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A computational study of adiposity-associated factors in the inflammatory process of osteoarthritis

Juntong Lai[a,b,1], Damien Lacroix[a,b,*,2]

[a]Insigneo Institute, University of Sheffield, Sheffield, UK
[b]School of Mechanical, Aerospace and Civil Engineering, University of Sheffield, Sheffield, UK

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ABSTRACT

Chronic inflammation is a key factor in the degenerative changes of osteoarthritic joints. Obesity significantly raises the risk of osteoarthritis (OA), since excess body fat (adipose tissue) not only systemically increases the level of inflammation but also locally stimulates the inflammatory responses within osteoarthritic joints. In this context, physical activity is a practical approach in OA prevention and intervention, whereas current therapeutic strategies remain empirical and lack patient-specific tailoring. This makes it challenging to determine the appropriate dose and timing of physical activity therapy for diverse individuals. Building on our previous work of an adipokine-mediated inflammation model, this study aimed to analyse the effects of obesity and physical activity on OA inflammation by parameterising the inflammatory activities. In this model, five key mediator groups (pro- and anti-inflammatory cytokines, matrix metalloproteinases, adipokines and fibronectin fragments) were included. A global sensitivity analysis was conducted in the estimated parametric space and revealed the critical role of adiposity-associated factors in regulating inflammation. In addition, the inflammatory activities were simulated by tuning two adiposity-associated parameters, body mass index (BMI) and physical activity level (PAL), factoring in a simulated injury. The effectiveness of three physical activity intervention strategies was assessed by examining the inflammatory responses of the representative cases with four BMI profiles. A marked sensitivity to the timing (window period) of physical activity implementation was found. Results underscored the importance of accounting for both the adiposity level and the extent of tissue damage when designing intervention strategies of physical activity and optimising their timing for managing OA inflammation. This novel computational study analyses the adiposity-associated effects of physical activity on OA inflammation, illustrating that the effective window period of physical activity interventions varies from 0 to 15 months, depending on the level of adiposity and mechanical damage. Outcomes from the evaluation of the time window can strategically contribute to optimising physical activity interventions for the management of OA risk at an early stage.

1. Introduction

Osteoarthritis (OA) is a chronic pathological outcome within the whole synovial joint, resulting from the intricate interactions of pathogenic pathways across multiple scales (Tang et al., 2025). These include metabolism-driven inflammation at the molecular and cellular scale and loading-induced mechanical injury at the tissue scale. As a prominent and modifiable risk factor of OA, obesity has become a global health issue at a pandemic level over the course of the last 50 years (Blüher, 2019). The increasing exposure to the risk of obesity is significantly contributing to the worldwide burden of OA. By 2050, the global population with OA is anticipated to reach 642 million, where there may be over 20% of OA cases associated with obesity (Steinmetz et al., 2023). The resulting financial burden is projected to be as high as 2.5% of gross national product (GNP) in developed countries (Leifer et al., 2022). To date, the emphasis of OA treatments is in the management of symptoms, including pain relief and improvements in joint function, through education, lifestyle modification, physical activity therapy or pharmacological prescriptions (Tang et al., 2025). The precise mechanisms underlying OA remain unclear at present, rendering it unattainable to develop effective treatments. Modern consensus acknowledges the crucial roles of metabolic disturbance and biomechanical abnormalities in OA pathology (Tang et al., 2025). Emerging evidence reveals that low-grade inflammation is present

*Corresponding author
ORCID(s): 0009-0009-5488-8619 (J. Lai); 0000-0002-5482-6006 (D. Lacroix)
[1]Email address: jlai10@sheffield.ac.uk
[2]Email address: D.Lacroix@sheffield.ac.uk

prior to the structural signs of OA (Sokolove and Lepus, 2013; Robinson et al., 2016). Adipose tissue has been shown to regulate the inflammatory process in the pathogenesis of OA (Chang et al., 2018; Zeng et al., 2020; Collins et al., 2021; Zhou et al., 2022). Body mass index (BMI) is the most common metric for the estimation of adiposity and the identification of obesity (González-Muniesa et al., 2017). The elevation in per unit BMI correlates with a 15% increased risk of developing OA (Reyes et al., 2016; Duclos, 2016). At a high level of BMI, the excessive production of adipokines (Dumond et al., 2003; Poonpet, 2014; Kroon et al., 2019; Zhang et al., 2022) can stimulate OA inflammation, and the risk of tissue damage increases due to abnormal mechanical loading (Felson, 2013).

The cycle of the inflammatory process in OA can be activated by a variety of risk factors such as genetics, age, obesity, and injury (Tang et al., 2025). Pattern-recognition receptors (PRRs) and damage-associated molecular patterns (DAMPs) are recognised by the innate immune system (Orlowsky and Kraus, 2015) when inflammatory mediators are released in response to the inflammation. The inflammatory mediator groups can be categorised by different metabolic roles. Primarily, pro- and anti-inflammatory cytokines (PICs and AICs) (Wojdasiewicz et al., 2014; Nees et al., 2019) modulate the catabolic and anabolic processes reciprocally. Matrix metalloproteinases (MMPs) (Mehana et al., 2019) and chemokines (Scanzello, 2017) are two key enzymes involved in the regulation of tissue composition. In the progression of OA, tissue composition degrades with the release of fibronectin fragments (Fn-fs) (Pérez-García et al., 2019). As a type of damaging products within cartilage tissue, Fn-fs can stimulate inflammatory responses. In addition, adipokines serve as a critical mediator family that induces inflammation and tissue degradation by disrupting the metabolic balance within the inflammatory cycle (Wang and He, 2018).

Despite the improved understanding of OA inflammation, it is still difficult to facilitate consensus on identifying drivers of early OA due to the complex and simultaneous cascades of molecular signal transduction (Mahmoudian et al., 2021). In the current understanding of OA, molecular signalling pathways differ not only across pathogenic tissue types, but also temporally interrelate over the progression of OA. This understanding could be responsible for the manifestation of OA as a whole-joint disease. The lack of consensus on specific OA phenotypes and endotypes is a main factor underlying challenges in developing valid treatments (Hunter and Deveza, 2025). Empirical evidence shows that exercise contributes to OA management by influencing the heterogeneity of phenotypes and endotypes at both systemic and local levels. Specifically, exercise can ultimately modulate the levels of inflammatory mediators (Griffin et al., 2012, 2020; Messier et al., 2004, 2013; Sakamoto et al., 2023; Hahn et al., 2021; Hsieh and Yang, 2018; Castrogiovanni et al., 2019; Huesa et al., 2022; Runhaar et al., 2019) through the channel of mechanical transduction (Segarra-Queralt et al., 2024; Kong et al., 2022) and the alteration of metabolic environments such as the reduction of adipose tissue (Thompson et al., 2012; Drenowatz et al., 2015; Saeidi et al., 2021), thereby reducing the overall risk of OA. Physical activity has accordingly become the mainstream strategy to manage OA (Roos and Arden, 2016; Barrow et al., 2019; Skou et al., 2018; Huffman et al., 2024). Since the degeneration of joints in OA is progressive, proper physical activities play a positive role in the prevention of OA, adapting to the population with different risk levels. In addition to the aforementioned metabolism-related outcomes, physical activity can improve general health, muscle strength and joint stability, serving as primary intervention by contributing to the protection of joints from the onset of OA in susceptible populations (Roos and Arden, 2016). The implementation of physical activity can also be considered as secondary prevention by aiming to slow the progressive degeneration of joints in individuals with early OA (Roos and Arden, 2016). Nevertheless, there is no clear consensus yet on the specific criteria for physical activity prescriptions to maximise therapeutic benefits in OA (Huffman et al., 2024).

The heterogeneity of OA pathology leads to diverse and interacting degenerative pathways across the entire joint. This makes it challenging to identify and examine the underlying mechanisms for different phenotypes and endotypes. To overcome this challenge, computational modelling approaches exhibit the advantages in exploring the pathological mechanisms of OA (Mukherjee et al., 2020). Aside from reducing environmental and experimental costs, computational approaches are exceptionally suited to integrate the fragmented knowledge of different pathways in OA onset and development. This knowledge-based integration allows for the classification and analysis of distinct, simultaneously interacting pathological pathways. As a result of that, emerging mathematical models (Baker et al., 2017; Kar et al., 2016; Kapitanov et al., 2016; Campbell et al., 2019; Lesage et al., 2022; Segarra-Queralt et al., 2022, 2023; Rahman et al., 2023; Ferrao Blanco et al., 2024; Lai and Lacroix, 2025) have been recently established to study cartilage degeneration and inflammation. However, only one mathematical model with five variables considers the metabolic effects of adipokines in the context of obesity, which was developed in our previous work (Lai and Lacroix, 2025). This general model includes the signalling pathways of adipokines that mediate OA inflammation for the first time. While other models (Kapitanov et al., 2016; Segarra-Queralt et al., 2023; Rahman et al., 2023) incorporate mechanical loading as a stimulus, our model uniquely introduces physical activity level (PAL) as a parameter that

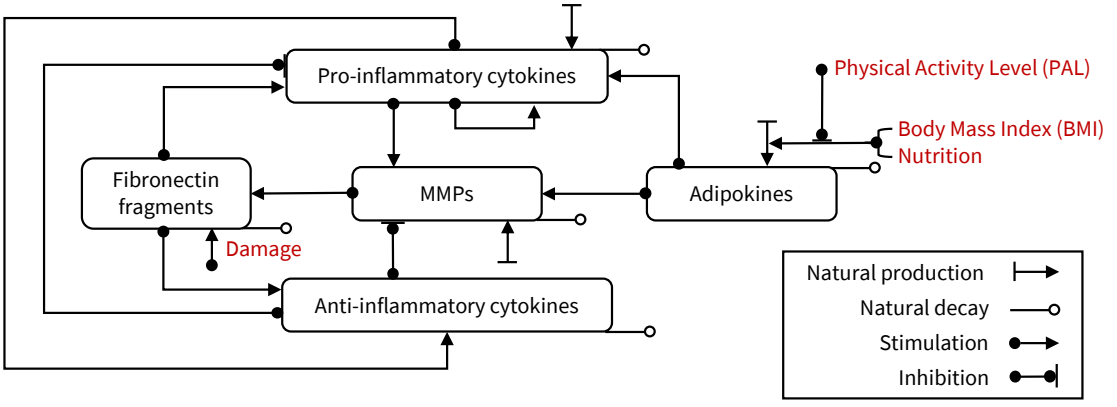

Figure 1: The regulatory network of the PICs, AICs, MMPs, adipokines and Fn-fs in OA inflammation. Reproduced from Lai and Lacroix (2025) under CC BY 4.0. PICs, AICs, MMPs, adipokines and Fn-fs interact to mediate the inflammatory process of OA. Damage is an external source to stimulate the production of Fn-fs due to the tissue injury resulting from mechanics. The production of adipokines is associated with the level of adiposity. PAL, BMI and nutrition are three modifiable system attributes that measure the adiposity level to govern the adipokine production.

regulates adiposity in conjunction with BMI and nutrition. This enables the possibility to computationally analyse the overall adiposity-associated effects on the inflammatory process of OA. Due to the difficulty in acquiring data, parameters were non-dimensionalised in the development of the general five-variable model (Lai and Lacroix, 2025) and the focus was the analysis of inflammation dynamics in OA. Nevertheless, the roles of physical activity and adiposity in OA inflammation remain unclear for different cohorts stratified by BMI levels. Moreover, the nondimensionalisation of this model hindered the optimisation of the strategy to reduce OA inflammation risk through physical activity within a temporal framework, due to the uncertainty in the global parametric space. Therefore, this study aimed to parameterise this dimensionless model using literature-based estimates, and to examine the effects of adiposity-associated factors (BMI and PAL) on the inflammatory activities through the pathway of altering adiposity, with identifying various temporal strategies of physical activity intervention. The representative molecular half-lives were estimated as an approximation of time granularity for the parameterisation of this five-variable model. A global sensitivity analysis was performed to identify the critical correlations between inflammatory responses and the estimated parameter space by a global mapping of system behaviours. The inflammatory processes were simulated to analyse the effects of physical activity when varying the mechanical damage level and BMI to represent different cohorts.

