.6), 0.699	-28.0 (-56.4 to 0.3), 0.052
Cortical Thickness (mm)	Baseline – Year-1	-0.29 (-0.5 to -0.04), 0.024*	-1.9 (-3.4 to -0.5), 0.011**
	Baseline – Year-2	0.02 (-0.05 to 0.09), 0.540	-0.2 (-0.4 to -0.003), 0.048**
Cortical CSA (mm^2)	Baseline – Year-1	-8.0 (-22.5 to 6.5), 0.269	2.6 (-48.1 to 53.3), 0.916
	Baseline – Year-2	0.1 (-2.7 to 2.9), 0.920	-7.6 (-17.0 to 1.7), 0.103
PMI (mm^4)	Baseline – Year-1	766.7 (-1350.6 to 2805.3), 0.481	1247.2 (-6308.7 to 8803.0), 0.737
	Baseline – Year-2	16.8 (-328.8 to 362.5), 0.921	-709.3 (-1926.4 to 507.8), 0.241
Participants with incomplete SCI (AIS C/D)			
Cortical vBMD (mg/cm^3)	Baseline – Year-1	-7.0 (-16.7 to 2.7), 0.150	5.9 (-18.5 to 30.3), 0.617
	Baseline – Year-2	-7.5 (-17.5 to 2.5), 0.133	-0.9 (-25.2 to 23.3), 0.936
Cortical Thickness (mm)	Baseline – Year-1	-0.2 (-0.5 to 0.02), 0.069	-1.3 (-3.3 to 0.6), 0.167
	Baseline – Year-2	-0.1 (-0.2 to -0.01), 0.037*	-0.3 (-0.6 to -0.1), 0.012**
Cortical CSA (mm^2)	Baseline – Year-1	-2.1 (-7.3 to 3.0), 0.398	-7.0 (-20.1 to 6.2), 0.280
	Baseline – Year-2	-4.9 (-9.7 to -0.1), 0.047*	-13.1 (-25.0 to -1.3), 0.032**
PMI (mm^4)	Baseline – Year-1	1632.4 (-810.6 to 4075.4), 0.180	-992.3 (-6901.9 to 4917.3), 0.729
	Baseline – Year-2	-364.7 (-939.8 to 210.4), 0.200	-815.5 (-2264.6 to 633.5), 0.250

n=32 Baseline – Year-1 in Participants with complete SCI; Time post injury in years [mean ±SD (Min, Max)] = 16.8 ± 10.8 (2, 41)
n=29 Baseline – Year-2 in Participants with complete SCI; Time post injury in years [mean ±SD (Min, Max)] = 17.2 ± 10.7 (2, 41)
n=23 Baseline – Year-1 in Participants with incomplete SCI; Time post injury in years [mean ±SD (Min, Max)] = 12.0 ± 9.0 (2, 30)
n=20 Baseline – Year-2 in Participants with incomplete SCI; Time post injury in years [mean ±SD (Min, Max)] = 12.7 ± 9.3 (2, 30)

Abbreviations: SCI, spinal cord injury; vBMD, volumetric bone mineral density; CSA, cross-sectional area; PMI, polar moment of inertia; CI, confidence interval
[a]Adjusted for sex, time post injury and bisphosphonate use: Simple linear regression analysis using change from baseline values.
*$p \leq 0.05$ for unadjusted values
**$p \leq 0.05$ for adjusted values

2.4.5 Changes in muscle density

At baseline, mean muscle density was 55.81 ± 11.47 mg/cm^3 when examined at the 66% tibia site (muscle cross-sectional area). The changes in muscle density have already been published (143). There was a statistically significant reduction in muscle density between baseline and year-1 (mean difference: -0.94 [95% CI: -1.80 to -0.11] mg/cm^3, p=0.028) and between baseline and year-2 (mean difference: -1.04 [95% CI: -1.94 to -0.14] mg/cm^3, p=0.024) (143). Among subgroups, the only statistically significant change in muscle density was between baseline and year-1 in participants with an incomplete SCI (mean difference: -1.31 [95% CI: -2.46 to -0.15] mg/cm^3, p=0.028) (143). After outliers were omitted, there was still a statistically significant reduction in muscle density (mean difference: -1.04 [95% CI: -1.87 to -0.22] mg/cm3, p = 0.014 and mean difference: - 1.21 [95% CI: -2.10 to -0.32] mg/cm3, p = 0.009 for baseline-year 1 and baseline-year 2, respectively) among the entire cohort but not the subgroups (143). Given that there were no statistically significant trabecular bone changes but there were cortical bone changes, we only examined the relationship between changes in muscle density and changes in cortical bone. The bivariate regression analyses indicated that the change in muscle density was not a potential correlate for the observed cortical bone changes.

2.5 Discussion

We observed no changes in TrabvBMD over two years in our cohort of individuals with chronic SCI, but there was a statistically significant decline in cortical vBMD, cortical thickness and CSA. Therefore, individuals with chronic SCI may have reached a plateau in bone loss with respect to trabecular bone, but cortical loss can continue well into the chronic stages. Given that our analysis was exploratory, the findings needs to be confirmed in future studies. In addition, there were individuals who experienced changes in TrabvBMD that were greater than the LSC, suggesting that there is a need

to identify modifiable risk factors among those who continue to lose bone in the chronic stages of SCI. Changes in muscle density were not associated with the decrease observed in cortical vBMD, thickness and CSA. Our findings suggest that individuals with chronic SCI should be assessed for modifiable risk factors for bone loss and fractures, and treatment options should be discussed.

There was high variability in the participants' two-year changes in TrabvBMD. The largest ranges in TrabvBMD were observed among individuals with a complete SCI; between the maximum and minimum values there was a difference of 391 mg/cm^3 in year-1 (n=30) and 265 mg/cm^3 in year-2 (n=29) among participants with a complete SCI versus a difference of 39 mg/cm^3 in year-1 (n=23) and 60 mg/cm^3 in year-2 (n=20) among participants with an incomplete SCI. The majority of our study population (64%) was comprised of individuals with a complete SCI. The wide variability in the TrabvBMD changes were also observed in two studies involving only individuals with complete SCI (102,106) and one study compromised of participants with both complete and incomplete SCI (144). In a *post hoc* exploratory examination of individual data, it appears that the participant who experienced the greatest TrabvBMD loss of -188.2 mg/cm^3 was a male subject with a complete injury who was prescribed bisphosphonates and was 8 years post injury. The participant who experienced the greatest gain of 76.4 mg/cm^3 was also a male with a complete injury however he was not on bisphosphonates and was 17 years post SCI. In addition, both subjects had a normal body mass index. Therefore, the variability may have made it more challenging to detect any significant changes in TrabvBMD and the modifiable risk factors remain undetermined.

Cross-sectional studies have found that the loss in TrabvBMD occurs at a much faster rate than the loss in cortical bone (101,102). As a result, it should not be surprising that cortical bone changes post-SCI take longer to reach a steady state than trabecular bone changes. However, it is important to note that there was variability in cortical bone changes among participants thus suggesting that changes may continue in some but not all people with chronic SCI. For example, although our study demonstrated that there was a statistically significant reduction in cortical vBMD between baseline and year-1, the range of changes were between -267.7 to 90.3 mg/cm^3. In addition, the reduction was no longer

considered statistically significant when it was adjusted for sex, time post injury and bisphosphonate use thus indicating that there are modifiable and non-modifiable risk factors that can determine cortical vBMD loss. In our exploratory prospective study, we noticed that individuals with chronic SCI are losing cortical bone thickness over time, consistent with the findings of a cross-sectional study (102). In contrast, Frotzler et al. did not observe changes in cortical bone in their prospective study (106). A possible explanation could be that the study sample also included participants with acute injuries (not strictly chronic SCI) and as a result they could still be predominantly losing trabecular bone (106). Furthermore, at this time, it remains unclear whether severity of injury is a significant factor affecting cortical changes as the majority of studies in this field are limited to men with complete SCI. It is important to consider severity of injury as our study findings indicated that cortical thickness as well as CSA continue to decline in individuals with incomplete SCI. When assessed in the full sample and among participants with a complete SCI there was a statistically significant reduction between baseline and year-1 in cortical thickness but not in cortical CSA. A possible explanation as to why in some cases there was a statistically significant reduction in cortical thickness, but not cortical CSA was likely due to the greater variability in cortical CSA changes among the participants. For instance, when examined in the full sample, the change in cortical thickness between baseline to year-1 ranged from -5.6 to 2.9 mg/cm^3, while the change in cortical CSA for that same time period ranged from -206.5 to 28.0 mg/cm^3. However, there was a statistically significant reduction in both cortical thickness and CSA between baseline and year-2 after adjusting for sex, time post injury and bisphosphonate use among the full sample and in people with an incomplete SCI. Although we did not observe statistically significant reductions in cortical CSA among people with a complete SCI, a cross-sectional study demonstrated that cortical CSA was 1.5-2 times lower in men with a complete chronic SCI (n=8) compared with age-matched healthy control subjects (n=6) (145). Discrepancy between our findings and the cross-sectional study was likely due to the smaller sample size, the use of a different imaging modality (magnetic resonance imaging vs. pQCT) to measure cortical CSA, the different skeletal site examined (femur vs. tibia), and bisphosphonate use (i.e., none of the participants in the cross-sectional study were

taking bisphosphonates) (145). Overall, it appears that beyond the first few years post-SCI, variable amounts of cortical bone loss may persist and likely depend on sex, time post injury and bisphosphonate use, while trabecular bone loss may plateau. Another explanation could be that there are bone microarchitectural changes that we are unable to detect with the currently available technology.

The longitudinal changes in muscle density may not influence changes in bone quality in people with a chronic SCI. Our team has previously reported in a cross-sectional study that muscle density was positively associated with TrabvBMD, as well as cortical thickness and cortical vBMD (146). Nevertheless, our exploratory findings revealed no associations between changes in muscle density and changes in cortical vBMD, cortical thickness or cortical CSA. We expected that with lower muscle density there would be a decrease in the muscle force-generating capacity. However, the expected reductions in muscle density or in muscle force may have not been substantial enough to contribute to the cortical bone changes. It is possible that much of the change in muscle density and force was lost acutely after the SCI. Another explanation could be the presence of spasticity among those with a motor complete injury. There are currently no other studies examining the prospective changes in the muscle-bone unit in the chronic state of SCI. Future prospective studies should consider assessing changes in muscle function or strength along with muscle density when examining the association with bone changes in people with a chronic SCI.

2.5.1 Limitations

We would like to acknowledge some study limitations. First, we would like to emphasize that all of the analyses in this study are considered exploratory and should be interpreted with caution. Further large-scale multicentre studies are required to confirm our findings. Given that there is accelerated bone loss at skeletal sites with a higher proportion of trabecular bone, TrabvBMD at the distal tibia was chosen as the primary outcome. However, the most common fracture sites in people with a SCI also include the distal femur and proximal tibia which were not assessed in this exploratory study. With respect to participants, we chose not to exclude participants on bisphosphonates because it was not pragmatic.

Therefore, the true extent of bone mass decline in chronic SCI may be underestimated as 73% of the cohort was prescribed bisphosphonate therapy; adherence was self-reported during the study period. However, some participants were experiencing reductions in bone mass despite being on bisphosphonates. Also, a recent propensity-matched case-control analyses demonstrated that bisphosphonate therapy did not significantly affect fracture risk in people with SCIs or disorders (147). Furthermore, individuals with a history of fracture may have underlying risk factors that we did not control for in the analysis, and as a result may have different rates of bone loss, contributing to variability in our estimates. We have observed differences in bone strength at baseline in individuals with SCI who have a history of fractures compared to those who have no history (127). We limited the number of potential covariates because of sample size, and it is possible that there are other covariates that should be explored in future studies. Another study limitation was that some participants did not complete the final scans at two-year follow up, and the sample size for the subgroup analyses was small, thus the analyses may have been underpowered. Nevertheless, there are few studies of prospective longitudinal bone changes after SCI. In addition, when examining whether there was an association between changes in muscle density and changes in bone, exploratory analysis was conducted for only those that were statistically significant in order to avoid multiple assessments. However, it is possible for an association to be observed in the bone variables that did not show a statistically significant change. Finally, there were a few limitations with respect to image acquisition in individuals with SCI (e.g., presence of lower leg edema, spasticity) that may have prevented accurate analysis. Also, there was risk of exposing participants to ionizing radiation when acquiring the images via pQCT. Participants were fully informed about all the risks during the informed consent process.

2.6 Conclusion

This two-year longitudinal study found no changes in TrabvBMD at the 4% tibia site, but reported a decline in cortical vBMD, cortical thickness and CSA at the 38% tibia site among a diverse population of individuals with chronic SCI. Risk factors such as sex, time post injury and bisphosphonate use may

contribute to cortical bone changes. Overall, the findings of this study emphasize that people with a chronic SCI could continue to benefit from interventions to prevent loss in bone mass. However, given that this is an exploratory study the findings need to be confirmed in future studies. Furthermore, although pertinent studies tend to focus mainly on complete SCI, the study results demonstrate that individuals with an incomplete SCI also undergo extensive bone loss and thus future intervention studies should include participants with motor complete as well as incomplete SCI.

Chapter 3: Study 2

Title: Resistance Training and Health in Adults: An Overview of Systematic Reviews

3.1 Overview

The objective of this overview of systematic reviews was to determine the benefits and harms of resistance training (RT) on health outcomes in adults aged 18 years or older, compared to not participating in RT. Four electronic databases were searched in February 2019 for systematic reviews published in the past 10 years. Eligibility criteria were determined *a priori* for population (community dwelling adults), intervention (exclusively RT), comparator (no RT or different doses of RT), and health outcomes (critical: mortality, physical functioning, health-related quality of life, and adverse events (AEs); important: cardiovascular disease, type 2 diabetes mellitus, mental health, brain health, cognitive function, cancer, fall-related injuries or falls, and bone health). We selected one review per outcome and we used the GRADE process to assess the strength of evidence. We screened 2089 records and 375 full-text articles independently, in duplicate. Eleven systematic reviews were included, representing 364 primary studies and 382,627 unique participants. RT was associated with a reduction in all-cause mortality and cardiovascular disease incidence, and an improvement in physical functioning. Effects on health-related quality of life or cognitive function were less certain. AEs were not consistently monitored or reported in RT studies, but serious AEs were not common. Systematic reviews for the remaining important health outcomes could not be identified. Overall, RT training improved health outcomes in adults and the benefits outweighed the harms. PROSPERO; Registration no. CRD42019121641

3.2 Introduction

The previous Canadian Physical Activity Guidelines (2011) recommended that to improve health outcomes, healthy adults (18-64 years of age) and older adults (≥65 years of age) should engage in at least 150 minutes per week of moderate-to-vigorous intensity aerobic physical activity in bouts of at least 10 minutes (148). The previous guidelines also recommended adults and older adults engage in "muscle and bone strengthening activities using major muscle groups, at least 2 days per week" (148). As we move forward with the new guidelines, *The Canadian 24-Hour Movement Guidelines for Adults aged 18-64 years and 65 years and older: An Integration of Physical Activity, Sedentary Behaviour, and Sleep*, we wanted to consider whether there was new evidence to update the resistance training (RT) recommendations.

Given the growth in the number of published systematic reviews, we chose to complete an overview of systematic reviews to identify evidence pertaining to the effects of RT on health outcomes (149,150). The evidence from this overview informed the development of the Physical Activity component of the 24-hour Movement Guidelines. The objective of this overview was to determine the benefits and harms of RT on health outcomes in adults aged 18 years or older, compared to not participating in RT. We also explored whether there was evidence that age, exposure dose, or type of RT influenced the effects on health outcomes.

3.3 Methods

3.3.1 Protocol and registration

We established a Content Working Group to lead systematic reviews and overviews of reviews to inform the 24-hour Movement Guidelines. The protocol was developed and registered *a priori* via a consensus process among working group members [International Prospective Register of Systematic Reviews (PROSPERO); Registration no. CRD42019121641]. The methods used in this overview were informed by *The Cochrane Handbook for Systematic Reviews of Interventions* and a scoping review that provided methodological guidance for conducting overviews (151,152). The reporting of this

review is consistent with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (153).

3.3.2 Search methods for identification of reviews

A comprehensive literature search was conducted in February 2019 and May 2019 by a librarian with expertise in systematic reviews (ARW) (Appendix B1). The following electronic databases were searched: core health and medicine databases (MEDLINE and EMBASE – Ovid interface); specialized databases (Cochrane Controlled Register of Trials, Cochrane Database of Systematic Reviews – Ovid interface, Cumulative Index to Nursing and Allied Health Literature – Ebsco interface); and a multidisciplinary database (Web of Science Core Collection – Clarivate interface). Other potential databases (e.g., Scopus) were not considered due to workload, time management, and duplications with selected databases. The literature searches were restricted to published papers in English or French language, and limited to studies involving humans aged 18 years or older. The search was limited to systematic reviews that were published within the past 10 years (February 2009 to May 2019), but there were no date restrictions for primary studies within the reviews. The 2009 cut-off was selected to manage scope, and also because reviews in the last 10 years would include the most recent body of evidence. Bibliographic records resulting from the search were imported into a reference management software (Covidence, Veritas Health Innovation, Melbourne, Australia). The full search strategy can be accessed via this link: https://qspace.library.queensu.ca/handle/1974/27648.

3.3.3 Inclusion criteria for reviews

3.3.3.1 Study design

Published or in press peer-reviewed systematic reviews as defined by the Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0, Chapter 1.2.2 (http://handbook-5-1.cochrane.org/) were eligible for inclusion (151). Systematic reviews must have searched at least two relevant databases and provided a keyword or search strategy. Justifying language restrictions was not required, so long as the review included publications in English or French. Some or all of the primary studies contained

in the systematic reviews must have been randomized controlled trials (RCTs) or cohort studies. If only a subset of the primary studies contained within an included systematic review met the eligibility criteria then only that subset of studies was included in the overview. Systematic reviews with or without meta-analyses were eligible.

3.3.3.2 Population

The population of interest was healthy community dwelling adults aged 18 years and older. We excluded studies of individuals who were pregnant, residents in long-term care, patients in acute care or a hospital setting, people who were unable to move under their own power, and elite athletes (e.g., varsity/provincial level athletes or Masters' athletes). We also excluded studies that exclusively targeted a disease-specific population (e.g., prospective cohort studies that only studied participants who had heart disease at baseline), with the exception of adults with obesity, adults with metabolic syndrome, or adults who had one or more falls in the past year. Reviews of mixed populations (i.e., with primary studies of individuals who met and did not meet the eligibility criteria) were eligible for inclusion if the results pertaining to the population of interest were reported separately. If results for the population of interest were not reported separately, studies with a mixed population were eligible if 80% or more of the study population, as described above, met the inclusion criteria (or if the sample average met the criteria). For example, a systematic review with no sub-group analyses that included some studies from the general population, and some from disease-specific populations, was eligible if 80% or more of participants in the systematic review were from primary studies performed in the general population.

3.3.3.3 Intervention and comparators

The intervention of interest was RT. The RT program was required to meet the definition provided by the Prevention of Fall Network Europe (ProFaNE) Taxonomy: "contracting the muscles against a resistance to 'overload' and bring about a training effect in the muscular system. The resistance is an external force, which can be one's own body placed in an unusual relationship to gravity (e.g. prone

back extension) or an external resistance (e.g. free weight)." (68). Systematic reviews needed to state that RT was used as the intervention or exposure; measurement of or reporting on the actual training done was not required. For systematic reviews that included primary experimental studies, the interventions must have targeted RT exclusively and not multiple exercise types or health behaviors (e.g., both RT and aerobic exercise, or both RT and diet). If there were no systematic reviews for an outcome where the intervention was exclusively RT (or where there was a subgroup or sensitivity analysis with RT only, or the data from individual studies were reported separately), we considered reviews where 80% or more of the included studies examined RT only. All exercise settings were accepted (e.g., home exercises, exercises performed at centres outside the home). In addition, the interventions could have been provided in a group setting or one-on-one. Comparators included placebo/no intervention or different doses (i.e., frequency, intensity, time) or types of RT programs (e.g., free weight programs, body-weight exercises, power training, isometric training).

3.3.3.4 Outcome measures

The outcomes were selected based on relevance and were chosen *a priori* via a consensus process among Content Working Group members (52). The outcomes were prioritized into critical and important measures as per the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach (154). The critical outcomes were: mortality, physical functioning (e.g., muscle strength, physical performance), health-related quality of life, and serious and non-serious adverse events (AEs). Our original protocol included the outcome "function and disability". We revised the name, but not the concept of the outcome to "physical functioning" to better capture the concept we were referring to using language from the International Classification of Functioning, Disability and Health framework (155). The following were selected as important outcomes: incident cardiovascular disease (CVD), incident type 2 diabetes mellitus, incident depression or other mental health (e.g., anxiety, psychological distress), brain health (e.g., incident neurodegenerative disease such as Alzheimer's disease or Parkinson's disease), cognitive function (e.g., attention, memory, problem

solving), incident cancer, fall-related injuries or falls, and bone health (e.g., osteoporosis, bone mineral density, incident fractures). We considered indirect indicators (e.g., blood pressure as an indirect marker for the outcome "incident CVD") only if no data on any of the above-mentioned outcomes were available.

3.3.4 Data collection and analysis

3.3.4.1 Selection of systematic reviews

Using Covidence (Veritas Health Innovation, Melbourne, Australia), de-duplication of records was first performed and then there were two levels of screening to select systematic reviews that met the inclusion criteria. For Level 1 screening, titles and abstracts were screened by two independent reviewers (RE and MP). Full text copies of all articles deemed potentially eligible by at least one reviewer during Level 1 screening were obtained for Level 2 screening. During Level 2 screening, the same two reviewers (RE and MP) independently reviewed the full-text documents and any supplementary materials (e.g., online appendices, published protocols) to ensure reviews met the eligibility criteria. Disagreements were resolved by consensus and all reasons for excluding full-text reviews were documented.

We used the "Assessing the Methodological Quality of Systematic Reviews 2" (AMSTAR 2) tool to assess study quality, and systematic reviews that did not receive a "yes" or "partial yes" for items 4 (adequacy of literature search) and 9 (risk of bias from individual studies being included in the review) were excluded as these characteristics were considered critical flaws (156). We planned to select one review per outcome to avoid overlap in primary studies between multiple eligible reviews. Therefore, once we identified all of the reviews that met the eligibility criteria, they were further screened to identify the review to include per outcome. First, studies that reported direct outcome measures were prioritized over studies that reported indirect markers of the outcome. It was possible for one selected review to be used for more than one outcome measure if it was considered the highest quality review available for each outcome examined. If no systematic reviews reported on a critical or important

outcome, then systematic reviews reporting on the most pertinent indirect marker of the outcome were included (e.g., for CVD, blood pressure was prioritized over lipid profile). We prioritized muscle strength over muscle mass, although some organizations consider muscle mass to also be an indirect outcome related to bone health, cardiovascular or diabetes risk (157,158).

If multiple reviews reported an outcome, we prioritized reviews that examined the effect of population age (i.e., if the effects were different in adults aged 18-64 years versus aged ≥65 years) or exposure dose or dose-response profile (i.e., frequency per week, or intensity of exercise) or type (e.g., power training, traditional strength training) on the estimate of effect. If there was more than one review that addressed these criteria, we selected the review that was of highest quality based on full AMSTAR 2 assessment. If there were multiple reviews of high quality we prioritized the most recent review. If a review did not address, or addressed only one of population age, exposure dose or exposure type, we considered whether estimates of effect from more than one review could be included to address whether the effect varied with age, dose or type of exposure. For example, if no reviews assessed the effect of age, we considered including estimates of effect from one systematic review that included adults aged 18-64 years, and an estimate of effect from a second systematic review that included adults aged 65 years or older. The same strategy was applied for "exposure" and "dose-response". If there were no reviews that considered age, exposure dose/type or dose-response, we included the most comprehensive systematic review (defined as having the highest number of included, relevant primary studies) that addressed the outcome of interest.

If estimates of effect from more than one systematic review had to be included for a given outcome (i.e., to be able to evaluate the effect of age, exposure dose or type), we assessed and reported on the degree of overlap in primary studies between systematic reviews using the corrected covered area (CCA) (159). The extent of primary study overlap among the systematic reviews was interpreted as either slight (0-5), moderate (6-10), high (11-15) or very high (>15) (159).

3.3.5 Data extraction and management

Data extraction was completed by one reviewer (RE) and verified by another reviewer (LG). Data-extraction forms were designed *a priori* to collect the following information from the included systematic reviews: author, publication year, study designs and number of primary studies included, pooled sample size, countries of primary studies, age, intervention, comparator, outcome, main findings, and quality of evidence as reported by the authors. Information related to intervention frequency, training volume or intensity was extracted, where available.

If the systematic review pooled studies that did and did not meet our inclusion criteria, but the results pertaining to studies that met our criteria were reported separately (e.g., as primary studies in a forest plot), the results from the primary studies were extracted (and the results from the pooled analysis not extracted). Whether the review reported differences by age, sex, race/ethnicity, socioeconomic status, chronic disease and weight status was extracted. Where multiple models were reported in systematic reviews, results were extracted from the most fully-adjusted model. If this included adjustment for the other movement behaviours (e.g., sedentary behaviour, sleep), results were also extracted from the most adjusted model that was not adjusted for the other movement behaviours to examine the effect of adjustment (this information was recorded separately to avoid double counting). If data were presented for the complete sample as well as by subgroups of interest, both sets of data were extracted but were recorded separately to avoid double counting. Reviewers were not blinded to the authors or journals when extracting data.

3.3.6 Assessment of methodological quality of included reviews

3.3.6.1 Quality assessment of included systematic reviews

Two reviewers (MP and TJ) independently assessed the methodological quality of each systematic review using the AMSTAR 2 rating scale. All assessments were verified by a third reviewer (RE). The included systematic reviews were categorized as "high", "moderate", "low" or "very low" quality based on the AMSTAR 2 criteria (156). We considered the following items non-critical: 2 (pre-registration

of protocol), 3 (explanation of included study designs), 7 (justification for exclusion of individual studies), and 10 (reporting sources of funding for individual studies). The item on conflict of interest, required that conflict of interest for the systematic review and all primary studies be assessed. We modified this item to assess whether potential conflict of interest was documented only for the review itself.

3.3.6.2 Quality assessment of primary studies within included systematic reviews

Once reviews were selected for inclusion, we extracted information on the tools used to assess the quality of primary studies by the authors of the systematic reviews and the outputs of those assessments. The information was reported as indicated by the systematic review authors (e.g., "the authors concluded that the evidence was low to moderate quality").

3.3.7 Strategy for data synthesis

We summarized the data via narrative synthesis, grouped by outcome. Data from reviews of observational studies were presented separately from that of reviews of RCTs, where possible. Results were described as reported by the systematic review authors, such as reporting available summary estimates and confidence intervals. We reported both pooled estimates and results from primary studies that were not included in pooled estimates but described in systematic reviews. We presented the results outlining the benefits and harms of RT in summary of findings tables (Table 3.1 and Table 3.2). We used the GRADE process to assess the strength of evidence available for each outcome.

If there were no systematic reviews for a critical outcome for which 80% or more of the participants met the population inclusion criteria, then we selected the review with the highest number of primary studies involving the population of interest, and only the data from the relevant subset of studies were synthesized. A meta-analysis using fixed effects was performed with the data that were sufficiently homogeneous in terms of statistical, clinical, and methodological characteristics using Review Manager Software 5.3. Funnel plots were used to assess publication bias. If studies were deemed not appropriate

for a meta-analysis, qualitative synthesis structured around the type of health indicator was conducted and the results were presented narratively.

3.3.8 Analysis of subgroups or subsets

We presented a narrative description of any subgroup analyses included in the systematic reviews, involving short-term versus long-term effects of RT, or pertinent subgroup-specific findings (e.g., differences according to age, sex, race/ethnicity, socioeconomic status, and weight status, or differences related to frequency or intensity of RT). We planned to summarize any reported analyses exploring potential sources of heterogeneity in the effect estimates, but no studies reported this.

3.4 Results

3.4.1 Included reviews

The search identified 2089 records after duplicates were removed (Figure 3.1). Titles and abstracts were initially screened which lead to 375 full-text articles that were assessed for eligibility. 344 articles were excluded since they did not meet the inclusion criteria, and then an additional 20 articles were excluded when the reviews were prioritized within each outcome (Appendix B2). A total of 11 systematic reviews were included in this overview paper (Tables 3.1 and 3.2). Across all systematic reviews, there were 364 primary studies [322 RCTs (no RT as a control group), 31 randomized trials that were comparing different doses of RT (e.g., comparing low versus high intensity RT), 10 cohort studies, and 1 crossover study] involving 382,627 unique participants (12,613 participants from experimental studies and 370,014 from observational studies) from 28 countries.

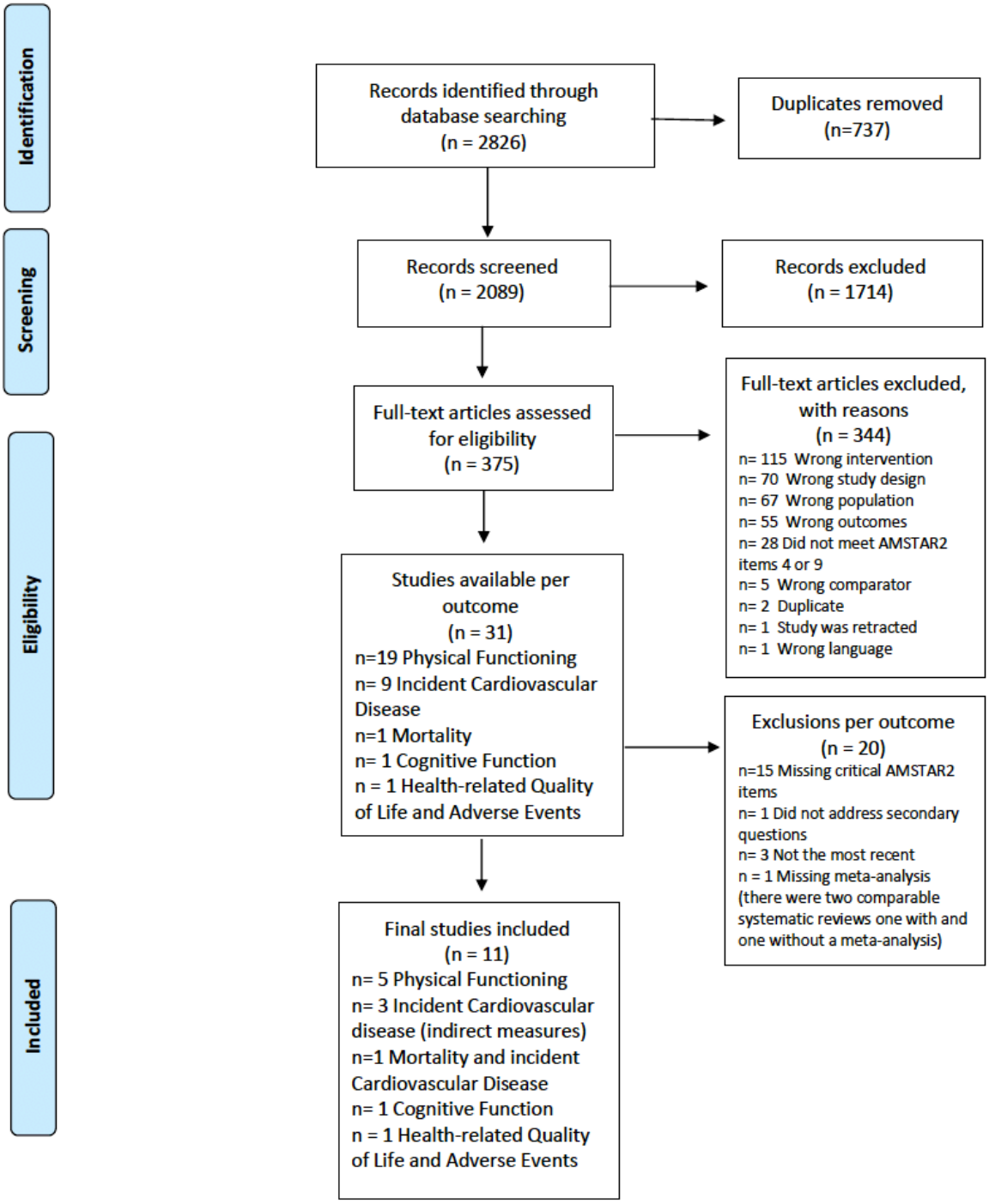

Figure 3.1 PRISMA flow diagram for the identification, screening, eligibility, and inclusion of reviews

3.4.2 Data synthesis

3.4.2.1 Critical outcomes

3.4.2.1.1 Mortality

One systematic review mainly comprised of cohort studies (1 RCT, 10 cohort studies) in 370, 256 adults aged 18-75 years from 2 countries was selected (160). Compared with no RT, performing RT was associated with 21% lower risk of all-cause mortality [hazard ratio (HR): 0.79, 95% CI :0.69–0.91] and a borderline but not statistically lower risk of CVD mortality (HR: 0.83, 95% CI: 0.67–1.03) (160). RT was not associated with cancer mortality (HR: 0.81, 95% CI: 0.54–1.20) (160). The included systematic review conducted subgroup analysis to compare the effect of RT frequency per week (low: 1 or 2, moderate: 2-5, and high: ≥ 5 sessions per week) versus no RT. Performing 1 to 2 sessions of RT was associated with lower all-cause mortality (HR: 0.79, 95% CI: 0.66–0.95), but the effects of more than two sessions of RT per week were not statistically significant (2-5 sessions per week, HR: 0.85, 95% CI: 0.69–1.06; ≥ 5 sessions per week, HR: 1.07, 95% CI: 0.90–1.26) (160). Also, the meta-analysis showed that performing RT ≥ 2 times a week was not statistically significantly different from <2 times a week in terms of all-cause mortality (HR: 1.00, 95% CI: 0.89–1.11) (160). Using the Cochrane Collaboration tool, within-study risk of bias was rated by the systematic review authors as "low to moderate" in all of the included primary studies except one that was "moderate" (160). The AMSTAR 2 assessment of the systematic review was rated as "moderate". Overall, the certainty of evidence was considered "low" due to potential risk of bias, because the results were mostly based on observational studies, there was no evidence of a dose-response effect, and because of the presence of heterogeneity across studies.

3.4.2.1.2 Physical functioning

To assess the effect of RT on physical functioning, a total of 5 systematic reviews were selected since each addressed a different component of the research question (e.g., type, frequency or duration of RT) (161–165) (Table 3.1). Physical functioning was assessed via muscle strength [5 studies reported 1

repetition maximum (RM) using various exercises (161–165); 1 study reported maximal voluntary contraction (163)], and physical performance [1 study administered a chair-stand test (165)].

