

“Menopause and joints: friend or foe?”

Menopause Society, Brussels, November 22, 2025

Molecular Immunology and Inflammation Team (MIIT)
Inflammation Research Center VIB Ghent &
Department of Rheumatology, Ghent University Hospital

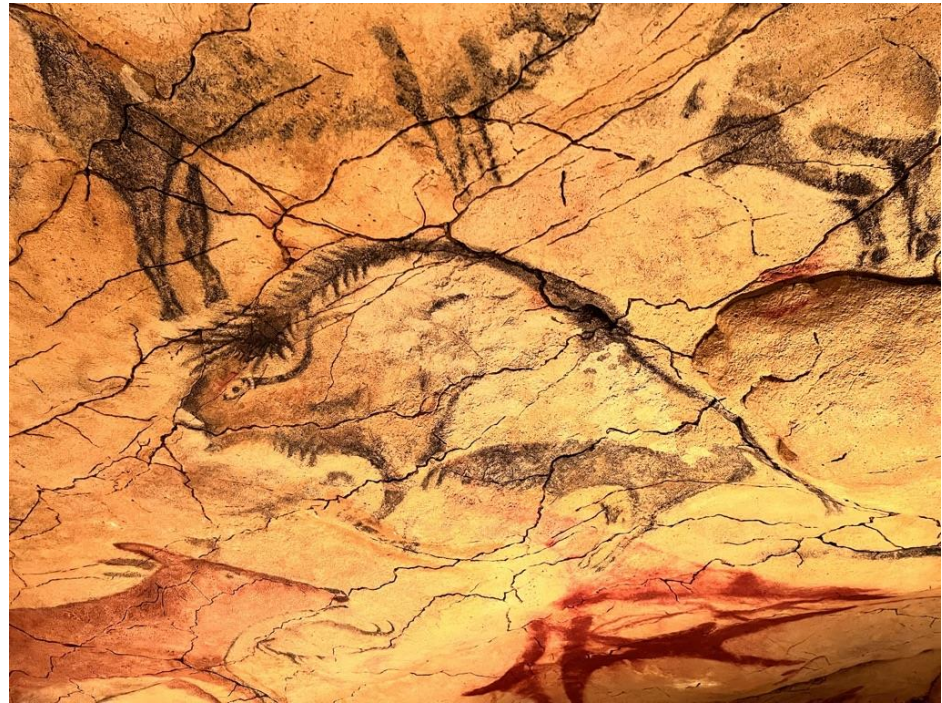
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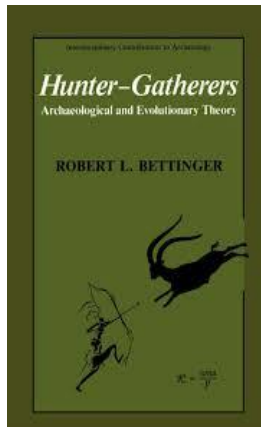
The cave of Altamira, Spain...



First discovery from prehistory that palaeolithic people were capable of creating art works such as painting (Marcelino Sanz de Sautuola)

Take home message 1

The musculoskeletal system in male differs evolutionary from females



NOVEMBER 1, 2023 | 13 MIN READ

Scientific American

The Theory That Men Evolved to Hunt and Women Evolved to Gather Is Wrong

The influential idea that in the past men were hunters and women were not isn't supported by the available evidence

PLOS ONE

RESEARCH ARTICLE

The Myth of Man the Hunter: Women's contribution to the hunt across ethnographic contexts

