Table 1. Comparison of published randomized control trial and the OAI target trial.

Characteristic	Sanghi et al	McAlindon et al	Arden et al	Jin et al	OAI target trial
Country	India	United States	United Kingdom	Australia	United States
Key eligibility criteria	**Inclusion:** • Age ≥ 40 years. • ACR criteria for KOA. • Knee pain for 6 months with WOMAC pain score > 4 out of 20. • Conventional treatment for OA for at least 6 months. **Exclusion:** • BMI < 30 kg/m2 • Previous fracture or surgeries on knee • Secondary OA. • Chronic disease including asthma, obstructive pulmonary disease, renal failure, and malignancy.	**Inclusion:** • Age ≥ 45 years. • ACR criteria for symptomatic KOA. • Mild pain on one of the weight-bearing questions of WOMAC. • Knee pain/discomfort confirmed by physical exam. **Exclusion:** • Daily supplemental vitamin D > 800 IU. • Serum calcium > 10.5 mg/dL. • Hypercalciuria. • Supplements on cartilage (e.g., glucosamine). • Oral corticosteroid use. • Inflammatory joint disease and comorbidities that precluded MRI.	**Inclusion:** • Age > 50 years. • Radiographic KOA. • Knee pain for most days of the previous month. **Exclusion:** • Secondary OA. • Inflammatory arthritis. • Early morning knee stiffness > 30 minutes • Cod liver oil or vitamin D supplement containing Vit D > 200 IU. • Glucosamine or chondroitin use for < 3 months. • Osteoporotic fracture. • Previous knee surgery or arthroscopy within 6 months. • Use of bisphosphonates within 2 years.	**Inclusion:** • Age 50 to 79 years. • ACR criteria for symptomatic KOA. • Knee pain for at least 6 months with VAS 20-80 mm on a 100 mm scale. • ACR function class I, II and III. • Serum 25(OH)D 12.5 – 60 nmol/L. **Exclusion:** • Severe radiographic KOA • Rheumatoid or psoriatic arthritis, lupus, or cancer. • Contra-indication to having MRI. • vitamin D supplement within the last 30 days. • Conditions affecting oral absorption of vitamin D.	**Inclusion:** • Age 45 to 79 years • Symptomatic KOA defined as: ○ KL grade ≥ 2. ○ Knee pain on most days for at least one month within the past year. **Exclusion:** • KL grade 4. • Used prescription vitamin D in the previous 30 days. • Rheumatoid arthritis or inflammatory arthritis. • Cancer or other malignancy.
Treatment strategy	**Intervention:** Daily 60,000 IU for 10 days then monthly 60,000 IU for 12 months. **Control:** Placebo capsule at the same regime	**Intervention:** Daily 2000 IU of oral vitamin D_3 **Control:** Identical placebo capsule.	**Intervention:** Daily 800 IU of oral vitamin D_3 **Control:** Matched placebo.	**Intervention:** Monthly 50,000 IU of oral vitamin D_3 capsule. **Control:** Identical inert placebo.	**Exposure:** Daily 1,000 IU vitamin D^*, at least 4 days a week. **Control:** No use of vitamin D in the past 30 days
Assignment procedures	Simple randomization at 1:1 ratio	Block randomization stratified by KL grades	Simple randomization at 1:1 ratio stratified by site	Simple randomization at 1:1 ratio stratified by site	Propensity score matching with exact match in age, sex, race, BMI, KL grade, smoking status, pain medication use status.
Follow-up period	1 year	2 years	3 years	2 years	2 years
Outcomes	**Primary outcomes:** Knee pain and function **Secondary outcomes:** Serum calcium, phosphorus, alkaline phosphatase, and 25(OH)D.	**Primary outcomes:** • WOMAC pain • Cartilage volume loss **Secondary outcomes:** • Global physical function. • WOMAC function. • Cartilage thickness. • Bone marrow lesion and radiographic JSW.	**Primary outcome:** Joint space narrowing at medial compartment. **Secondary outcomes:** • Joint space narrowing at lateral compartment. • KL grade. • WOMAC VAS score. • Get up and Go test.	**Primary outcomes:** • Tibial cartilage volume • WOMAC pain **Secondary outcomes:** • WOMAC function • Cartilage defects • Bone marrow lesions • Effusion synovitis	**Primary outcome:** WOMAC pain **Secondary outcomes:** • WOMAC function • Quantitative JSW
Causal contrast of interest	Intention-to-treat.	Intention-to-treat	Intention-to-treat	Intention-to-treat.	Intention-to-treat.
Analysis plan	Student's t-test.	Linear mixed model.	Linear mixed model.	linear mixed model.	linear mixed model with inverse propensity score weighting.