Ralston et al. (2018), comprised of 12 studies [2 RCTs, and 10 randomized trials without a control group (i.e., comparing different frequencies of RT interventions)], examined the effect of RT frequency on muscle strength in 299 adults aged 40 ± 19.9 years from 5 countries. The results showed no differences pre vs. post-intervention in muscle strength gain (1 RM) between low frequency (1 day per week) and high frequency (at least 3 days per week) [mean effect size (ES): ES: 0.03, 95% CI: - 0.20–0.27] of equal volume (i.e., number of repetitions and sets) (161). However, the effect of low and high frequency may depend on whether the RT exercises involve the upper or lower body [Upper body: Muscle strength gain was statistically significantly greater when high frequency was compared with low frequency (mean ES: 0.48, 95% CI: 0.20–0.76); Lower Body: There was no statistically significant difference in muscle strength between high and low frequency (mean ES: 0.21, 95% CI: - 0.55–0.13)] (161). Risk of bias was assessed using the Physiotherapy Evidence Database scale and the authors reported that the scores ranged from 4-6; scores ≥ 4 were considered to have adequate internal validity and were included in the systematic review analysis (161). No further interpretation of the scores was provided by the authors. The AMSTAR 2 assessment was rated as "high".

Cirer-Sastre et al. (2017) investigated the effect of different types of RT programs in 10 RCTs enrolling 409 participants from 5 countries and found that eccentric exercise (vs. concentric and isometric) and performing a prescribed number of repetitions (vs. performing repetitions to failure) resulted in greater muscle strength (maximal voluntary contraction) improvements (ES: 1.05, 95% CI: 0.56 –1.52 and ES: 0.74, 95% CI: 0.55–0.93, respectively) in people who were 14-50 years of age. In general, using the Cochrane Collaboration bias assessment tool, the included primary studies were considered to have a high risk of bias when assessed by the systematic review authors (163). The AMSTAR 2 assessment was rated as "moderate".

Davies et al. (2017) studied the effect of fast vs slow-moderate speed progressive RT in 15 studies (8 RCTs and 7 non-RCTs) involving 509 participants from 5 countries and reported no differences in

muscle strength (1RM) between the two protocols when assessed in adults aged 19–73 years. Using the Downs and Black quality assessment tool, the mean quality of the primary studies was rated as "good" by the systematic review authors (164). The AMSTAR 2 assessment was rated as "moderate".

Muñoz-Martínez et al. (2017) identified 8 studies (6 RCTs, 2 randomized trials that were comparing different types of RT programs), enrolling 237 participants from 4 countries examined the effect of circuit progressive RT on muscle strength in adults 21-36 years of age. The results showed greater muscle strength improvements in participants who engaged in circuit RT three times a week in comparison to no RT (ES: 1.15, 95% CI: 0.64–1.24). Greater muscle strength improvements were observed in exercise sessions that were less than 60 minutes in duration versus ≥60 min (ES: 1.27 and 0.41, respectively) and performed at a low versus high intensity (ES: ≥ 60% 1 RM = 0.56; <60% 1 RM = 1.75) (162). However, the systematic review authors cautioned that there was lack of homogeneity among the groups and therefore inferences about duration and intensity should be interpreted with caution (162). There were no differences in muscle strength gains when comparing the total number of exercise sessions for the whole intervention or the duration of the RT program (162). The systematic review authors assessed methodological quality of the primary studies using the Physiotherapy Evidence Database scale and reported an overall average score of "moderate" (6.6 out of 11 points) (162). The AMSTAR 2 assessment was rated as "moderate".

Lai et al. (2018) included 21 RCTs (N=18 of muscle strength and N=5 for physical performance) involving 875 participants from 8 countries examined muscle strength and physical performance among older adults (age range 68-92). A minimum of 6 weeks RT improved muscle strength [1RM, mean difference (MD): 12.8 kg, 95% CI: 8.5–17.0)] and physical performance (Chair-stand test, MD: 2.6 more chair stands, 95% CI: 1.3–3.9) compared with usual care. Using the Cochrane Collaboration tool, the overall risk of bias of the included primary studies was considered "low" or "unclear" by the systematic review authors (165). The AMSTAR 2 assessment was rated as "moderate".

There was a "slight"' (CCA= 4) degree of overlap between Cirer-Sastre et al. (2017) and Davies et al. (2017), but the review authors used the same primary study to address different secondary research questions (i.e., concentric vs. eccentric vs. isometric RT, and fast vs. slow RT, respectively). For the physical functioning outcome, the quality of evidence of the included primary studies ranged from "low" to "moderate" as reported by the systematic review authors, and the quality of the systematic reviews ranged from "moderate" to "high" as assessed by AMSTAR 2. Overall, there was "moderate" certainty in the evidence due to potential risk of bias.

3.4.2.1.3 Health-related quality of life

We were unable to find a systematic review that met our inclusion criteria for the effect of RT on health-related quality of life. Since health-related quality of life was a critical outcome, we selected a systematic review that had the highest percentage of primary studies that met the inclusion criteria (166) (62% of the primary studies met the inclusion criteria; 4.96% of the primary studies that met the inclusion criteria assessed health-related quality of life) and we re-analyzed only that subset of data (Appendix B3). The re-analysis was based on 6 RCTs from 3 countries involving a total of 357 older adults (mean age range: 68 to 84.8 years) (166). Health-related quality of life was assessed using the physical function domains in the Short Form Health Survey 36-item or 12 item, and pain and vitality domains in the Short Form Health Survey 36-item. There was no statistically significant effect of RT on any of the health-related quality of life domains (Physical function, standardized MD: 0.19, 95% CI: -0.04–0.42; Pain, standardized MD: 0.03, 95% CI: -0.30–0.37; and vitality, standardized MD: 0.12; 95% CI -0.21–0.45) compared to no RT. Based on the findings of one primary study, there were no differences in pain or vitality scores when comparing high vs. low intensity RT [MD: -0.21, 95% CI: -0.97 – 0.55 and MD: 5.40, 95% CI: -0.85 – 11.65, respectively) (166). The systematic review authors used the Cochrane Bone, Joint and Muscle Trauma Group's evaluation tool and indicated that all of the included primary studies were of poor methodological quality (166). The AMSTAR 2 assessment was

rated as “low”. Overall, the certainty of evidence was considered “very low” due to risk of bias, imprecision, and inconsistency.

3.4.2.1.4 Adverse events

We were unable to identify a systematic review that met the inclusion criteria and thus we selected a systematic review that had the highest percentage of primary studies that were eligible for the AE outcome (25.6% of the primary studies that met the inclusion criteria assessed AEs; 56.2% of the studies provided comments on AEs). Out of 121 RCTs identified by Liu and Latham (2009), we included 31 RCTs (Appendix B4) from 8 countries, involving a total of 1687 people with an age range from 50–93 years. Out of the 31 RCT studies, 21 reported non-serious AEs, 4 reported serious AEs, 6 reported that no AEs occurred, 3 studies had no comments at all on AEs, and 5 provided a vague description of the AEs so it was unclear whether they were serious or not (166). For the 21 studies that reported non-serious AEs, 14 studies reported musculoskeletal AEs (e.g., muscle strain, bruising, or joint pain), 3 studies reported falls, 2 studies reported cardiovascular reactions (e.g., angina, dyspnea, fainting), and 3 studies reported aggravation of already existing injuries. For the 4 studies that reported serious AEs in the intervention group, one was related to the intervention (inguinal hernia occurred during strength testing and required surgical repair), 2 were not related to the intervention (1 clavicle fracture, and 1 hip fracture) and one was unclear (death due to myocardial infarction). There were 2 studies that reported serious AEs in control group (3 wrist fractures). Generally, AEs were not consistently monitored or reported, and serious AEs were not common. The systematic review authors used the Cochrane Bone, Joint and Muscle Trauma Group's evaluation tool and indicated that all of the included primary studies were of poor methodological quality (166). The AMSTAR 2 assessment was rated as “moderate”. Overall, the certainty of evidence was “very low” due to risk of bias, imprecision, and inconsistency.

Table 3.1 Overview of key systematic reviews that examined the relationship between resistance training and *critical* health outcomes in adults

Author (year)	Study Designs and Numbers of Primary Studies Included	Population	Intervention / Exposure and Comparison	Outcome Measure	Main findings	Quality of Evidence	AMSTAR Rating and Rationale
Outcome: Mortality							
Saeidifard (2019)	Systematic review and meta-analysis of randomized controlled trials (RCTs) and cohort studies N=11 included in the meta-analysis (1 RCT, 10 cohort studies)	N= 370,256 from 2 countries (USA, Canada) Age: 18-75 years	**Intervention:** The mean follow-up for all of the included studies was 8.85 years RT was self-reported in the 10 cohort studies (91%). **RT intervention** details for the 1 RCT: two sets of 8–12 repetitions of nine different exercises at 60%–70% of estimated 1-repetition maximum (RM). Resistance increased by 10% when participants completed > 12 repetitions. **Comparator** (for cohort and RCT studies): No RT	**Mortality**: all-cause, cardiovascular mortality, and cancer mortality.	21% lower all-cause mortality in those who participated in RT compared to those who did not (HR: 0.79, 95% CI:0.69–0.91) . No statistically significant association with cardiovascular mortality in those who participated in RT compared to those who did not (HR: 0.83, 95% CI: 0.67–1.03). No statistically significant association with cancer mortality in those who participated in RT compared to those who did not (HR:	Used Cochrane tool to assess risk of bias. Within-study risk of bias was low to moderate in all of the included studies, except one that was moderate. Two studies had serious-to-critical risk of bias, one in the 'blinding' domain and one in the 'selection of the reported result' domain. In some domains, some studies had an unclear risk of bias or not enough information was provided in the study to make a judgement.	**MODERATE**[a] Non-critical weaknesses: No explanation for study design selection for inclusion in the review Sources of funding not reported for included primary studies

					0.81, 95% CI: 0.54–1.20) **Dose-exposure:** >0 to 2 sessions/week of RT was associated with lower all-cause mortality than no RT (HR:0.79, 95% CI: 0.66–0.95) 2–3 sessions of resistance training per week was not statistically significantly different from lower frequencies of RT in terms of all-cause mortality (HR: 1.00, 95% CI: 0.89–1.11)		
Outcome: Physical Functioning							

Ralston (2018)	Systematic review and meta-analysis of randomized trials (RANs; i.e., no control group) and RCTs N=12 included in the meta-analysis (2, RCT, 10 RAN)	N = 299 from 5 countries (Australia, Brazil, Canada, Iran, and USA) Age: 40 ± 19.9 years	**Intervention:** RT program length ranged from 8 to 24 weeks (mean 10.5 ± 4.75 weeks), frequency ranged from 1 to 3 days per week[b] and the exercise repetition ranged from 3 to 15 repetitions. Number of sets ranged from 1 to 8 sets. **Comparator:** Control not included in the 10 RAN studies; comparing different frequencies of RT. 1 RCT did not specify the control, 1 RCT used no RT as the control.	**Muscle Strength** was assessed using 1RM (squat, bench press, lat pulldown, tricep press, bicep curl, lateral raise, chest fly, leg curl, seated dip, leg extension, hack squat, tricep pulley), 3-5 RM (leg press, chest press), and max elbow extensor torque	Volume-equated pre- to post-intervention strength gain was not significantly different when low frequency (LF; 1 day per week) was compared to high frequency (HF; ≥ 3 days per week) (mean ES: 0.03, 95% CI: -0.20–0.27) Upper body pre- to post-intervention strength gain was greater when HF was compared with LF (mean ES:0.48, 95% CI: 0.20–0.76) with significant differences between frequencies. Upper body pre- to post-intervention strength gain was not significantly different when medium frequency (MF; 2 days per week) was compared with LF (ES: 0.12, 95% CI: -0.22–0.47). There was no significant difference in lower body strength gain mean ES between HF and LF (mean ES:0.21, 95% CI: - 0.55–0.13).	Risk of bias was assessed using the Physiotherapy Evidence Database (PEDro) scale. The scale has 11 criteria, with a maximum score of 10 (the first item is a yes/no question). Total PEDro scores ranged from 4-6 across the included primary studies.	**HIGH** Non-critical weakness: Sources of funding not reported for included primary studies

Cirer-Sastre (2017)	Systematic review and meta-analysis of RCTs N=10 included in the meta-analysis	N= 409 from 5 countries (Australia, Canada, Finland, Norway, USA Age: 14[c]-50 years	**Intervention:** Isometric, concentric and eccentric or mixed unilateral strength training programs. Mean intervention duration 6.3 ± 2.31 weeks, mean frequency 3.5 ± 0.7 per week. In two studies, subjects completed 1-3 sets and performed the maximum number of repetitions to failure, which were considered fatigue protocols. The remaining 8 organized the training protocol in sets and repetitions, involving a mean volume of 4.4 ± 1.7 sets and 10 ± 3.5 repetitions. **Comparator:** The non-trained side	**Muscle Strength** was assessed using isometric MVC and 1RM arm curl	There was a statistically significantly higher, effect size observed in eccentric protocols (ES:1.05, 95% CI: 0.56 –1.52) than isometric and concentric. There was a statistically significantly higher, effect size found in protocols with sets of repetitions (ES:0.74, 95% CI: 0.55–0.93) compared to repetitions to failure.	Used the Cochrane Collaboration bias assessment tool. Overall, the included studies were considered to have a high risk of bias owing to the lack of blinding of participants and personnel or owing to the methodologies used to determine the limb dominance of the participants.	**MODERATE** Non-critical weaknesses: No explanation for study design selection for inclusion in the review Sources of funding not reported for included primary studies Did not assess the potential impact of RoB on the results No explanation for the heterogeneity observed
Davies (2017)	Systematic review and meta-analysis of randomized and non-randomized comparative studies N=15 included in	N= 509 from 5 countries (Australia, Brazil, Japan, Spain, USA) Age: 19-73 years	**Intervention:** Fast group in which the concentric and/or eccentric phase of each repetition was performed in ≤1 second or described as lifting with maximal concentric velocity (e.g., 'explosive')	**Muscle Strength** All studies tested dynamic muscular strength using the 1 RM (squat, bench press, leg extension, bicep curl, leg press, chest press,	There were no significant differences between fast and moderate-slow training when studies were restricted to low (<60% 1 RM, ES: -0.06, 95% CI: -0.45 – 0.32) or high intensities (≥80% 1	Downs and Black quality assessment tool was used. The mean quality of studies was rated as "good". The mean ± SD quality rating score was 20.8 ± 2.2 out of a possible score of 29.	**MODERATE** Non-critical weaknesses: No explanation for study design selection for inclusion in the review

	the meta-analysis (7 Non-RCT, 8 RCT)		**Comparator:** Moderate-slow group that performed repetitions (i.e., concentric plus eccentric phase) at a slower movement velocity or not intending to lift with maximal concentric velocity. Both fast and moderate-slow interventions used the same RT program: 1–6 sets of 2–13 repetitions at loads of either 30–95% 1 or 6–12 RM. Six studies stated that exercise was performed to concentric failure. Fast: explosive concentric phase (n=8 studies), w 1-s tempo concentric and eccentric phase 1- to 3-s tempo or instruction on "moderate-slow" (n=7 studies) Moderate-slow: concentric phase tempo of 1.7–3 s or with deliberate intent to reduce velocity, eccentric phase tempo of 1.7–3 s	dumbbell pull, hamstring curl).	RM, ES: -0.08, 95% CI: -0.41 – 0.25). **Age:** No significant effects were found between fast and moderate-slow training when studies were restricted to older adults (mean age ranged from 66.3 ± 4.8 years to 73.2 ± 4.6 years across 4 primary studies) (ES: 0.20, 95% CI: -0.17 – 0.57) and younger adults (mean age ranged from 19.9 ± 0.8 years to 30.3 ± 5.6 years across 10 primary studies) (ES: 0.02, 95% CI: -0.21 – 0.25).		Sources of funding not reported for included primary studies Did not assess the potential impact of RoB on the results

			or verbal instruction to be moderate-slow and controlled.				
Munoz-Martinez (2017)	Systematic review and meta-analysis of RCTs and RANs (i.e., no control group) N=8 included in the meta-analysis (6 RCT, 2 RAN)	N= 237 from 4 countries (Brazil, Iran, Spain, USA) Age: 21-36 years	**Intervention:** Resistance circuit training comprised single sets of several different exercises completed in succession, with little rest between exercises. **Comparator:** In the 6 RCT the control group was no RT. In the 2 RAN: one study was comparing 2 different types of resistance circuit training programs. The other study was comparing manual resistance training versus resistance circuit training.	**Muscle Strength** 1 RM bench press	There were statistically significant improvements in muscle strength among participants who performed resistance circuit training compared with no RT (ES: 1.15; 95% CI 0.64–1.24) **Dose-exposure:** There were statistically significantly greater changes in the workout sessions <60 min compared with those who exercised ≥ 60 min (ES: <60 min = 1.27; ≥60 min = 0.41). There were statistically significantly greater changes with low versus high training intensities (ES: ≥ 60% 1 RM = 0.56; <60% 1 RM = 1.75). There were no statistically significant differences found between the total	Used PEDro scale to assess methodological quality. The overall average score across primary studies was moderate (6.6 out of 11 possible points).	**MODERATE** Non-critical weaknesses: Did not specify inclusion criteria for comparator group No explanation for study design selection for inclusion in the review Data extraction was not performed in duplicate Sources of funding not reported for included primary studies

					number of exercise sessions (ES: ≥ 30 = 0.64, n=7; <30= 0.71, n=6) and duration of program (ES:≥10 weeks = 0.64; <10 weeks= 0.71).		
Lai (2018)	Systematic review and meta-analysis of RCTs N= 18 for muscle strength and N=5 for physical performance	N= 875 from 8 countries (Portugal, Denmark, Greece, Australia, Spain, Brazil, Japan, USA) Age: 68-92	**Intervention:** RT programs that are consistent with the American College of Sports Medicine recommendations for older adults. The included RT programs ranged in duration from 6 to 32 weeks, 1-4 sets, 8-30 repetitions, 40-80% 1RM, 1-4 days per week, and the number of exercises ranged from 2-8. **Comparator:** Usual care (including placebo-based interventions such as education or stretching).	**Muscle Strength:** 1 RM leg extension **Physical Performance:** Chair-stand test	RT (minimum of 6 weeks) was associated with a significantly greater improvement in muscle strength (1 RM leg extension) compared to usual care (MD: 12.8 kg, 95% CI: 8.5–17.0). RT (minimum of 6 weeks duration) was associated with a significantly greater improvement in physical performance (based on chair-stand test results) than usual care (MD: 2.6 times greater, 95% CI: 1.3–3.9). **Dose-exposure:** The meta-regression analysis found no evidence that effects on muscle strength or physical performance were affected by intervention duration.	Used the Cochrane Collaboration's tool. The overall risk of bias across primary studies was low or unclear.	**MODERATE** Non-critical weaknesses: Study selection was not performed in duplicate Data extraction was not performed in duplicate Sources of funding not reported for included primary studies Did not assess the potential impact of RoB on the results
Outcome: Health-Related Quality of Life							

Liu (2009)	Systematic review and meta-analysis of RCTs N= 6[d]	N= 357 from 3 countries (USA, Australia, Netherlands) Age: The mean age ranged between 68-84.8 years	**Intervention:** RT programs The RT programs ranged from 10-12 weeks in duration, 2-3 times per week, 8-16 repetitions, 1-3 sets, and 55-85% 1RM. **Comparator:** No exercise or different intensity of RT programs.	**Health-related quality of life** The physical function domains of the SF-36 or SF-12; pain and vitality of the SF-36.	We analyzed data from a subset of trials that met the inclusion criteria for population. There was no difference in the physical function domains of health-related quality of life between RT and control (SMD 0.19, 95% CI: -0.04–0.42, 6 studies). 3 out of the 6 studies assessed pain and vitality using SF-36; there was no differences between RT and control (SMD: 0.03, 95% CI: -0.30–0.37 and SMD: SMD: 0.12; 95% CI -0.21–0.45, respectively). **Dose-exposure:** There were no differences in pain or vitality scores for high intensity RT compared to low intensity (MD: -0.21, 95% CI: -0.97 – 0.55 and MD: 5.40, 95% CI: -0.85 – 11.65, respectively, 1 study).	The Cochrane Bone, Joint and Muscle Trauma Group's evaluation tool was used to assess risk of bias. Overall, the included studies were of poor methodological quality.	**LOW** Critical weakness: Did not perform graphical or statistical test for publication bias and did not discuss the likelihood or magnitude of impact Non-critical weaknesses: No explanation for study design selection for inclusion in the review Sources of funding not reported for included primary studies
Outcome: Adverse Events							
Liu (2009)	Systematic review of RCT N= 31[e]	N= 1687 from 8 countries (Greece, Australia, New	**Intervention:** RT programs. The intervention programs ranged in intensity from 20%-85% 1 RM, had the	**Serious Adverse events** Fracture, hospitalization or death.	3 studies had no comments at all on adverse events (AEs). 6 studied reported no AEs occurred. 5	The Cochrane Bone, Joint and Muscle Trauma Group's evaluation tool was used to assess risk of bias.	**MODERATE[f]** Non-critical weaknesses:

		Zealand, Finland, UK, Canada, USA, Netherland) Age: 50-93	frequency of 2- 3 times a week, performed 6-16 repetitions of 1-4 sets, and lasted between 8-52 weeks. **Comparator:** No exercise or different intensity, or types of RT programs.	**Non-serious Adverse Events**	studied provided a vague description of AEs: 2 studies indicated that no "significant adverse events" occurred but did not provide a further description. 1 study indicated that exercise-related injuries were infrequent without any further explanation. 2 studies indicated that there were injuries but did not specify what kind. 21 studies reported non-serious AEs: 14 studies reported musculoskeletal AEs (e.g., muscle strain, bruising, or joint pain), 3 studies reported falls, 2 studies reported cardiovascular reactions (e.g., angina, dyspnea, fainting), and 3 studies reported aggravation of already existing injuries. 4 studies reported serious AEs in intervention groups: Related: 1 inguinal hernia (during strength	Overall, the included studies were of poor methodological quality.	No explanation for study design selection for inclusion in the review Sources of funding not reported for included primary studies

					testing) requiring surgical repair Unclear: Death due to myocardial infarction Not-related: 1 clavicle fracture, 1 hip fracture. 2 studies reported serious AEs in control groups: 3 wrist fractures		

Abbreviations: AE, Adverse Events, AMSTAR, A MeaSurement Tool to Assess systematic Reviews; CI, Confidence Interval; ES, Effect Size; HF, High Frequency; HI, High Intensity; HR, Hazard Ratio; LF, Low Frequency; LO, Low Intensity; MD, Mean Difference; MF, Medium Frequency; MO, Moderate Intensity; MVC, Maximal Voluntary Contraction; PEDro, Physiotherapy Evidence Database; PT, Power Training; RAN, Randomized Trials; RCT, Randomized Controlled Trials; RM, Repetition Maximum; RoB, Risk of Bias; RT, Resistance Training; SF, Short Form Survey; SMD, Standard Mean Difference.

[a]The study was upgraded from "low" to "moderate" since the systematic review authors sent us the missing funnel plot (AMSTAR2 Item 15) and the results cannot be used to refute or deny any publication bias.
[b]Frequency defined as low (LF; 1 day per week), medium (MF; 2 days per week), or high (HF; ≥ 3 days per week).
[c]Only one study out of the nine was in people less than 18 years of age; met the 80% rule for population inclusion criteria.
[d]Only the primary studies that met the inclusion criteria were re-analyzed for this outcome.
[e]Only the primary studies that met the inclusion criteria interest were included for this outcome.
[f]The authors did not do a meta-analysis for adverse events and thus it was not rated down based on the missing critical item related to the meta-analysis.

3.4.2.2 Important outcomes

3.4.2.2.1 Incident cardiovascular disease

Four systematic reviews, one of which included a single relevant cohort study, were selected to assess the effect of RT on incident CVD (167–170). The three included systematic reviews assessed indirect markers of CVD (e.g., blood pressure) and more than one review was chosen since they addressed different components of the research question (e.g., effect of frequency, duration and type).

The systematic review by Saeidifard et al. (2019) identified only one primary study to examine the association between RT and incident CVD. The included primary study was a cohort study that included 44,452 men 40-75 years of age from the United States (167). Men who engaged in RT for 30 minutes or more had significantly reduced incident fatal coronary heart disease and non-fatal myocardial infarction by 23% compared with men who did not train with weights (167). The risk of bias in this cohort study was not assessed by the systematic review authors. The AMSTAR 2 assessment was rated as "moderate". There was "low" certainty in the evidence due to potential risk of bias and imprecision.

Ashton et al. (2018) included 173 RCTs, involving 6,169 participants from 28 countries ranging from 18-89 years of age. Both medium-term (7-23 weeks) and long-term (≥ 24 weeks) RT programs reduced systolic blood pressure (SBP) (MD: - 4.02, 95% CI: -5.92 – -2.11; MD -5.08, 95% CI: -10.04 – -0.13, respectively) and diastolic blood pressure (DBP) (MD: -1.73, 95% CI: - 2.88 – -0.57); MD: -4.93, 95% CI: -8.58 – -1.28, respectively) compared to habitual or no RT and that the effect was significantly greater in adults ≥ 41 years of age (170). The authors used the Cochrane Collaboration tool and indicated that the risk of bias ranged from "low" to "high" across the included primary studies (170). To assess the strength of evidence, the authors used GRADE and indicated that the score ranged from "very low" to "low" (170). The AMSTAR 2 assessment was rated as "moderate".

MacDonald et al. (2016) identified 64 studies (52 RCTs, 12 non-RCTs) enrolling 2,344 people with a mean age of 47.2 ± 19.0 years from 15 countries. The results indicated that moderate intensity (i.e., 65% – 70% 1RM), dynamic RT elicited small-to-moderate reductions in SBP and DBP [predicted

weighted mean effect size (d+) = -0.31, 95% CI: -0.43 – -0.19, -3.0 mm Hg; d+ = -0.30, 95% CI: -0.38 – -0.18, -2.1 mm Hg, respectively] compared to the no RT control group and the effect was significantly greater in individuals with higher resting blood pressure (169). Greater reductions in DBP relative to the control group were associated with performing RT at least 3 days a week vs. less than 3 days a week (d+ = -0.50, 95% CI: -0.76 – -0.23, -4.5 mm Hg; d+ = -0.10, 95% CIs: -0.31 – 0.11, -0.9 mm Hg, respectively) (169). The authors used a modified version of Downs and Black Checklist and indicated that the included primary studies were of "moderate" methodological quality (169). The AMSTAR 2 assessment was rated as "moderate".

Inder et al. (2016) identified 11 studies (10 RCTs, 1 crossover) enrolling 302 participants age 16-80 years from 3 countries. Isometric RT reduced SBP (MD: -5.20mmHg, 95% CI: -6.08 − -4.33), DBP (MD: -3.91mmHg, 95% CI: -5.68 − -2.14) and mean arterial pressure (MAP) (MD: - 3.33mmHg, 95% CI: -4.01− -2.66) compared to no RT. The effect of isometric RT was greater among participants who engaged in ≥ 8 weeks of training vs. less than 8 weeks of training (SBP, MD: -7.26mmHg, 95% CI -8.47 − -6.04 and MAP, MD: -4.22mmHg, 95% CI: -5.08 − -3.37; SBP, MD: -2.99mmHg, 95% CI: -4.25 to − -1.73, and MAP, MD:-1.85mmHg, 95% CI: -2.95 − -0.74, respectively), who were ≥45 years of age vs. less than 45 years of age (MAP, MD: -5.51mmHg, 95% CI: -6.95 − -4.06; MD: -2.72mmHg, 95% CI: - 3.49 to − -1.96, respectively), or who had hypertension vs. normotension (MAP, MD: -5.91mmHg, 95% CI: -7.94 − -3.87; MD: -3.01mmHg, 95% CI: -3.73− -2.29, respectively) (168). To assess the methodological quality of the included primary studies, the authors used the Tool for the Assessment of Study Quality and Reporting in Exercise scale and reported a median score of 10 out of 15 (168). The authors stated that a higher score indicated better methodological quality, but they did not provide any further interpretation of their score. The AMSTAR 2 assessment was rated as "moderate".

There was a "moderate"' (CCA=7) degree of overlap between Ashton et al. (2018) and MacDonald et al. (2016), but the review authors used the same primary studies to address different components of the research question (i.e., effect of RT duration or intensity). For the CVD outcome, the quality of evidence

of the included primary studies ranged from “very low” to “moderate” as reported by the systematic review authors, and the quality of the systematic reviews was “moderate” as assessed by AMSTAR 2. Overall, there was “very low-to-moderate” certainty in the evidence due to potential risk of bias, imprecision, and inconsistency.

3.4.2.2.2 Cognitive function

Cognitive function was assessed as a secondary outcome measure in one review (171). Raymond et al. (2013) included two RCTs that assessed cognitive function in 104 adults 61– 86 years of age from 2 countries. One RCT showed an improvement in cognitive function after moderate (55 – 65% 1RM) and high (75– 85% 1RM) intensities of RT 3 times a week compared to a control group that performed the same exercises but without overload and only once a week (172). However, the other RCT reported no RT treatment effects for neurocognitive function when compared to no RT (173). The systematic review authors assessed the methodological quality of the two primary studies using the Physiotherapy Evidence Database scale and reported a score of 5 and 6 out of 10; no further interpretation of the scores was provided (171). The AMSTAR 2 assessment was rated as “moderate”. Overall, the certainty of evidence was considered “very low” due to risk of bias, inconsistency and imprecision.

3.4.2.3 Other important outcomes

We identified no systematic reviews that met the inclusion criteria for the effect of RT on 6 important outcomes: incident type 2 diabetes mellitus, incident depression, brain health, incident cancer, fall-related injuries or falls, or bone health.

Table 3.2 Overview of key systematic reviews that examined the relationship between resistance training and *important* health outcomes in adults

Author (year)	Study Designs and Numbers of Primary Studies Included	Population	Intervention / Exposure and Comparison	Outcome Measure	Main findings	Quality of Evidence	AMSTAR Rating and Rationale
Outcome: Incident Cardiovascular Disease							
Saeidifard (2019)	Systematic review and meta-analysis Only one primary study (a cohort study) in this systematic review was relevant to the CVD outcome.	The population for the one cohort study included: N= 44, 452 from USA Age: 40-75 years	**Intervention:** Self-reported weight training per week **Comparator:** Self-reported no weight training per week	**Coronary heart disease** Newly diagnosed cases	The results of the cohort study showed a 23% risk reduction (RR: 0.77, 95% CI: 0.61 – 0.98) among men who trained with weights for 30 min or more per week compared with men who did not train with weights.	Used Cochrane tool to assess risk of bias. All of the included primary studies had a low overall risk of bias.	**MODERATE** Non-critical weaknesses: No explanation for study design selection for inclusion in the review Sources of funding not reported for included primary studies
Ashton (2018)	Systematic review and meta-analysis of RCTs N=173 included	N= 6,169 from 28 countries (USA, Iran, Norway, Denmark, India,	**Intervention:** Resistance training (RT) exercise interventions that are short-term, medium-term, and long-term.	**Indirect markers of CVD:** Systolic blood pressure (SBP), diastolic	Favourable reductions in SBP (Medium-term, MD: -4.02, 95% CI: - 5.92 – -2.11); Long-term, MD: -5.08, 95% CI: -10.04 – -0.13)	Risk of bias was assessed using the Cochrane Risk of Bias tool. The risk of bias ranged from "low"	**MODERATE** Non-critical weaknesses: No explanation for study design selection for inclusion in the review

	in the meta-analysis	Brazil, Canada, New Zealand, Italy, Spain, Germany, Australia, Ireland, UK, Greece, Turkey, Finland, Belgium, Japan, Switzerland, Korea, Taiwan, Portugal, South Africa, Sweden, Netherlands, Austria) Age: 18-89	RT programs mainly used weight machines (n=90 studies; 52%), a mix of free weights, bodyweight and machine exercises (n=43 studies; 25%), elastic resistance bands (n=13 studies; 8%), circuit exercises (n=12 studies; 7%), free weights (n=10 studies; 6%), ankle/leg weights (n=2 studies; 1%), isometric hand grip (n=2 studies; 1%) and isometric exercise with whole body vibration (n=1 study). The majority of interventions were supervised by an exercise professional (n=105 studies; 61%). One study reported data from an unsupervised intervention, and 13 (8%) used a combi- nation of supervised and unsupervised	blood pressure (DBP) and mean arterial pressure (MAP).	and DBP (Medium-term, MD: -1.73, 95% CI: -2.88 – -0.57); Long-term, MD: -4.93, 95% CI: -8.58 – -1.28) were apparent after medium-term and long-term term RT interventions compared to habitual or no RT. There were non-statistically significant effects for MAP after short-term and medium-term RT interventions compared to habitual or no RT. **Age:** When comparing healthy young adults ≤40 years (n=44) with healthy older adults ≥41 years (n=50), there were significant reductions in SBP with medium-term RT interventions for healthy older adults compared with healthy younger adults (MD: -4.36, 95% CI: -5.73 – -2.99 vs MD: -0.56, 95% CI: -1.57 – 0.44, respectively).	to “high” across the primary studies. The strength of evidence was assessed using The Grading of Recommendations Assessment, Development and Evaluation (GRADE). The strength of evidence ranged from very low to low across the primary studies.	Sources of funding not reported for included primary studies

			programmes. Fifty-four studies (31%) did not report the level of supervision. The duration of the intervention varied from ≤6 weeks (n=13), 7–23 weeks (n=129) and ≥24 weeks (n=31). The most common frequency of training was three sessions per week (n=110), followed by two sessions per week (n=36), though some studies required participants to complete the programme in one, four or five sessions per week (n=1, n=7 and n=5, respectively). The remaining studies stipulated either two to three sessions per week (n=8), three to four sessions per week (n=1) or did not report the frequency (n=5). **Comparator:**		In the healthy older adults, there were statistically significantly greater improvements in SBP, DBP, and MAP following medium-term interventions compared with younger adults for the same intervention duration. Statistically significantly greater improvements after long-term interventions were also apparent for DBP in healthy older adults ≥41 years compared with younger adults.		

