Association Between Physical Activity and Risk of Fracture

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ABSTRACT
Prospective studies that have examined the association between physical activity and fracture risks have reported conflicting findings. We performed a meta-analysis to evaluate this association. We searched MEDLINE (1966 to February 1, 2013), EMBASE (1980 to February 1, 2013), and OVID (1950 to February 1, 2013) for prospective cohort studies with no restrictions. Categorical, heterogeneity, publication bias, and subgroup analyses were performed. There were 22 cohort studies with 1,235,768 participants and 14,843 fractures, including 8874 hip, 690 wrist, and 927 vertebral fractures. The pooled relative risk (RR) of total fractures for the highest versus lowest category of physical activity was 0.71 (95% confidence interval [CI], 0.63–0.80). The analysis of fracture subtypes showed a statistically significant inverse relationship between a higher category of physical activity and risk of hip and wrist fracture. The risk of hip or wrist fracture was 39% and 28% lower, respectively, among individuals with the highest category of physical activity than among those with the lowest category (95% CI, 0.54–0.69 and 0.49–0.96, respectively). The association between physical activity and vertebral fracture risk was not statistically related (RR, 0.87; 95% CI, 0.72–1.03). There was no evidence of publication bias. There was a statistically significant inverse association between physical activity and total fracture risk, especially for hip and wrist fractures. Additional subject-level meta-analyses are required for a more reliable assessment of subgroups and types of physical activity. © 2014 American Society for Bone and Mineral Research.

KEY WORDS: PHYSICAL ACTIVITY; FRACTURE; META-ANALYSIS; PROSPECTIVE STUDY

Introduction
Fracture represents a major health concern, leading to substantial disability, morbidity, and a loss of quality of life. In addition, medical costs place a tremendous burden on families and on society.1-4 Hence, identifying and characterizing the potential risk factors for fracture have significance for public health and clinical medicine. Increased age, smoking, alcohol consumption, and body mass index (BMI) are of major importance for controlling fractures.5-7 However, considering other lifestyle factors, a regular and appropriate amount of physical activity is advocated as an efficient means of preventing osteoporosis and subsequent probabilities of fracture. Several prospective cohort studies have verified that physical activity may contribute to the prevention of fracture through various means.8-10 However, the results of these studies are inconsistent.11,12 We therefore performed a meta-analysis of prospective cohort studies with the following objectives: (1) to assess the association between physical activity and fracture; and (2) to evaluate the association between physical activity and subtypes of fracture.

Materials and Methods
We performed a meta-analysis of prospective cohort studies in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and performed a systematic review of the existing literature.13-15

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Search strategy

We searched MEDLINE (1966 to February 1, 2013), EMBASE (1980 to February 1, 2013), and OVID (1950 to February 1, 2013) for prospective cohort studies with no restrictions. We used medical subject headings (MeSH) or free-text words to perform all of the searches. We combined search terms for the outcome (fracture, hip fracture, wrist fracture, and vertebral fracture) and the influence factor (physical activity, leisure time physical activity, work physical activity, and sport). In addition, we searched the reference lists and reviewed studies from all of the identified relevant publications. We inspected the entire text of any citation that appeared relevant. Moreover, we hand-searched abstracts of meetings related to sports medicine, presbyatrics, and osteoporosis that provided printed or electronic publications. However, none of these meeting abstracts are quoted in the present study.

Selection criteria

Two reviewers (XHQ and XYZ) independently evaluated studies for their content. We first reviewed the titles to ascertain the possible fit to the selection criteria, followed by an assessment if we were unable to determine the relevance based on title review. Review of the abstracts and observation of the methods and results of each remaining article were conducted to reduce the pool of potential articles. We (ZZJ, HWL, and KRD) resolved discrepancies by discussion and reached a consensus on study inclusion and data interpretation after discussion. Studies were included in the meta-analyses if they met the following criteria: (1) prospective design; (2) adult population; (3) the exposure of interest was physical activity; (4) the outcome of interest was fracture; and (5) the risk estimates such as relative risks (RRs), odds ratios, hazard ratios, or other measures, could be transformed into RRs with 95% confidence intervals (CIs). Those studies that did not meet the inclusion criteria were excluded during the initial review phase. If different studies came from the same cohort, we used the one that was the most detailed with respect to the types of physical activity.

