Can/should we complement animal models with advanced in vitro and in silico models, including organ-on-chip approaches and AI-driven models?

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Response/Recommendation: Advanced in vitro and in silico models, including organs-on-chips and AI-driven approaches, can effectively complement animal models to mechanistically model some cellular and molecular aspects of obesity-associated osteoarthritis (OA). However, despite the limitations of animal models, they cannot be replaced by advanced in vitro or in silico systems. Animal models remain indispensable for validating systemic responses, assessing the efficacy and safety of novel interventions, and conducting OA pain research. An integrated research strategy that incorporates all these models can optimize research efficiency and ensure clinical relevance.

Level of Evidence: Moderate; **Delegate Vote:** Agree: ___%, Disagree: ___%, Abstain: ___%

Rationale: Obesity-associated OA is a complex joint disease influenced by systemic metabolic inflammation and overweight-related mechanical stress [1]. Its pathogenesis involves chronic low-grade inflammation and adipokine dysregulation, which exacerbate joint damage beyond mechanical load alone [2, 3]. Animal models of this disease can be classified into: (1) diet-induced obesity (DIO) models without intentional joint injury [4-13], (2) DIO combined with classic surgical post-traumatic OA models [14-21], (3) DIO combined with mild focal cartilage injury models [21-24], (4) obesogenic diet-superimposed spontaneous or age-related OA models [25-27], (5) adipose-centric genetic/metabolic models [28-34], and (6) controlled mechanical overloading after DIO or in genetically obese mice [35, 36]. Primary species include mice [4, 5, 10-15, 17, 19, 25, 29-34, 37, 38], rats [6-9, 18, 21-24], guinea pigs [27], and rabbits [39, 40]. These models recapitulate systemic physiology and long-term pathology in obesity-associated OA, but face inherent translational limitations: interspecies genetic discrepancies, complex intercellular crosstalk within multi-tissue joints, limited scalability for drug screening and personalized medicine, and the inability to mimic human individual variability [41][42][43]. Ethical imperatives (3Rs: Replacement, Reduction, and Refinement) [44], along with high costs and long study durations, further constrain their utility [45]. Advanced in vitro models and in silico tools offer human-relevant platforms to dissect mechanisms, enable high-throughput screening, and support personalized medicine, mitigating some translational bottlenecks of animal models.

1. Conventional Co-Culture & Conditioned Medium Models

Conventional in vitro approaches model tissue crosstalk via co-culture or conditioned medium. Direct-contact co-culture of infrapatellar fat pad (IPFP) with cartilage recapitulates native proximity and metabolic reciprocity (e.g., IPFP-stimulated proteoglycan synthesis) but hinders isolation of soluble mediator effects [46]. Transwell-type co-culture separates tissues while allowing diffusion, clarifying paracrine roles of IPFP-derived cytokines, adipokines, and MMPs [47]. IPFP-conditioned medium applied to cartilage cultures defines effects of IPFP-secreted factors [48]. These models are low-cost, standardized, compatible with high-throughput analyses, and enable precise variable control, but lack systemic context, multi-tissue biomechanics, and native tissue architecture/function, limiting translational relevance.

2. Organ-on-a-Chip & Organoid Systems

Organ-on-a-chip (OoC) platforms typically use microfluidics to culture cells in controlled 3D microenvironments with precise spatiotemporal biochemical and biomechanical cues [49]. A human "miniJoint" system integrating osteochondral, synovial-like fibrous, and adipose tissues recapitulates IL-1β-mediated inflammation and crosstalk and support drug evaluation [50]. These systems address species differences and the low throughput of in vivo studies, capture human OA pathophysiology, resolve inter-tissue crosstalk, shorten cycles, and enable high-throughput analyses. Integrating "miniJoint" concepts with advanced multi-cellular white adipose tissue-on-a-chip modules [51, 52] could s capture regional and systemic obesity-related OA phenotypes, accounting for diverse adipose secretory profiles [53], longitudinal changes, and comorbidity contexts [54].

Organoids, self-organized 3D constructs typically derived from human stem cells, recapitulate cellular diversity and core tissue functions [55]. OA cartilage organoids exposed to inflammatory cytokines reproduce chondrocyte hypertrophy, matrix mineralization, and catabolic enzyme overexpression consistent with human OA [56]. Scaffold-free adipose organoids model adipocyte hypertrophy and lipolysis dysfunction under obesogenic conditions [57]. Together, human OoC and organoid models reduce species differences, better reflect human tissue function, support scalable mechanistic studies, and allow flexible human cell/tissue combinations versus in vivo approaches.

