Osteoarthritis: a systemic inflammatory and metabolic disease of primary care

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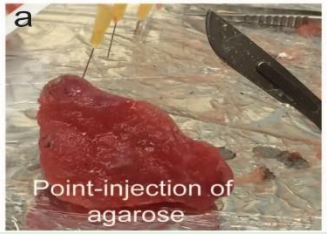
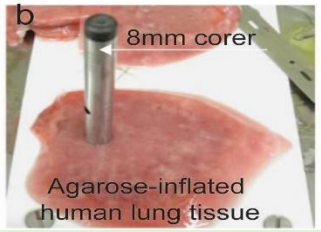
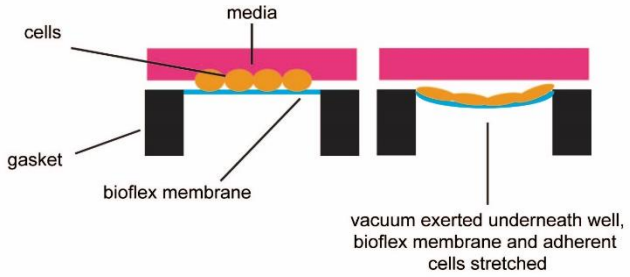
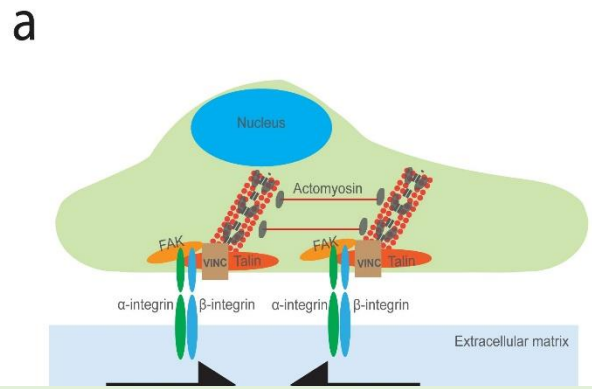
background: **Academic Clinical Fellow in primary care / mechanobiologist**

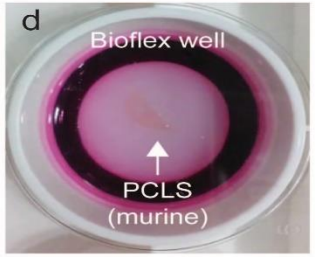


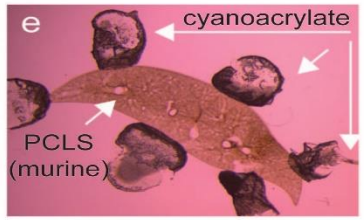


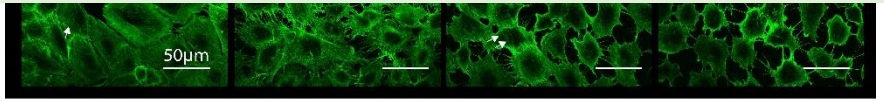


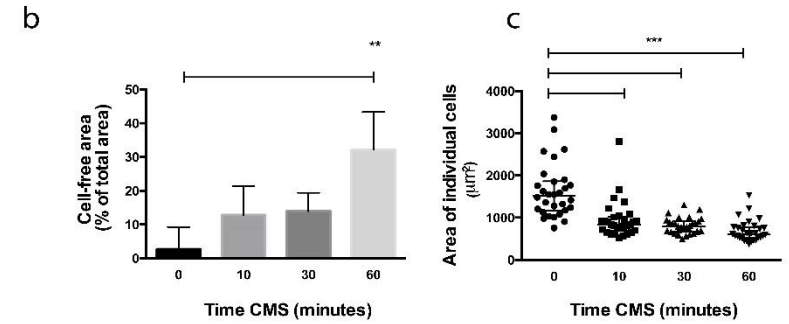


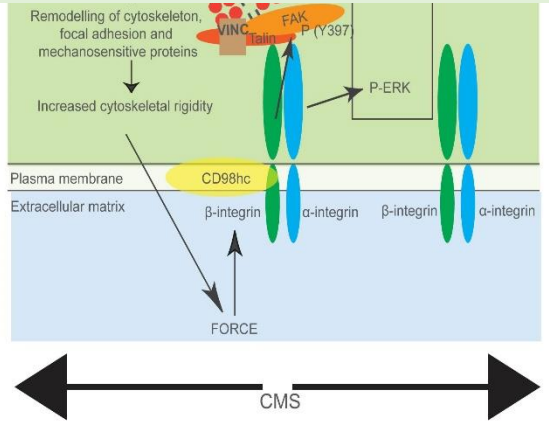
Cells and tissues are adapted to respond to mechanical force









