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Author/s:
Giangregorio, LM;Papaioannou, A;MacIntyre, NJ;Ashe, MC;Heinonen, A;Shipp, K;Wark, J;McGill, S;Keller, H;Jain, R;Laprade, J;Cheung, AM

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Too Fit To Fracture: Exercise recommendations for individuals with osteoporosis or osteoporotic vertebral fracture

Giangregorio LM[1,2,3], Papaioannou A[4], MacIntyre NJ[5], Ashe M[6], Heinonen A[7], Shipp K[8], Wark J[9], McGill S[1], Keller H[1,2], Jain R[10], Laprade J[10,11], Cheung, AM[12]

[1]Department of Kinesiology, University of Waterloo, Canada

[2]Toronto Rehabilitation Institute – University Health Network, Canada

[3]Research Scientist with the Schlegel -UW Research Institute for Aging

[4]Department of Medicine, McMaster University, Canada

[5]School of Rehabilitation Science, McMaster University, Canada

[6]Dept. of Family Practice, University of British Columbia, Canada

[7]Department of Physiotherapy, Health Sciences, University of Jyvaskyla, Finland

[8]Department of Community and Family Medicine, Duke University, United States of America

[9]Royal Melbourne Hospital Department of Medicine, University of Melbourne, Australia

[10]Ontario Osteoporosis Strategy & Osteoporosis Canada

[11]Division of Anatomy, University of Toronto

[12]Department of Medicine, University of Toronto, Canada

Corresponding author:

Lora Giangregorio
University of Waterloo
200 University Ave W
Waterloo ON, N2L 3G1
519 888 4567 x 36357

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Abstract

Purpose: The aim was to develop consensus on exercise recommendations for individuals: 1) with osteoporosis; and 2) with osteoporotic vertebral fracture(s).

Methods: The Grading of Recommendations Assessment, Development and Evaluation (GRADE) method was used to evaluate the quality of evidence and develop recommendations. Outcomes important for decision-making were nominated by an expert panel and patient advocates and included falls, fractures, BMD and adverse events for individuals with osteoporosis/vertebral fractures, and pain, quality of life and function for those with vertebral fracture. Meta-analyses evaluating the effects of exercise on the outcomes were reviewed. Observational studies or clinical trials were reviewed when meta-analyses were not available. Quality ratings were generated, and informed the recommendations.

Results: The outcome for which evidence is strongest is falls. Point estimates of the effects of exercise on falls, fractures and BMD vary according to exercise type. There is not enough evidence to quantify the risks of exercise in those with osteoporosis or vertebral fracture. Few trials of exercise exist in those with vertebral fracture. The exercise recommendations for exercise in individuals with osteoporosis or osteoporotic vertebral fracture are conditional. The panel strongly recommends a multicomponent exercise program including resistance and balance training for individuals with osteoporosis or osteoporotic vertebral fracture. The panel recommends that individuals with osteoporosis or vertebral fracture do not engage in aerobic training to the exclusion of resistance or balance training.

Conclusions: The preliminary consensus of our international panel is that exercise is recommended for individuals with osteoporosis or vertebral fracture, but our recommendations are conditional.

Osteoporosis-related fragility fractures are a significant source of morbidity and mortality. Vertebral and hip fractures are a common consequence of osteoporosis, and can result in pain, depression, functional impairment and increased mortality [1]. One woman in five who have a vertebral fracture will suffer from another vertebral fracture within a year, and the risk of death is 2.7 times higher than those with no fracture (adjusted hazard ratio 2.7, 95% confidence interval 1.1-6.6) [2;3]. Individuals who are identified at high risk of fracture, such as those with a prevalent vertebral fracture, or with risk factors that place them in the high risk category of available risk assessment tools, represent groups that should be targeted for preventative therapies.

A number of pharmacological therapies are available that have been shown to reduce fracture risk in individuals with osteoporosis, and are recommended for individuals at risk, along with ensuring calcium and vitamin D sufficiency. National (e.g., Osteoporosis Canada, National Osteoporosis Foundation, Osteoporosis Australia) and international (International Osteoporosis Foundation, IOF) organizations emphasize the importance of physical activity or exercise for the prevention of bone loss, falls and fractures. Physical activity refers to "…any bodily movement produced by skeletal muscles that results in energy expenditure" whereas exercise is defined as "…physical activity that is planned, structured, repetitive and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective" [4]. Older adults at high risk of fracture pose specific challenges when it comes to prescribing exercise. Specific questions include: How can we safely modify exercise when mobility or posture is altered; and will exercise increase the risk of falls, or fractures? Clinical practice guidelines for the management of osteoporosis advocate for exercise [5], but their scope in informing exercise prescription is limited, especially as they do not differentiate between risk groups (e.g., with versus without vertebral fractures). There have been several recent meta-analyses addressing the impact of exercise on outcomes related to fracture risk [6-10]. There are structured methods for establishing consensus, evaluating evidence and making recommendations, so there is a need to translate current evidence into exercise recommendations that can inform practice.

The Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach, is a structured, transparent approach for evaluating the quality of existing evidence

around a clinical question and developing recommendations. The GRADE approach is used or endorsed by the World Health Organization and the Cochrane Collaboration (http://www.gradeworkinggroup.org/society/index.htm) [11]. One of the benefits of the GRADE process is that it considers both the benefits and potential harm when making recommendations. We established an international expert panel to use the GRADE process to evaluate the quality of existing evidence and generate recommendations for exercise prescription for two target groups: 1) individuals with a diagnosis of osteoporosis but no fracture history; and 2) individuals with a history of vertebral fracture.

METHODS:

Forming the expert panel

We convened an expert panel of researchers and clinicians from Australia, Canada, Finland and the United States, as well as partners from Osteoporosis Canada (Appendix A). Criteria used to select panel members were previous experience with guideline development, prior experience in conducting clinical trials of exercise in individuals with osteoporosis or vertebral fracture, or having clinical or anatomy/biomechanics expertise related to exercise prescription in the target groups. Members of the expert panel included expertise in physical therapy, geriatrics, endocrinology, internal medicine, gerontology, biomechanics and kinesiology.

Deciding on outcomes and formulating the research questions

Prior to the first meeting, panel members were notified that they were to identify important clinical questions around the efficacy of exercise in the management of osteoporosis, and were to make decisions about scope of the recommendations, namely the population(s), intervention(s), comparator(s) and outcomes of interest (PICO format).