Data extraction and quality assessment

Two reviewers (XHQ and ZZ) independently abstracted all of the essential information using a standardized data collection form. We (XYZ, HWL, and KRD) resolved discrepancies by discussion with other investigators and by consulting original articles. The following data were collected from each study: the first author’s last name, publication year, country, duration of follow-up, recruitment time, size of study population, participant sex and age, number of cases, measure and range of exposure, adjustment variables, types of fracture (eg, hip, wrist, vertebral), and the risk estimates with corresponding CIs. Quality was assessed using elements of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort studies by two reviewers (XHQ and XYZ). A third reviewer (ZZJ) was enlisted to resolve disagreements regarding the abstracted data.

Data synthesis and statistical analysis

We used RRs as the common measure of association across studies.16,17 Hazard ratios and odds ratios were transformed into RRs.16,17 The RRs were pooled to summarize associations for the highest versus the lowest activity categories for physical activity.

We only extracted the RRs and 95% CIs that reflected the greatest degree of control for potential confounders for use in our main analyses.

For the meta-analysis, we used random-effects models for all analyses.18 Heterogeneity between studies was assessed using I² statistics.19 As suggested by Higgins and Thompson,20 I² values of 25%, 50%, and 75% were defined as low, moderate, and high, respectively. Subgroup analyses were used to identify associations between the risk of fracture and relevant study characteristics (sex, mean age, follow-up period, and geographical location) as possible sources of heterogeneity. Funnel plot asymmetry was used to detect publication bias, and the Egger and Begg regression tests were applied to measure funnel plot asymmetry.21,22 We also performed the “trim and fill” procedure to further assess the possible effect of publication bias in our meta-analysis. This method considers that hypothetical, “missing” studies exist, imputes their RRs, and recalculates a pooled RR that incorporates the hypothetical missing studies as though they had actually been performed.23 All of the analyses were conducted using Stata 10 (StataCorp, College Station, TX, USA). Probability values of <0.05 were considered to be statistically significant.

Results

The process of the study selection is presented in Fig. 1. There were 1295 studies identified from the initial database search. After title and abstract evaluations, we excluded duplicated studies and those that did not satisfy the criteria, and therefore, only 57 articles remained. Of these, a few studies were excluded because of their case-control or cross-sectional design or because data were missing. After the evaluation, we included 22 studies in the meta-analysis.18,24–40 Observers reached good agreement on which studies should be included (Cohen’s unweighted κ = 0.92).