			In the majority of studies, control participants were instructed to continue with their habitual activity (n=115/173) or were allocated to usual care (n=15). Three studies provided lifestyle advice to the control group and discussion about physical activity levels, but no structured/supervised exercise (n=3). Forty studies did not report the requirements of the control group.				
MacDonald (2016)	Systematic review and meta-analysis RCTs and non-RCTs N = 64 included in meta-analysis (52 were RCTs and 12	N = 2,344 from 15 countries (Australia, Belgium, Brazil, Canada, China, Denmark, Finland, India, Iran, Japan, Korea, Norway, Spain, South	**Intervention:** Dynamic RT was performed 2.8±0.6 days/week for 14.4±7.9 weeks using moderate loads/intensity that corresponded to 65% to 70% of 1 repetition maximum (1 RM), averaging 64.7±13.0% of 1 RM. RT programs generally targeted the whole body	**Indirect markers of CVD:** SBP and DBP	Moderate-intensity dynamic RT elicited small-to-moderate reductions in SBP (d+ = -0.31; 95% CI: -0.43 – -0.19, -3.0 mm Hg) and DBP (d+ = -0.30, 95% CI: -0.38 – -0.18, -2.1 mm Hg) compared to controls. Greater blood pressure reductions occurred among samples with higher resting SBP/ DBP: ~6/5 mm Hg for	Assessed using a modified version of the Downs and Black Checklist. It addresses 5 subscales of quality (i.e., reporting, external validity, bias, confounding, and power). The overall methodological quality was gauged as percentage of items satisfied out of a possible 29-point	**MODERATE** Non-critical weaknesses: No explanation for study design selection for inclusion in the review Sources of funding not reported for included primary studies No discussion of the source or impact of

	non-RCT)	Africa, Taiwan, Turkey, UK, USA) Age: 47.2 ± 19.0 years	(91%), but varied widely in their prescription of other acute program variables (e.g., RT protocols consisted of 1–5 sets/exercise of 5–30 repetitions/set for 1–16 RT exercises/session). On average, dynamic RT programs prescribed 2.8±0.9 sets of 11.0±3.8 repetitions for 7.9±2.9 dynamic RT exercises per session. One-fourth of studies (27%) failed to disclose the level of supervision during the dynamic RT intervention; of those that did, 63% reported direct supervision. The overall adherence to dynamic RT was high (92.3%±8.9%), but adherence was only reported in 65% of the studies. **Comparator:** Most interventions involved a non-		hypertension, ~3/3 mm Hg for prehypertension, and ~0/1 mm Hg for normal blood pressure. Greater DBP reductions occurred among studies that prescribed dynamic RT ≥3 (d+ = -0.50, 95% CI: -0.76 – -0.23, -4.5 mm Hg) versus <3 days/week (d+ = -0.10, 95% CIs: -0.31 – 0.11, -0.9 mm Hg)	total and was quantified as: low (≤14 points, <50%), moderate (>14–23 points, 50–79%), or high (≥24 points, ≥80%). Included studies achieved "moderate" methodological study quality (~63%), despite widely varying scores (41–85%). Studies were most likely to satisfy reporting (78.6%) and internal validity (bias=70.2% and confounding=51.5%) quality subscales, but least likely to satisfy external validity (46.5%) and power (9.2%). None of the subscales emerged as significant moderators in analyses; only 7 studies satisfied ≥80% of quality items (~83.3%).	heterogeneity on the results

			exercise/wait-listed control group (86%); 9 studies involved a "placebo" control/comparison group.				
Inder (2016)	Systematic review and meta-analysis of RCTs N = 11 included in meta-analysis (10 RCTs, 1 crossover)	N = 302 from 3 countries (Canada, UK, USA) Age: 16-80 years	**Intervention:** Isometric RT (IRT) Six studies used handgrip and five studies used leg exercise. 4 studies used unilateral contractions, 7 used bilateral. All interventions included 4 x 2 min contractions, separated by a rest period. Frequency: All were 3 days/week, with one study including an additional group at 5 days/week. Duration: Range of 3-10 weeks, with the majority of studies doing 8 weeks. **Comparator:** 5 studies did not specify the control, 1 did not have a	**Indirect markers of CVD:** SBP, DBP and MAP.	IRT reduced SBP (MD: -5.20mmHg, 95% CI: -6.08 − -4.33), DBP (MD: -3.91mmHg, 95% CI: -5.68 − -2.14) and MAP (MD: - 3.33mmHg, 95% CI: -4.01− -2.66) compared to no RT. **Age**: Subjects aged ≥ 45 years demonstrated larger reductions in MAP (MD: -5.51mmHg, 95% CI: -6.95 − -4.06) than those < 45 years (MD: -2.72mmHg, 95% CI: - 3.49 to − -1.96). Subjects undertaking ≥ 8 weeks of IRT demonstrated a larger reduction in SBP (MD: -7.26mmHg, 95% CI -8.47 − -6.04) and MAP (MD: -4.22mmHg, 95% CI: -5.08 − -3.37) than those who performed less than 8 weeks of	Study quality was assessed by using the Tool for the assEssment of Study qualiTy and reporting in EXercise (TESTEX) scale. Median score was 10 out of a scale of 15 (higher score indicates better quality). Four studies scored 9 and seven scored 10.	**MODERATE** Non-critical weaknesses: Did not specify inclusion criteria for comparator group No explanation for study design selection for inclusion in the review Data extraction was not performed in duplicate Sources of funding not reported for included primary studies Did not assess the potential impact of RoB on the results

			control group, 4 had a non-exercising control, and 1 had the controls engage in a 10min weekly one-on-one session relating to hypertension.		training (SBP, MD: -2.99mmHg, 95% CI: -4.25 to − -1.73, and MAP, MD: -1.85mmHg, 95% CI: -2.95 − -0.74). Hypertensive participants in IRT demonstrated a larger reduction in MAP (MD: -5.91mmHg, 95% CI: -7.94 − -3.87) than normotensive participants (MD: -3.01mmHg, 95% CI: -3.73− -2.29).		
Outcome: Incident Type 2 Diabetes Mellitus							
No eligible systematic reviews were identified for this outcome.							
Outcome: Incident Depression							
No eligible systematic reviews were identified for this outcome.							
Outcome: Brain Health							
No eligible systematic reviews were identified for this outcome.							
Outcome: Cognitive Function							
Raymond (2013)	Systematic review and meta-analysis of RCT N = 2 RCT[a] included in the meta-analysis	N= 104 from 2 countries (USA, Brazil) Age: 61-86	**Intervention:** RT intervention program was provided in both studies (100%) Exercise interventions details: One study had 2 exercise groups: High intensity/low volume (EXH: 2 sets of 8 to 10 repetitions for 75	**Cognitive function** including short- and long-term memory, attention, mental arithmetic, and mirror drawing	One study reported improvements in cognitive functioning for both high and moderate training intensities (compared to a control group that performed the same exercises but without overload and only once a week) in some areas of cognitive testing (Digit Span Forward, Corsi BlockTapping Task	Physiotherapy Evidence Database (PEDro) scale was used to assess study quality. One study scored 6 out of 10 and the other 5 out of 10.	**MODERATE[b]** Non-critical weaknesses: No explanation for study design selection for inclusion in the review Study selection was not performed in duplicates

			to 85% of 1 RM) and low intensity/high volume (EXL: 2 sets of 14 to 16 repetitions for 55 to 65% of 1 RM). The EXH and EXL groups attended 3 supervised strength training sessions per week for 12 consecutive weeks. 12 weight machine exercises were used. The second study also 2 exercise groups: EMODERATE (50% 1RM) and EHIGH (80% 1RM). They attended three 1-hr sessions per week for 24 weeks. Sessions included a warm-up, stretching, and 6 exercises targeting main muscle groups. Participants worked in twos, one performing the exercise, the other counting the reps, taking note of breathing and technique.		Backward, similarities, Rey-Osterreith Complex Figure Immediate Recall), with no difference between intensities. This population had at least 8 years of schooling and a Mini-Mental State Examination score of ≥ 24 (out of 30). The other study reported no RT treatment effects for neurocognitive function when compared to no RT. The participants were healthy but sedentary older adults with at least a high school education.		Sources of funding not reported for included primary studies Did not assess the potential impact of RoB on the results No discussion on the impact of heterogeneity on the results

			Comparator: One study used no exercise as the control, the other study had their control group attend sessions at the centre 1x per week to do warm-up, stretching, and the same 6 exercises as the exercise group but without overload.				
Outcome: Incident Cancer							
No eligible systematic reviews were identified for this outcome.							
Outcome: Fall-related Injuries or Falls							
No eligible systematic reviews were identified for this outcome.							
Outcome: Bone Health							
No eligible systematic reviews were identified for this outcome.							

Abbreviations: AMSTAR, A MeaSurement Tool to Assess systematic Reviews; CI, Confidence Interval; DBP, Diastolic Blood Pressure; EXH, High Intensity/Low Volume; EXL, Low Intensity/High Volume; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; IRT, Isometric Resistance Training; MAP, Mean Arterial Pressure; MD, mean difference; PEDro, Physiotherapy Evidence Database; RCT, randomized controlled trial; RET, resistance exercise training; RM, Repetition Maximum; RR, Relative Risk; RT, Resistance Training; SBP, Systolic Blood Pressure; TESTEX, Tool for the assEssment of Study qualiTy and reporting in EXercise.

[a]Only 2 studies out of the 21 studies assessed cognitive function as a secondary outcome. The columns are all complete based on the findings of those two studies only.
[b]We did not downgrade for publication bias since only 2 studies assessed cognitive function as a secondary outcome

3.5 Discussion

This overview of reviews synthesized peer-reviewed evidence from 11 systematic reviews examining the association between RT and health outcomes in adults aged 18 years and older. The included systematic reviews were mainly comprised of RCTs (88%) involving a total of 382,627 unique participants from 28 countries. Across outcomes, the overall quality of evidence of the included primary studies ranged from "very low" to "moderate" as reported by the systematic review authors, and the quality of the systematic reviews ranged from "low" to "high" as assessed by AMSTAR 2. This overview showed that RT was favourably associated with a reduction in all-cause mortality, a reduction in incident CVD, a reduction in BP, and an improvement in muscle strength and physical function (e.g., chair-stand test). There was evidence that different doses and types of RT programs were associated with improving health outcomes. AEs in trials of RT were not consistently monitored or reported, but when they were, they were infrequent. In general, within community-dwelling healthy adults and older adults (age range:18-93) the benefits of RT outweighed the harms.

3.5.1 Benefits

We have "very low" to "moderate" certainty evidence to support that engaging in RT was favourably associated with health outcomes related to all-cause mortality, incident CVD, and physical functioning. The mortality data were mostly based on cohort studies that assessed the frequency of participation in RT via self-report (160). For instance, participants were asked to report how often in the past 30 days they engaged in muscle strengthening exercise (e.g., weight lifting, push-ups or sit-ups). Unfortunately, these cohort studies did not assess the intensity or duration of the RT sessions. Furthermore, our overview showed that RT alone was favourably associated with all-cause mortality, however other studies have demonstrated that RT in combination with aerobic exercise was also favourably associated with a reduction in all-cause mortality, in addition to cardiovascular (160) and cancer mortality (174).

The characteristics of RT programs may influence strength gains, but different types of programs may be effective. For example, circuit RT and RT programs that involved eccentric exercise or followed a prescribed number of repetitions were all shown to be effective for improving muscle strength (162,163). While we reported that RT was associated with lower incident CVD (167), data were from a cohort study that only included men, and RT was self-reported. However, RT was shown in this overview to be associated with a reduction in indirect markers of CVD such as blood pressure, which provides additional support for a favourable association between RT and cardiovascular health. Although we did not identify reviews that examined the effect of RT on some important outcome measures in healthy adults, RT has been shown to improve glycemic control in people with diabetes (175), and improve parkinsonian motor symptoms in individuals with early-moderate Parkinson's disease (176). Therefore, RT has a favourable effect on a number of health outcomes.

3.5.2 Effect of dose: Frequency, duration, intensity, and type

There was a variety of frequency, intensity and duration of RT programs reported in the included systematic reviews. Several studies suggested that engaging in at least 2 days of RT was associated with a reduction in all-cause mortality, an improvement in muscle strength, and a reduction in DBP (MacDonald et al., 2016; Ralston et al., 2018; Saeidifard et al., 2019). As for the other characteristics of the RT program, there were diverse findings across outcomes. The duration of RT interventions ranged from 3 to 52 weeks across all the systematic reviews. Lai et al. (2018) included only older adults (68-92 years of age) and demonstrated that individuals may start to achieve health benefits (e.g., muscle strength gain) after the first 6 weeks of a RT program. A large range of RT intensities (20%- 95% 1RM) were reported in the included studies. Low intensity RT was associated with improvements in muscle strength (162), and moderate to high intensity RT programs were associated with an improvement in muscle strength and physical performance (40-80% 1RM), as well as resting SBP and DBP (65-70% 1RM) (165,169).

The type of RT programs varied across primary studies. For instance, cohort studies used self-reported participation in any activities to strengthen muscles (e.g., sit-ups and push-ups), weight lifting, or activities using exercise machines or free weights. In contrast, RT interventions in RCTs were defined with variable prescribed sets, repetitions and intensity, where sources of resistance also varied widely and included weight machines, free weights, bodyweight exercises, elastic resistance bands, circuit exercises, ankle/leg weights, or isometric exercise. A consistent feature of RT interventions was that the activities required a high degree of effort, which was consistent with the American Physical Activity Guidelines (2018) that recommend a moderate or greater intensity of muscle strengthening activities (54).

3.5.3 Effect of age

There was no evidence that the effect of RT was different in adults aged 18-64 compared to older adults aged 65 years or older. Out of the 11 included systematic reviews, 7 were inclusive of adults greater than 65 years of age. There were 4 systematic reviews that included a range of young and older adults [18-75 years of age (N= 370, 256) (160); 19-73 years of age (N=15) (164); 18-89 years of age (N=6,169) (170); 16-80 years of age (N=302) (168)], and 3 systematic reviews that only included older adults [68-92 years of age (N=875) (165); mean age range of 68-84.5 years (N=357) for health related quality of life and 50-93 years of age (N=1,687) for AEs (166); 61-86 years of age (N=104) (171)]. Out of the 4 studies that included a range of young and older adults, 3 studies conducted subgroup analysis by age (164,168,170). We have low quality evidence (based on the included primary studies as rated by systematic review authors) that the effect of RT on blood pressure was greater in adults over the age of 40 compared to younger adults (168,170). Therefore, the effect of RT on health outcomes may not significantly differ based on age among the healthy population.

3.5.4 Harms

AEs were not consistently monitored or reported in RT studies. Studies either had no comment at all on AEs or provided a vague description regarding the frequency or nature of the AEs. Most of the studies only reported AEs if they occurred in the intervention group or if they were reasons for withdrawal. Similarly, a more recent systematic review involving RT demonstrated that 71.1% of the included primary studies made no comments at all regarding AEs (170). In studies of high intensity RT trials that included participants with health conditions or functional limitations, AEs were reported more often (177). Among healthy participants, however, non-serious AEs (e.g., muscle soreness or pain) were common whereas serious AEs (e.g., death or fractures) were uncommon. In general, there needs to be consistency in AE reporting across studies to determine the harms of RT.

3.5.5 Limitations

Limitations of this overview include the lack of evidence for some important outcome measures, methodological limitations of the primary studies within the systematic reviews and methodological limitations of the systematic reviews identified for the health-related quality of life and cognitive function outcomes. Out of the 8 important health outcome measures chosen, we were unable to identify systematic reviews for 6 outcomes (type 2 diabetes mellitus, depression or other mental health, brain health, cancer, fall-related injuries or falls and bone health).

The purpose of this overview was to look for evidence that would be generalizable to the general Canadian population and thus we did not include studies where the inclusion criteria specified the presence of a chronic disease. As a result, a possible explanation for the lack of information for certain important outcomes is that the effect of RT on these outcomes has only been examined in individuals at risk of those specific outcomes. For instance, many studies that used RT interventions to address diabetes or brain health included individuals with type 2 diabetes or Parkinson's disease, respectively. Furthermore, for some outcomes, the primary studies included in the systematic reviews were rated by

the authors as having “low” and even “very low” quality evidence. For example, all of the primary studies (N=6 RCTs) included in the health-related quality of life systematic review were rated as having “low” quality evidence (166). In addition, the synthesized results for the all-cause mortality outcome were mainly (90.9%) based on cohort studies that included self-reported data (160). Furthermore, one of the systematic reviews comprising of the greatest number of RCTs (N=173) across all reviews, included primary studies that ranged from “very low” to “low” quality evidence when examining the indirect markers of CVD (170). As for the quality of the included systematic reviews, the one identified for the health-related quality of life received a "low" AMSTAR rating. Also, the systematic review identified for cognitive function (assessed as a secondary measure) included only 2 RCTs with conflicting findings. Therefore, our overview showed uncertain evidence with respect to the effect of RT on health-related quality of life and cognitive function.

3.6 Conclusion

RT was associated with a reduction in all-cause mortality and incident CVD, and an improvement in muscle strength and physical function among community dwelling healthy adults aged 18 years and older. AEs related to RT were not consistently monitored or reported, but overall the benefits appeared to outweigh the harms. There was evidence that a variety of RT programs (e.g., different intensities, durations and types) were favourably associated with health outcomes.

Study 3

Adverse events (AEs) are not being consistently monitored or reported in resistance training (RT) studies. We took a multimethod approach to: 1) explore the experiences and perspectives of individuals with chronic health conditions who had an AE as a result of RT; 2) understand researchers' current practices and perspectives on AE reporting in RT, and identify barriers and facilitators of AE reporting; and 3) generate exercise-specific AE-reporting recommendations.

Chapter 4: Study 3 – Stage 1

Title: A Qualitative Study Exploring Participants' Perspectives on Adverse Events Due to Resistance Training

4.1 Overview

Objectives: The objective of this study was to explore the experiences and perspectives of individuals with chronic health conditions who had an adverse event (AE) as a result of resistance training (RT).

Methods: Web conference or telephone-based one-on-one semi-structured interviews were conducted with 12 participants with chronic health conditions (arthritis, heart disease, cancer, mood or anxiety disorder, hypertension, asthma, diabetes and osteoporosis) who had an AE as a result of RT. Interview data were analyzed using the thematic framework method.

Results: Six themes were identified: 1) personal experiences with aging influence perceptions of RT; 2) physical and emotional consequences of AEs limit activities and define future RT participation; 3) injury recovery defines severity of AE; 4) health conditions influence the perceived risks and benefits of participating in RT; 5) RT setting and trained supervision influences exercise behaviors and risk perceptions; and 6) experiencing a previous AE influences future exercise behavior.

Conclusions: Despite participant awareness of the value and benefits of RT in both the context of aging and chronic health conditions, there is concern about experiencing exercise-related AEs. The perceived risks of RT influenced the participants' decision to engage or return to RT. Consequently, to promote RT participation, the harms, not just the benefits, of RT should be properly reported in future studies, translated and disseminated to the public.

4.2 Introduction

According to a cross-sectional analysis of the Canadian Longitudinal Study on Aging, 32.5% of active older adults reported engaging in resistance training (RT) (178). Among older adults, the barriers to

participate in RT included pain, and the perceived risk of injury, heart attack, stroke, or death (179–182). Injuries can influence future participation or adherence in RT studies, so when participants are excluded because of injuries or poor adherence, it may provide an inflated estimate of the efficacy and an underestimate of harm (179–182). People with health conditions (e.g., osteoporosis) are not only interested in which exercises are considered effective at improving or managing their health condition, but also which are considered safe (181). Given that participants are concerned regarding adverse events (AEs) as a result of exercise, it emphasizes the importance of accurate AE reporting in RT studies.

An adverse event (AE) is defined by Health Canada as "Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product [or exercise] and which does not necessarily have to have a causal relationship with this treatment" (183). Despite the public's interest in safe exercise, AEs are inconsistently or not often reported in exercise trials involving healthy individuals or people with health conditions (84,166,184–188). Although AE reporting became more common after the Consolidated Standards of Reporting Trials (CONSORT) statement was released in 2001, there are still no recommendations or consensus as to what types of AEs to look for, when to report and how to classify AEs in exercise studies (84,177). Accurate reporting of AEs will determine whether benefits of RT outweigh the harms in individuals who are healthy and in people with common health conditions, and the absence of accurate AE reporting creates limitations when developing physical activity guidelines, especially when patients or clinicians may have concerns about the safety of RT (52,181,188,189).

Participants are involved in reporting AEs in exercise trials. For example, a descriptive comparative study examining the safety of endurance and RT during oncological treatment demonstrated that 20% of AEs were reported by the exercise trainers while 28% of AEs were self-reported by the participants (190). Furthermore, the potential for minor AEs (e.g., musculoskeletal issues or pain) to limit

functioning is underestimated and not often reported as an AE in RT studies, but they can be important to the participants who experience them (84,166,184–188). Therefore, it is critical to consider the participant perspective when examining AE reporting practice in exercise trials. In accordance with the Knowledge-To-Action framework, to improve AE reporting in RT studies we need to understand the participant viewpoint to appropriately select, tailor and implement interventions (90). Therefore, the objective of this study was to explore the experiences and perspectives of individuals with chronic health conditions who had an AE as a result of RT.

4.3 Methods

4.3.1 Context

This study is part of a multi-stage project; this study reports on stage 1 only (Figure 4.1). The study was conducted during the COVID-19 pandemic. Accordingly, all data were collected online or via telephone; there was no in-person data collection. The reporting for this study was informed by the Consolidated Criteria for Reporting Qualitative Research (191). All research activity was conducted according to the Tri-Council Policy Statement (http://www.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/). The study received ethics approval from University of Waterloo research ethics board (ORE # 42207). All participants provided informed verbal consent.

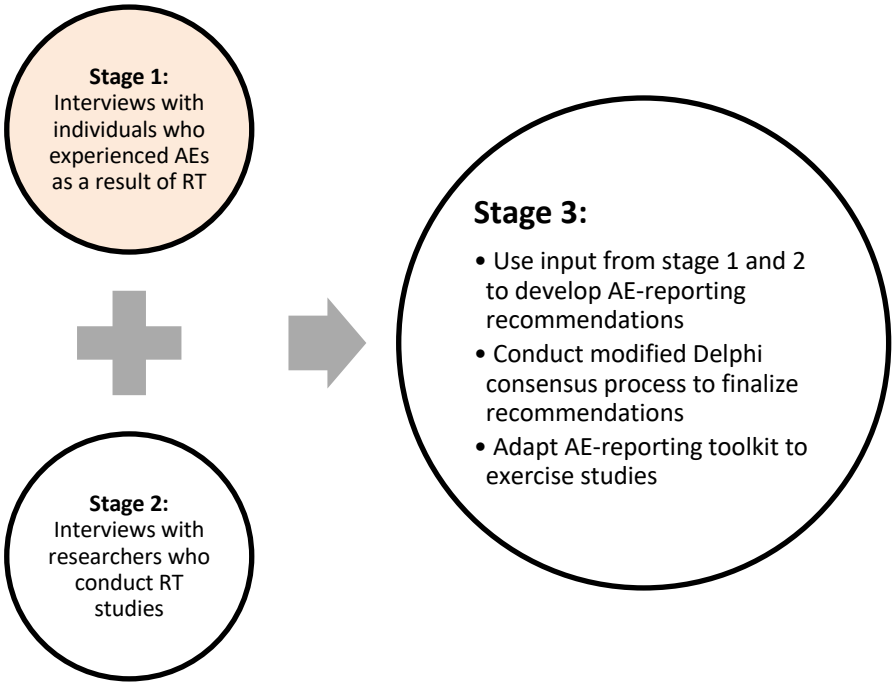

Figure 4.1 Summary of the multi-stage project.

4.3.2 Participant selection

We used purposeful and convenience sampling techniques to recruit participants. Multiple strategies were used: A participant pool (Waterloo Research in Aging Participant pool), the University of Waterloo Bone Health and Exercise Science Lab email distribution list and website, social media, and a newspaper advertisement. All interested potential participants were screened over the telephone using a screening questionnaire. The inclusion criteria were: can speak English fluently; had at least one of the following common health conditions: hypertension, arthritis, osteoarthritis, mood or anxiety disorders, osteoporosis, diabetes, asthma, chronic obstructive pulmonary disorder, ischemic heart disease, or cancer; and had experienced any AE (e.g., pain, discomfort, injury) as a result of RT. The RT program must meet the definition provided by the Prevention of Fall Network Europe Taxonomy: "contracting the muscles against a resistance to 'overload' and bring about a training effect in the

muscular system. The resistance is an external force, which can be one's own body placed in an unusual relationship to gravity (e.g. prone back extension) or an external resistance (e.g. free weight)" (68).

4.3.3 Data collection

We asked participants to first complete an online pre-interview questionnaire (using https://www.surveymonkey.com/). If they did not wish to complete the online questionnaire, we collected the information during the scheduled interview. The pre-interview questionnaire included demographic and health-related questions (e.g., age, sex, education level, exercise habits, and current health). The interviewer (RE: woman, MSc degree, PhD Candidate) then conducted a one-on-one semi-structured interview by telephone or web conference (using Microsoft Teams) to discuss the participant's experience with AEs that occurred as a result of RT, what they consider as serious or minor injuries, and their thoughts and concerns pertaining to AEs and RT (List of interview questions in Appendix C1). All interviews were audio-recorded.

4.3.4 Sample size and data analyses

We recruited and interviewed participants until data saturation was reached (i.e., no new themes emerged) (192–194). Therefore, data collection and data analyses occurred simultaneously (193). Data saturation often occurs after about 12 interviews (195). We used Microsoft Excel (Version 2016; Redmond, WA: Microsoft Corporation) to perform descriptive statistics. Age was presented as mean (SD), while sex, education, ethnicity, use of mobility, personal income, living situation, number of adults living with the participant, health condition(s), meets exercise guidelines, currently participating in RT, and types of AEs experienced were expressed as counts (n) and percentages (%). To analyze the interviews, we used NVivo 12 software (12.6.0; QRS International). We used the thematic framework method for qualitative data analyses (196). We adopted an inductive (coding and theme development are led by the data content), semantic (coding and theme development explicitly reflect data content),

and realist (reporting an assumed reality present in the data) analysis approach (196–199). Consistent with the thematic framework method, we analyzed the interview data via multiple steps described below.

1. Transcription: All of the recorded interviews were transcribed verbatim by a research team member (RE, JP or AS) using an online transcription software (https://otranscribe.com/). The interview transcripts were then deidentified and reviewed by another research team member, who did not initially transcribe the interview, for accuracy (RE, JP or AS).

2. Familiarization with the interviews: Two research team members (RE and LG) independently read and familiarized themselves with the first four completed transcripts.

3. Coding: The same two researchers (RE and LG) then independently performed "open coding" to the same four transcripts.

4. Developing a working analytical framework: The researchers (RE and LG) met to compare and agree on the set of codes applied (i.e., developed a working analytical framework) (196). A third research team member (CS) reviewed the same transcripts as well as the analytical framework and provided feedback.

5: Applying the analytical framework: The lead student investigator (RE) familiarized herself with the remaining transcripts and applied the final analytical framework to all the transcripts. The process was reviewed by another team member (AS).

6. Charting data into the framework matrix: A research team member (JP) then charted the data into a framework matrix using Microsoft Excel.

7. Interpreting the data: The lead student investigator (RE) generated themes from the data by reviewing the matrix and making connections across the interviews. Themes were generated based on the study objective as well as any new concepts that emerged from the interviews.

The generated themes were discussed and agreed upon during a meeting (i.e., peer de-briefing) with team members not involved in interviews or analyses.

4.4 Results

4.4.1 Participant characteristics

We interviewed 12 participants who experienced an AE as a result of RT (Table 4.1). The interviews lasted an average of 29 minutes (SD: 11 minutes, range: 16-56 minutes) and 58% were conducted via web conference (42% over telephone). Participants had a mean age of 60.9 years (SD: 17.9 years; range: 25-91 years). The majority of the participants were female (66.7%), attended graduate school (58.3%), Caucasian (91.7%), not using a mobility aid (91.7%), living at home (91.7%) with one other adult (58.3%), indicated that they meet the exercise guidelines of 150 minutes per week of moderate-vigorous physical activity (75%), and were currently participating in RT (66.7%). The participants had at least one health condition such as arthritis, heart disease, cancer, mood or anxiety disorders, hypertension, asthma, diabetes or osteoporosis. The most common type of AE reported as a result of RT was pain (91.7%).

Table 4.1 Demographic characteristics of the individuals who experienced an adverse event due to resistance training (n=12)

Characteristics	Participants
Sex, n (%)	
Male	4 (33.3)
Female	8 (66.7)
Age (in years)	
Mean (± SD)	60.9 (17.9)
Range	25-91
Education, n (%)	
College	1 (8.3)
University	3 (25.0)
Graduate School	7 (58.3)
Professional School	1 (8.3)
Ethnicity, n (%)	
Caucasian	11 (91.7)

Southeast Asian	1 (8.3)
Use of Mobility Aids, n (%)	
Yes (cane, as needed)	1 (8.3)
No	11 (91.7)
Personal Income, n (%)	
$20,000-$40,000	2 (16.7)
$40,001-$60,000	2 (16.7)
$60,001–$80,000	4 (33.3)
$80,001–$100,000	1 (8.3)
Greater than $100,000	2 (16.7)
I prefer not to say	1 (8.3)
Living Situation, n (%)	
At home	11 (91.7)
In a retirement community	1 (8.3)
Number of Adults Living with Participant, n (%)	
0	3 (25.0)
1	7 (58.3)
2	1 (8.3)
I prefer not to say	1 (8.3)
Health Condition(s), n (%)	
Arthritis (osteoarthritis, rheumatoid, and psoriatic arthritis)	4 (33.3)
Heart Disease	4 (33.3)
Cancer	3 (25)
Mood or Anxiety Disorders	2 (16.7)
Hypertension	1 (8.3)
Asthma	1 (8.3)
Diabetes	1 (8.3)
Osteoporosis	1 (8.3)
Meets Exercise Guidelines (150 min/week of moderate-vigorous activity), n (%)	
Yes	9 (75.0)
No	3 (25.0)
Currently Participating in RT, n (%)	
Yes	8 (66.7)
No	4 (33.3)
Types of AEs Experienced as a Result of RT, n (%)	
Pain	11 (91.7)
Discomfort	9 (75.0)
Muscle strain	9 (75.0)
Bruising	2 (16.7)
Dizziness	2 (16.7)
Fall(s)	1 (8.3)
Shortness of Breath	1 (8.3)
Other (frozen shoulder, an impact that required stitches)	2 (16.7)

Abbreviations: SD, Standard Deviation; RT, Resistance Training; AE, Adverse Event

4.4.2 Themes

Six major themes emerged: 1) Personal experiences with aging influence perceptions of RT; 2) Physical and emotional consequences of AEs limit activities and define future RT participation; 3) Injury recovery defines severity of AE; 4) Health conditions influence the perceived risks and benefits of participating in RT; 5) RT setting and trained supervision influences exercise behaviors and risk perceptions; and 6) Experiencing a previous AE influences future exercise behavior (Table 4.2; Quotations examples in Appendix C2, Table C2.1).

Table 4.2 Themes related to the experiences and perspectives of individuals with chronic health conditions who had an adverse event due to resistance training

Theme	Description	Code(s)
Personal Experiences with Aging Influence Perceptions of RT	Participants were concerned or unacquainted with the available RT resources for older adults.	Aging and RT
	Participants were aware with respect to muscle loss and the importance of RT training when it comes to aging.	
Physical and emotional consequences of AEs limit activities and define future RT participation	Individuals who experienced an AE sought health services, and were limited in their daily activities as well as hobbies.	Consequences
	The presence of pain influenced the decision to participate in RT.	
	Participants worried about reinjury and future injury when considering or engaging in RT.	
Injury Recovery Defines Severity of AE	A minor injury was determined by the length of recovery time (e.g., quick recovery).	Perception of minor injury
	A serious injury was determined by the length of recovery time (e.g., slow recovery).	Perception of a serious injury
Health Conditions Influence the Perceived Risks and Benefits of Participating in RT	Concerns with experiencing an AE as a result of RT in the context of chronic health conditions.	Relevance to chronic condition
	Practicality of RT in the context of chronic health conditions.	Value of RT
RT Setting and Trained Supervision Influences Exercise Behaviors and Risk Perceptions	Participants were less motivated when exercising on their own or at home. Participants were less confident and experienced greater concern with respect to injury when exercising without supervision. Participants were more likely to push themselves due to social pressure,	RT setting
		Social pressure

	but felt that they are at a greater risk of experiencing an injury.	
Experiencing a Previous AE Influences Future Exercise Behavior	Participants wanted to be safely challenged by avoiding exacerbating past injuries and making sure to manage past injuries while engaging in RT.	Want to be safely challenged
		Willingness to return to RT

Abbreviations: AE, Adverse Event, RT, Resistance Training

Theme 1: Personal experiences with aging influence perceptions of RT

Some participants were concerned or unacquainted with the available RT resources for older adults. For instance, participant 03 indicated: "I feel vulnerable to the aging process . . . I suspect a couple of things, one is probably lack of availing myself to better training methods i.e., qualified trainers that could offer me some reliable evidence-based protocols to follow." Also, some participants were aware of the importance of RT when it comes to aging, particularly to manage or prevent muscle loss. For example, participant 06 stated: ". . . I do feel that you lose strength faster as you age so you need to keep up a more regular [RT] schedule."

Theme 2: Physical and emotional consequences of AEs limit activities and define future RT participation

As a result of AEs, participants indicated that they were limited in their daily activities such as sleep, getting dressed, doing the laundry, pushing a vacuum cleaner, opening jars, grooming (e.g., blow dry hair), cooking limitations (e.g., unable to hold a heavy pot of water), and unable to reach for items on high shelves. Other activities mentioned included limiting hobbies (e.g., gardening, riding a bike) or the ability to work (e.g., unable to type on a computer). Participant 02 said: "Yes, it [AE] is affecting my life because of this injury I have to stop working and then after I stopped working I had to be very cautious when I'm doing exercise, especially the ones with weight [lifting]." Also, the presence of pain influenced the participants' decision to engage in RT. For instance, participant 05 explained: "If I'm having a high period of pain and discomfort then I feel like it's more of a major problem. But if I'm

having a good couple of weeks where my pain is less and I'm able to work out more, then that concern [for experiencing an AE] gets lower and then my risk for tolerance like goes high." Furthermore, participants worried about reinjury and future injury when considering or engaging in RT. Participant 22 stated: "Yeah and just there's that ever-present fear, you know, kind of doing really drastic harm."

Theme 3: Injury recovery defines severity of AE

Participants defined a minor injury based on the quick recovery time. The examples of minor injuries they mentioned included muscle strain, muscle stiffness, muscle ache, soreness, joint pain, and little aching pain. Some participants were willing to return to RT shortly after experiencing a minor injury. Participant 07 indicated: "I mean, it's a little set back but as long as I was able to recognize that it was a minor injury and I was able to recognize the conditions that allowed for that injury to occur and able to correct those conditions then I would just carry on [with RT]." While others were more reluctant. For example, participant 19 said: ". . . because I feel like my health is pretty fragile overall I would probably pull back and try to do less [as a result of a minor AE]." On the other hand, participants defined a serious injury based on the slow recovery time. The examples mentioned included fractures, chronic tendonitis, torn ligament, severe pain, and any injury that required hospitalization. Participants were less willing to return to RT shortly after experiencing a serious injury. Participant 01 explained: "Well that would be stop [due to a serious AE] until I strengthen, like heal and regain my strength."

Theme 4: Health conditions influence the perceived risks and benefits of participating in RT

Some participants were concerned with experiencing an AE as a result of RT in relevance to their chronic health condition. Participant 04 expressed: "My concerns with my osteoarthritis . . . I'm probably a little less likely to take chances pushing [during RT] because I don't know if I'm doing more harm to myself when I do that." However, some participants considered the benefits of RT in relevance to their chronic health condition. Participant 03 explained: ". . . from my understanding of coronary

artery disease is I'm liable to get a lot more healthy, enjoyable years of life if I engage in strength training exercises and do it on a regular basis."

Theme 5: RT setting and trained supervision influences exercise behaviors and risk perceptions

Some participants were less motivated when exercising on their own or at home. Participant 07 stated: "I would say on the whole, my performance is better [at the gym]. My focus is better at the gym. My enthusiasm and my attitude are better." Also, some participants were less confident and experienced greater concern with respect to injury when exercising without supervision. Participant 26 said: ". . . when I stopped having that supervision, I did tend to be a little bit more cautious, and I was less likely to push myself in fear of hurting myself and not having that supervision." Furthermore, some participants were more likely to push themselves due to social pressure, but felt that they are at a greater risk of experiencing an injury. For example, participant 04 explained: ". . . when you're in a group situation, there are a lot of other people who are doing it so you should be able to do it too and you have an instructor that is encouraging you to pull, to keep . . . And then when you're not listening to your body, you're apt to make those mistakes."