During the first teleconference the panel established its purposes to: a) evaluate the effects of exercise, when compared to no intervention, on outcomes critical for decision making; and b) develop exercise recommendations for individuals over the age of 65 years with osteoporosis, with or without vertebral fracture. There was interest in developing recommendations for those with a history of hip fracture, or those with low or moderate risk of fracture, but these additions were considered too broad a scope. Further, it was noted that most

exercise literature to date has defined osteoporosis based on bone density definitions outlined by the World Health Organization, rather than on risk categories (e.g., high, moderate or low risk).

Each panel member was asked to nominate outcomes, both desirable and undesirable, that were important to patients, or important for decision-making, and a list of potential outcomes was generated during the first teleconference. Panel members were asked to independently vote on all of the outcomes for each patient group, using a 9-point Likert scale (0 = "low importance", 5 = "important, but not critical for decision-making" and 9 = "critical for decision-making"). Responses were compiled by a non-panel member. All outcomes with an average score of 8 or higher were included as a separate research question for the review. The Likert scale identified scores of 7-9 as those deemed critical for decision making, but scores below 5 were infrequently used, so a cutoff of 8 was chosen to ensure consensus around the most important outcomes.

Four patient advocates (including one male) were nominated from the Canadian Osteoporosis Patient Network to provide input on outcomes important to patients. Based on input from the patient advocates, three additional questions about bone mineral density and function (activities of daily living [ADL] and mobility) were also included. Panel members were notified of the results, and had the opportunity to request further discussion prior to finalizing the research questions (Table 1).

Evidence retrieval, assessment and synthesis

As several reviews and meta-analyses were available, some of which included studies that focused on our two target groups, these were the focus of this analysis. For most of the outcomes of interest one or more recent (2011 -2013) systematic reviews from the Cochrane Collaboration or other peer-reviewed journals were available and reviewed. To address the question about the effect of exercise on pre-specified outcomes for individuals with osteoporosis, recent meta-analyses were identified [6-9;12]. Because sufficiently powered randomized controlled trials had not been conducted, a 2008 meta-analysis of observational studies, and more recent observational studies examining the relationship between fractures and exercise were identified (13-18) [19-25] via literature search of OVID, EMBASE and CINAHL, performed by a librarian using search terms related to exercise, physical activity and fractures. To address the question about the effect of exercise on pre-specified outcomes for individuals with a history of vertebral fracture, a Cochrane Collaboration systematic review that synthesized all randomized controlled

trials of exercise in individuals with osteoporotic vertebral fractures was used [10]. An additional meta-analysis was reviewed for the ADL outcome [26]. To address the question about the risk of adverse events, we reviewed the adverse events reported in two meta-analyses of exercise interventions [6;10] and one systematic review about adverse event reporting in resistance training trials in older adults [27]. Searches for articles published after the included meta-analyses were not performed unless explicitly stated above.

Four panel members were assigned to each research question and assessed the quality of evidence for each outcome independently using the criteria proposed by the GRADE Working Group [28]. Panel members were given instructions on the GRADE process adapted from the GRADE toolbox (http://www.gradeworkinggroup.org/toolbox/index.htm) [11;29]. Each panel member assigned a rating (High, Moderate, Low, or Very Low) that pertained to the quality of evidence available to answer each of their assigned questions for the patient group of interest. The quality ratings were assigned as follows, in accordance with the GRADE process:

High quality— Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality— Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality— Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality— Any estimate of effect is very uncertain

The panel members were asked to consider how the ratings they generated would inform a recommendation (strong or conditional or no recommendation) for or against exercise in the context of their assigned questions. The panel reconvened at a consensus meeting. For each research question, the assigned panel members voiced their quality ratings and rationale, and there was a discussion among the entire group. A consensus was established by the entire panel for the quality rating and the rationale for the rating for each question, and for preliminary exercise recommendations for each of the two patient groups. We did not pool data to generate relative or absolute effects, but we used tables to summarize the effects, quality ratings and associated rationales.

Formulation of the recommendations

The quality ratings, recommendations and associated evidence summaries were independently reviewed by the working group, consistent with the approach recommended by the GRADE Working Group [11;29]. The panel met to discuss the draft and finalize the ratings and generate recommendations (strong or conditional or no recommendation) for or against exercise for each patient group, and an associated rationale. The strength of the recommendations (strong or conditional or no recommendation) and the direction (for or against) took into consideration the quality of the available evidence, the balance between the benefits and risks associated with exercise, and the patient groups' values and preferences (e.g., would most individuals with vertebral fracture want to participate in exercise as part of chronic disease management?) [11;29]. We were unable to assess cost-effectiveness as there were no studies that quantify the cost versus benefit of exercise in our target groups. The costs of exercise prescription are often incurred by the patient rather than the health care system, so the costs of care were considered to factor into the patient groups' values and preferences. Strong recommendations were worded as "We strongly recommend…" and conditional recommendations were worded as "We recommend…" with any conditions placed specified.

Stakeholder input

The report was circulated to the following stakeholder groups for input on its utility and clarity: the Osteoporosis Canada Clinical Practice Guidelines committee, representatives from the Canadian Osteoporosis Patient Network, the National Osteoporosis Foundation exercise and rehabilitation advisory council, the International Osteoporosis Foundation, the Finnish Osteoporosis Association, Osteoporosis Australia, and the Canadian Physiotherapy Association.

RESULTS:

The quality of evidence evaluating the effect of exercise on most of the outcomes of interest for each target group was LOW or VERY LOW, with the exception of the falls outcome (Table 2). The evidence summaries are outlined with the quality ratings, and Table 3 contains a summary of the meta-analyses reviewed and the reported effects. The final recommendations are listed in Table 4.

Falls

Two meta-analyses provide strong evidence that exercise can reduce falls in older adults. The effect varies depending on the type and frequency of exercise [7;8]. The ProFANE taxonomy is a naming and classification system aimed at standardizing elements of falls prevention interventions (http://www.profane.eu.org/taxonomy.html). Home-based or group-based exercise programs that emphasize balance training and a higher overall dose of exercise, or include exercises from more than one category in the ProFaNE taxonomy (i.e., gait/balance/functional training, strength/resistance training, flexibility, three-dimensional training like Tai Chi, general physical activity, endurance training or other) were able to significantly reduce falls [7;8]. Both reviews suggested that walking or resistance training alone may not have a significant effect on falls [7;8].