![Fig. 1. Flowchart for study selection.](image-url)
<table>
<thead>
<tr>
<th>Study, cohort study name (country)</th>
<th>Sex/Age, y</th>
<th>Recruitment Time (Follow-up, y)</th>
<th>No of cases (cohort size)</th>
<th>Physical Activity Assessment</th>
<th>RR (95% CI) for Highest vs Lowest Category of Physical Activity</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorock et al, 1988 Dunedin Program (New Zealand)</td>
<td>Male/Female, ≥65</td>
<td>1976–1977 (NA)</td>
<td>104 Fractures (3,110)</td>
<td>Mailed questionnaire</td>
<td>Regular physical activity versus no regular physical activity; Male: 0.41 (0.17, 1.01); Female: 0.76 (0.50, 1.15)</td>
<td>Age, BMI, fracture history, thiazide diuretic use, OA, and poor circulation to legs and feet.</td>
</tr>
<tr>
<td>Wickham et al, 1989 / (Britain)</td>
<td>Male/Female, ≥65</td>
<td>1973–1974 (15)</td>
<td>44 Hip Fractures (1,419)</td>
<td>Interview</td>
<td>Outdoor activity index ≥70 versus &lt;50 in men and ≥57 versus &lt;44 in women 0.23 (0.04, 1.43)</td>
<td>BMI and smoking.</td>
</tr>
<tr>
<td>Paganini-Hill et al, 1991 Leisure World Study (United States)</td>
<td>Male/Female, Mean age 73</td>
<td>1981 (7)</td>
<td>418 Hip Fractures (13,987)</td>
<td>Mailed questionnaire</td>
<td>Activity exercise ≥1 h/d versus &lt;1/2 h/d Male: 0.51 (0.31, 0.86) Female: 0.62 (0.47, 0.80) Both: 0.59 (0.45, 0.73)</td>
<td>Age.</td>
</tr>
<tr>
<td>Cummings et al, 1995 (United States)</td>
<td>Female, ≥65</td>
<td>1986–1988 (4.1)</td>
<td>192 Hip Fractures (9,516)</td>
<td>Questioned and examined in outpatient clinics.</td>
<td>Walking for exercise versus not walking for exercise 0.70 (0.50, 0.90)</td>
<td>Age.</td>
</tr>
<tr>
<td>Gregg et al, 1998 Study of Osteoporotic Fracture (United States)</td>
<td>Female, ≥65</td>
<td>1986–1988 (7.6)</td>
<td>1,330 Total Fractures, 424 Hip Fractures, 519 Wrist Fractures, 387 Vertebral Fractures (9,704)</td>
<td>Using a modified version of the Harvard Alumni Questionnaire.</td>
<td>Quintile of total physical activity (5th versus 1st) Hip: 0.64 (0.45, 0.89) Wrist: 0.85 (0.63, 1.15) Vertebral: 0.84 (0.59, 1.19)</td>
<td>Age, weight, smoking, HRT, dietary calcium, falls, alcohol intake, self-rated health, and functional difficulty.</td>
</tr>
<tr>
<td>Mussolino et al, 1998 NHANES I and NHEFS (United States)</td>
<td>Male, 45–74</td>
<td>1992 (22)</td>
<td>71 Hip Fractures (2,879)</td>
<td>Questionnaire.</td>
<td>High versus low non-recreational physical activity 1.58 (0.71, 3.53)</td>
<td>Age, previous fracture, smoking, alcohol intake, PA at work, chronic disease prevalence, calcium intake, calories, intake of protein, weight.</td>
</tr>
<tr>
<td>Høidrup et al, 2001 Copenhagen Center for Prospective Population Studies (Denmark)</td>
<td>Male/Female, 20–93</td>
<td>1964–1992 (27)</td>
<td>1,121 Hip Fractures (30,228)</td>
<td>Self-administered questionnaire</td>
<td>Moderate activity versus sedentary Male: 0.76 (0.54, 1.07) Female: 0.72 (0.57, 0.92)</td>
<td>Age, PA at work, smoking, alcohol intake, BMI, and education.</td>
</tr>
<tr>
<td>Study, cohort study name (country)</td>
<td>Sex/Age, y</td>
<td>Recruitment Time (Follow-up, y)</td>
<td>No of cases (cohort size)</td>
<td>Physical Activity Assessment</td>
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<tr>
<td>Lau et al, 2001 (Asia)</td>
<td>Male/Female, ≥50</td>
<td>1997–1998 (/)</td>
<td>1,176 Hip Fractures (2,338)</td>
<td>Standardized questionnaire</td>
<td>Activity every day versus none Male: 0.68 (0.48, 0.88) Female: 0.63 (0.44, 0.82)</td>
<td>Age and center.</td>
</tr>
<tr>
<td>Feskanich et al, 2002 Nurses’ Health Study (United States)</td>
<td>Female, 40–77</td>
<td>1986 (12)</td>
<td>415 Hip Fractures (61,200)</td>
<td>Questionnaire</td>
<td>Activity ≥ 24 MET-h/wk versus &lt;3 MET-h/wk 0.45 (0.32, 0.63)</td>
<td>MET-hours, BMI, age, smoking, HRT, and intake of calcium, vitamin D, retinol, protein, vitamin K, alcohol, and coffee.</td>
</tr>
<tr>
<td>Roy et al, 2003 European Prospective Osteoporosis Study (EVOS) (Europe)</td>
<td>Male/Female, 50–79</td>
<td>/ (3.8)</td>
<td>224 Vertebral Fractures (6,575)</td>
<td>Interviewer-administered questionnaire</td>
<td>Heavy/very heavy versus Light/moderate Male: 1.02 (0.66, 1.38) Female: 0.90 (0.65, 1.14)</td>
<td>Age and center.</td>
</tr>
<tr>
<td>Nevitt et al, 2005 Study of Osteoporotic Fractures (United States)</td>
<td>Female, ≥65</td>
<td>1986–1988 (3.7)</td>
<td>181 Vertebral Fractures (5,822)</td>