3. In Silico & AI-driven Models

In silico models, including physiologically based pharmacokinetic (PBPK) approaches, integrated with multi-organ chip (MOC) and body-on-a-chip (BOC) data [58], predict human-relevant drug metabolism, efficacy, and toxicity, reducing reliance on animal testing. MOCs recapitulate inter-organ crosstalk via simulated vascular perfusion [59, 60], quantitatively predict human drug responses and metabolic disruptions, and overcome interspecies differences. For example, an MOC with hepatocytes, adipose tissue, and endothelial cells sustained glucose and fatty acid homeostasis, simulating obesity-related perturbations and drug responses [61]. A five-variable mathematical model centered on adipokines linked obesity to OA inflammatory dynamics, incorporating pro- and anti-inflammatory cytokines, MMPs, adipokines, and fibronectin fragments to quantify obesity-mediated OA inflammatory risk [62]. MOC/BOC complexity is rapidly advancing, with pharmacological models incorporating up to 10 and 18 organs, respectively [63].

AI can optimize in vitro model design, predict disease progression, and integrate multi-omics and clinical data for patient stratification. Algorithms process high-dimensional organoid/OoC data (imaging, biosensors, molecular profiles); convolutional neural networks track drug responses and detecting abnormalities; and generative AI assesses physiological relevance and enables automated high-throughput screening, accelerating compound testing and drug development [64].

Conclusions

Conventional in vitro models are cost-effective for early mechanistic studies in obesity-associated OA but lack systemic, biomechanical, and multi-tissue fidelity. OoC and organoid systems address gaps, and in silico PBPK models calibrated with chip data further reduce reliance on animal testing for drug evaluation. Integrated with computational approaches, these non-animal methods complement animal models by partially mitigating translational limits. Animal models remain essential to validate systemic responses, long-term progression, and organism-level efficacy and safety. Combining high-throughput in vitro, in silico, and AI tools with targeted animal studies optimizes efficiency and clinical relevance in preclinical research on obesity-associated OA.

