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PRONOUNCEMENT

Effects of Physical Activity in Knee and Hip Osteoarthritis: A Systematic Umbrella Review

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ABSTRACT

KRAUS, V. B., K. SPROW, K. E. POWELL, D. BUCHNER, B. BLOODGOOD, K. PIERCY, S. M. GEORGE, and W. E. KRAUS, FOR THE 2018 PHYSICAL ACTIVITY GUIDELINES ADVISORY COMMITTEE. Effects of Physical Activity in Knee and Hip Osteoarthritis: A Systematic Umbrella Review. *Med. Sci. Sports Exerc.*, Vol. 51, No. 6, pp. 1324–1339, 2019. **Introduction:** We conducted a systematic umbrella review to evaluate the literature relating to effects of physical activity on pain, physical function, health-related quality of life, comorbid conditions and osteoarthritis (OA) structural disease progression in individuals with lower-extremity OA. **Methods:** Our primary search encompassed 2011 to February 2018 for existing systematic reviews (SR), meta-analyses (MA) and pooled analyses dealing with physical activity including exercise (not mixed with any other intervention and compared to a no-activity control group). A supplementary search encompassed 2006 to February 2018 for original research related to physical activity (including exercise) and lower limb OA progression. Study characteristics were abstracted, and risk of bias was assessed. **Results:** Physical activity decreased pain and improved physical function (strong evidence) and improved health-related quality of life (moderate evidence) among people with hip or knee OA relative to less active adults with OA. There was no evidence to suggest accelerated OA progression for physical activity below 10,000 steps per day. Both physical activity equivalent to the 2008 Physical Activity Guidelines for Americans (150 $\min \cdot wk^{-1}$ of moderate-intensity exercise in bouts ≥10 min) and lower levels of physical activity (at least 45 total minutes per week of moderate-intensity) were associated with improved or sustained high function. No SR/MA addressing comorbid conditions in OA were found. Measurable benefits of physical activity appeared to persist for periods of up to 6 months following cessation of a defined program. **Conclusions:** People with lower-extremity OA should be encouraged to engage in achievable amounts of physical activity, of even modest intensities. They can choose to accrue minutes of physical activity throughout the entire day, irrespective of bout duration, and be confident in gaining some health and arthritis-related benefits. **Key Words:** PAIN, FUNCTION, QUALITY OF LIFE, PROGRESSION, KNEE, HIP

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There are approximately 100 different arthritic conditions with a total of 54.4 million Americans estimated to have physician-diagnosed arthritis (1). Among these, osteoarthritis (OA) is the most common joint disorder in the US, affecting an estimated 30.8 million adults (13.4% of the civilian adult US population) (2). Osteoarthritis affects a broad spectrum of age groups in the US, including 2 million Americans under the age of 45 yr with knee OA (3). By the year 2040, an estimated 78.4 million (25.9% of the projected total adult population) adults 18 yr and older are expected to have physician-diagnosed arthritis (4), the majority of whom will have OA. Methodological issues, such as the current inability to reliably diagnose early nonradiographic OA and traditional accounting of OA in only a limited number of joint sites (hip and knee), make it highly likely that the real burden of OA has been underestimated (5). The risk of mobility disability (defined as needing help walking or climbing stairs) attributable to knee OA alone is greater than that attributable to any other medical condition in people 65 yr and older (6). As expected, based on these prevalence and disability figures, OA is associated with an extremely great economic burden—by one national estimate equal to US $185.5 billion in aggregate annual medical care expenditures (7).

To provide recommendations to the Department of Health and Human Services for updating the *Physical Activity Guidelines for Americans*, the Physical Activity Guidelines Advisory Committee (PAGAC) chose to investigate seven chronic conditions, among them OA (8). The choice of OA was predicated on the large portion of the general population having this chronic condition, the high disability associated with OA (9), and the potential public health importance of physical activity in people with OA. The overall goal of this systematic umbrella review was to evaluate the literature relating to effects of physical activity on 1) pain, 2) physical function, 3) health-related quality of life (HRQoL), 4) disease progression, and 5) risk of comorbid conditions in individuals with existing lower limb (hip and/or knee) OA. As a secondary goal, we also evaluated the literature for evidence of variation in the relationship of physical activity and these outcomes based on (a) the dose of physical activity exposure; (b) age, sex, race/ethnicity, socioeconomic status, or weight status; and (c) frequency, duration, intensity, mode (type), or means of measuring physical activity. This article represents the scientific research performed to inform the 2018 Physical Activity Guidelines for Americans (10) with an extension of the literature search by 1 yr through February 2018.

METHODS

The overarching methods used to conduct systematic reviews (SR) informing the 2018 Physical Activity Guidelines Advisory Committee Scientific Report (search strategy development, article triage, data abstraction, bias assessment, and quality control processes and methods for analysis) have been described in detail elsewhere (11). The searches were conducted of electronic databases (PubMed®, CINAHL, and Cochrane) and were supplemented by authors (experts in the area) to provide additional articles identified through their expertise and familiarity with the literature. The full search strategies are available online (12). The inclusion criteria were predefined and searches were registered in PROSPERO CRD42018092365. Studies were included if they were published in English; were meta-analyses (MA), SR or pooled analyses published from 2011 through February 2018, and investigated individuals of all ages with preexisting OA of the hip or knee; the association between all types and intensities of physical activity, including exercise, not mixed with any other interventions (such as diet); and one of the health outcomes of interest (pain, physical function, HRQoL, disease progression or risk of comorbid conditions). Physical activity was defined as bodily movement produced by skeletal muscles that results in energy expenditure. Exercise was defined as a form of physical activity that is planned, structured, repetitive, and designed to improve or maintain physical fitness, physical performance, or health. Physical function was defined as the ability of a person to move around and to perform types of activity; in the studies included in this summary, this was most often measured by a standardized instrument used routinely in OA clinical trials, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (13). Health-related quality of life was defined as a multidimensional concept including domains related to physical, mental, emotional, and social functioning.

Studies of nonambulatory adults, hospitalized patients, or animals were excluded. We also excluded studies of multimodal interventions not presenting data on physical activity alone and studies of single, acute sessions of physical activity. The titles, abstracts, and full-text of the identified articles were independently screened by two reviewers. Disagreement between reviewers was resolved by discussion or by a third member of the PAGAC committee.

The amended literature search yielded 20 MA and SR meeting the inclusion criteria for our analysis of OA and pain, physical function, and HRQoL outcomes (14–31); however, the studies identified included significant overlap. In an attempt to minimize redundancy, the Committee reviewed the overlap of studies within all the MA/SR; those with considerable overlap, with three or fewer unique additional studies, and that did not add additional information to the larger studies, were not retained for purposes of the final summary. This procedure resulted in retention of six MA (14–16,18,22,32) and three SR for the purposes of the summary related to OA pain, physical function, and HRQoL (17,33,34) (Table 1); from the amended search, one additional MA and two additional SR were added to the original search conducted as part of the governmental report.

Upon completion of triage based on the MA, SR, and pooled analyses, the authors observed a paucity of MA and SR dealing with physical activity and knee OA progression defined as structural worsening of OA based on imaging (radiographic or magnetic resonance imaging [MRI]), worsening function (based on patient-reported outcomes or gait speed) or

TABLE 1. Summary of included studies assessing the relationship of physical activity with pain, function and quality of life in individuals with lower-extremity OA (14–18,22,32–34).

Author (Year)	Type of Study; Joints; Mean Age and/or Range	Sample Size and No. Studies	Type(s) of Physical Activity	Outcome Measures	Effect Sizes (95% CI)*
Bartels (2016) (14)	MA; Knee & Hip; 68 yr	Total: 1190 participants from 13 studies Pain: 971 participants from 12 trials Physical Function: 1059 participants from 12 trials HRQoL: 971 participants from 10 trials	Range of motion, strength training, and aerobic exercise in a therapeutic/heated indoor pool	Pain: WOMAC, VAS, SF-36, HAQ, Lequesne algofunctional index, AIMS, KSPS, McGill Pain Questionnaire, ASES, SES, and NRS Physical Function: WOMAC, SF-36, PCS, HAQ, PDI, ASES HRQoL: SF-36/SF-12/SF-8, EuroQoL, KOOS Subscore: QOL, Quality of well-being, AIMS, others	**Pain:** **SMD −0.31 (−0.47 to −0.15)** **Physical Function:** **SMD −0.32 (−0.47 to −0.17)** **HRQoL:** **SMD −0.25 (−0.49 to −0.01)**
Bartholdy (2017) (33)	SR; Knee; 64 yr;	4699 participants from 45 studies	ACSM[a] Interventions (29% of included studies) and non-ACSM Interventions	Strength: knee extension Pain: WOMAC, NRS, KOOS, pain score, AIMS2, OASI, and VAS Physical Function: WOMAC, Lequesne Index, KOOS, functional incapacity score, SF-36 AIMS2, OASI, subjective rating of daily activity, and KOOS ADL	**Strength: SMD 0.448 (0.091 to 0.805)** Pain: SMD 0.106 (−0.239 to 0.451) Physical Function: SMD 0.153 (−0.243 to 0.549)
Beumer (2016) (15)	SR/MA; Hip; 52–77 yr	1213 participants from 19 studies	Land- and aquatic-based therapeutic strength and aerobic exercises	Pain: VAS, WOMAC	Pain: **(WOMAC): SMD −0.53 (−0.96 to −0.10)** **(VAS): SMD −0.49 (−0.70 to −0.29)**
Chang (2016) (16)	SR/MA; Knee; Mean age of study participants ranged from 61.15 to 79.01 yr	508 participants from 11 studies	Tai Chi Chuan	Pain: WOMAC Physical function: WOMAC, 6 min-walk test, stair climb test, and SAFE	Pain (WOMAC): **SMD −0.41 (−0.67 to −0.74)** Physical Function **(WOMAC): SMD −0.16 (−0.44 to −0.11)** **(6-min walking test): SMD −0.16 (−1.23 to 0.90)** **(Stair climb test): SMD −0.76 (−1.34 to 0.15)** **(SAFE): SMD −0.63 (−0.98 to −0.27)**
Escalante (2011) (17)	SR; Hip & Knee; Mean age range 54.4–74 yr (discoverable for 19 studies)	2145 participants from 20 studies	Land-based (strength, tai chi, aerobic, and mixed) and aquatic exercise	Physical function: 6 min walk test	Physical Function (6-min walk test): **Strength: SMD 0.31 (0.06 to 0.56)** **Pooled Tai Chi: SMD 0.66 (0.23 to 1.09)** **Pooled Aerobic: SMD 0.90 (0.70 to 1.10)** **Pooled Mixed: SMD 0.47 (0.032 to 0.62)** Pooled Hydrotherapy: SMD 0.00 (−0.38 to 0.39)