2. Methods

2.1. Governing equations

A minimal model of adipokine-mediated inflammation was developed in a previous study (Lai and Lacroix, 2025). The general inflammation model includes five state variables (Fig. 1): PICs, AICs, MMPs, adipokines and Fn-fs, as denoted respectively by P_c, A_c, M, A_d, F. The mathematical formation of this minimal model is based on several assumptions and simplifications. The dynamical effects of cells including macrophages and chondrocytes are not explicitly included, and the inflammatory process is confined to the synovial joint where a homogeneous environment is assumed. In addition, inflammatory mediators are signalled as an entire group in this minimal model, and the same mediator group exhibits similar metabolic effects on OA inflammation. Accordingly, the reaction kinetics of each mediator group is approximated by a specific molecular phenotype that dominates the group concentration or the average of different phenotypes. The kinetics of mediator reactions is formulated in Eqs. (1) to (6), where n is the Hill coefficient (Lai and Lacroix, 2025) of reaction kinetics. In addition to stimulation and inhibition, each production group contains a term of decay rate depending on the half-life of the representative mediator.

PICs and AICs concurrently regulate the inflammatory activities in OA and interact with other mediators. The production of PICs results from the response of the immune system as well as local chondrocytes, whereas AICs are primarily released due to the stimulation of immune cells (Wojdasiewicz et al., 2014). The production source of PICs

is characterised by a local natural production term supplemented by three stimulation pathways, which is modelled as Eq. (1). Interleukin-6 (IL-6) was selected for the representation of PIC group (Nees et al., 2019) to reduce the complexity of the model, meanwhile, interleukin-4 (IL-4) represents AIC group in this model where there are two stimulating feedback from PICs and Fn-fs. The production of AICs is modelled as Eq. (2).

$$\frac{dP_c(t)}{dt} = \left[C_0 + C_1 \cdot \frac{P_c^n(t)}{C_2^n + P_c^n(t)} + C_3 \cdot \frac{A_d^n(t)}{C_4^n + A_d^n(t)} + C_5 \cdot \frac{F^n(t)}{C_6^n + F^n(t)}\right] \cdot \frac{C_7^n}{C_7^n + A_c^n(t)} - D_1 \cdot P_c(t) \quad (1)$$

$$\frac{dA_c(t)}{dt} = C_8 \cdot \frac{P_c^n(t)}{C_9^n + P_c^n(t)} + C_{10} \cdot \frac{F^n(t)}{C_{11}^n + F^n(t)} - D_2 \cdot A_c(t) \quad (2)$$

where C_0, C_1, C_3, C_5, C_7 are the rate parameters and C_2, C_4, C_6, C_7 are the saturation parameters in PIC production; C_8, C_{10} are the rate parameters and C_9, C_{11} are the saturation parameters in AIC production; and D_1, D_2 are the clearance parameters for PICs and AICs, respectively.

MMP-1 and MMP-13 are two main pivotal types of MMPs, and their half-lives were averaged to estimate the production of MMPs (Moise and Friedman, 2019). Excessive levels of PICs and adipokines can drive the release of MMPs to enhance tissue remodelling activities, leading to two stimulation terms. The inhibition sources are from AICs applied to all the pathways involved in the production of MMPs. The production of MMPs is modelled as Eq. (3).

$$\frac{dM(t)}{dt} = \left[C_{12} + C_{13} \cdot \frac{P_c^n(t)}{C_{14}^n + P_c^n(t)} + C_{15} \cdot \frac{A_d^n(t)}{C_{16}^n + A_d^n(t)}\right] \cdot \frac{C_{17}^n}{C_{17}^n + A_c^n(t)} - D_3 \cdot M(t) \quad (3)$$

where C_{12}, C_{13}, C_{15}, C_{17} are the rate parameters and C_{14}, C_{16}, C_{17} are the saturation parameters in MMP production, and D_3 is the clearance parameter for MMPs.

Due to the lack of documented data on adipokines, leptin is selected to represent the primary behaviour of adipokine group. Leptin level is positively correlated to BMI level (Dumond et al., 2003), which aligns with the assumptions of adipokine production behind this model. Specifically, the production of adipokines is determined by two main sources, the number and size of adipocytes (C_{18} and C_{19}). The variations of adiposity primarily depend on the adipocyte size that can be varied by BMI, nutrition and PAL, therein the nutritional term is defined by the proportion of daily calorie intake ($DailyCal$) to basal metabolic rate (BMR). The production of adipokines is modelled as Eq. (4) and Eq. (5) is the function of BMI^{meas} scaling the production rate driven by the size of adipocytes.

$$\frac{dA_d(t)}{dt} = C_{18} + \left[C_{19} \cdot f(BMI^{meas}) \cdot \frac{DailyCal}{BMR \cdot PAL}\right] \cdot \frac{C_{20}^{nex}}{C_{20}^{nex} + A_d^{nex}(t)} - D_4 \cdot A_d(t) \quad (4)$$

$$f(BMI^{meas}) = \frac{BMI^{meas}}{BMI^{std}} \quad (5)$$

where C_{18}, C_{19} are the rate parameters and BMI^{meas}, $DailyCal$, BMR, PAL, C_{20}, nex are the adiposity-associated parameters altering the production rate of adipokines. D_4 is the clearance parameter for adipokines. BMI^{std} is the standard BMI in measuring obesity (González-Muniesa et al., 2017). In particular, C_{20} and nex are the parameters determined by PAL and BMI^{meas} respectively, approximating the nonlinear effects of physical activity on adipokine production at different levels of BMI (Thompson et al., 2012; Drenowatz et al., 2015).

As the damage breakdowns, Fn-fs are released from the tissue degradation that is governed by two parameters (C_{21} and C_{22}). C_{21} is associated with the level of MMPs when C_{22} measures the level of mechanical damage. The production of Fn-fs is modelled as Eq. (6).

$$\frac{dF(t)}{dt} = C_{21} \cdot M(t) + C_{22} - D_5 \cdot F(t) \quad (6)$$

where C_{21}, C_{22} are the rate parameters in the production of Fn-fs, and D_5 is the clearance parameter for Fn-fs.

2.2. Parameterisation

Since capturing all the chemical-biological reactions is not viable yet, the illustrative parameterisation of this model is essential to exhibit the net effects of signal transduction on the mediator production according to the molecular decay rates. The decay rates can delineate the time scale of mediator production, converted by Eq. (7) according to the estimated half-life of each representative mediator.

$$D_{im} = \frac{\ln 2}{T^{im}_{half-life}}, \left(im = P_c, A_c, M, A_d, F\right) \tag{7}$$

where D_{im} is the decay rate of each mediator, and $T^{im}_{half-life}$ is the half-life of the constituent at each generation.

The estimated decay rates and the corresponding production parameters are presented in Tables 1 to 5. The half-lives of IL-6 (Moise and Friedman, 2019) and IL-4 (Liu et al., 2021) are estimated as 4 days and 20 minutes respectively, leading to the decay rates of PICs and AICs (D_1 and D_2). The half-life of MMPs is approximated as 120 hours by the average of MMP-1 and MMP-13 to estimate the decay rate of MMPs (D_3) (Rahman et al., 2023). The half-life of leptin is reported as 25 mins (Klein et al., 1996), from which the decay rate of adipokines (D_4) is estimated. The decay rate of Fn-fs (D_5) is estimated based on its approximate half-life of 7 days (Homandberg et al., 1998).

For simplicity, the natural production rates (C_0, C_{12}) are estimated as 1 percent of the corresponding decay rates so that natural production is not dominant in prompting inflammation. Additionally, the stimulated production parameters of PICs and MMPs (C_1, C_3, C_5, C_8, C_{10}, C_{13}, C_{15}) are 10 times the values of decay rates to play a primary role in regulating inflammatory processes. To maintain the balance of MMPs and Fn-fs production, the effects of MMPs are not negligible so C_{21} is set to match the magnitude of the Fn-fs decay rate. Since the variability of mediator concentration has yet to be thoroughly assessed and there exists a limited amount of data demonstrating the saturating effects of inflammatory mediators in OA, the saturation constants (C_2, C_4, C_6, C_7, C_9, C_{11}, C_{14}, C_{16}, C_{17}) are estimated to be an order of magnitude smaller than the corresponding stimulated production rate in Hill functions. This assumption helps to minimise bias from overestimating or underestimating saturation effects due to the uncertainty in mediator concentration. Accordingly, the level of mediator is illustrative to exhibit the minimally essential system behaviours of inflammation. C_{22} is an arbitrary parameter measuring the level of mechanical damage within tissue. Hill coefficient (n) is set to 2 for all the signalling feedback from multiple receptors in inflammatory regulations (Baker et al., 2017).

Table 1: Descriptions of the estimated parameters in the production of PICs.

Parameter	Description	Value	Reference
C_0	Natural production rate of PICs	0.05	Estimated
C_1	Stimulated production rate of PICs by PICs	50	Estimated
C_2	Saturation constant at which the capability of stimulating PIC production signalled by PICs is half of maximum	5	Estimated
C_3	Stimulated production rate of PICs by adipokines	50	Estimated
C_4	Saturation constant at which the capability of stimulating PIC production signalled by adipokines is half of maximum	5	Estimated
C_5	Stimulated production rate of PICs by Fn-fs	50	Estimated
C_6	Saturation constant at which the capability of stimulating PIC production signalled by Fn-fs is half of maximum	5	Estimated

Continued on next page

Table 1: Descriptions of the estimated parameters in the production of PICs. (Continued)

C_7	Saturation constant at which the capability of inhibiting PIC production signalled by AICs is half of maximum	5	Estimated
D_1	Clearance rate of PICs	5.2	(Moise and Friedman, 2019)
n	Hill coefficient	2	(Baker et al., 2017)

Table 2: Descriptions of the estimated parameters in the production of AICs.

Parameter	Description	Value	Reference
C_8	Stimulated production rate of AICs by PICs	1×1.5^4	Estimated
C_9	Saturation constant at which the capability of stimulating AIC production signalled by PICs is half of maximum	1×1.5^3	Estimated
C_{10}	Stimulated production rate of AICs by Fn-fs	1×1.5^4	Estimated
C_{11}	Saturation constant at which the capability of stimulating AIC production signalled by Fn-fs is half of maximum	1×1.5^3	Estimated
D_2	Clearance rate of AICs	1.5×10^3	(Liu et al., 2021)
n	Hill coefficient	2	(Baker et al., 2017)

Table 3: Descriptions of the estimated parameters in the production of MMPs.

Parameter	Description	Value	Reference
C_{12}	Natural production rate of MMPs	0.05	Estimated
C_{13}	Stimulated production rate of MMPs by PICs	50	Estimated
C_{14}	Saturation constant at which the capability of stimulating MMP production signalled by PICs is half of maximum	5	Estimated
C_{15}	Stimulated production rate of MMPs by adipokines	50	Estimated
C_{16}	Saturation constant at which the capability of stimulating MMP production signalled by adipokines is half of maximum	5	Estimated
C_{17}	Saturation constant at which the capability of inhibiting MMP production signalled by AICs is half of maximum	5	Estimated
D_3	Clearance rate of MMPs	4.2	(Rahman et al., 2023)

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Table 3: Descriptions of the estimated parameters in the production of MMPs. (Continued)

n	Hill coefficient	2	(Baker et al., 2017)

Table 4: Descriptions of the estimated parameters in the production of adipokines.

Parameter	Description	Value	Reference
C_{18}	The background production rate of adipokines due to the number of adipocytes	500	Estimated
C_{19}	The background production rate of adipokines due to the size of adipocytes	500	Estimated
BMI_{std}	The standard BMI	25	(González-Muniesa et al., 2017)
C_{20}	Saturation constant at which the capability of reducing adiposity through physical activity is half of maximum	Dependent on PAL	Estimated
$\frac{DailyCal}{BMR}$	The nutritional term defined by the ratio of daily calorie intake to BMR	1	Estimated
nex	The coefficient that governs the nonlinearity of physical activity effects at different BMI levels	Dependent on BMI^{meas}	Estimated
D_4	Clearance rate of adipokines	1.2×10^3	(Klein et al., 1996)

Table 5: Descriptions of the estimated parameters in the production of Fn-fs.

Parameter	Description	Value	Reference
C_{21}	Stimulated production rate of Fn-fs by MMPs	3	Estimated
C_{22}	Stimulated production rate of Fn-fs due to mechanical damage	0	Estimated
D_5	Clearance rate of Fn-fs	3	(Homandberg et al., 1998)

The production rates driven by the number and size of adipocytes (C_{18}, C_{19}) are estimated to be 500 for the baseline in analysis. This confines the system so that the stability of steady states is sensitive to the production of adipokines governed by BMI and PAL, as presented in **Fig. (A.1)**. Based on the given values of C_{18} and C_{19}, a sensitivity analysis on the coefficients (nex, C_{20}) related to BMI and PAL was performed to estimate their boundaries, as shown in Fig. 2. Accordingly, two piecewise functions are given to determine the aforementioned coefficients, as detailed in Eqs. (8) and (9). The calibration of the two piecewise functions ensures that the relationship between PAL and adipokine production is aligned with the present knowledge in general (Lai and Lacroix, 2025). In addition, the ranges of BMI and PAL are constrained according to (Lai and Lacroix, 2025), and the nutrition term ($\frac{DailyCal}{BMR}$) is assumed to be 1 for the dietary control in this study.