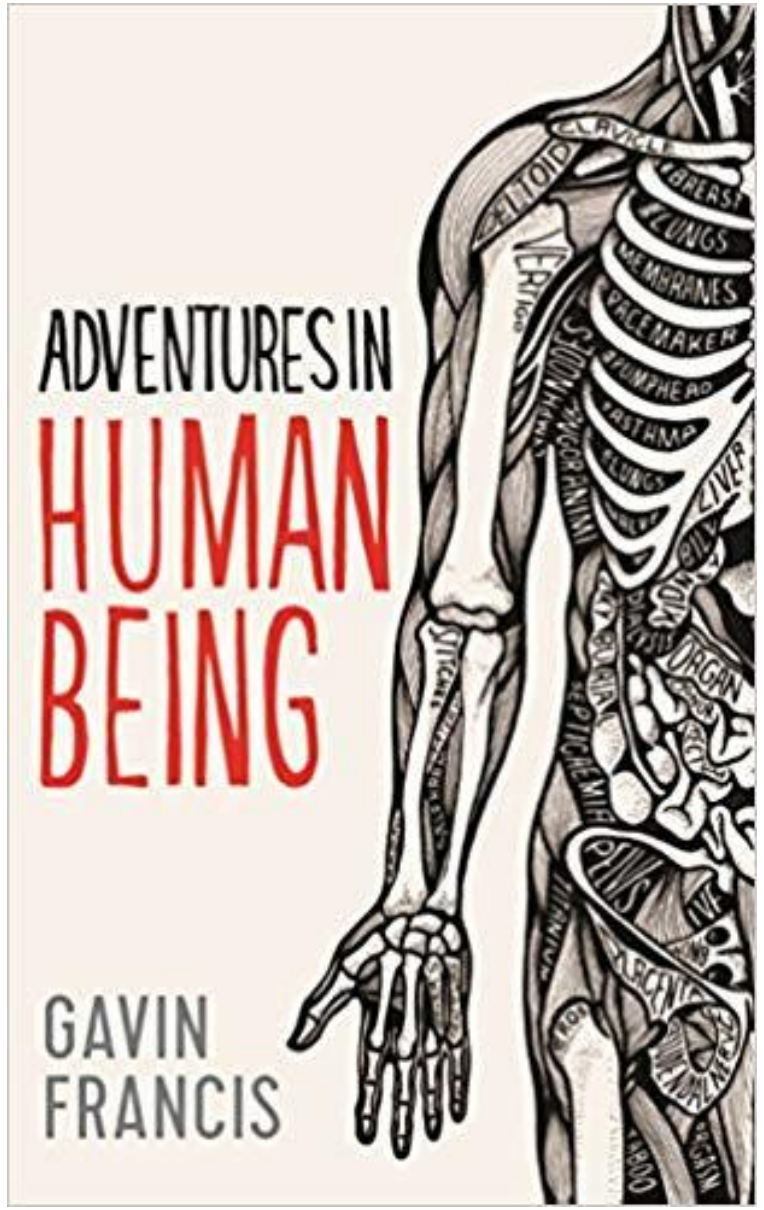


background: Academic Clinical Fellow in primary care / musculoskeletal sciences

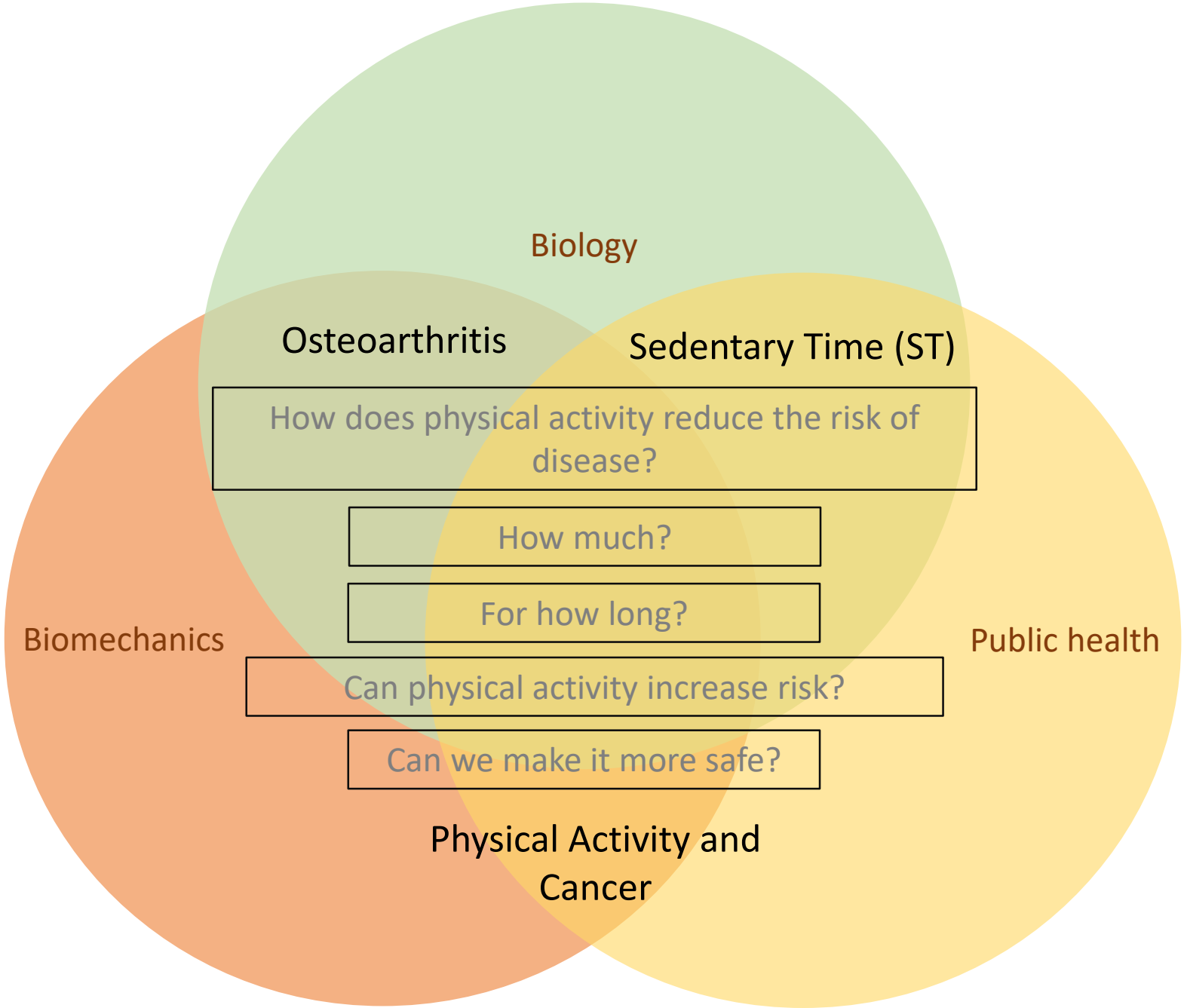
Disease

Prevention → Treatment → Palliation

- Academic trainee in primary care from 2017-2021
- Aim to practice as a GP with interest in sports and exercise, and academic component
- The messy of world of preventative/ lifestyle medicine



strategy: **Where biomechanics meets biology and public health**



osteoarthritis: a significant burden

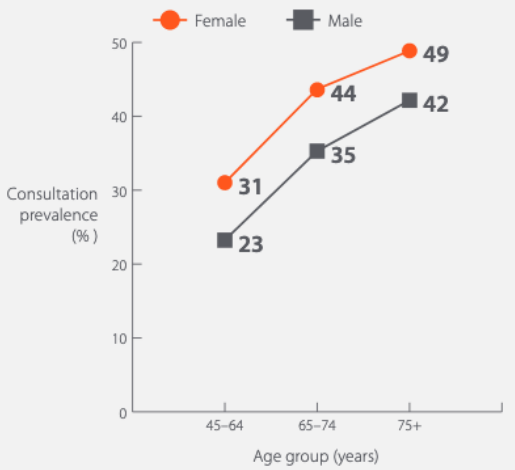
ARUK 2013

- Most common joint disease worldwide Woolf 2003
- Is a disease of primary care: 1/3rd of people aged over 45 in the UK have sought treatment for osteoarthritis from their GP ARUK 2013
- Is a significant socio-economic burden: In developed countries cost between 1 and 2.5% GDP Hiligsman 2013 OA accounts for >90% of lower limb joint replacements Hartvigsen 2014
- Burden is increasing: predicted to affect over 130 million individuals worldwide Breedveld 2004