The consensus of the panel was that the observed effects of exercise on falls in older adults would be similar in individuals with osteoporosis, so the panel rated the quality of evidence as HIGH. However, it was noted that hyperkyphotic posture (excessive kyphotic curvature of the thoracic spine) may modify fall risk or the effect of exercise on fall risk. The indirectness of the evidence was identified to be more of a concern when applying the findings to individuals with a history of vertebral fracture, where impaired gait and balance and hyperkyphotic posture may be more prevalent [30-33]. However, a single subgroup analysis suggested that the effect of exercise on falls in individuals at high risk was not different than in those at low risk [7]. Therefore, the quality of evidence around the effects of exercise on fall risk was downgraded to MODERATE for individuals with vertebral fracture (Table 2).

Fractures

No randomized trials of exercise completed to date have been powered to investigate fracture (hip, vertebral, or non-vertebral) as a primary outcome. One 12-year study identified fracture as a primary outcome but participants self-selected to exercise or control groups; the risk ratio for fracture risk reduction was 0.32 [95% CI, 0.08 to 1.05] and was not statistically significant [15]. Both randomized trials and observational studies have reported that physical activity or exercise may reduce fracture risk, but there are important inconsistencies in the size and direction of the effect, and there is a high risk of bias among studies (Table 3). Two meta-analyses of randomized controlled trials of exercise in older adults report an estimate of effect on incident fractures [6;7], but the reported effects should be viewed with caution given the inclusion of

largely underpowered studies where the primary outcome was not fracture (Table 3). One was a meta-analysis of exercise interventions aimed at reducing falls in older adults, which reported a significant reduction of fractures (RR 0.36 [95% CI 0.19 to 0.70]; 719 participants, 5 trials), however it was fractures reported as adverse events, rather than as a study outcome that were pooled, and the study designs were diverse (e.g., one was a 6-week trial of PT in individuals with Parkinson's disease, another was a multifaceted intervention). The other meta-analysis examined whether exercise could improve bone density in post-menopausal women, and reported no significant effect of exercise on fractures, with wide confidence intervals (odds ratio, OR 0.61; [95% CI 0.23 to 1.64]; four studies and 539 participants). Three of the trials excluded women on osteoporosis medication and one trial started all participants on 5 mg of alendronate.

A meta-analysis of prospective observational studies reported that participation in physical activity was associated with reduced hip fracture risk; the fracture risk reduction attributable to physical activity participation in men and women was 45% [95% CI, 31-56%] and 38% [95% CI, 31-44%], respectively [19]. Subsequent observational studies have confirmed that physical activity participation is associated with a reduced risk of hip fracture [20-22;24;25;34;35] or osteoporosis-related fractures [23]. However, a few recent observational studies suggest that the effect of exercise may vary with exercise type, fracture type or season, and that in some cases the risk of fracture may be increased with increased physical activity participation [16;18;36;37]. The risk of self-reported fractures has been reported to be increased among women who participated in at least 3 hours (odds ratio (OR) 1.51 [95% CI 1.01–2.24]) or 6 bouts of walking weekly (OR 1.56 [95% CI 1.07–2.27], and was also increased in men who walked more than 3 hours per week (OR 2.30 [95% CI 1.06-4.97]) when compared with men who reported no walking. The effects were specific to walking; the time spent in physical activity in general was not associated with self-reported fractures.

The finding that higher physical activity may not reduce the risk of fractures other than hip fractures [20;22], or may be associated with an increased risk of wrist fractures has been reported in several studies [13;36]. Rikkonen et al (2010) reported that being in the highest quintile of physical activity participation was associated with an increased risk of wrist fractures, hazard ratio 1.4 [95% CI 1.14–1.69], happening more often in winter. A recent analysis of data from the Women's Health Initiative suggests that compared to those participating in no physical activity, the increased risk of wrist fracture attributable to participating in the highest levels of

physical activity (>17.5 MET-hours/week) is modest (HR=1.10, 95% CI: 0.96, 1.27). Further, there was a negative association between high physical activity participation and hip fractures (HR= 0.63, 95% CI: 0.48, 0.81), clinical vertebral fractures (HR=0.80, 95% CI 0.66, 0.98) and total fractures (HR=0.95, 95% CI: 0.89, 1.02) [16]. In contrast, a population-based case-control study suggested that active commuting reduced the risk of wrist fracture, but leisure walking did not [37]. Notably, adjusting for confounding variables has been shown to weaken or eliminate any observed associations between physical activity level and fracture incidence in observational trials [13;14].

Although osteoporotic fractures can often occur as a result of a fall, vertebral fractures can occur during other events or movements, and therefore activities that increase or decrease fall risk may not have the same effect on the incidence of vertebral fractures as it would on the incidence of other fracture types in individuals with osteoporosis, or with a history of osteoporotic vertebral fracture. In individuals with vertebral fractures, there have been reports of fractures during exercise (e.g., when rolling from supine to prone, or when weights were dropped on foot) but the between-group differences in risk were not examined [38]. Because of the sparse data, inconsistency in the reported size and direction of effect and high risk of bias, the panel put forward a VERY LOW quality rating for the fractures outcome for both target groups, and suggested that both the risks and benefits of exercise be considered in the recommendations.

Bone mineral density (BMD)

A meta-analysis evaluating exercise in postmenopausal women provides evidence of a modest between-group difference in favour of the effects of exercise on BMD at the lumbar spine and trochanter, but no significant differences at the total hip or femoral neck, suggesting inconsistency in the effect [6]. Subgroup analyses also revealed that the effects varied depending on the type of exercise. In general, it was suggested that the effects of exercise at the total hip and trochanter were slightly larger for dynamic, weight-bearing high force exercise, but that this type of exercise did not improve spine BMD. Multicomponent exercise programs had a significant effect on BMD at the trochanter and neck of femur, such that the between-group difference at the spine in favour of exercise was greater than 3%. Although small between-group differences in favour of exercise have been observed, the clinical significance of the changes

with respect to fracture prevention is unclear. As well, the evidence to date is indirect, as only two of the included trials studied women with osteoporosis exclusively. The evidence provided by those trials would not be sufficient to upgrade the quality rating as they only assessed effects at the lumbar spine, and there were other sources of bias (e.g., co-intervention with osteoporosis medication, low power, unclear risk on other items) [39;40].