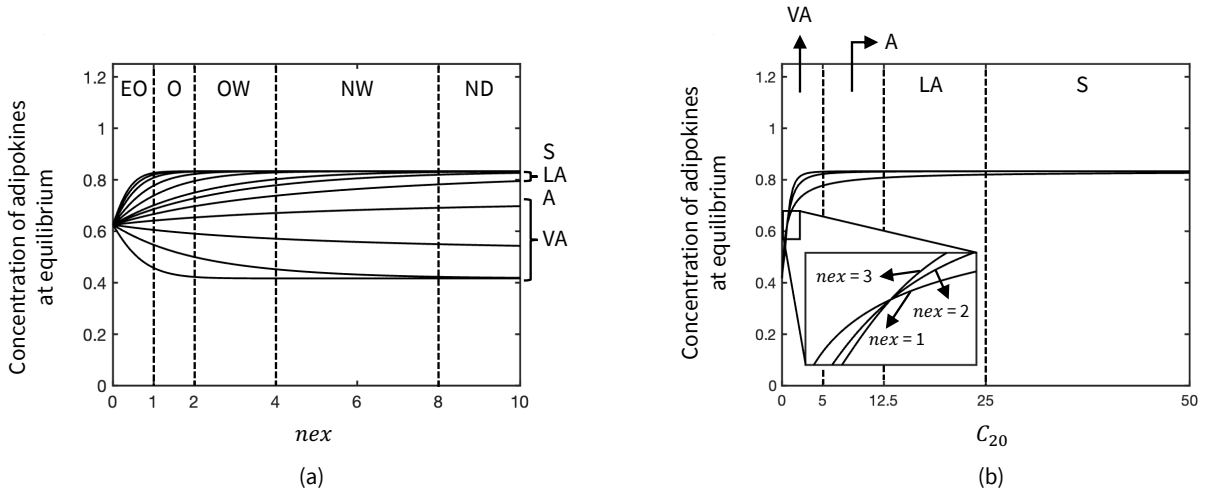

Figure 2: The calibration of boundaries for the coefficients governing the decrease of adiposity: (a) nex; (b) C_{20}. The level of BMI includes extreme obesity (EO), obesity (O), overweight (OW), normal weight (NW) and nutritional deficiency (ND). The level of physical activity includes sedentary (S), low active (LA), active (A) and very active (VA). The BMI and PAL ranges are presented in Table 6.

$$nex = \begin{cases} B_{ND} - BMI^{meas} \cdot \dfrac{B_{ND} - B_{NW}}{R_{ND} - R_{ND_{min}}}, & if\ R_{ND_{min}} < BMI^{meas} < R_{ND} \\ B_{NW} - \left(BMI^{meas} - R_{ND}\right) \cdot \dfrac{B_{NW} - B_{OW}}{R_{NW} - R_{ND}}, & if\ R_{ND} \leqslant BMI^{meas} \leqslant R_{NW} \\ B_{OW} - \left(BMI^{meas} - R_{NW}\right) \cdot \dfrac{B_{OW} - B_{O}}{R_{OW} - R_{NW}}, & if\ R_{NW} < BMI^{meas} \leqslant R_{OW} \\ B_{O} - \left(BMI^{meas} - R_{OW}\right) \cdot \dfrac{B_{O} - B_{EO}}{R_{O} - R_{OW}}, & if\ R_{OW} < BMI^{meas} < R_{O} \\ \dfrac{R_O}{BMI^{meas}}, & if\ BMI^{meas} \geqslant R_{O} \end{cases} \tag{8}$$

$$C_{20} = \begin{cases} B_S - \left(PAL - R_{S_{min}}\right) \cdot \dfrac{B_S - B_{LA}}{R_S - R_{S_{min}}}, & if\ R_{S_{min}} \leqslant PAL \leqslant R_S \\ B_{LA} - \left(PAL - R_S\right) \cdot \dfrac{B_{LA} - B_A}{R_{LA} - R_S}, & if\ R_S < PAL \leqslant R_{LA} \\ B_A - \left(PAL - R_{LA}\right) \cdot \dfrac{B_A - B_{VA}}{R_A - R_{LA}}, & if\ R_{LA} < PAL \leqslant R_A \\ B_{VA} - \left(PAL - R_A\right) \cdot \dfrac{B_{VA}}{R_{VA} - R_A}, & if\ R_A < PAL \leqslant R_{VA} \end{cases} \tag{9}$$

where the boundaries of nex and C_{20} are estimated to be $B_{ND} = 10$, $B_{NW} = 8$, $B_{OW} = 4$, $B_O = 2$, $B_{EO} = 1$, $B_S = 50$, $B_{LA} = 25$, $B_A = 12.5$, $B_{VA} = 5$. The range parameters of BMI level and PAL follow their categorised definitions (González-Muniesa et al., 2017; Brooks et al., 2004) in Table 6.

2.3. Sensitivity analysis of inflammation and obesity

Parameter sensitivity analysis was performed for the production of those five mediators in a global parameter space using Latin hypercube sampling/partial rank correlation coefficient (LHS/PRCC). LHS/PRCC is a global sensitivity

Table 6
The categories and ranges of BMI and PAL

Level of obesity	Interval of BMI^{meas}
Nutritional deficiency (ND)	$(R_{ND_{min}}, R_{ND}) \equiv (0, 18.5)$
Normal weight (NW)	$[R_{ND}, R_{NW}] \equiv [18.5, 24.9]$
Overweight (OW)	$(R_{NW}, R_{OW}] \equiv (24.9, 29.9]$
Obesity (O)	$(R_{OW}, R_O) \equiv (29.9, 40)$
Extreme obesity (EO)	$[R_O, \infty) \equiv [40, \infty)$
Level of physical activity	**Interval of PAL**
Sedentary (S)	$[R_{S_{min}}, R_S] \equiv [1, 1.39]$
Low active (LA)	$(R_S, R_{LA}] \equiv (1.39, 1.59]$
Active (A)	$(R_{LA}, R_A] \equiv (1.59, 1.89]$
Very active (VA)	$(R_A, R_{VA}] \equiv (1.89, 2.5]$

analysis method for measuring the correlation between model inputs and outputs (Marino et al., 2008). The inputs are the model parameters sampled by LHS, and 1,000 samples were uniformly generated, varying from 0.5 to 2 times the estimated baseline parameter values of reaction kinetics. BMI and PAL are in the range of $(0, 50]$ and $[1, 2.5]$ respectively. PRCCs and corresponding p-values were calculated for the level of each mediator at a steady state in this model, where a significance threshold of $p < 0.01$ was applied (Moise and Friedman, 2019).

2.4. Computational configurations of the inflammatory process

By implementing the baseline parameters, the system of ODEs was solved with a relative accuracy of 0.001 using *ode15s* of implicit method in MATLAB (R2024a, The Math Works, Inc., Natick, MA, USA) to simulate the inflammatory process. The threshold of mechanical damage level (C_{22}) that results in inflammation was computed for various cases, while considering the variations in BMI and PAL. To analyse the effects of physical activity intervention, the temporal variations of inflammatory mediators were simulated according to different levels of BMI (Fig. 3). Normal weight (NO), overweight (OW), low obesity (LO) and high obesity (HO) were four representative cases in simulations. The level of PICs serves as a marker for measuring the level of inflammation. At baseline, the levels of inflammatory mediators stay in a healthy state with the PIC level at a low value of approximately 0.5. A damage level ($C_{22} = 1.2$) was applied at month 12 to induce inflammation, resulting in an increase in the PIC level over 15 in an inflamed state. Meanwhile, different physical activity intervention strategies were performed in the time domain with a mild increased level ($PAL = 1.5$) to neglect the negative effects of overloading. The interval between introducing mechanical damage and the latest allowable start of physical activity intervention that remained effective for preventing inflammation was quantified as the window period. To explore the sensitivity of three main factors (the mechanical damage level, BMI, and the level of physical activity for intervention), the variations of window period were measured in the inflammatory process when varying their values respectively. As the illustrative case, mechanical damage level, BMI and PAL were controlled at 1.2, 25 and 1.5 respectively while serving as covariables. Interventions were simulated over all possible contiguous time frames within the 36-month period.

3. Results

3.1. Parameter sensitivity

The correlations between parameters and the level of each inflammatory mediator were presented by PRCC values in Fig. 4. The higher absolute value of PRCC that is from 0 to 1 reflects the stronger correlation between input samples and measured outputs. Within the given sample space, the production and decay rates exhibited significant correlations with the level of each corresponding mediator, excluding the natural production rates (C_0, C_{12}) in the secretion of PICs and MMPs. This suggested that the activation of the inflammatory process was primarily associated with the stimulating pathways rather than the natural releases of PICs and MMPs that maintain the metabolic balance. In addition, Figs. 4a

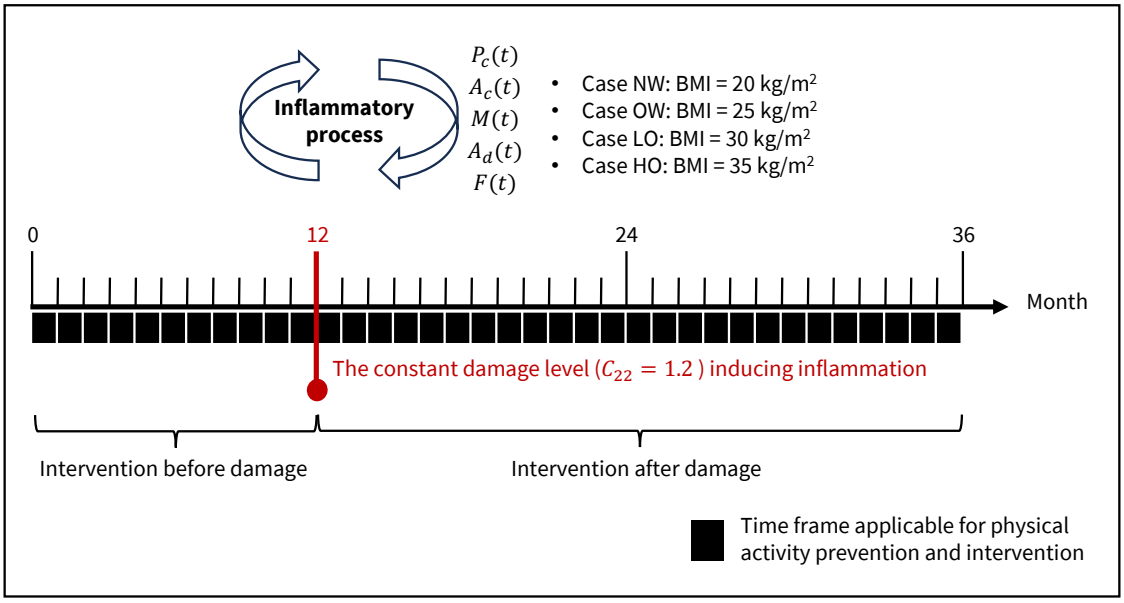

Figure 3: The strategies of physical activity intervention in the inflammatory process for four representative cases (NW: Normal weight; OW: Overweight; LO: Low obesity; HO: High obesity).

and 4b illustrate that the production of Fn-fs (C_{21}, C_{22}) was more correlated to the release of inflammatory cytokines compared with the production of MMPs (C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}). This aligns with their regulatory roles, since MMPs mainly degrade the cartilage tissue to facilitate the release of Fn-fs, the accumulation of which can provoke the immune response (Robinson et al., 2016).

As a predominant risk factor of OA inflammation, the biological effects of obesity result from the regulation of adipokines in this model. The parameters governing adipokine production (C_{18}, C_{19}, BMI^{meas}, PAL, D_4) revealed a significant correlation not only in the level of adipokines (Fig. 4d) but also in the levels of the other four inflammatory mediators (PICs, AICs, MMPs and Fn-fs). Specifically, the relationship between BMI and the inflammatory mediators included in this model was significantly positive whereas PAL negatively correlated to inflammation, as presented in Figs. 4a to 4c and 4e.

It is notable that the parameters of AIC production (C_8, C_9, C_{10}, C_{11}) exhibited a significant correlation only in the level of AICs (Fig. 4b). This implies that AICs, which are released by the stimulation of PICs and damaging products, might play a secondary role in counterbalancing inflammation whilst simultaneously acting as inhibitors of PICs and MMPs.

