JOR Consensus Obesity and OA Q17: Can/should we determine whether obesity accelerates aging using OA as a model - structurally, molecularly, and functionally?

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Response/Recommendation: YES

Chronological age/aging and overweight/obesity are both well recognized risk factors for structural and symptomatic OA in humans and in rodents. Biological aging (measured by telomere shortening, DNA methylation, transcriptomic clocks, cell senescence, mitochondrial dysfunction, etc.) is also associated with worsening obesity and OA structural and symptomatic disease. Chronic low-grade inflammation is characteristic of both aging (inflammaging) and obesity (metabolic syndrome) and has direct impacts on structural and symptomatic OA onset and progression. Pre-clinical models commonly used to study the effects of chronological age on different diseases including OA are confounded by increasing adiposity and obesity in older/aged animals (particularly in rodents) that is both strain- and sex-dependent. Using pre-clinical models to explore the isolated effects on OA of chronological aging, biological aging and obesity (as well as the potential bi-directional effects of OA on obesity and biological aging) requires deliberate experimental planning and data interpretation. However, while the necessary methods, resources and pre-clinical models (including specific genetically modified mouse strains) to conduct such detailed studies are available, many gaps in knowledge persist. Importantly from a translational perspective, over two-thirds of individuals with OA have one or more additional chronic conditions, this co/multi-morbidity increases with age and obesity, and the concept of differential organ-aging is an emerging paradigm in human disease and global patient well-being. Research to define the mechanisms driving the interaction between OA and obesity, chronological aging, and systemic and joint-tissue biological aging is needed and will have high translational significance by increasing the likelihood of identifying and validating disease-modifying therapies for OA and its common co-morbid conditions.

Level of evidence for the response/recommendation: Strong that the question has translational relevance to the human/clinical condition (i.e. “we should”) **Moderate-Strong** that the tools and methods are available to address the question (i.e. “we can”).

Delegate Vote: Agree: Disagree: Abstain:

Rationale: ***Aging, obesity and OA risk - clinical evidence.*** The most consistently cited risk factors for OA, both structural and symptomatic disease, are aging (years lived), overweight and obesity (including measures such as increased body mass index (BMI), height-waist-ratio (HWR), adiposity, dyslipidemia), joint injury (both destabilizing and chronic repetitive loading), and female sex[1-18]. There are complex mediating and moderating inter-relationships between these (and other) OA risk factors, as well as specificity for which play greater or lesser roles in OA in particular joints (e.g. hip, knee, ankle). Critically, the precise mechano-biological mechanisms driving OA risk associated with the different risk factors, and the inter-relationships between these, remains incompletely defined necessitating ongoing research to identify potential diagnostic and therapeutic targets.

Chronological vs biological age/aging**.** While years-lived since birth (chronological age) is a readily defined variable, not all people show equivalent age-associated disease risk, trajectory or burden[19; 20]. The latter are features of “biological age/aging”, which encompasses a range of clinical, functional

and biological measures that may better predict individual ageing status and outcomes in longitudinal aging cohorts, including those related to chronic pain, musculoskeletal conditions and OA[5; 19-38]. Key processes associated with and used as measures and biomarkers of biological aging, include telomere shortening, DNA methylation, transcriptomic features, cell senescence and the senescence-associated secretory phenotype (SASP), disabled autophagy, and mitochondrial dysfunction[7; 19; 22-26; 28; 34; 38-73]. These biological-aging changes can be identified systemically (e.g. in circulating leukocytes) and in organ-specific cells, with disparity between biological-age in different organs and tissues, including those of the musculoskeletal system, increasingly recognized as part of variable human age-associated morbidity and mortality[74; 75]. The role and importance of the different systemic and joint-tissue/cell (e.g. chondrocyte, osteoblast, synovial fibroblast) biological aging processes in the incidence and progression of OA structural and symptomatic disease, remains an area of controversy and active clinical research[9; 22; 23; 30; 37; 38; 46; 51; 52; 55; 76]. Importantly, there is evidence of a bi-directional relationship between obesity and biological aging in different cells and organs[5; 77]. While the mechanisms driving the obesity/aging interaction remain to be fully elucidated, the systemic and local chronic low-grade inflammation associated with both conditions is implicated, and is also associated with OA structural and symptomatic disease pathophysiology and risk[62; 69; 77-84].

Aging, obesity, OA and multi-morbidity. There is an enormous volume of epidemiological data from populations in many countries, on the number of people living with 2 or more chronic health conditions.[8; 36; 85-135]. The prevalence of this co- or multi-morbidity increases with both age and obesity. OA is highly associated with numerous co-morbid conditions with over two thirds of individuals having one or more additional health problems. The significant co-morbid disease associations are seen both before and after OA diagnosis suggesting bi-directional interaction. The pathobiological mechanisms driving OA co-morbid disease association and any modifying effects of age and obesity have not been determined. Further, OA therapies may be less or more effective in patients with multi-morbidity, and testing new interventions in settings where aging, obesity, OA and co-morbid conditions intersect, is critical to define efficacy in real-world patient populations.