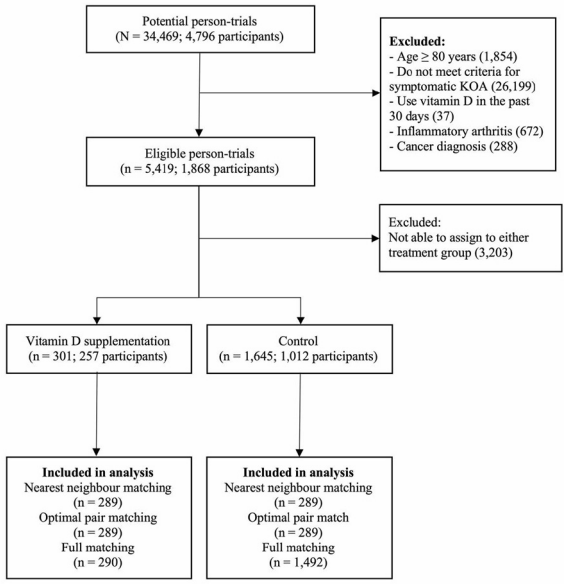
OA, osteoarthritis; KOA, knee osteoarthritis; BMI, body mass index; 25(OH)D, 25-hydroxycholecalciferol; IU, international unit.
ACR, American College of Rheumatology; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; KL, Kallgren-Lawrence Classification System of Osteoarthritis.
*Australian Therapeutic Guidelines recommend 1000-2000 IU/day for people with mild vitamin D deficiency (30-40 nmol/L).

Table 2. Comparison of results between OAI target trial and published RCTs

Study	Vitamin D		Control		Between-group difference
	n	Mean [95%CI]	n	Mean [95%CI]	SMD [95% CI]
WOMAC pain					
Published RCTs					
Jin 2016	209	-9.9 [-12.4, -4.5]	204	-7.0 [-9.6, -4.5]	-0.16 [-0.35, 0.03]
McAlindon 2013	73	-11.6 [-16.2, -3.0]	73	-7.3 [-11.7, -3.0]	-0.23 [-0.55, 0.10]
Arden 2016	236	-0.1 [-1.2, 1.0]	232	0.7 [-0.4, 1.8]	-0.09 [-0.28, 0.09]
Sanghi 2013	52	-2.8 [-0.4, 7.4]	51	5.8 [4.1, 7.4]	-0.39 [-0.78, 0.00]
OAI target trial					
Optimal matching	289	-3.1 [-5.0, -1.1]	289	-0.8 [-2.8, 1.1]	-0.13 [-0.30, 0.03]
Nearest neighbour matching	289	-3.1 [-5.0, -1.1]	289	-1.3 [-3.2, 0.6]	-0.10 [-0.27, 0.06]
Full matching	290	-3.1 [-5.1, -1.0]	1,492	-4.7 [-5.6, -3.7]	0.09 [-0.04, 0.23]
WOMAC function					
Published RCTs					
Jin 2016	209	-10.0 [-12.2, -3.5]	204	-5.7 [-8.0, -3.5]	-0.26 [-0.46, -0.07]
McAlindon 2013	73	-10.2 [-14.3, -2.5]	73	-5.6 [-8.8, -2.5]	-0.30 [-0.62, 0.03]
Arden 2016	236	0.4 [-0.6, 1.4]	232	1.1 [0.0, 2.1]	-0.08 [-0.26, 0.10]
Sanghi 2013	52	-2.0 [-2.8, 2.1]	51	1.0 [-0.0, 2.1]	-0.92 [-1.32, -0.51]
OAI target trial					
Optimal matching	289	-9.0 [-15.0, -3.0]	289	-1.7 [-7.5, 4.1]	-0.13 [-0.28, 0.02]
Nearest neighbour matching	289	-9.1 [-15.1, -3.1]	289	-1.8 [-7.6, 3.9]	-0.13 [-0.28, 0.02]
Full matching	290	-9.0 [-14.9, -3.2]	1,492	-13.1 [-15.9, -10.2]	0.07 [-0.05, 0.19]
Joint space width					
Published RCTs					
McAlindon 2013	73	-0.3 [-0.5, -0.0]	73	-0.2 [-0.4, -0.0]	-0.15 [-0.47, 0.18]
Arden 2016	236	0.0 [-0.2, 0.1]	232	-0.1 [-0.2, 0.1]	0.07 [-0.11, 0.25]
OAI target trial					
Optimal matching	289	-1.5 [-2.6, -0.5]	289	-1.0 [-1.5, -0.5]	-0.08 [-0.26, 0.11]
Nearest neighbour matching	289	-1.5 [-2.6, -0.4]	289	-1.0 [-1.5, -0.5]	-0.08 [-0.28, 0.11]
Full matching	290	-1.5 [-2.9, -0.2]	1,492	-1.4 [-1.7, -1.2]	-0.01 [-0.23, 0.21]

WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; RCTs, randomized controlled trials; CI, confidence intervals; SMD, standard mean difference.
WOMAC scores presented in table are normalized to a scale of 0-100 to allow comparison across studies.

Figure 1. Flowchart of person-trials in the OAI target trial.



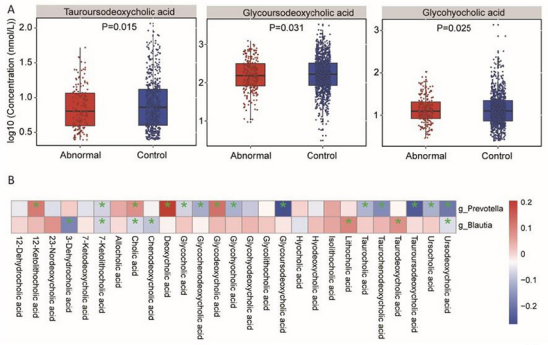
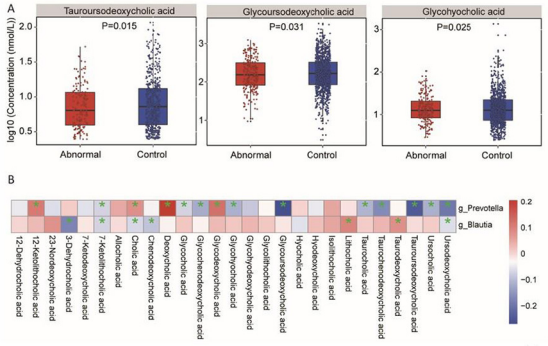


Figure 2 Profiling of the plasma bile acids and correlations of microbiota with the levels of plasma bile acids. (A) Differentiated plasma bile acids between participants with hand synovial abnormality and control group after adjusting for age, sex and body mass index. (B) Correlations of significantly altered microbiota genera with the levels of plasma bile acids, as determined by Spearman's rank test (* P<0.05).



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EFFECTIVENESS OF VITAMIN D SUPPLEMENTATION ON KNEE

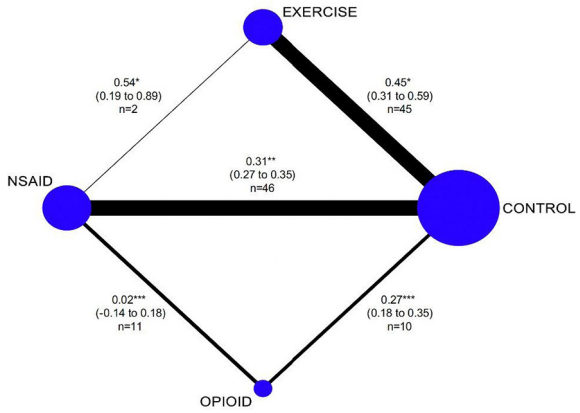

Figure 1 Osteoarthritis and Cartilage

Graphic presentation of comparisons between control interventions (placebo or control), exercise therapy, NSAIDs and opioids with standardized mean differences (SMD), 95% confidence intervals and number of trials (n). No estimate available for exercise therapy vs opioids. *=favour exercise therapy, **=favour NSAIDs, ***=favour opioids.