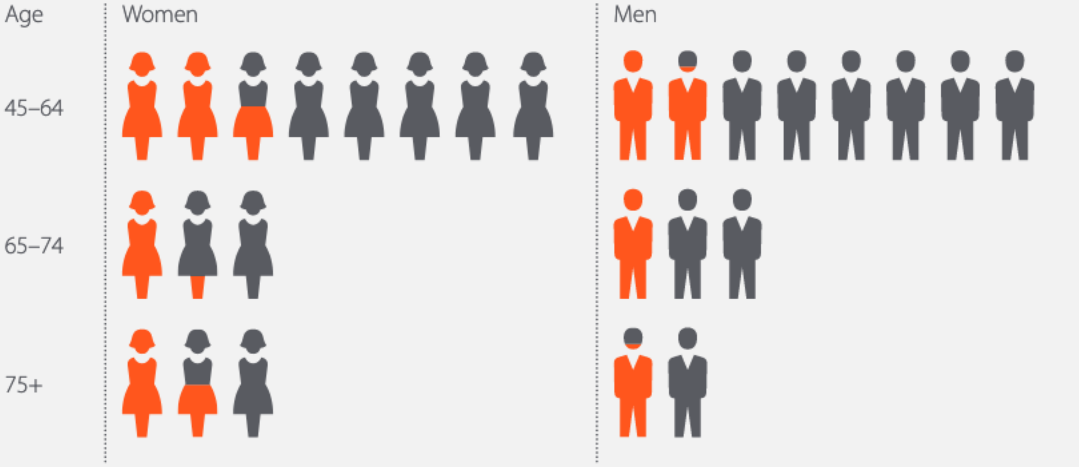
4.1: How many people in the UK have osteoarthritis?

This graph shows the estimated number of people in the UK who have sought treatment for osteoarthritis, by gender and age group. A total of **8.75 million people** in the UK have sought treatment about osteoarthritis.*

4.2: How common is osteoarthritis in the UK?



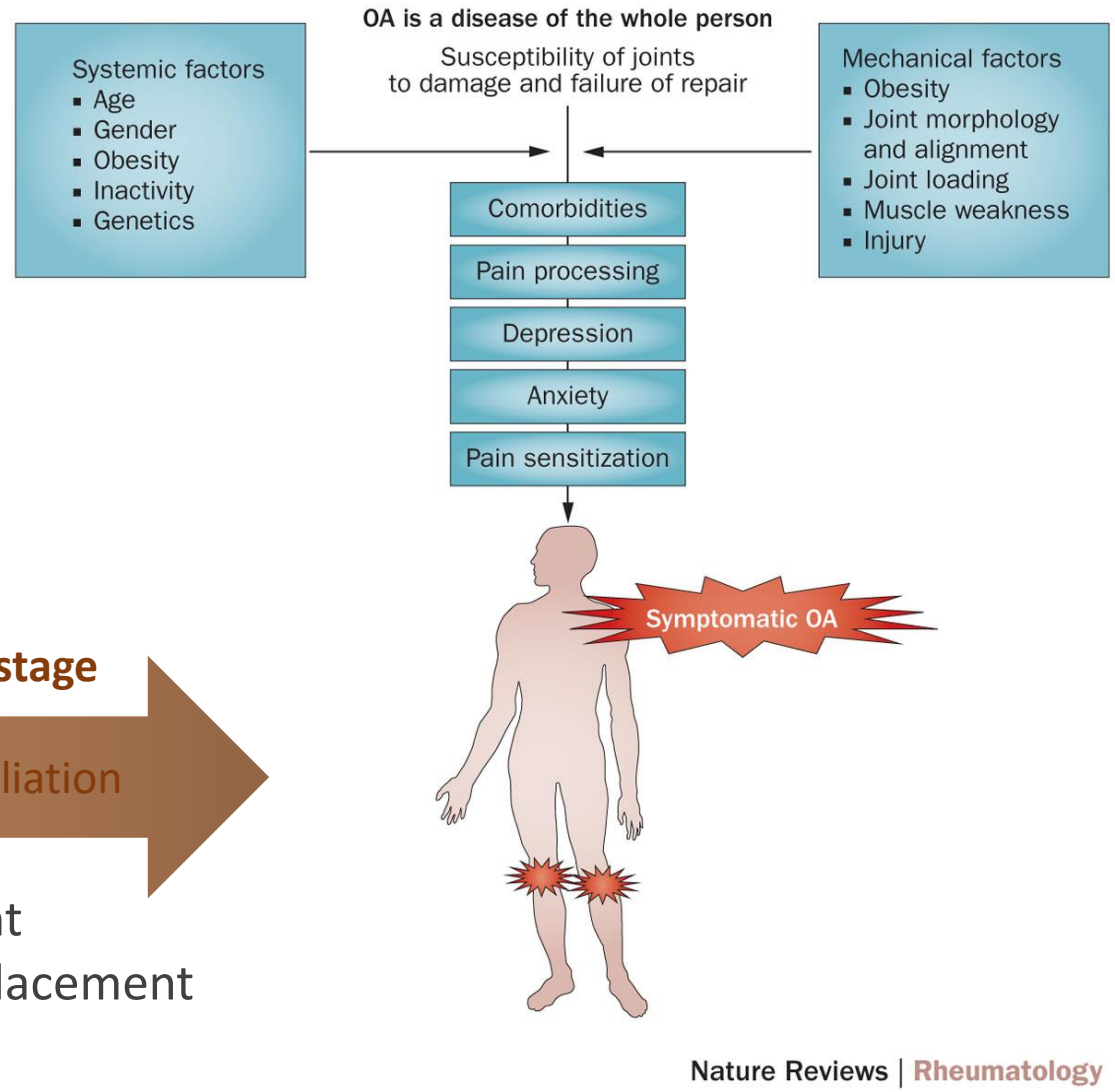
This graph shows the estimated proportion of people in the UK who have sought treatment for osteoarthritis, by gender and age group. In all, **one third of the population** aged 45 and over have sought treatment about osteoarthritis.*