Pre-clinical models. Many different animal models have been developed and used to study OA structural and symptomatic disease pathophysiology and treatment[136-142]. With the diversity of models has come recognition that different OA disease phenotypes can have distinct cellular and molecular mechanisms underpinning both structural and symptomatic disease[137-149]. In particular, there has been burgeoning comparison of spontaneous age-associated OA and surgically or mechanically induced post-traumatic OA, and both of these with and without diet induced obesity[136; 137; 142; 145; 147; 150-155]. These studies have provided novel insight into OA-associated modulation of different biological-aging processes including telomere shortening, mitochondrial dysfunction, cell senescence and inflammation, including SASP[25; 60; 64; 65; 156-164]. Chronological aging models of spontaneous OA, however, can be confounded by sex-dependent increasing dyslipidemia, adiposity and obesity in older/aged animals[165-170]. Further, both spontaneous and diet-induced obesity are strain- and sex-dependent and can be modified by factors such as age, previous pregnancy etc[151; 153; 169; 171-175]. While reflecting age-associated co-morbidity and biological aging changes in people[75; 176; 177], this limits dissection of the specific effects and bi-directional interactions of age, obesity and OA. However, there are implementable experimental methods/protocols (e.g. caloric restriction, appetite modifying drugs[172; 178; 179]), and mouse strains with modified aging and adiposity (e.g. lipodystrophic (LD) mice[180; 181], senescence accelerated & resistant (SAM/SAMPR) mice[182-186], and others[159; 167; 184; 187-189]) that can enable the individual effects of age and obesity and their bi-directional cross talk with OA to be investigated, the cellular and biological mechanisms defined, and new therapies tested in more clinically and heterogenous patient relevant setting.

Summary: Age and obesity are clinically relevant risk factors for OA, which in turn can modify biological-aging and drive co-morbid disease. Using appropriate pre-clinical models and designing studies to define distinct and shared mechanisms driving this common and costly disease interaction will advance understanding of the role of OA in obesity/aging and may ultimately lead to improved therapeutic discovery and development.

References cited

1. Dell'Isola A, Recenti F, Giardulli B, et al. 2025. Osteoarthritis year in review 2025: Epidemiology and therapy. Osteoarthritis Cartilage 33:1300-1306.
2. Duong V, Abdel Shaheed C, Ferreira ML, et al. 2025. Risk factors for the development of knee osteoarthritis across the lifespan: A systematic review and meta-analysis. Osteoarthritis Cartilage 33:1162-1179.
3. Eckstein F, Wirth W, Putz R. 2024. Sexual dimorphism in articular tissue anatomy - Key to understanding sex differences in osteoarthritis? Osteoarthritis Cartilage 32:1019-1031.
4. Hawker GA, King LK. 2022. The Burden of Osteoarthritis in Older Adults. Clin Geriatr Med 38:181-192.
5. He Q, Mei J, Xie C, et al. 2025. The Relationship Between Central Obesity and Osteoarthritis in US Adults: The Mediating Role of Biological Aging Acceleration. J Am Nutr Assoc 44:29-39.
6. Hernandez PA, Bradford JC, Brahmachary P, et al. 2024. Unraveling sex-specific risks of knee osteoarthritis before menopause: Do sex differences start early in life? Osteoarthritis Cartilage 32:1032-1044.
7. Lin C, Yang J, Su H, et al. 2025. The Bidirectional Role of Obesity and Aging in the Pathogenesis of Osteoarthritis: Molecular Mechanisms, Epigenetic Insights, and Therapeutic Implications. J Inflamm Res 18:12637-12676.
8. Losina E, Walensky RP, Reichmann WM, et al. 2011. Impact of obesity and knee osteoarthritis on morbidity and mortality in older Americans. Ann Intern Med 154:217-226.
9. Luo Q, Zhang S, Yang Q, et al. 2024. Causal factors for osteoarthritis risk revealed by mendelian randomization analysis. Aging clinical and experimental research 36:176.
10. Misra D, Fielding RA, Felson DT, et al. 2019. Risk of Knee Osteoarthritis With Obesity, Sarcopenic Obesity, and Sarcopenia. Arthritis & rheumatology (Hoboken, NJ) 71:232-237.
11. Niu J, Clancy M, Aliabadi P, et al. 2017. Metabolic Syndrome, Its Components, and Knee Osteoarthritis: The Framingham Osteoarthritis Study. Arthritis & rheumatology (Hoboken, NJ) 69:1194-1203.
12. Segal NA, Nilges JM, Oo WM. 2024. Sex differences in osteoarthritis prevalence, pain perception, physical function and therapeutics. Osteoarthritis Cartilage 32:1045-1053.
13. Strand MP, Neogi T, Niu J, et al. 2017. No association between metabolic syndrome and radiographic hand osteoarthritis: Data from the Framingham study. Arthritis Care Res (Hoboken).
14. Tang S, Zhang C, Oo WM, et al. 2025. Osteoarthritis. Nat Rev Dis Primers 11:10.
15. Wang Y, Tang X, Peng JR, et al. 2025. Global, regional, and national burden of osteoarthritis among middle-aged and older adults: estimates from the global burden of disease study 2021 and projections to 2050. Front Med (Lausanne) 12:1696929.
16. Witkam R, Gwinnutt JM, Selby DA, et al. 2022. Does body mass index mediate the relationship between socioeconomic position and incident osteoarthritis? Semin Arthritis Rheum 56:152063.
17. Yasuda E, Nakamura R, Matsugi R, et al. 2017. Association between the severity of symptomatic knee osteoarthritis and cumulative metabolic factors. Aging clinical and experimental research.
18. Salis Z, Gallego B, Nguyen TV, et al. 2023. Association of Decrease in Body Mass Index With Reduced Incidence and Progression of the Structural Defects of Knee Osteoarthritis: A Prospective Multi-Cohort Study. Arthritis & rheumatology (Hoboken, NJ) 75:533-543.
19. Johnson AA, Shokhirev MN. 2025. First-generation versus next-generation epigenetic aging clocks: Differences in performance and utility. Biogerontology 26:121.
20. Hamczyk MR, Nevado RM, Barettino A, et al. 2020. Biological Versus Chronological Aging: JACC Focus Seminar. J Am Coll Cardiol 75:919-930.
21. Arsenis NC, You T, Ogawa EF, et al. 2017. Physical activity and telomere length: Impact of aging and potential mechanisms of action. Oncotarget 8:45008-45019.