Theme 6: Experiencing a previous AE influences future exercise behavior.

Some participants wanted to be safely challenged by avoiding exacerbating past injuries and making sure to manage past injuries while engaging in RT. For example, participant 18 said: "I was in the hospital for a couple of times because of back incidents . . . There are a few things in the gym where I see people doing stuff [exercises] with their back and so I kind of avoid all that kind of stuff." Also, not all participants were willing to re-engage in RT after experiencing an AE. Participant 21 indicated: ". . . I have no way of deciding how much I can do or how little, so I think it's better if I don't do it [squatting]."

4.5 Discussion

Participants value RT and recognized that it may help improve their health or manage chronic health conditions. However, the perceived or actual physical and emotional consequences of RT may influence participants' decisions to exercise. Therefore, participants were particularly interested in safe exercises more so than effective exercises. Furthermore, some participants were less motivated when exercising on their own or at home, and were less confident and more concerned with respect to injury when exercising without supervision. Overall, accurate AE reporting along with translation and dissemination of the safety findings may influence people's decision to participate in RT as well as allow health care providers to make evidence-based decisions when prescribing RT to patients.

The presence of pain and worry about injury influenced the participants' decision to engage in RT. A qualitative study in individuals with osteoporosis reported that pain even hindered participants who are highly motivated to regularly exercise (181). Lack of awareness regarding safety of exercise can result in fear of injury which influences psychological capability to engage in exercise (e.g., lack of confidence and exercise self-efficacy) (181,200). Simply being aware of the benefits of exercise may not necessarily increase RT participation among older adults (180,201). Therefore, participants' concern of experiencing an AE due to exercise may be stronger than their motivation to participate in RT to achieve health benefits. As such, accurate AE reporting may influence decisions to participate in RT, or provide an understanding of what types of exercises or movements are risky. A possible strategy to promote (or discourage) RT participation, would be for health care providers to thoroughly discuss exercise safety with their patients.

The study findings demonstrated that participants were concerned with experiencing an AE related to their chronic health condition, while also being aware of the benefits of RT for their specific health condition. A recent report released by the Chartered Society of Physiotherapy found that people living with long-term health conditions fear that their condition could deteriorate if they participate in RT

(202). On the other hand, a review of reviews demonstrated that a motivator for older adults to participate in RT and balance activities was to prevent deterioration of their current health condition (179). A qualitative study demonstrated that a barrier to implementing physical activity recommendations is the presence of fear among rehabilitation professionals to provide safe and effective exercises to people who are considered to have high-risk health conditions (189). Consequently, to help individuals as well as health care providers make an evidence-based decision about participating in RT to improve chronic health condition, the harms, not just the benefits, of RT should be properly reported in future studies, translated and disseminated to the public.

Furthermore, participants were less motivated when exercising on their own or at home, and were less confident and experienced greater concern with respect to injury when exercising without supervision. The report released by the Chartered Society of Physiotherapy provided tips on how to promote and discuss RT from the perspective of people living with long-term health conditions (202). Examples included to convey that RT is easy as it can be done at home without special equipment and to show that RT is accessible without using patronizing terms (e.g., lifting "small" bottles) (202). A systematic review and meta-analysis reported that supervised RT was more effective (i.e., induced larger effects in measures of muscle strength and power) than unsupervised RT among healthy older adults (203). Therefore, it is possible that the concern with AEs may discourage participants from exerting too much effort during unsupervised RT and thus may be less effective than when supervised. Future RT studies can incorporate fully or semi-supervised exercise sessions not only to effectively improve muscle strength and power, but also to reduce participant concern regarding AEs. Furthermore, there is currently insufficient data to support whether AEs occur more often during unsupervised RT than supervised. Addressing this knowledge gap could potentially influence participants' perceptions regarding AEs during unsupervised RT.

One possible solution to improve AE reporting in RT studies is to adapt existing AE guidelines to exercise trials. Patient and public involvement is considered an essential element when developing guidelines and should be prioritized (204). The consideration of the patient/public perspective in guideline development can have "organizational (developer) outcomes" as well as "guideline outcomes" (204). An example of organizational outcomes includes "highlighting personal impact of disease" and an example of guideline outcomes includes "identifying issues that may be overlooked by medical professionals" (204). Consistent with our study, capturing the participant perspective highlighted the impact of AEs on their personal life, and even though not all researchers see value in reporting AEs when conducting exercise trials, safety findings can influence people's decision to engage in RT. Consequently, to promote RT participation, exercise researchers should value the reporting of harms and adopt a consistent AE reporting approach to allow adequate comparisons across exercise interventions. Furthermore, researchers and participants may have different perceptions of what is considered a minor or serious AE. For example, pain may be classified as a minor AE by a researcher, but the impact of pain on the participant's personal life may be considered serious. Therefore, researchers should provide a description of any AEs that occurred during the exercise trial. For instance, instead of vaguely reporting that minor AEs occurred, researchers should provide examples of the minor AEs that occurred. Accurate reporting of AEs can provide individuals with the ability to decide whether to participate in RT based on their own perception of safety risk.

4.5.1 Limitations

We acknowledge some study limitations. Despite our broad recruitment strategies, all of the participants were considered well educated and thus may have different experiences or perspectives related to RT than the general population. Furthermore, the majority of the participants were female (sex), Caucasian, and did not use a mobility aid thus further limiting the external validity of the findings. A randomized controlled trial and qualitive study involving women (gender) demonstrated that

participants' perceptions regarding the RT intervention did not vary by race/ethnicity (205). However, compared to Caucasian women, women of color placed greater emphasis on parental and marital obligations as barriers to adhering to the RT intervention (205). In this study, we collected sex but not gender data, and we did not look at differences in responses based on sex. A cross-sectional study reported gender and found that, compared to men, there was a statistically significant ($\chi 2(18, n = 643) = 43.49$, $p < 0.001$) higher percentage of women who reported pain as a reason for not participating in RT (180). With respect to exercise behavior, because we were purposefully recruiting individuals who experienced an AE during RT, most of the participants were considered physically active (i.e., met the exercise guidelines or are currently participating in RT). Individuals who are not active may have different perceptions regarding AEs and RT. Also, the interview responses may have been subject to social-desirability bias as the participants were being interviewed by a PhD candidate conducting RT-related research.

4.6 Conclusion

The perceived or previously experienced physical and emotional consequences of RT, and the perceived risks of RT in relation to a chronic health condition may influence people's decision to engage or return to RT. Participant risk perception was also influenced by RT setting and supervision status. Despite participant awareness of the value and benefits of RT in both the context of aging and chronic health conditions, participants may place greater emphasis on safety rather than effectiveness of exercise. Consequently, to promote RT participation, the harms, not just the benefits, of RT should be properly reported in future studies, translated and disseminated to the public and health care providers should discuss exercise safety when prescribing RT to patients.

Chapter 5: Study 3 – Stage 2

Title: A Qualitative Study of Researchers' Perspectives on Adverse Event Reporting in Resistance Training Trials

5.1 Overview

Objectives: The objectives of this study were to understand researchers' current practices and perspectives on adverse event (AE) reporting in clinical trials of resistance training (RT), and identify barriers and facilitators to AE reporting.

Methods: We conducted web conference or telephone-based one-on-one semi-structured interviews with 14 researchers from six countries (Canada, USA, UK, Australia, Greece, and Puerto Rico) who have published RT studies in individuals with or without health conditions. We audio-recorded and transcribed the interviews, and analyzed data using the thematic framework method.

Results: Four themes were identified in the context of RT studies: 1) researchers lack guidance, resources, or motivation for rigorous AE reporting; 2) to facilitate AE reporting, researchers educate and value participants, use trained personnel, and implement standardized guidelines; 3) there is suboptimal implementation of existing AE reporting standards, or the perception that the available guidelines do not apply to exercise trials; and 4) the acceptability and feasibility of an exercise-specific guide for AE reporting depends on its content and format. Major sources of bias and heterogeneity included only reporting AEs deemed related to intervention, choosing not to report AEs in academic publications, and varying AE reporting methods based on participants' characteristics.

Conclusions: Our findings demonstrate that researchers acknowledge that AE reporting methods in the field of exercise science do not align with established guidelines. Based on the barriers and facilitators identified in this study, behavioural change strategies should be considered to reduce inconsistent and suboptimal AE reporting in RT trials.

5.2 Introduction

An adverse event (AE) is defined by Health Canada as "Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product [or exercise] and which does not necessarily have to have a causal relationship with this treatment" (183). An overview of systematic reviews and a Cochrane review demonstrated that AEs are not consistently monitored or reported in resistance training (RT) studies (166,188). Although AE reporting became more common after the Consolidated Standards of Reporting Trials (CONSORT) statement was released in 2001, there are still no recommendations or consensus as to what types of AEs to look for, when to report AEs and how to classify AEs in exercise studies (84,177). In a Cochrane review, only 7.4% of the included primary RT studies indicated *a priori* what type of AEs were monitored and reported (e.g., only serious AEs that occurred in the intervention groups, all AEs that occurred in each group) (166). Furthermore, in RT studies, AEs were reported more often if they occurred in the intervention group, if they were reasons for study withdrawal, or if the study involved participants with health conditions (e.g., osteoarthritis, cardiovascular disease) (177,188). Thus, the occurrence of AEs may be over or underestimated in RT studies based on the researchers' AE reporting methods.

Although AE reporting guidelines already exist, the available recommendations are either inconsistent with respect to exercise or are drug trial-focused (85–87). For instance, the Consensus on Exercise Reporting Template indicates that investigators should "Describe the type and number of AEs that occur during exercise", whereas the CONSORT for harms recommends to report AEs that occurred in all groups (i.e., not just AEs that occurred during exercise) (85,86). Furthermore, there are nuances specific to exercise that are not addressed in the drug trial-focused guidelines (85,87). For example, transient mild muscle soreness is a common occurrence due to exercise, but could be considered an AE if caused by a pharmaceutical drug. Therefore, the suboptimal AE reporting practice in exercise research studies may be influenced by the lack of awareness of AE reporting standards, the uncertainty

of AE reporting recommendations with respect to exercise, or the belief that existing AE reporting standards only apply to pharmaceutical trials.

Accurate reporting of AEs will determine whether benefits of RT outweigh the harms in individuals who are healthy and in people with common health conditions, and the absence of accurate AE reporting creates limitations when developing physical activity guidelines, especially when patients or clinicians may have concerns about the safety of RT (52,181,188,189). In accordance with the Knowledge-To-Action framework, to improve AE reporting, we must first understand the gap between guidelines and practice, and any barriers to AE reporting in exercise trials (90). Therefore, to inform future guidance, the objectives of this study were to identify barriers and facilitators to AE reporting, and to understand researchers' current practices and perspectives on AE reporting in RT studies among adults with or without health conditions.

5.3 Methods

5.3.1 Context

This study is part of a multi-stage project; this study reports on stage 2 only (Figure 5.1). The study was conducted during the COVID-19 pandemic. Accordingly, all data were collected online or via telephone; there was no in-person data collection. The reporting for this study was informed by the Consolidated Criteria for Reporting Qualitative Research (191). All research activity was conducted according to the Tri-Council Policy Statement (http://www.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/). The study received ethics approval from University of Waterloo research ethics board (ORE # 42207). All participants provided informed verbal consent.

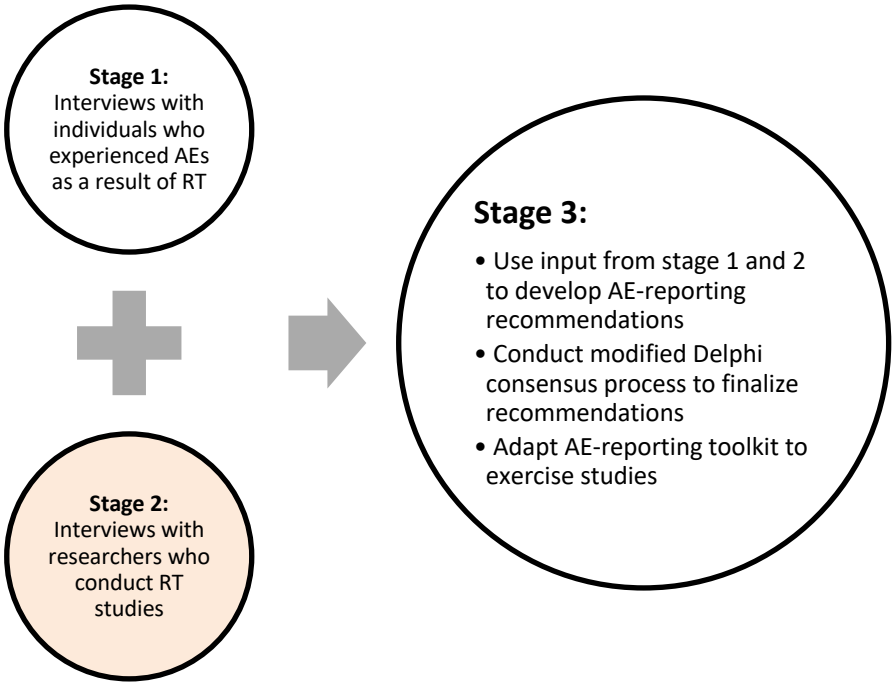

Figure 5.1 Summary of the multi-stage project.

5.3.2 Participant selection

We used purposeful and convenience sampling techniques to recruit participants. We directly emailed the authors of clinical trials that were in the systematic review that was included in our overview paper to examine benefits and harms of RT, used to inform the Canadian 24-Hour Movement Guidelines (166,188). We also conducted a literature search to identify additional researchers and emailed them directly. Using MEDLINE, we filtered article type to only show "clinical trials" and we used the following search terms: resistance training, strength training, adults, or adverse events. In addition, we directly emailed authors based on referrals from other researchers (snowball sampling). The inclusion criteria were: can speak English fluently; conducted at least one clinical trial involving RT; recruited adults with or without a health condition in their RT trials. The RT program must meet the definition provided by the Prevention of Fall Network Europe Taxonomy: "contracting the muscles against a resistance to 'overload' and bring about a training effect in the muscular system. The resistance is an

external force, which can be one's own body placed in an unusual relationship to gravity (e.g. prone back extension) or an external resistance (e.g. free weight)" (68).

5.3.3 Data collection

We asked participants to first complete a pre-interview questionnaire either online (using https://www.surveymonkey.com/) or during the scheduled interview. The pre-interview questionnaire included demographic questions (e.g., age, sex, and academic background). The interviewer (RE, woman, MSc degree, PhD Candidate) then conducted a one-on-one semi-structured interview by telephone or web conference (using Microsoft Teams) to discuss the participant's experience with AE reporting in their RT trials, the types of AEs that occurred in their RT trials, and their thoughts regarding the challenges of AE reporting in RT trials (List of interview questions in Appendix D1). All interviews were audio-recorded.

Participants were instructed to use their assigned identification number, instead of their names, when completing the online pre-interview questionnaire. Interview transcripts were deidentified by substituting the participants' names with their identification number. All of the participants were aware that the interviewer's PhD thesis focused on considerations for designing RT studies including AE reporting. However, the interviewer made a conscious effort not to share their own perspectives or experiences when asking questions.

5.3.4 Data analyses

We recruited and interviewed participants until data saturation was reached (i.e., no new themes emerged) (192–194). Therefore, data collection and data analyses occurred simultaneously (193). Data saturation often occurs after about 12 interviews (195). We used Microsoft Excel (Version 2016; Redmond, WA: Microsoft Corporation) to perform descriptive statistics. Age was presented as mean (SD), while sex, education, academic discipline, career stage, and country were expressed as counts (n)

and percentages (%). To analyze the interviews, we used NVivo 12 software (12.6.0; QRS International). We adopted an inductive (coding and theme development are led by the data content), semantic (coding and theme development explicitly reflect data content), and realist (reporting an assumed reality present in the data) analysis approach (196–199). We used the thematic framework method for qualitative data analyses (196). Consistent with the thematic framework method, we analyzed the interview data via multiple steps described below.

1. Transcription: All of the recorded interviews were transcribed verbatim by a research team member (RE, JP or AS) using an online transcription software (https://otranscribe.com/). The interview transcripts were then deidentified and reviewed by another research team member, who did not initially transcribe the interview, for accuracy (RE, JP or AS).

2. Familiarization with the interviews: Two research team members (RE and LG) independently read and familiarized themselves with the first four completed transcripts.

3. Coding: The same two researchers (RE and LG) then independently performed "open coding" to the same four transcripts.

4. Developing a working analytical framework: The researchers (RE and LG) met to compare and agree on the set of codes applied i.e., developed a working analytical framework (196). A third research team member (JP) reviewed the same transcripts and the analytical framework and provided feedback.

5: Applying the analytical framework: The lead student investigator (RE) familiarized herself with the remaining transcripts and applied the final analytical framework to all the transcripts. The process was reviewed by another team member (JP).

6. Charting data into the framework matrix: A research team member (JP) then charted the data into a framework matrix using Microsoft Excel.

7. Interpreting the data: The lead student investigator (RE) generated themes from the data by reviewing the matrix and making connections across the interviews. Themes were generated based on the study objective as well as any new concepts that emerged from the interviews. The generated themes were discussed and agreed upon during a meeting (i.e., peer de-briefing) with team members not involved in interviews or analyses.

5.4 Results

5.4.1 Participant characteristics

Out of the 60 emails that were submitted, a total of 14 researchers from six countries (Canada, USA, UK, Australia, Greece, and Puerto Rico) agreed to participate in this study (Table 5.1). The interviews lasted an average of 44 minutes (SD: 12 minutes, range: 22-60 minutes) and 92.9% were conducted via web conference (7.1% over telephone). Participants had a mean age of 52.8 years (SD: 9.8 years; range: 36-72 years), 42.9% were female, and 78.6% identified as a senior researcher.

Table 5.1 Demographic characteristics of the researchers (n=14)

Characteristics	Participants
Sex, n (%)	
Male	7 (50.0)
Female	6 (42.9)
Prefer not to say	1 (7.1)
Age (in years)	
Mean (SD)	52.8 (9.8)
Range	36-72
Education, n (%)	
PhD	11 (78.6)
PhD and MD	2 (14.3)
EdD	1 (7.1)
Academic Discipline, n (%)	
Kinesiology	6 (42.9)
Rehabilitation Science	2 (14.3)
Health Studies	2 (14.3)
Sport Sciences	1 (7.1)
Medical Sciences	1 (7.1)
Psychology	1 (7.1)

Exercise Physiology	1 (7.1)
Career Stage, n (%)	
Junior	2 (14.3)
Intermediate	1 (7.1)
Senior	11 (78.6)
Country, n (%)	
Canada	6 (42.9)
USA	3 (21.4)
UK	2 (14.3)
Australia	1 (7.1)
Greece	1 (7.1)
Puerto Rico	1 (7.1)

Abbreviations: SD, Standard Deviation; PhD, Doctor of Philosophy; MD, Doctor of Medicine; EdD, Doctor of Education; USA, United States of America; UK, United Kingdom.

5.4.2 Themes

Four major themes emerged: 1) Lack of guidance, resources, motivation or interest are barriers to AE reporting; 2) Valuing and educating participants, having access to trained personnel and to standardized and enforced recommendations are facilitators to AE reporting; 3) There is suboptimal implementation of existing AE reporting standards, or the perception that the available guidelines do not apply to exercise trials; and 4) The acceptability and feasibility of a guide for AE reporting depends on its content and format (Table 5.2; Quotation examples in Appendix D2, Table D2.1).

Table 5.2 Themes and subthemes related to researchers' practices and perspectives on adverse event reporting

Theme	Subtheme	Description	Code(s)
Lack of guidance, resources, motivation or interest are barriers to AE reporting	Lack of a Standardized AE Reporting Protocol	Across researchers, there was variability in monitoring and recording AEs, and there were various opinions regarding the definitions of AEs and attributable AEs.	Inconsistent Documentation of AEs
			Lack of Universal Definitions
	Lack of Access to Resources	Resources include time and money.	Resources
	Lack of Motivation or Interest to	Some researchers were resistant to improving AE reporting in their	Resistance to Oversight

	Improve AE Reporting	RT studies and perceived the research ethics boards' requirements as excessive or unrealistic.	
Valuing and educating participants, having access to trained personnel and to standardized and enforced recommendations are facilitators to AE reporting	Valuing and Educating Participants	Creating a culture where participants feel valued. Prior to starting an exercise intervention, providing participants with a protocol familiarization period and ensuring participant safety during exercise. Educating and communicating with participants about the expected side effects that may occur as a result of RT.	Enhancing the Participant Experience Educating Participants
	Access to Trained Personnel	Training research staff to monitor and record AEs appropriately.	Training Staff
	Access to Standardized and Enforced AE Reporting Recommendations	Standardizing and enforcing AE reporting recommendations by involving ethics boards, exercise organizations and Journals.	Standardization and Enforcement of AE Recommendations
There is suboptimal implementation of existing AE reporting standards, or the perception that the available guidelines do not apply to exercise trials		There were potential sources of bias including variability in reporting AEs based on the participants' characteristics (healthy versus people with health conditions), excluding participants who experienced an AE and could no longer perform the exercise at the required level, only reporting	AE Reporting Based on Population Excluding Participants No AE Reporting Outside of Study Not Acknowledging Risk Involved Not Publishing AEs Value of Balanced Reporting of AEs

	AEs related to the exercise intervention, not acknowledging the level of risk involved, and not publishing AEs in journals. Furthermore, not all researchers saw value in reporting AEs for both intervention and control group.	
The acceptability and feasibility of a guide for AE reporting depends on its content and format	Researchers preferred a concise and visually appealing guide that can be applied to various types of RT studies.	Preferred Guide Format and Content

Abbreviations: AE, Adverse Event, RT, Resistance Training

Theme 1: Lack of guidance, resources, motivation or interest are barriers to AE reporting

A major barrier to clear, comprehensive AE reporting is the lack of awareness of existing guidelines or how to apply them in exercise trials. For example, participant 11 stated: "I think most of the people [researchers] do their own thing and they go with their own approach." Using AE reporting guidelines that are drug trial-centered were considered to be problematic. For example, participant 16 explained "Well, I think that the guidelines for drug trials are going to have a lot of details surrounding doses of drugs and they won't mention exercise extensively. Like a good example would be if someone has an AE and they left the intervention, but then they came back. You know, we can reduce the dose of exercise training, but I don't think that's outlined in a typical guideline that's made for drugs." Also, due to a lack of exercise-specific guidance, researchers have personal opinions regarding how to define AEs and attributable AEs in the context of RT. Participant 23 said: ". . . it's pretty normal to have certain things happen, like muscle soreness in a RT program - if I reported that as an AE, it's not AE, it's an adaptive response." And participant 13 explained: "I would say that in order to attribute it [AE] to the intervention, that you need to be able to directly say there was something happening that our [RT] intervention caused that led directly to this AE."

Another barrier is limited access to time and money for comprehensive AE reporting. Some researchers expressed that to eliminate recall bias, AEs need to be continually monitored in all participants and that involves costs (e.g., hiring enough staff) as well as time commitment (e.g., calling each participant). Researchers emphasized that ongoing monitoring of AEs is especially challenging in large sample studies or long-duration trials. For instance, participant 25 was concerned that ". . . if you got 150 or 200 people in an exercise arm, it can become challenging trying to continually monitor minor complaints, AEs, or minor AEs as well."

Furthermore, to have a data safety monitoring board (DSMB), researchers need to find people who have an academic background relevant to the RT intervention and who are willing to dedicate their time to become board members. Participant 09 cautioned that "It [having a DSMB] of course means more time for people who are external to the study, and they're not paid so it's not always easy to find people willing to do that." Finally, some researchers may be resistant to improving AE reporting in their RT studies and perceive the research ethics boards' requirements as excessive or unrealistic. For example, participant 23 said that ". . . if one would expect everyone undergoing [an] RT trial to report what I consider minor AEs, I think that's probably too much." And the research ethics board's requirements were described by participant 08 as follows: "I think the whole IRB [Institutional Review Board] process is out of control. I think IRB has gone way overboard on their objection, way overboard."

Theme 2: Valuing and educating participants, having access to trained personnel and to standardized and enforced recommendations are facilitators to AE reporting

A facilitator to AE reporting is creating a culture where participants feel valued, and educating participants. To establish a rapport with study participants in RT trials, participant 11 indicated: ". . . we have given them [the participants] our phone numbers to give us a call whenever they feel like. So, we are in close contact with them and we want to make sure that nothing bad happens . . . and if it happens we have to be there." Another way that researchers made participants feel valued was by

providing participants with a protocol familiarization period prior to starting an exercise intervention, designing individually tailored exercise programs, and ensuring participant safety during exercise. Participant 15 stated: "I usually conduct multiple method studies so it's not just you know, 'can we deliver it [RT program]', but actually also finding out from the study participants what's important to them, is this important, are they able to do it?" Researchers educated and communicated with participants in regards to what AEs are, the importance of monitoring AEs, and the expected side effects (e.g., delayed onset muscle soreness) of the RT intervention. For instance, participant 25 said: "So I think what we do try to do is explain to participants in our studies, the importance of reporting minor aches and pains or AEs essentially, and that we do want to monitor them because it's important for us to evaluate the safety of the program."

Another facilitator to AE reporting is access to research personnel who are trained to monitor and record AEs appropriately. For instance, participant 17 explained: ". . . making them [exercise trainers] feel comfortable with reporting things [AEs], so not making them feel like they messed up or they did something wrong if something happened and they have to kind of try and cover it up or hide it. So, making them aware of the importance of reporting these things." Some researchers indicated they would value standardized AE reporting exercise-specific recommendations that are required by ethics boards, exercise organizations and scientific journals. Researchers indicated that professional exercise organizations can assist with disseminating recommendations for AE reporting in exercise studies. For instance, participant 10 suggested: "I'm not sure about how you go about getting that [the recommendations] out. Maybe with the help of university IRB [Institutional Review Board] committee chairs, so the director of research, or the chair of an IRB committee at the smaller schools . . . I guess another way would be posting on some of our professional organizations that are featured and if this is going to have a, kind of a focus more of, on more of exercise trials, then maybe American College of Sports Medicine or other organizations might be willing to post something in their virtual reports where

they do a weekly kind of news, or something like that would be a way." Also, to improve publishing AEs, participant 14 explained: "I think that if journals require that you report AEs, that, of course would make it, you know, obligatory. People will have to then be more formal about the way the data are collected."

Theme 3: There is suboptimal implementation of existing AE reporting standards, or the perception that the available guidelines do not apply to exercise trials

There were sources of bias and heterogeneity in AE reporting practice. Sources of bias involved excluding participants who experience an AE and can no longer perform the exercise at the required level, not reporting AEs that occur outside the exercise sessions, not acknowledging the level of risk involved with RT, not publishing AEs in journals, and not reporting AEs in the control group. Heterogeneity in AE reporting may be related to the characteristics of the participants. For example, some researchers stated that they would monitor AEs more closely in older adults versus younger adults, and in people with chronic health conditions versus healthy individuals. For example, participant 17 expressed that: ". . . if you're running an exercise trial in undergrads, then that [AEs] might not be on your mind because you're like, 'oh, they are healthy young undergrads, they should be able to do anything' and you know, they're not as prone to injury or, AEs. And so, just making sure that all researchers are aware, regardless of the population that they're working with, that this is something that needs to be reported, because I think there is a bias to these things being monitored and reported, more so with the older adult population and not necessarily with younger adults." Some researchers excluded participants who experienced an AE and could no longer perform the exercise at the required level. For instance, participant 08 explained that if someone experienced an AE: ". . . the person [participant] would say, well, 'I'll try to work out today', and then you [the researcher] can observe the first exercise or the first few repetitions and, and realize, no, this person cannot do their activity, therefore they'll have to withdraw." In some cases, researchers limited AE reporting to only events that occurred during

the study sessions (e.g., testing or exercise sessions). Participant 20 indicated: ". . . she [the participant] was like, 'Oh actually I've just come back from hospital because this has happened, a fall'. So, it wasn't formally recorded because at that time we would just be recording things that happened in [the exercise] class." Not all researchers acknowledged the risk involved when participants engaged in an RT intervention. Participant 13 said: "AEs are so rare that in all of these populations — . . . It's rare in young people, it's rare in older people." In terms of not publishing AEs in journals, participant 12 stated: "It's [AEs] something that we report to the REB [Research Ethics Board] and we just say that 'this was done, it's resolved'. We don't report in the paper. Why that's the case? Again, I just think its part and parcel of doing the [RT] program, to be honest with you." Finally, not all researchers saw value in monitoring AEs in both the intervention and control group. For example, participant 17 said: "The control group was listening to music and we didn't have an adverse [event] log for that. But you know if something did come up—so we weren't actively monitoring for adverse events—if something did come up, then we would of course report it to the Research Ethics Board, but it wasn't something that we were actively monitoring." In contrast, participant 15 indicated: "I'm interested in looking at any sort of health-related event that might affect people in both groups and by doing [AE monitoring] both groups, we can also actually look to see if are there differences between the two [groups]."

Theme 4: The acceptability and feasibility of a guide for AE reporting depends on its content and format

To develop an acceptable and feasible AE-reporting guide adapted for exercise trials, researchers indicated that it should be concise and include valuable content that could be applied to various types of RT studies. For instance, participant 24 said: ". . . it [guide] has to be quite short and, clear and concise, so I think that's the first thing. It should not take much time to put into practice, but it should be also valuable, there should be the value seen in that." Also, participant 25 suggested: "I guess it [the guide] needs to be partly adaptable for the different types of [RT] intervention trials, because there are

interventions where they're highly rigorous in terms of their supervision and support." Researchers suggested features such as including exercise examples in the guide, making it visually appealing by involving a decision tree or diagram, modifying existing AE template standard forms and definitions specifically to exercise, and incorporating technology if possible (e.g., phone application).

5.5 Discussion

To improve AE reporting in RT studies we need to address barriers including the appropriate use of existing AE and clinical trial reporting standards, and the perceived limited access to resources for comprehensive AE reporting. Furthermore, we need to incorporate facilitators like creating a culture where participants feel valued and having trained personnel conduct the reporting of AEs. To disseminate and enforce reporting recommendations, researchers suggested involving ethics boards, exercise organizations and scientific journals. We also need to address potential bias (e.g., not reporting AEs in the control group) and sources of heterogeneity (e.g., AE reporting methods varied based on participants' characteristics).

A key barrier to AE reporting is the lack of awareness of existing guidelines or how to apply them in exercise intervention trials. Good Clinical Practice (GCP) is an international quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials (206). The GCP guidelines define an AE as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment" (207). The definition highlights "pharmaceutical product" and thus researchers may overlook the guidelines in the context of exercise. Furthermore, in the existing guidelines, the different types AEs are presented from the perspective of drug trials. For instance, an unexpected AE is defined as an event that occurs that is not listed in the drug's current labeling (207). Consequently, the fact that AE reporting guidelines are not inclusive of language specific to exercise may explain the inconsistent reporting observed across researchers who conduct RT trials. Furthermore,

the methods for monitoring and recording AEs are not described in RT studies thus further reinforcing the lack of awareness of existing standards and the inconsistent AE reporting practice (166,188). In our study, researchers indicated that comprehensive AE reporting in RT trials require access to time and money. RT studies are already considered resource intensive especially if the participants are classified as inexperienced with respect to exercise (208). Therefore, researchers should find a balance between available resources and the need to include an AE reporting protocol for future RT studies. Overall, the study findings demonstrate the need for tailored communication strategies to the exercise community regarding the AE reporting standards and the required resources.

Furthermore, to improve AE reporting we need to incorporate facilitators such as enhancing the participant experience when designing RT interventions, having access to trained personnel, and the involvement of relevant institutions to disseminate and enforce reporting recommendations. Consistent with the position statement from the National Strength and Conditioning Association, researchers can create a culture where participants feel valued by designing individualized RT programs and ensuring there is appropriate exercise spotting while older adults are engaging in RT (209). If RT interventions are individualized, participant-centered (e.g., based on preferences), and feel safe, this will enhance the participant experience and create a rapport between the research staff and the participant. Research staff, trained in AE reporting, are better able to monitor AEs if they remain in close contact with the study participants and educate them in regards to what constitutes an AE. To raise awareness with respect to AE reporting standards, researchers suggested the involvement of ethics boards (e.g., university affiliated ethics boards), exercise organizations (e.g., American College of Sports Medicine) and academic journals. Relevant institutions can improve AE reporting by disseminating and enforcing the existing standards in the context of exercise trials.

AE reporting in RT studies are subject to sources of bias and heterogeneity. Muscle soreness and exacerbation of pre-existing injuries were most commonly reported as minor AEs in RT studies,

however not all the researchers who were interviewed defined such events as AEs (188). Furthermore, some researches defined AEs as only those events that were attributable to the exercise intervention. However, in the GCP guidelines, the AE definition indicates that the event does not need to have a causal relationship with the treatment investigated and thus could be any harmful event that occurred during the span of the study (207). Therefore, the findings indicate that AE reporting methods in the field of exercise science do not align with what is considered GCP. Moreover, the results demonstrated that publishing AEs is not commonly observed, and not everyone reported AEs in the control group. The findings were consistent with our overview study that showed 71.1% of the included primary studies involving the generally healthy population did not mention AEs at all (188). Among people with health conditions, a recent systematic review and meta-analysis demonstrated that 51% of the included primary studies did not report AEs in exercise trials (84). Furthermore, a recent Cochrane systematic review that examined fall prevention exercise among older adults indicated that only one out of the 81 included primary studies closely monitored AEs in both the exercise and control group for the entire duration of the study (210). However, the extension CONSORT statement for better reporting of harms in RCTs recommends to report AEs in publications and to do so for all treatment groups (85). Our work suggests that some researchers presume that the existing standards do not apply to exercise, or they are unaware or have different interpretations of the standards. Finally, with respect to heterogeneity, AE reporting should not differ based on whether the participants are considered healthy, frail older adults, or people with health conditions (211–213). However, researchers may consider participant characteristics, and develop a list of potentially expected AEs *a priori* that they would like to monitor for the duration of the study. For example, if a participant has hypertension, blood pressure should be closely monitored during the RT intervention (209). In future RT studies, researchers can choose to perform unsolicited AE data collection (i.e., asking open ended questions about whether

any AEs occurred) or solicited (e.g., questionnaires asking about specific AEs) or both solicited and unsolicited.

Overall, to reduce inconsistent and suboptimal AE reporting in the field of exercise science, we can consider the behaviour change wheel (BCW) framework which is comprised of three components: sources of behavior, intervention functions, and policy categories (200). The researchers interviewed in this study expressed the importance of having access to concise AE reporting recommendations that include exercise-specific AE definitions and examples which can be applied to various types of RT studies. Producing and disseminating exercise-specific AE reporting guidelines would align with the "policy category" of the BCW (200). However, based on our findings there are other categories that can also be considered. For instance, consistent with intervention functions of the BCW, the presence of bias in AE reporting within the exercise community emphasizes the importance of educating and training exercise researchers in GCP of AE reporting. Furthermore, to address motivation which is a source of behavior, we need to raise awareness of the existing AE reporting standards among exercise researchers. Finally, using the intervention functions "enablement" and "restriction", we can enforce GCP AE reporting standards by involving relevant institutions (e.g., journals can make GCP AE reporting a requirement when submitting manuscripts).