<td>Questionnaire and interview</td>
<td>High to moderate activity versus none 1.02 (0.05, 2.09)</td>
<td>Age, fracture, and BMD.</td>
</tr>
<tr>
<td>Samelson et al, 2006 Framingham Study (United States)</td>
<td>Male/Female, 47–72</td>
<td>1967–1969 (25)</td>
<td>135 Vertebral Fractures (704)</td>
<td>Structured questionnaire</td>
<td>High activity versus low Male: 0.53 (0.18, 1.64) Female: 0.61 (0.26, 1.44)</td>
<td>Age, height, weight, prevalent vertebral fracture, smoking, and alcohol intake.</td>
</tr>
<tr>
<td>Thorpe et al, 2006 First Adventist Health Study (AHS-1) (United States)</td>
<td>Female, ≥25</td>
<td>1976 (25)</td>
<td>171 Wrist Fractures (1,865)</td>
<td>The 1976 and 2002 Adventist Health Study lifestyle questionnaires.</td>
<td>Physical activity index: high activity versus low or none 0.61 (0.41, 0.87)</td>
<td>Age, diabetes, RA, ever pregnant, smoking, alcohol intake.</td>
</tr>
<tr>
<td>Michaelsson et al, 2007 Uppsala Longitudinal Study of Adult Men (ULSAM) (Sweden)</td>
<td>Male, 49–51</td>
<td>1970–1973 (35)</td>
<td>482 Total Fractures, 134 Hip Fractures (2,205)</td>
<td>Reliability-tested questionnaire</td>
<td>High activity versus low Hip: 0.39 (0.24, 0.65) Total: 0.64 (0.48, 0.83)</td>
<td>Change in physical activity during follow-up, weight, height, smoking, perceived health, PA at work, diabetes mellitus; any musculoskeletal disorder, and alcohol intake.</td>
</tr>
<tr>
<td>Robbins et al, 2007 Women’s Health Initiative (WHI) (United States)</td>
<td>Female, 50–79</td>
<td>/ (8.0)</td>
<td>1,132 Hip Fractures (93,676)</td>
<td>Standardized medical update questionnaire</td>
<td>Activity ≥ 12 METs versus 0 METs 0.61 (0.46, 0.81)</td>
<td>Age, self-reported health, height, weight, smoking status, parent broke hip, corticosteroid use, use of hypoglycemic agent and race/ethnicity.</td>
</tr>
<tr>
<td>Study, cohort study name (country)</td>
<td>Sex/Age, y</td>
<td>Recruitment Time (Follow-up, y)</td>
<td>No of cases (cohort size)</td>
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<tr>
<td>Appleby et al, 2008 (European Prospective Investigation into Cancer and Nutrition (EPIC) (Britain))</td>
<td>Male/Female, 20–89</td>
<td>1993–1999 (5.2)</td>
<td>1,898 Fractures (34,696)</td>
<td>Main questionnaire</td>
<td>Quartile of activity (4th versus 1st) Male: 1.34 (1.05, 1.62) Female: 1.18 (1.00, 1.35)</td>
<td>Age, energy and calcium intake, smoking, alcohol intake, BMI, marital status, and, for women, menopausal status, HRT, and number of children.</td>
</tr>
<tr>
<td>Lee et al, 2010 Korean Health and Genome Study (KHGS) (Korea)</td>
<td>Male/Female, 40–69</td>
<td>2001 (3.8)</td>
<td>195 Fractures (9,351)</td>
<td>Standardized self-administered questionnaire</td>
<td>Regular exercise ≥ 30 min versus &lt;30 min 0.59 (0.36, 0.97)</td>
<td>Age, BMI, menopausal status, previous fracture, hip circumference, weekly dairy product consumption, regular exercise duration, alcohol intake, and history of RA and OA.</td>
</tr>
<tr>
<td>Trimpou et al, 2010 Multifactor Primary Prevention Study (Sweden)</td>
<td>Male, 46–56</td>
<td>1970–1973 (30)</td>
<td>451 Hip Fractures (7,495)</td>
<td>Questionnaire</td>
<td>Leisure activity: regular and hard versus sedentary; work activity: very heavy versus Sedentary 1.34 (0.63, 2.05)</td>
<td>Age, height, BMI, LTPA, occupational class, smoking, coffee, alcohol intake, stroke before fracture, dementia before fracture.</td>
</tr>
<tr>
<td>Armstrong et al, 2011 Million Women Study (Britain)</td>
<td>Female, ≥53</td>
<td>1996–2001 (6.2)</td>
<td>2,582 Hip Fractures (925,345)</td>
<td>Self-administered questionnaire</td>
<td>Any activity: ≥ 3 times/w versus rarely/never 0.68 (0.63, 0.73)</td>
<td>Age, socioeconomic status, smoking, alcohol intake, parity, HRT, height, heart disease/thrombosis, diabetes mellitus, thyroid disease, RA/OA, and strenuous activity or BMI.</td>
</tr>
<tr>
<td>Nikander et al, 2011 Australian Diabetes, Obesity and Lifestyle Study (AusDiab) (Australia)</td>
<td>Male/Female, ≥50</td>
<td>1999–2000 (5)</td>
<td>462 Fractures (4,909)</td>
<td>Household interview and biomedical evaluation</td>
<td>Physical activity: Sufficient, ≥2.5 h/week versus Sedentary, 0 min/week Male: 1.17 (0.53, 2.61) Female: 1.00 (0.64, 1.43)</td>
<td>Age, BMI, QOL, history of CVD, previous history of fractures, smoking, calcium intake and serum 25(OH)D.</td>
</tr>
</tbody>
</table>
The characteristics of included studies