22. Bao C, Zhu W, Bao T, et al. 2025. The application of epigenetic clocks in degenerative musculoskeletal diseases: A systematic review. Osteoarthritis Cartilage 33:1052-1065.
23. Brawner CM, Sturdy C, Arbeeva L, et al. 2026. Borderline acceleration in blood epigenetic age of unclear biological importance in knee osteoarthritis progression: Specimens and data from the Osteoarthritis Initiative and Johnston County Osteoarthritis Project. Osteoarthritis Cartilage 34:372-379.
24. Diekman BO, Hsueh MF. 2025. Biomarkers of aging as it relates osteoarthritis: we can't improve what we can't measure. Connect Tissue Res 66:352-358.
25. Diekman BO, Loeser RF. 2024. Aging and the emerging role of cellular senescence in osteoarthritis. Osteoarthritis Cartilage 32:365-371.
26. Ferrucci L, Gonzalez-Freire M, Fabbri E, et al. 2020. Measuring biological aging in humans: A quest. Aging cell 19:e13080.
27. Fuggle NR, Laskou F, Harvey NC, et al. 2022. A review of epigenetics and its association with ageing of muscle and bone. Maturitas 165:12-17.
28. Gems D, Carver A, Zhao Y. 2025. Aging as a multifactorial disorder with two stages. Aging 17:2989-3002.
29. Hassett AL, Epel E, Clauw DJ, et al. 2012. Pain is associated with short leukocyte telomere length in women with fibromyalgia. J Pain 13:959-969.
30. He Q, Luo H, Mei J, et al. 2024. The association between accelerated biological aging and the risk of osteoarthritis: a cross-sectional study. Front Public Health 12:1451737.
31. Jia L, Zhang W, Chen X. 2017. Common methods of biological age estimation. Clinical interventions in aging 12:759-772.
32. Kalson NS, Brock TM, Mangino M, et al. 2018. Reduced telomere length is associated with fibrotic joint disease suggesting that impaired telomere repair contributes to joint fibrosis. PLoS One 13:e0190120.
33. Rippberger PL, Emeny RT, Mackenzie TA, et al. 2018. The association of sarcopenia, telomere length, and mortality: data from the NHANES 1999-2002. European journal of clinical nutrition 72:255-263.
34. Sibille KT, Witek-Janusek L, Mathews HL, et al. 2012. Telomeres and epigenetics: potential relevance to chronic pain. Pain 153:1789-1793.
35. Steward AM, Morgan JD, Espinosa JP, et al. 2017. Chronic Pain and Telomere Length in Community-Dwelling Adults: Findings From the 1999 to 2002 National Health and Nutrition Examination Survey. J Pain 18:1517-1525.
36. Thompson MQ, Theou O, Yu S, et al. 2017. Frailty prevalence and factors associated with the Frailty Phenotype and Frailty Index: Findings from the North West Adelaide Health Study. Australasian journal on ageing.
37. Yagi M, Mizukoshi R, Maruiwa R, et al. 2025. Accelerated biological aging in patients with degenerative spine diseases: the impact of modifiable lifestyle factors on phenotypic age. Spine J 25:2369-2381.
38. Yau MS, Okoro PC, Haugen IK, et al. 2024. Assessing the association of epigenetic age acceleration with osteoarthritis in the Multicenter Osteoarthritis Study (MOST). Osteoarthritis Cartilage 32:585-591.
39. Aviv A, Shay JW. 2018. Reflections on telomere dynamics and ageing-related diseases in humans. Philosophical transactions of the Royal Society of London Series B, Biological sciences 373.
40. Benetos A, Toupance S, Gautier S, et al. 2018. Short Leukocyte Telomere Length Precedes Clinical Expression of Atherosclerosis: The Blood-and-Muscle Model. Circ Res 122:616-623.
41. Brown L, Zhang Y, Mitchel C, et al. 2018. Does Telomere Length Indicate Biological, Physical and Cognitive Health Among Older Adults? Evidence from the Health and Retirement Study. J Gerontol A Biol Sci Med Sci.
42. Epel ES, Prather AA. 2018. Stress, Telomeres, and Psychopathology: Toward a Deeper Understanding of a Triad of Early Aging. Annual review of clinical psychology.