A meta-analysis of the results of three trials in adult males (aged 41-79 years) suggested a medium effect of exercise (Effect size, g = 0.53 95% CI [0.031, 1.153], p=0.04) on BMD at the femoral neck, and the effect of exercise on BMD at the lumbar spine was not significant (g = 0.190 [-0.036, 0.416], p=0.10). There was no statistically significant effect of exercise on BMD at the total hip. The studies did not include males with osteoporosis, were heterogeneous in their observed effect of exercise at the femoral neck, and the data related to our research questions were sparse. A subsequent randomized controlled trial of unilateral training 7 days a week (where non-trained leg was used as the control) in adult males reported a significant effect of exercise on femoral neck BMD, but no statistically significant effect on lumbar spine BMD or total hip, which is consistent with the results of the meta-analysis [41]. There has been only one trial examining the effects of exercise on BMD in women with vertebral fractures; no significant between-group difference was reported, but there were sources of bias (e.g., subgroup analysis from larger trial, co-intervention with osteoporosis medication, high or unclear risk on other items) that may have affected the ability to detect an exercise effect [42]. The panel rated the overall quality of evidence supporting a positive effect of exercise on BMD as LOW for individuals with osteoporosis and VERY LOW for individuals with vertebral fractures.

Harms

Adverse event reporting in exercise trials is subject to a high probability of reporting bias [43]. Data are sparse regarding adverse events in the reviewed literature. Rarely do randomized controlled trials report if and how adverse event data were collected in the methodology section, and they are reported inconsistently or under-reported. Commonly reported adverse events in exercise trials include muscle soreness/strain, joint pain, cardiovascular reactions, and falls [6;10;43]. Although our review of current evidence concluded that the risks of exercise do not outweigh the benefits, there is evidence from both observational trials and randomized controlled trials that exercise may increase the risk of fractures under certain conditions, such as walking

during slippery weather, or performing twisting movements too quickly during transitions between positions [18;36;38]. The panel assigned the rating of VERY LOW to the quality of evidence around harms associated with exercise, and noted the importance of considering both the risks and benefits when making recommendations for individuals at risk of fractures.

Pain

In individuals with vertebral fractures, there are a few reports of reduced pain after short-term (10-weeks) exercise programs, but no effect reported after longer-term (24 week) exercise, suggesting imprecision in the estimate [38;44-46]. The data are sparse, and the risk of bias in some cases is a concern. There were only four trials that examined this question, and one was a study of a multicomponent physical therapy intervention that included exercise. Not all studies examined individuals with significant pain at baseline. The quality rating around the evidence for exercise effects on pain was VERY LOW.

Quality of Life

There were three trials that reported the effects of exercise in individuals with vertebral fracture on health-related quality of life using generic or disease-specific scales. The effects were not consistent across subscale areas, although any positive effects were more likely to be observed in longer-term, rather than short-term follow-up. This inconsistency coupled with the sparse data and the risk of bias associated with lack of blinding of participants completing the self-report questionnaire, as well as other sources of bias resulted in a quality rating of VERY LOW for this body of evidence.

Mobility

There were only four trials that examined the effects of exercise on mobility. Pooled analyses of two trials [46;47] revealed a small but significant between groups difference in favour of exercise for Timed Up and Go test performance. Yet these findings should be viewed with caution given that two other trials not included in the pooled analysis did not find significant between-group differences, suggesting inconsistency in the reported effects [44;48]. Walking speed was reported in one trial; there was a small but significant effect in favour of exercise [47]. The significant effects of exercise on mobility outcomes are promising, but the magnitude of the

effects were small and the clinical significance needs to be confirmed (between-group differences ~1 second for Timed Up and Go and ~2 seconds for walking speed over 20 metres). Further, there was substantial variability in quality across all studies. Despite the inconsistency, risk of bias and sparse data, small positive effects were observed in more than one trial, so the panel upgraded the quality rating to LOW.

Activities of Daily Living (ADL)

Our assessment of the effects of exercise on ADLs in individuals with vertebral fractures was limited to three trials that examined this outcome indirectly via activity restriction or ADL subscales of a quality of life measure, which was a self-report measure (risk of bias due to lack of participant blinding). There was inconsistency in the reported effect. The sparse data, risk of bias and inconsistency resulted in a VERY LOW quality rating. We reviewed a meta-analysis of the effects of exercise on ADL performance in frail older adults [26], but the poor quality of available evidence did not warrant upgrading the quality rating.

Recommendations

Exercise is a very broad term; the evidence reviewed included walking, Tai Chi, resistance training, dance, jogging, gymnastics, balance exercises, and multicomponent programs in the category of exercise. The expert panel concluded that strong recommendations could not be made for exercise in general and that conditions must be placed on any exercise recommendations made for individuals with osteoporosis or osteoporotic vertebral fractures. The main recommendations that arose from the consensus process are (Table 4):

For individuals with osteoporosis:

1) We strongly recommend that individuals with osteoporosis engage in a multicomponent exercise program that includes resistance training in combination with balance training.
2) We recommend that individuals with osteoporosis do not engage in aerobic training to the exclusion of resistance or balance training.

For individuals with osteoporotic vertebral fracture:

3) Consultation with a physical therapist is suggested to ensure safe and appropriate exercise. We strongly recommend that individuals with osteoporotic vertebral fracture engage in a multicomponent exercise program that includes resistance training in combination with balance training.
4) We recommend that individuals with osteoporotic vertebral fracture do not engage in aerobic training to the exclusion of resistance or balance training.

The potential risk of falls or fractures during exercise should be considered in the design and execution of exercise programs in the target groups. Individuals at high risk of fracture should consider consulting a physical therapist with expertise in osteoporosis prior to initiating a new exercise program, and all individuals with osteoporosis should learn how to move safely or take precautions when performing twisting or bending during transitions between movements, when working with loads, when performing movements that challenge balance or when performing activities outdoors in slippery weather. In developing the more detailed recommendations related to specific exercise domains below, we also considered the physical activity guidelines for older adults put forward by the Canadian Society for Exercise Physiology (CSEP) (http://www.csep.ca/english/view.asp?x=587), the Centers for Disease Control (CDC) (http://www.cdc.gov/physicalactivity/everyone/guidelines/olderadults.html) and the American College of Sports Medicine (ACSM) (http://journals.lww.com/acsm-msse/Fulltext/2009/07000/Exercise_and_Physical_Activity_for_Older_Adults.20.aspx), so as not to negate the benefits of physical activity for other health domains, and also to maintain consistency with national guidelines when appropriate to do so. For individuals with osteoporosis who are sedentary, have comorbid conditions that affect activity participation, or have high fracture risk, consultation with a physical therapist is recommended when starting a new exercise program.