3.2. Effects of physical activity intervention

The inflammatory mediators were initially at a relatively low level within the system with the estimated baseline parameters in Tables 1 to 5. The increase of PIC level was measured to indicate inflammation in this model. Fig. 5 illustrates the minimum degree of mechanical damage that triggers inflammation when encompassing all levels of BMI and physical activity. In Fig. 5a, the deeper hue indicates the reduced resistance of the system to inflammation induced by mechanical damage. The elevation of PAL can enhance the resistance to inflammation by increasing the threshold for minimal mechanical damage that may initiate an inflammatory response. Compared to the cases of nutritional deficiency and extreme obesity, the increase of low PAL (sedentary and low active) was more effective when BMI level was between normal weight and obesity. Conversely, the case of extreme obesity remained at a high risk of inflammation from mechanical damage, as the sedentary physical activity failed to elevate the damage threshold.

Fig. 5b shows a threshold of BMI leading to inflammation without mechanical damage. Namely, the minimum damage is zero when the BMI value is over the threshold. In this model, the threshold was found in the case of obesity and its value could be decided by the system parameters. In particular, it could be seen that increasing sedentary PAL led to a transition in the BMI threshold within the cases classified as obese and extremely obese in Fig. 5a. This suggests that the enhancement of PAL may effectively increase the threshold.

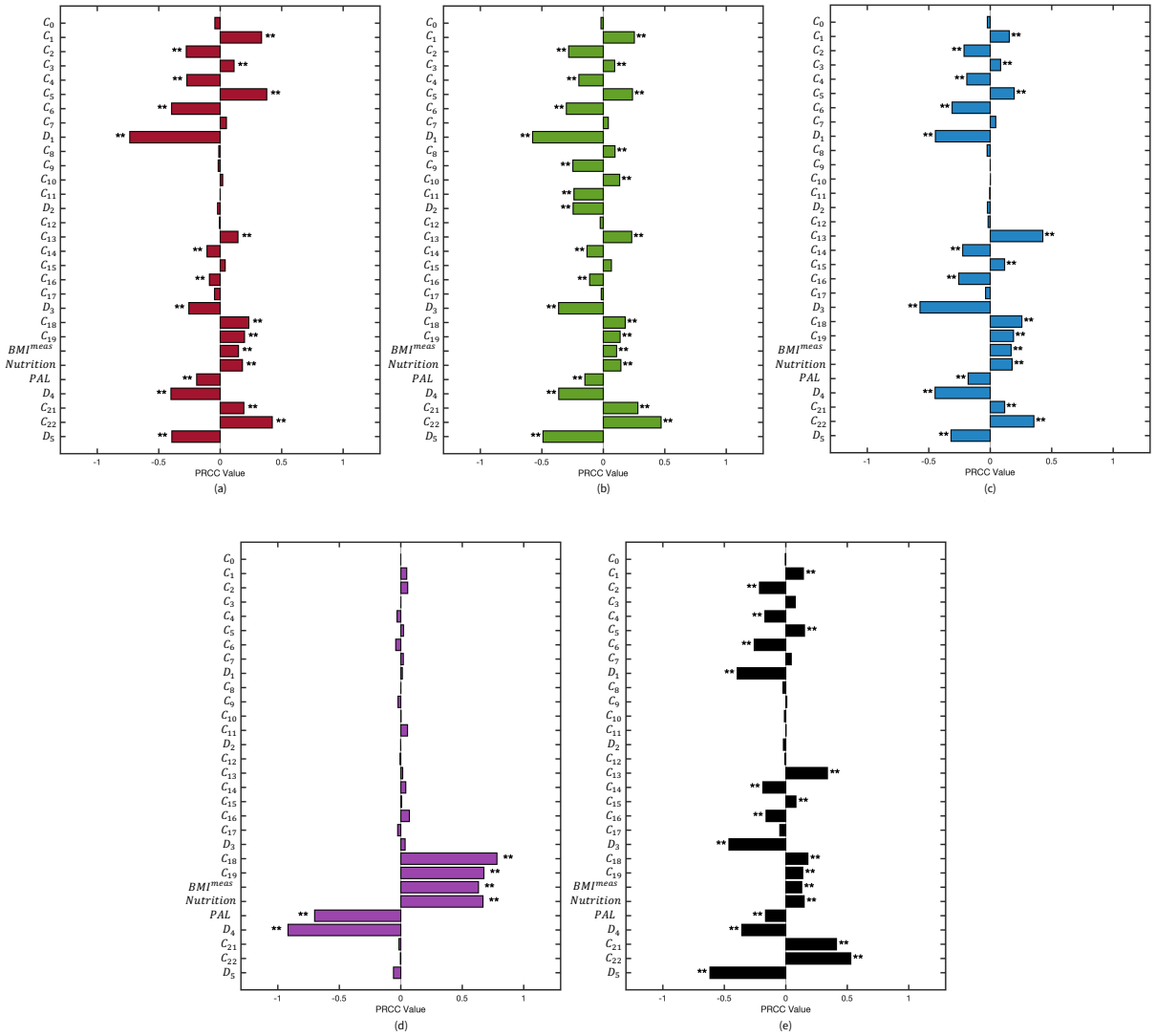

Figure 4: PRCC analysis of the parameters in the inflammatory process. The correlations between parameters and (a) the level of PICs, (b) the level of AICs, (c) the level of MMPs (d) the level of adipokines, and (e) the level of Fn-fs are measured by PRCC values. The significance of correlation is denoted by (**) when p-value is less than 0.01, and PRCC varies from -1 to 1, implying negative and positive correlations between changes in parameters and mediator level.

The inflammatory activities of three cases (NW, OW, LO), applying different strategies of physical activity intervention under the control of mechanical damage ($C_{22} = 1.2$), are shown in Figs. 6 to 8. The sign of inflammation appeared after the introduction of an instant mechanical damage in the case of NW, OW and LO (Figs. 6a to 6c, 7a to 7c and 8a to 8c). This suggests that the intervention of physical activity for reducing adiposity only prior to the onset of damage was insufficient in preventing the activation of inflammatory response. However, a window period of 15 months was found for the case of NW when physical activity interventions began after damage occurred (Figs. 6d to 6f), and the window period decreased to 2 months in the OW case (Figs. 7d to 7f). Within the window period, the activated inflammatory response was attenuated through a reduction in adipokine levels as a result of the continuous physical activity intervention following injury (Figs. 6e and 7e). Nevertheless, the intervention strategy subsequent to injury was ineffective beyond the window period for NW and OW cases (Figs. 6f and 7f). The states of NW, OW and

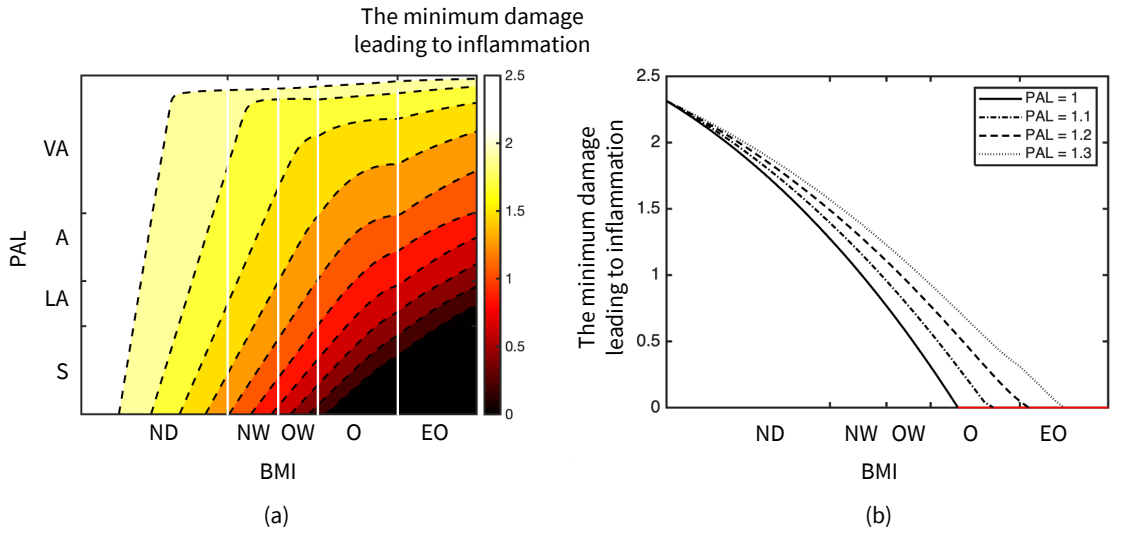

Figure 5: The sensitivity of the mechanical damage threshold leading to inflammation: (a) The distribution of damage threshold (C_{22}) when PAL is from sedentary to very active and BMI is from nutritional deficiency to extreme obesity; (b) The representative relation between damage threshold and BMI at different sedentary PALs, where the red line represents the inflammation state without damage ($C_{22} = 0$).

LO stabilised in the inflammatory state respectively at months 30, 20 and 16 (Figs. 6a, 7a and 8a).This indicated that the progression of inflammatory processes was faster with a higher BMI.

Different to NW and OW cases, LO (Fig. 8) and HO (**Fig. (A.2)**) cases did not exhibit the presence of a window period and any intervention strategies of physical activity were ineffective in hindering the progression of inflammation. Inflammatory activities evolved from a heathy state alongside the mechanical damage in case LO, whilst the case of HO has already stabilised at an inflammation state at the beginning of the simulation time frame (**Fig. (A.2)**). In the case with LO, the intervention of physical activity could still delay the inflammatory responses. When the mixed physical activity intervention persisted until month 18, inflammation reached a stable state at month 22 (Fig. 8g). Extension of the intervention period postponed the time when inflammation was stable to month 32 (Fig. 8i).

Mixed strategies of physical activity intervention appeared to be less effective if the intervention failed to persist after damage occurs, as illustrated in Figs. 6g to 6i and 7g to 7i. This suggested that the duration of physical activity, during which the level of adipokines was downregulated, might play a pivotal role in the evolution of inflammatory processes, in conjunction with the aforementioned window period. Despite being ineffective in preventing inflammation, the mixed intervention strategies that was interrupted at a later time point could still postpone the activation of inflammation. Notably, the temporal delayed effect of mixed intervention strategies in mitigating inflammation also depended on BMI level. The physical activity intervention, maintained until month 24 could effectively control the inflammatory mediators to a relatively low level at month 36, when the BMI level was normal weight (Fig. 6h). In turn, the case of OW evolved into an inflammatory state by month 36 in response to the damage at month 12 (Fig. 7g).

3.3. Window period of physical activity intervention

A window period, where inflammation did not reach steady state, was predicted when a physical activity intervention was simulated. Fig. 9 presents the illustrative variations of the window period, indicating that the mechanical damage level and BMI were more responsive to the outcomes of physical activity interventions in comparison to PAL. By incorporating the variations in damage level, BMI, and PAL, three states of the system were identified with the implementation of physical activity, as summarised in Table 7. The window period decreased dramatically to zero from nearly 15 months when the arbitrary value of mechanical damage increased to 1.5 or BMI level was from normal weight to obesity (Figs. 9a and 9b). However, the elevation of PAL was not able to significantly