43. Herrmann M, Pusceddu I, Marz W, et al. 2018. Telomere biology and age-related diseases. Clin Chem Lab Med.
44. Martin J, Buckwalter J. 2001. Telomere erosion and senescence in human articular cartilage chondrocytes. J Gerontol Biol Sci 56A:B172-B179.
45. Martin JA, Buckwalter JA. 2002. Aging, articular cartilage chondrocyte senescence and osteoarthritis. Biogerontology 3:257-264.
46. Martin JA, Buckwalter JA. 2003. The role of chondrocyte senescence in the pathogenesis of osteoarthritis and in limiting cartilage repair. J Bone Joint Surg Am 85-A Suppl 2:106-110.
47. McCulloch K, Litherland GJ, Rai TS. 2017. Cellular senescence in osteoarthritis pathology. Aging cell 16:210-218.
48. Ong SM, Hadadi E, Dang TM, et al. 2018. The pro-inflammatory phenotype of the human non-classical monocyte subset is attributed to senescence. Cell death & disease 9:266.
49. Osler M, Bendix L, Rask L, et al. 2016. Stressful life events and leucocyte telomere length: Do lifestyle factors, somatic and mental health, or low grade inflammation mediate this relationship? Results from a cohort of Danish men born in 1953. Brain, behavior, and immunity 58:248-253.
50. Rask L, Bendix L, Harbo M, et al. 2016. Cognitive Change during the Life Course and Leukocyte Telomere Length in Late Middle-Aged Men. Frontiers in aging neuroscience 8:300.
51. Sibille KT, Chen H, Bartley EJ, et al. 2017. Accelerated aging in adults with knee osteoarthritis pain: consideration for frequency, intensity, time, and total pain sites. Pain reports 2:e591.
52. Sibille KT, Langaee T, Burkley B, et al. 2012. Chronic pain, perceived stress, and cellular aging: an exploratory study. Mol Pain 8:12.
53. Strazhesko ID, Tkacheva ON, Akasheva DU, et al. 2017. Growth Hormone, Insulin-Like Growth Factor-1, Insulin Resistance, and Leukocyte Telomere Length as Determinants of Arterial Aging in Subjects Free of Cardiovascular Diseases. Frontiers in genetics 8:198.
54. Toh WS, Brittberg M, Farr J, et al. 2016. Cellular senescence in aging and osteoarthritis. Acta Orthop 87:6-14.
55. Vidal-Bralo L, Lopez-Golan Y, Mera-Varela A, et al. 2016. Specific premature epigenetic aging of cartilage in osteoarthritis. Aging 8:2222-2231.
56. Zgheib NK, Sleiman F, Nasreddine L, et al. 2018. Short Telomere Length is Associated with Aging, Central Obesity, Poor Sleep and Hypertension in Lebanese Individuals. Aging and disease 9:77-89.
57. McDonnell E, Orr SE, Barter MJ, et al. 2024. The methylomic landscape of human articular cartilage development contains epigenetic signatures of osteoarthritis risk. Am J Hum Genet 111:2756-2772.
58. Abbas M, Cruz CJ, Tamargo JA, et al. 2025. Exploring senescence markers as potential drivers of osteoarthritis pain in aging adults. Exp Gerontol 212:112950.
59. Childs BG, Gluscevic M, Baker DJ, et al. 2017. Senescent cells: an emerging target for diseases of ageing. Nat Rev Drug Discov 16:718-735.
60. Collins JA, Diekman BO, Loeser RF. 2018. Targeting aging for disease modification in osteoarthritis. Curr Opin Rheumatol 30:101-107.
61. Coryell PR, Diekman BO, Loeser RF. 2021. Mechanisms and therapeutic implications of cellular senescence in osteoarthritis. Nat Rev Rheumatol 17:47-57.
62. Freund A, Orjalo AV, Desprez PY, et al. 2010. Inflammatory networks during cellular senescence: causes and consequences. Trends Mol Med 16:238-246.
63. Kelly PN. 2017. Targeting senescence to combat osteoarthritis. Science 356:595-596.
64. Liu Y, Zhang Z, Li T, et al. 2022. Senescence in osteoarthritis: from mechanism to potential treatment. Arthritis Res Ther 24:174.
65. Loeser RF. 2013. Aging processes and the development of osteoarthritis. Curr Opin Rheumatol 25:108-113.
66. Su W, Liu G, Mohajer B, et al. 2022. Senescent preosteoclast secretome promotes metabolic syndrome associated osteoarthritis through cyclooxygenase 2. Elife 11.

67. Patusco R, Gyasi K, Kaufmann A. 2026. Exploring the nexus between inflammation and mobility through the lens of healthy aging: current scenario and future perspectives. Aging clinical and experimental research 38:60.
68. Prasoon P, Nguyen KL, Fathi PA, et al. 2026. Pathophysiological mechanisms linking osteoarthritis and neurodegenerative disease risk. Osteoarthritis Cartilage 34:193-212.
69. Ramos ELP, Sousa Neto IV, Pinto AP, et al. 2025. Mechanisms underlying the interplay between autophagy and the inflammasome in age-related diseases: Implications for exercise immunology. Ageing research reviews 110:102821.
70. Meyer DH, Schumacher B. 2021. BiT age: A transcriptome-based aging clock near the theoretical limit of accuracy. Aging cell 20:e13320.
71. Qi H, Zhao H, Li E, et al. 2025. DeepQA: A Unified Transcriptome-Based Aging Clock Using Deep Neural Networks. Aging cell 24:e14471.
72. Caramés B, Olmer M, Kiosses WB, et al. 2015. The relationship of autophagy defects to cartilage damage during joint aging in a mouse model. Arthritis & rheumatology (Hoboken, NJ) 67:1568-1576.
73. Lorenzo-Gómez I, Nogueira-Recalde U, García-Domínguez C, et al. 2023. Defective chaperone-mediated autophagy is a hallmark of joint disease in patients with knee osteoarthritis. Osteoarthritis Cartilage 31:919-933.
74. Salimi S, Raftery D, Ferrucci L. 2026. Genomic Perspective on Heterogeneity of Organs and Body Aging. Aging cell 25:e70353.
75. Salimi S, Vehtari A, Salive M, et al. 2025. Health octo tool matches personalized health with rate of aging. Nature communications 16:4007.
76. Henriques J, Berenbaum F, Mobasheri A. 2024. Obesity-induced fibrosis in osteoarthritis: Pathogenesis, consequences and novel therapeutic opportunities. Osteoarthr Cartil Open 6:100511.
77. Mustari MN, Massi MN, Usman MA, et al. 2023. Dynamic interaction of obesity, age, MCP-1 Level, and ACE-1 gene with the severity of knee osteoarthritis: a cross-sectional study. Ann Med Surg (Lond) 85:3845-3851.
78. Binvignat M, Sellam J, Berenbaum F, et al. 2024. The role of obesity and adipose tissue dysfunction in osteoarthritis pain. Nat Rev Rheumatol 20:565-584.
79. De Roover A, Escribano-Núñez A, Monteagudo S, et al. 2023. Fundamentals of osteoarthritis: Inflammatory mediators in osteoarthritis. Osteoarthritis Cartilage 31:1303-1311.
80. Goh IY, Ghosh U, Harasymowicz NS. 2025. Advancements in understanding the role of obesity in osteoarthritis. Connect Tissue Res 66:345-351.
81. Herrero-Beaumont G, Castro-Dominguez F, Migliore A, et al. 2024. Systemic osteoarthritis: the difficulty of categorically naming a continuous condition. Aging clinical and experimental research 36:45.
82. Shivappa N, Stubbs B, Hebert JR, et al. 2018. The Relationship Between the Dietary Inflammatory Index and Incident Frailty: A Longitudinal Cohort Study. Journal of the American Medical Directors Association 19:77-82.
83. Wallace IJ, Felson DT, Kraus VB, et al. 2026. Dampened inflammation and reduced risk of osteoarthritis among non-industrialized societies. Osteoarthritis Cartilage 34:18-27.
84. Wu Z, Li J, Li R, et al. 2026. Chronic Inflammation and Aging in Rheumatic Diseases. Aging and disease.
85. Buch A, Carmeli E, Boker LK, et al. 2016. Muscle function and fat content in relation to sarcopenia, obesity and frailty of old age--An overview. Exp Gerontol 76:25-32.
86. Duffield SJ, Ellis BM, Goodson N, et al. 2017. The contribution of musculoskeletal disorders in multimorbidity: Implications for practice and policy. Best Pract Res Clin Rheumatol 31:129-144.
87. Alonso Monteiro Bezerra M, Hellwig N, da Rocha Castelar Pinheiro G, et al. 2018. Prevalence of chronic musculoskeletal conditions and associated factors in Brazilian adults - National Health Survey. BMC public health 18:287.