Fernandopulle, (2017) (32)	SR/MA; Hip & Knee; 54–73 yr	3233 participants from 27 studies	Land-based generic physical activity interventions on pain, physical function, and physical performance	Pain: pain intensity, VAS, WOMAC Physical Function: WOMAC, AIMS, KOOS, Japanese Knee OA measurement, customized measure of disability Physical Performance: 6MWT, TUG, timed stair climbing	Recreational Activity **Physical Function (WOMAC) at 3 months from randomization: SMD –9.56 (–13.95 to –5.17)** Conditioning Exercise **Physical Performance (6MWT) 6 months from randomization: SMD 42.72 (27.28 to 57.66)**; **Physical Function (WOMAC) 6 months from randomization: SMD –3.74 (–5.70 to –1.78);** Physical Performance (Timed-stair climbing test) at 6 months randomization: SMD –2.29 (–4.65 to .006); **Physical Performance (Timed-stair climbing test) at 18 months: SMD –0.49 (–0.75 to –0.23)** Walking **Physical Function at 6 months from randomization: SMD, –10.38 (–12.27 to –8.49);** Physical Function at 12 months from randomization: SMD, –0.03 (–0.035 to 0.28); Physical Performance 6MWT at 12 months from randomization: SMD, –1.88 (–43.46 to 39.71); Pain 3 months from randomization: SMD 0.19 (–0.31 to 0.68); Pain 6 months from randomization: SMD, –1.55 (–3.62 to 0.52)
Fransen (2015) (18)	SR/MA; Knee; Mean age range 55–73 yr	6345 participants from 54 studies Pain (immediately post-treatment): 3537 participants from 44 studies Physical Function (immediately post-treatment): 3913 participants from 44 studies HRQoL (immediately post-treatment): 1073 participants from 13 studies	Land-based strength and aerobic exercises (muscle strengthening, balance training, aerobic walking, cycling, Tai Chi)	Pain: WOMAC, global pain scores, Lequesne OA Index (2–6 months in and >6 months) Physical function: WOMAC, global disability scores, Sickness Impact profile (2–6 and >6 months) HRQoL: SF-12	Pain: **Pooled SMD 0.49 (0.39 to 0.59)**; 12 studies (1468 participants) **SMD 0.24 (95% CI, 0.14–0.35)** at 2–6 months post-exercise training; 6 studies SMD 0.08 (95% CI, –0.15 to 0.30) after more than 6 months post-exercise training Physical Function: **Pooled SMD 0.52 (95% CI, 0.39–0.64);** 10 studies (1279 participants) **SMD 0.15 (95% CI, 0.04–0.26)** at 2–6 months post-exercise training; seven studies **SMD 0.20 (95% CI, 0.08–0.32)** after more than 6 months post-exercise training HRQoL: **SMD 0.28 (0.15 to 0.40)**

(continued next page)

TABLE 1. *(Continued)*

Author (Year)	Type of Study; Joints; Mean Age and/or Range	Sample Size and No. Studies	Type(s) of Physical Activity	Outcome Measures	Effect Sizes (95% CI)*
Juhl (2014) (22)	SR/MA; Knee; 64.3 yr	4418 participants from 48 studies	Single or combination exercises (aerobic, resistance, and performance training)	Pain: WOMAC, VAS, SF-36, AIMS, BPI, KOOS, OASI Physical function: WOMAC, AIMS, Self-Reported from FAST, SF-36, KOOS, OASI	Pain: **Overall pooled SMD 0.50 (0.39 to 0.62); Aerobic Exercise SMD 0.67; Resistance Exercise SMD 0.62; Performance Exercise SMD 0.48** Physical Function: **Overall Pooled SMD 0.49 (0.35 to 0.63); Aerobic Exercise SMD 0.56; Resistance Exercise SMD 0.60; Performance Exercise SMD.56**
Young (2018) (34)	SR; Knee; Mean age range 54.4–70 yr	2173 participants from 24 studies (that included effect sizes related to knee OA)	To identify specific doses of exercise (aerobic, balance, and strength) related to improved outcomes of pain and function in individuals with common knee disorders	Pain: WOMAC, KOOS, VAS Physical Function: WOMAC, KOOS, Step Test, SF-36, 6MWT	Pain (Land based): WOMAC: SMD 0.28 to SMD 1.39; KOOS: SMD 0.64 to SMD 0.76; VAS: SMD 0.48 to SMD 2.44 Physical Function (Land based): WOMAC: SMD 0.01 to SMD 1.83; KOOS: SMD 0.45 to SMD 0.99; Step Test: SMD 0.45; SF-36: SMD 0.68 to SMD 1.49; 6MWT: SMD 0.58 Pain (aquatic based): KOOS: SMD 0.17 to SMD 0.58; VAS: SMD 1.78 to SMD 2.43 Physical Function (aquatic based): KOOS: SMD 1.19; SF-36: SMD 0.58; 6MWT: SMD 0.72

*Statistically significant results favoring exercise are shown in bold font (note sign can be positive or negative depending upon coding of data within the study).

[a]ACSM Interventions, a voluntary contraction against an external resistance typically performed in especially designed equipment or with free weights. The external load should be above 40% of 1 repetition maximum (1RM) corresponding to very light to light intensity, and the exercises performed in 2–4 sets of 8–12 repetitions; preferably to contraction failure or muscular exhaustion. The exercise program should consist of at least two to three sessions per week. Non-ACSM interventions, exercise interventions that in their description were considered not to follow all of the above definitions were categorized as "not-ACSM interventions," and include all other types of interventions.

Additional Results for Juhl 2014.

Overall.

- When the studies that evaluated only a single exercise type were pooled, the SMD for pain 0.61 (95% CI, 0.48–0.75), and for the SMD for disability was 0.58 (95% CI, 0.40–0.75) but with large heterogeneity.
- Exercise programs that included a combination of resistance, aerobic, and performance exercise were not significantly better than control treatments in reducing pain (SMD 0.16 [95% CI, ⩾0.04 to 0.37], I2 = 44.0%) and had only a small effect in reducing disability (SMD 0.22 [95% CI, 0.08–0.37], I2 = 0%). The difference between exercise programs focusing on one type of exercise compared with programs mixing two or more types was significant for both outcomes (SMD for pain 0.45 [95% CI, 0.20–0.69], $P < 0.001$ and SMD for disability 0.36 [95% CI, 0.13–0.58], $P < 0.002$) in favor of using only one type of exercise.

Aerobic Training.

- The effect of aerobic exercise on pain relief increased with an increased number of supervised sessions (slope 0.022 [95% confidence interval 0.002,0.043]).
  Resistance Training.
- More pain reduction occurred with quadriceps-specific exercise than with lower limb exercise (SMD 0.85 vs 0.39; $P = 0.005$) and when supervised exercise was performed at least three times a week (SMD 0.68 vs 0.41; $P = 0.017$).

Disease Severity.

- Stratified analysis showed similar effects for pain in patients with severe knee OA (SMD 0.60 [95% CI, 0.38–0.82], I2 = 36.1%) and those with mild/moderate knee OA (SMD 0.66 [95% CI, 0.34–0.99], I2 = 77.0%) ($P = 0.736$).
- Although exercise therapy seemed to reduce patient-reported disability less in patients with severe knee OA (SMD 0.39 [95% CI, 0.05–0.74], I2 = 73.6%) than in patients with mild/moderate knee OA (SMD 0.66 [95% CI, 0.32–0.99], I2 = 84.6%) ($P = 0.282$), the differences did not reach significance.