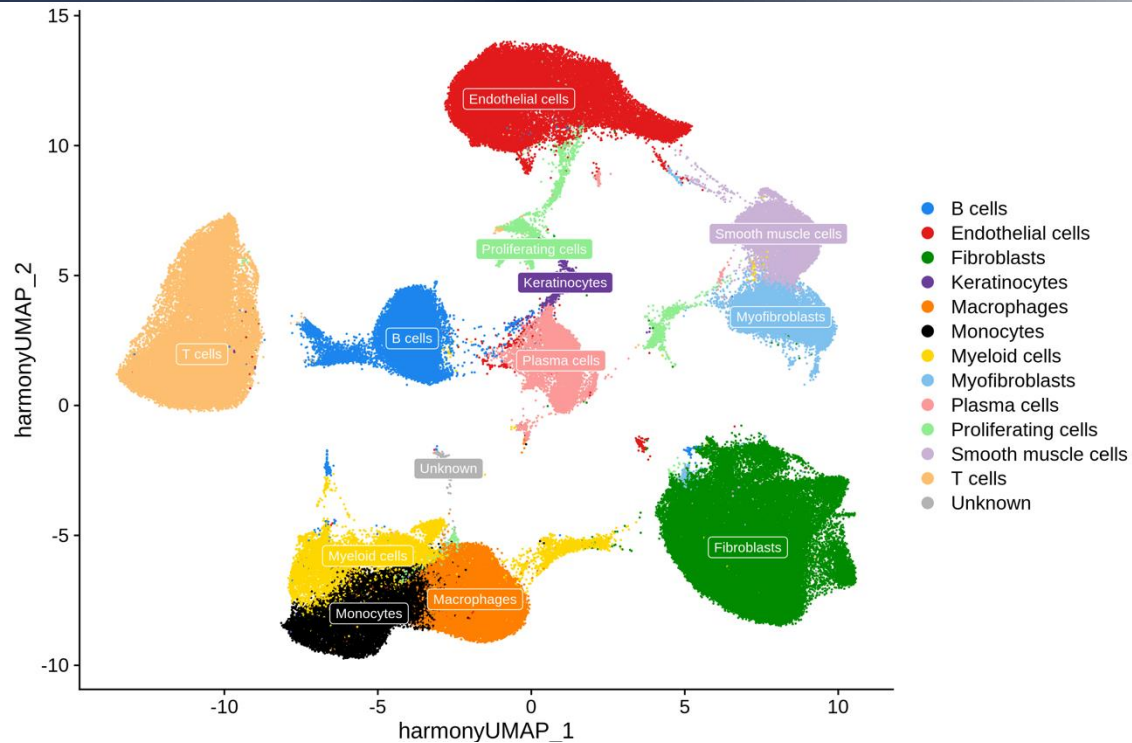
Abigail Anderson¹, Sophia Chilczuk¹, Kaylie Nelson¹, Roxanne Ruther¹, Cara Wall-Scheffler^{1,2*}

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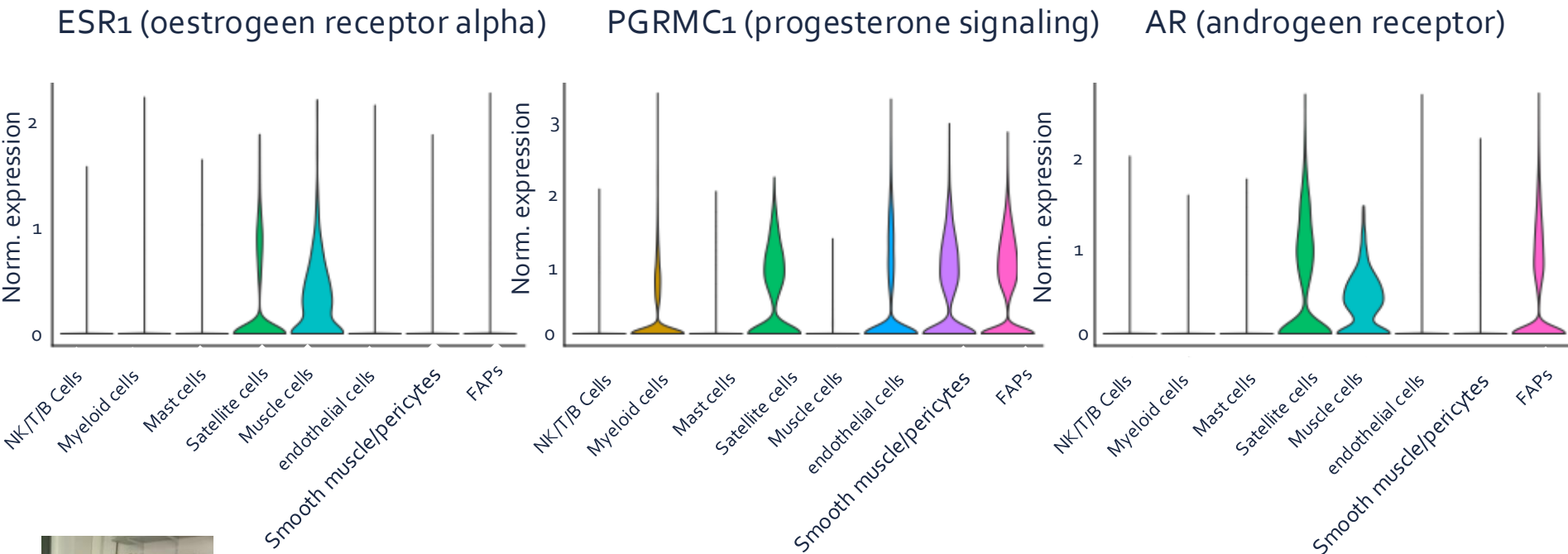
* cwallisch@spu.edu