88. Calderon-Larranaga A, Santoni G, Wang HX, et al. 2018. Rapidly developing multimorbidity and disability in older adults: does social background matter? Journal of internal medicine.
89. de Santos Machado V, Valadares AL, Costa-Paiva LH, et al. 2013. Aging, obesity, and multimorbidity in women 50 years or older: a population-based study. Menopause (New York, NY) 20:818-824.
90. Ferrer A, Formiga F, Sanz H, et al. 2017. Multimorbidity as specific disease combinations, an important predictor factor for mortality in octogenarians: the Octabaix study. Clinical interventions in aging 12:223-231.
91. Guccione AA, Felson DT, Anderson JJ, et al. 1994. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health 84:351-358.
92. Guisado-Clavero M, Roso-Llorach A, Lopez-Jimenez T, et al. 2018. Multimorbidity patterns in the elderly: a prospective cohort study with cluster analysis. BMC geriatrics 18:16.
93. Held FP, Blyth F, Gnjidic D, et al. 2016. Association Rules Analysis of Comorbidity and Multimorbidity: The Concord Health and Aging in Men Project. J Gerontol A Biol Sci Med Sci 71:625-631.
94. Jindai K, Nielson CM, Vorderstrasse BA, et al. 2016. Multimorbidity and Functional Limitations Among Adults 65 or Older, NHANES 2005-2012. Preventing chronic disease 13:E151.
95. Koyanagi A, Lara E, Stubbs B, et al. 2018. Chronic Physical Conditions, Multimorbidity, and Mild Cognitive Impairment in Low- and Middle-Income Countries. Journal of the American Geriatrics Society.
96. Lowe DB, Taylor MJ, Hill SJ. 2017. Cross-sectional examination of musculoskeletal conditions and multimorbidity: influence of different thresholds and definitions on prevalence and association estimates. BMC research notes 10:51.
97. Lowe DB, Taylor MJ, Hill SJ. 2017. Associations between multimorbidity and additional burden for working-age adults with specific forms of musculoskeletal conditions: a cross-sectional study. BMC Musculoskelet Disord 18:135.
98. Marengoni A, Rizzuto D, Wang HX, et al. 2009. Patterns of chronic multimorbidity in the elderly population. Journal of the American Geriatrics Society 57:225-230.
99. Mikula-Noble N, Cormie V, McCowan RE, et al. 2025. Identifying clusters of multimorbid disease and differences by age, sex, and socioeconomic status: A systematic review. PLoS One 20:e0329794.
100. Prados-Torres A, Calderon-Larranaga A, Hancco-Saavedra J, et al. 2014. Multimorbidity patterns: a systematic review. Journal of clinical epidemiology 67:254-266.
101. Taylor CJ, Harrison C, Britt H, et al. 2017. Heart failure and multimorbidity in Australian general practice. Journal of comorbidity 7:44-49.
102. Teh RO, Menzies OH, Connolly MJ, et al. 2018. Patterns of multi-morbidity and prediction of hospitalisation and all-cause mortality in advanced age. Age and ageing 47:261-268.
103. Vancampfort D, Stubbs B, Koyanagi A. 2017. Physical chronic conditions, multimorbidity and sedentary behavior amongst middle-aged and older adults in six low- and middle-income countries. The international journal of behavioral nutrition and physical activity 14:147.
104. Xu X, Mishra GD, Jones M. 2017. Evidence on multimorbidity from definition to intervention: An overview of systematic reviews. Ageing research reviews 37:53-68.
105. Yokota RT, Van der Heyden J, Nusselder WJ, et al. 2016. Impact of Chronic Conditions and Multimorbidity on the Disability Burden in the Older Population in Belgium. J Gerontol A Biol Sci Med Sci 71:903-909.
106. Zambon S, Siviero P, Denkinger M, et al. 2016. Role of Osteoarthritis, Comorbidity, and Pain in Determining Functional Limitations in Older Populations: European Project on Osteoarthritis. Arthritis Care Res (Hoboken) 68:801-810.
107. Parkinson L, Waters DL, Franck L. 2017. Systematic review of the impact of osteoarthritis on health outcomes for comorbid disease in older people. Osteoarthritis Cartilage 25:1751-1770.