Resistance Training

The panel strongly recommends that individuals with osteoporosis or osteoporotic vertebral fractures participate in a multicomponent exercise program that includes progressive resistance training program for all major muscle groups, a minimum of twice weekly. Resistance training has been defined in the ProFaNE Taxonomy (http://www.profane.eu.org/documents/Falls_Taxonomy.pdf) as: “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. trunk extension in prone lying) or an external resistance (e.g. free weight)." The intensity and type of exercise should be tailored to tolerance and ability, especially in the presence of pain. Two sets of at least one exercise for each major muscle group should be performed, at a target intensity of 8-12 repetitions maximum for those that can tolerate it, recognizing that some individuals, such as those who are previously sedentary or unfamiliar with resistance training, should begin training at a lower intensity. Resistance training exercises can include those that use resistance bands or cables, free weights, or body weight to provide resistance. Resistance training machines often require forward bending and twisting to perform the exercise or to adjust the equipment and to ensure proper positioning. Resistance training machines should be avoided in individuals at high risk of vertebral fracture unless there is certainty that it can be used and adjusted with proper form. Instruction on proper handling of equipment and transitions between movements is important for individuals at risk of fracture. A few fractures in individuals with vertebral fracture have occurred when weights were dropped or when turning from supine to prone [38]. Slow, controlled movements are recommended. The panel highlighted the importance of including strengthening exercises targeting muscles important for posture, and that individuals with osteoporosis or vertebral fracture are educated about proper posture during exercise and every day activities. There is growing evidence that hyperkyphotic posture is associated with balance impairment and other adverse outcomes [30-33]. There is some weak evidence that exercise can improve posture in individuals with osteoporosis or hyperkyphosis [44;47;49-53]. Exercise to increase strength in functional movements, such as stair climbing and squats or sit-to-stand, are also suggested. Previous work suggests that women with low bone mass are able to adhere to resistance and agility training [54].

Balance Training

The panel strongly recommends that individuals with osteoporosis or osteoporotic vertebral fracture participate in daily balance training as part of a multicomponent exercise program, and aim to accumulate two hours of balance training weekly (~15-20 minutes per day), where daily training can be performed all at once, in short bouts throughout the day, or incorporated into daily activities. Indeed, a recent study demonstrated that teaching lifestyle-integrated exercise

(where people learn to incorporate activities or exercises into their daily activities, e.g., tandem stance while washing dishes) may work as well as a structured exercise program [55]. Balance training is defined as "…the efficient transfer of bodyweight from one part of the body to another or challenges specific aspects of the balance systems (e.g., vestibular systems)" and balance retraining is defined as "… from the re-education of basic functional movement patterns to a wide variety of dynamic activities that target more sophisticated aspects of balance." Exercises should be chosen that provide a sufficient challenge to balance, by reducing the person's base of support or amount of sensory input, perturbing their centre of mass or challenging muscles important for posture or balance, and may need to be individually tailored [56]. Examples of exercises included in clinical trials that have reported a significant reduction in falls are listed in Table 5. Three-dimensional exercises are defined by the ProFaNE taxonomy as "involves constant movement in a controlled, fluid, repetitive way through all 3 spatial planes or dimensions", and include Tai Chi or dance. Three-dimensional exercises could be incorporated as part of balance training because they require weight-transfer, upright posture, and dynamic balance. Another strategy may be to incorporate exercises that challenge both strength and balance, such as squats, lunges, or calf raises. There must be a progressive increase in the balance challenge or intensity of exercise over time. Precautions should be put in place to prevent accidental falls (e.g., the use of support objects, having support objects like a sink or corner wall nearby, performing the exercises in areas with soft flooring, wearing flat-soled shoes that increase the traction between the foot and ground).

Aerobic Training

Physical activity guidelines from CSEP, CDC and ASCM include recommendations around aerobic exercise because of the benefits of aerobic exercise for multiple health domains. The panel proposed conditional recommendations against prescribing aerobic exercise to the exclusion of resistance training and balance training. It is not uncommon for health care providers to recommend that walking is the best type of exercise for individuals with osteoporosis, and to neglect other types of exercise, which arguably may be of equal or greater benefit [57]. Therefore, for individuals with osteoporosis or osteoporotic vertebral fractures, aerobic exercise alone may not be sufficient for fall or fracture prevention; health care providers should emphasize the importance of resistance training combined with balance training for individuals with osteoporosis or osteoporotic vertebral fractures.

To achieve health benefits across multiple health domains, in addition to bone health, aerobic exercise can be combined with resistance and balance training. Individuals with osteoporosis or vertebral fractures can aim to achieve the recommended intensity, frequency and duration of aerobic exercise set out by the CDC, the ACSM and CSEP (150-300 minutes per week of moderate intensity aerobic physical activity *or* 75-150 minutes per week of vigorous intensity aerobic physical activity), in bouts of 10 minutes or more. The ACSM and CDC use a 0-10 scale to define intensity, where 0 = sitting and 10 = working as hard as you can; moderate is 5-6, and vigorous is 7-8. Previously sedentary individuals or those with low endurance or aerobic capacity, fractures or comorbid conditions that affect activity participation may not be able to achieve the recommended frequency, intensity or duration, and may need to start at much lower levels. Shorter activity bouts or lower intensity may be more appropriate in individuals with fractures or other limitations. The panel recommends that weight-bearing aerobic exercise be emphasized over non-weight bearing exercise, because of its potential impact on BMD. Exercises that included dynamic, weight-bearing high force exercise, such as jumping or running, were more likely to have an effect on hip BMD, but for individuals at high risk of vertebral fracture, the risks associated with these exercise types, or vigorous exercise in general, may outweigh the benefits. Dynamic, weight-bearing low force exercise, such as Tai Chi or walking, may have a modest effect on spine BMD [6]. However, patient or client values and preferences should be considered, and if there is a preference for non-weight bearing exercise such as swimming, it does not need to be discouraged, rather the client or patient should be counseled on how to add resistance and balance training to their regime. Finally, for individuals at risk of fracture, performing aerobic exercise outside in rainy or icy weather, or on slippery surfaces should be discouraged, because of the potential for increased fall and fracture risk [18;36]. Instead, developing a plan for engaging in exercise indoors when outdoor conditions pose a high fall risk should be encouraged. That said, the risk factors for indoor falls and outdoor falls may be different; some data suggests that many falls occur in the home in frail, inactive older people, whereas highly active people may be more likely to fall outdoors [58]. Ultimately, the safety of the exercise prescription and the environment in which it is performed must be considered in individuals at risk of falls and fractures.