**Could sex hormones be a major driver in
musculoskeletal system?**

The universe of single cell RNA sequencing

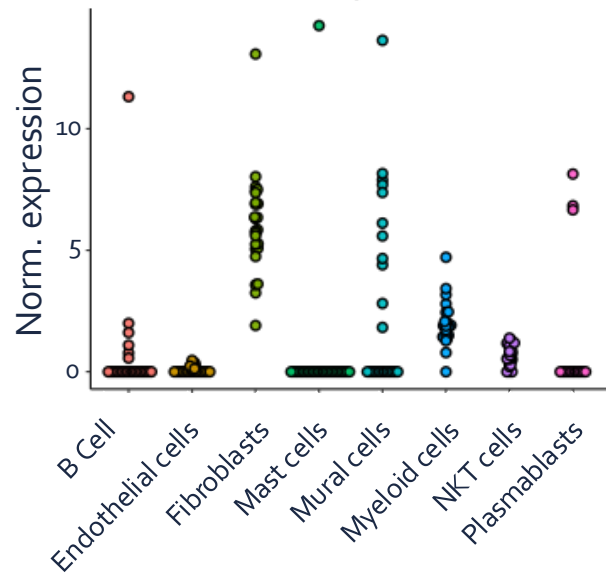


Expression of sex hormone receptors in human muscle

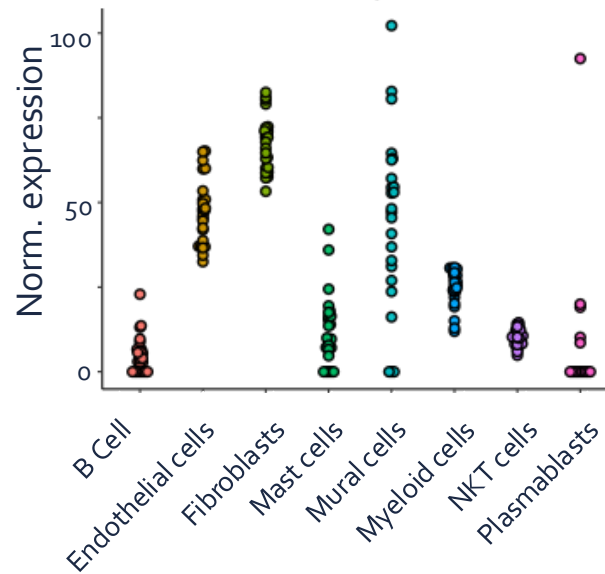


Expression of sex hormone receptors in human synovium (AMP consortium)