108. Baghbani-Naghadehi F, Armijo-Olivo S, Prado CM, et al. 2023. Obesity, Comorbidities, and the Associated Risk among Patients Who Underwent Total Knee Arthroplasty in Alberta. J Knee Surg 36:744-751.
109. Chen H, Dang Q, Shi Y, et al. 2026. The Comorbidity Burdens of Osteoarthritis and 174 Diseases, 1990-2021: A Modeling Study Based on the Global Burden of Disease Study 2021. Int J Rheum Dis 29:e70548.
110. Constantino de Campos G, Mundi R, Whittington C, et al. 2020. Osteoarthritis, mobility-related comorbidities and mortality: an overview of meta-analyses. Ther Adv Musculoskelet Dis 12:1759720x20981219.
111. Cook MJ, Verstappen SMM, Lunt M, et al. 2022. Increased Frailty in Individuals With Osteoarthritis and Rheumatoid Arthritis and the Influence of Comorbidity: An Analysis of the UK Biobank Cohort. Arthritis Care Res (Hoboken) 74:1989-1996.
112. Dell'Isola A, Pihl K, Turkiewicz A, et al. 2022. Risk of Comorbidities Following Physician-Diagnosed Knee or Hip Osteoarthritis: A Register-Based Cohort Study. Arthritis Care Res (Hoboken) 74:1689-1695.
113. Dell'Isola A, Recenti F, Englund M, et al. 2024. Twenty-year trajectories of morbidity in individuals with and without osteoarthritis. RMD open 10.
114. Dell'Isola A, Turkiewicz A, Zhang W, et al. 2022. Does osteoarthritis modify the association between NSAID use and risk of comorbidities and adverse events? Osteoarthr Cartil Open 4:100253.
115. Dell'Isola A, Vinblad J, Turkiewicz A, et al. 2024. The coexistence of diabetes, hypertension and obesity is associated with worse pain outcomes following exercise for osteoarthritis: A cohort study on 80,893 patients. Osteoarthritis Cartilage 32:1308-1318.
116. Ding L, Dai R, Jin D, et al. 2025. Age-specific comorbidity risks in osteoarthritis: implications for healthy aging across diverse populations. Arch Public Health 83:174.
117. Graham J, Novosat T, Sun H, et al. 2023. Medication use and comorbidities in an increasingly younger osteoarthritis population: an 18-year retrospective open-cohort study. BMJ Open 13:e067211.
118. Gustafsson K, Kvist J, Eriksson M, et al. 2021. Health status of individuals referred to first-line intervention for hip and knee osteoarthritis compared with the general population: an observational register-based study. BMJ Open 11:e049476.
119. Haue AD, Armenteros JJA, Holm PC, et al. 2022. Temporal patterns of multi-morbidity in 570157 ischemic heart disease patients: a nationwide cohort study. Cardiovasc Diabetol 21:87.
120. Kamps A, Runhaar J, de Ridder MAJ, et al. 2023. Comorbidity in incident osteoarthritis cases and matched controls using electronic health record data. Arthritis Res Ther 25:114.
121. Kamps A, Runhaar J, de Ridder MAJ, et al. 2023. Occurrence of comorbidity following osteoarthritis diagnosis: a cohort study in the Netherlands. Osteoarthritis Cartilage 31:519-528.
122. Karim M, Hossen MD, Ratna TT, et al. 2026. Mapping the intersection of social status and comorbidity in knee osteoarthritis: A WOMAC-based study. PLoS One 21:e0324767.
123. Kobayashi K, Otani K, Sekiguchi M, et al. 2024. Relationship between lumbar facet joint osteoarthritis and comorbidities: A cross-sectional study in the Japanese community. J Orthop Sci 29:769-774.
124. Lentz TA, Hellkamp AS, Bhavsar NA, et al. 2021. Assessment of Common Comorbidity Phenotypes Among Older Adults With Knee Osteoarthritis to Inform Integrated Care Models. Mayo Clin Proc Innov Qual Outcomes 5:253-264.
125. Li B, Yang Z, Li Y, et al. 2024. Exploration beyond osteoarthritis: the association and mechanism of its related comorbidities. Frontiers in endocrinology 15:1352671.
126. Li X, Pan F, Zhu R, et al. 2024. Cross-Sectional and Longitudinal Associations of Comorbidities with Knee Symptoms and Radiographic Abnormalities of Osteoarthritis. Rheumatol Ther 11:129-142.