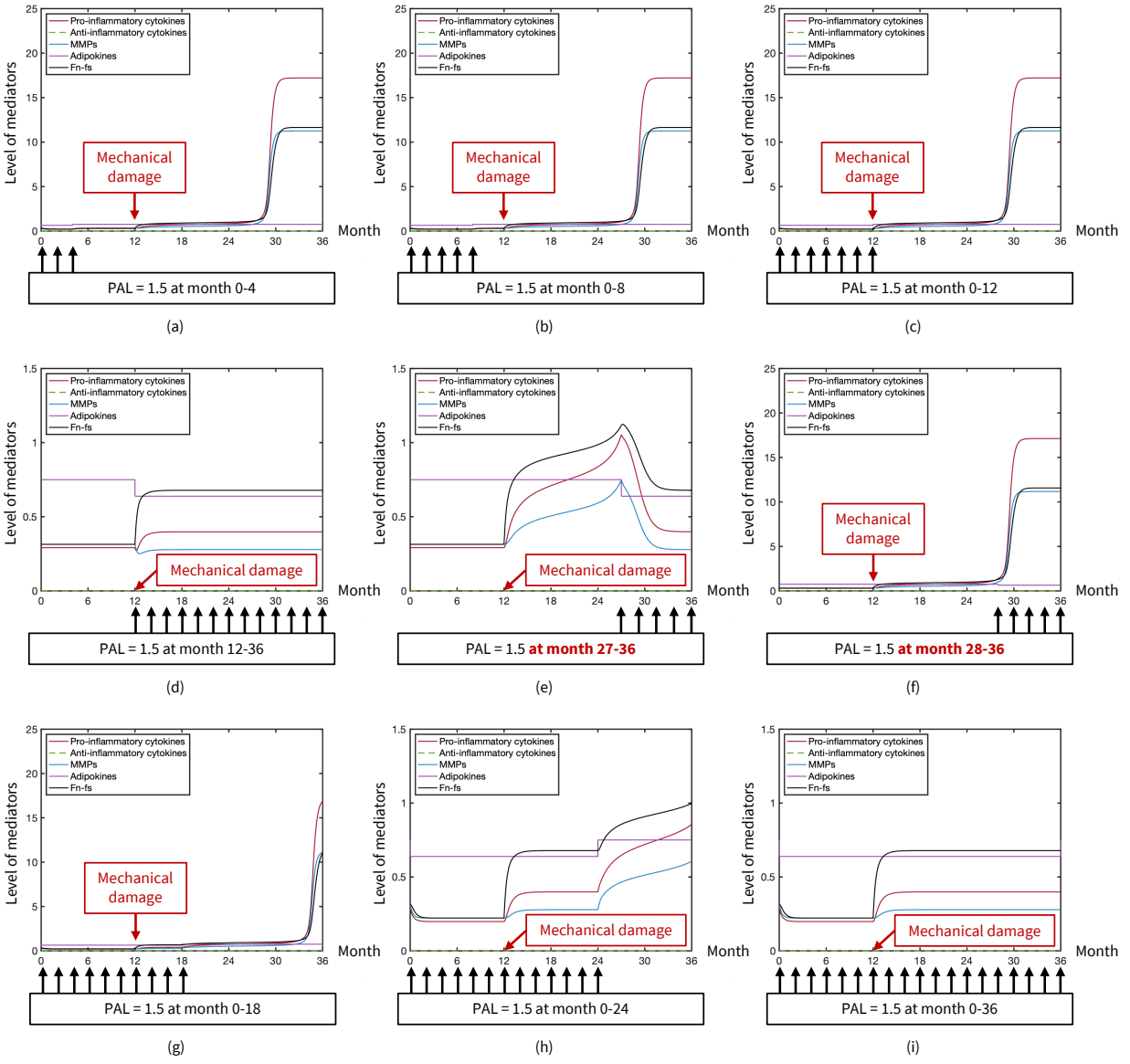

Figure 6: Physical activity interventions in the inflammatory process when BMI level is normal weight: (a)– (c) Only before damage; (d) – (f) Only after damage; (g) – (i) Mixed strategy. The durations of physical activity intervention that are highlighted in red signify the transition from a healthy consequence to an inflamed result due to missing a time window after damage.

extend the span of the window period (Fig. 9c), suggesting that the window period principally depended on the levels of damage and adiposity.

4. Discussion

The effects of adiposity-associated factors, BMI and PAL, were first qualitatively evaluated at a temporal scale in the inflammatory process, based on an established OA inflammation model (Lai and Lacroix, 2025). In this study, BMI and PAL concurrently govern the production of adipokines in inflammatory activities. The time scale was estimated according to the half-life of representative mediators. A global sensitivity analysis exhibited significant correlations

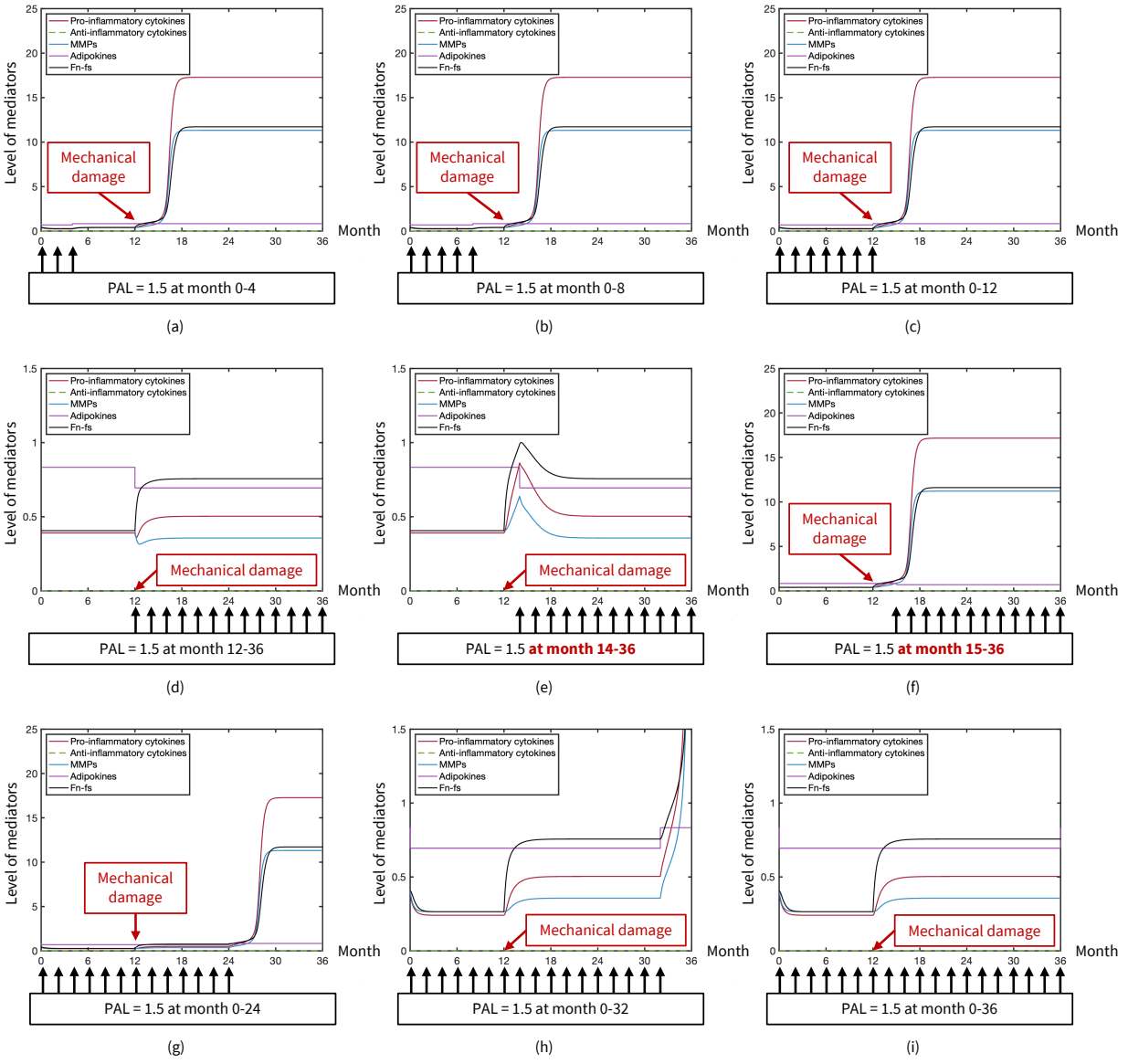

Figure 7: Physical activity interventions in the inflammatory process when BMI level is overweight: (a)– (c) Only before damage; (d) – (f) Only after damage; (g) – (i) Mixed strategy. The durations of physical activity intervention that are highlighted in red signify the transition from a healthy consequence to an inflamed result due to missing a time window after damage.

between the parameters of adipokine production and inflammatory responses, using the LHS/PRCC method. From normal BMI level to obesity, a variety of physical activity intervention strategies were assessed during the onset and progression of inflammation in response to an instant mechanical damage. It was found that the effects of physical activity on OA inflammation differ. This depended on the intervention strategies and BMI levels. The timely and continuous physical activity interventions had the potential to diminish the individual susceptibility to inflammatory responses triggered by damage. This accordingly contributed to delaying and preventing inflammation. In addition, a window period of physical activity interventions was predicted and depended on BMI, PAL and damage level.

Obesity has been regarded as a condition of inflammation in OA due to its role in prompting the release of inflammatory mediators (Wang and He, 2018). The regulatory effects of adipokines are critical in OA inflammation at

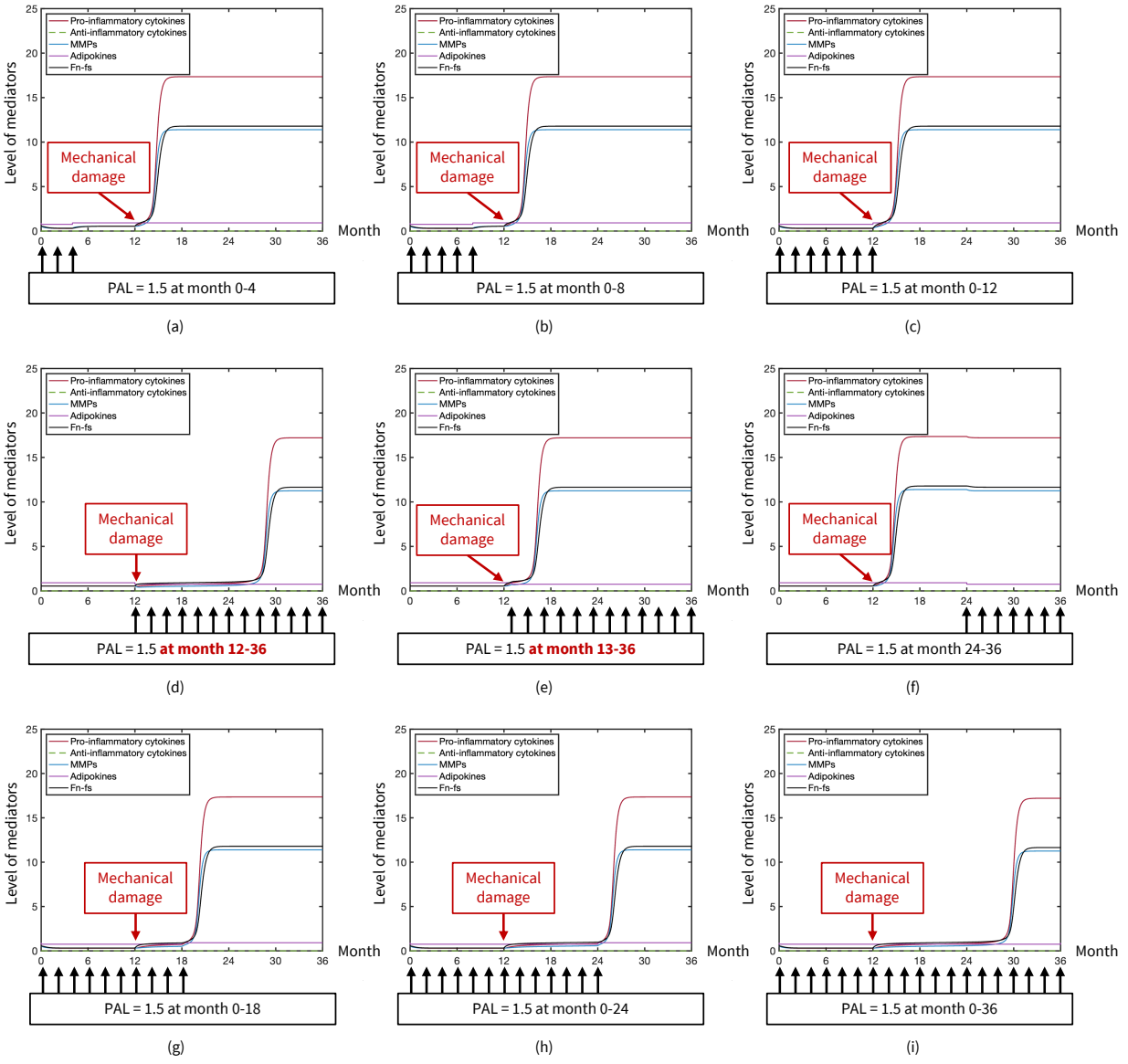

Figure 8: Physical activity interventions in the inflammatory process when BMI level is low obesity: (a)– (c) Only before damage; (d) – (f) Only after damage; (g) – (i) Mixed strategy. The durations of physical activity intervention that are highlighted in red signify no transition from a healthy consequence to an inflamed result after damage.

a molecular level (Zhang et al., 2022; Collins et al., 2021; Chang et al., 2018). The PRCC analysis of the adipokine-mediated inflammation model showed a significant correlation between adipokine production and inflammation. The BMI level and nutrient term positively correlated to the level of inflammatory mediators whilst the correlation between PAL and inflammatory mediators was negative. These correlations suggest the possibility of downregulating OA inflammation through reducing adiposity. In fact, weight management (Miller et al., 2008), dietary control (Griffin et al., 2020; Messier et al., 2013) and physical activity (Sakamoto et al., 2023; Griffin et al., 2012) were reported as effective methods to alleviate inflammation levels in OA, by reducing adiposity. Despite the complexity and multifaceted nature of the regulatory mechanisms associated with adipokines and exercise (Zhang et al., 2022; Kong et al., 2022), their effects ultimately converge on the upregulation and downregulation of inflammatory mediators. This

Table 7
The system states resulting from physical activity intervention when varying the mechanical damage level, BMI and PAL.