Supplementary Materials

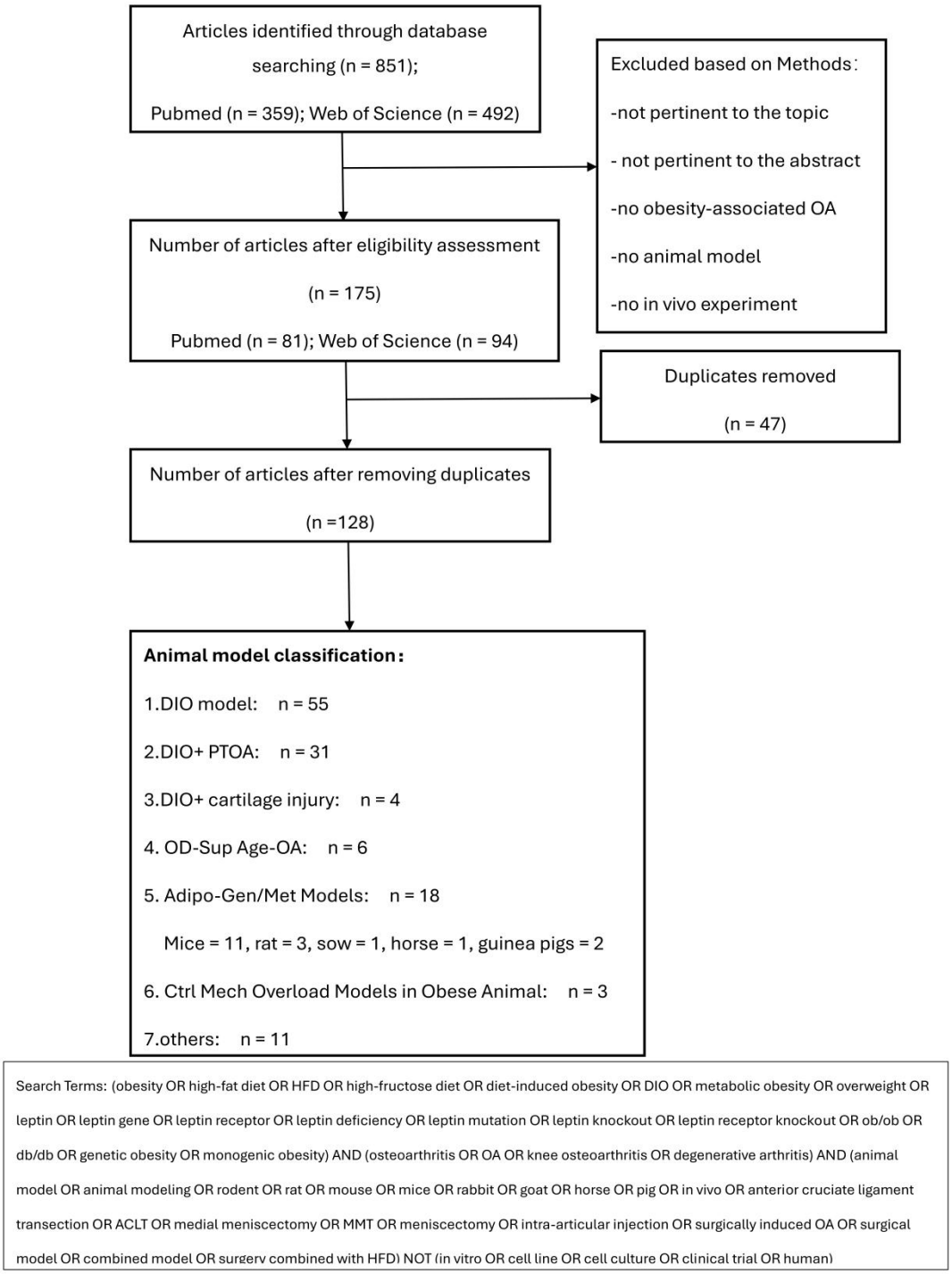

Figure S1 Flow diagram illustrating the identification, screening, eligibility assessment, and inclusion of studies evaluating obesity-associated OA animal models. A total of 851 records were identified across PubMed and Web of Science. After exclusion of irrelevant studies and removal of 47 duplicates, 128 studies met inclusion criteria and were classified into seven types of obesity-associated OA animal models.