5.5.1 Limitations

We acknowledge some study limitations. We did not appreciate the need to define a distinction between AE and adverse effect (i.e., an event that is attributable to the intervention) prior to conducting the interviews, and some individuals used these terms interchangeably. Therefore, the participants' responses may have differed if we clarified prior to conducting the interviews that we are asking about adverse events and not adverse effects, and defined each term. Furthermore, we indicated that the practice of AE reporting varied across researchers who conduct RT studies. However, their practices may differ because of varying expectations between institutions or ethics boards. We did not compare

the AE reporting practices of researchers who are affiliated with the same ethics board. For external validity purposes, we included a diverse group of researchers who are associated with various ethics boards involving distinctive AE reporting requirements. With respect to participant characteristics, there was a disproportionate number of researchers from Canada and we reported sex but not gender. We are uncertain whether or how the responses of the researchers would vary based on sex or gender.

5.6 Conclusion

There are sources of bias and heterogeneity in AE reporting, which may be the reason AEs are not consistently monitored or reported in RT studies. We revealed barriers to AE reporting related to a perceived lack of guidance, resources, or motivation, and the perception that available guidelines do not apply to exercise trials. Facilitators of AE reporting included valuing and educating participants, having access to trained personnel and enforcing AE reporting recommendations. Our findings demonstrate that AE reporting methods in the field of exercise science do not align with what is considered GCP. To change behavior among exercise researchers, we need to raise awareness of the existing AE reporting standards, promote education and training in AE reporting, involve relevant institutions to enforce GCP relevant to AE reporting, and provide access to exercise-specific AE recommendations that are adaptable to various types of RT studies.

Chapter 6: Study 3 - Stage 3

Title: A Modified Delphi Process to Adapt Adverse Event Reporting Guidelines to Resistance Training Studies

6.1 Overview

Objective: The objective of this study was to adapt existing adverse event (AE) reporting guidelines to resistance training (RT) studies.

Methods: To adapt the guidelines, we conducted purposeful and convenience sampling to identify researchers who published RT studies and we invited them to participate in a modified Delphi consensus process. Out of the 80 researchers who were invited, 19 researchers from six countries (Canada, USA, UK, Australia, Greece, and Puerto Rico) agreed to participate (~24% response rate). First, exercise-specific AE-reporting recommendations were generated based on interviews with people who have common health conditions and experienced any AE as a result of RT (n=12), and researchers who published RT studies (n=14). The recommendations were turned into a survey and were sent electronically to the Delphi participants to be rated. We conducted three rounds of review until there was consensus (minimum 74% agreement) on each recommendation.

Results: All 19 participants responded to the three survey rounds (100% response rate). After each round, the recommendations were revised based on the participants' feedback. For the first round, there were ten out of 24 recommendations that were below the consensus cut off. For the second round, there was one out of 28 recommendations that was below the consensus cut off. For the final round, the remaining recommendation reached consensus. The agreed upon recommendations were used to develop an exercise-specific AE-reporting toolkit (i.e., checklist, template AE form, and decision tree).

Conclusion: Our modified Delphi consensus process resulted in an exercise-specific AE-reporting toolkit that researchers can use to apply AE guidelines in RT studies, and improve the quality of trial conduct and reporting.

6.2 Introduction

An adverse event (AE) is defined by Health Canada as "Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product [or exercise] and which does not necessarily have to have a causal relationship with this treatment" (183). An overview of systematic reviews and a Cochrane review demonstrated that AEs are not consistently monitored or reported in resistance training (RT) studies (166,188). Although AE reporting became more common after the Consolidated Standards of Reporting Trials (CONSORT) statement was released in 2001, there are still no recommendations or consensus as to what types of AEs to look for, when to report AEs and how to classify AEs in exercise studies (84,177).

AE reporting guidelines already exist and are endorsed by randomized clinical trial (RCT) reporting recommendations (85–87). The Consensus on Exercise Reporting Template is a 16-item checklist encompassing the minimum requirements for reporting exercise intervention studies (86). Item eleven indicates that investigators should "Describe the type and number of AEs that occur during exercise" and refers readers to the CONSORT for harms for further details (86). The CONSORT for harms is an extension of the CONSORT statement that includes ten recommendations for reporting harms in RCTs (85). The National Institute on Aging (NIA) AE guidelines provide elaborate AE definitions (e.g., how to categorize severity, expectedness, and relatedness), an AE template form, and a decision tree for when an AE occurs (87).

Despite available AE reporting guidelines, there are limitations when applying them to exercise studies. For instance, contrary to the Consensus on Exercise Reporting Template, the CONSORT for harms recommends to report AEs that occurred in all groups (i.e., not just AEs that occurred during exercise) (85). Furthermore, the examples included in the CONSORT for harms and NIA are related to drug trials and as such do not provide exercise-specific considerations. There are nuances specific to exercise that are not addressed in the drug trial-focused guidelines. For example, transient mild muscle soreness is a

common occurrence due to exercise, but could be considered an AE if caused by a pharmaceutical drug. Therefore, adapting and disseminating AE reporting guidelines for RT trials may help researchers be more aware of existing practices, and demonstrate the expectations that are considered acceptable by the exercise community.

Overall, exercise-specific AE reporting guidelines can increase the quality of published research with respect to RT interventions, and allow researchers and clinicians to make evidence-based decisions as to whether the benefits of RT truly outweigh the harms in individuals who are healthy and in people with common health conditions. In accordance with the Knowledge-To-Action framework, to appropriately adapt and tailor the existing AE reporting guidelines to the exercise research context, we must first understand the participant as well as the researcher perspective, understand the gap between guidelines and practice, and assess barriers to AE reporting in RT studies (90). Therefore, we interviewed people with health conditions who experienced any AE as a result of RT (stage 1), and researchers who report AEs in their RT studies (stage 2). The objective of this study was to use the interview data from stage 1 and stage 2 to tailor an exercise-specific AE-reporting toolkit (i.e., checklist, template AE form, and decision tree).

6.3 Methods

6.3.1 Context

This study is part of a multi-stage project; this study reports on stage 3 only (Figure 6.1). The study was conducted during the COVID-19 pandemic. Accordingly, all data were collected online or via telephone; there was no in person data collection. The reporting for this study was informed by the Consolidated Criteria for Reporting Qualitative Research (191). All research activity was conducted according to the Tri-Council Policy Statement (http://www.ethics.gc.ca/eng/policy-

politique/initiatives/tcps2-eptc2/Default/). The study received ethics approval from University of Waterloo research ethics board (ORE # 42207). All participants provided informed verbal consent.

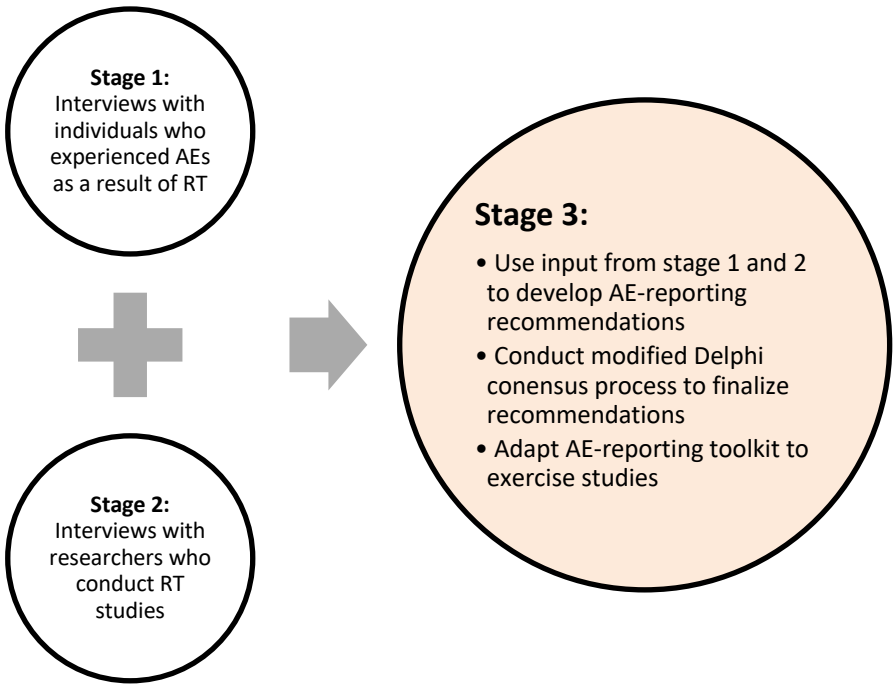

Figure 6.1 Summary of the multi-stage project.

6.3.2 Participant selection

We used purposeful and convenience sampling techniques to recruit participants. We invited the researchers who completed stage 2 (n=14) to participate in the modified Delphi process (stage 3). To identify additional participants, we directly emailed the authors of clinical trials that were in the systematic review that was included in our overview paper to examine benefits and harms of RT, used to inform the Canadian 24-Hour Movement Guidelines (166,188). We also conducted a literature search to identify additional researchers and emailed them directly. Using MEDLINE, we filtered article type to only show "clinical trials" and we used the following search terms: resistance training, strength training, adults, or adverse events. In addition, we directly emailed authors based on referrals from other researchers (snowball sampling). The inclusion criteria were: can speak English fluently;

conducted at least one clinical trial involving RT; recruited adults with or without a health condition in their RT trials. The RT program must meet the definition provided by the Prevention of Fall Network Europe Taxonomy: "contracting the muscles against a resistance to 'overload' and bring about a training effect in the muscular system. The resistance is an external force, which can be one's own body placed in an unusual relationship to gravity (e.g. prone back extension) or an external resistance (e.g. free weight)" (68).

6.3.3 Data collection

We asked participants to first complete an online demographic and descriptive questionnaire (using https://www.surveymonkey.com/) regarding age, sex, education, academic discipline, and career stage. To reduce participant burden, participants who already competed the questionnaire for stage 2 did not have to re-submit their responses.

To adapt the existing AE reporting guidelines, the modified Delphi process applied was a hybrid approach that was informed by three separate papers (57,214,215). Two research team members (RE and JP) generated recommendations based on the interviews with people who have common health conditions and experienced any AE as a result of RT (stage 1, n=12), and researchers who conduct RT studies (stage 2, n=14). The recommendations were turned into a survey (using https://www.qualtrics.com/) and were sent electronically to the Delphi study participants to be rated. The participants rated their agreement with each statement on a scale of 1 to 9, where 1 means strongly disagree and 9 means strongly agree (Figure 6.1) (215). Recommendations with median scores in the 1-3 range were classified as "disagree with recommendation", those in the 4-6 range were classified as "uncertain", and those in the 7-9 range were classified as "agree with recommendation" (215). However, regardless of the median, if a score was spread across the entire 1 to 9 rating scale then it indicated that there was no consensus and thus the recommendation was classified as uncertain (215). Under each rating there was also a text box that allowed participants to provide a rationale for their

score. Given that the recommendations will be used to develop a guide, we decided *a priori* to revise recommendations based on the feedback provided. In the second round, each participant received an individualized survey showing the distribution of all the participants' first round ratings along with their own personal rating and were asked to confirm or re-rate their response (Figure 6.2) (215). The provided feedback was used to improve clarity or address concerns before asking participants to re-rate their responses.

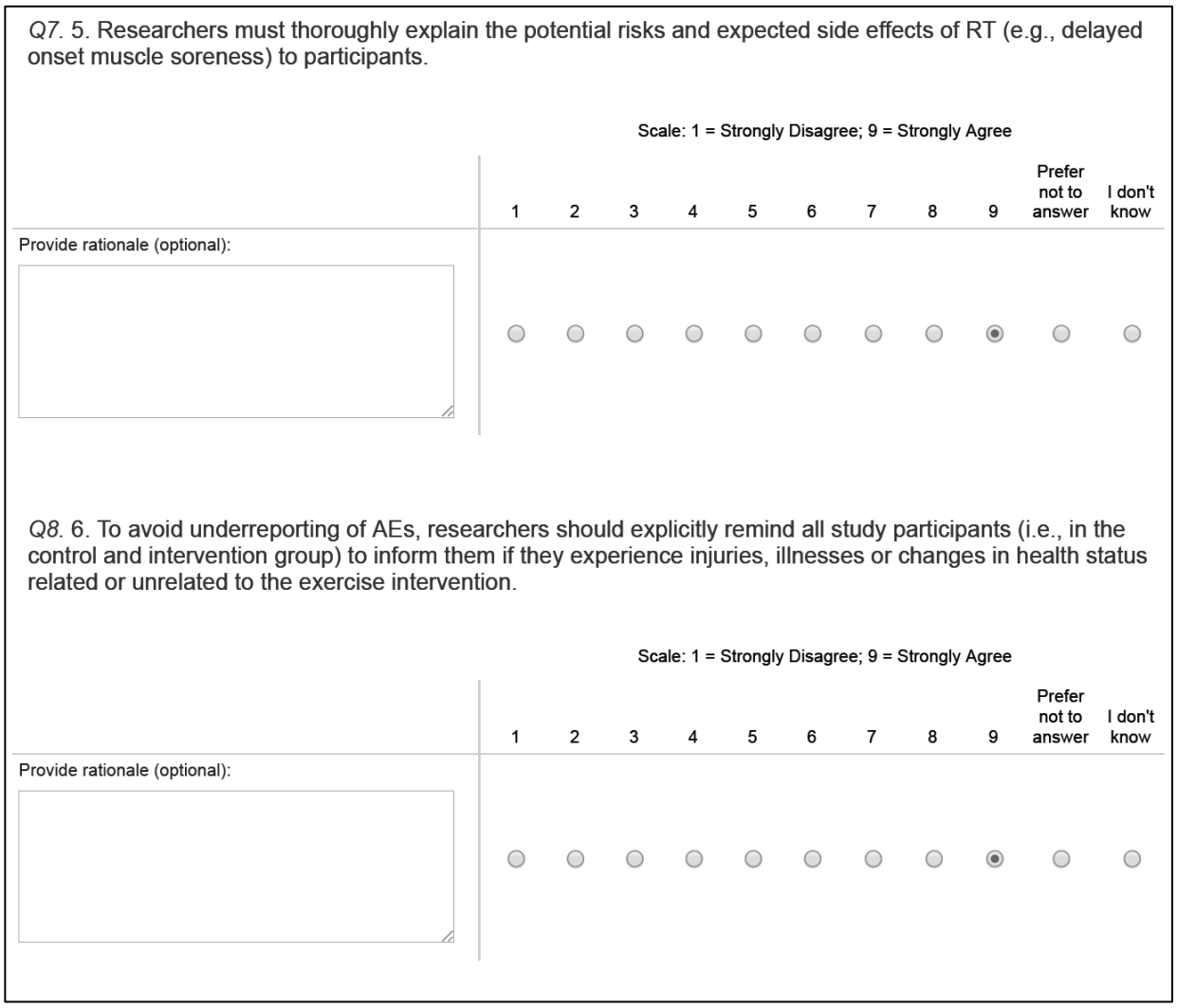

Figure 6.1 Scoring sheet example for the first round

Q55. 5. Researchers should educate participants about the expected side effects of RT (e.g., delayed onset muscle soreness).
<statement has been revised from first round>

Scale: 1 = Strongly Disagree; 9 = Strongly Agree

(Median: 9.0, Standard Deviation: 2.7)

	1	2	3	4	5	6	7	8	9*	Prefer not to answer	I don't know
	2	***0***	***0***	***1***	***0***	***0***	***0***	***2***	***14***	***0***	***0***
Provide rationale (optional):	○	○	○	○	○	○	○	◉	○	○	○

Q98. 6. If researchers are using solicited AE monitoring, they should provide participants with a list of relevant potential AEs.
<statement has been added since first round>

Scale: 1 = Strongly Disagree; 9 = Strongly Agree

	1	2	3	4	5	6	7	8	9	Prefer not to answer	I don't know
Provide rationale (optional):	○	○	○	○	◉	○	○	○	○	○	○

Q56. 7. To avoid underreporting of AEs, researchers should use a standardized protocol to regularly remind all study participants (i.e., in the control and intervention group) to inform them if they experience injuries, illnesses or changes in health status, whether related or unrelated to the study.
<statement has been revised from first round>

Scale: 1 = Strongly Disagree; 9 = Strongly Agree

(Median: 9.0, Standard Deviation: 0.6)

	1	2	3	4	5	6	7	8	9*	Prefer not to answer	I don't know
	0	***0***	***0***	***0***	***0***	***0***	***1***	***6***	***12***	***0***	***0***
Provide rationale (optional):	○	○	○	○	○	○	○	○	◉	○	○

Figure 6.2 Scoring sheet example for the second round. The participant's own response is represented by an asterisk. The number of the remaining participants and their specific rating was added in for each recommendation.

The participants were given two weeks to provide feedback after each round; responses were still accepted if they were within four weeks. Reminders were sent 1-2 weeks apart to participants to complete the survey. We conducted 2-3 rounds of review via email until there was consensus on each recommendation. In case consensus was not reached, we decided *a priori* to conduct a maximum number of three rounds to minimize participant burden. Based on the panel size, consensus was determined by counting the number of panelists whose rating was outside the 3-point region containing the median (1-3, 4-6, 7-9) (Table 6.1) (215). The definition of consensus by percent agreement varies across Delphi studies (range between 50-97%) with a median consensus threshold of 75% which is consistent with our method (216).

Table 6.1 Determining consensus based on panel size

Panel Size	**Number of panelists rating outside the 3-point region containing the median (1-3, 4-6, 7-9)**	**Calculated Minimum Percentage of Consensus Based on Panel Size**
8-9-10	≤ 2	75% - 78% - 80%
11-12-13	≤ 3	73% - 75% - 77%
14-15-16	≤ 4	71% - 73% - 75%
17-18-19	≤ 5	71% - 72% - 74%
20-21-22	≤ 6	70% - 71% - 73%

*This table was adapted from Table 4 by Fitch et al., 2001 (215).

Once consensus was reached, the survey recommendations were used to develop an exercise-specific AE-reporting guideline toolkit (i.e., checklist, template AE form, and decision tree) which was sent to the participants for feedback. Recommendations that were deemed as "in agreement" were included in the guidelines, recommendations that were deemed uncertain were included as optional recommendations, and recommendations that were deemed as "no agreement" were not included in the guidelines. In the case that consensus was not reached after three rounds, the respective

recommendations were included as "other supplementary material" in the guidelines while making it clear that there was no consensus around it.

6.3.4 Sample size and data analyses

There is no definitive standard for the number of panelists who are required to participate in a Delphi consensus process (215,217). For our study, we invited all researchers who met the inclusion criteria based on our search results or referrals and recruited the participants who responded. We used Microsoft Excel (Version 2016; Redmond, WA: Microsoft Corporation) to perform descriptive analysis of the participants. Age was presented as mean (± SD), while sex, education, academic discipline, career stage, and country were expressed as counts (n) and percentages (%). For the modified Delphi process, the median percentage agreement was calculated for each recommendation using Microsoft Excel. Percentage agreements were reported for each round to determine if consensus was reached (i.e., minimum percentage agreement based on panel size number).

6.4 Results

6.4.1 Participant characteristics

All 14 researchers from stage 2 agreed to participate in the Delphi process. Out of the 80 emails submitted, five additional researchers agreed to participate in this study. Overall, a total of 19 researchers from six countries (Canada, USA, UK, Australia, Greece, and Puerto Rico) participated in the Delphi process (Table 6.2). The sample size is in line with other recent studies that conducted a modified Delphi process (217–219). In this study, participants had a mean age of 50.8 years (SD: 10.3 years; range: 34-72 years), 47.4% were female, and 73.7% identified as a senior researcher (Table 6.3).

Table 6.2 List of researchers who contributed to the development of the exercise-specific adverse event reporting recommendations

Name	Credentials	Affiliations

Maureen C. Ashe	PhD	Centre for Hip Health and Mobility, The University of British Columbia, Vancouver, BC, Canada Department of Family Practice, The University of British Columbia, Vancouver, BC, Canada
Belinda Beck	PhD, FACSM	School of Health Sciences and Social Work & Menzies Health Institute Queensland, Griffith University Gold Coast Campus, Gold Coast, Queensland, Australia The Bone Clinic, Brisbane, Queensland, Australia
Lee E. Brown	EdD, CSCS*D, FNSCA, FACSM	Center for Sport Performance and Human Performance Lab, Department of Kinesiology, California State University, Fullerton, Fullerton, California, USA
Phil Chilibeck	PhD	College of Kinesiology, University of Saskatchewan, Saskatoon, SK, Canada
Robin Daly	PhD, FSMA, FASBMR	Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Science, Deakin University, Melbourne, Australia
Ioannis G. Fatouros	PhD, CSCS	Department of Physical Education and Sport Science, University of Thessaly, Trikala, Greece
Walter R. Frontera	MD, PhD	Department of Physical Medicine, Rehabilitation, and Sports Medicine, University of Puerto Rico School of Medicine, San Juan, Puerto Rico Department of Physiology, University of Puerto Rico School of Medicine, San Juan, Puerto Rico
Jenna Gibbs	PhD	Department of Kinesiology and Physical Education, McGill University, Montreal, QC, Canada
Andrea Josse	PhD	Muscle Health Research Centre, York University, Toronto, ON, Canada School of Kinesiology and Health Science, Faculty of Health, York University, Toronto, ON, Canada
Saija Kontulainen	PhD	College of Kinesiology, University of Saskatchewan, Saskatoon, SK, Canada
Lindsay Nagamatsu	PhD	Faculty of Health Sciences, School of Kinesiology, Western University, London, ON, Canada Exercise, Mobility and Brain Health Lab, Western University, London, ON, Canada Brain and Mind Institute, Western University, London, ON, Canada
Kate Mangione	PT, PhD, FAPTA	Department of Physical Therapy, Arcadia University, Glenside, PA, USA

Jeanne F. Nichols	PhD, FACSM, CBDT	Exercise and Physical Activity Resource Center (EPARC), Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego (UCSD), La Jolla, CA, USA School of Exercise and Nutritional Sciences, San Diego State University, San Diego, CA, USA
Gladys Pearson	PGCAP, PhD, FHEA, FPhysiol	Musculoskeletal Science and Sports Medicine Research Centre, Department of Sport and Exercise Sciences, Manchester Metropolitan University, Manchester, UK
Stuart Phillips	PhD, FCAHS, FACSM, FACN	Exercise Metabolism Research Group, Department of Kinesiology, McMaster University, Hamilton, ON, Canada
Robert Ross	PhD	School of Kinesiology and Health Studies, Queen's University, Kingston, ON, Canada
Chip Rowan	PhD, CSEP-CEP, R.Kin	School of Kinesiology and Health Science, York University, Toronto, ON, Canada
Jeff Schlicht	PhD	Department of Health Promotion and Exercise Sciences, Western Connecticut State University, Danbury, CT, USA
Dawn Skelton	PhD, MD h.c., FCSP, FRCP (Edin)	Research Centre for Health (ReaCH), School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, UK

Abbreviations: CBDT, Certified Bone Densitometry Technologist; CSCS, Certified Strength and Conditioning Specialist; CSCS*D, Certified Strength and Conditioning Specialist with Distinction; CSEP-CEP, Canadian Society for Exercise Physiology – Certified Exercise Physiologist; EdD, Doctor of Education; FACN, Fellow of the American College of Nutrition; FACSM, Fellow of the American College of Sports Medicine; FAPTA, Fellow of the American Physical Therapy Association; FASBMR, Fellow of the American Society of Bone and Mineral Research; FCAHS, Fellow of the Canadian Academy of Health Sciences; FCSP, Fellow of the Chartered Society of Physiotherapy (UK); FHEA, Fellow of the Higher Education Academy; FNSCA, Fellow of the National Strength and Conditioning Association; FPhysiol, fellow of the Physiological Society; FRCP (Edin), Fellow of the Royal College of Physicians of Edinburgh (UK); FSMA, Fellow of Sports Medicine Australia; MD, Doctor of Medicine; MD h.c., Honorary Doctor of Medicine; PGCAP, Postgraduate Certificate in Academic Practice; PhD, Doctor of Philosophy; PT, Physical Therapist; R. Kin, Registered Kinesiologist

Table 6.3 Demographic characteristics of the researchers who participated in the Delphi process (n=19)

Characteristics	Participants
Sex, n (%)	
Male (%)	9 (47.4)
Female (%)	9 (47.4)
Prefer not to say (%)	1 (5.3)

Age (in years)	
Mean (± SD)	50.8 (10.3)
Range	34 – 72
Education, n (%)	
PhD	17 (89.5)
PhD and MD	1 (5.3)
EdD	1 (5.3)
Academic Discipline, n (%)	
Kinesiology	10 (52.6)
Rehabilitation Science	2 (10.5)
Health Studies	2 (10.5)
Sport Sciences	1 (5.3)
Medical Sciences	1 (5.3)
Psychology	1 (5.3)
Physical therapy	1 (5.3)
Exercise Physiology	1 (5.3)
Career Stage, n (%)	
Junior	4 (21.1)
Intermediate	1 (5.3)
Senior	14 (73.7)
Country n (%)	
Canada	9 (47.4)
USA	4 (21.1)
UK	2 (10.5)
Australia	2 (10.5)
Greece	1 (5.3)
Puerto Rico	1 (5.3)

Abbreviations: SD, Standard Deviation; PhD, Doctor of Philosophy; MD, Doctor of Medicine; EdD, Doctor of Education; USA, United States of America; UK, United Kingdom.

6.4.2 Delphi results

All 19 participants responded to the three survey rounds (100% response rate). Based on Table 6.1, the consensus cut off for each recommendation was set at 74%. For round one, the average consensus was 81%. There were ten recommendations (out of 24) that were below the consensus cut off. Many respondents who did not fully agree with the recommendation suggested a revision or alternative recommendations, which we used to revise the recommendations. For the second round, the average consensus was 89%. However, there was one recommendation (out of 28) that was below the consensus

cut off. Therefore, we proceeded to round three and asked participants to confirm or re-rate only the one recommendation that did not reach consensus. The recommendation was revised based on the feedback from round two, and reached consensus (~79% agreement) in round three. Also, during round three, we provided for review the first draft of the exercise-specific AE-reporting toolkit (i.e., checklist, template AE form, and decision tree) that was developed using the agreed upon recommendations as well as the NIA AE definitions and template form (87). The toolkit was revised based on the feedback from the respondents (checklist in Appendix E1, template AE form and definitions in Appendix E2, decision tree in Appendix E3).

Topics where there was a lack of consensus in the first two rounds:

How to define AEs when they happen

There was inconsistency across the respondents in regards to the definition of AE versus adverse effect. Therefore, in the second round we defined the terms at the very beginning of the survey highlighting that AE is not synonymous with adverse effect. That an AE is any harmful event that a participant experienced while in the study, and may or may not be related to the intervention. An adverse effect, on the other hand, is an AE that is attributable to study participation (e.g., strength testing, exercise intervention). Furthermore, the NIA AE definitions and classifications were modified specifically to exercise (Appendix E2). Due to the revisions, the consensus for the recommendation listed below increased from around 79% in round one to 95% in round two:

- To ensure consistent AE reporting, all researchers conducting exercise trials should use the modified NIA AE definitions and classifications regardless of age and sex.

With respect to the examples of AEs that could occur with exercise that one might want to consider monitoring for, there was no consensus (round 1 and 2: 58%) on whether muscle soreness should be included in the list. After two rounds of revisions the following recommendation reached consensus (round 3: 79%):

- Researchers should monitor and report transient episodes of mild muscle soreness, joint pain or shortness of breath, but should not count it as an AE unless the symptoms are more severe or persist longer than would be expected with initiation of a new exercise program, or result in a participant missing a subsequent session(s) or having to modify their exercise program.

The full list of exercise-specific examples of AEs that reached consensus can be found at the end of the checklist (Appendix E1).

What methods need to be in place to monitor AEs

During the first round, there was no consensus (58%) as to when researchers should consider a data safety monitoring board (DSMB). After elaborating and clarifying the criteria for having a DSMB, the following recommendation reached consensus in round two (89%):

- Researchers should consider the need for a data safety monitoring board (DSMB) when recruiting participants with health conditions or if testing an intervention where AEs may be expected. A DSMB should be used when studying an intervention that involves side effects that cause serious morbidity or mortality, or are irreversible, when the study involves vulnerable participants (e.g., studies with high morbidity or mortality, or impaired ability to consent), when mortality is a study endpoint, or when interim analyses or stopping rules are being used.

Also, there was no consensus (round 1: 58%) that providing a greater number of exercise trainers to supervise the exercise sessions is considered a feasible strategy to reduce AEs in study participants who are considered at a greater risk of experiencing an AE. Some respondents cautioned that it may depend on study funding, resources and nature of the intervention (e.g., home vs. center-based; individual vs. group; virtual vs. in-person). Moreover, some respondents questioned whether it would be a necessary or even an effective strategy. Therefore, the recommendation was revised to the following and reached consensus in round two (84%):

- Providing a greater number of exercise trainers to supervise the exercise sessions or having a limited number of participants per session if recruiting participants who are at a greater risk of experiencing AEs or who are unfamiliar with RT.

How to classify AEs as attributable or not when they happen

Respondents indicated that the recommendation for what to do if it is unclear whether an AE is attributable to the intervention, was not clearly described in the first round (63% consensus). Therefore,

a more elaborate description was included and the following recommendation reached consensus in round two (94%):

- If it is unclear whether an AE attributable to the intervention, the primary investigator (PI) or trained delegate should thoroughly discuss the AE with the participant or their delegate to get additional information, including their perspective on the event, to report on the event or determine if it is attributable.

Furthermore, there was no consensus (round 1: 53% consensus) that if there is a DSMB, the designated chair should determine whether the AE is considered definitely or possibly related to the intervention. The respondents highlighted the importance of consulting other parties and thus the recommendation was revised to the following (round 2: 79% consensus):

- If there is a DSMB, the designated chair should make the final decision as to whether the AE is considered definitely or possibly related to the intervention based on the available information, and in consultation with the rest of the committee, the PI, and only if necessary, with a health care professional independent of the study team.

The decision tree (Appendix E3) outlines the process with respect to AEs that occur in a study with or without a DSMB.

What actions to take when AEs happen

The respondents indicated that the principal investigator (PI) and the participant are not the only two who decide whether the participant should withdraw from the study if they experience an AE (round 1: 63% consensus). The respondents suggested to consider involving the DSMB as well as the participant's delegate. Therefore, the recommendation was revised to the following (round 2: 89% consensus):

- The DSMB or PI and the participant or their delegate should agree on whether the participant should withdraw wholly or in part from the intervention/control activities if they experience an AE. If the participant is willing, they should remain in the study even if they withdraw from intervention/control activities. Any data that can be collected safely from that participant should be collected and included in intention to treat analyses for the group to which they were allocated.

For round one, there was no consensus (68%) on the recommendation that researchers should follow up with participants and specify the outcome of AE as one of the following: resolved-no sequel, AE still present no treatment, AE still present- being treated, residual effects present-not treated, residual effects present-treated, death, unknown. Respondents indicated that it was important to provide further details regarding treatment. Therefore, in the second round, two recommendations were included to address the feedback (100% consensus on both):

- On the AE reporting form, researchers should specify the action taken regarding any type of AE as follows:

Action Taken/Treatment Regarding AE (select all that apply)
☐ None ☐ Medication ☐ Health care provider ☐ Hospitalization: ___ nights ☐ Emergency room visit ☐ Undisclosed ☐ Other (specify): _____ Notes:

- On the AE reporting form, researchers should follow up with participants or their delegate and specify the outcome of any type of AE as follows:

Outcome of AE
☐ Resolved ☐ AE still present ☐ Residual effect of AE present ☐ Death ☐ Undisclosed Notes:

The full template AE form is in Appendix E2.

How to report AEs in publications

In the first round there was no consensus pertaining to which AEs should researchers report in their publications. There was 68% consensus on reporting mild, moderate and severe AEs, 53% consensus on reporting only serious AEs, and 53% consensus on reporting AEs that are related and unrelated to the exercise intervention. For the second round, the AE definitions were modified to exercise and the recommendations were grouped differently. The results demonstrated an 84% agreement on reporting mild, moderate, severe and serious AEs in publications. As for relatedness, along with the exercise-related definitions and examples, the recommendation was re-worded to "related and unrelated AEs that occurred in the intervention group (reported separately)" and there was 89% consensus agreement.

6.5 Discussion

In the guidelines for AE methods and reporting, it is important to convey the distinction between AE and adverse effect to the exercise community to avoid having people consider the terms as interchangeable. Furthermore, access to exercise-specific AE examples, along with modifications of definitions and template forms in the context of exercise may reduce inconsistent AE reporting in RT studies. Adapting the AE reporting guidelines to exercise is not enough to change behavior or practice and thus we should consider and plan for dissemination and implementation strategies.

The findings demonstrated that, despite the different meanings, the terms AE and adverse effect are used interchangeably within the exercise community. The available guidelines define an AE as an unfavorable occurrence that does not necessarily have to have a causal relationship with the treatment or intervention (87,183,207). Whereas an adverse effect is an AE that is attributable to study participation (e.g., strength testing, exercise intervention) (84). The terminology used to report harms is considered to be poorly standardized and thus may lead to misleading conclusions (85). Furthermore, a methods guide for assessing harms by Chou et al. cautioned that classifying AEs as only those that are intervention-related is considered a subjective measure of harms (220). Our findings, and the fact

that AEs are poorly reported in exercise trials, suggest that many exercise researchers may be either unaware of the existing AE definition and reporting guidelines, or assume they are only relevant to pharmaceutical trials. In the second survey round, the inclusion of a clear distinction between AE and adverse effect in the context of exercise studies did not only contribute to the increase in percentage agreement on the recommended AE definition, but it also likely contributed to the increase in overall consensus (round 1: 81% vs. round 2: 89% agreement). All of the suggested recommendations were centered around AEs and thus, as expected, the participants' interpretation of what constitutes an AE influenced their survey response. Therefore, the distinction between AE and adverse effect must be clearly communicated to the exercise community, and defined in any exercise-specific AE guidelines. Furthermore, access to exercise-specific AE examples may reduce inconsistent AE reporting among the exercise community. Given that the available AE guidelines are drug-trial focused, the examples used to classify intervention-related AEs may not be applicable to exercise (87,183,207). For instance, a review of systematic reviews examining the benefits and harms of RT showed that in 14 trials muscle soreness was reported as a "non-serious AE" (188). However, in this study not all participants agreed that muscle soreness should count as an AE since it is a normal response to exercise. Furthermore, some participants indicated that muscle soreness should still be monitored and reported even if it doesn't count as an AE, while others disagreed. How and when to report AEs related to muscle soreness in exercise trials was the only recommendation that had to undergo a third survey round to reach consensus. Therefore, the findings of this study emphasize the complexity of AEs in the context of exercise and the necessity of exercise-specific AE reporting guidelines.