System state	Description
I	The state where the system remains in a healthy state without the activation of inflammation
II	The state where the system transits to an inflamed state from a healthy state when inflammation is activated, where a window period exists for the intervention of physical activity
III	The state where the system remains in an inflamed state after the activation of inflammation, where there is no effective window period for the intervention of physical activity

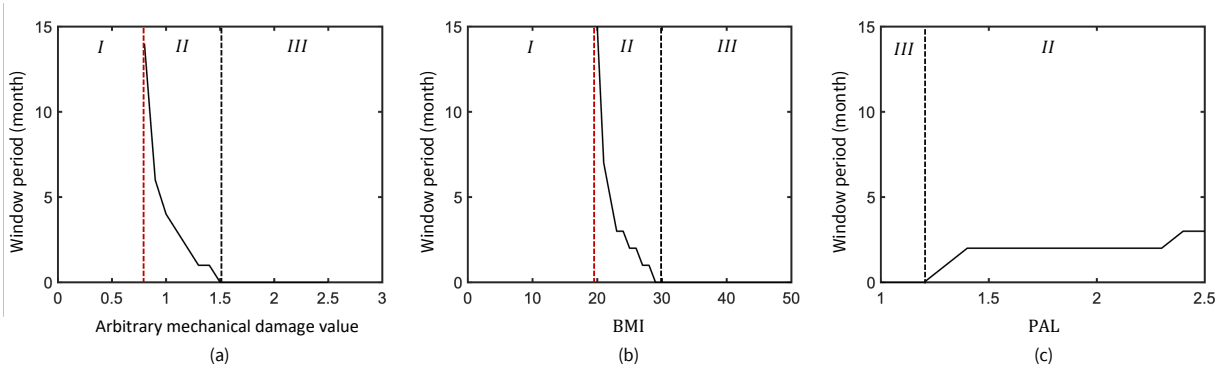

Figure 9: The variations of the window period for effective physical activity interventions in the evolution of the inflammatory process: (a) Sensitivity to the mechanical damage level when BMI = 25 and PAL = 1.5; (b) Sensitivity to the level of BMI when the mechanical damage level = 1.2 and PAL = 1.5; (c) Sensitivity to PAL when the mechanical damage level = 1.2 and BMI = 25.

model provided minimally essential simulations to analyse the effects of BMI and PAL regulating the level of adiposity during inflammatory processes.

In this model, the level of BMI describes the baseline of inflammatory mediators, thereby the increase of BMI results in the higher susceptibility of inflammation in response to mechanical damage. A threshold of BMI was found to maintain the system in chronic inflammation, which is consistent with a previous non-dimensional study (Lai and Lacroix, 2025). This threshold was nearly 33 in this estimated model when PAL was sedentary ($PAL = 1$), and it depended on the variations of parameters. Chronic OA inflammation could be the systemic and local consequence of excessive adipose tissue (Chang et al., 2018). Collins et al. (2021) suggested that the signalling pathways of adipokines might induce systemic inflammation and eventually activate the inflammatory responses within local joints. This regulatory effect of adipokines may also contribute to a state that is more susceptible to inflammation driven by mechanical damage, which could explain the illustrative sensitivity of the damage threshold triggering inflammation when varying BMI and PAL. Similarly, Hahn et al. (2021) suggested that the threshold effect of adiposity might be the cause of the increase of OA incidence in the cohort of high-fat diet induced obesity. Despite the prevailing awareness regarding the importance of mechanical damage in inducing OA inflammation (Sokolove and Lepus, 2013; Robinson et al., 2016; Shumnalieva et al., 2023), it is not yet possible to examine how adiposity affects the susceptibility of damaged cartilaginous tissue to inflammation, due to the complex molecular interplays between joint compartments. In the present paradigm of inflammation, tissue damage signals to the innate immune system to activate a repairing metabolism through PRRs and DAMPs (Orlowsky and Kraus, 2015). This metabolic balance may be disrupted by either excessive tissue damage or adiposity, leading to chronic inflammation. The variations in the BMI threshold and the minimum damage level that induce inflammation could be attributed to changes in metabolic balance driven by alterations in adiposity.

Comparing the effects of physical activity intervention across different levels of BMI (NW, OW, LO, HO), the identical moderate PAL was more effective in managing OA inflammation for cases NW and OW. Furthermore, sustained and long-term intervention strategies demonstrated the capability to inhibit inflammation. Several animal experiments (Hsieh and Yang, 2018; Castrogiovanni et al., 2019; Griffin et al., 2012, 2020; Sakamoto et al., 2023; Huesa et al., 2022) indicated the protective role of physical activity in OA inflammation from the perspective in the outcome of early intervention. Particularly, Huesa et al. (2022) examined the positive effect of exercise on reducing adipose tissue in OA pathology. However, obesity might diminish the benefits of physical activity in the OA pathology. In the study by Griffin et al. (2020), obesity induced by a high-fat diet reduced both systemic and local impacts of exercise on OA. This is consistent with the dependence of intervention outcomes on BMI levels observed in this computational study. Moderate PAL might not be sufficiently effective to reduce the baseline level of inflammation through the loss of adipose tissue in obese cases. Previous studies (Messier et al., 2004, 2013) have also shown the limited effect of physical activity intervention alone and suggested that the combination of dietary and exercise intervention exhibited improvements on OA pathology. Thus, a proper integration of diverse strategies, aiming for the decrease in adiposity level, might be more adaptive to manage OA inflammation for obese cases. It is notable that Runhaar et al. (2019) stressed the anti-inflammatory effects of diet and exercise intervention independent of BMI. This independence might result from the minimal variations in body weight but significant changes in fat mass when BMI remained relatively constant (Thompson et al., 2012; Duclos, 2016).

Although the adiposity-associated factors (BMI and PAL) were evaluated during OA inflammation in this computational study, there are still a number of limitations. As a standard measure of obesity, BMI is the ratio of body weight to height and lacks the accuracy to identify abdominal adiposity compared to the waist circumference (González-Muniesa et al., 2017). This may result in a weaker correlation between BMI and inflammation level (Runhaar et al., 2019). Despite the strong association between both BMI and waist circumference with OA risk (Duclos, 2016; Vasilic-Brasnjevic et al., 2016), BMI has been widely used in the present evidence of adipokine production in OA (Dumond et al., 2003; Poonpet, 2014; Wang and He, 2018). This limited the calibration of this model, and BMI was accordingly considered as a parameter that directly regulates the production of adipokines to alter the inflammatory process. In the model calibration, the variability in PAL-dependent adipokine production was not included due to the lack of data. In addition, the mechanism of early OA pathology has yet to be elaborated due to unmeasurable parameters. As the main intervention strategy of OA inflammation, the regulatory pathway of physical activity was based only on the alteration of adipokine levels. However, exercise can regulate the inflammatory process by the simultaneous actions of mechanical transduction and endocrine effects in vivo studies (Segarra-Queralt et al., 2024). The mechanical effect (Segarra-Queralt et al., 2024) and acute regulation (Runhaar et al., 2019) of physical activity were not assessed by this minimally essential model. Due to the unclear and complex interplay of molecules, this study focused on the ultimate outcomes of tuning the damage level, BMI and PAL rather than exclusively examining different signalling pathways. This model can be further extended by specifying the phenotypes of inflammatory mediators and signal transduction pathways resulting from exercise.

To date, the diagnosis of early OA still lacks a validated standard (Mahmoudian et al., 2021). In this computational study, inflammatory processes were simulated at a continuous time frame from a steady state without mechanical damage. The structural changes at a late stage of OA were not considered. The inflammatory responses in relation to the damage reflected the fluctuation of molecular levels, exhibiting a window period for the effectiveness of physical activity intervention. This window period was tightly associated with the attributes of the inflammation, such as the mechanical damage level and BMI. Namely, the existence of a window period for exercise intervention may vary depending on more complex regulations in the inflammatory process. The duration of the window period was found to range from one month to over 15 months. This stresses the significance of stratifying the risk of OA inflammation in different susceptible groups. For the simplicity of this model, the level of adipokines negatively correlates to PAL on a short-term scale. Nevertheless, the reduction of adiposity requires a long-term implementation of exercise (Saeidi et al., 2021). This could lead to a smaller window period for effective physical activity interventions. The assessment of the baseline factors contributes to the development of diagnostic criteria for early OA (Runhaar et al., 2021; Wang et al., 2022). Interestingly, acquired interventions of physical activity were effective within the window period but might not be sensitive to the span of the window period. This could be explained by the regulatory mechanism of physical activity in this model. Since the effect of physical activity depends on the level of adiposity (Drenowatz et al., 2015), PAL is a parameter that regulates the production of adipokines in the evolution of inflammation. This is different from BMI in this model. From the view point of OA prevention strategies, minimising the risk factors of OA, such as

mechanical damage and obesity, is critical to the primary prevention (Roos and Arden, 2016). Regarding obese cases, proper exercise intervention can be effective in the secondary prevention strategies (Barrow et al., 2019).

In the future, different biochemical entities can be specified to extend and predefine the regulatory network of this inflammation model based on available in vitro and in vivo data (Chow and Chin, 2020; Zhang et al., 2022). Due to challenges in acquiring high-quality longitudinal data, calibration of reaction kinetics is required for specified biomarkers based on their corresponding levels profiled in subject-specific samples, such as synovial fluid, serum or plasma, together with general information including BMI, body weight, diet and physical activity. Samples can be stratified by imaging-based OA assessment to score the tissue damage (Li et al., 2023). The levels of specified biomarkers correspond to the primary variables in this mathematical model, which can be characterised by integrated analysis of untargeted multiomics profiles from subject-specific samples to facilitate model calibration at high resolution (Collins et al., 2025). In addition, the temporal variations in BMI and body weight can be collected through longitudinal anthropometric measures. Lifestyle parameters (PAL and calorie consumptions) can be monitored daily by wearable trackers such as triaxial accelerometer and heart rate sensors (Brooke et al., 2017). Dietary intake can be estimated through food frequency questionnaires (FFQs) (Bailey, 2021; Zheng et al., 2021). Predictive mediator levels from the calibrated model can be compared with independent datasets containing above measurable data to provide more accurate estimations on the window period and the temporal effects of physical activity on the inflammatory process. This may contribute to the personalised development of physical activity strategies of managing OA.

5. Conclusion

This computational study provides novel insights into the interplay between adiposity-associated factors and OA inflammation, using a mechanistic adipokine-mediated inflammation model. For the first time, the critical role of managing adiposity in mitigating the risk of OA inflammation was evaluated using a computational model. It was found that a high BMI increased the baseline level of inflammation, which, in turn, diminished the efficacy of physical activity interventions. This attenuation was particularly pronounced when mechanical joint damage was present. The sensitivity of inflammatory responses to physical activity was modulated by this adiposity-driven inflammation baseline, which underscores the importance of obesity management in OA prevention. Furthermore, the window of physical activity interventions was found to range broadly from 0 to 15 months, and it was more responsive to BMI and mechanical damage than to PAL alone. While long-term physical activity can effectively prevent inflammation in response to the mechanical damage for non-obese cases, its protective benefits are limited for those obese cases without other countermeasures such as dietary control or protection against injury. These results provide insights for designing multi-modal intervention strategies, tailored to subject-specific adiposity and joint health profiles, to better optimise the management of OA inflammation.

6. CRediT authorship contribution statement

Juntong Lai: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Visualisation; Writing - original draft; Writing - review & editing. **Damien Lacroix**: Conceptualisation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Resources; Writing - review & editing.

7. Declaration of competing interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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9. Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used Google Gemini in order to improve readability. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

A. Appendices

Fig. (A.1) The bifurcation of the adipokine production parameter (C_{19}) governed by BMI.

Fig. (A.2) Physical activity interventions in the inflammatory process when BMI level is high obesity: (a)– (c) Only before damage; (d) – (f) Only after damage; (g) – (i) Mixed strategy. The durations of physical activity intervention that are highlighted in red signify no transition from a healthy consequence to an inflamed result after damage.

Fig. (A.3) The sensitivity of the window period to the mechanical damage level when (a) BMI = 20 and PAL = 1.5, (b) BMI = 30 and PAL = 1.5, (c) BMI = 25 and PAL = 2, (d) BMI = 30 and PAL = 2.