Summary of Rationale for Recommendations: The available evidence suggests that multicomponent exercise programs that combine muscle strengthening and balance training can reduce falls. Multicomponent exercise programs may also have the most potential for improving BMD, although it is unclear if any effects on BMD are observed in individuals with established osteoporosis or vertebral fractures. The strong recommendations for multicomponent exercise and the conditional recommendations against emphasizing aerobic exercise to the exclusion of resistance and balance training arose because of the strength of the evidence regarding the effects of exercise on fall risk and the fact that many individuals would want the intervention (e.g., when values and preferences were considered). There is some evidence that a home-based exercise program aimed at reducing falls is cost-effective in individuals at high risk of falls [59;60]. The frequency and intensity were informed by the published research and by recommendations put forward by the CDC, CSEP and ACSM. Exercises strengthening muscles important for posture (e.g., improving back extensor muscle endurance) are were included in all of the published research studies of exercise in women with vertebral fracture. Because there is increasing evidence that hyperkyphosis is associated with an increased risk of falls, and may increase the risk of vertebral fractures, the panel noted the importance of posture exercises/education for the two target groups. Our recommendations also identify areas where caution is needed to reduce harms associated with exercise, based on current evidence. Table 6 is a quick reference summary of our recommendations, with details around frequency and intensity informed by national physical activity guidelines from the CDC, CSEP and ACSM.

Recommendations for Future Research

During the process of reviewing the evidence, the panel identified key research gaps and limitations and generated recommendations for future research.

<u>Recommendation 1: Systematic evaluation of harms</u>

Future studies need to systematically collect and report adverse events as a study outcome, and clearly identify any adverse events that are directly related to the intervention. Trials should have a Data Safety Monitoring Board or Committee to review adverse events. Adverse events are not always reported, and when they are it is unclear if they were systematically assessed throughout the trial or if they were reported inconsistently. Trial investigators should outline the protocol

used to collect information about adverse events in the trial methodology. Understanding what events led to an adverse outcome may inform future research or practice.

Recommendation 2: Assess outcomes that will inform cost-effectiveness analyses

To inform policy, it is important to understand the cost of implementing an intervention relative to the benefits observed. The cost of implementing an intervention may also assist other investigators or community-based organizations planning to develop similar interventions. Although it is possible to estimate cost-benefit once a trial is complete using indirect sources of information, it would be more compelling and valid to embed measures of health utilities and resource use into the design of the trial.

Recommendation 3: Clinical trials in individuals at high risk of vertebral or other fractures

Our review of the evidence revealed that very few clinical trials of exercise have been conducted in individuals with osteoporosis or osteoporotic vertebral fractures. The effects of exercise on patient-important outcomes (e.g., adverse events, falls, fractures, BMD, ADL performance, quality of life) may be different in these groups. In many cases it is only when the presence of chronic disease, namely osteoporosis, is identified, that the patient's need for information about how to incorporate chronic disease management strategies such as exercise becomes apparent. Our patient advocates and clinicians have reported that questions about safe and effective exercise rank among the most frequent questions asked by patients. However, the available evidence to inform exercise prescription in individuals at high risk of fracture is limited.

Recommendation 4: Good clinical trial design and reporting

To inform practice, the details around the frequency, intensity, duration and type of exercise are needed. Further, attention to clinical trial design (e.g., how missing data is handled, randomization procedures, blinding) can reduce bias. Researchers and clinicians designing or interpreting clinical research should refer to the Consolidated Standards of Reporting Trials (CONSORT) Statement, and its extensions (http://www.consort-statement.org/consort-statement/). One of the extensions is specific to non-pharmacological interventions.

Recommendation 5: Consider multiple disciplines, including basic science, psychology, implementation science, and observational data in the design of clinical trials

It was of interest to the panel that basic science suggests that shorter, more frequent bouts of exercise may be more osteogenic, yet interventions in clinical trials often implement thrice-weekly bouts of exercise of longer (e.g., 60 minutes) duration [61]. Similarly, unusual movement patterns or high impact loads have been proposed as osteogenic in basic science experiments, yet there is a fear that these movements may increase the risk of falls or fractures in high risk individuals, or not be feasible in older adults because of the high prevalence of osteoarthritis. Progressively increasing impact exercise may be tolerable in older adults with osteoarthritis and does not contribute to disease progression [62]. Barriers to implementation of basic science evidence in clinical trials with vulnerable populations need to be identified. Finally, it was evident that a key gap in trials of older adults is the ability to maintain long-term sustainability of and adherence to exercise interventions. Long-term adherence to exercise interventions is often low, particularly when exercise is unsupervised. Future trials may consider designing interventions that include both exercise prescription and behavioural interventions. Thorough review of basic science, observational trials, and relevant research in other disciplines, in addition to existing clinical trials, should be used to identify important gaps and inform the design of future interventions.

Next Steps for Too Fit To Fracture

In consultations with patients, clinicians and advocacy groups, it was clear that there were a number of questions around exercise that were important to patients for which there is no evidence to guide practice. There is little information on how to adapt exercise according to different case presentations. For example, would the exercise goals or prescription for someone with a history of osteoporotic vertebral fracture vary depending on the presence of pain or hyperkyphosis? Therefore, we intend to get broader input on the recommendations we have developed by seeking out the opinion of important stakeholders. The *Too Fit To Fracture* team is conducting a Delphi consensus process that will engage clinicians, researchers and patient advocates to come to consensus on how to make and apply exercise recommendations depending on case presentation, to answer questions important to patients and to inform future research priorities. The next step will be to combine the GRADE recommendations presented in this paper with the results of the Delphi consensus process, resulting in more detailed exercise recommendations for individuals with osteoporosis or osteoporotic vertebral fractures.

Acknowledgements and Endorsements:

These recommendations were reviewed and endorsed by Osteoporosis Canada, by the National Osteoporosis Foundation, and by Osteoporosis Australia's Medical and Scientific Advisory Committee. We are grateful for the International Osteoporosis Foundation's contribution and review of this document, as well as reviews by Susan Muir and Bonny O'Hare representing the Canadian Physiotherapy Association, and reviews by Dr. Harri Sievänen and Dr. Maarit Piirtola representing the Finnish Osteoporosis Association. We would like to acknowledge financial support from the University of Waterloo, Osteoporosis Canada and the Schlegel-University of Waterloo Research Institute for Aging. We would like to thank Celina Lin, Michael McLeod and Caroline Jeon for their assistance with the literature review process.