VAS, visual analog scale for pain; SF, Short Form (-8, -12, or -36 item) Health Survey; HAQ, Health Assessment Questionnaire; AIMS, Arthritis Impact Measurement Scales; KSPS, Knee Specific Pain Scale; ASES, Arthritis Self-Efficacy Scale; SES, Schmerzempfindungsskala; NRS, Numeric Rating System (of pain); PCS, Physical Composite Score; PDI, Pain Disability Index; EuroQoL, an instrument for measuring HRQoL; KOOS, Knee Injury and Osteoarthritis Outcome score; SAFE, Survey of Activities and Fear of Falling in the Elderly; OASI, Osteoarthritis Screening Index; FAST, Fitness Arthritis and Senior Trial; KOOS ADL, KOOS scale of activities of daily living; 6MWT, 6-min walk test; TUG, timed up and go test; BPI, Brief Pain Inventory; FAST, Fitness Arthritis and Seniors Trial.

progression to total joint arthroplasty (replacement) for OA. Based on the paramount importance of the issue of disease progression for individuals with OA, we elected to perform a separate literature search, using the same search strategy, process, and inclusion/exclusion criteria used for the pain, physical function and HRQoL outcomes but including two additional specific criteria: only inclusion of original research published from 2006 through February 2018 and only inclusion of the outcome of OA progression. Of note, we did not identify any studies examining the effects of physical activity on progression based on systemic biomarkers associated with disease state.

The search for MA, SR, and pooled analyses, and reports failed to identify any literature to address the question of the effects of physical activity on comorbid conditions in OA. The term comorbid condition referred to any other existing chronic condition identified by a medical diagnosis (e.g., coronary heart disease) or by clinical events (e.g., cardiovascular mortality); therefore, this question was not pursued.

The quality of each MA, SR and pooled analysis, summarized in Supplemental Digital Content 1 (see Table, Supplemental Digital Content 1, quality assessment chart, http://links.lww.com/MSS/B518), was assessed using $\text{AMSTAR}_{\text{ExBP}}$ (35), a modified version of "A Measurement Tool to Assess Systematic Reviews" (AMSTAR) (36,37); the majority of the studies met 11 of the 18 AMSTAR criteria. Risk of bias, or internal validity was assessed for each original study using an adapted version of the USDA NEL Bias Assessment Tool (BAT) (38) as summarized in Supplemental Digital Content 2 (see Table, Supplemental Digital Content 2, original research bias assessment chart, http://links.lww.com/MSS/B519); the majority of the studies met 8 of the 10 applicable criteria. The bias assessment of the original research and the full search strategy is available (12). Recently, the method of data extraction has been published in detail (11). Literature trees summarize the selection of MA, SR, and pooled analyses and reports in Supplemental Digital Content 3 (see Figure, Supplemental Digital Content 3, providing details of literature tree search for reviews related to OA pain, physical function, HRQoL, progression and risk of comorbid conditions, http://links.lww.com/MSS/B520) and original research related to OA progression in Supplemental Content (see Figure, Supplemental Digital Content 4, providing details of literature tree search for original research related to OA progression, http://links.lww.com/MSS/B521).

RESULTS

OA and Pain, Physical Function, and HRQoL as Outcomes

Most of the retained MA (six) and SR (three) publications evaluated randomized controlled trials (RCT) reviewing the effects of one or more modalities of exercise (land-based and aquatic, aerobic, muscle strengthening, and Tai Chi) on knee and hip OA. Most used the WOMAC scale—common in the OA research arena—to assess pain and physical function, and SF-12 to assess HRQoL. One SR examined land-based exercise studies exclusively (18); another examined pool-based exercise effects only (14). In sum, these references encompassed 261 studies related to knee and/or hip OA involving 25,924 individuals with pain, physical function or HRQoL as an outcome. A total of 240 studies involving 24,583 participants included knee OA; a total of 52 studies involving 4803 participants included hip OA.

Taken together, the evidence demonstrated that physical activity reduces pain and improves physical function and HRQoL for persons with lower limb OA. The effect sizes (based on standardized mean differences [SMD]) favored exercise: maximal SMD reported were 0.53 for pain (15), 0.76 for physical function (16) and 0.28 for HRQoL (18) (Table 1). For pain, physical function, and HRQoL, the effect sizes for those with hip OA did not vary from those with knee OA only. Although there were some modest differences in effect sizes across different exposures, in general, the reviews were consistent in finding that physical activity is associated with reductions in pain and improvements in physical function and HRQoL for both knee and hip OA, irrespective of the mode (aquatic vs land-based exercise) or muscle strengthening versus aerobic versus Tai Chi (Table 1). Following cessation of the intervention, the beneficial effects of physical activity persisted up to 6 months for pain, and beyond 6 months for physical function (18) (Table 1).

The findings on pain, physical function, and HRQoL are illustrated in Figures 1 and 2, which present results from one review addressing land-based exercise effects on the knee (from Fransen et al. (18)) and one review addressing aquatic exercise effects on the knee (from Bartels et al. (14)). In Figure 1, the direction to the left favors exercise (decreased pain and improved physical function), whereas, improved HRQoL is to the right. In Figure 2, the direction to the left favors exercise (decreased pain, improved physical function and HRQoL).

Mode and Dose of Exercise

Most studies of the effects of physical activity on pain, physical function, and HRQoL were RCT of one mode, intensity, or duration; there was significant heterogeneity for these factors among the studies included within each MA/SR. Limited information was available on dose–response or different modes (types of exercise). Overall, the literature search revealed four MA/SR (22) addressing mode and/or dose of exercise for OA (Table 1). One MA/SR of 48 RCT (4028 patients with pain data) (22) observed similar pain reduction for aerobic, resistance, and performance exercise (practicing a specific activity with the lower extremity); single-type exercise programs were more efficacious than programs that included different exercise types. The effect of aerobic exercise on pain relief increased with an increased number of supervised sessions; overall, more pain reduction occurred when supervised exercise was performed at least three times a week. The authors recommended supervised exercise three times a week, noting that such programs have a similar effect, regardless of patient characteristics, including radiographic disease severity and baseline pain.

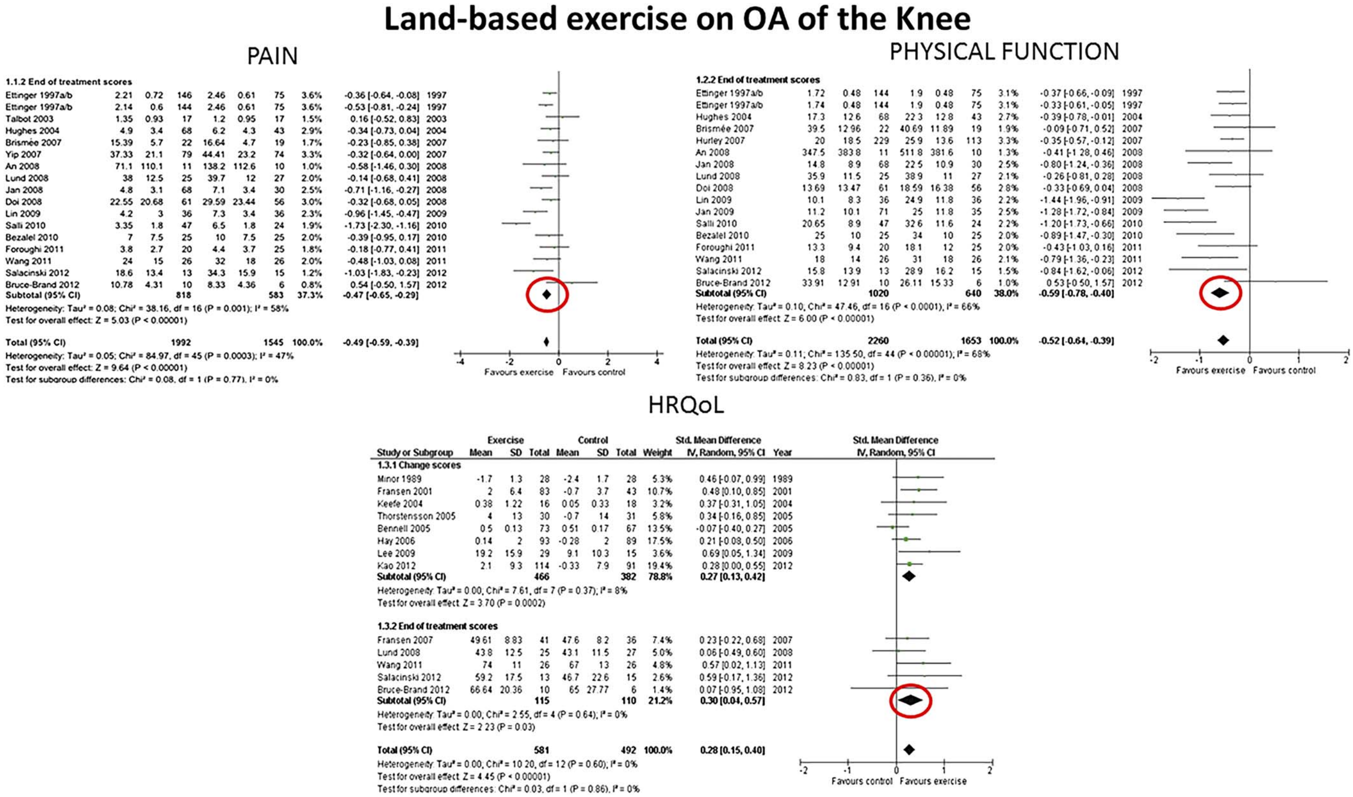

FIGURE 1—Effects of land-based exercise on pain, physical function and HRQoL in knee OA. Negative SMD represent improvements in pain and physical function (lower scores represent better pain and/or physical function) whereas positive SMD represent improvements in HRQoL (higher scores represent better HRQoL). Reproduced with permission from Fransen M, McConnell S, Harmer AR, et al. Exercise for osteoarthritis of the knee: a Cochrane systematic review. *Br J Sports Med.* 2015;49:1554–7. Copyright © 2015 BMJ Publishing Group Ltd.