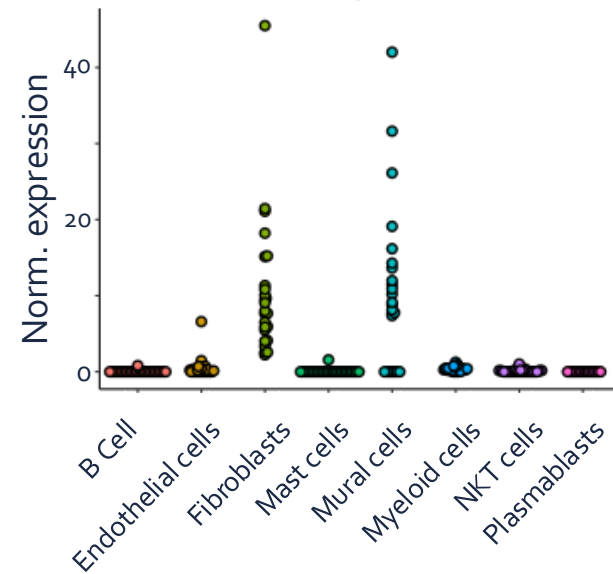
ESR1 (oestrogen receptor alpha)



PGRMC1 (progesterone signaling)



AR (androgen receptor)



Take home message 2

Broad expression within muscle

Tissue resident cells (fibroblasts & mural cells)
express sex hormone receptors

Endothelial cells selectively express progesterone receptors

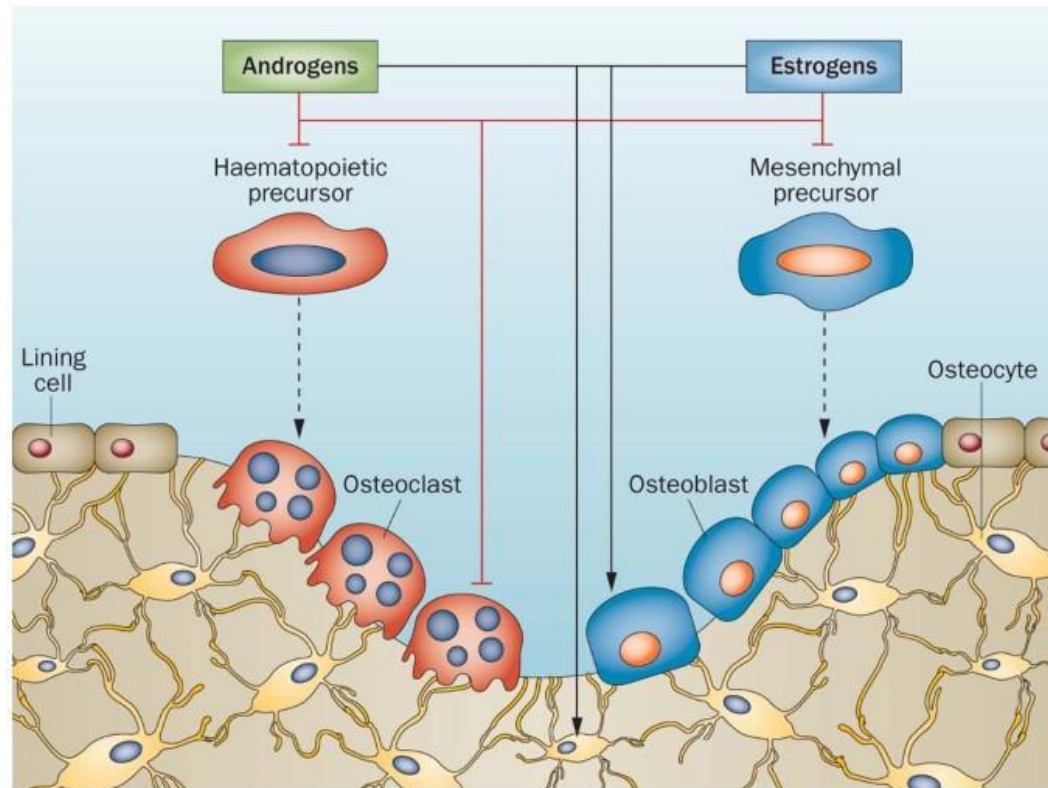
Myeloid cells express estrogen and progesterone receptor
but not androgen receptor

Overall surprisingly cellular selectivity of
sex hormone receptors within synovium