Appendix A: Members of the Expert Panel for GRADE recommendations process

Member Name, Title, Affiliation
Lora Giangregorio, Associate Professor, Department of Kinesiology, University of Waterloo, Canada, Research Scientist, Research Institute for Aging
Alexandra Papaioannou, Professor, Department of Medicine, McMaster University, Canada
Angela Cheung, Professor, Department of Medicine, University of Toronto, Canada
Ari Heinonen, Professor, Department of Health Sciences, University of Jyvaskyla, Finland
John Wark, Professor of Medicine, University of Melbourne, Australia
Kathy Shipp, Assistant Professor, Department of Medicine, Duke University, United States of America
Maureen Ashe, Assistant Professor, Dept. of Family Practice, University of British Columbia, Canada
Norma MacIntyre, Associate Professor, School of Rehabilitation Science, McMaster University, Canada
Stuart McGill, Professor, Department of Kinesiology, University of Waterloo, Canada
Heather Keller, Professor, Department of Kinesiology, University of Waterloo, Canada

Osteoporosis Canada partners

Ravi Jain, Director, Ontario Osteoporosis Strategy & Osteoporosis Canada

Judi Laprade, Lecturer, Division of Anatomy, University of Toronto, Lead Consultant, Bone Fit™ Training Program

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Table 1: PICO Questions

Population, Intervention, Comparator	**Patient-Important Outcomes**
Among individuals with osteoporosis but no history of vertebral fracture, does exercise, when compared to no intervention:	• reduce the risk of falls? • reduce the risk of fracture? • increase bone density? • increase the risk of adverse events?
Among individuals with a history of osteoporotic vertebral fracture, does exercise, when compared to no intervention:	• reduce the risk of falls? • reduce the risk of fracture? • increase bone density? • reduce pain? • improve health-related quality of life? • improve function (i.e., activities of daily living, mobility outcomes)? • increase the risk of adverse events?

Table 2: Quality Rating and Rationale for Evidence Addressing Effects of Exercise on Priority Outcomes of Interest in Target Groups

Outcome	Individuals with diagnosis of osteoporosis	Individuals with osteoporotic vertebral fracture(s)
Falls	**HIGH** -Two meta-analyses provide evidence for effect -Evidence indirect but effect not suspected to be different -Effect similar in high and low risk individuals -Effect may be modified by hyperkyphotic posture -Balance exercises or multicomponent exercise programs	**MODERATE** -Two meta-analyses provide evidence for effect -Evidence indirect and effect may be different -Effect similar in high and low risk individuals -Effect may be modified by hyperkyphotic posture -Balance exercises or multicomponent exercise programs
Fractures	**VERY LOW** -Imprecise or sparse data -Inconsistency in direction and size of effect -Most data supporting an effect are observational -High risk of bias in available data	**VERY LOW** -Imprecise or sparse data -Inconsistency in direction and size of effect -Most data supporting an effect are observational -High risk of bias in available data
BMD	**LOW** -Indirect evidence: uncertain if effects on BMD are different in the presence of osteoporosis -Imprecise or sparse data -Risk of bias	**VERY LOW** -Indirect evidence: effects on BMD may be different in people with osteoporotic spine fracture -Imprecise or sparse data -Risk of bias, participants on bone drugs
Harm (adverse events)	**VERY LOW** -Inconsistency in direction and size of effect	**VERY LOW** -Inconsistency in direction or size of effect

	-High probability of reporting bias	-High probability of reporting bias
	-Imprecise or sparse data	-Imprecise or sparse data, indirect evidence
Pain	n/a	**VERY LOW**
		-Imprecision and risk of bias
		-Inconsistency in direction and size of effect
QOL	n/a	**VERY LOW**
		-Imprecise or sparse data, risk of bias
Mobility	n/a	**LOW**
		-Imprecise or sparse data, variable risk of bias
		-Inconsistency in size and direction of effect
		-Small positive effects in more than one trial
ADL	n/a	**VERY LOW**
		-Imprecise or sparse findings, variable risk of bias
		-Inconsistency in size and direction of effect

Table 3: Meta-analyses used to develop GRADE quality ratings*

Source	**Study Population**	**Outcome(s)**	**Reported effect** (effect [95% confidence intervals]
Howe et al. Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database Syst Rev. 2011	Postmenopausal women	• BMD • Fractures • Rate of falls/Risk of falling • Adverse events	• Largest effect on FN BMD - progressive resistance strength training (MD 1.03 [0.24 to 1.82]). • Largest effect on spine BMD - combination exercise programmes (MD 3.22 [1.80 to 4.64]) • Fractures and falls were reported as adverse events in some studies. No effect on numbers of fractures (OR 0.61 [0.23 to 1.64])[1]
Kelley et al. Exercise and bone mineral density in men: a meta-analysis	Adult men	• BMD	• FN BMD - Effect size, g = 0.53 95% CI [0.031, 1.153], p=0.04 • LS BMD - (g = 0.190 [-0.036, 0.416], p=0.10)
Giangregorio et al. Exercise for improving outcomes in individuals with osteoporotic vertebral fracture (Cochrane review in progress)	Individuals with a history of osteoporotic vertebral fracture	• BMD • Fractures • Adverse events • Quality of life • Pain • Function (ADL, mobility)	• No significant effect on BMD • No study with fracture as an outcome • No between-group comparison of adverse events. 3 exercise-related fractures. • Inconsistent effects on QOL – no pooled data • Inconsistent effects on pain – no pooled data • Inconsistent effects on ADLs – no pooled data • Improved TUG time (MD -1.13 seconds [-1.85 to -0.42]) • Improved 20metre walking speed (effect size 0.5)
Sherrington et al. Exercise to prevent falls in older adults. N S W Public Health Bull. 2011	Older adults (≥ 65 years old)	• Rate of falls/Risk of falling	Effect on falls varied by intervention or population: • Exercise (RaR 0.84 [0.77 to 0.91]) • Balance training, no walking training, higher exercise dose (RaR 0.62 [0.54 to 0.73]) • High fall risk population (RaR 0.90 [0.80 to 1.00])