This graphic shows the number of people in the UK by gender and age. Each figure represents 1 million people; the orange figures represent people with osteoarthritis. The UK population size decreases with age, but a greater proportion of people living to older age have osteoarthritis.

osteoarthritis: a changing paradigm

- Traditionally seen as an inevitable disease of joint use with age: 'Wear and Tear'
- However: it is a complex and multifactorial disease
- Failure of the joint as an organ: whole-person disease
- Disease of structure, function and nociception: pain, stiffness and reduced function
- Disconcordance betweeen structural signs and symptoms Javaid 2012
- Biomechanical, inflammatory, and metabolic disease
- 'Wear and repair': abnormal bone modelling in response to inflammation (Robinson 2016)

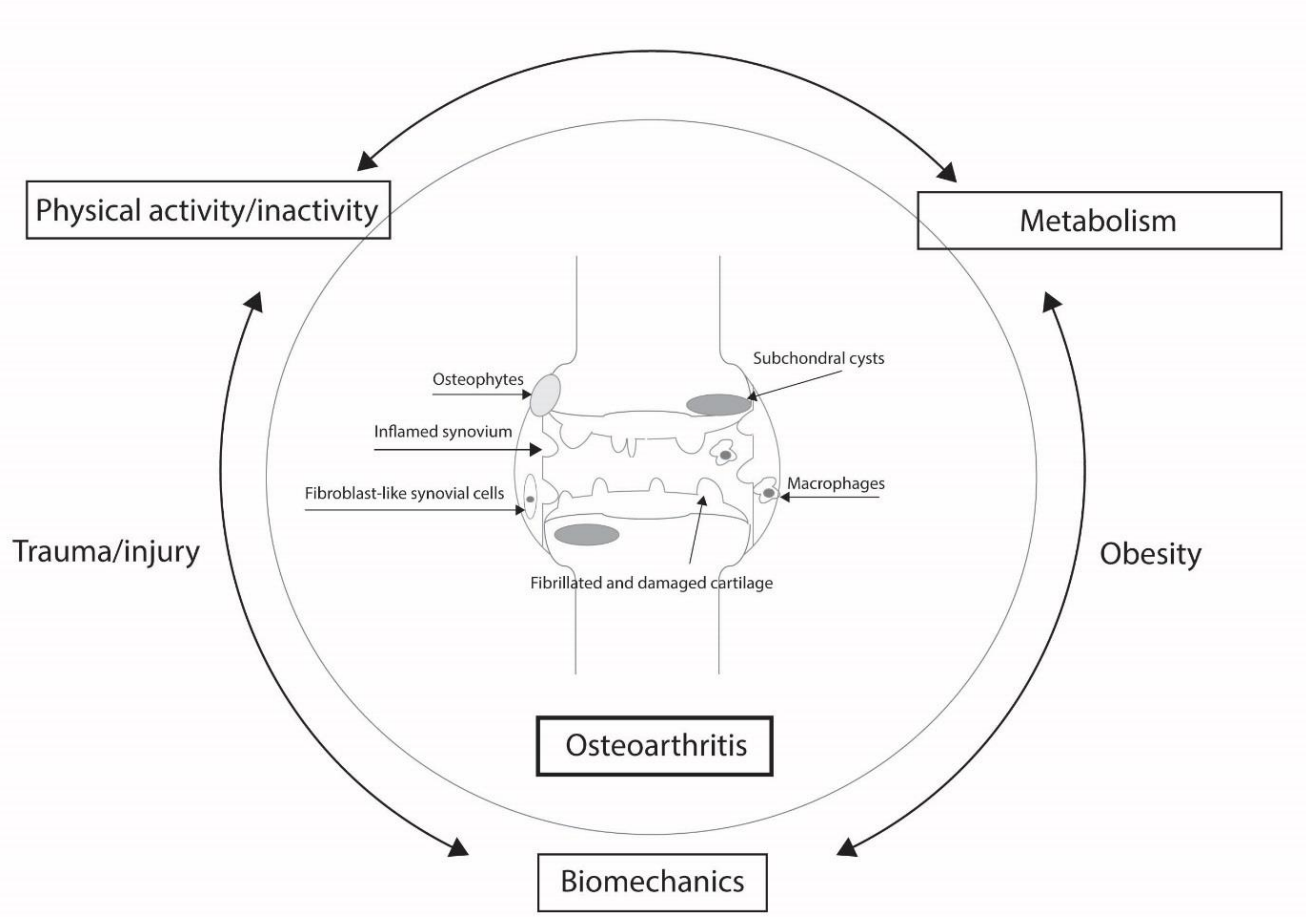


No symptoms	Symptoms	End-stage
Prevention	Treatment	Palliation
• Diet • Physical activity • Injury prevention	• Steroid injection • Physiotherapy • Weight reduction	• Joint replacement

Roos 2015

osteoarthritis: a systemic biomechanical and metabolic disease

- **Age and Sex**: Lawrence 2008
- **Previous injury**: Muthuri 2011, Showery 2016
- **Biomechanics**: increased risk with hip dysplasia/ FAI/ limb alignment
- **Metabolic**: obesity and metabolic syndrome are linked to OA Roos 2016
- **Physical activity**: Exercise is more protective than causative (?)
- **Genetic factors:** Klein 2019



osteoarthritis: an inflammatory disease

- Degradation of articular cartilage
- Synovial inflammation: pre-dates radiographic damage Sokolove 2013
- Bone disease: thickening/ osteophyte formation/ subchondral sclerosis and cysts, microfractures and microcracks