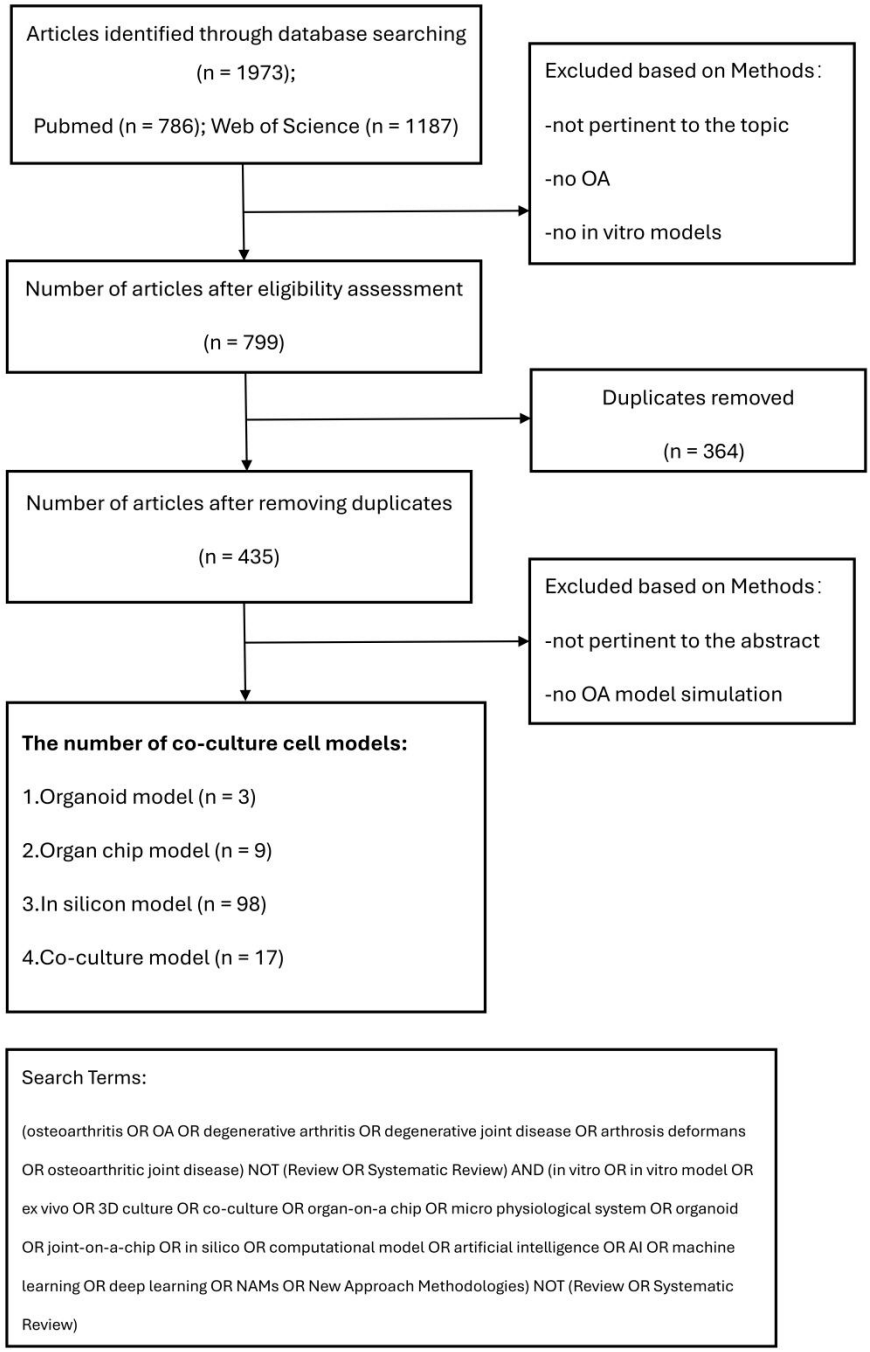

Figure S2 Flow diagram illustrating the identification, screening, eligibility assessment, and inclusion of studies evaluating in vitro and in silico models of OA. A total of 1973 records were identified across PubMed and Web of Science. After exclusion of irrelevant studies and removal of 364 duplicates, 435 studies met inclusion criteria and were classified into four types of in vitro/in silico OA models.