For most AE methods and reporting recommendations, we found that we reached consensus in the second round after clarification, elaboration, or modification of the guidelines, and providing exercise-specific examples. The revised AE recommendations for exercise trials provide clear criteria for when to have a DSMB, feasible strategies to reduce AEs, and options for consulting other parties to aid in

decision-making. The NIA guidelines already have an AE reporting template form, however similar to the AE definitions it is drug trial-focused (87). For instance, if an AE occurs, the options for actions taken regarding study intervention include “reduced dose”, “increased dose”, or “delayed dose” which could be a possible reason as to why exercise researchers do not commonly use these existing AE forms (87). Therefore, in our adapted AE reporting toolkit the options for actions taken were modified to the exercise context such as “exercise modified”, “exercise paused” and “exercise terminated”. Also, in the NIA AE reporting template form, the outcome of AE included a combination of both outcome as well as treatment status (87). However, the participants in this study preferred to report outcome and treatment of AE as two separate categories and to elaborate with respect to method of treatment (e.g., medication, health care provider, hospitalization). The adapted AE form can be used for different types of exercise studies and even suggests the option of adding another column for “Action Taken Regarding Exercise Control” if the control group is also engaging in exercise (e.g., a different type of exercise than the intervention). Furthermore, given that definitions with respect to relatedness and expectedness of AEs already exist, they just needed to be modified to include exercise terms and examples (87). Once we outlined the AE definitions (e.g., relatedness, expectedness) in the second round, we reached consensus on the AEs that should be reported in publications. Overall, an exercise-adapted AE reporting template form provides clear instructions on how the existing guidelines can be applied to RT studies.

Based on our prior work (stages 1 and 2), we identified education and mass-media/communication campaigns as dissemination strategies and engaging stakeholders and access to planning tools as implementation strategies. Guideline development without dissemination and implementation plans is not enough to change behavior or practice (221). In the context of our study, dissemination of the guidelines involves purposive distribution of the adapted exercise-specific AE reporting guidelines to researchers who conduct RT studies (91,92). As for implementation of the guidelines, it involves the actions required to support researchers in following the guidelines when conducting RT studies (91,92).

Dissemination can include education strategies such as presenting the adapted guidelines at research institutions, graduate university courses, or at relevant conferences (91,92). Mass-media/communication campaign dissemination strategies can include distributions of the adapted guidelines via relevant websites and social media (91,92). It is essential to concurrently consider and use dissemination and implementation strategies, as dissemination strategies on their own are not enough to change behavior or improve adherence to guidelines (91). Implementation strategies can include engaging stakeholders such as exercise organizations who would be interested in improving the quality of reporting harms in RT studies (91,92). Also, involving journals to make AE reporting guidelines a requirement when submitting manuscripts. Furthermore, having planning tools such as our AE reporting checklist can help guide action steps related to changing AE reporting behavior among exercise researchers (91,92). The objective of this study was to adapt existing tools to RT trials as opposed to developing new ones. Therefore, commonly used tools such as the CONSORT checklist, as well as already existing AE reporting forms (i.e., NIA AE reporting template form and decision tree) were adapted specifically for AE reporting in RT trials. In the future, to evaluate impact of the dissemination and implementation strategies, we can examine AE reporting practice in RT studies published after the adapted guidelines were released.

6.5.1 Limitations

We acknowledge a few study limitations. We did not invite participant or lay voices to the consensus process. We did, however, interview lay people about their experience with AEs, to inform the development of the recommendations that were included in the consensus process. The "ideal" contribution from the patient/participant representative is unclear with respect to the guideline development process (204). However, according to the implementability framework, guidelines are more implementable when they consider the patient/public perspective (222). The Appraisal of Guidelines for Research and Evaluation II instrument indicates that guideline developers should seek

the view of the target population (223). Therefore, given that the target population for the adapted guidelines are researchers, we decided it was sufficient to consider patient/public perspective when generating the recommendations, but not during the consensus process. With respect to participant characteristics, even though we recruited five more researchers there was still a disproportionate number of participants from Canada. Also, we reported sex but not gender and thus we are uncertain whether or how the survey responses would vary based on sex or gender.

6.6 Conclusion

A modified Delphi consensus process was performed to develop an exercise-specific AE-reporting toolkit (i.e., checklist, template AE form, and decision tree). After a total of three survey rounds (100% response rate) there was consensus on each suggested recommendation. To reach consensus, the results depicted the importance of distinguishing between AE and adverse effects, providing exercise-specific AE examples, and modifying existing AE definitions and template forms to exercise intervention studies. The overall aim of the developed toolkit along with dissemination and implementation strategies is to improve AE reporting in RT studies.

Chapter 7: General Discussion

7.1 Summary of findings and implications

The overarching objective of this thesis was to inform resistance training (RT) interventions with respect to timing, benefits and the proper reporting of harms. The secondary data analysis exploring changes in bone mass in individuals with a chronic spinal cord injury (SCI) demonstrated that bone loss reached a plateau in trabecular bone, but there was still cortical bone loss. Therefore, exercise interventions aimed to reduce the risk of fracture should be considered during the chronic stage of SCI, not just the acute stage. The overview of systematic reviews showed that RT programs were associated with improving health outcomes (e.g., reduction in all-cause mortality) among the generally healthy adult population (≥ 18 years). Given the health-related benefits, RT interventions programs should be considered as treatment or prevention options for chronic disease. However, the findings indicated that adverse events (AEs) were not being consistently monitored or reported in RT studies. The qualitative study identified AE reporting knowledge gaps from both the participant and researcher perspective and was used to inform and develop an exercise-specific AE-reporting toolkit via a consensus process. Consistent AE reporting in RT studies will allow researchers, health care providers, and patients to make well-informed evidence-based decisions as to whether the benefits of RT interventions truly outweigh the harms. The thesis findings and implications are summarized in Table 7.1.

Table 7.1 Summary of thesis findings and implications

	Title	Overarching Objective	Findings	Implications
Study 1	Exploring changes in bone mass in individuals with a chronic spinal cord injury	To inform exercise interventions with respect to timing (i.e., timing effective interventions aimed to reduce the risk of fracture).	There were no changes in trabecular bone (trabecular volumetric BMD at the 4% tibia site), but reported a decline in cortical bone (cortical volumetric BMD, cortical thickness and cross-sectional area at the 38% tibia site) in people with a chronic SCI.	Exercise interventions aimed to reduce the risk of fracture should be considered beyond the acute stage of SCI.
Study 2	Resistance training and health in adults: An overview of systematic reviews	To inform RT interventions with respect to benefits.	RT was associated with a reduction in all-cause mortality and cardiovascular disease incidence, and an improvement in physical functioning. However, AEs were not being consistently monitored or reported in RT studies.	RT interventions programs should be considered as treatment or prevention options for chronic disease.
Study 3	Stage 1: A qualitative study exploring participants' perspectives on adverse events due to resistance training Stage 2: A qualitative study of researchers' perspectives on adverse event reporting in resistance training trials Stage 3: A modified Delphi process to adapt adverse event reporting guidelines to resistance training studies	To inform proper reporting of harms in RT interventions.	Knowledge gaps with respect to AE reporting were identified from the participant and researcher perspective. An exercise-specific AE-reporting toolkit was developed via a consensus process and knowledge translation strategies were identified.	Consistent AE reporting in RT studies will allow researchers, health care providers, and patients to make well-informed evidence-based decisions as to whether the benefits of RT interventions truly outweigh the harms.

Abbreviations: BMD, Bone Mineral Density; SCI, Spinal Cord Injury; RT, Resistance Training; AE, Adverse Event

7.1.1 Timing of exercise interventions

People with a chronic SCI could continue to benefit from exercise interventions to prevent loss in bone mass. Sublesional bone loss occurs rapidly the first six months after a SCI and is thought to stabilize after 12 months (224). Therefore, it is not surprising that most exercise interventions studies aimed to prevent or treat SCI-related osteoporosis are more commonly conducted in the acute phase of a SCI. However, the results of our exploratory secondary data analysis revealed that there was a statistically significant decline in cortical volumetric bone mineral density (BMD), cortical thickness and cross-sectional area in individuals with a chronic SCI (≥ 2 years). Currently, there is no high-quality evidence to indicate that exercise interventions can prevent or treat SCI-related bone loss due to small sample size, high risk of bias, and significant heterogeneity across studies (109). Comparisons of BMD changes across studies were challenging as some used dual energy X-ray absorptiometry (DXA) while others used peripheral quantitative computed tomography (pQCT) (109). Exercise intervention studies that show small changes in aBMD (i.e., using DXA) may be considered ineffective at improving bone strength (70). However, animal model exercise studies demonstrated that even small changes in bone mass were able to significantly improve bone strength by favorably altering bone geometry (70). Therefore, BMD along with bone geometry measures (e.g., shape and size) assessed via pQCT may be a better assessment of exercise effectiveness at improving bone strength than simply using aBMD via DXA (70). Provided that our exploratory study showed that bone loss does not reach a steady state in people with a chronic SCI, the effectiveness of exercise interventions at reducing fracture risk (via assessment of BMD and bone geometry) may need to be examined beyond the acute phase of injury.

7.1.2 Considering resistance training interventions as therapy

In addition to aerobic exercise, specific and clear RT recommendations are required to prevent or treat chronic health conditions. The findings of our overview of systematic reviews showed that RT was associated with a reduction in all-cause mortality and cardiovascular disease incidence, and an

improvement in physical functioning. Therefore, performing RT, at least twice a week, can serve as a preventative strategy for chronic disease among the generally healthy population (52). Exercise interventions have also been prescribed to treat or manage existing chronic health conditions, but there tends to be greater emphasis and more guidance with respect to aerobic exercise. For instance, the American College of Sports Medicine's (ACSM) recommendations for exercise preparticipation health screening provide clear instructions for people with chronic health conditions (e.g., cardiovascular disease, diabetes) regarding aerobic exercise participation only (225). A possible reason why aerobic exercise prescription or participation may be preferred is because RT often requires some initial instruction and depends on knowledge of exercise technique and, in some cases, on equipment availability (208). RT guidelines for the clinical population are not as consistent or well-established as those for the generally healthy population. For example, numerous exercise (aerobic and RT) prescription guidelines exist for people with multiple sclerosis, stroke and Parkinson's disease (226). Furthermore, there are specific RT considerations depending on the target clinical population, such as performing strength exercises in a seated position to reduce risk of falls among people post-stroke (227,228). In addition to safety considerations based on the target population, the goal of the exercise recommendations should depend on the characteristics of the chronic condition. For instance, exercise prescription for people with osteoporosis should be primarily focused on improving bone health (i.e., osteogenic exercise). Overall, RT guidelines for people with chronic disease should incorporate population-specific safety considerations and include effective exercise properties that can improve or manage the underlying health condition.

7.1.3 Proper reporting of harms in resistance training studies

Before RT can be appropriately prescribed as prevention or treatment for chronic health conditions, AE reporting in exercise trials should be systematically conducted across studies. Exercise intervention studies involving healthy participants as well as people with health conditions do not

consistently monitor or report AEs (84,188). To improve AE reporting, our qualitative study findings were used to inform and adapt existing AE reporting guidelines to exercise trials. The adapted AE reporting guidelines were designed to be applicable to different types of exercise trials and for various populations. Proper reporting of AEs in RT intervention studies is necessary to inform clinical decision making; it is necessary for clinicians who are prescribing RT as a therapy for their patients (229,230). Furthermore, patients cannot provide fully informed consent if the harms of the RT intervention are ambiguous (231).

Consistent with the knowledge-to-action framework (KTA), we identified the problem, conducted knowledge synthesis, assessed barriers, as well as adapted and tailored knowledge related to AE reporting practice in RT interventions (90). Knowledge synthesis "represents the aggregation of existing knowledge" and this was collected via our overview of systematic reviews as well as via the semi-structured interviews with the general public and researchers (90). The purpose of knowledge tools or products "is to present knowledge in clear, concise, and user-friendly formats and ideally provide explicit recommendations with the intent of influencing what stakeholders do and to meet stakeholders' knowledge or informational needs, thereby facilitating the uptake and application of knowledge" (90). The knowledge tool that we derived was the adapted exercise-specific AE-reporting toolkit (i.e., checklist, template form, and decision tree). Furthermore, while using the KTA framework, appropriate dissemination and implementation strategies were selected with the intention to change AE reporting practice. Overall, access to standardized AE reporting guidelines for RT studies along with dissemination and implementation strategies can potentially improve reporting of harms.

7.2 Limitations

An overarching limitation was that the although the three included studies were used to inform one overall theme, they involved various populations. To inform timing, benefits and proper reporting

of harms in RT interventions we examined people with a chronic SCI, the generally healthy population, and people with common chronic health conditions, respectively. Furthermore, the secondary data analysis involving people with chronic SCI was primarily focused on bone changes whereas the benefits and harms of RT interventions were not specifically investigated with respect to bone health. The original thesis plan was primarily focused on osteoporosis and the purpose of the exercise clinical trial, that was suspended due to COVID-19, was to investigate bone changes among women who are taking osteoporosis medications. Shortly after the exercise clinical trial was suspended, a new study was devised based on the results of the overview of systematic reviews (study 2). Largely, although the modified thesis plan did not mainly focus on bone adaptations in response to disuse or exercise, it was selected based on identified knowledge gaps, research activity restrictions (i.e., no in-person data collection due to COVID-19), and available resources.

7.3 Future research

The findings of this thesis can be used to inform future research with respect to exercise interventions. To determine whether exercise interventions can manage or prevent bone loss among people with chronic SCI, there needs to be homogeneity in selection of outcome measurement (i.e., use pQCT instead of DXA to assess bone mass and geometry) across studies. Furthermore, since sample size tends to be small in SCI studies, researchers should consider conducting multi-center exercise clinical trials. In terms of reporting harms in exercise studies, consistent with the KTA framework, future studies are required to monitor and evaluate use of the adapted AE reporting guidelines. As a next step, to supplement the guidelines, it would important to consider the clinician perspective on how they use AE reporting data in exercise trials when prescribing RT as treatment for their patients. More specifically, another qualitative study could be conducted to interview clinicians and understand how AE reporting impacts decision making around rehabilitative exercise interventions.

7.4 Conclusions

The timing, benefits and harms of RT interventions are important considerations when used to prevent, manage or treat health outcomes. In terms of timing, exercise interventions aimed to improve bone health should be considered and assessed in the acute as well as the chronic phase of a SCI. The benefits and recommendations for RT are clear with respect to prevention of chronic disease among the generally healthy population. For individuals with chronic health conditions, specific RT program recommendations should be considered to provide safe (e.g., RT performed in a seated position) and effective (e.g., osteogenic RT to improve bone health) treatment or management of the underlying health condition. Finally, an exercise-specific AE-reporting toolkit along with dissemination and implementation strategies will ultimately allow people with common health conditions, researchers, and health care providers to make evidence-based decisions as to whether the benefits of RT truly outweigh the harms.

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Appendices

Appendix A: Suspended study

The study below was suspended due to COVID-19.

Title: Bone Response to Resistance and Impact Exercise (BRRIE) in Women on Antiresorptive Medications: A Randomized Controlled Trial

Introduction

Pharmacological and exercise interventions aimed to treat osteoporosis are typically examined separately. A common pharmacological treatment for osteoporosis involves antiresorptive medications, which has been previously shown to blunt the bone response to exercise (66,232,233). Many studies have shown that moderate-high intensity progressive resistance training (RT) and impact exercise is required to stimulate bone (58–67). There are only two RCT studies that examined the effect of progressive resistance training or impact exercise on bone response in participants taking antiresorptive medications (232,233). One study showed that the combination of antiresorptive medications and resistance training did not increase bone mineral density (BMD) to a greater extent than medications alone in postmenopausal women (232). Another study demonstrated no additive effect of antiresorptive medications and progressive impact exercise on reducing bone turnover markers (BTMs) in postmenopausal women (233). However, there are currently no available studies that examine the effect of both progressive resistance training along with impact exercise on the bone response in women taking antiresorptive medications. Most exercise studies exclude people taking medications that affect bone, or are heterogeneous with respect to antiresorptive medication use. Further, there is little data on the safety of moderate-high intensity progressive RT and impact exercise in individuals at moderate or high risk for fracture.

The bone response to medications and exercise can be measured via the assessment of bone biomarkers present in the blood. For instance, sclerostin is a protein secreted by osteocytes and it can influence the bone remodeling process by inhibiting bone formation (234). Human genetic disorders deficient in sclerostin, such as sclerosteosis and Van Buchem's disease, have been associated with significant increases in bone mass (235). Therefore, decreasing sclerostin levels may be a potential treatment for people with low bone mass conditions (236). A case-control study demonstrated that postmenopausal women who adequately responded to bisphosphonates (e.g., did not experience a fracture while on treatment) had significantly lower serum sclerostin concentrations than those who experienced a fracture while taking bisphosphonates (237). There is also a link between sclerostin and exercise as a previous cross-sectional study reported an association between low serum sclerostin levels and increased physical activity duration (238). In addition, RT and high impact exercise interventions have been shown to decrease sclerostin levels in healthy pre-menopausal women and thus may eventually increase bone mass or prevent bone loss (238,239). Therefore, changes in serum sclerostin levels can be used to provide insight regarding the bone response to antiresorptive medications as well as exercise.

We plan to conduct a single-blinded parallel-group randomized controlled trial (RCT) with 1:1 allocation ratio to determine whether participants with low bone mass are able to adhere and safely perform RT and impact exercises at an intensity that is hypothesized to stimulate bone. Specifically, the primary aim will be to determine the effects of moderate-high RT and impact training on sclerostin in women on antiresorptive medication. The secondary aims will be: a) to explore the effects of moderate-high RT and impact training on BTMs [serum N-terminal procollagen of type I collagen (P1NP), C-terminal cross-linked of type I collagen (CTX), parathyroid hormone (PTH), Vitamin D and serum calcium], physical function and quality of life and body composition; b) to determine the feasibility of the intervention by assessing adherence, participant satisfaction with the intervention, and the acceptability of the attention control group; and c) to determine if there are any adverse events (AEs), including falls, fractures, or other adverse health outcomes attributable to the exercise intervention.

Methods

Study setting

This is a sub-study of an observational case-control multicentre study examining the clinical and genetic risk factors for atypical femur fractures (AFF) in women taking antiresorptive medications for osteoporosis. However, all research activity related to this sub-study will only take place at the University of Waterloo site in Waterloo, Ontario, Canada.

Trial design

This study is a single-blinded RCT comparing moderate-high RT and impact exercise to an attention control that receives static posture and balance exercises. Using a computer-generated random selection process, the participants will be randomized in a 1:1 allocation ratio in blocks of variable sizes (2, 4 or 6 per block) which will be randomly determined. The randomization sequence will be created and maintained using a secure web application known as Research Electronic Data Capture (REDCap). After the baseline assessment, an unblinded study investigator will access the randomization and determine the group allocation for each participant. Allocation will be concealed from all but the person performing the randomization, the participants, and the exercise trainers. Although the participants cannot be blinded to the assigned exercise group, they will simply be informed that the purpose of the study is to compare two different exercise programs with no indication regarding the study hypothesis.

Participants

Individuals will be eligible for inclusion if they are women over the age of 18 years and are taking antiresorptive medications for at least 12 months such as risedronate (Actonel), alendronate (Fosamax, Fosavance), etidronate (Didronel, Didrocal), zolendronic acid (Aclasta, Reclast, Zometa), pamidronate (Aredia), and denosumab (Prolia, Xgeva). Exclusion criteria will include: not able to communicate in English; already participating in a structured progressive resistance exercise or impact training exercise program; presence of any progressive neurological disorders that can possibly prevent study completion; unable to stand or walk 10 m with or without a gait aid; does not have the mental capacity to provide informed consent; or if they have any contraindications to exercise as determined by a physician. If individuals have had a fracture in the last 6 months, they need to have completed any immobilization (e.g.,

casting) and post-fracture rehabilitation, and they need physician consent to participate in the study. We will not exclude individuals who have had any fractures in the past (> 6months ago).

Intervention exercise:

Setting and supervision

Exercise training will be performed at the Centre for Community, Clinical, and Applied Research Excellence (CCCARE) at the University of Waterloo. The exercises will be performed under the supervision of Certified Exercise Physiologists (Canadian Society for Exercise Physiology) or BoneFit™ trained exercise instructors. The first exercise session will involve 1:1 supervision to provide coaching on proper form and selecting appropriate exercise intensity progression. In the following 2-3 months the exercise sessions will be offered in a small group setting with a maximum of five participants per trainer. If less supervision is required, the remainder of the exercise sessions will be offered with a maximum of nine participants per trainer. The exercise instructors will receive a training manual that provides guidance on how to deliver and progress the exercises.

Goal and exercise modes

The primary goal of the exercise program is to increase bone and muscle strength. Each exercise session will include a 5-10 minute warm up involving repetitive dynamic range of motion exercises that mimic the movement patterns of the exercise program, completed at a low intensity. Following exercise, each session will be concluded with a cool down of range of motion exercises targeting joints that are often restricted (e.g., hips, shoulders, ankles). The initial session will include a screening of body mechanics during an unweighted overhead reach, hip hinge and squat movement. Participants will be individually prescribed variations of the main exercises they can safely complete, and accessory exercises to help develop movement patterns. Exercises will challenge both the upper and lower body using functional movement patterns. Each muscle group will be trained twice a week: Day 1 will include a squat, deadlift or hinge, vertical press, horizontal pull, weighted carry, and accessory exercises to address specific weaknesses, and complement the development of basic movements. Day 2 will include a squat, step up or lunge, vertical pull, vertical press, horizontal press and weighted carry. Exercise trainers will assess each participant during

the performance of each exercise using body weight or low weight as resistance, and will select the appropriate exercise variation.

Frequency and duration

Full body resistance and impact exercises will be performed twice a week and each training session will be approximately 30-45 minutes long. There will be at least one day of rest between each scheduled exercise session.

Intensity

During the first month, participants will focus on completing exercises with good form at a low intensity. Once form is mastered, exercises will be progressed (by increasing load, or challenge of the movement) so that the participant can complete a maximum of 8 repetitions with 1-2 repetitions in reserve for 3 sets and a rating of perceived exertion (RPE) of 8-9. Further progressions will follow the two for two rule, increasing load by 2.5-10% once a participant can perform 2 or more additional repetitions in the final set of an exercise, over 2 consecutive sessions, to a maximum 85% 1 repetition maximum (1RM). 1RM is the maximum weight someone can lift with proper form for one repetition (240). The exercises will be performed at a moderate to high exercise intensity (80-85% 1RM) where 8 (~80% 1RM) or 6 (~85% 1RM) repetitions can be performed with good form will be determined for each exercise using multiple RM testing.

Time

The exercise training program will be performed over a span of 6 months.

Comparator

The participants in the attention control group will perform static posture and balance exercises (e.g., low intensity yoga poses) and will be given the same attention as the participants in the intervention group. The frequency and duration of the exercise program will be the same as the intervention group (i.e., twice a week, 30-45 minutes per session, over 6 months) with at least one day of rest between each session. The small group exercises will also be performed at CCCARE under the supervision of a certified personal

trainer and yoga instructor that is BoneFit™ trained. Each exercise session will include a warm up and a cool down as part of the class.

Data collection and management

Consent forms, standard operating procedures, case report forms, and exercise training programs will be available in the BRRIE Study Manual. Research staff blinded to group allocation will have access to the assessment forms. An alternate research staff member will collect or enter data that may cause unblinding (e.g., randomization, exercise adherence logs). Exercise trainers who are unblinded to group allocation will have access to the exercise training manual. The schedule for recruitment and screening, assessments, and the exercise training for the intervention and control group is outlined in Table A1.1. Password protected Microsoft Excel sheets will be used to input and manage all data. Completed outcome assessments and exercise training related data will be stored in separate files to avoid exposing group allocation.

Table A1.1 Time schedule of enrolment, assessments and interventions

Activity	Staff Member	T-2: Pre-screening	T-1: Screening/ Consent	T0: Baseline	T1	T2-T14	T15: 3-month follow-up	T16-T28	T29: 6-month follow-up
Recruitment and Screening									
AFF study informed consent	Staff blinded[a]	X							
Screening Questionnaire	Staff blinded[a]		X						
BRRIE study informed consent	Staff blinded[a]		X						
Assessments									
Demographic and medical history information	Staff blinded[a]			X					
Physical activity level	Staff blinded[a]			X					
Dietary Intake	Staff blinded[a]			X			X		X
Bone biomarkers	Staff blinded[a]			X			X		X
Physical function and mobility	Staff blinded[a]			X			X		X
Quality of life	Staff blinded[a]			X			X		X

Body Composition	Staff blinded[a]			X					X
Randomization	Staff unblinded[b]				X				
Exit Interview	Staff unblinded[b]								X
Feasibility outcomes: participants recruited and retained, exercise adherence and acceptability of attention control	Staff blinded[a]								X
Fracture/fall ascertainment questionnaire	Staff blinded[a]	As needed throughout the study							
Serious/non-serious adverse events	Staff blinded[a]								
Exercise Program									
Intervention group: RT and impact exercise program	Exercise Trainers					X		X	
Control Group: Posture and balance exercises	Exercise Trainers					X		X	

T: time point; AFF: atypical femur fractures; BRRIE: bone response to resistance and impact exercise; RT: resistance training

[a]Refers to a research coordinator or research assistant who is blinded to group allocation.

[b]Refers to a research coordinator or research assistant who is unblinded to group allocation.

Primary outcome: Sclerostin

The primary outcome measure will be serum sclerostin. Venous blood samples will be taken by experienced phlebotomists between 8:00 and 10:00 am, after an overnight fast (8-12 hours). Participants will also be instructed to refrain from exercise for 48 hours prior to blood collection. An assessor who is blind to group allocation will measure sclerostin using ab221836 Human SOST SimpleStep ELISA® (Enzyme-Linked Immunosorbent Assay) supplied by Abcam (Abcam Inc., Toronto, Ontario, Canada). To ensure consistency in precision, the same assessor will measure sclerostin at baseline, at the 3-month, and at the 6-month follow-up.

Secondary outcomes

Other bone biomarkers

Serum P1NP, CTX, PTH, vitamin D and calcium will be also be measured by the same single blinded assessor. P1NP will be measured using Human Total Procollagen Type I Intact N-Terminal Propeptide (TP1NP) ELISA Kit supplied by MyBioSource (MyBioSource Inc., San Diego, California, USA). Beta-crosslaps CTX will be measured using Human beta-crosslaps (bCTx) ELISA Kit supplied by Cusabio (Cusabio Technology LLC, Houston, Texas, USA). Parathyroid hormone will be measured using ab230931 Human PTH SimpleStep ELISA® Kit supplied by Abcam (Abcam Inc., Toronto, Ontario, Canada). Vitamin D will be measured using Human 25-Hydroxyvitamin D-1 Aplha Hydroxylase Mitochondrial (CYPB27B1) ELISA® Kit supplied by Cusabio (Cusabio Technology LLC, Houston, Texas, USA). Calcium will be measured using ab112115 Calcium Quantification Kit – Red Fluorescence supplied by Abcam (Abcam Inc., Toronto, Ontario, Canada). To ensure consistency in precision, the same assessor will measure sclerostin at baseline, at the 3-month, and at the 6-month follow-up.

Physical function and mobility

Physical function and mobility will be assessed using the following tests: 40 m fast-paced walk test, 30-second sit-to-stand test, 4-square step test, and stair climb test. A brief description of each test is provided below:

40 m Fast-paced Walk Test is a test for short distance walking activity, walking speed over short distances and changing direction during walking. It is a fast-paced walking test that is timed over 4 x 10 m for a total of 40 m. Participants are asked to walk as quickly and safely as possible for 10 m down a walkway, turn around and repeat for a total distance of 40 m (3 turns). Time is recorded from when the participant starts the test until they complete the 40 m walk.

The test was found to be a reliable measure [Inter-tester Intraclass Correlation (ICC) of 0.95, 95% CI: 0.90-0.98] with a minimal clinically important improvement of 0.2-0.3m/sec in people with hip osteoarthritis (mean age of 66.5 ± 9.4 years) (241).

30-second Chair Stand Test is a test of sit-to-stand activity that also includes lower body strength and dynamic balance. The participants are asked to sit in a straight back chair with no armrests, with their arms crossed at the wrists against their chest. From the seated position, the participant stands up completely, then back down and repeats this as many times as possible for 30 seconds. The maximum number chair stands completed in 30 seconds is recorded.

The test was found to be a reliable [Test-retest ICC of 0.89 (95% CI: 0.79-0.93)] and valid (r=0.77, 95% CI: 0.64-0.85) indicator of lower body strength in healthy older adults (mean age of 70.5 ± 5.5) (242). A minimal clinically important improvement of 2-3 stands was found in people with hip osteoarthritis (mean age of 66.5 ± 9.4 years) (241).

4-square Step Test is a test for dynamic balance and has a strong cognitive component. Four canes are placed on the ground to make four squares. Participants start in square one, facing square two. The participants step forward into square two, sideways into square three, backwards into square four and sideways into square one. The sequence is then reversed so the participants step sideways into square

four, forwards into square 3, sideways into square 2 and backwards into square 1. The full sequence includes 1, 2, 3, 4, 1, 4, 3, 2, 1. Both of the participant's feet should contact the floor in each square. The time form when the first foot contacts the floor in square two to when the last foot contacts the floor in square one is recorded.

The test was found to be a reliable test (Inter-rater ICC=0.99; Test-retest ICC= 0.98) in community dwelling older adults [mean age of multiple fallers: 74.00 ± 5.68 years; mean age of non-multiple fallers (less than 2 falls in the last six months): 73.78 ± 6.09 years; and mean age of non-fallers 74.14 ± 6.07 years] (243). When comparing multiple fallers (identified as having scores greater than 15 seconds) to non-multiple fallers and non-fallers (both identified as having scores ≤ 15 seconds) the test showed a sensitivity of 89%, specificity of 85% and a positive predictive value of 86% (243).

Stair Climb Test is a test for ascending and descending stair activity as well as lower body strength and dynamic balance. The participant is asked to ascend and descend a flight of stairs as quickly and safely as possible. Time begins on the signal to start and stops when the participant returns with both feet on the ground. The time it takes to ascend and descend the flight of stairs is recorded as well as the number of stairs in the flight, the step height and the use of hand rail (for ascent, descent, both), side of hand rail and use of walking aids.

The test was found to be a reliable indicator in people with hip and knee osteoarthritis (Intra-tester ICC of 0.94-0.96, 95% CI: 0.75-0.99; mean age of 69.4 ± 5.9 years), in people following knee joint replacement (Inter-tester ICC of 0.94, 95% CI: 0.55-0.98; mean age of 68 ± 8 years), and in people in end-stage hip and knee osteoarthritis awaiting joint replacement (Test-retest ICC of 0.90, 95% CI: 0.79-0.96; mean age of 63.7 ± 10.7 years) (244–246).

Quality of life

The 5 level EQ-5D instrument (EQ-5D-5L) and the QUALEFFO-41 questionnaire will be used to assess the quality of life of the participants. The EQ-5D-5L instrument includes a descriptive system

that is comprised of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. There is also a visual analogue scale that is used to measure the individuals self-rated overall health. The QUALEFFO-41 questionnaire is specific to people with osteoporosis and includes the following domains: pain, activities of daily living, mobility, leisure and social activity, general health perception, and mental function.

Body composition

Certified technologists, blind to group allocation, will assess body composition using a dual energy X-ray absorptiometry (DXA) scan (Hologic Inc, Bedford, MA). The following variables will be collected: Spine (L1-L4) BMD (g/cm^2), femoral neck BMD (g/cm^2), body weight, whole body fat- and bone-free lean mass (FBFM, in kg), appendicular lean mass (ALM, in kg) and its index (ALMI, in kg/m^2).

Feasibility

The current trial will inform future research and knowledge translation related to the feasibility of moderate-high intensity resistance training in individuals with established osteoporosis. Feasibility outcomes will include: the number of participants recruited and retained, the proportion of exercise adherence, and the acceptability of the attention control group (e.g., low dropout rate after randomization). The exercise trainers will be provided with an attendance sheet at every exercise session to monitor participant exercise adherence. An MSc student (E.M) will conduct one exit to determine the participants' perspective on the intervention and if they understood the purpose of the study. All of the feasibility outcomes will be reported at the end of the study.

Falls and fractures

As recommended by the Prevention of Falls Network Europe and Outcomes Consensus Group, falls will be recorded using a prospective notification system in order to assess the number of falls, the number of fallers/non-fallers/frequent fallers and the fall rate (247). A fall will be defined as "an unexpected event in which the participants come to rest on the ground, floor, or lower level" (247). On

a weekly basis, participants will be asked to report any falls that occurred outside as well as during the exercise training program. Specifically, participants will be asked "in the past week, have you had any fall including a slip or trip in which you lost your balance and landed on the floor or ground or lower level?" (247). Participants will be instructed to provide their weekly assessments to their exercise trainers when they attend their scheduled exercise sessions. The exercise trainers will check if the weekly falls assessments were complete and will follow-up with participants who have missing assessments. The falls assessment forms will also be reviewed to confirm the date, injuries and hospitalization after a fall has been reported. In addition, participants will be asked to report any new fractures or injuries, related or unrelated to the exercise training. An exercise trainer will complete an AE report to ascertain the cause and timing of any injuries. To verify fracture details, written consent will be obtained to abstract data from medical records. If possible and with a physician's approval, participants will remain in their randomized exercise group and will be provided with modified exercises.

Adverse events

According to Health Canada a serious AE is defined as ". . . an event (experience) or reaction is any untoward medical occurrence that at any dose (a) results in death, (b) is life-threatening, (c) requires inpatient hospitalization or prolongation of existing hospitalization, (d) results in persistent or significant disability/ incapacity, or (e) is a congenital anomaly/birth defect" (183). Whereas a non-serious AE includes bone/limb pain, myalgia or muscle cramps (e.g. pain, cramps or aches), and injuries. Participants will be asked to report any serious and non-serious AEs as soon as they happen. Any AEs that are a result of the exercise training or that interfere with training (e.g., exercise cessation) will be reported separately. All AEs that occur will be recorded and the research ethics board will be notified.

Descriptive data

We will collect descriptive data such as demographic information, medical history, physical activity level and dietary intake. Demographic information will include date of birth, race, formal education, marital status, alcohol consumption, and current smoking status. Current and past medical history information will be collected as well as any recent or past drug therapies in addition to bone-related medications. We will also record reproductive history (e.g., age at menarche or menopause), family history, past surgical history, falls risk (e.g., number of falls within the last 12 months), and fracture history. Baseline physical activity levels of the participants will be assessed using accelerometers (ActiGraph GT3X+, v3.2.1, Pensacola, FL 32502). Participants will be instructed to wear the accelerometer on their waist for one continuous week (7 days) prior to participating in the exercise training program. In addition, a Bone-specific Physical activity Questionnaire will be administrated at baseline. To assess dietary energy, calcium and protein intake, participants will be asked to complete an Automated Self-Administered 24-hour (ASA24®) Dietary Assessment Tool (Canada Version) at baseline, 3-months and 6-months. ASA24®-Canada (http://asa24.ca/) is a guided web-based tool used to recall dietary intake in a 24-hour period. Participants will be asked to report all food and drinks consumed on one weekday and one weekend day (2 days total). Each participant will be provided with a specific log in username and password to ensure that only the researcher and the participant are able to access the data. E-mail or telephone reminders will be provided for when the recall is to be completed. If participants do not have access to a computer or internet, the tool will be administered over the phone.