The extracted data and the characteristics of the included prospective studies are summarized in Table 1. There were 22 cohort studies with 1,235,768 participants and 14,843 fractures, including 8874 hip, 690 wrist, and 927 vertebral fractures. The cohorts were from different countries (nine studies from the United States, 10 from Europe, five from Asia, and one from Australia). Eleven studies recruited male and female participants, and another eight recruited only women. The study lengths ranged from 3.7 to 35 years. The physical activity assessment methods included questionnaires, interviews, and self-report for physical activities. Fracture was identified using self-reports of fracture experience, X-ray radiologic diagnosis, or hospital admission records. The most frequent confounders, other than age, that were adjusted in the studies included BMI, height, weight, smoking, alcohol intake, any fracture history, and calcium intake. In addition, hormone-replacement therapy (only in female participants) was adjusted for in three studies.

Physical activity and fracture risk

In the sum of all of the selected studies, the multivariate-adjusted RRs for highest versus lowest physical activity are shown in Fig. 2. In our meta-analysis, the participants with the highest category of physical activity had an approximately 29% lower risk of total fractures compared to those in the lowest category, with 95% CIs of 0.63–0.80 (p < 0.01) and moderate heterogeneity across studies (p = 0.0, I^2 = 74.2%). Moreover, the analysis for subtypes of fracture showed a statistically significant inverse relationship between higher category of physical activity and risk of hip or wrist fracture (39% and 28% lower risk, respectively), among individuals in the highest category of physical activity than among those in the lowest category (95% CIs were 0.54–0.69 and 0.49–0.96, respectively, all p < 0.01). The association between physical activity and vertebral fracture risk was not statistically significant (RR, 0.87; 95% CI, 0.72–1.03; p < 0.01) (Table 2).