References

Bailey, R.L., 2021. Overview of dietary assessment methods for measuring intakes of foods, beverages, and dietary supplements in research studies. Current Opinion in Biotechnology 70, 91–96. doi:10.1016/j.copbio.2021.02.007.

Baker, M., Brook, B.S., Owen, M.R., 2017. Mathematical modelling of cytokines, mmps and fibronectin fragments in osteoarthritic cartilage. Journal of Mathematical Biology 75, 985–1024. doi:10.1007/s00285-017-1104-y.

Barrow, D.R., Abbate, L.M., Paquette, M.R., Driban, J.B., Vincent, H.K., Newman, C., Messier, S.P., Ambrose, K.R., Shultz, S.P., 2019. Exercise prescription for weight management in obese adults at risk for osteoarthritis: Synthesis from a systematic review. BMC Musculoskeletal Disorders 20, 610. doi:10.1186/s12891-019-3004-3.

Blüher, M., 2019. Obesity: Global epidemiology and pathogenesis. Nature Reviews Endocrinology 15, 288–298. doi:10.1038/s41574-019-0176-8.

Brooke, S.M., An, H.S., Kang, S.K., Noble, J.M., Berg, K.E., Lee, J.M., 2017. Concurrent validity of wearable activity trackers under free-living conditions. The Journal of Strength & Conditioning Research 31, 1097. doi:10.1519/JSC.0000000000001571.

Brooks, G.A., Butte, N.F., Rand, W.M., Flatt, J.P., Caballero, B., 2004. Chronicle of the institute of medicine physical activity recommendation: How a physical activity recommendation came to be among dietary recommendations. The American Journal of Clinical Nutrition 79, 921S–930S. doi:10.1093/ajcn/79.5.921S.

Campbell, K., Naire, S., Kuiper, J.H., 2019. A mathematical model of cartilage regeneration after chondrocyte and stem cell implantation – i: The effects of growth factors. Journal of Tissue Engineering 10, 204173141982779. doi:10.1177/2041731419827791.

Castrogiovanni, P., Di Rosa, M., Ravalli, S., Castorina, A., Guglielmino, C., Imbesi, R., Vecchio, M., Drago, F., Szychlinska, M.A., Musumeci, G., 2019. Moderate physical activity as a prevention method for knee osteoarthritis and the role of synoviocytes as biological key. International Journal of Molecular Sciences 20, 511. doi:10.3390/ijms20030511.

Chang, J., Liao, Z., Lu, M., Meng, T., Han, W., Ding, C., 2018. Systemic and local adipose tissue in knee osteoarthritis. Osteoarthritis and Cartilage 26, 864–871. doi:10.1016/j.joca.2018.03.004.

Chow, Y.Y., Chin, K.Y., 2020. The role of inflammation in the pathogenesis of osteoarthritis. Mediators of Inflammation 2020, 1–19. doi:10.1155/2020/8293921.

Collins, K.H., Haugen, I.K., Neogi, T., Guilak, F., 2025. Osteoarthritis as a systemic disease. Nature Reviews Rheumatology , 1–13doi:10.1038/s41584-025-01332-8.

Collins, K.H., Lenz, K.L., Pollitt, E.N., Ferguson, D., Hutson, I., Springer, L.E., Oestreich, A.K., Tang, R., Choi, Y.R., Meyer, G.A., Teitelbaum, S.L., Pham, C.T.N., Harris, C.A., Guilak, F., 2021. Adipose tissue is a critical regulator of osteoarthritis. Proceedings of the National Academy of Sciences 118, e2021096118. doi:10.1073/pnas.2021096118.

Drenowatz, C., Hand, G.A., Sagner, M., Shook, R.P., Burgess, S., Blair, S.N., 2015. The prospective association between different types of exercise and body composition. Medicine & Science in Sports & Exercise 47, 2535–2541. doi:10.1249/MSS.0000000000000701.

Duclos, M., 2016. Osteoarthritis, obesity and type 2 diabetes: The weight of waist circumference. Annals of Physical and Rehabilitation Medicine 59, 157–160. doi:10.1016/j.rehab.2016.04.002.

Dumond, H., Presle, N., Terlain, B., Mainard, D., Loeuille, D., Netter, P., Pottie, P., 2003. Evidence for a key role of leptin in osteoarthritis. Arthritis & Rheumatism 48, 3118–3129. doi:10.1002/art.11303.

Felson, D., 2013. Osteoarthritis as a disease of mechanics. Osteoarthritis and Cartilage 21, 10–15. doi:10.1016/j.joca.2012.09.012.

Ferrao Blanco, M.N., Lesage, R., Kops, N., Fahy, N., Bekedam, F.T., Chavli, A., Bastiaansen-Jenniskens, Y.M., Geris, L., Chambers, M.G., Pitsillides, A.A., Narcisi, R., Van Osch, G.J., 2024. A multi-model approach identifies alw-ii-41-27 as a promising therapy for osteoarthritis-associated inflammation and endochondral ossification. Heliyon 10, e40871. doi:10.1016/j.heliyon.2024.e40871.

González-Muniesa, P., Mártinez-González, M.A., Hu, F.B., Després, J.P., Matsuzawa, Y., Loos, R.J.F., Moreno, L.A., Bray, G.A., Martinez, J.A., 2017. Obesity. Nature Reviews Disease Primers 3, 17034. doi:10.1038/nrdp.2017.34.

Griffin, T.M., Batushansky, A., Hudson, J., Lopes, E.B.P., 2020. Correlation network analysis shows divergent effects of a long-term, high-fat diet and exercise on early stage osteoarthritis phenotypes in mice. Journal of Sport and Health Science 9, 119–131. doi:10.1016/j.jshs.2019.05.008.

Griffin, T.M., Huebner, J.L., Kraus, V.B., Yan, Z., Guilak, F., 2012. Induction of osteoarthritis and metabolic inflammation by a very high-fat diet in mice: Effects of short-term exercise. Arthritis & Rheumatism 64, 443–453. doi:10.1002/art.33332.

Hahn, A.K., Batushansky, A., Rawle, R.A., Lopes, E.B.P., June, R.K., Griffin, T.M., 2021. Effects of long-term exercise and a high-fat diet on synovial fluid metabolomics and joint structural phenotypes in mice: An integrated network analysis. Osteoarthritis and Cartilage 29, 1549–1563. doi:10.1016/j.joca.2021.08.008.

Homandberg, G.A., Wen, C., Hui, F., 1998. Cartilage damaging activities of fibronectin fragments derived from cartilage and synovial fluid. Osteoarthritis and Cartilage 6, 231–244. doi:10.1053/joca.1998.0116.

Hsieh, Y.L., Yang, C.C., 2018. Early intervention of swimming exercises attenuate articular cartilage destruction in a rat model of anterior cruciate ligament and meniscus knee injuries. Life Sciences 212, 267–274. doi:10.1016/j.lfs.2018.10.013.

Huesa, C., Dunning, L., MacDougall, K., Fegen, M., Ortiz, A., McCulloch, K., McGrath, S., Litherland, G.J., Crilly, A., Van 'T Hof, R.J., Ferrell, W.R., Goodyear, C.S., Lockhart, J.C., 2022. Moderate exercise protects against joint disease in a murine model of osteoarthritis. Frontiers in Physiology 13. doi:10.3389/fphys.2022.1065278.

Huffman, K.F., Ambrose, K.R., Nelson, A.E., Allen, K.D., Golightly, Y.M., Callahan, L.F., 2024. The critical role of physical activity and weight management in knee and hip osteoarthritis: A narrative review. The Journal of Rheumatology 51, 224–233. doi:10.3899/jrheum.2023-0819.

Hunter, D.J., Deveza, L.A., 2025. Deconstructing the "types" of osteoarthritis. Osteoarthritis Imaging 5, 100257. doi:10.1016/j.ostima.2024.100257.

Kapitanov, G.I., Wang, X., Ayati, B.P., Brouillette, M.J., Martin, J.A., 2016. Linking cellular and mechanical processes in articular cartilage lesion formation: A mathematical model. Frontiers in Bioengineering and Biotechnology 4. doi:10.3389/fbioe.2016.00080.

Kar, S., Smith, D.W., Gardiner, B.S., Li, Y., Wang, Y., Grodzinsky, A.J., 2016. Modeling il-1 induced degradation of articular cartilage. Archives of Biochemistry and Biophysics 594, 37–53. doi:10.1016/j.abb.2016.02.008.

Klein, S., Coppack, S.W., Mohamed-Ali, V., Landt, M., 1996. Adipose tissue leptin production and plasma leptin kinetics in humans. Diabetes 45, 984–987. doi:10.2337/diab.45.7.984.

Kong, H., Wang, X.Q., Zhang, X.A., 2022. Exercise for osteoarthritis: A literature review of pathology and mechanism. Frontiers in Aging Neuroscience 14. doi:10.3389/fnagi.2022.854026.

Kroon, F., Veenbrink, A., de Mutsert, R., Visser, A., van Dijk, K., le Cessie, S., Rosendaal, F., Kloppenburg, M., 2019. The role of leptin and adiponectin as mediators in the relationship between adiposity and hand and knee osteoarthritis. Osteoarthritis and Cartilage 27, 1761–1767. doi:10.1016/j.joca.2019.08.003.

Lai, J., Lacroix, D., 2025. Mathematical modelling of inflammatory process and obesity in osteoarthritis. PLOS ONE 20, e0323258. doi:10.1371/journal.pone.0323258.

Leifer, V.P., Katz, J.N., Losina, E., 2022. The burden of oa-health services and economics. Osteoarthritis and Cartilage 30, 10–16. doi:10.1016/j.joca.2021.05.007.

Lesage, R., Ferrao Blanco, M.N., Narcisi, R., Welting, T., van Osch, G.J.V.M., Geris, L., 2022. An integrated in silico-in vitro approach for identifying therapeutic targets against osteoarthritis. BMC Biology 20, 253. doi:10.1186/s12915-022-01451-8.

Li, X., Roemer, F.W., Cicuttini, F., MacKay, J.W., Turmezei, T., Link, T.M., 2023. Early knee oa definition–what do we know at this stage? an imaging perspective. Therapeutic Advances in Musculoskeletal Disease 15, 1759720X231158204. doi:10.1177/1759720X231158204.

Liu, C., Chu, D., Kalantar-Zadeh, K., George, J., Young, H.A., Liu, G., 2021. Cytokines: From clinical significance to quantification. Advanced Science 8, 2004433. doi:10.1002/advs.202004433.

Mahmoudian, A., Lohmander, L.S., Mobasheri, A., Englund, M., Luyten, F.P., 2021. Early-stage symptomatic osteoarthritis of the knee — time for action. Nature Reviews Rheumatology 17, 621–632. doi:10.1038/s41584-021-00673-4.

Marino, S., Hogue, I.B., Ray, C.J., Kirschner, D.E., 2008. A methodology for performing global uncertainty and sensitivity analysis in systems biology. Journal of Theoretical Biology 254, 178–196. doi:10.1016/j.jtbi.2008.04.011.

Mehana, E.S.E., Khafaga, A.F., El-Blehi, S.S., 2019. The role of matrix metalloproteinases in osteoarthritis pathogenesis: An updated review. Life Sciences 234, 116786. doi:10.1016/j.lfs.2019.116786.

Messier, S.P., Loeser, R.F., Miller, G.D., Morgan, T.M., Rejeski, W.J., Sevick, M.A., Ettinger Jr., W.H., Pahor, M., Williamson, J.D., 2004. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: The arthritis, diet, and activity promotion trial. Arthritis & Rheumatism 50, 1501–1510. doi:10.1002/art.20256.

Messier, S.P., Mihalko, S.L., Legault, C., Miller, G.D., Nicklas, B.J., DeVita, P., Beavers, D.P., Hunter, D.J., Lyles, M.F., Eckstein, F., Williamson, J.D., Carr, J.J., Guermazi, A., Loeser, R.F., 2013. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: The idea randomized clinical trial. JAMA 310, 1263. doi:10.1001/jama.2013.277669.

Miller, G.D., Nicklas, B.J., Loeser, R.F., 2008. Inflammatory biomarkers and physical function in older, obese adults with knee pain and self-reported osteoarthritis after intensive weight-loss therapy. Journal of the American Geriatrics Society 56, 644–651. doi:10.1111/j.1532-5415.2007.01636.x.

Moise, N., Friedman, A., 2019. Rheumatoid arthritis - a mathematical model. Journal of Theoretical Biology 461, 17–33. doi:10.1016/j.jtbi.2018.10.039.

Mukherjee, S., Nazemi, M., Jonkers, I., Geris, L., 2020. Use of computational modeling to study joint degeneration: A review. Frontiers in Bioengineering and Biotechnology 8, 93. doi:10.3389/fbioe.2020.00093.