Recruitment

We plan to recruit a total of 46 participants (N=23 per group). Women who are eligible and who first consent to participate in the AFF study at the Waterloo site can consent to this sub-study. Potential participants will be contacted by phone or in person. Recruitment strategies will include brochures,

posters, emails, social media posts, online websites and the involvement of local family practice physicians or osteoporosis specialists.

Strategies to enhance retention

The attention control group will receive the same attention as the intervention group. The only difference between the control and the intervention group will be the training intensity of the exercises performed. We will inform participants that we are comparing two different exercise interventions but we will conceal the hypothesis.

Sample size estimation

The sample size estimation was determined using data from a cross-sectional study by Ardawi et al. who reported an association between low physical activity duration and high serum sclerostin levels (238). Women who engaged in less than 30 minutes of exercise per week had statistically significantly higher serum sclerostin levels than women who engaged in 60-120 minutes of physical activity per week (27.84 ± 4.98 pmol/L vs. 21.64 ± 6.21 pmol/L; $p<0.0001$, respectively) (238).The study by Ardawi et al. used a manual ELISA® kit to assess sclerostin which is consistent with our study protocol. Based on the study findings, to detect a difference in serum sclerostin of 6.2 pmol/L with a standard deviation of 1.23 pmol/L we will need 38 participants using an alpha level of 0.05 and a power of 90% (238). We assumed a 20% attrition rate and thus the estimated sample size was increased to 46 participants.

Analyses

The study protocol was prepared according to the Standard Protocol Items: Recommendations for Interventional Trial (SPIRIT) guidelines. Reporting will be consistent with Consolidated Standards of Reporting Trials (CONSORT) non-pharmacological trials extension. The proposed study protocol is summarized in the flowchart below (Figure A1.1). Participant characteristics and outcomes that are considered continuous variables will be reported as mean ± standard deviation or median and

interquartile range. Categorical data will be reported as number (%). Analyses of the feasibility and safety of the exercise intervention will be descriptive. A participant flow diagram will be used to demonstrate the number of participants who were randomly assigned to each group, who completed the exercise training program and who were analyzed for each outcome. For each group, losses or exclusions after randomization will be recorded along with reasons. Intention-to-treat analysis will be performed and thus all participants will be included in the analysis and analyzed according to the group to which they were randomized. Differences in outcome measures will be assessed using analysis of covariance while adjusting for baseline demographic and clinical characteristics (e.g., age, smoking status, physical activity level, dietary intake). Body composition and exit interview data will be analyzed separately by an MSc student (E.M). We will also perform sensitivity analysis to determine if participants with ≥80% adherence criteria to the exercise intervention experience greater benefits. At the end of the study, we will assess whether allocation concealment was maintained among the blinded research staff and whether participants were aware of the study hypothesis. Statistical significance will be set at $p \leq 0.05$. All data analysis will be conducted using IBM SPSS version 24 (Armonk, NY: IBM Corp).

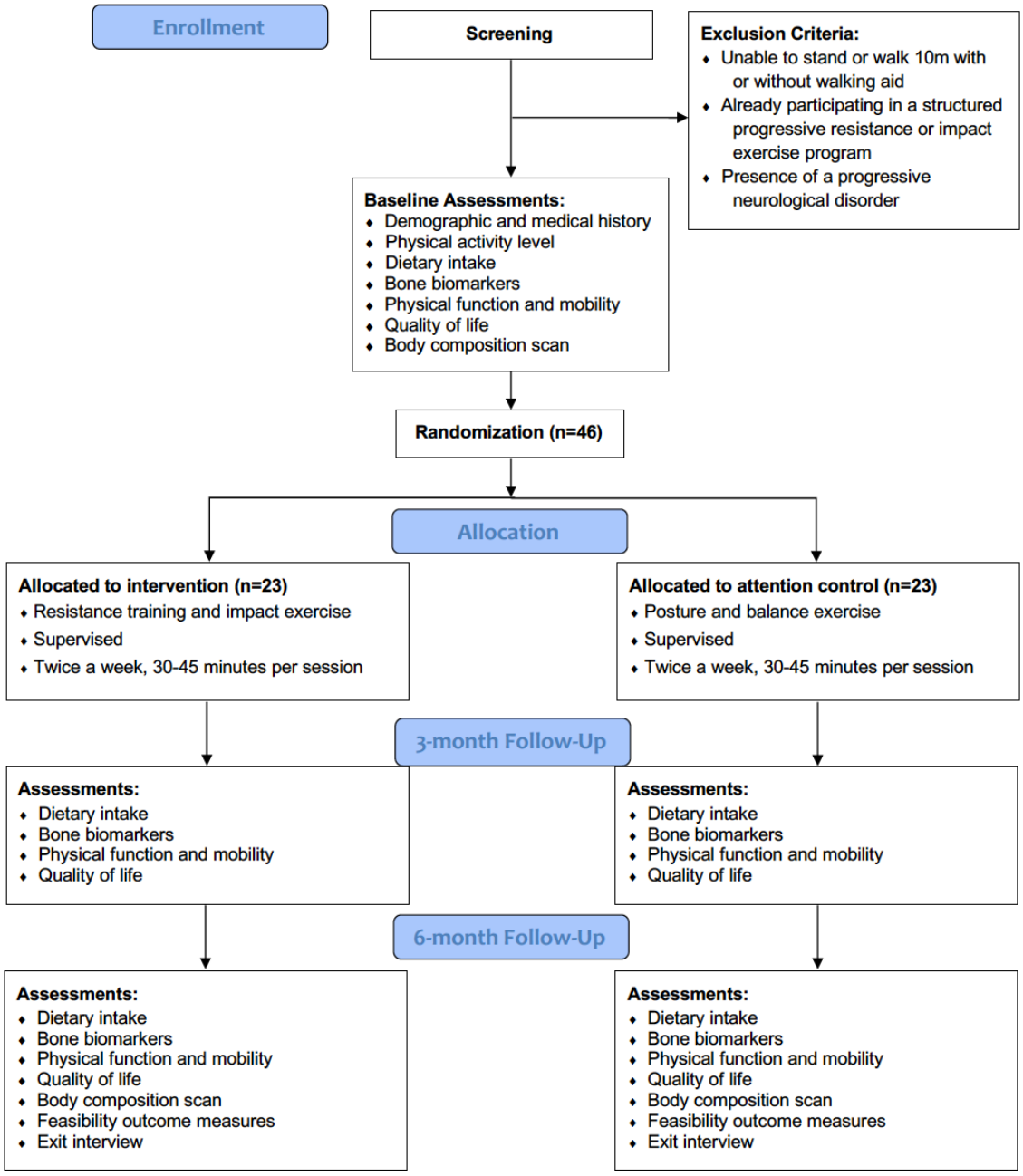

Figure A1.1 Flow chart describing proposed study protocol

Ethics and confidentiality

All research activity will be conducted according to the Tri-Council Policy Statement (http://www.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/). A research ethics application has already been submitted at the University of Waterloo and we are currently waiting for approval (ORE #41153). All participants will be assigned an identification number that will be reported on data collection forms and used in data management systems. A key file linking the participant's contact information with their identification number will be kept in a separate password protected file on the network drive. Hard copies of de-identified data will be stored in a secure cabinet at the University of Waterloo. Only research personnel directly involved in this study will be allowed to collect, enter, view and analyze the data. The study findings will be published in an academic journal and will be presented at conferences.

Results (Incomplete due to Covid-19):

- Number of participants recruited: 26 (Target sample size with 20% attrition rate is 46 participants).
- Number of participants who completed baseline assessments with the exception of the DXA scan: 14 (assessments included a fasting blood sample, physical function and mobility tests, 7-day physical activity level assessed via an accelerometer, and questionnaires related to demographics, medical history, dietary intake, physical activity level, and quality of life)
- Number of participants who completed a DXA scan: 8
- None of the participants started the exercise program as it was scheduled to begin the same week that the University announced it will be closing.

Appendix B1: Search strategy

The search strategy followed a two-step process. An initial search was developed in Ovid MedLine with a goal to develop the initial group of subject headings and keywords and sent to all authors for review. Once the initial review was considered by the team, additional keywords and subject headings were added to the search to ensure completeness. Only once a satisfactory search was completed in Ovid MedLine were additional databases added and the search translated to Embase and PsycInfo, both using the Ovid platform and CINAHL (Ebsco). Initial searches were conducted in February 2019 and all searches were completed the week of May 6-10, 2019. For searches in MedLine, Embase and CINAHL, the initial topic keywords and subject headings were combined with the Scottish Intercollegiate Guidance Network (SIGN) search filters for reviews (available at: https://www.sign.ac.uk/search-filters.html). The SIGN search filters for reviews was modified for the PsycInfo database by ARW.

Table B1.1 Resistance training search strategy

	Ovid Medline	Ovid Embase	Ebsco CINAHL	Ovid PsycInfo
Subject Headings	Resistance Training/	Resistance training/ resistance training/ muscle strength/ AND (exercis* or train*).mp. 11 1 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (49475)	(MH "Muscle Strengthening") OR (MH "Resistance Training")	
Keywords	(weight bear* or weight lift* or load bear* or axial bear*) adj3 (exercise* or strengthen*) resistance train* strength train*	resistance train*.mp. functional strength*.mp. postural control*.mp. functional train*.mp. strength train*.mp. ((weight bear* or weight lift* or load bear* or axial bear*) adj3 (exercise* or strengthen*)).mp.	TX "resistance train*" TX "strength train*" TX ((weight bear* or weight lift* or load bear* or axial bear*) N3 (exercise* or strengthen*)) TX "functional strength*"	(weight bear* or weight lift* or load bear* or axial bear*) adj3 (exercise* or strengthen*) resistance train* strength train*

			TX "functional train*" TX "postural control*"	
SIGN review	1. Meta-Analysis as Topic/ 2. meta analy$.tw. 3. metaanaly$.tw. 4. Meta-Analysis/ 5. (systematic adj (review$1 or overview$1)).tw. 6. exp Review Literature as Topic/ 7. or/1-6 8. cochrane.ab. 9. embase.ab. 10. (psychlit or psyclit).ab. 11. (psychinfo or psycinfo).ab. 12. (cinahl or cinhal).ab. 13. science citation index.ab. 14. bids.ab. 15. cancerlit.ab. 16. or/8-15 17. reference list$.ab. 18. bibliograph$.ab. 19. hand-search$.ab. 20. relevant journals.ab. 21. manual search$.ab. 22. or/17-21 23. selection criteria.ab. 24. data extraction.ab. 25. 23 or 24 26. Review/ 27. 25 and 26 28. Comment/ 29. Letter/	12 exp Meta Analysis/ 13 ((meta adj analy$) or metaanalys$).tw. 14 (systematic adj (review$ or overview$)).tw. 15 12 or 13 or 14 16 (cancerlit or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or "science citation index" or bids).ab. 17 ("reference lists" or bibliograph$ or hand-search$ or "manual search$" or "relevant journals").ab. 18 ("data extraction" or "selection criteria").ab. 19 review.pt. 20 18 and 19 21 letter.pt. 22 editorial.pt. 23 animal/ 24 human/ 25 23 not (23 and 24) 26 21 or 22 or 25 27 15 or 16 or 17 or 20 28 27 not 26 29 11 and 28	(MH "Meta Analysis") TX "Meta analys*" TX Metaanaly* (MH "Literature Review") OR (MH "Scoping Review") OR (MH "Systematic Review") TX (systematic N1 (review or overview))	(meta analy$ OR metaanaly$).tw. (systematic adj (review$1 or overview$1)).tw. (cochrane OR embase OR (cinahl or cinhal) OR science citation index OR bids OR cancerlit OR reference list$ OR bibliograph$ OR hand-search$ OR relevant journals OR manual search$).ab

	30. Editorial/ 31. animal/ 32. human/ 33. 31 not (31 and 32) 34. or/28-30,33 35. 7 or 16 or 22 or 27 36. 35 not 34			
Limits	Human Adults English or French 2009-present NOT exp pregnancy/	Human Adults English or French 2009-present NOT exp pregnancy/ Article	Human Adults English or French 2009-present NOT (MH "Pregnancy+") Journal Article	Human Adults English or French 2009-present
TOTAL # citations	717	1735	1355	10

Appendix B2: List of excluded systematic reviews and reasons for exclusion when prioritized by outcome

Systematic Review Authors	Reasons for Exclusion
Borde et al. (2015) Casonatto et al. (2016) De Oliveira et al. (2017) Granacher et al. (2013) Grgic et al. (2018) Guizelini et al. (2018) Hortobágyi et al. (2015) Lemes et al. (2016) Liu et al (2017) López-Valenciano et al. (2019) Moran et al. (2018) Raymond et al. (2013) Roig et al. (2009) Schoenfeld et al. (2017) Steib et al. (2010)	Missing critical AMSTAR 2 items
Carlson et al. (2014)	Did not address any of the secondary research questions (e.g., age, exposure dose, or type of RT)
Cornelissen et al. (2013) Paterson et al. (2010) Rossi et al. (2013)	Not the most recent systematic review available
Katsoulis et al. (2019)	Missing meta-analysis*

Abbreviations: AMSTAR, A MeaSurement Tool to Assess systematic Reviews; RT, Resistance Training

*There were two systematic reviews that examined older adults only and they were both published in the same year and had a "moderate" AMSTAR 2 rating. However, one systematic review performed a meta-analysis and one did not. Therefore, we chose to include the systematic review with the meta-analysis.

References for the excluded systematic reviews:

1. Borde, R., Hortobágyi, T., & Granacher, U. (2015). Dose–Response Relationships of Resistance Training in Healthy Old Adults: A Systematic Review and Meta-Analysis. Sports Medicine, 1693–1720. https://doi.org/10.1007/s40279-015-0385-9
2. Carlson, D. J., Dieberg, G., Hess, N. C., Millar, P. J., & Smart, N. A. (2014). Isometric exercise training for blood pressure management: A systematic review and meta-analysis. Mayo Clinic Proceedings, 89(3), 327–334. https://doi.org/10.1016/j.mayocp.2013.10.030
3. Casonatto, J., Goessler, K. F., Cornelissen, V. A., Cardoso, J. R., & Polito, M. D. (2016). The blood pressure-lowering effect of a single bout of resistance exercise: A systematic review and meta-analysis of randomised controlled trials. European

Journal of Preventive Cardiology, 23(16), 1700–1714. https://doi.org/10.1177/2047487316664147
4. Cornelissen, V. A., & Smart, N. A. (2013). Exercise training for blood pressure: a systematic review and meta-analysis. Journal of the American Heart Association, 2(1), 1–9. https://doi.org/10.1161/JAHA.112.004473
5. De Oliveira, P. A., Blasczyk, J. C., Junior, G. S., Lagoa, K. F., Soares, M., De Oliveira, R. J., … Martins, A. W. R. (2017). Effects of Elastic Resistance Exercise on muscle strength and functional performance in healthy adults: A systematic review and meta-analysis. Journal of Physical Activity and Health, 14(4), 317–327. https://doi.org/10.1123/jpah.2016-0415
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8. Guizelini, P. C., de Aguiar, R. A., Denadai, B. S., Caputo, F., & Greco, C. C. (2018). Effect of resistance training on muscle strength and rate of force development in healthy older adults: A systematic review and meta-analysis. Experimental Gerontology, 102(June 2017), 51–58. https://doi.org/10.1016/j.exger.2017.11.020
9. Hortobágyi, T., Lesinski, M., Gäbler, M., VanSwearingen, J. M., Malatesta, D., & Granacher, U. (2015). Effects of Three Types of Exercise Interventions on Healthy Old Adults' Gait Speed: A Systematic Review and Meta-Analysis. Sports Medicine, 45(12), 1627–1643. https://doi.org/10.1007/s40279-015-0371-2
10. Katsoulis, K., Stathokostas, L., & Amara, C. E. (2019). The effects of high- versus low-intensity power training on muscle power outcomes in healthy, older adults: A systematic review. Journal of Aging and Physical Activity, 27(3), 422–439. https://doi.org/10.1123/japa.2018-0054
11. Lemes, Í. R., Ferreira, P. H., Linares, S. N., MacHado, A. F., Pastre, C. M., & Netto, J. (2016). Resistance training reduces systolic blood pressure in metabolic syndrome: A systematic review and meta-analysis of randomised controlled trials. British Journal of Sports Medicine, 50(23), 1438–1442. https://doi.org/10.1136/bjsports-2015-094715
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13. López-Valenciano, A., Ruiz-Pérez, I., Ayala, F., Sánchez-Meca, J., & Vera-Garcia, F. J. (2019). Updated systematic review and meta-analysis on the role of isometric resistance training for resting blood pressure management in adults. Journal of Hypertension, 37(7), 1320–1333. https://doi.org/10.1097/HJH.0000000000002022

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16. Raymond, M. J., Bramley-Tzerefos, R. E., Jeffs, K. J., Winter, A., & Holland, A. E. (2013). Systematic Review of High-Intensity Progressive Resistance Strength Training of the Lower Limb Compared With Other Intensities of Strength Training in Older Adults. Archives of Physical Medicine and Rehabilitation, 94(8), 1458–1472. https://doi.org/10.1016/j.apmr.2013.02.022
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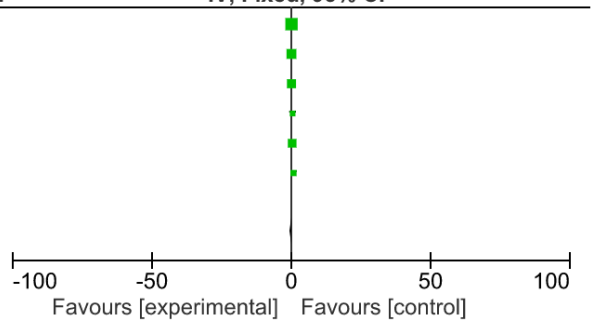
Appendix B3: Meta-analysis of primary studies that met the inclusion criteria for the outcome health related-quality of life

a)

	Experimental			Control				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Chandler 1998	44.2	20.4	44	42.5	25.8	43	29.2%	0.07 [-0.35, 0.49]	
Damush 1999	81.8	18.8	33	80.7	24.2	29	20.7%	0.05 [-0.45, 0.55]	
de Vreede 2007	50.1	9.2	28	49.6	9	26	18.1%	0.05 [-0.48, 0.59]	
Mangione 2005	57.7	21.1	11	48	18.9	10	6.8%	0.46 [-0.41, 1.33]	
Miller 2006	35.3	11.1	25	32.1	9.8	26	16.9%	0.30 [-0.25, 0.85]	
Tsutsumi 1997	91.9	7.5	13	75.7	26.4	14	8.3%	0.80 [0.01, 1.59]	
Total (95% CI)			**154**			**148**	**100.0%**	**0.19 [-0.04, 0.42]**	

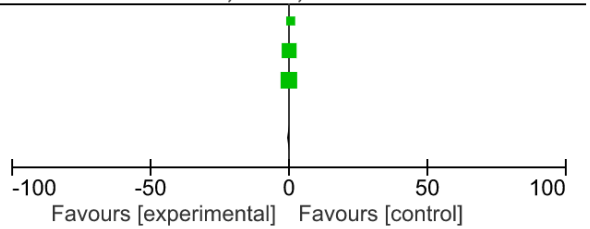
Heterogeneity: Chi² = 3.65, df = 5 (P = 0.60); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)



b)

	Experimental			Control				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Tsutsumi 1997	75.8	6.7	13	70.4	9.7	14	18.1%	0.62 [-0.15, 1.40]	
de Vreede 2007	72.3	16.1	28	71.3	17.5	26	38.2%	0.06 [-0.48, 0.59]	
Damush 1999	61.8	19.6	33	62.4	21.3	29	43.7%	-0.03 [-0.53, 0.47]	
Total (95% CI)			**74**			**69**	**100.0%**	**0.12 [-0.21, 0.45]**	

Heterogeneity: Chi² = 2.01, df = 2 (P = 0.37); I² = 1%
Test for overall effect: Z = 0.73 (P = 0.47)



c)

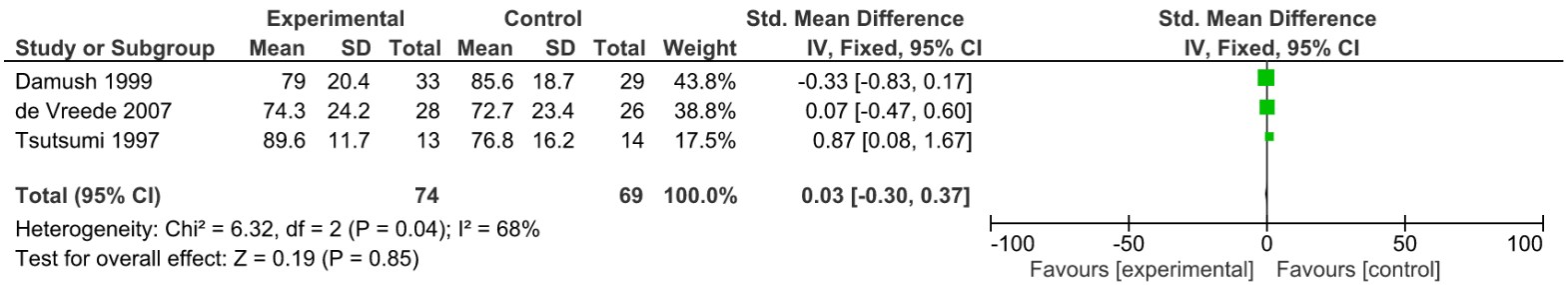


Figure B3.1 Meta-analysis of primary studies that met the inclusion criteria for the outcome health related-quality of life. a) No difference in the physical function domains between resistance training and control. b) No difference in vitality between resistance training and control. c) No difference in pain between resistance training and control. Squares represent the weight given to each study in the analysis; larger squares represent bigger weights. Vertical lines represent no effect.

Appendix B4: Reference list for the 31 primary studies that met the inclusion criteria for the adverse events outcome

1. Bean JF, Herman S, Kiely DK, Frey IC, Leveille SG, Fielding RA, et al. Increased Velocity Exercise Specific to Task (InVEST) training: a pilot study exploring effects on leg power, balance, and mobility in community-dwelling older women. Journal of the American Geriatrics Society. 2004; 52(5):799–804. [PubMed: 15086665]
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3. Buchner DM, Cress ME, de Lateur BJ. The effect of strength and endurance training on gait, balance, fall risk and health services use in community-living older adults. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 1997; 52(4):M218–24.
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6. DeBeliso M, Harris C, Spitzer-Gibson T, Adams KJ. A comparison of periodised and fixed repetition training protocol on strength in older adults. Journal of Science & Medicine in Sport. 2005; 8(2):190–9. [PubMed: 16075779]
7. DiFrancisco-Donoghue J, Werner W, Douris P. Comparison of once-weekly and twice-weekly strength training in older adults. British Journal of Sports Medicine. 2007; 41(1):19–22. [PubMed: 17062657]
8. Fatouros IG, Kambas A, Katrabasas I, Nikolaidis K, Chatzinikolaou A, Leontsini D, et al. Strength training and detraining effects on muscular strength, anaerobic power, and mobility of inactive older men are intensity dependent. British Journal of Sports Medicine. 2005; 39(10):776–80. [PubMed: 16183776]
9. Fielding RA, LeBrasseur NK, Cuoco A, Bean J, Mizer K, Fiatarone Singh MA. High-velocity resistance training increases skeletal muscle peak power in older women. Journal of the American Geriatrics Society. 2002; 50(4):655–62. see comment. [PubMed: 11982665]
10. Galvao DA, Taaffe DR. Resistance exercise dosage in older adults: Single- versus multiset effects on physical performance and body composition. Journal of the American Geriatrics Society. 2005; 53(12):2090–7. [PubMed: 16398892]
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13. Haykowsky M, McGavock J, Vonder Muhll I, Koller M, Mandic S, Welsh R, et al. Effect of exercise training on peak aerobic power, left ventricular morphology, and muscle strength in healthy older women. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2005; 60(3):307–11.

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30. Jette AM, Lachman M, Giorgetti MM, Assman SF, Harris BA, Levenson C, et al. Exercise - it's never too late: The strong-for-life program. American Journal of Public Health. 1999; 89(1):66–72. [PubMed: 9987467]
31. Krebs DE, Scarborough DM, McGibbon CA. Functional vs. strength training in disabled elderly outpatients. American Journal of Physical Medicine & Rehabilitation. 2007; 86(2):93–103. [PubMed: 17251692]

Appendix C1: List of interview questions – Stage 1

1. Tell me about your experience with harms that occurred during strength training.

Prompts:

a. How did it affect your life?
b. How did it limit your activities? Which activities did it limit?
c. How did it affect your ability to exercise? How did it change how you exercised? How do you feel about having to modify your exercises?
d. How did it relate to your chronic condition?
e. Did it persist?
f. How did you connect it to strength training?

2. What harms are you most concerned about when it comes to strength training?

Prompts:

a. Can you tell me how it relates to your chronic condition?
b. Can you describe how you deal with that concern?
c. How does pain, or worrying about it, affect your willingness to do certain exercises? Is having pain a minor concern, or more serious?
d. Can you tell me about your concerns with falling during strength training?

3. What do you consider as serious injuries and what do you consider as minor injuries? *provide examples*

Prompts:

a. Can you tell me more about what you think a minor injury is versus a serious one?
b. How would you define a serious injury? What about it makes it serious?

4. What types of risks are not acceptable to you when it comes to strength training?

Prompts:

a. If you experience minor injury, how would that influence your decision to participate in strength training?
b. If you experience a serious injury, how would that influence your decision to participate in strength training?
c. What do you consider as unacceptable risks?

Appendix C2: Quotation examples – Stage 1

Table C2.1 Examples of themes related to individuals' experiences and perspectives on adverse events that occurred due to resistance training

Theme	Description	Code(s)	Relevant Quotes
Personal Experiences with Aging Influence Perceptions of RT	Participants were concerned or unacquainted with the available RT resources for older adults. Participants were aware with respect to muscle loss and the importance of RT training when it comes to aging.	Aging and RT	03: "I feel vulnerable to the aging process . . . I suspect a couple of things, one is probably lack of availing myself to better training methods i.e. qualified trainers that could offer me some reliable evidence-based protocols to follow." 03: "Well actually what I value about it [strength training] is being able to do things that - because I am a senior citizen and I think I can do some surprising things and so it's probably vanity." 04: "In terms of maintaining the muscles . . . I think that's really important. I think it's extremely important as I've watched both my parents become frail and how that plays into - I mean it's the chicken or egg situation - but how that plays into illness. And you know when they get very frail, that's actually a condition, it's considered a condition."

	04: “I just really felt like somebody looked at how old I was and just sort of said well you can't do those things so they had me working at a really basic level . . . that didn't really reflect somebody who's looked at you and developed the program that was individualized to what you would be able to do given your age and the types of abilities that you had related to your chronic conditions.”
	06: “. . . I do feel that you lose strength faster as you age so you need to keep up a more regular schedule.”

Physical and Emotional Consequences of AEs Limit Activities and Define Future RT Participation	Individuals who experienced an AE were limited in their daily activities as well as hobbies. The presence of pain influenced the decision to participate in RT. Participants worried about reinjury and future injury when considering or engaging in RT.	Consequences	02: “Yes, it [AE] is affecting my life because of this injury I have to stop working and then after I stopped working I had to be very cautious when I'm doing exercise, especially the ones with weight [lifting].” 03: “. . . I just got back to it now, but with a - I guess with a 33% reduction in weight . . . .” 05: “If I'm having a high period of pain and discomfort then I feel like it's more of a major problem. But if I'm having a good couple of weeks where my pain is less and I'm able to workout more, then that concern gets lower and then my risk for tolerance like goes high.” 05: “. . . I just have to be careful like I don't want to get any more injuries to have to deal with.” 06: “. . . basically just trying to avoid injury is the biggest thing that I'm trying to do and because of the arthritis.” 07: “My intention absolutely was to continue the program with the modified options.”

			18: “I'm just sort of being a little cautious about it. I might eventually go back to that, but at this point I'm just going to kind of ease back in and do this other stuff which is not quite as strenuous.” 22: “Yeah and just there's that ever-present fear, you know, kind of doing really drastic harm.”
Injury Recovery Defines Severity of AE	A minor injury was determined by the length of recovery time (e.g., quick recovery).	Perception of minor injury	06: “. . . I would probably just avoid the area of the minor injury, but I would continue with the other areas of strength training.” 07: “I mean, it's a little set back but as long as I was able to recognize that it was a minor injury and I was able to recognize the conditions that allowed for that injury to occur and able to correct those conditions then I would just carry on.” 19: “. . . because I feel like my health is pretty fragile overall I would

			probably pull back and try to do less [as a result of a minor AE]."
	A serious injury was determined by the length of recovery time (e.g., slow recovery).	Perception of a serious injury	01: "Well that would be stop until I strengthen, like heal and regain my strength." 03: "Well so it wouldn't lessen my resolve, but it would lessen the frequency until I recover from that injury." 05: "So I feel like that decision would be made and I would, you know, I think at that point too, I would listen to the advice of my doctor or my physio if they're like telling, no you can't workout . . . then I would stop."
Health Conditions Influence the Perceived Risks and Benefits of Participating in RT	Concerns with experiencing an AE as a result of RT in the context of chronic health conditions.	Relevance to chronic condition	04: "My concerns to my osteoarthritis . . . I'm probably a little less likely to take chances pushing because I don't know if I'm doing more harm to myself when I do that." 06: "OK, so whenever I lift a weight or get into a compromising kind of position there starts to be pain, particularly in certain joints like the wrist and shoulder and so forth, and I think this is a result of my psoriatic arthritis . . . also when I start to increase the weight so I want to lift

			heavier weights then it starts to create pressure at certain joints and in certain positions as well." 07: " . . . as a cancer patient I developed neuropathy . . . so my balance is compromised already, but I know that . . . my trainers are aware of that and that they're tailoring the exercises that I do specifically to help that particular piece and so I welcome the exercise."
	Practicality of RT in the context of chronic health conditions.	Value of RT	01: ". . . keeping myself strong and flexible - I, it does relate to my depression and the fact that I feel that helps me, you know, achieve, a good lifestyle." 03: "Oh yeah for me, from my understanding of coronary artery disease is I'm liable to get a lot more healthy, enjoyable years of life if I engage in strength training exercises and do it on a regular basis." 04: "So if you talk about my [osteo]arthritis, it's important for me to have good posture and to have good posture I have to have good stomach muscles and if I want to have good stomach muscles I have to do strength training of the abdominal muscles and

all of them, not just the the ones that are closest to the surface, right?"

06: "So, with my arthritis, I find that strength training actually reduces the pain that I experience during daily activities."

07: ". . . it's one thing when you're going through treatment as a cancer patient and things are done to you all the time that you know are good for you. But there you have no control over something, how you're going to react to the chemotherapy or to the radiation, or the fact that you got shingles or that you know there's a lot of things beyond your control, but if you have the energy to get out and move, that gives you a little sense of, you're not just a victim, right? You can do things."

19: "Why is it important for me to get back to strength training? My fitness level, I already have heart problems. I've already had two kinds of cancer. I've gotta do something to improve my health overall, and fitness is a part of that."

26: "I have osteoporosis so I know strength training is really important to

			maintain my bone mass and so it's something I do try to prioritize and ensure that I do keep as part of my routine, so it's frustrating when I have to stop or if I can't do something because I'm like I want this to be part of my routine for my well-being."
RT Setting and Trained Supervision Influences Exercise Behaviors and Risk Perceptions	Participants were less motivated when exercising on their own or at home. Participants were less confident and experienced greater concern with respect to injury when exercising without supervision. Participants were more likely to push themselves due to social pressure, but felt that they are at a greater risk of experiencing an injury.	RT setting	04: ". . . my concern is that I'm not going to be able to provide myself with the right feedback and then I'll do something that will cause me harm . . ." 07: "I would say on the whole, my performance is better. My focus is better at the gym. My enthusiasm and my attitude are better." 26: ". . . when I had that very structured, very well supervised environment, I was much more likely to make bigger, like step-ups in my resistance training. So I was willing to take on more weight, or willing to try different exercises when I had that supervision. As I mentioned, when I stopped having that supervision, I did tend to be a little bit more cautious, and I was less likely to push myself in fear of hurting myself and not having that supervision."

		26: “And I think for a lot of individuals without that direct supervision, or without that guidance, it's far too intimidating to start into and can be something very easy that they shy away from and not even start doing some smaller things just because it's like, ‘oh, I don't use that section of the gym’ or especially now, it's like ‘I don't have that at home, so I'm not going to do it. I'll just go for my walks’.”
	Social pressure	04: “. . . when you’re in a group situation, there are a lot of other people who are doing it so you should be able to do it too and you have an instructor that is encouraging you to pull, to keep - perhaps not to listen to your own body as much as to listen to the messages around ‘you gotta go past the burn’ or ‘you can and you have to push yourself a little harder’ ‘you’re just not trying hard’ and that kind of stuff. And then when you're not listening to your body, you’re apt to make those mistakes.” 04: “I can remember one time the instructor having us to do abdominal strengthening exercises and again that kind of same situation where you are in a class situation you know you've done

	as much as you, your muscles are capable of doing it and you do it one more time and it ends up wrecking your back, right?" 05: "I think, again I push myself more like in a class or something like that if I'm surrounded by people I find that I'm like I want to- not be better than them, but at least like be doing the exercises right? So you get that kind of like, crowd. Like saying where you you're like 'everyone else is doing it. I can do it too'." 26: "I was always like 'I'm going to try to be like them', so I think there'd be an element of peer pressure in there of people do what they see, and so, I continued."

Experiencing a Previous AE Influences Future Exercise Behavior	Participants wanted to be safely challenged by avoiding exacerbating past injuries and making sure to manage past injuries while engaging in RT.	Want to be safely challenged	05: “So it kind of affected the way I work out because I really wanted to try and build more muscle, but I'm always constantly afraid of like irritating it, right? So I kind of sometimes will go a bit higher in the weight and sometimes not depending on how I'm feeling that day.” 05: “I'm on this mission now to build more muscle, that it's in my head that fight, like fight between like wanting to, you know, use more weight to try and gain the muscle but then on the other hand trying to be like try to think about "I don't want to damage this even more or create more issues"?” 07: “I'm not supposed to push my shoulder, my arm outside of where it's frozen, so the area where I have mobility, I can move that, but I shouldn't push outside of that because then that could result in just greater trauma and so anything that you know, lifting weights over my head with my right arm right now I would say that's out.” 18: “I was in the hospital for a couple of times because of back incidents. . . There's a few things in the gym where I see people doing stuff with their back

and so I kind of avoid all that kind of stuff."

22: "I'm not young and I have to—my mind and my body are very disconnected. My mind says one thing and my body's telling me something different, and they haven't even yet caught up with each other. So, it affected me in that I have to seriously take a look at what can I do, and what can't I do. And when I feel good, I feel I can conquer the world and then I pay for it after."

22: "So it's finding that place somehow with your own body and I don't know what that is at the moment. I need to sort out what's going on with me generally right now and figure out what I can do. . . Like my body is not resilient like it was, like the ligaments aren't going back, you know, after each thing I do. And so I have to find some place that's going to be right for me."