Subgroup and sensitivity analyses

The subgroup analyses for the associations between physical activity and fracture stratified by study characteristics are shown in Table 2. We examined sex of the participants, mean age, follow-up period, and geographical location as possible sources of heterogeneity. The analyses indicated that follow-up period and geographical location influence the inverse associations between physical activity and fracture risk. The RR was 0.78 (95% CI, 0.63–0.93; p < 0.01) for male participants and 0.72 (95% CI, 0.64–0.80; p < 0.01) for female participants; no significant interactions were observed between subgroups (p = 0.37). With respect to follow-up periods, the RRs were 0.79 (95% CI, 0.65–0.92; p < 0.01) for <11 years and 0.63 (95% CI, 0.52–0.75; p < 0.01) for ≥11 years (p = 0.02). We also examined geographical location as a possible source of heterogeneity for physical activity. The RRs were 0.62 (95% CI, 0.54–0.71; p < 0.01) for studies conducted in the United States, 0.81 (95% CI, 0.65–0.96; p < 0.01) for studies in Europe, 0.68 (95% CI, 0.52–0.87; p < 0.01) for studies in Asia, and 0.61 (95% CI, 0.27–0.95; p < 0.01) for the 1 study conducted in Australia. Significant interactions were observed between subgroups (p = 0.02), and no heterogeneity was found (p = 0.72; I^2 = 0%) for the analysis of studies conducted in Asia. Sensitivity analysis showed that the exclusion
of any one study from the pooled analysis did not vary substantially (RRs ranged from a low of 0.67 [95% CI, 0.62–0.73; \( p < 0.01 \)] to a high of 0.73 [95% CI, 0.65–0.81; \( p < 0.01 \)]).

**Publication bias**

Visual inspection of the funnel plot showed no asymmetry. Egger’s test \( p = 0.58 \) and Begg’s test \( p = 0.18 \) showed no evidence of publication bias, and the “trim and fill” method confirmed that there were no missing studies (Supplemental Fig. S1).

**Discussion**

**Main findings**

After the publication of many independent studies investigating the association between physical activity and fracture risk, this meta-analysis of 22 prospective cohort studies supports the view that being more physically active is associated with a lower risk of fracture. Our findings suggest that individuals who were more physically active had a 29% lower risk of all types of fracture compared with those performing no physical activity. An analysis stratified by subtypes of fractures suggests that performing a greater amount of physical activity is associated with 39% and 28% lower risk of hip and wrist fracture, respectively. However, we did not observe statistical relevance between physical activity and vertebral fracture risk.

Kemmner and colleagues \(^{41} \) preformed a meta-analysis to evaluate the effect of exercise on fracture reduction in the elderly. They included 10 controlled exercise trials for overall fractures and three exercise trials for vertebral fractures, and found that exercise may reduce overall fractures (36 fractures among 754 subjects in the exercise group and 73 fractures among 670 subjects in the control group; RR, 0.49; 95% CI, 0.31–0.76). A nonsignificant reduction in vertebral fractures was observed (19 fractures among 103 subjects in the exercise group and 31 fractures among 102 subjects in the control group; RR, 0.56; 95% CI, 0.30–1.04) in the elderly. Their results were consistent with those of the current meta-analysis.