Nees, T.A., Rosshirt, N., Zhang, J.A., Reiner, T., Sorbi, R., Tripel, E., Walker, T., Schiltenwolf, M., Hagmann, S., Moradi, B., 2019. Synovial cytokines significantly correlate with osteoarthritis-related knee pain and disability: Inflammatory mediators of potential clinical relevance. Journal of Clinical Medicine 8, 1343. doi:10.3390/jcm8091343.

Orlowsky, E.W., Kraus, V.B., 2015. The role of innate immunity in osteoarthritis: When our first line of defense goes on the offensive. The Journal of Rheumatology 42, 363–371. doi:10.3899/jrheum.140382.

Pérez-García, S., Carrión, M., Gutiérrez-Cañas, I., Villanueva-Romero, R., Castro, D., Martínez, C., González-Álvaro, I., Blanco, F.J., Juarranz, Y., Gomariz, R.P., 2019. Profile of matrix-remodeling proteinases in osteoarthritis: Impact of fibronectin. Cells 9, 40. doi:10.3390/cells9010040.

Poonpet, T., 2014. Adipokines: Biomarkers for osteoarthritis? World Journal of Orthopedics 5, 319. doi:10.5312/wjo.v5.i3.319.

Rahman, M.M., Watton, P.N., Neu, C.P., Pierce, D.M., 2023. A chemo-mechano-biological modeling framework for cartilage evolving in health, disease, injury, and treatment. Computer Methods and Programs in Biomedicine 231, 107419. doi:10.1016/j.cmpb.2023.107419.

Reyes, C., Leyland, K.M., Peat, G., Cooper, C., Arden, N.K., Prieto-Alhambra, D., 2016. Association between overweight and obesity and risk of clinically diagnosed knee, hip, and hand osteoarthritis: A population-based cohort study. Arthritis & Rheumatology 68, 1869–1875. doi:10.1002/art.39707.

Robinson, W.H., Lepus, C.M., Wang, Q., Raghu, H., Mao, R., Lindstrom, T.M., Sokolove, J., 2016. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. Nature Reviews Rheumatology 12, 580–592. doi:10.1038/nrrheum.2016.136.

Roos, E.M., Arden, N.K., 2016. Strategies for the prevention of knee osteoarthritis. Nature Reviews Rheumatology 12, 92–101. doi:10.1038/nrrheum.2015.135.

Runhaar, J., Beavers, D.P., Miller, G.D., Nicklas, B.J., Loeser, R.F., Bierma-Zeinstra, S., Messier, S.P., 2019. Inflammatory cytokines mediate the effects of diet and exercise on pain and function in knee osteoarthritis independent of bmi. Osteoarthritis and Cartilage 27, 1118–1123. doi:10.1016/j.joca.2019.04.009.

Runhaar, J., Kloppenburg, M., Boers, M., Bijlsma, J.W.J., Bierma-Zeinstra, S.M.A., and the CREDO expert group, 2021. Towards developing diagnostic criteria for early knee osteoarthritis: Data from the check study. Rheumatology 60, 2448–2455. doi:10.1093/rheumatology/keaa643.

Saeidi, A., Haghighi, M.M., Kolahdouzi, S., Daraei, A., Abderrahmane, A.B., Essop, M.F., Laher, I., Hackney, A.C., Zouhal, H., 2021. The effects of physical activity on adipokines in individuals with overweight/obesity across the lifespan: A narrative review. Obesity Reviews 22, e13090. doi:10.1111/obr.13090.

Sakamoto, J., Miyahara, S., Motokawa, S., Takahashi, A., Sasaki, R., Honda, Y., Okita, M., 2023. Regular walking exercise prior to knee osteoarthritis reduces joint pain in an animal model. PLOS ONE 18, e0289765. doi:10.1371/journal.pone.0289765.

Scanzello, C.R., 2017. Chemokines and inflammation in osteoarthritis: Insights from patients and animal models: Chemokines in osteoarthritis. Journal of Orthopaedic Research 35, 735–739. doi:10.1002/jor.23471.

Segarra-Queralt, M., Crump, K., Pascuet-Fontanet, A., Gantenbein, B., Noailly, J., 2024. The interplay between biochemical mediators and mechanotransduction in chondrocytes: Unravelling the differential responses in primary knee osteoarthritis. Physics of Life Reviews 48, 205–221. doi:10.1016/j.plrev.2024.02.003.

Segarra-Queralt, M., Neidlin, M., Tio, L., Monfort, J., Monllau, J.C., González Ballester, M.Á., Alexopoulos, L.G., Piella, G., Noailly, J., 2022. Regulatory network-based model to simulate the biochemical regulation of chondrocytes in healthy and osteoarthritic environments. Scientific Reports 12, 3856. doi:10.1038/s41598-022-07776-2.

Segarra-Queralt, M., Piella, G., Noailly, J., 2023. Network-based modelling of mechano-inflammatory chondrocyte regulation in early osteoarthritis. Frontiers in Bioengineering and Biotechnology 11, 1006066. doi:10.3389/fbioe.2023.1006066.

Shumnalieva, R., Kotov, G., Monov, S., 2023. Obesity-related knee osteoarthritis—current concepts. Life 13, 1650. doi:10.3390/life13081650.

Skou, S.T., Pedersen, B.K., Abbott, J.H., Patterson, B., Barton, C., 2018. Physical activity and exercise therapy benefit more than just symptoms and impairments in people with hip and knee osteoarthritis. Journal of Orthopaedic & Sports Physical Therapy 48, 439–447. doi:10.2519/jospt.2018.7877.

Sokolove, J., Lepus, C.M., 2013. Role of inflammation in the pathogenesis of osteoarthritis: Latest findings and interpretations. Therapeutic Advances in Musculoskeletal Disease 5, 77–94. doi:10.1177/1759720X12467868.

Steinmetz, J.D., Culbreth, G.T., Haile, L.M., Rafferty, Q., Lo, J., Fukutaki, K.G., Cruz, J.A., Smith, A.E., Vollset, S.E., Brooks, P.M., Cross, M., Woolf, A.D., Hagins, H., Abbasi-Kangevari, M., Abedi, A., Ackerman, I.N., Amu, H., Antony, B., Arabloo, J., Aravkin, A.Y., Argaw, A.M., Artamonov, A.A., Ashraf, T., Barrow, A., Bearne, L.M., Bensenor, I.M., Berhie, A.Y., Bhardwaj, N., Bhardwaj, P., Bhojaraja, V.S., Bijani, A., Briant, P.S., Briggs, A.M., Butt, N.S., Charan, J., Chattu, V.K., Cicuttini, F.M., Coberly, K., Dadras, O., Dai, X., Dandona, L., Dandona, R., De Luca, K., Denova-Gutiérrez, E., Dharmaratne, S.D., Dhimal, M., Dianatinasab, M., Dreinhoefer, K.E., Elhadi, M., Farooque, U., Farpour, H.R., Filip, I., Fischer, F., Freitas, M., Ganesan, B., Gemeda, B.N.B., Getachew, T., Ghamari, S.H., Ghashghaee, A., Gill, T.K., Golechha, M., Golinelli, D., Gupta, B., Gupta, V.B., Gupta, V.K., Haddadi, R., Hafezi-Nejad, N., Halwani, R., Hamidi, S., Hanif, A., Harlianto, N.I., Haro, J.M., Hartvigsen, J., Hay, S.I., Hebert, J.J., Heidari, G., Hosseini, M.S., Hosseinzadeh, M., Hsiao, A.K., Ilic, I.M., Ilic, M.D., Jacob, L., Jayawardena, R., Jha, R.P., Jonas, J.B., Joseph, N., Kandel, H., Karaye, I.M., Khan, M.J., Kim, Y.J., Kolahi, A.A., Korzh, O., Koteeswaran, R., Krishnamoorthy, V., Kumar, G.A., Kumar, N., Lee, S.w., Lim, S.S., Lobo, S.W., Lucchetti, G., Malekpour, M.R., Malik, A.A., Mandarano-Filho, L.G.G., Martini, S., Mentis, A.F.A., Mesregah, M.K., Mestrovic, T., Mirrakhimov, E.M., Misganaw, A., Mohammadpourhodki, R., Mokdad, A.H., Momtazmanesh, S., Morrison, S.D., Murray, C.J.L., Nassereldine, H., Netsere, H.B., Neupane Kandel, S., Owolabi, M.O., Panda-Jonas, S., Pandey, A., Pawar, S., Pedersini, P., Pereira, J., Radfar, A., Rashidi, M.M., Rawaf, D.L., Rawaf, S., Rawassizadeh, R., Rayegani, S.M., Ribeiro, D., Roever, L., Saddik, B., Sahebkar, A., Salehi, S., Sanchez Riera, L., Sanmarchi, F., Santric-Milicevic, M.M., Shahabi, S., Shaikh, M.A., Shaker, E., Shannawaz, M., Sharma, R., Sharma, S., Shetty, J.K., Shiri, R., Shobeiri, P., Silva, D.A.S., Singh, A., Singh, J.A., Singh, S., Skou, S.T., Slater, H., Soltani-Zangbar, M.S., Starodubova, A.V., Tehrani-Banihashemi, A., Valadan Tahbaz, S., Valdez, P.R., Vo, B., Vu, L.G., Wang, Y.P., Yahyazadeh Jabbari, S.H., Yonemoto, N., Yunusa, I., March, L.M., Ong, K.L., Vos, T., Kopec, J.A., 2023. Global, regional, and national burden of osteoarthritis, 1990–2020 and projections to 2050: A systematic analysis for the global burden of disease study 2021. The Lancet Rheumatology 5, e508–e522. doi:10.1016/S2665-9913(23)00163-7.

Tang, S., Zhang, C., Oo, W.M., Fu, K., Risberg, M.A., Bierma-Zeinstra, S.M., Neogi, T., Atukorala, I., Malfait, A.M., Ding, C., Hunter, D.J., 2025. Osteoarthritis. Nature Reviews Disease Primers 11, 1–22. doi:10.1038/s41572-025-00594-6.

Thompson, D., Karpe, F., Lafontan, M., Frayn, K., 2012. Physical activity and exercise in the regulation of human adipose tissue physiology. Physiological Reviews 92, 157–191. doi:10.1152/physrev.00012.2011.

Vasilic-Brasnjevic, S., Marinkovic, J., Vlajinac, H., Vasiljevic, N., Jakovljevic, B., Nikic, M., Maksimovic, M., 2016. Association of body mass index and waist circumference with severity of knee osteoarthritis. Acta reumatologica portuguesa 2016.

Wang, Q., Runhaar, J., Kloppenburg, M., Boers, M., Bijlsma, J.W.J., Bierma-Zeinstra, S.M.A., 2022. Diagnosis for early stage knee osteoarthritis: Probability stratification, internal and external validation; data from the check and oai cohorts. Seminars in Arthritis and Rheumatism 55, 152007. doi:10.1016/j.semarthrit.2022.152007.

Wang, T., He, C., 2018. Pro-inflammatory cytokines: The link between obesity and osteoarthritis. Cytokine & Growth Factor Reviews 44, 38–50. doi:10.1016/j.cytogfr.2018.10.002.

Wojdasiewicz, P., Poniatowski, Ł.A., Szukiewicz, D., 2014. The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. Mediators of Inflammation 2014, 1–19. doi:10.1155/2014/561459.

Zeng, N., Yan, Z.P., Chen, X.Y., Ni, G.X., 2020. Infrapatellar fat pad and knee osteoarthritis. Aging and disease 11, 1317. doi:10.14336/AD.2019.1116.

Zhang, C., Lin, Y., Yan, C.H., Zhang, W., 2022. Adipokine signaling pathways in osteoarthritis. Frontiers in Bioengineering and Biotechnology 10, 865370. doi:10.3389/fbioe.2022.865370.

Zheng, S., Wu, F., Winzenberg, T., Cicuttini, F., Wluka, A.E., Antony, B., Aitken, D., Blizzard, L., Ding, C., 2021. The cross-sectional and longitudinal associations of dietary patterns with knee symptoms and mri detected structure in patients with knee osteoarthritis. Osteoarthritis and Cartilage 29, 527–535. doi:10.1016/j.joca.2020.12.023.

Zhou, S., Maleitzke, T., Geissler, S., Hildebrandt, A., Fleckenstein, F.N., Niemann, M., Fischer, H., Perka, C., Duda, G.N., Winkler, T., 2022. Source and hub of inflammation: The infrapatellar fat pad and its interactions with articular tissues during knee osteoarthritis. Journal of Orthopaedic Research 40, 1492–1504. doi:10.1002/jor.25347.