Gillespie et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev. 2009	Older adults (≥ 65 years old)	• Rate of falls/Risk of falling • Fractures	Effect on fractures in older adults: (RR 0.36, [0.19 to 0.70][1] Effect on falls varied by intervention or population: • Multiple-component group exercise (RaR 0.78, [0.71 to 0.86]; RR 0.83 [0.72 to 0.97]) • Tai Chi (RaR 0.63 [0.52 to 0.78]; RR 0.65 [0.51 to 0.82]) • Multiple-component home-based exercise (RaR 0.66 [0.53 to 0.82]; RR 0.77 [0.61 to 0.97]) • Gait/balance/ functional training (RaR 0.73 [0.54 to 0.98]); (RR 0.77 [0.58 to 1.03]) • Other exercise types had no significant effect • High risk population (RaR 0.75 [0.62 to 0.89], RR 0.88 [0.78-0.99]) Effect on fractures: (RR 0.36 [0.19 to 0.70]
Moayyeri 2008 The Association Between Physical Activity and Osteoporotic Fractures: A Review of the Evidence and Implications for Future Research[2]	Middle-aged and older adults	• Hip fracture	Effect of moderate-to-vigorous physical activity on hip fracture risk: • (RR 0.55 [0.44-0.69]) for men • (RR=0.62 [0.56-0.69]) for women

FN = femoral neck, BMD = bone mineral density in g/cm^2, OR = odds ratio, ADL = Activities of Daily Living, RaR = rate ratio, RR = risk ratio, TUG = Timed Up and Go, MD = mean difference, data in [] are 95% confidence intervals

*individual randomized controlled trials or observational trials were also used to inform quality ratings, but are not listed here

[1]The effect of exercise on fractures was examined in two separate meta-analyses; one was conducted among studies of postmenopausal women, and one in studies of interventions for falls in older adults. Both analyses should be interpreted with caution

as they may be largely influenced by a study by Korpelainen et al (2006) that was not designed or powered to examine fractures as a primary outcome (n=133) and the reported effect was large; six women (7%) in the intervention group and 15 (20%) in the control group sustained a fracture.

[2]A meta-analysis of observational trials. The rest of the meta-analyses are of randomized controlled trials

Table 4: Exercise recommendations for individuals with osteoporosis or osteoporotic vertebral fractures

Recommendations for individuals with osteoporosis:

5) We strongly recommend that individuals with osteoporosis engage in a multicomponent exercise program that includes resistance training in combination with balance training.
6) We recommend that individuals with osteoporosis do not engage in aerobic training to the exclusion of resistance or balance training.

Recommendations for individuals with osteoporotic vertebral fracture:

1) We strongly recommend that individuals with osteoporosis engage in a multicomponent exercise program that includes resistance training in combination with balance training. Consultation with a physical therapist is recommended to ensure safe and appropriate exercise.
2) We recommend that individuals with osteoporotic vertebral fracture do not engage in aerobic training to the exclusion of resistance or balance training.

Table 5: Example balance training exercises that have been used in clinical trial interventions for fall prevention

What is balance training?	Example exercises
Balance training is defined as "…the efficient transfer of bodyweight from one part of the body to another or challenges specific aspects of the balance systems (e.g., vestibular systems)" and balance retraining is defined as "… from the re-education of basic functional movement patterns to a wide variety of dynamic activities that target more sophisticated aspects of balance." http://www.profane.eu.org/taxonomy.html	**Reducing Base of Support in Static Stance:** • One-legged stand • Tandem or semi-tandem stand • Standing on heels only • Standing on toes only **Shifting Weight, Moving to Limits of Stability** • Shifting weight between heels and toes **Dynamic balance exercises:** • Walking on toes only • Walking on heels only • Tandem Walk • Figure 8s • Sit-to-stand or squat • Walking backwards **Three-dimensional Movement** • Tai Chi • Dancing **Additional ways to progress balance challenges:** • Gradually reduce contact with support objects • Add weight shifting to activities with reduced base of support • Close eyes during static tasks • Dual-tasking – doing another activity or mental challenge at the same time

Table 6: Exercise prescription details for individuals with osteoporosis or osteoporotic vertebral fracture. Bold text is used to highlight the exercise domains that are emphasized in the recommendations.

Type	How often per week?	How hard should it be?	Examples	Comments
Resistance Training	2 days a week minimum*	One exercise for each major muscle group, 2 sets per exercise, 8-12 repetitions*: If > 12 reps can be performed → too easy If < 8 reps → too hard	Exercises that result in work being performed against resistance (e.g., body weight relative to gravity, or external resistance)	Individuals who are previously sedentary, with comorbid conditions that affect activity participation, at high fracture risk or unfamiliar with resistance training may need to train at a lower intensity, at least initially.
Balance Training	15-20 minutes per day, accumulating 2 hours per week.	Start with static balance exercises and progress to dynamic	Table 5	Can be performed in short bouts throughout the day, or embedded in daily activities. Consultation with a health care provider on exercise selection and progression is recommended
Aerobic Exercise*,[1] (for general health benefits)	3-5 days per week for 30-60 minutes per day	Moderate- to vigorous-intensity	Weight-bearing e.g., dancing, walking	Shorter, more frequent bouts (e.g., 10 minutes at a time) are acceptable, and may be preferable for individuals with vertebral fractures, with comorbid conditions that limit activity participation, or who were previously

				sedentary.
Total exercise time = Minimum of 150 minutes of moderate- or vigorous-intensity exercise per week*,[2]				

* in accordance with physical activity guidelines for older adults put forward by the Canadian Society for Exercise Physiology (http://www.csep.ca/english/view.asp?x=587), the Centers for Disease Control (http://www.cdc.gov/physicalactivity/everyone/guidelines/olderadults.html) or the American College of Sports Medicine (http://journals.lww.com/acsm-msse/Fulltext/2009/07000/Exercise_and_Physical_Activity_for_Older_Adults.20.aspx

[1]Included to reinforce recommendations in CSEP, CDC and ASCM physical activity guidelines for achieving general health benefits

[2]Physical activity guidelines from CSEP, CDC and ACSM recommend 150 minutes of moderate- to vigorous-intensity aerobic physical activity per week for general health benefits. Sherrington et al reported that at least two hours per week of exercise (that included challenging balance exercises) was most effective for fall prevention. Therefore, a minimum of 150 min per week of exercise is proposed. In the event that time is limited, aerobic exercise should not supplant resistance and balance training.