In agreement with the individual studies, we have shown a protective effect of physical activity on fracture risk. All types of physical activities, including both leisure-time and incidental physical activities, are widely recognized as a key determinant of fracture risk. Other physical activities such as walking or work activity involve daily movements in ordinary life that do not impose large forces on the skeleton and muscle; such activities are believed to be associated with increases in or protection of muscle mass and its neuromuscular function. A prevailing theory of skeletal mechanisms proposes that bone tissue responds to local mechanical stimuli by deforming, which can be transformed into biologically active signals during the process of mechanotransduction. \(^{42} \)

Activities such as running, walking, cycling, or climbing specifically indicate a lifestyle that includes outdoor recreation, which corresponds to more exposure to fresh air and sunshine. Sunshine has a beneficial influence on the metabolism of vitamin D, which plays a significant role in serum calcium and phosphorus balance. A lack of vitamin D may result in lower serum calcium levels and detrimental effects on ossification, ultimately predisposing individuals to a higher risk of fracture. \(^{43} \)

Although food is the largest source of vitamin D, sunshine may supplement dietary intake by up to 90%. A subset of the “U Find Out” (UFO) cohort found that low vitamin D level was a risk factor for hip fractures. \(^{44} \)

Physical activity, especially aerobic exercise, is advocated to promote a healthier lifestyle. Aerobic exercise is characterized by low-capacity, rhythmic movement, and should be performed for long durations (>30 minutes). Aerobic exercises such as swimming, jogging, tennis, and cycling, can help burn carbohydrate, reduce fat, adjust the psychological state, and strengthen and improve cardiopulmonary function, while at the same time preventing osteoporosis. \(^{45} \) Moreover, epidemiological studies indicate that increased physical activity is associated with an increase in bone mineral density (BMD), a concomitant decrease in BMI, and retarded bone loss, and thus contributes to a reduction of fracture risk. \(^{46,47} \)

During physical activity, nutrients and oxygen are required for muscle contraction. Activity of a longer duration requires the cardiopulmonary system to work harder to contract and expand to offer sufficient oxygen to the muscle, thus strengthening muscles, improving flexibility, and eventually reducing fracture risk. However, Junno and colleagues \(^{48} \) investigated the association between physical activity and vertebral strength parameters such as cross-sectional size and BMD during late adolescence, and found that frequent physical activity did not directly affect the strength of lumbar vertebrae. Moreover, approximately 90% hip fractures result from simple falls, and wrist fractures always occur concomitantly with hip fractures, whereas only 25% of vertebral fractures are caused by falls. \(^{49} \) These findings may help explain why physical activity does not influence vertebral strength and hence fracture risk.

**Strengths and limitations**

There were three advantages to this meta-analysis. First, we were able to include a substantial number of participants and fracture cases (up to 1,235,768 participants and 14,843 fracture cases), which significantly enhances the statistical power of our analysis. Second, the quantitative assessment of the analysis was based on prospective cohort studies, which minimized the possibility of recall or selection bias. Third, two independent investigators cooperated to perform the data extraction, data analysis, and quality assessment of the methods, and an arbitrator confirmed the consistency of these two sets of reports, thus improving the accuracy of the data used in our meta-analysis.

Despite these strengths, our meta-analysis also revealed several limitations. First, the quality of individual studies varied; some of these may have had limited adjustments for potential statistical confounders. Our meta-analysis was subject to confounding factors within the included studies, which is an inherent limitation of all observational studies and meta-analyses. As most of the included studies were adjusted for age, BMI, height, weight, smoking, alcohol intake, fracture history, and calcium intake, confounding known or unknown risk factors may potentially explain the observed findings.

Second, the classification of the quantity of physical activity is difficult to evaluate, a fact that inevitably weakens the strength of the identified association. Certain studies adopted public health physical activity guidelines \(^{39} \) whereas others used metabolism equivalents to assess the quantity of physical activity. \(^{9,35,38} \) Because the participants’ physical activity was primarily estimated by questionnaires, interviews, or self-reports, and the content of affecting factors also varied, there may be an inevitable underestimation of the RRs.
Fig. 2. Adjusted RR of physical activity (95% CI) and total fracture (highest versus lowest categories) using the random-effects model. RR = relative risk; CI = confidence interval.