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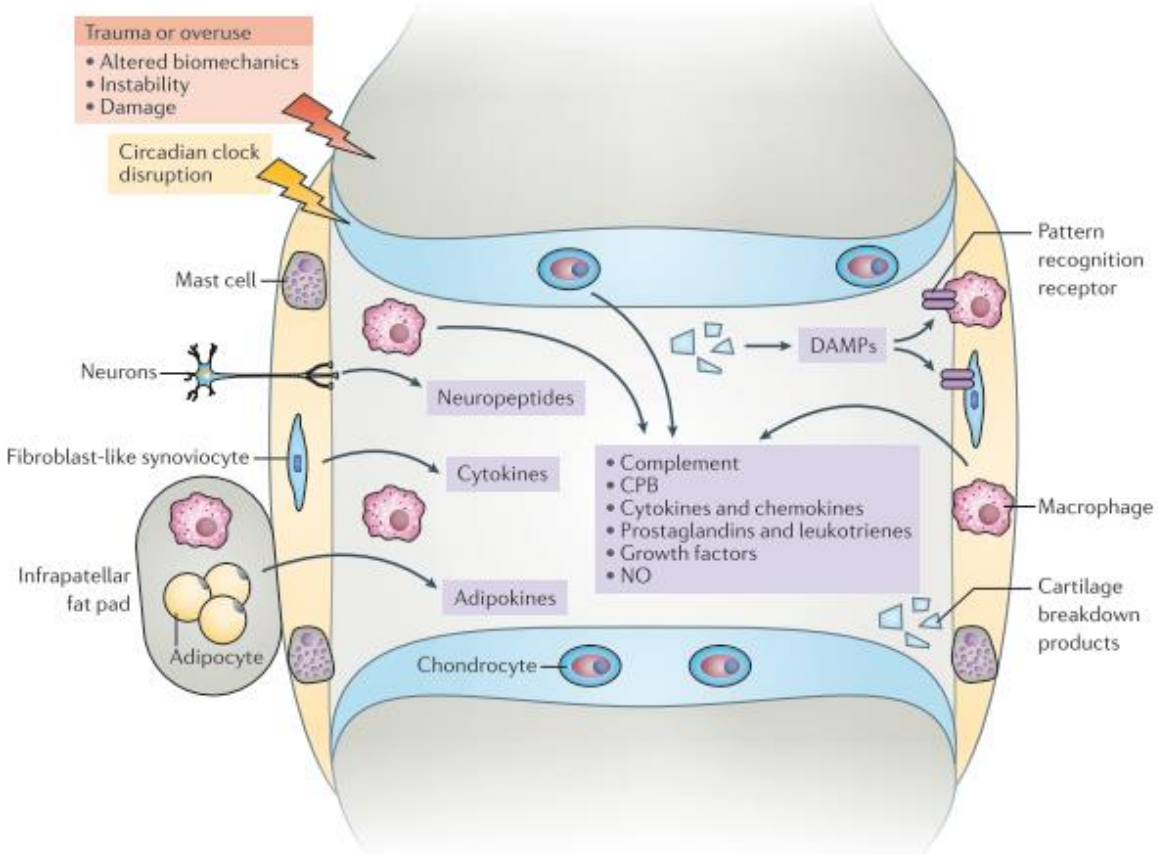
- Systemic inflammation: C-reactive protein predictive of OA development and progression Pelletier 2001
- Innate immunity: DAMP-PRR Sokolove 2013,Scanzello 2012, complement Wang 2011, Macrophages/mast cells
- Adaptive immunity: antibodies and immune complexes Gobezie 2007
- Local and circulating inflammatory mediators: cytokines eg IL-1β/ TNF - modest when compared to RA Sohn 2012
- Chemokines: promote breakdown of cartilage matrix and promote bone remodelling Borzi 2000
- Growth factors: TGF-β, FGF, VEGF, NGF Thysen 2015
- Adipokines: Kluzek 2015
- Prostaglandins: PGE2 Martel-Pelletier 2003, LTB4 Pelletier 2002
- BUT: blocking cytokine pathways alone (anti-TNF/ anti-IL-1β) ineffective in OA Chevalier 2013

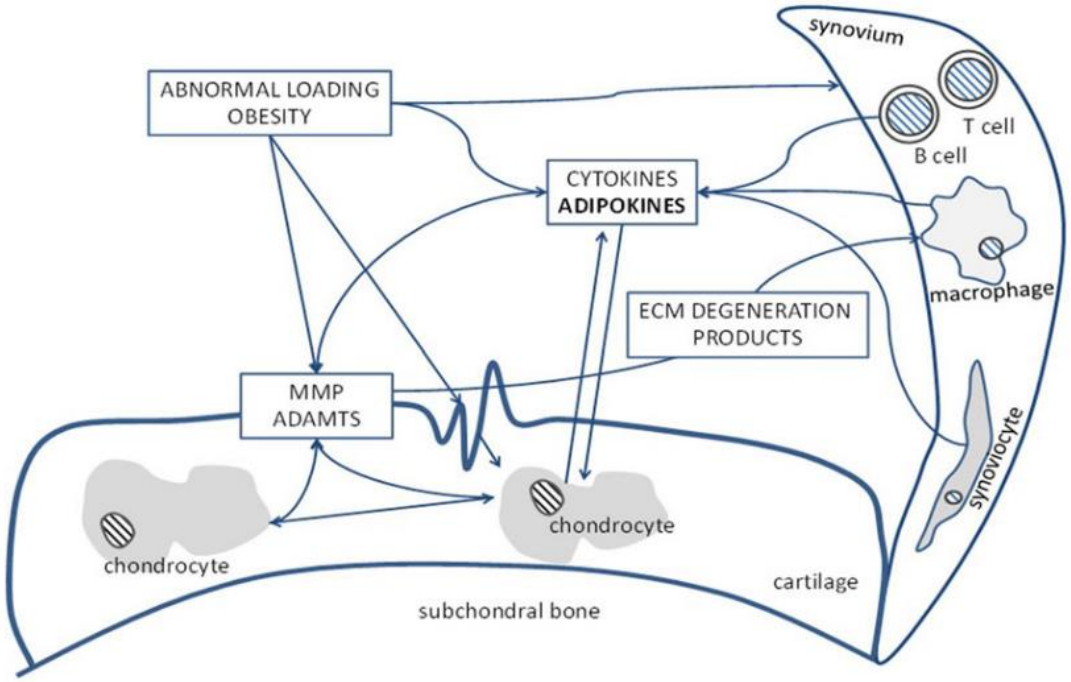


Robinson 2016

osteoarthritis: a metabolic disease

- OA associated with risk of cardiovascular disease and mortality Hawker 2014, Nuesch 2011, Haugen 2015
- Metabolic syndrome: hypertension, dyslipidaemia, insulin resistance: twice as high in patients with OA and **increased risk of symptomatic knee OA** Engstrom 2009
- Type 2 diabetes, dyslipidaemia and central obesity: all linked with development of OA Kluzek 2015
- Obesity: increased risk of knee and hand OA Gobezie 2007