Another SR, encompassing 45 trials (4699 participants), addressed mode and dose of exercise for knee OA (33). This review concluded that knee extensor strength significantly improved following American College of Sports Medicine (ACSM) recommendations (39) (described in Table 1 footer) versus all other types (i.e., any that did not deliver the intervention according to the ACSM recommendation) of strength training for older or sedentary patients. Although a dose–response association was identified between knee extensor strength gain and improvement in pain and physical function, there was no difference in pain and function outcomes comparing ACSM versus other types of exercise interventions.

A third SR, encompassing 24 trials (1747 participants), addressed dose of exercise for knee OA (34). Large differences among studies in the type, duration, and volume of exercise made it difficult to discern specific variables influencing the effects of treatment. A few generalizations based on self-reported pain and function were possible: 1) 24 or more total exercise sessions were most often related to large effect sizes (studies ranged from 3 to 108 sessions), 2) 8- and 12-wk exercise durations most often exhibited larger effect sizes (studies ranged from 4 to 36 wk), and 3) a frequency of one time per week exercise showed no effect.

A fourth MA/SR, encompassing 27 trials (3060 participants), addressed different modes of land-based exercise (recreational activities, walking or conditioning exercise consisting of a combination of strength training, flexibility, and aerobic interventions) (32). In contrast to studies lasting 12 months, walking and conditioning exercise lasting 6 months had a significant impact on physical function and/or physical performance (6-min walk test or timed stair climbing test) but not on pain. Conditioning exercise also had a moderate level of evidence for effectiveness on physical function in individuals with knee OA in both the short (6 months) and longer (18 months) terms. Adherence to the interventions is very likely to have an effect on the significance of the results.

Although not an MA or SR, and therefore not used in the PAGAC report, we found one original research article worth noting related to dose of exercise and function. In this study, Dunlop et al. (40) assessed the association of accelerometer measured physical activity and physical function in 1647 participants with lower-extremity symptoms in the OA Initiative (OAI) cohort. Moderate-to-vigorous physical activity (MVPA) was defined as greater than 2020 counts per minute corresponding to 3 METs or a level of exertion corresponding to a ~3.5 mph walk (41). Physical function based on measured (gait speed) and self-reported (SF-12) function was assessed 2 yr later. Improved or sustained high function was achieved by 34% of participants. Compared with participants performing ≤45 total minutes of MVPA per week (including bouts <10 min in duration), those performing >45 min·wk^{-1} were more likely to improve gait speed (relative risk [RR], 1.8;

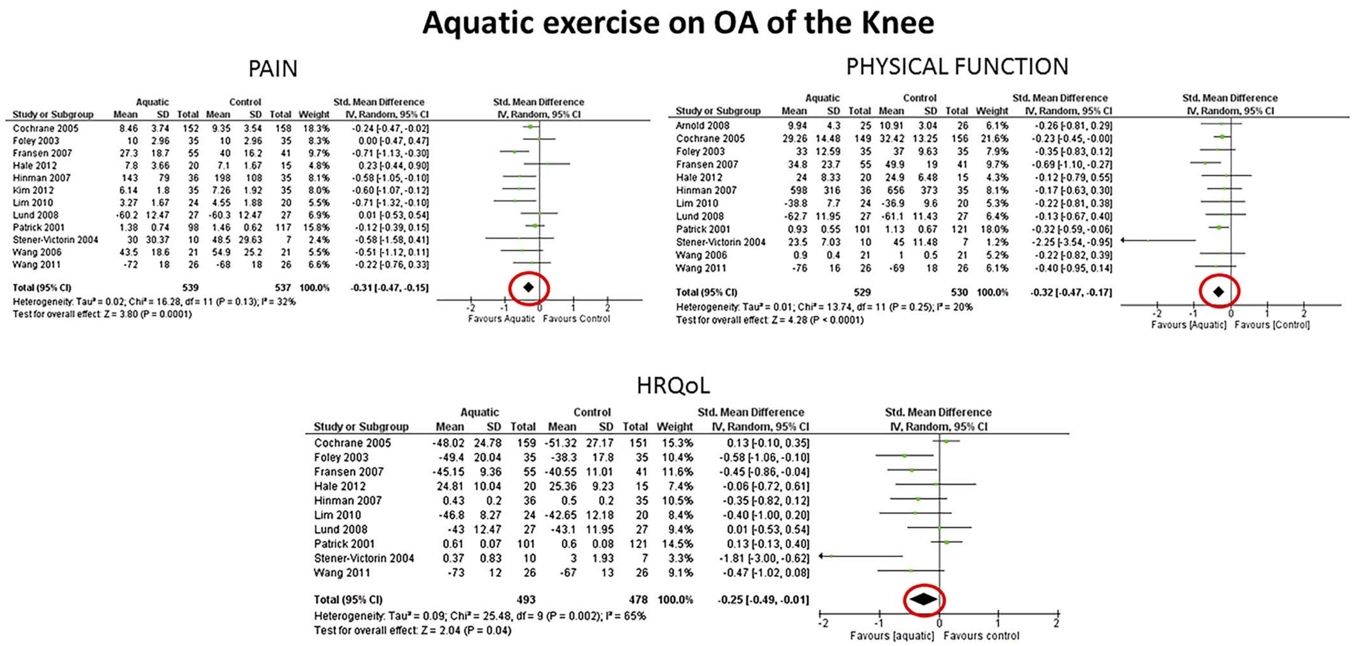

FIGURE 2—Effects of Aquatic Exercise on Pain, Physical Function and HRQoL in Knee OA. A multitude of measures were used in the included studies; standardized instruments used most often were WOMAC for pain and function and SF-36, SF-12 or SF-8 for physical function. Negative SMD represented improvements in pain, physical function and/or HRQoL (lower scores mean better pain, physical function and/or HRQoL). Reproduced with permission from Bartels EM, Juhl CB, Christensen R, et al. Aquatic exercise for the treatment of knee and hip osteoarthritis. *Cochrane Database Syst Rev.* 2016;3: CD005523. Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

95% confidence interval [CI], 1.6–2.1) and self-reported function (RR, 1.4; 95% CI, 1.3–1.6). Individuals performing or exceeding the 2008 Physical Activity Guidelines for Americans of >150 min·wk^{-1} of MVPA in bouts lasting ≥10 min also improved gait speed (RR, 1.4; 95% CI, 1.3–1.6) and self-reported function (RR, 1.3; 95% CI, 1.2–1.4). Results were consistent across varying knee OA severities. Thus, it is evident that important health improvements can be achieved even with levels of physical activity below those recommended by the 2008 Physical Activity Guidelines for Americans.

Demographic factors and weight status. Dunlop et al. (40) determined that the results for the intermediate level of physical activity (≥45 min·wk^{-1} moderate-vigorous activity) were consistent across sex, body mass index and age. However, effect modifications by sex, age, race/ethnicity and socioeconomic status were not addressed in any of the MA/SR identified for this umbrella review. Although a relationship between body mass index (BMI) and OA is generally well recognized (42), to our knowledge, there are no MA evaluating whether BMI modifies the physical activity–OA relationship.

OA Disease Progression as an Outcome

Existing SR and MA. A concern about the potential harm that high intensity and large amounts of weight-bearing exercise may cause for OA progression prompted a targeted review for this outcome.

We identified one SR/MA (29) that assessed the association of self-reported running or jogging (including running-related sports such as triathlon and orienteering) with knee OA onset or progression defined by any definition of diagnosed knee OA, radiographic or imaging markers of knee OA, knee arthroplasty for OA, knee pain and/or disability specifically associated with the knee (Table 2). Although this SR/MA included incident as well as progressive OA, the data are instructive for understanding the potential role of running in the development and/or progression of OA. With this evidence, the authors concluded that it was not possible to determine the role of running in knee OA. However, they noted that a key finding of their review was the result of their MA (2172 individuals) of three case-control studies (two of the three controlled for joint injury), which suggested that runners (running for 1 yr up to a lifetime) had around a 50% reduced odds of undergoing a total knee replacement for OA than nonrunners (pooled odds ratio, 0.46, $P = 0.0004$, Table 2). Evidence relating to symptomatic outcomes was sparse and inconclusive. Because retrospective case-control studies are subject to several types of bias, these data have to be interpreted with caution; these biases include recall and observer bias, bias related to choice of control groups, and selection bias. Selection bias could occur if individuals with joint symptoms or injury ceased their participation in physical activity and went on to eventual joint replacement; therefore, individuals with total knee replacement would be identified as having engaged in less physical activity leading to an apparent protective effect of physical activity on knee replacement.

We also identified one SR that included 49 studies (43) assessing the safety of physical activity in older adults with knee pain (summarized in Table 2). The SR (43) examined 49 longitudinal studies (comprising 48 RCT and one case

TABLE 2. Summary of included studies assessing the relationship of physical activity and OA progression in individuals with lower-extremity OA. (29,40,43–48).