OSTEOARTHRITIS - A TARGET TRIAL EMULATION STUDY USING DATA FROM THE OSTEOARTHRITIS INITIATIVE COHORT

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Purpose: Previous observational studies suggested an inverse relationship between serum vitamin D level and symptoms in knee osteoarthritis (KOA). However, randomized controlled trials (RCTs) to date investigating the efficacy of vitamin D supplementation in knee OA have reported conflicting results. Target trial emulation is a research method that incorporates idealized RCT design to improve the quality and interpretability of observational research. This study aims to assess the effectiveness of vitamin D supplementation in patients with KOA and to test whether the treatment effect estimates from four previous RCTs can be replicated.
Methods: This study utilized a target trial emulation framework and used 11-year data from the Osteoarthritis Initiative (OAI) - a longitudinal cohort of people who had or were at risk for symptomatic KOA. Participants that were 45 years or older, had symptomatic KOA and did not take vitamin D supplementation in the past 30 days were eligible to be included in the target trial at baseline. Symptomatic KOA was defined as having knee pain on most days for at least one month within the past year and showing Kellgren-Lawrence (KL) grade 2 or above on plain knee radiograph. Participants were excluded if they had severe KOA (defined by KL grade 4), inflammatory arthritis or active diagnosis of cancer. Participants were allocated to the vitamin D group if they reported taking 1,000 IU per day for at least 4 days a week in the past 30 days at the first follow-up visit after they were included at the target trial at baseline. Participants were allocated to the control group if they indicated no use of vitamin D in the past 30 days. Propensity score matching (PSM) using optimal matching method was performed to address imbalance in observed confounders between the two groups. Sex, race, body mass index (BMI) category, KL grade, use of pain medication and smoking status were matched in exact balance between the two groups. Other match covariates included age, Charlson comorbidity index, glucosamine use, chondroitin use, depression score and physical activity.
The primary outcomes were the mean difference in change of knee pain after two years measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) on a scale of 0-100. Secondary outcomes were WOMAC physical function and quantitative measure of joint space width (JSW) on radiograph. Linear mixed modelling was used to analyze the marginal mean differences in the outcomes between the vitamin D group and the control group. Standardized mean difference (SMD) was calculated as a measure of effect size to compare the findings with those reported in published RCTs. Sensitivity analyses were conducted to compare the treatment effect resulting from using different PSM methods, including nearest neighbour matching and full matching.
Results: Figure 1 shows the flow of study participants. A total of 1,946 participant-trials (1,189 participants) were eligible for the analysis, with 301 receiving vitamin D supplementation and 1,645 not receiving vitamin D (control group). Participant characteristics that were associated with KOA were balanced after PSM. A total of 289 participant-trials in the vitamin D group were pair-matched at a 1:1 ratio by nearest neighbour method and optimal matching method. For full matching, 290 participant-trials in the vitamin D group were matched to 1,492 participant-trials in the control group. Compared to the control group, vitamin D supplementation did not reach statistically significant difference (Table 2) in change of WOMAC pain (SMD = -0.13, 95%CI [-0.30, 0.03]), physical function (SMD = -0.13, 95%CI [-0.28, 0.02]) and radiographic JSW (SMD = -0.08, 95%CI [-0.26, 0.11]). The SMDs from the OAI target trial were consistent with the effect sizes previously reported in the four published RCTs. Sensitivity analysis comparing different PSM methods showed similar results.
Conclusions: Applying target trial emulation to OAI cohort in this study resulted in results close to those published in RCTs. These findings support future use of target trial emulation when evaluating other systemic therapies for KOA.

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COMPARISON OF EXERCISE THERAPY, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS, AND OPIOIDS FOR KNEE OSTEOARTHRITIS PAIN: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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Purpose: Exercise therapy, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are all treatments commonly used to address knee osteoarthritis (OA) pain, but the comparative effectiveness of these interventions are not well studied. The clinical value of comparing effects across interventions obtained from randomized trials in pairwise meta-analysis is limited, when no direct statistical comparison can be made between all relevant interventions. To provide valid estimates on the comparative effectiveness of opioids, NSAIDs and exercise therapy for knee OA pain, we performed a systematic review and network meta-analysis.
Methods: We searched Medline, EMBASE, and CENTRAL from inception to April 15th 2021 for randomized controlled trials comparing exercise therapy, NSAIDs, and opioids in any combination for knee OA pain. The study was pre-registered in PROSPERO (CRD42018106484). Study screening, data extraction and risk of bias assessment (using the Cochrane Collaborations risk of bias tool) was performed by two authors independently. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach adjusted for network meta-analysis framework to assess the overall quality of the evidence. We applied a meta-analysis to combine the results from