Table 2. Stratified Analyses of Relative Risk of Fracture According to Physical Activity

<table>
<thead>
<tr>
<th>Fracture subtypes</th>
<th>No of studies</th>
<th>RR (95%CI)</th>
<th>I² (%)</th>
<th>p Value for Heterogeneity</th>
<th>p Value Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip Fracture</td>
<td>13</td>
<td>0.61 (0.54, 0.69)</td>
<td>50.3</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Wrist Fracture</td>
<td>2</td>
<td>0.72 (0.49, 0.96)</td>
<td>45.5</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Vertebral Fracture</td>
<td>4</td>
<td>0.87 (0.72, 1.03)</td>
<td>0</td>
<td>0.56</td>
<td></td>
</tr>
</tbody>
</table>

Subgroup analyses for total fracture

<table>
<thead>
<tr>
<th>Sex</th>
<th>No of studies</th>
<th>RR (95%CI)</th>
<th>I² (%)</th>
<th>p Value for Heterogeneity</th>
<th>p Value Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>12</td>
<td>0.78 (0.63, 0.93)</td>
<td>65.1</td>
<td>&lt;0.01</td>
<td>0.37</td>
</tr>
<tr>
<td>Women</td>
<td>18</td>
<td>0.72 (0.64, 0.80)</td>
<td>71.6</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

| Age(years)                |               |                |        |                           |                        |
| <62 y                     | 11            | 0.76 (0.60, 0.91) | 85.0   | 0                          | 0.52                   |
| ≥62 y                     | 10            | 0.69 (0.61, 0.76) | 28.7   | 0.18                      |                        |

| Length of follow-up (years) |               |                |        |                           |                        |
| <11                        | 10            | 0.79 (0.65, 0.92) | 84.6   | 0                          | 0.02                   |
| ≥11                        | 10            | 0.63 (0.52, 0.75) | 46.4   | 0.05                      |                        |

| Geographical location      |               |                |        |                           |                        |
| United States             | 9             | 0.62 (0.54, 0.71) | 27.2   | 0.20                      | 0.02                   |
| Europe                    | 10            | 0.81 (0.65, 0.96) | 85.1   | 0                          |                        |
| Asia                      | 2             | 0.64 (0.52, 0.77) | 0      | 0.72                      |                        |
| Other                     | 1             | 0.61 (0.27, 0.95) | /      | /                         | /                      |
Third, differences in methodology between studies may also introduce heterogeneities. With subgroup analyses, we confirmed follow-up period and geographical location as possible sources of heterogeneity. Most of the $I^2$ estimates calculated in this meta-analysis were assessed as moderate. Although these issues may reduce the strength of our conclusions, visual inspection of forest plots suggests considerable consistency in RR across the studies.

Implication

A few questions remain to be answered, with this meta-analysis as a foundation. First, because our study did not conduct a dose-response analysis, the existence of a dose-response relationship between physical activity and fracture risk remains unknown. Although the quantity of activity is difficult to assess, a unified evaluation scale should be established to estimate this parameter among individuals. Further studies should be conducted to quantitatively assess the dose-response relationship between physical activity and fracture risk. This assessment will help to clarify the upper end of the dose-response curve and enable future studies to obtain additional quantitative evaluations. Second, whereas work-time physical activity is diverse and can include leisure-time and other types of activities, does activity at work help to reduce fracture risk? To address this question, several well-designed and stratified cohort studies should be conducted with adequate controls for different types of activities.

Conclusion

In conclusion, physical activity shows a significant inverse association with the overall risk of total fractures. Additional subject-level meta-analyses are required that include more reliable subgroup analyses and types of physical activity.

Disclosures

All authors state that they have no conflicts of interest.

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Authors’ roles: XHQ, XYZ, and ZJJ were responsible for the initial plan, study design, data collection, data extraction, data interpretation, manuscript drafting, statistical analysis, and conducting the study. HWL, QXL, and GWL were responsible for data collection, extraction, and critical revisions of the manuscript. HWL, ZAZ, YQH, and KRĐ were responsible for data interpretation, manuscript drafting, supervision, and critical revisions of the manuscript for important intellectual content. This article’s contents are solely the responsibility of the authors. KRĐ is the guarantor for this article and has full responsibility for this study.

References