Author (Year)	Type of Study, Joints, Mean Age and/or Range	Sample Size & Number of Studies	Type of Physical Activity	Outcome Measures	Measures of Association (95% CI)
Quicke (2015) (43)	SR, Knee, 45 yr or older	8920 participants from 49 studies 46 studies measured pain 43 measured physical function 3 measured TKR	Three months or more of physical activity intervention or exposure	OA Progression (structural OA biomarker imaging and TKR) between three and 30 months of physical activity intervention	There was no evidence of progression of structural OA by imaging or increased TKR at a group level (n = 8 TKR within the physically active groups compared to n = 10 TKR in the nonphysically active) The case control study concluded that increasing levels of regular physical activity was associated with lower risk of progression to TKR; OR, 0.91 (0.31 to 2.63) and OR, 0.56 (0.30 to 0.93) in men and women, respectively, with low cumulative hours of physical activity; OR, 0.35 (0.12 to 0.95) and OR, 0.56 (0.32 to 0.98) in men and women, respectively, with a high number of accumulative hours of physical activity
Timmins (2017) (29)	SR/MA, Knee, 28–69 yr	15 studies: 110 cohort and 4 case–control	Any form of running or jogging	OA Progression defined by one of the following outcomes and a minimum of 1 yr of running/jogging: 1. Any definition of diagnosed knee OA 2. Radiographic or imaging markers of knee OA 3. Knee arthroplasty for OA 4. Knee pain 5. Disability specifically associated with the knee	Findings of studies with a diagnostic OA outcome were mixed. Some radiographic differences were observed in runners, but only at baseline within some subgroups. MA suggested a protective effect of running against surgery due to OA: pooled OR, 0.46 (0.30 to 0.71)
Kwee (2016) (47)	ORes, Knee, 62.2 yr	100	Physical Activity Scale for the Elderly (PASE)	OA Progression was measured via cartilage damage progression in medial tibiofemoral compartment using 2-yr follow-up MRI in participants with denuded areas of subchondral bone (dAB) at the central weight-bearing medial femur (cMF) at baseline MRI examination	Standardized Regression Coefficient: Mean cMF.ThCtAB change: −0.15762 mm; cMF.dAB% change: 0.11479; MT.ThCtAB change: −0.08589; MT.dAB% change: 0.13846
Lin (2013) (48)	ORes, Knee, 52.8 yr	205 participants from the OAI without symptomatic or radiographic evidence of OA	Physical Activity Scale for the Elderly (PASE)	OA Progression was measured with MRI T2 relaxation time over a 4-yr period	T2 progression was increased in the highest tertile of physical activity compared to the mid-tertile at the medial tibia (P = 0.041), patella (P = 0.019), and average T2 of all knee compartments combined (P = 0.033). Participants with the lowest 15% PASE scores showed significantly higher T2 progression compared to the mid-level physical activity group at the lateral femur (P = 0.025), lateral tibia (P = 0.043), medial femur (P = 0.044), tibiofemoral compartment (P = 0.017), patellofemoral compartment (P = 0.016), lateral compartments (P = 0.003), and average of all compartments (P = 0.043)
Felson (2013) (45)	ORes, Knee, 61 yr	2,073 participants (3,542 knees)	Physical Activity Scale for the Elderly (PASE)	OA Progression was measuring with long limb radiographs. Participants were followed for 30 months (in MOST) and 48 months (in OAI), respectively, with at least one of the following incident outcomes: Symptomatic tibiofemoral OA (radiographic OA and knee pain) Tibiofemoral narrowing	Incident Tibiofemoral Symptomatic Knee OA: Lower 75%: OR, 1.0 Upper 25%: OR, 0.60 (0.03 to 1.3) Joint Space Loss: Lower 75%: OR, 1.0 Upper 25%: OR, 0.9 (0.05 to 1.5)
Oiestad (2015) (46)	ORes, Knee, 67 +/− 7.6 yr	1179 participants (2008 knees)	Steps/Day using a ccelerometer	OA Progression measured by radiographic and MRI assessment with a follow-up of 2 yr	Radiographic Worsening: <5859 steps per day: OR, 0.91 (0.64 to 1.27); 5859–7846 steps per day: OR, 1.0; >7846 steps per day: OR, 0.99 (0.69 to 1.42) Intensity minutes: OR, 1.01 (0.99 to 1.02); Lateral Cartilage Loss: <6078 steps per day: OR, 0.82 (0.45 to 1.51) 6078–7938 steps per day: OR, 1.0 >7938 steps per day; Medial Cartilage Loss: <6078 steps per day: OR, 1.37 (0.81 to 2.32); 6078–7938 steps per day: OR, 1.0; >7938 steps per day: 1.37 .80 to 2.33); MVPA minutes: OR, 0.99 (0.97 to 1.01)

Dore (2013) (44)	ORes, Knee, 51–81 yr	405 participants	Steps per day	OA Progression between objectively measured steps per day and knee structural change using MRI with approximately a 2.7-yr follow-up	≥10,000 steps per day increases BML: RR, 1.97 (1.19 to 3.27) ≥10,000 steps per day had a 1.52 times (1.05 to 2.20) greater risk of increasing meniscal pathology score, which increased to 2.49 (1.05 to 3.93) in those with adverse meniscal pathology at baseline. ≥10,000 steps per day was associated with a greater risk of increasing cartilage defect score in those with prevalent BML at baseline: RR, 1.36, (1.03 to 1.69) Steps per day was protective against volume loss in those with more baseline cartilage volume but led to increased cartilage loss in those with less baseline cartilage volume. ($P = 0.046$ for interaction)

TKR, total knee replacement; OR, odds ratio; ORes, original research; cMF.ThCtAB, mean cartilage thickness over total subchondral bone area at the central medial femur in mm; cMF. dAB%, % denuded area of subchondral bone (dAB) at the central medial femur; MT.ThCtAB, mean cartilage thickness over total subchondral bone area at the medial tibia in mm; MT.dAB%, % denuded area of subchondral bone (dAB) at the medial tibia; OAI, the Osteoarthritis Initiative cohort; BML, bone marrow lesion (MRI measure); SF-12, Short Form (12 item) Health Survey; PRO, patient-reported outcome;

control study) of 8614 total participants with knee pain and/or a diagnosis of knee OA ranging in radiographic severity from Kellgren and Lawrence (49) grades 1 to 4. All physical activity interventions were low-impact, most often combining muscle-strengthening, stretching, and aerobic elements for 3 to 30 wk. None of the primary literature studies in this SR dealt with hip OA. Comparing groups with greater amounts of low-impact physical activity to groups with the least amounts, this SR provided no evidence of serious adverse events defined as increased pain, decreased physical function, progression of structural OA on imaging or increased total knee replacement at a group level. In addition, although the total numbers were small and total follow-up brief, based on four RCT (985 participants), there were no more total knee replacements over a 2- to 24-month observation period within physical activity groups compared to nonphysical activity groups (n = 8 vs n = 10 total knee replacements, respectively).

Original research. We identified five original research studies that examined the relationship between physical activity and disease progression (40,44–48) (Table 2); no additional studies were identified as part of the extended search for this summary. All studies were prospective cohort studies (published 2013 to 2016). The analytical sample size ranged from 100 (47) to 2073 (45); four were US studies (40,45–48), one Australian (44). Three studies used self-reported physical activity via the Physical Activity Scale for the Elderly (PASE) (45,47,48). Two studies had device-measured physical activity via accelerometer or pedometer (40,44,46). The five included studies determined OA progression based on change in radiographic imaging (34), change in MRI imaging (cartilage loss) (44,47,48) or both (46). Collectively, these five studies focused on one of three longitudinal cohort studies: the OAI (40,45,47,48), the Multicenter Osteoarthritis (MOST) study (34,35) and a longitudinal cohort study of 405 community dwelling adults from Australia (33). The OAI assessed physical activity with the PASE survey (34,36,37) and accelerometry (29); the MOST study and the Australian cohort assessed exposure by objective step count measures. Overall, the findings in these studies were mixed.

Three progression-related studies quantified physical activity with PASE at baseline and quantified OA progression by imaging (radiographic or MRI) outcomes. Kwee et al. (47) assessed 2-yr knee OA progression based on MRI of 100 participants in the OAI with symptomatic OA and baseline full-thickness cartilage defects of the knee; although OA progressed, there was no association of disease progression and levels of physical activity as measured by PASE (mean, 2-yr score 156; range, 42–334). Lin et al. (48) assessed 4-yr knee OA progression based on knee MRI (increasing T2 signal) of 205 asymptomatic individuals with (80%) and without (20%) risk factors for knee OA in the OAI. Greater OA progression was identified in the individuals with the 15% highest (score range, 242–368) and 15% lowest (score range, 31–120) PASE scores compared with the 70% mid-range (score range, 153–207) scores of the reference group. The moderate activity mid-range group consistently showed the lowest (best) T2 values at baseline and 48-month follow-up. This study supported a potential U-shaped relationship of physical activity and OA progression for individuals at high risk for radiographic OA (80% with risk factors) or who had radiographic OA (Kellgren Lawrence grade 1), although the overall proportion of this subset was not reported. Potential interactions of baseline MRI lesion severity and physical activity for OA progression were not evaluated. Felson et al. (45) assessed 30- to 48-month knee OA progression based on radiograph or symptoms of 2073 participants (3542 knees, 50% symptomatic) with or at high risk of knee OA; there was no relation of quartiles of PASE scores with any OA progression outcomes (radiographic joint space loss or incident symptomatic knee OA) and no difference by degree of knee malalignment. The upper quartile of PASE scores (median score 250 for women, 300 for men) corresponded to regular work with some walking, "walks outside the home 1–2 $h \cdot d^{-1}$ occasionally," light house or yard work in the prior 7 d but no extensive sports participation.