- Adipokines and inflammatory cytokines: leptin, resistin, chemerin, TNF, IL-1, IL-6 Kluzek 2015
- Leptin: associated with reduced cartilage thickness, symptoms and radiographic changes and bone disease Stannus 2013, Peruccio 2014, Karvonen-Gutierrez 2014



Kluzek 2015

osteoarthritis: is predictable (?)

Biomechanics

Early knee OA: postural deficits in one-leg stand and altered hip adduction moments, increased activity of gluteus medius, quadriceps and hamstrings Duffell 2014

Later gait adaptations: increased knee adduction moment (KAM) Landry 2007

Neuromuscular adaptations: reduced strength and proprioception of quadriceps Hurley 1997

Reduced balance: falls Levinger 2011 and postural sway Tarigan 2009

Biological markers

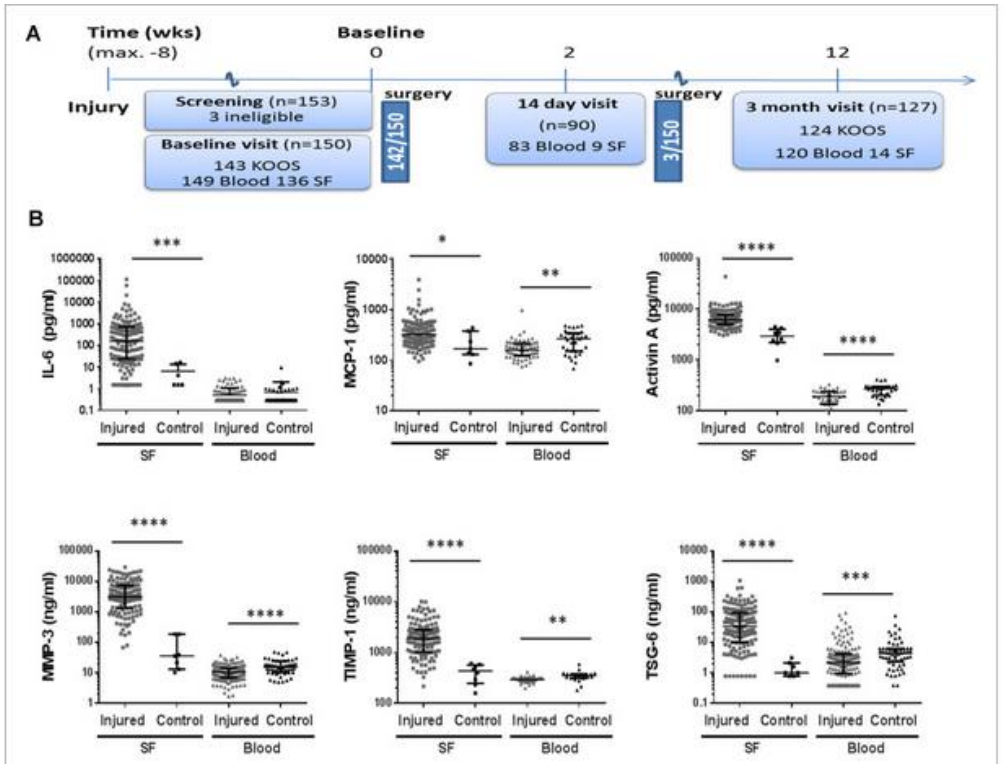
Post-knee injury: KICK study: high synovial fluid levels of IL-6, MCP-1, activin A, MMP-3, TIMP-1 and TSG-6 Watt 2016

IL-6: increased levels correlated with worse scores at 3 months

Glutamate: levels increased in synovial fluid in OA Flood 2007

IL-1: causes cartilage degradation and increased in SF Irie 2003

uCTX-II/serum cartilage oligomeric protein/ serum MMP degraded type II collagen: minimal clinical utility in predicting OA Valdes 2014



Watt 2016

osteoarthritis: is predictable (?)