127. Mulrooney E, Neogi T, Dagfinrud H, et al. 2023. Comorbidities in people with hand OA and their associations with pain severity and sensitization: Data from the longitudinal Nor-Hand study. Osteoarthr Cartil Open 5:100367.
128. Pineda-Moncusí M, Dernie F, Dell'Isola A, et al. 2023. Classification of patients with osteoarthritis through clusters of comorbidities using 633330 individuals from Spain. Rheumatology (Oxford) 62:3592-3600.
129. Schwetlik SN, Baldock KL, Hill CL, et al. 2025. Exploring the relationship between allostatic load and osteoarthritis: A cross-sectional analysis from the North West Adelaide Health Study. Osteoarthr Cartil Open 7:100689.
130. Swain S, Coupland C, Mallen C, et al. 2021. Temporal relationship between osteoarthritis and comorbidities: a combined case control and cohort study in the UK primary care setting. Rheumatology (Oxford) 60:4327-4339.
131. Swain S, Coupland C, Strauss V, et al. 2022. Clustering of comorbidities and associated outcomes in people with osteoarthritis - A UK Clinical Practice Research Datalink study. Osteoarthritis Cartilage 30:702-713.
132. Swain S, Fernandes GS, Sarmanova A, et al. 2022. Comorbidities and use of analgesics in people with knee pain: a study in the Nottingham Knee Pain and Health in the Community (KPIC) cohort. Rheumatol Adv Pract 6:rkac049.
133. Tekaya AB, Bouzid S, Kharrat L, et al. 2023. Health-Related Quality of Life and Associated Factors Among Patients With Knee Osteoarthritis. Curr Rheumatol Rev 19:355-361.
134. Zemedikun DT, Lee H, Nirantharakumar K, et al. 2022. Comorbidity phenotypes and risk of mortality in patients with osteoarthritis in the UK: a latent class analysis. Arthritis Res Ther 24:231.
135. Zou Y, Zhang Y, Sun X, et al. 2025. Osteoarthritis as a clinical marker of cardiovascular-kidney-metabolic multimorbidity: a population-based cohort study in China. Frontiers in endocrinology 16:1660319.
136. Blaker CL, Clarke EC, Little CB. 2017. Using mouse models to investigate the pathophysiology, treatment, and prevention of post-traumatic osteoarthritis. J Orthop Res 35:424-439.
137. Blaker CL, Shu CC, Soul J, et al. 2025. The utility of animal models in understanding osteoarthritis (OA) pathogenesis - an update on the impact of genetically modified mice. Connect Tissue Res 66:399-406.
138. Little CB, Hunter DJ. 2013. Post-traumatic osteoarthritis: from mouse models to clinical trials. Nat Rev Rheumatol 9:485-497.
139. Little CB, Zaki S. 2012. What constitutes an "animal model of osteoarthritis"--the need for consensus? Osteoarthritis Cartilage 20:261-267.
140. Malfait AM, Little CB. 2015. On the predictive utility of animal models of osteoarthritis. Arthritis Res Ther 17:225.
141. Malfait AM, Little CB, McDougall JJ. 2013. A commentary on modelling osteoarthritis pain in small animals. Osteoarthritis Cartilage 21:1316-1326.
142. Zaki S, Blaker CL, Little CB. 2022. OA foundations - experimental models of osteoarthritis. Osteoarthritis Cartilage 30:357-380.
143. Blaker CL, Clarke EC, Little CB. 2019. Adding insult to injury: synergistic effect of combining risk-factors in models of post-traumatic osteoarthritis. Osteoarthritis Cartilage 27:1731-1734.
144. Julovi SM, Dao A, Trinh K, et al. 2023. Disease-modifying interactions between chronic kidney disease and osteoarthritis: a new comorbid mouse model. RMD open 9.
145. Little CB. 2023. Cholesterol, systemic inflammation, interleukin-1β, and osteoarthritis risk - aligning animal models with specific patient endotypes provides novel insights. Osteoarthritis Cartilage 31:298-299.
146. Little CB, Fosang AJ. 2010. Is cartilage matrix breakdown an appropriate therapeutic target in osteoarthritis--insights from studies of aggrecan and collagen proteolysis? Curr Drug Targets 11:561-575.

147. Soul J, Barter MJ, Little CB, et al. 2021. OATargets: a knowledge base of genes associated with osteoarthritis joint damage in animals. Ann Rheum Dis 80:376-383.
148. Zaki S, Smith MM, Little CB. 2021. Pathology-pain relationships in different osteoarthritis animal model phenotypes: it matters what you measure, when you measure, and how you got there. Osteoarthritis Cartilage 29:1448-1461.
149. Zaki S, Smith MM, Smith SM, et al. 2020. Differential patterns of pathology in and interaction between joint tissues in long-term osteoarthritis with different initiating causes: phenotype matters. Osteoarthritis Cartilage 28:953-965.
150. Griffin TM, Huebner JL, Kraus VB, et al. 2012. Induction of osteoarthritis and metabolic inflammation by a very high-fat diet in mice: effects of short-term exercise. Arthritis Rheum 64:443-453.
151. Griffin TM, Lopes EBP, Cortassa D, et al. 2024. Sexually dimorphic metabolic effects of a high fat diet on knee osteoarthritis in mice. Biol Sex Differ 15:103.
152. Collins KH, Hart DA, Seerattan RA, et al. 2018. High-fat/high-sucrose diet-induced obesity results in joint-specific development of osteoarthritis-like degeneration in a rat model. Bone & joint research 7:274-281.
153. Collins KH, MacDonald GZ, Hart DA, et al. 2020. Impact of age on host responses to diet-induced obesity: Development of joint damage and metabolic set points. J Sport Health Sci 9:132-139.
154. Gathercole LL, Nikolaou N, Harris SE, et al. 2022. AKR1D1 knockout mice develop a sex-dependent metabolic phenotype. J Endocrinol 253:97-113.
155. Karjalainen K, Tanska P, Collins KH, et al. 2024. Independent and combined effects of obesity and traumatic joint injury to the structure and composition of rat knee cartilage. Connect Tissue Res 65:117-132.
156. Bolduc JA, Collins JA, Loeser RF. 2019. Reactive oxygen species, aging and articular cartilage homeostasis. Free Radic Biol Med 132:73-82.
157. Greene MA, Loeser RF. 2015. Aging-related inflammation in osteoarthritis. Osteoarthritis Cartilage 23:1966-1971.
158. Jeon OH, Kim C, Laberge RM, et al. 2017. Local clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment. Nat Med 23:775-781.
159. Cornelis FMF, de Roover A, Storms L, et al. 2019. Increased susceptibility to develop spontaneous and post-traumatic osteoarthritis in Dot1l-deficient mice. Osteoarthritis Cartilage 27:513-525.
160. Thompson SD, Pichika R, Lieber RL, et al. 2021. Systemic transplantation of adult multipotent stem cells prevents articular cartilage degeneration in a mouse model of accelerated ageing. Immun Ageing 18:27.
161. Ghezai YT, Farhat NM, Ibrahim SMS, et al. 2025. Epigenetics in osteoarthritis: emerging mechanistic and translational landscape. Connect Tissue Res 66:313-322.
162. Izda V, Dunn CM, Prinz E, et al. 2022. A Pilot Analysis of Genome-Wide DNA Methylation Patterns in Mouse Cartilage Reveals Overlapping Epigenetic Signatures of Aging and Osteoarthritis. ACR Open Rheumatol 4:1004-1012.
163. Kenny J, Mullin BH, Tomlinson W, et al. 2023. Age-dependent genetic regulation of osteoarthritis: independent effects of immune system genes. Arthritis Res Ther 25:232.
164. Rice SJ, Beier F, Young DA, et al. 2020. Interplay between genetics and epigenetics in osteoarthritis. Nat Rev Rheumatol 16:268-281.
165. Kyostio-Moore S, Nambiar B, Hutto E, et al. 2011. STR/ort mice, a model for spontaneous osteoarthritis, exhibit elevated levels of both local and systemic inflammatory markers. Comp Med 61:346-355.
166. Uchida K, Urabe K, Naruse K, et al. 2009. Hyperlipidemia and hyperinsulinemia in the spontaneous osteoarthritis mouse model, STR/Ort. Exp Anim 58:181-187.