Two progression-related studies quantified physical activity with pedometers or accelerometers at baseline and quantified OA progression by imaging (radiographic or MRI) outcomes. Oiestad et al. (46) assessed 2-yr knee OA progression based on both knee radiographs (X-rays) and MRI (cartilage loss) of 1179 participants in the MOST study, at risk of or with mild knee OA with physical activity measured at baseline by accelerometer (steps). There were no significant associations between daily walking or more time spent walking at a moderate to vigorous intensity with radiographic worsening or cartilage loss. Dore et al. (44) assessed ~2.7-yr knee OA progression based on knee MRI (with four structural measures) of 405 Australian individuals (age, 50–80 yr) in a community-based sample with physical activity measured at baseline by pedometer. There was no association of steps and OA progression for individuals with baseline MRI joint pathology performing fewer than 10,000 steps per day. However, in the context of baseline joint pathology compared with the individuals performing fewer than 10,000 steps per day, there was greater OA progression (more meniscal pathology, more bone marrow lesions and/or lower cartilage volume by MRI) related to performing ≥10,000 steps per day (Fig. 3). Thus, the effect of physical activity was modified by baseline OA status. When steps were analyzed as a continuous variable, there was a significant association of steps and risk of progression of cartilage defects and bone marrow lesions; there was also an interaction of steps and baseline severity of OA for MRI-based cartilage volume and meniscal pathology. Taken together, these data support a potential J-shaped

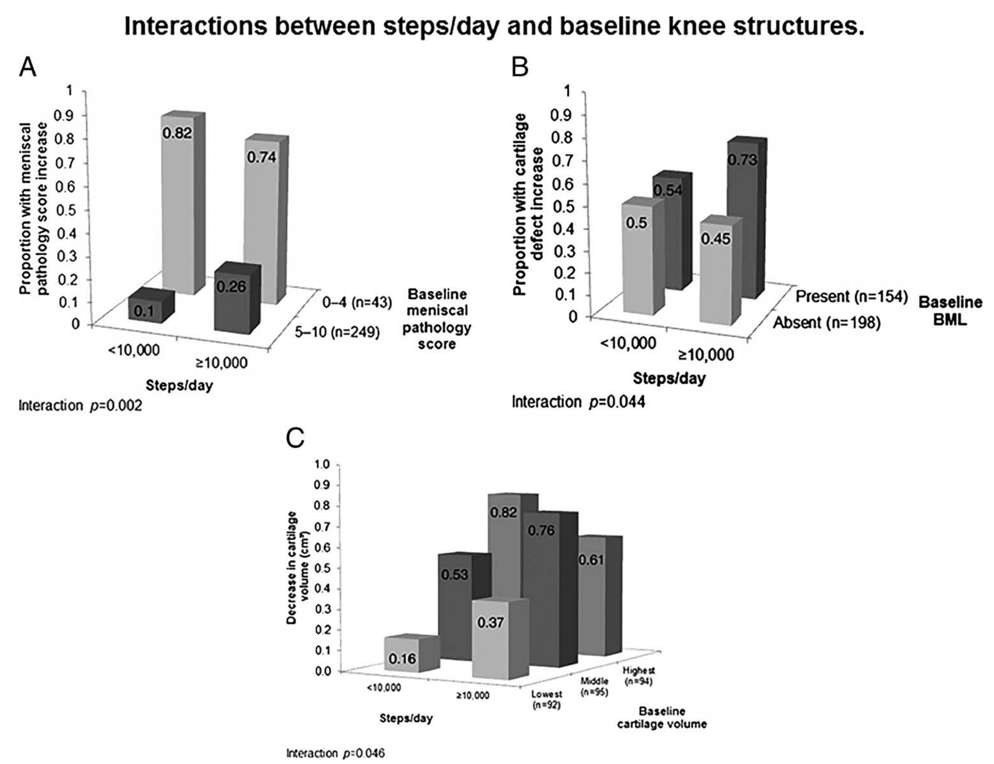

FIGURE 3—Interaction of underlying joint pathology by MRI and ambulatory physical activity amounts (step counts) on OA progression, as shown on MRI. Greater meniscal pathology scores, presence of BML and less cartilage volume all indicate more severe disease. BML are areas of increased signal adjacent to the subcortical bone at the medial tibial, medial femoral, lateral tibial, and lateral femoral sites and indicate more severe joint pathology. All figures show an interaction effect, wherein for those individuals with less baseline osteoarthritis pathology, steps are not related to pathology score increases. In contrast, in adults with greater baseline pathology scores, a greater percent of adults with more than 10,000 steps per day show worsening of pathology scores over time (26%) compared to adults with fewer than 10,000 steps per day (10%). BML, bone mineral lesions. Reproduced with permission from Doré DA, Winzenberg TM, Ding C, et al. The association between objectively measured physical activity and knee structural change using MRI. *Ann Rheum Dis.* 2013;72:1170–5. Copyright © 2013 BMJ Publishing Group Ltd.

relationship of physical activity and OA progression for those with preexisting OA.

DISCUSSION AND NEEDS FOR FUTURE RESEARCH

Over an entire week, as many as 40% of adults with lower-extremity joint conditions do not engage in even a single session of moderate physical activity lasting 10 min (40). However, as is clear from our review, regular exercise at amounts up to those consistent with the 2008 Physical Activity Guidelines for Americans—150 $min \cdot wk^{-1}$ of moderate-intensity aerobic exercise, 2 $d \cdot wk^{-1}$ of muscle-strengthening exercise—has a substantial beneficial impact on health of individuals with preexisting knee and hip OA. The evidence suggests that up to 10,000 steps per day of activity does not accelerate OA progression in individuals with preexisting OA. Land-based exercise appears to be as efficacious as water-based exercise for these outcomes. Benefits related to pain relief, physical function, and HRQoL appear to be applicable for aerobic exercise, muscle-strengthening exercise, and Tai Chi. Although not tested head to head, effect sizes for joint pain reduction by physical activity are comparable to those reported for analgesics (20). Although this review did not identify any MA/SR related to risk of comorbid conditions, a recent large cohort study (16,362 individuals age ≥55 yr; median, 13.5 yr follow-up) demonstrated that the presence and burden of radiographic hip and/or knee OA was significantly associated with increased risk (16%–25%) for incident diabetes (controlled for confounders) with 37% to 46% of this relationship explained by baseline limitations in walking (50). This excellent study begins to address the important question of physical activity and comorbidities in OA and underscores the necessity of further studies to determine means of counteracting the incidence or reversing established serious comorbidities, such as diabetes, in individuals with OA. A summary of the overall conclusions and grade of the evidence, based on a consensus of the 2018 PAGAC, are provided in Table 3.

There are a number of barriers to physical activity for individuals with OA. For people with lower-extremity joint symptoms, even 10-min bouts of activity can be a challenge. Moreover, greater knee pain and BMI can both contribute to poorer compliance with exercise (51). One study suggested a potential U-shaped, and another a J-shaped, dose–response relationship of physical activity with OA progression (40,44,48). Interestingly, this U-shaped dose–response relationship is supported by an MA of exercise studies in healthy animals (52).

Evidence addressing some of the barriers to physical activity for individuals with joint disease are provided by Dunlop et al. (40) where an intermediate level of accumulated physical activity—minimum of 45 $min \cdot wk^{-1}$ of at least moderate intensity, irrespective of bouts—benefited function of individuals with lower-extremity OA. Given the ready accessibility to the general public of mobile health devices—including individuals with arthritis—it is useful for patients and arthritis health-related professionals to understand what is known about the relation of step counts to health outcomes in those with OA. The goal of 150 $min \cdot wk^{-1}$ of MVPA (walking at least 3.3 mph) equates to ~2500 steps per day whereas the goal of 45 $min \cdot wk^{-1}$ of MVPA corresponds to ~750 steps per day. Considering a background of daily activity of 5000 steps per day (53), a computed translation of these recommendations yields estimates of a total of ~7500 steps per day (corresponding to a 'somewhat active' lifestyle (54)), and ~5750 steps per day (also considered a 'somewhat active' lifestyle (54)), respectively. It is possible that background daily activity in some individuals with OA does not exceed basal activity levels of 2500 steps per day (54); under these circumstances, the corresponding minimal estimates of activity would be a total of ~5000 steps per day and ~3250 steps per day (considered a "sedentary" lifestyle). Interestingly, all these goals fall within the apparent safe range for individuals with more severe lower limb OA of less than 10,000 steps per day. In a large (n = 4840) community-based sample, benefits are similar for both bouted and nonbouted physical activity (55,56). Moreover, a marked mortality benefit accrues from as little as 40–80 $min \cdot d^{-1}$ of moderate activity (56) defined as a threshold of 760 counts per minute using a waist-worn accelerometer—roughly equivalent to the level of exertion of activities of daily living. Taken together, these new insights provide encouraging news for individuals with OA for whom nonbouted activity and intermediate levels of activity below US guideline amounts are likely to be beneficial and more readily achieved on a regular basis.

Although umbrella reviews represent one of the highest levels of evidence synthesis currently available, they are subject to several limitations including: incomplete stratification of the evidence due to residual overlap within the included MA/SR; heterogeneity of exposures making it difficult to determine the exact relationships of physical activity and outcomes; and heterogeneity of studied populations potentially limiting the generalizability of results. In addition, this review was limited by the lack of studies related to HRQoL and OA progression and a lack of uniform definitions of OA—a current challenge to the OA research field as a whole. As a strength, this review has yielded insights into knowledge gaps that led us to formulate the recommendations described below for future research.