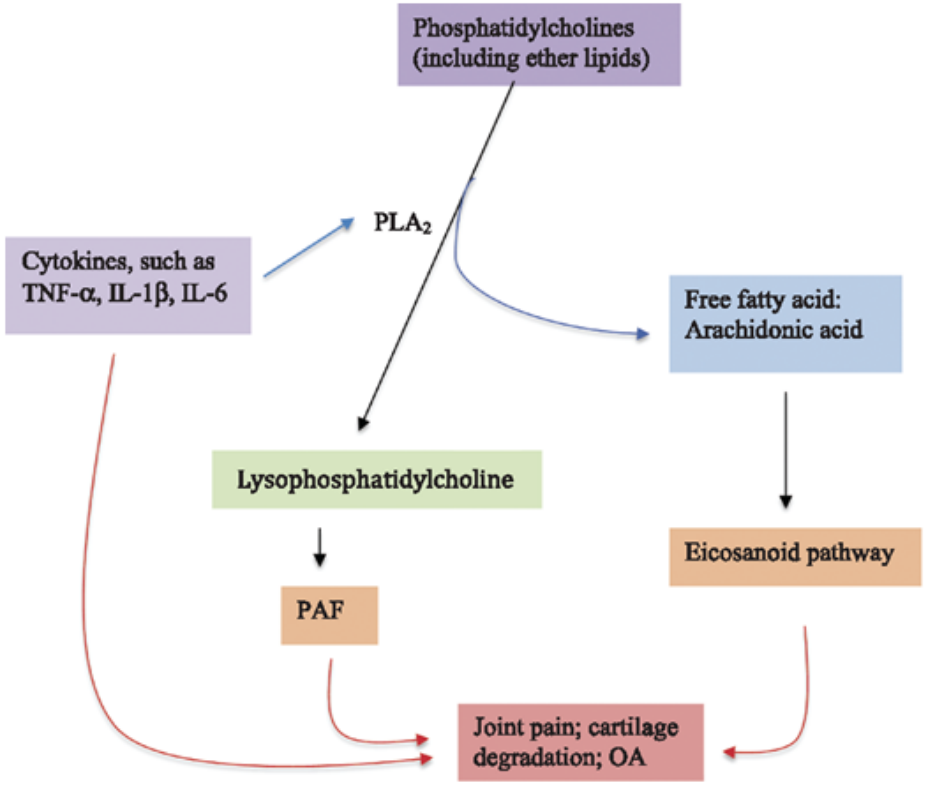
Metabolomics

Urine: NMR spectra discriminate OA and controls Lamers 2005
Synovial fluid: 11 metabolites discriminative Mickiewica 2015, differences in metabolites involved in energy metabolism Zhang 2014

Branched chain amino acids (BCAAs): BCAA to histidine ratio associated with knee OA (AUC 0.76) Zhai 2010, Zhang 2016

Plasma arginine: plasma concentrations reduced in knee OA patients: AUC 0.984, reduced arginine/ornithine ratio in OA patients Zhang 2016

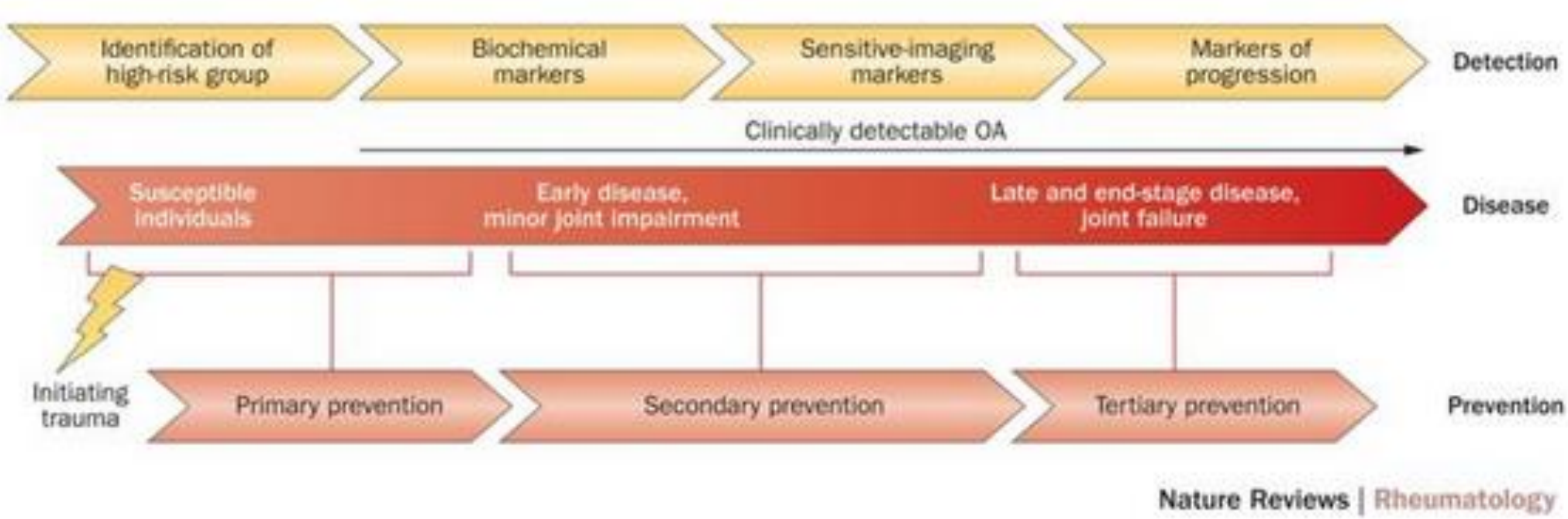
Phosphatidylcholines: PC acyl-alkyl C34:3 and PC acyl-alkyl C36:3 reduced in plasma and SF from knee OA patients Zhang 2015, lysophosphatidylcholine/phosphatidylcholine increased in OA patients when compared with controls: increased ratio predictive of knee replacement (phospholipase A2 pathway) Zhang 2016