167. Grover L, Sklioutovskaya-Lopez K, Parkman JK, et al. 2023. Diet, sex, and genetic predisposition to obesity and type 2 diabetes modulate motor and anxiety-related behaviors in mice, and alter cerebellar gene expression. Behav Brain Res 445:114376.
168. Horakova O, Janovska P, Irodenko I, et al. 2024. Postnatal surge of adipose-secreted leptin is a robust predictor of fat mass trajectory in mice. Am J Physiol Endocrinol Metab 327:E729-e745.
169. Kopcewicz M, Walendzik K, Bukowska J, et al. 2020. Cutaneous wound healing in aged, high fat diet-induced obese female or male C57BL/6 mice. Aging 12:7066-7111.
170. Kubota Y, Han Q, Reynoso J, et al. 2023. Old-age-induced obesity reversed by a methionine-deficient diet or oral administration of recombinant methioninase-producing Escherichia coli in C57BL/6 mice. Aging 15:4642-4648.
171. Burchfield JG, Kebede MA, Meoli CC, et al. 2018. High dietary fat and sucrose results in an extensive and time-dependent deterioration in health of multiple physiological systems in mice. J Biol Chem.
172. Casimiro I, Stull ND, Tersey SA, et al. 2021. Phenotypic sexual dimorphism in response to dietary fat manipulation in C57BL/6J mice. J Diabetes Complications 35:107795.
173. Dakin RS, Walker BR, Seckl JR, et al. 2015. Estrogens protect male mice from obesity complications and influence glucocorticoid metabolism. Int J Obes (Lond) 39:1539-1547.
174. Wei W, Bastiaansen-Jenniskens YM, Suijkerbuijk M, et al. 2017. High fat diet accelerates cartilage repair in DBA/1 mice. J Orthop Res 35:1258-1264.
175. Yuan R, Tsaih SW, Petkova SB, et al. 2009. Aging in inbred strains of mice: study design and interim report on median lifespans and circulating IGF1 levels. Aging cell 8:277-287.
176. Salimi S, Pettan-Brewer C, Ladiges W. 2021. PathoClock and PhysioClock in mice recapitulate human multimorbidity and heterogeneous aging. Aging Pathobiol Ther 3:107-126.
177. Snyder JM, Snider TA, Ciol MA, et al. 2019. Validation of a geropathology grading system for aging mouse studies. Geroscience 41:455-465.
178. Chlebek C, McAndrews C, Aaronson B, et al. 2026. In C57BL/6J mice, weight loss in previously obese mice reduced bone mass and shifted the cortical bone metabolome. Bone 202:117690.
179. Qin H, Yu J, Yu H, et al. 2026. Semaglutide ameliorates osteoarthritis progression through a weight loss-independent metabolic restoration mechanism. Cell Metab.
180. Collins KH, Lenz KL, Pollitt EN, et al. 2021. Adipose tissue is a critical regulator of osteoarthritis. Proc Natl Acad Sci U S A 118.
181. Collins KH, Lenz KL, Welhaven HD, et al. 2025. Adipose-derived leptin and complement factor D mediate osteoarthritis severity and pain. Sci Adv 11:eadt5915.
182. Beck J, Horikawa I, Harris C. 2020. Cellular Senescence: Mechanisms, Morphology, and Mouse Models. Vet Pathol 57:747-757.
183. Ding C, Yimiti D, Sanada Y, et al. 2024. High-fat diet-induced obesity accelerates the progression of spontaneous osteoarthritis in senescence-accelerated mouse prone 8. Mod Rheumatol 34:831-840.
184. Rae EA, Brown RE. 2015. The problem of genotype and sex differences in life expectancy in transgenic AD mice. Neuroscience and biobehavioral reviews 57:238-251.
185. Takeda T. 1999. Senescence-accelerated mouse (SAM): a biogerontological resource in aging research. Neurobiol Aging 20:105-110.
186. Chen WH, Hosokawa M, Tsuboyama T, et al. 1989. Age-related changes in the temporomandibular joint of the senescence accelerated mouse SAM-P/3 as a new murine model of degenerative joint disease. Am J Pathol 135:379-385.
187. Drechsler S, Lynch MA, Novella S, et al. 2016. With mouse age comes wisdom: A review and suggestions of relevant mouse models for age-related conditions. Mechanisms of ageing and development 160:54-68.
188. Hambright WS, Niedernhofer LJ, Huard J, et al. 2019. Murine models of accelerated aging and musculoskeletal disease. Bone 125:122-127.

189. Kõks S, Dogan S, Tuna BG, et al. 2016. Mouse models of ageing and their relevance to disease. Mechanisms of ageing and development 160:41-53.