1. Conduct additional research to assess effect sizes of physical activity on OA to determine the clinical impact exercise may have on particular outcomes.
   Rationale: There is a particular need to conduct prospective longer-term RCT of physical activity to evaluate OA disease progression, with objective quantification of physical activity exposures with molecular and imaging disease status biomarkers as outcomes. In addition, more data are needed to address the critical issues of varying amounts and intensities of physical activity and their relationship to incidence and progression of OA (tibiofemoral and patellofemoral) in the absence of underlying injury. Because it often takes years for disease activity to result in

TABLE 3. PAGAC recommendations.

Research Questions	Evidence Grade[a]
Amounts of physical activity and comorbidities in individuals with OA	Not assignable
Amounts of physical activity and decreased pain and improved physical function in adults with OA of the knee and hip	Strong (evidence is unlikely to be modified by more studies for these outcomes)
Amounts of physical activity and improved HRQoL in persons with OA of the knee and hip	Moderate
Relationships vary by age, sex, race, ethnicity, socioeconomic status, or body mass index	Not assignable
Dose–response relationship between physical activity and improved pain, physical function and HRQoL in individuals with OA	Not assignable
Intensity or duration of aerobic and muscle-strengthening physical activity is related to improvement in pain and functional capacity in individuals with OA of the knee and hip	Limited
Dose–response relationship between physical activity and disease progression in individuals with OA	Moderate for safety (the relationship appears to be U-shaped; up to the range of 10,000 steps per day, ambulatory physical activity does not accelerate OA of the knee); Limited for adverse effects (range of more than 10,000 steps per day may have an adverse effect on progression of OA of the knee in individuals with existing OA of the knee)

[a]The 5 grading criteria serving as the determinants of the final Evidence Grade are described in Torres 2018 (Table 1); in brief they were 1) applicability, 2) generalizability (to the US population of interest), 3) risk of bias or study limitations (as determined by NEL BAT and/or AMSTARExBP), 4) quantity and consistency (of the results across the available studies), and 5) magnitude and precision of effect.

structural, detectable radiographic changes in the joint, sophisticated imaging modalities, such as MRI, and biological biomarkers of disease activity (circulating systemic or intra-articular) are needed to measure the outcomes. Recently (after the timeframe of the searches for this review), the first MA of synovial fluid, serum, and urine biomarkers in individuals with established knee OA was published (57). It concluded that 4 to 24 wk of exercise therapy (strengthening and or aerobic) was not harmful as it did not increase the concentration of molecular biomarkers related to inflammation and cartilage turnover, associated with cartilage breakdown. The overall quality of evidence was graded as low because of the limited number of RCT available underscoring the need for more biomarker research in this field.

2. Conduct research to clarify how OA progression is modified by baseline demographic and disease characteristics as well as pain responses to exercise.
   Rationale: For the outcome of disease progression induced by physical activity, some evidence suggests that baseline disease status plays a role in modifying the effect of physical activity; but this role has not yet been fully explained. In addition, although a relationship between BMI and OA is generally recognized, no studies have investigated through MA whether BMI modifies the physical activity–OA relationship. More studies on OA progression need to evaluate groups of individuals with clear evidence of OA (defined biochemically, by MRI or radiograph) at baseline as well as those “at risk” of OA.

3. Conduct direct head-to-head comparisons of the relative effectiveness of physical activity and analgesics for pain control in individuals with OA.
   Rationale: Our review of the literature revealed that the effect sizes for pain control from exercise interventions is very similar to that of analgesics, including narcotic analgesics (20). If true, this would be a critical observation with profound implications for patient care, especially as the effects of physical activity on OA-related pain seem to be durable for up to 6 months following cessation of an intervention. Determining the comparative effects of physical activity and analgesics on OA pain could contribute greatly to effective clinical management of OA and potentially to greater third-party payment of exercise treatments for OA.

4. Conduct research to determine the optimal physical activity dose, mode, intensity, duration and frequency to optimize efficacy and sustainability of physical activity for different types and severity of OA.
   Rationale: Different modalities or amounts of physical activity (using the same modality) have not been compared head-to-head to ascertain their relative effects on OA progression, as well as pain, physical function, and HRQoL. Dose–response investigations on the relationship of daily step counts and other device-based measures of physical activity and OA disease progression are particularly needed. Given that varying pain intensities and structural severities of OA have been associated with reduced compliance with exercise therapy, it is important to develop approaches to personalize physical activity prescriptions for individuals with OA to minimize discontinuation due to exacerbation of symptoms and/or disease progression.

5. Determine the capacity of individuals with OA to perform physical activity at intensities and amounts of exercise that are able to modify comorbidities.
   Rationale: Obesity is a risk factor for OA incidence and progression. Obesity is also a significant risk factor for OA-related comorbidities, including diabetes, cardiovascular disease, and cancer. However, few to no data address the relationships of physical activity and modification of OA-related comorbidities and mortality in those with OA. New longitudinal cohort studies, facilitated by device-based measures of physical activity, will be required to adequately address this question. In addition, more data are needed to determine whether those with advanced OA can safely exercise at intensities or amounts that are able to modify the risk of developing disease comorbidities without subjecting themselves to a greater risk of disease progression.

6. Develop biomarkers of exercise responsiveness and trajectories for different types and severity of OA, to determine who is likely to respond favorably to physical activity interventions versus who is at risk of disease progression.
   Rationale: As for many human conditions and physiologic states, even when controlling for possible effect modifiers, individuals with different OA characteristics (pain, physical function, HRQoL, and disease structural severity) demonstrate a range of individual responses to the same exercise exposure. Developing technologies (such as biomarkers) and approaches to better understand the demographic, physiologic, and molecular basis of disease will be valuable for predicting and monitoring responses to exercise and thereby for developing the best exercise regimen to elicit specific responses at the individual level.

CONCLUSIONS

Physical activity decreases pain, improves physical function and HRQoL among people with hip and/or knee OA relative to less active adults with OA. Given the strength of the evidence (261 studies of various physical activity modes of exposure including land and pool, aerobic, resistance and flexibility), it is highly unlikely that the conclusions will be modified by more RCT for these outcomes. There is currently no evidence to suggest accelerated progression of OA in individuals with preexisting joint pathology for physical activity below 10,000 steps per day. A total of at least 45 $\text{min}\cdot\text{wk}^{-1}$ of MVPA can improve or sustain function of individuals with lower-extremity OA. Thus, people with lower-extremity OA should be encouraged to engage in achievable amounts of physical activity, of even modest intensities, accrued throughout the entire day, irrespective of bouts, and be confident of gaining some health and arthritis-related benefits.

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Role of the Funder/Sponsor: HHS staff provided general administrative support to the Committee and assured that the Committee adhered to the requirements for Federal Advisory Committees. HHS also contracted with ICF, a global consulting services company, to provide technical support for the literature searches conducted by the Committee. HHS and ICF staff collaborated with the Committee in the design and conduct of the searches by assisting with the development of the analytical frameworks, inclusion/exclusion criteria, and search terms for each primary question; using those parameters, ICF performed the literature searches.

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REFERENCES

1. Barbour K, Helmick C, Boring M, Brady T. Vital signs: prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation—United States, 2013–2015. *MMWR Morb Mortal Wkly Rep*. 2017;66(9):246–53.
2. Cisternas MG, Murphy L, Sacks JJ, Solomon DH, Pasta DJ, Helmick CG. Alternative methods for defining osteoarthritis and the impact on estimating prevalence in a US population-based survey. *Arthritis Care Res*. 2016;68(5):574–80.
3. Deshpande BR, Katz JN, Solomon DH, et al. Number of persons with symptomatic knee osteoarthritis in the US: impact of race and ethnicity, age, sex, and obesity. *Arthritis Care Res*. 2016;68(12):1743–50.
4. Hootman JM, Helmick CG, Barbour KE, Theis KA, Boring MA. Updated projected prevalence of self-reported doctor-diagnosed arthritis and arthritis-attributable activity limitation among US adults, 2015–2040. *Arthritis Rheumatol*. 2016;68(7):1582–7.
5. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis*. 2014;73(7):1323–30.
6. Guccione AA, Felson DT, Anderson JJ, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham study. *Am J Public Health*. 1994;84(3):351–8.
7. Kotlarz H, Gunnarsson CL, Fang H, Rizzo JA. Insurer and out-of-pocket costs of osteoarthritis in the US: evidence from national survey data. *Arthritis Rheum*. 2009;60(12):3546–53.
8. 2018 Physical Activity Guidelines Advisory Committee. *2018 Physical Activity Guidelines Advisory Committee Scientific Report*. In. Washington, DC: Department of Health and Human Services; 2018.
9. Neogi T. The epidemiology and impact of pain in osteoarthritis. *Osteoarthr Cartil*. 2013;21(9):1145–53.
10. U.S. Department of Health and Human Services. *Physical Activity Guidelines for Americans*. In: USDoHaH Services editor. Washington, DC; 2018.
11. Torres A, Tennant B, Ribeiro-Lucas I, Vaux-Bjerke A, Piercy K, Bloodgood B. Umbrella and systematic review methodology to support the 2018 Physical Activity Guidelines Advisory Committee. *J Phys Act Health*. 2018;15:805–10.
12. Physical Activity Guidelines Advisory Committee. Evidence portfolio—chronic conditions subcommittee, question 2. 2018 [cited 2018]. Available from: https://health.gov/paguidelines/second-edition/report/supplementary_material/pdf/Chronic_Conditions_Q2_Osteoarthritis_Evidence_Portfolio.pdf.
13. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*. 1988;15(12):1833–40.
14. Bartels EM, Juhl CB, Christensen R, et al. Aquatic exercise for the treatment of knee and hip osteoarthritis. *Cochrane Database Syst Rev*. 2016;3:CD005523.
15. Beumer L, Wong J, Warden SJ, Kemp JL, Foster P, Crossley KM. Effects of exercise and manual therapy on pain associated with hip osteoarthritis: a systematic review and meta-analysis. *Br J Sports Med*. 2016;50(8):458–63.
16. Chang WD, Chen S, Lee CL, Lin HY, Lai PT. The effects of Tai Chi Chuan on improving mind-body health for knee osteoarthritis patients:

a systematic review and meta-analysis. *Evid Based Complement Alternat Med*. 2016;2016:1813979.
17. Escalante Y, Garcia-Hermoso A, Saavedra JM. Effects of exercise on functional aerobic capacity in lower limb osteoarthritis: a systematic review. *J Sci Med Sport*. 2011;14(3):190–8.
18. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee: a Cochrane systematic review. *Br J Sports Med*. 2015;49(24):1554–7.
19. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S. Exercise for osteoarthritis of the hip. *Cochrane Database Syst Rev*. 2014;4:CD007912.
20. Henriksen M, Hansen JB, Klokker L, Bliddal H, Christensen R. Comparable effects of exercise and analgesics for pain secondary to knee osteoarthritis: a meta-analysis of trials included in Cochrane systematic reviews. *J Comp Eff Res*. 2016;5(4):417–31.
21. Jansen MJ, Viechtbauer W, Lenssen AF, Hendriks EJ, de Bie RA. Strength training alone, exercise therapy alone, and exercise therapy with passive manual mobilisation each reduce pain and disability in people with knee osteoarthritis: a systematic review. *Aust J Phys*. 2011;57(1):11–20.
22. Juhl C, Christensen R, Roos EM, Zhang W, Lund H. Impact of exercise type and dose on pain and disability in knee osteoarthritis: a systematic review and meta-regression analysis of randomized controlled trials. *Arthritis Rheum*. 2014;66(3):622–36.
23. Li Y, Su Y, Chen S, et al. The effects of resistance exercise in patients with knee osteoarthritis: a systematic review and meta-analysis. *Clin Rehabil*. 2016;30(10):947–59.
24. Regnaux JP, Lefevre-Colau MM, Trinquart L, et al. High-intensity versus low-intensity physical activity or exercise in people with hip or knee osteoarthritis. *Cochrane Database Syst Rev*. 2015;29(10): Cd010203.
25. Sampath KK, Mani R, Miyamori T, Tumilty S. The effects of manual therapy or exercise therapy or both in people with hip osteoarthritis: a systematic review and meta-analysis. *Clin Rehabil*. 2016;30(12): 1141–55.
26. Tanaka R, Ozawa J, Kito N, Moriyama H. Efficacy of strengthening or aerobic exercise on pain relief in people with knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Clin Rehabil*. 2013;27(12):1059–71.
27. Tanaka R, Ozawa J, Kito N, Moriyama H. Effect of the frequency and duration of land-based therapeutic exercise on pain relief for people with knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *J Phys Ther Sci*. 2014; 26(7):969–75.
28. Tanaka R, Ozawa J, Kito N, Moriyama H. Does exercise therapy improve the health-related quality of life of people with knee osteoarthritis? A systematic review and meta-analysis of randomized controlled trials. *J Phys Ther Sci*. 2015;27(10):3309–14.
29. Timmins KA, Leech RD, Batt ME, Edwards KL. Running and knee osteoarthritis: a systematic review and meta-analysis. *Am J Sports Med*. 2017;45(6):1447–57.
30. Uthman OA, van der Windt DA, Jordan JL, et al. Exercise for lower limb osteoarthritis: systematic review incorporating trial sequential analysis and network meta-analysis. *BMJ*. 2013;347:f5555.
31. Zhang Y, Huang L, Su Y, Zhan Z, Li Y, Lai X. The effects of traditional Chinese exercise in treating knee osteoarthritis: a systematic review and meta-analysis. *PLoS One*. 2017;12(1): e0170237.
32. Fernandopulle S, Perry M, Manlapaz D, Jayakaran P. Effect of land-based generic physical activity interventions on pain, physical function, and physical performance in hip and knee osteoarthritis: a systematic review and meta-analysis. *Am J Phys Med Rehabil*. 2017;96(11):773–92.
33. Bartholdy C, Juhl C, Christensen R, Lund H, Zhang W, Henriksen M. The role of muscle strengthening in exercise therapy for knee osteoarthritis: a systematic review and meta-regression analysis of randomized trials. *Semin Arthritis Rheum*. 2017;47(1):9–21.
34. Young JL, Rhon DI, Cleland JA, Snodgrass SJ. The influence of exercise dosing on outcomes in patients with knee disorders: a systematic review. *J Orthop Sports Phys Ther*. 2018;48(3): 146–61.
35. Johnson BT, MacDonald HV, Bruneau ML Jr, et al. Methodological quality of meta-analyses on the blood pressure response to exercise: a review. *J Hypertens*. 2014;32(4):706–23.
36. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol*. 2007;7:10.
37. US Department of Agriculture (USDA). 2015 Dietary Guidelines Advisory Committee (DGAC) nutrition evidence library methodology. 2017. Available from: https://www.cnpp.usda.gov/sites/default/files/usda_nutrition_evidence_flbrary/2015DGAC-SR-Methods.pdf.
38. Guidelines SRotD, Advisory Committee. Table C.2, NEL grading rubric. 2015. Available from: https://health.gov/dietaryguidelines/2015-scientific-report/05-methodology.asp.
39. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc*. 2011; 43(7):1334–59.
40. Dunlop D, Song J, Lee J, et al. Physical activity minimum threshold predicting improved function in adults with lower-extremity symptoms. *Arthritis Care Res*. 2017;69(4):475–83.
41. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. *Med Sci Sports Exerc*. 2008;40(1):181–8.
42. Deveza LA, Melo L, Yamato TP, Mills K, Ravi V, Hunter DJ. Knee osteoarthritis phenotypes and their relevance for outcomes: a systematic review. *Osteo & Cartilage*. 2017;25(12):1926–41.
43. Quicke JG, Foster NE, Thomas MJ, et al. Is long-term physical activity safe for older adults with knee pain? A systematic review. *Osteoarthr Cartil*. 2015;23(9):1445–56.
44. Dore D, Winzenberg T, Ding C, et al. The association between objectively measured physical activity and knee structural change using MRI. *Ann Rheum Dis*. 2013;72(7):1170–5.
45. Felson D, Niu J, Yang T, et al. Physical activity, alignment and knee osteoarthritis: data from MOST and the OAI. *Osteoarthr Cartil*. 2013;21(6):789–95.
46. Oiestad B, Banion MK, Quinn E, et al. No association between daily walking and knee structural changes in people at risk of or with mild knee osteoarthritis. Prospective data from the multicenter osteoarthritis study. *J Rheumatol*. 2015;42(9):1685–93.
47. Kwee R, Wirth W, Hafezi-Nejad N, Zikria B, Guermazi A, Demehri S. Role of physical activity in cartilage damage progression of subjects with baseline full-thickness cartilage defects in medial tibiofemoral compartment: data from the osteoarthritis initiative. *Osteoarthr Cartil*. 2016;24(11):1898–904.
48. Lin W, Alizai H, Joseph G, et al. Physical activity in relation to knee cartilage T2 progression measured with 3 T MRI over a period of 4 years: data from the osteoarthritis initiative. *Osteoarthr Cartil*. 2013;21(10):1558–66.
49. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. *Ann Rheum Dis*. 1957;16(4):494–502.
50. Kendzerska T, King L, Lipscombe L, Croxford R, Stanaitis I, Hawker G. The impact of hip and knee osteoarthritis on the subsequent risk of incident diabetes: a population-based cohort study. *Diabetologia*. 2018;61:2290–9.
51. Rejeski W, Brawley L, Ettinger W, Morgan T, Thompson C. Compliance to exercise therapy in older participants with knee osteoarthritis: implications for treating disability. *Med Sci Sports Exerc*. 1997;29(8): 977–85.
52. Bricca A, Juhl CB, Grodzinsky AJ, Roos EM. Impact of a daily exercise dose on knee joint cartilage—a systematic review and

meta-analysis of randomized controlled trials in healthy animals. *Osteoarthr Cartil*. 2017;25(8):1223–37.
53. Tudor-Locke C, Bassett DR Jr. How many steps/day are enough? Preliminary pedometer indices for public health. *Sports Med*. 2004;34(1):1–8.
54. Tudor-Locke C, Craig CL, Aoyagi Y, et al. How many steps/day are enough? For older adults and special populations. *Int J Behav Nutr Phys Act*. 2011;8:80.
55. Saint-Maurice PF, Troiano RP, Matthews CE, Kraus WE. Moderate-to-vigorous physical activity and all-cause mortality: do bouts matter? *J Am Heart Assoc*. 2018;7(6).
56. Saint-Maurice PF, Troiano RP, Berrigan D, Kraus WE, Matthews CE. Volume of light versus moderate-to-vigorous physical activity: similar benefits for all-cause mortality? *J Am Heart Assoc*. 2018;7(7).
57. Bricca A, Struglics A, Larsson S, Steultjens M, Juhl CB, Roos EM. Impact of exercise therapy on molecular biomarkers related to cartilage and inflammation in people at risk of, or with established, knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Arthritis Care Res*. 2018. [Epub ahead of print]. doi:10.1002/acr.23786.