Zhai 2018

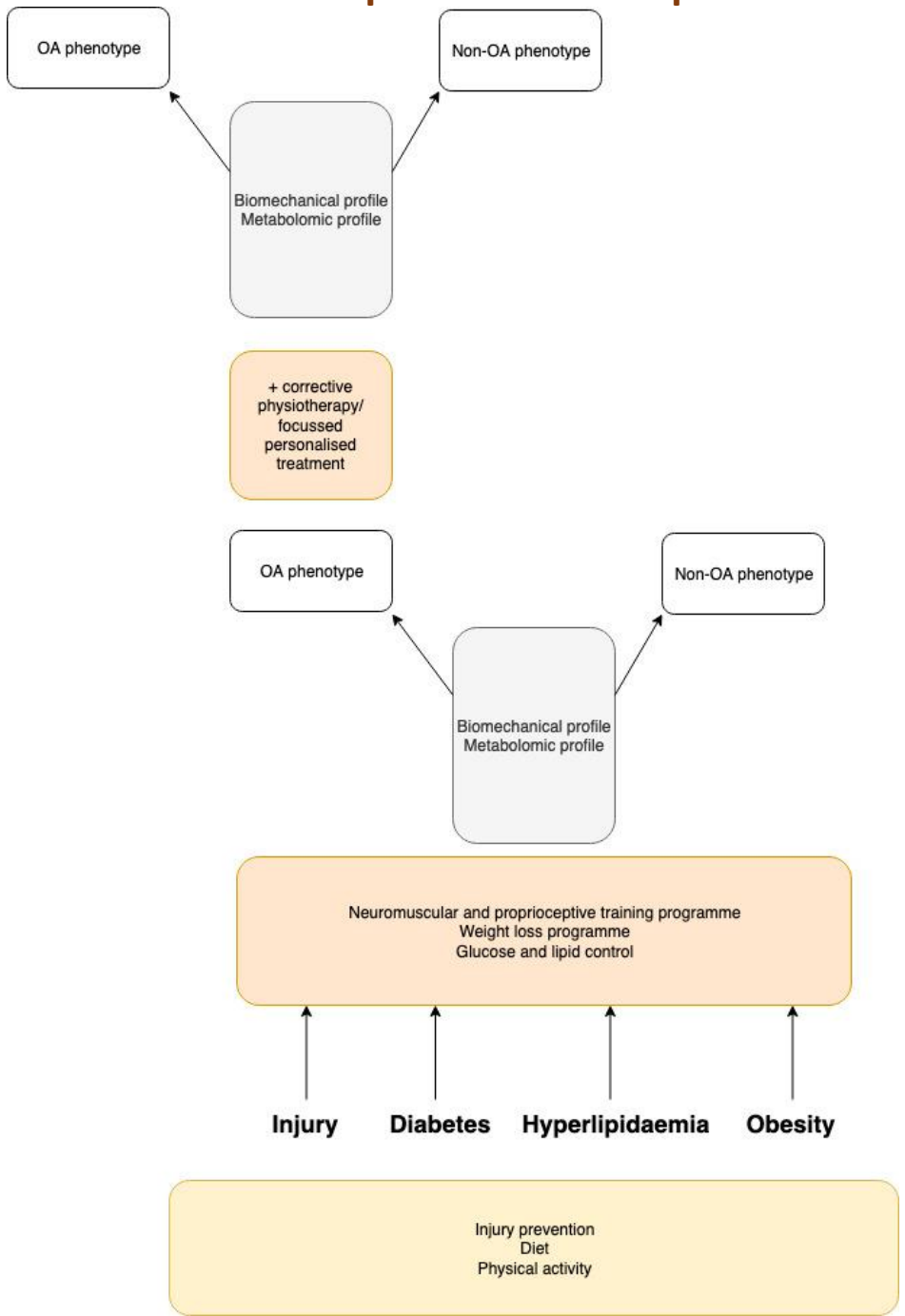
osteoarthritis: is preventable

Roos 2015



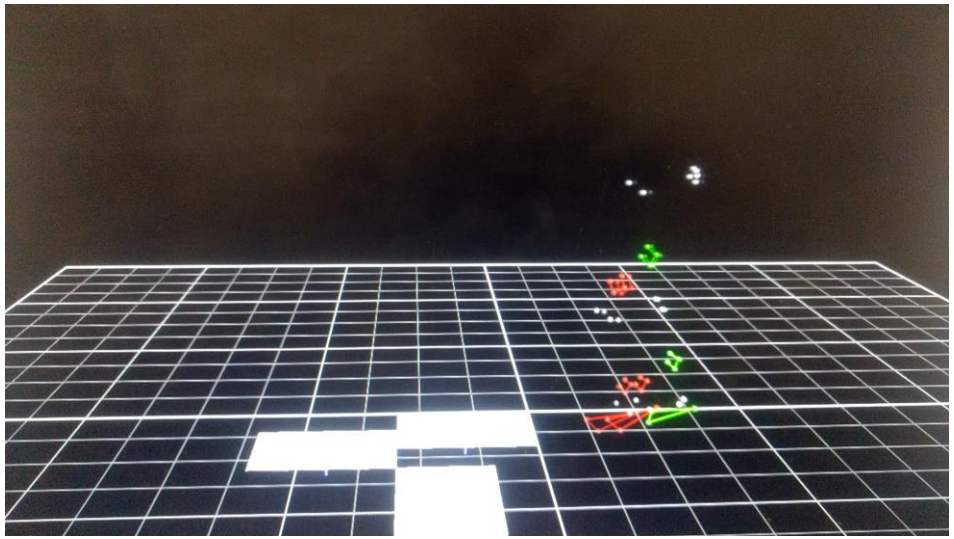
Injury Prevention: neuromuscular and proprioceptive training programmes prevent 50% of ACL injuries Gagnier 2013
Secondary prevention post injury: neuromuscular exercise also provides pain relief in OA Villadsen 2015
Weight loss: weight loss shown to reduce risk of knee OA in women Felson 1992
Lipid and diabetes control: Sturmer 1998, Schett 2013
Early cartilage defects are reversible: Ding 2010

osteoarthritis: is predictable and preventable



An Investigation of Knee Joint Functioning in People with and Without Knee Osteoarthritis: A Pilot Study

- Detecting early abnormalities in altered joint loading and serum/urine metabolomics in those with, or at risk from, OA
- 32 participants: 16 with OA and 16 at risk (eg. following knee injury)
- Blood and urine for detection of early metabolomic biomarkers of OA
- Physical activity scoring (Tegner/Koos)
- NMR-spectroscopy done
- Awaiting analysis and profiling of data



osteoarthritis	Working with Isabel Garcia on our metabolomics analysis for OA Accessing the UK biobank to obtain samples for metabolomics with correlating physical activity profiles with Alison and Isabel
physical activity and cancer	Supervising a medical student on a systematic review on wearable technologies and objective physical activity data with risk of cancer
sedentary time	?Module lead for physical activity aspect of lifestyle medicine and prevention phase one course with Edward Maile and Richard Pinder

ST3: Feb 2019-Feb 2020 (2 days/week)	**ST4: Feb 2020-Feb 2021 (3 days/week)**	**Post-CCT**
osteoarthritis: metabolomics analysis for OA		
physical activity and cancer: systematic review – wearables and cancer studies		
ST/OA/cancer: UK biobank - metabolomics	**grant applications/ CL**	
clinical: PGdip SEM/ biomechanics and gait analysis/ wearables and data/ MSK skills	**clinical**: SEM training?/ GP in MSK clinic?	
teaching: Research design and statistics (Richie Abel)/ Topic lead physical activity (PCPH)/ undergraduate (Alison)/ethics (PCPH)		

osteoarthritis: a systemic, biomechanical, inflammatory and metabolic disease of primary care

Summary

Risk factors for OA are diseases of primary care: obesity and metabolic syndrome
Prediction models for OA are within sight: combination of primary risk factors with inflammatory and metabolomic markers
Metabolomic screening in combination with biomechanical profiling: may offer phenotyping to allow for risk stratification and personalised treatment

Thank you!: d.salman11@imperial.ac.uk