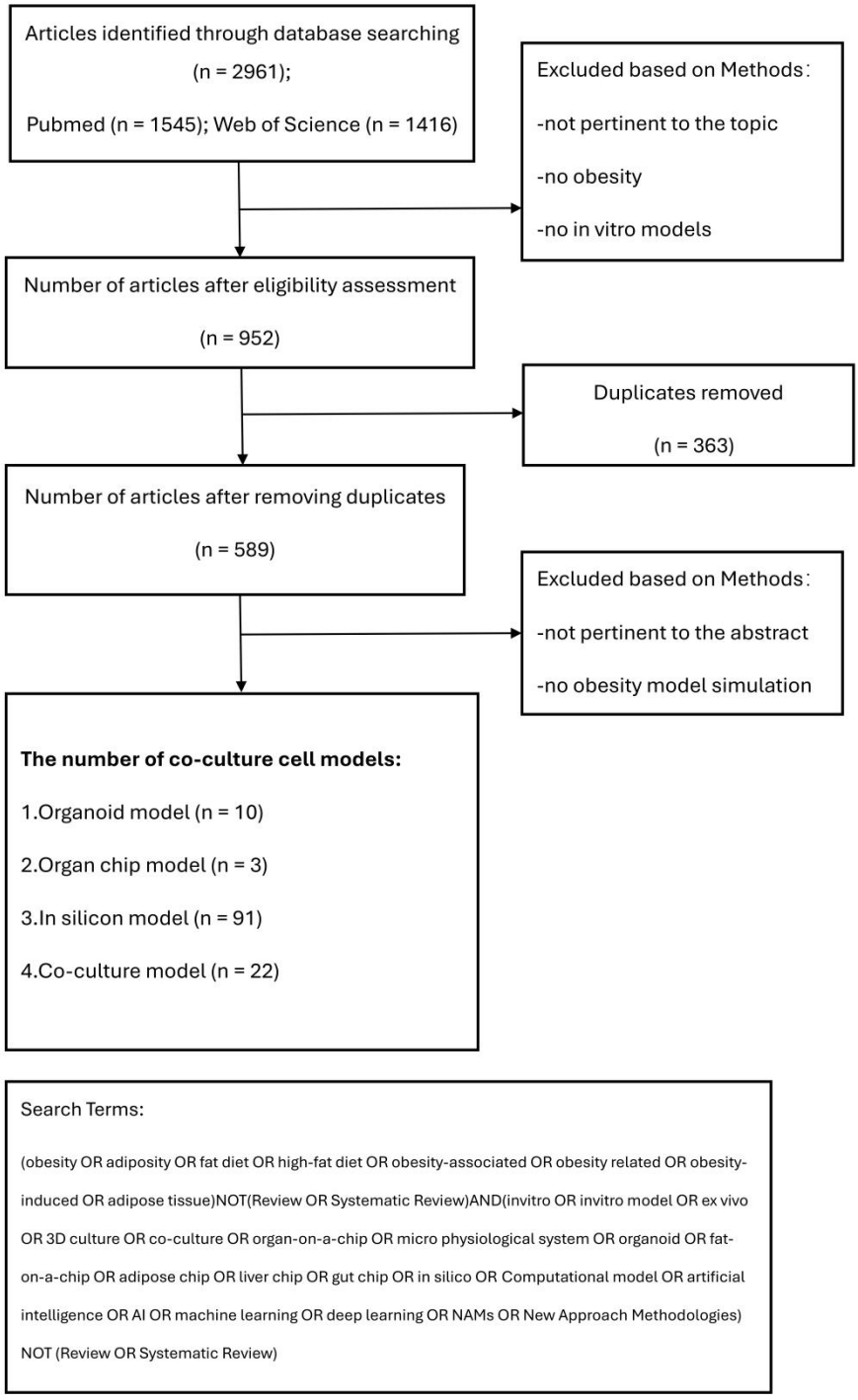

Figure S3 Flow diagram illustrating the identification, screening, eligibility assessment, and inclusion of studies evaluating in vitro models of obesity. A total of 2961 records were identified across PubMed and Web of Science. After exclusion of irrelevant studies and removal of 363 duplicates, 589 studies met inclusion criteria and were classified into four types of in vitro obesity models.

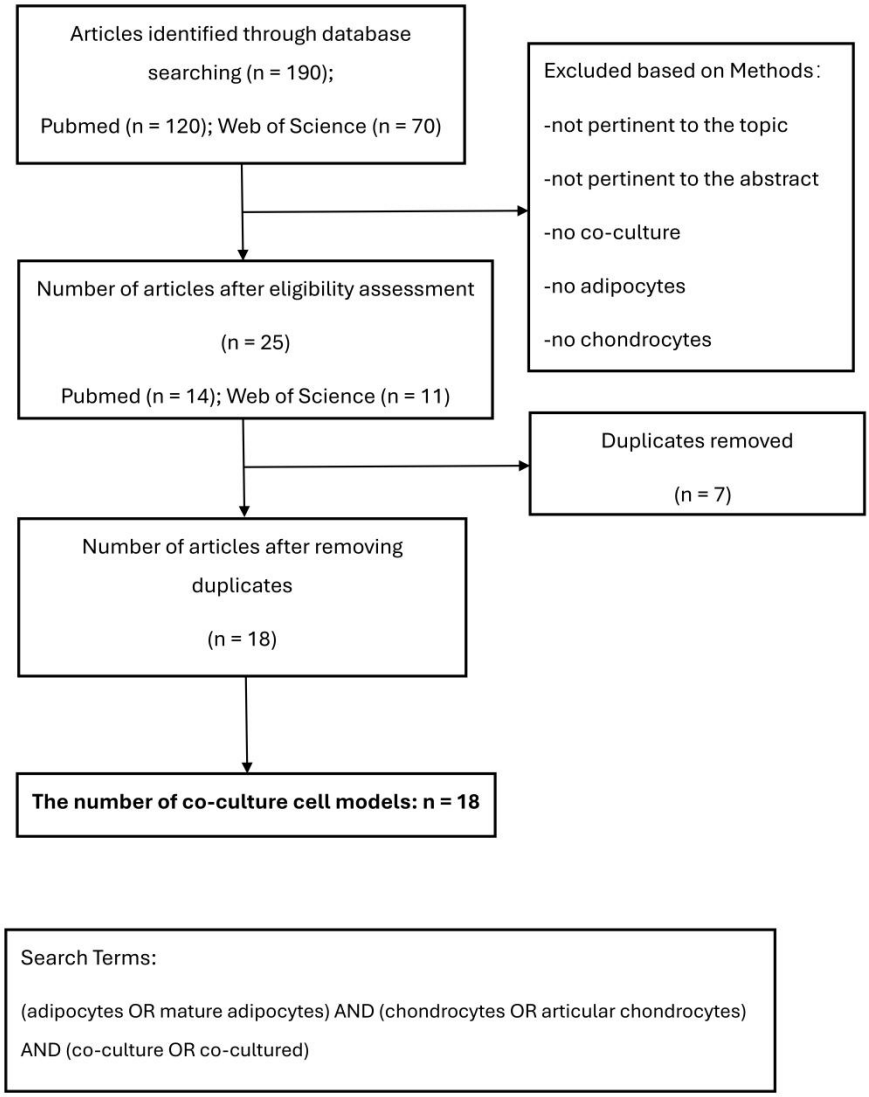

Figure S4 Flow diagram illustrating the identification, screening, eligibility assessment, and inclusion of studies evaluating adipocyte-chondrocyte co-culture models. A total of 190 records were identified across PubMed and Web of Science. After exclusion of irrelevant studies and removal of 7 duplicates, 18 studies met inclusion criteria and were included for analysis of co-culture cell models.

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