26: "So, it's sort of something that continues to linger in my mind if I'm doing something, like I tend not to do a lot of jumping exercises and that sort of because of other sort of challenges with my bones that I have developed compartmental syndrome, which is in

		my shins. It's more commonly referred to as to a shin splint, so like I don't like doing jumping exercises because that can aggravate that, and jumping exercises just lead to more opportunities to like be thrown off balance.”
	Willingness to return to RT	04: “I'm trying to think how much longer after that I ended up with a frozen shoulder - and then I couldn't do anything for a year. It took me a long time to come back.” 04: “ It [the harmful event experienced] certainly effects my willingness to push myself, but also at times if the exercises get done, then I tend not to do them, or I tend to do a couple of them but just that's it, I won't do anymore.” 05: “Yeah, I kinda still feel like I probably push myself too hard so I don't think the concern for harm is at

the moment like stopping me from doing anything because I still kind of push myself probably too much . . . if I have a bad week where I'm like, super sore then I kind of like will take a day off for less than a week anyway but then as soon as that's gone I'm like OK, I'm good again I can try and up my weight or do something again."

18: "But I haven't done, I haven't been as vigorous in my exercising. I've stopped doing the kettlebell thing now and I just, kind of do, you know push-ups, some light calisthenics, type of thing."

21: "And since it [AE] doesn't happen at the time I'm doing it [squatting], at least it doesn't hurt at the time I'm doing it, I have no way of deciding how much I can do or how little, so I think it's better if I don't do it [squatting]."

21: ". . . it took me most of the summer to gather up enough courage to actually do a full class again. So, when I did that full class again three weeks ago, it happened again. . . so I don't think I'm ever going to do the full exercise again."

Appendix D1: List of interview questions – Stage 2

1. Tell me about the methods you use for monitoring and reporting AEs in your exercise trials.
    Prompts:
    a. Can you describe how you report AEs for the intervention and the control group?
    b. Why do you think in general AE reporting is often done in the intervention group, but not in the control group?

2. What types of AEs are most common in the exercise trials you have done? What do you consider as serious AEs and what do you consider as minor AEs?
    Prompts:
    a. What are some expected AEs?

3. What is your experience with AEs that are attributable to the resistance training intervention?
    Prompts:
    a. How do you define an attributable AE?
    b. Who should be deciding if an AE is attributable to the RT intervention?
    c. What types of attributable AEs are most common?
    d. How often do they occur?

4. From your perspective, what are the barriers to monitoring and reporting AEs in exercise trials? What are some barriers that you have experienced?

5. What has helped you improve the quality of your AE reporting? What would it take to improve AE reporting in exercise trials?
    Prompts:
    a. What do you think is the bare minimum that we can do to improve AE reporting?
    b. What do you think is an ideal approach when it comes to AE reporting?

6. Are you familiar with the CONSORT for harms?
    Prompts:
    a. If yes, what do you think are the limitations?
    b. If no, share the resource and then ask about limitations

7. If we develop a guide to improve AE reporting in strength training studies, how can we make it acceptable and feasible for researchers to implement?
    Prompts:
    a. Are there important barriers that are likely to limit the acceptability and feasibility of implementing the guideline?

Appendix D2: Quotation examples – Stage 2

Table D2.1 Examples of themes and subthemes related to researchers' practices and perspectives on adverse event reporting

Theme	Subtheme	Description	Code(s)	Relevant Quotes
Lack of guidance, resources, motivation or interest are barriers to AE reporting	Lack of a Standardized AE Reporting Protocol	Across researchers, there was variability in monitoring and recording AEs, and there were various opinions regarding the definitions of AEs and attributable AEs.	Inconsistent Documentation of AEs	09: ". . . some of the studies had hardly any [AEs] and you knew they weren't being reported properly and we're constantly going back to the trial committee going, 'There's been nothing, what's going on?' Others, where there, to me there was too big a delay." 09: "We don't count minor [AEs], so if it is just delayed onset muscle discomfort for example, which is fairly common at the beginning of an [RT] intervention with older adults, and they're told by the instructor to expect that, so at the beginning, so we wouldn't count those." 11: "I think most of the people do their own thing and they go with their own approach." 12: ". . . when we setup the last two trials we sort of said "hey look this is a good [AE] form, we can modify it and use it". I don't know where it came from, honestly." 25: ". . . I think the challenge is collecting the information consistently from the different trials . . . because there's such diversity in how people run their trials. . ."
			Lack of Universal Definitions	14: "I'm not so sure that people define the term adverse events the same way across the board. I've seen different definitions in different places and different countries . . . What are we talking about when we say adverse event? And also, perhaps there is a little bit of a difficulty defining the severity. How do we define the severity?"

				16: “I think your exercise adverse events are going to be quite a bit different and variable [than drug AEs].” 23: “Now, obviously it depends on what you call an adverse event and what you decide to say falls into that category. . .” 23: “. . . if one would expect everyone undergoing [an] RT trial to report what I consider minor adverse events, I think that’s probably too much.” 23: “. . . it’s pretty normal to have certain things happen, like muscle soreness in a resistance training program - if I reported that as an adverse event, it’s not an adverse event, it’s an adaptive response.” 25: “I look at other published studies and they’ll report you know 12-month trial and so there was no adverse events which I find impossible, because people get muscle aches and soreness and everything, so your definition of an adverse event which is probably the gray area.”
	Lack of Access to Resources	Resources include time and money.	Resources	09: “It [having a DSMB] of course means more time for people who are external to the study, and they’re not paid so it’s not always easy to find people willing to do that. . . I’m never going to get named anywhere. I’m never going to get on a paper because it’s meant to be an independent group. So, you know, there is, apart from your CV, very little benefit to being on one of those committees.” 09: “I think it’s just that there’s never enough money in a study to follow everybody up in the same level. After all, a phone call to your control group is likely to not be less than five minutes, and

				you might have to ring five times to get a hold of them." 10: ". . . might be really valuable for new investigators for maybe doing their kind of first trials to be able to know a priori the requirement that it is going to take staff time, and that means money, time. So you know, working that into budgets and all . . . it is not something that you can do really haphazardly and quickly and be done with it." 11: ". . . if you need to always have a physician in your study, in the gym, you need to pay, so it's a matter of- it's an economical issue." 13: "So, [I] go to CONSORT and use CONSORT. Obviously, that seems to be what is accepted practice, so that's minimum that you would do for acceptable practice. So, using the consort statement as a guideline. I think that's the main one. I don't know that there is a lot more out there other than- other resources. 13: "Well, time, money, you know that whole thing, right? That, that's a problem for any experiment, because you can't call your subjects every day and say 'did something happen to you' and then once you don't do that, now you're dealing with memory and recall." 15: ". . . in an ideal world it would be good to have a health professional adjudicate them, but I also realize that that's probably challenging . . . but pragmatically, I would still advocate for a physician independent of the study to do the serious adverse event adjudication." 25: ". . . if you got 150 or 200 people in an exercise arm, it can become challenging trying to

				continually monitor minor complaints, adverse events, or minor adverse events as well."
	Lack of Motivation or Interest to Improve AE Reporting	Some researchers were resistant to improving AE reporting in their RT studies and perceived the research ethics boards' requirements as excessive or unrealistic.	Resistance to Oversight	08: "OK, so I think the whole IRB process is out of control. I think IRB has gone way overboard on their objection, way overboard." 23: ". . . if one would expect everyone undergoing resistance training trial to report what I consider minor adverse events, I think that's probably too much." 12: ". . . I think for some people the fear that, you know, if you report an adverse event, it somehow reflects badly on you as an investigator, that you didn't take the right precautions or something like that."
Valuing and educating participants, having access to trained personnel and to standardized and enforced recommendations are facilitators to AE reporting	Valuing and Educating Participants	Creating a culture where participants feel valued. Prior to starting an exercise intervention, providing participants with a protocol familiarization period and ensuring participant safety during exercise. Educating and communicating with participants about the expected side effects that may occur as a result of RT.	Enhancing the Participant Experience	10: ". . . we believe the tremendous success rate we had in terms of compliance, and so on, is largely due to the genuine perception of participants was that 'these people care about us'." 11: ". . . we have given them [the participants] our phone numbers to give us a call whenever they feel like. So, we are in close contact with them and we want to make sure that nothing bad happens . . . and if it happens we have to be there." 15: "I usually conduct multiple method studies so it's not just you know, 'can we deliver it [RT program]', but actually also finding out from the study participants what's important to them, is this important, are they able to do it?" 11: "So, with less fit individuals we have a longer familiarization period. We have to make sure that the strength gains are not due to a learning effect. So, we are very scholastic, very meticulous with this factor and we have to work with them in the gym. So, we teach them the movements, and then we'll go into the intervention."

				24: ". . . if we have individuals who might have some - who are more prone to some safety concerns or prone to have an injury for example. So then there should be a specification of the program that it was more tailored to them and it's also guided."
			Educating Participants	10: ". . . they [participants] would come in after a day of - especially when we advanced, you know we progressed to higher weights or did something new that likely caused soreness, and of course we talked a lot about what delayed onset muscle soreness is and that they're likely to experience it." 14: ". . . and of course, every time that you recruit people to work with you in an exercise study, you have to educate them and tell them why it's important to report these complaints and so on." 25: "So I think what we do try to do is explain to people- participants in our studies, the importance of reporting minor aches and pains or adverse events essentially, and that we do want to monitor them because it's important for us to, you know, evaluate the safety of the program and so forth."
	Access to Trained Personnel	Training research staff to monitor and record AEs appropriately.	Training Staff	15: "It's part of the clinical trial in terms of making sure everyone is aware what's an adverse event, what's a serious adverse event, and that is across the range of people involved in these trials from research assistants, to people delivering the intervention, to the team members and participants. . ." 17: ". . . making them [exercise trainers] feel comfortable with reporting things [AEs], so not making them feel like they messed up or they did something wrong if something happened and they

				have to kind of try and cover it up or hide it. So, making them aware of the importance of reporting these things." 23: ". . . we have great trainers that work with us, kin students as well as like bona fide trainers that have credentials and so they know, they've been taught and they know what to do, and we certainly go over stuff like that [AE reporting] before we start the study with them." 25: ". . . we make it a requirement that they [research staff] all do their GCP training, and a big part of that is around adverse event reporting and documenting adverse events."
	Access to Standardized and Enforced AE Reporting Recommendations	Standardizing and enforcing AE reporting recommendations by involving ethics boards, exercise organizations and Journals.	Standardization and Enforcement of AE Recommendations	10: "I'm not sure about how you go about getting that [the recommendations] out. Maybe with the help of university IRB [Institutional Review Board] committee chairs, so the director of research, or the chair of an IRB committee at the smaller schools . . . I guess another way would be posting on some of our professional organizations that are featured and if this is going to have a, kind of a focus more of, on more of exercise trials, then maybe American College of Sports Medicine or other organizations might be willing to post something in their virtual reports where they do a weekly kind of news, or something like that would be a way." 12: "And the journal didn't require it [publishing AEs]. So, you know nobody ever pushed us on that, but that's something that you know maybe needs to be a requirement." 14: "I think that if journals require that you report adverse events, that, of course would make it, you know, obligatory. People will have to then be more formal about the way the data are collected."

				20: "I think an ethics board should maybe keep us in check to say - to really look at what we're proposing to record." 24: ". . . the professional organizations, their websites, I think they're very good ones. And then the journals itself so that these sites have the journals . . . the key journals could also include that in their recommendation or what needs to be reported."
There is suboptimal implementation of existing AE reporting standards, or the perception that the available guidelines do not apply to exercise trials		There were potential sources of bias including variability in reporting AEs based on the participants' characteristics (healthy versus people with health conditions), excluding participants who experienced an AE and could no longer perform the exercise at the required level, only reporting AEs related to the exercise intervention, not acknowledging the level of risk involved, and not publishing AEs in journals. Furthermore, not all researchers saw value in reporting AEs for both intervention and control group.	AE Reporting Based on Population	16: "I would say with the older population we probably pay more attention to the adverse events and record them—I would say we probably record them more carefully." 17: ". . . you know, if you're running an exercise trial in undergrads, then that might not be, as you know on your mind because you're like, 'oh, they're healthy young undergrads, they should be able to do anything' and you know, they're not as prone to injury or, you know, adverse events, and so, you know, just making sure that all researchers are aware, regardless of the population that they're working with, that this is something that needs to be reported, because I think there is a bias to these things being monitored and reported, more so with the older adult population and not necessarily with younger adults."
			Excluding Participants	08: ". . . the person would say, well, 'I'll try to work out today', and then you can observe the 1st exercise or the first few repetitions and, and realize, no, this person cannot do their activity, therefore they'll have to withdraw." 11: "So, if they [participants] have an injury, light one, and they miss one or two sessions, it's OK. We just write it down and then report the participation rate in the publication, but if they are not able to continue the study or they miss quite a

				few sessions, then we don't include them, so we have to report them as missed ones, as drop-outs." 16: "I guess a serious adverse event, you know, if they [participants] had a fracture or, you know, a serious muscle injury, then they would probably be excluded." 24: "So, we have kept the children who have had fractures in the study and because they wanted to be part of it. But we have excluded the data from the analysis, so I think that depends on the research question, the sample of the participants you have there and then also, what's the really the design of the study."
			No AE Reporting Outside of Study	13: ". . . it's easy to record the ones [AEs] happening in the lab. . . It's the things that happen outside the lab that are the problem." 17: "So, we have had participants who on their own time have fallen, for instance, at home so not related to what they've done in the lab, and so we kind of make a note of it, but we haven't reported those specifically." 20: ". . . she [participant] was like, 'Oh actually I've just come back from hospital because this has happened, a fall'. OK, yeah. So it was more, yeah, it wasn't formally recorded because at that time we would just be recording things that happened in class."
			Not Acknowledging Risk Involved	08: "Expected? None. I do not expect there to be an adverse effect. There's a risk of an adverse effect, but I do not expect any to occur." 11: "I think that if you take the right measures you are on the safe side, so we didn't have a lot of incidents, so it's rarely I would say." 13: "Adverse events are so rare that in all of these populations—I mean because when you look at

				older adults that they all have some disease, so they are by definition disease. So, since it's so rare we don't need to change things. It's rare in young people, it's rare in older people." 16: "Older participants would have a fairly high number of mild musculoskeletal adverse events, like muscle soreness or joint pain. But rarely will we get something that's classified as more severe or serious adverse event, so those are quite rare."
			Not Publishing AEs	08: "I don't think it should be reported at all. I don't have, I never reported an adverse effect in a publication in my life. If I report it, it's going be to the IRB office, I'm not going to put that in my publication." 25: ". . . if you look through the publications, some people report no adverse events. They don't even report them, they don't report severities or nothing, and I guess we've gone to the other extreme probably too much in some of our papers." 12: "Like I said, it's something that we report to the REB and we just say that "this was done, it's resolved". We don't report in the paper. Why that's the case? Again, I just think it's part and parcel of doing the program, to be honest with you." 20: "And again, it's not something we reported in the paper. We just said "OK 20 people", I can't remember, "recruited. Now we have 18" . . . we usually write something like, "Due to circumstances unrelated to the to the study", we write words to that effect to say "OK, they've gone away", so we just kind of group it without giving any details, which I suppose is maybe not very helpful for the reader because they don't know why these people have gone away."

			Value of Balanced Reporting of AEs	08: "Well, generally the control group does not receive any intervention, so there's no need to report [AE] for them, because nothing happens to them." 09: "I think we should do the control group because you'll generally, I'm sure, find just as many adverse events in your control group. And actually, that might help you decide, what—if you have a whole host of possibly intervention-related adverse events, and then you had bothered to follow up your control group and they had just as many similar adverse events, but obviously not intervention related, cause they're not in the intervention group, that in itself would be a useful bit of information." 10: ". . . if I'm writing a paper that focuses on our exercise outcomes, all of our outcome measures are related to something involving exercise. Then I don't know if it would be really necessary to include any AEs that may have happened in other groups. And as I'm saying this I'm thinking well that's probably not very smart because you really, would be best to report for the entire group." 13: "I knew we were going to talk about the control group thing, which I think is the major issue with the literature right now. That, and the fact that people don't report [AEs] at all, right?" 15: ". . . I'm interested in looking at any sort of health-related event that might affect people in both groups [control and intervention group] and doing that in both groups, we can also actually look to see are there differences between the two?" 17: "The control group was listening to music and we didn't have an adverse log for that. But you know if something did come up—so we weren't actively monitoring for adverse events—if

				something did come up, then we would of course report it to the Research Ethics Board, but it wasn't something that we were actively monitoring." 23: ". . . it's in our best interest, and it's the right thing to do, to monitor the participants that are undergoing our intervention. The control is just that, it's a control for a reason. We want to leave them alone." 25: ". . . we didn't do [AE] monitoring in the control group and so the question we got asked was 'how is this different from what people would normally, this age group, normal musculoskeletal aches and pains that they would get?' So, we started recording [AEs] in the controls and that's essentially just following the same format [as intervention group]."
The acceptability and feasibility of a guide for AE reporting depends on its content and format		Researchers preferred a concise and visually appealing guide that can be applied to various types of RT studies.	Preferred Guide Format and Content	09: "I think a very good outcome of your work would be, 'Here's some examples . . . and detailed core set'. You know, this is a minimum that we should be reporting on." 13: "Develop a phone app that they could then implement in their trial. They could just say here's the phone app, upload this to your phone, and do it. So, if you did all that work on the front end, you've made it simple for someone to adopt it." 16: "Well, I think that the guidelines for drug trials are going to have a lot of details surrounding doses of drugs and they won't mention exercise extensively. Like a good example would be if someone has an AE and they left the intervention, but then they came back. You know, we can reduce the dose of exercise training, but I don't think that's outlined in a typical guideline that's made for drugs." 16: "Like a good example would be if someone has an adverse event and they left the intervention,

				but then they came back. You know, we can reduce the dose of your exercise training, but I don't think that that's outlined in a typical guideline that's made for drugs. You know, some might come—it might say that you know you can reduce the drug dosage. They don't mention anything, any guidelines about how you can modify the exercise with specific examples. Or how you can reduce the volume of exercise or intensity." 17: "I think simple, easy to read, you know, kind of like, you know visually appealing things like a flow diagram that's like, you know, 'did the participant report this? Yes or no'? Or just, like, you know, something that's like very visually colorful and easy to read . . . like a one page or two-pager that is kind of like a poster format that can then be placed in the lab that you know, then research personnel can refer to." 24: ". . . it [guide] has to be quite short and, and clear and concise, so I think that's the first thing. It should not take much time to put into practice, but it should be also valuable, there should be the value seen in that." 25: "I guess it needs to be partly adaptable for the different types of intervention trials, because there's interventions where they're highly rigorous in terms of their supervision and support."

Appendix E1: Checklist for researchers reporting adverse events in resistance training studies

This adverse event (AE) reporting checklist should be used during the protocol development stage as well as during the publication of resistance training (RT) studies.

Item #	Checklist Item	Completed	Not Applicable
HOW TO DEFINE AES WHEN THEY HAPPEN:			
1	Refer to the exercise-specific AE definitions and AE reporting template form to ensure consistent AE reporting across RT trials.	☐	☐
2a	Have a process in place a priori to collect data on AEs, and encourage participants to report any AEs or symptoms they have to the research team.	☐	☐
2b	Choose whether the AE data collection will be unsolicited (i.e., asking open ended questions about whether any AEs occurred) OR solicited (e.g., questionnaires asking about specific AEs) OR both solicited and unsolicited. If using solicited collection of AEs, prepare a questionnaire with a *list of potential AEs** a priori, that may be expected to occur and you would like to monitor for the duration of the study; if a participant reports an AE that is not on the list you should still document it.	☐	☐
3	Monitor and report transient episodes of mild muscle soreness, joint pain or shortness of breath, but do not count it as an AE unless the symptoms are more severe or persist longer than would be expected with initiation of a new exercise program, or result in a participant missing a subsequent session(s) or having to modify their exercise program.	☐	☐
WHAT METHODS NEED TO BE IN PLACE TO MONITOR AES:			
4	Have a protocol in place a priori to ensure ongoing monitoring of AEs (e.g., follow-up with participants at defined intervals) to reduce participant recall bias.	☐	☐
5	Educate participants about the expected side effects of RT (e.g., delayed onset muscle soreness) and ensure it is clearly outlined in the consent form.	☐	☐
6	To avoid underreporting of AEs, use a standardized protocol that includes reminding all study participants (i.e., in the control and intervention groups) to inform you if they experience injuries, illnesses or changes in health status, whether related or unrelated to the study.	☐	☐

Item #	Checklist Item	Completed	Not Applicable
7	Consider a DSMB when: a) studying an intervention that involves side effects that cause serious morbidity or mortality, or are irreversible; b) when the study involves vulnerable participants (e.g., studies with high morbidity or mortality, or impaired ability to consent); c) when mortality is a study endpoint; or d) when interim analyses or stopping rules are being used.	☐	☐
8a	To reduce AEs, provide participants with a "familiarization period" which accustoms participants to the exercises, and an individually tailored progressive exercise program (e.g., ensuring good technique before progressing to weights and ensuring good technique at each new weight).	☐	☐
8b	To reduce AEs, hire exercise trainers who are certified to run exercise programs or have a relevant academic background (e.g., kinesiology degree) and are trained with respect to monitoring and reporting AEs.	☐	☐
8c	To reduce AEs, provide a greater number of exercise trainers to supervise the exercise sessions or have a limited number of participants per session if recruiting participants who are at a greater risk of experiencing AEs or who are unfamiliar with RT.	☐	☐
WHO SHOULD BE MONITORED FOR AES:			
9	Use the same AE monitoring and reporting protocol for all participants, regardless of the participants' health status (e.g., people with chronic health conditions versus healthy individuals).	☐	☐
10	Monitor and report AEs in all participants in the study regardless of whether they receive the exercise intervention.	☐	☐
11	Monitor and report AEs that may occur outside the exercise sessions regardless of whether it is considered related or unrelated to the exercise intervention.	☐	☐
HOW TO CLASSIFY AES AS ATTRIBUTABLE OR NOT WHEN THEY HAPPEN:			
12	Classify relatedness of AEs as "definitely related", "possibly related" and "not related" to the intervention or study participation. Refer to the exercise-specific AE definitions and AE reporting template form.	☐	☐
13	If it is unclear whether an AE is attributable (i.e., definitely or possibly related) to the intervention, the PI or trained delegate should thoroughly discuss the AE with the participant or their delegate to get additional information, including their perspective on the event, to report on the event or determine if it is attributable.	☐	☐

Item #	Checklist Item	Completed	Not Applicable
14	If there is a DSMB, the designated chair should make the final decision as to whether the AE is considered definitely or possibility related to the intervention based on the available information, and in consultation with the rest of the committee, the PI, and only if necessary, with a health care professional independent of the study team.	☐	☐
15	For studies without a DSMB, the PI should make the final decision as to whether the AE is considered definitely or possibility related to the intervention based on the available information, and in consultation with the rest of the involved research team members, and if necessary with a health care professional independent of the study team.	☐	☐
WHAT ACTIONS TO TAKE WHEN AES HAPPEN:			
16	Inquire about and be aware of your respective university research ethics board or other involved clinical ethics boards' requirements with respect to what AEs to report and how soon they need to be reported.	☐	☐
17	If a participant experiences an AE, the DSMB or PI and the participant or their delegate should agree on whether the participant should withdraw wholly or in part from the intervention/control activities. If the participant is willing, they should remain in the study even if they withdraw from intervention/control activities. Any data that can be collected safely from that participant should be collected and included in intention to treat analyses for the group to which they were allocated.	☐	☐
18	If you choose to perform complete case analyses or per protocol analyses, you should identify it as such prior to initiation of the study, and you should indicate the number of participants not included in the analyses and why they were excluded.	☐	☐
19	Use the same AE monitoring and reporting protocol for unrelated AEs experienced by the control group as unrelated AEs experienced by the intervention group.	☐	☐
20	Specify the action taken regarding any type of AE. Refer to the exercise-specific AE reporting template form.	☐	☐
21	Specify the action taken regarding the exercise intervention after any type of AE. Refer to the exercise-specific AE reporting template form.	☐	☐
22	Have criteria for resuming, modifying, pausing, or terminating the exercise intervention (or control activities if active control is used) after any type of AE (e.g., consider when physician approval might be required).	☐	☐

Item #	Checklist Item	Completed	Not Applicable
23	Follow up with participants or their delegate and specify the outcome of any type of AE. Refer to the exercise-specific AE reporting template form.	☐	☐
24a	For AEs that are not resolved when the AE report is complete, you should follow-up until it is resolved, it is stable, or the participant withdraws from the intervention/control activities or study.	☐	☐
24b	Clearly outline the protocol for follow-up (e.g., calling participants on a monthly basis).	☐	☐
25	If AE data collection is solicited (refer to 2b), record whether the AE was expected or not expected using the list of potential AEs defined a priori. Refer to the exercise-specific AE definitions and AE reporting template form.	☐	☐
HOW TO REPORT AES IN PUBLICATIONS:			
26a	Report the total number of participants who experienced AEs per group.	☐	☐
26b	Report the number of AEs that resulted in withdrawal from intervention/control activities and withdrawal from study per group.	☐	☐
26c	Report mild, moderate, severe and serious AEs.	☐	☐
26d	If AE data collection is solicited (refer to 2b), report all expected and unexpected AEs.	☐	☐
26e	Report all related and unrelated AEs that occurred in the intervention group (reported separately).	☐	☐
26f	Report all actions taken regarding the exercise intervention (e.g. pausing or modifying exercise) for those who experienced AEs.	☐	☐
26g	Report all AE outcomes (e.g. resolved, death).	☐	☐
27	Explicitly indicate if no AEs occurred in the study.	☐	☐

Abbreviations:						
	AE	Adverse event	DSMB	Data safety monitoring board	PI	Principal investigator
	RT	Resistance training				

*__Exercise-specific examples of adverse events include:__

- Moderate or severe muscle discomfort/pain
- Muscle strain
- Moderate or severe joint pain
- Moderate or severe dizziness
- Exacerbation of pre-existing conditions
- Abnormal rise or drop in blood pressure (if measured)
- Hyper- or hypoglycemia confirmed by a finger stick/blood test (if measured)
- Fainting

- Moderate or severe shortness of breath
- Fractures
- Falls and fall-related injuries
- Cardiac events
- Arthritis flare-ups (e.g. more than just joint pain)
- New injuries or exacerbation of previous injuries
- Exercise-induced asthmatic response
- Ligament sprain confirmed by a health professional
- Edema in joint or tissues confirmed by a health professional
- Tendonitis
- Unexplained/persistent tremors or dyspraxia

Comments:

Appendix E2: Exercise-specific adverse event definitions and adverse event reporting template form

The definitions below were modified based on the National Institute on Aging adverse event definitions.

Reference: National Institute on Aging. (2018). NIA Adverse Event and Serious Adverse Event Guidelines. Retrieved from https://www.nia.nih.gov/sites/default/files/2018-09/nia-ae-and-sae-guidelines-2018.pdf

NOTE: Adverse event is not synonymous with adverse effect. An adverse event is any harmful event that a participant experienced while in the study, and may or may not be related to the intervention. An adverse effect is an adverse event that is attributable to study participation (e.g., strength testing, exercise intervention).

Adverse Event (AE): Any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the exercise study, whether or not considered related to the study (e.g., strength testing, exercise intervention). However, AEs related and unrelated to the exercise study should be reported separately. **Serious Adverse Event (SAE):** Any AE that: • Results in death • Is life threatening, or places the participant at immediate risk of death from the event as it occurred • Requires or prolongs hospitalization • Causes persistent or significant disability or incapacity • Results in congenital anomalies or birth defects • Is another condition which investigators judge to represent significant hazards	**Severity** Classifications often include the following: • *Mild:* Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient. • *Moderate:* Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning • *Severe:* Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating Severity is not synonymous with seriousness. A severe rash is not likely to be an SAE. Likewise, a severe headache is not necessarily an SAE. However, mild chest pain may result in a day's hospitalization and thus is an SAE.	**Expectedness** • *Unexpected* - nature or severity of the event is not consistent with information about the condition under study or exercise intervention in the protocol or consent form. • *Expected* - event is known to be associated with the exercise intervention or condition under study. **Relatedness** • *Definitely Related*: The AE is clearly related to the exercise intervention – i.e. an event that follows a reasonable temporal sequence from doing the exercise, follows a known or expected response pattern to the suspected exercise intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state. ***Example:*** *The participant injured their back immediately after lifting a heavy weight during the RT intervention*. • *Possibly Related*: An AE that follows a reasonable temporal sequence from doing the exercise follows a known or expected response pattern to the suspected exercise intervention, but that could readily have been produced by a number of other factors. ***Example:*** *The participant felt back pain the day after the RT intervention. However, that same day of the RT intervention the participant was helping a friend move furniture.* • *Not Related*: The AE is clearly not related to the exercise intervention- i.e. another cause of the event is most plausible; or a clinically plausible temporal sequence is inconsistent with the onset of the event and the exercise intervention; or a causal relationship is considered biologically implausible. ***Example:*** *The participant's initial onset of back pain occurred one week after the RT intervention.*

STUDY TITLE: _____	
Study Site: _____ **Participant ID:** _____	

Has the participant had any AEs during this study? ☐ **Yes** ☐ **No** ***(If yes, please list all AEs below)***

Serious AE?	**Severity**	**Expected**	**Study Intervention Relationship**	**Action Taken/Treatment Regarding AE (select all that apply)**	**Action Taken Regarding Exercise Intervention***	**Outcome of AE**
1 = Yes 2 = No	1 = Mild 2 = Moderate 3 = Severe	1 = Yes 2 = No	1 = Definitely related 2 = Possibly related 3 = Not related	1 = None 2 = Medication 3 = Health care provider 3 = Hospitalization: __ nights 4 = Emergency room visit 5 = Undisclosed 6 = Other (specify): _____	1 = No action taken 2 = Exercise modified 3 = Exercise paused 4 = Exercise terminated	1 = Resolved 2 = AE still present 3 = Residual effect of AE present 4 = Death 5 = Undisclosed

*****May need another column for "Action Taken Regarding Exercise Control" if the control group is also engaging in exercise (e.g., a different type of exercise than the intervention).*

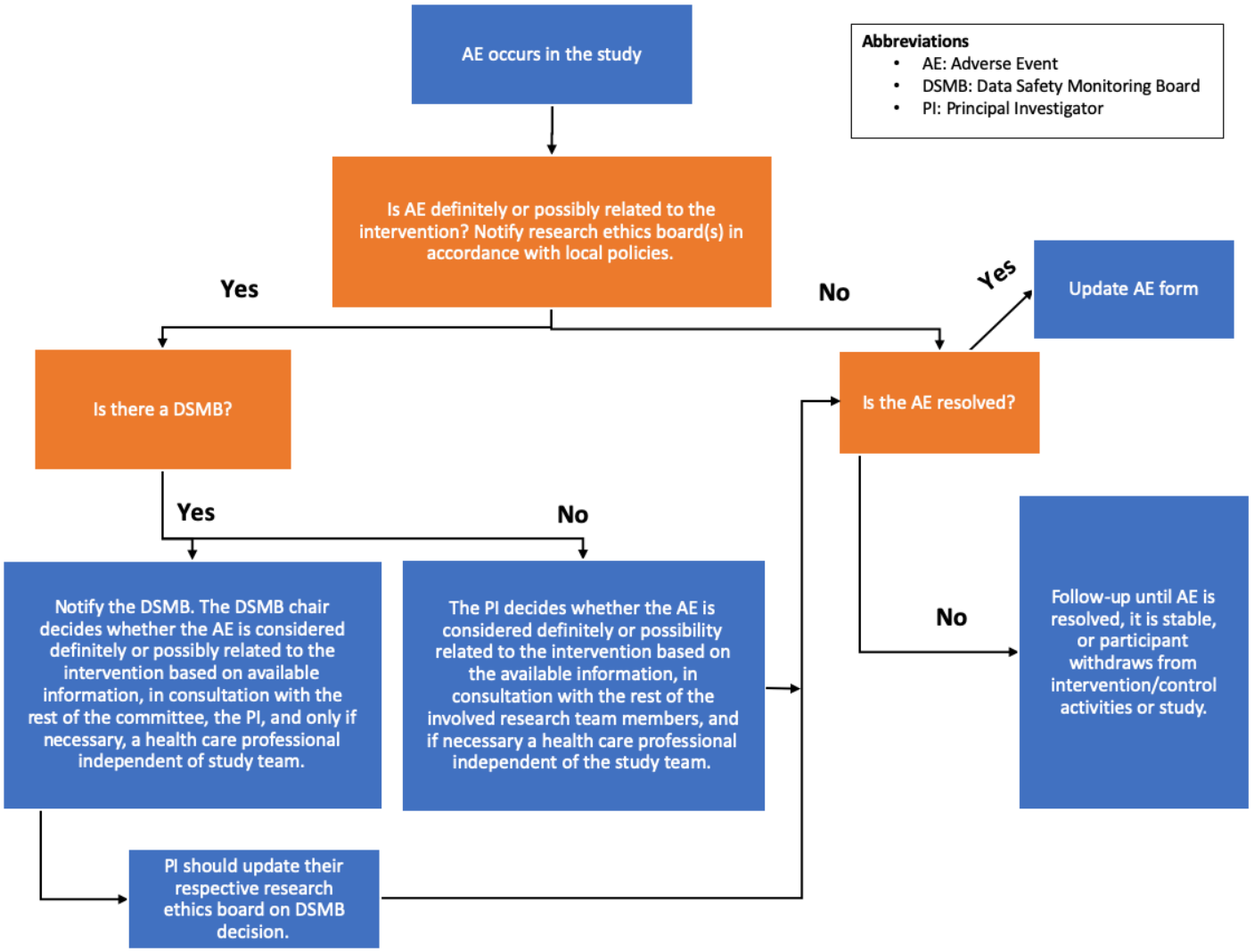
AE	Start Date	Stop Date	Serious AE?	Severity	Expected?	Study Intervention Relationship	Action Taken/Treatment Regarding AE	Action Taken Regarding Study Intervention	Outcome of AE	Notes	PI Initials & Date
1.											
2.											

3.											

Did you notify your research ethics board and data safety monitoring board (if applicable)? ☐Yes ☐ No (*If yes, please list all AEs below)*

AE	Date Reported
1.	
2.	
3.	

Appendix E3: Adverse event reporting decision tree


AE occurs in the study
Abbreviations
AE: Adverse Event
DSMB: Data Safety Monitoring Board
PI: Principal Investigator
Is AE definitely or possibly related to the intervention? Notify research ethics board(s) in accordance with local policies.
Yes
No
Yes
Update AE form
Is there a DSMB?
Is the AE resolved?
Yes
No
No
Notify the DSMB. The DSMB chair decides whether the AE is considered definitely or possibly related to the intervention based on available information, in consultation with the rest of the committee, the PI, and only if necessary, a health care professional independent of study team.
The PI decides whether the AE is considered definitely or possibility related to the intervention based on the available information, in consultation with the rest of the involved research team members, and if necessary a health care professional independent of the study team.
Follow-up until AE is resolved, it is stable, or participant withdraws from intervention/control activities or study.
PI should update their respective research ethics board on DSMB decision.