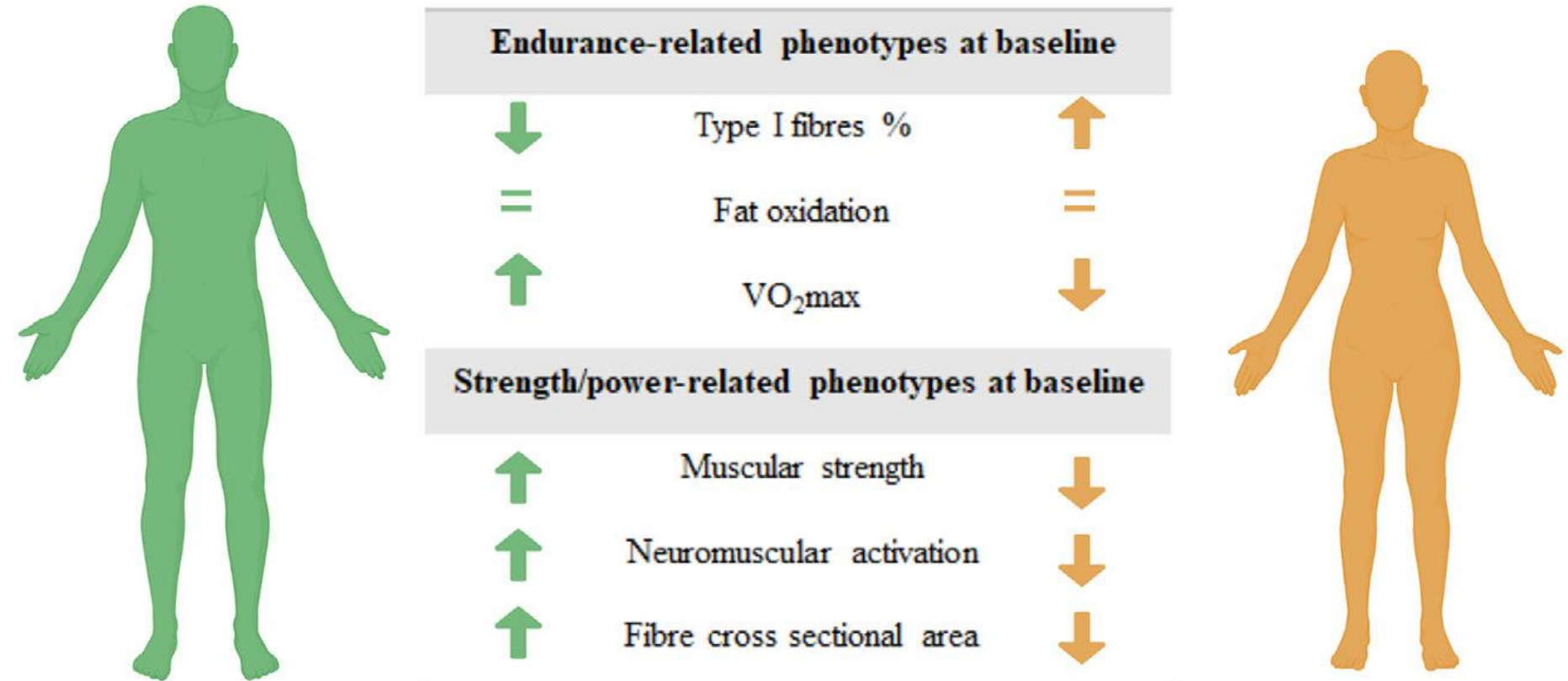
A positive control tissue

Normal bone remodeling process and its regulations



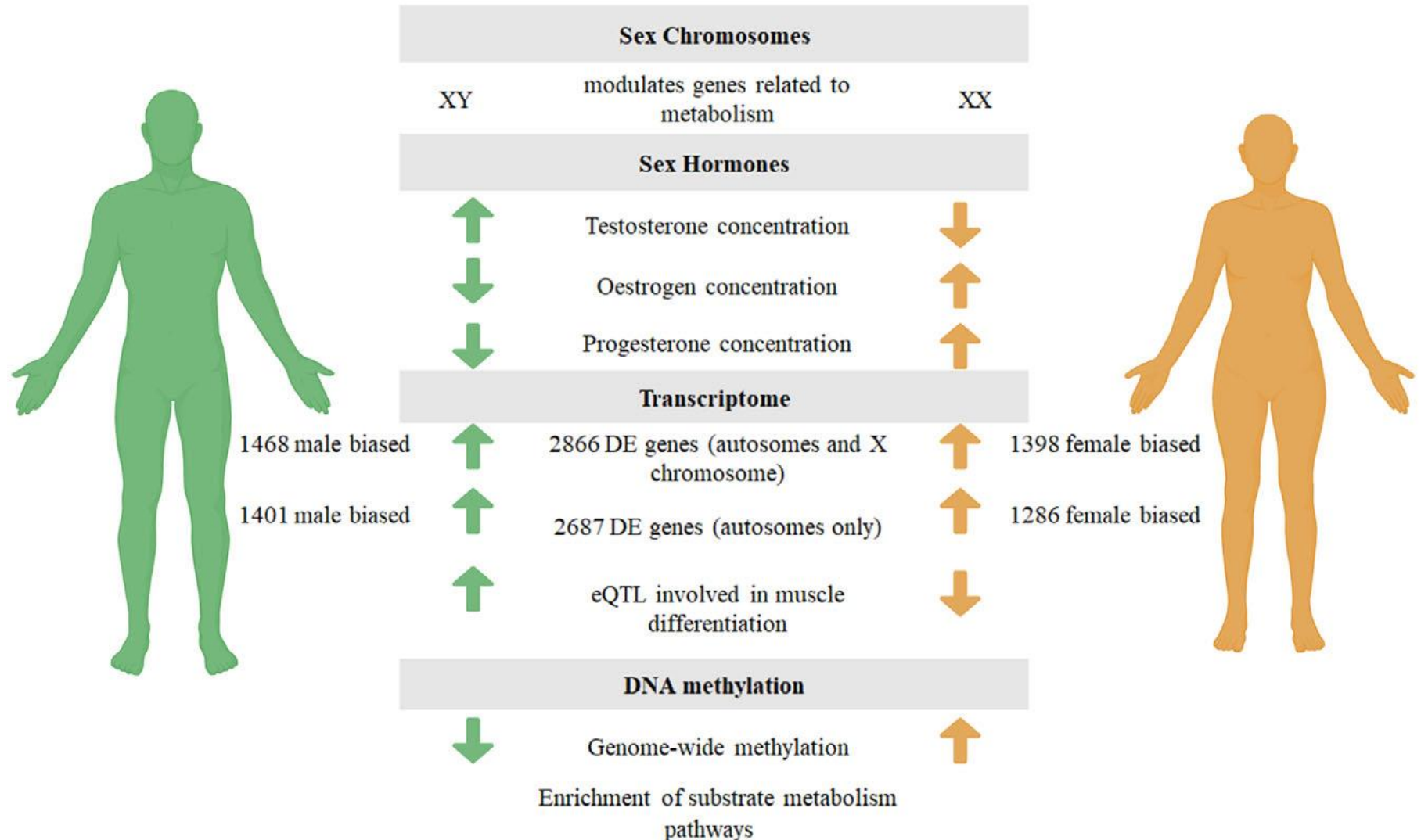
Physiological and molecular sex differences in human skeletal muscle in response to exercise training

Phenotypic sex differences at baseline



endurance- & strength/power-related factors

Sex-specific molecular mechanisms at rest



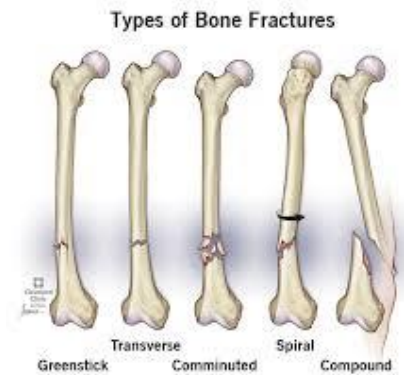
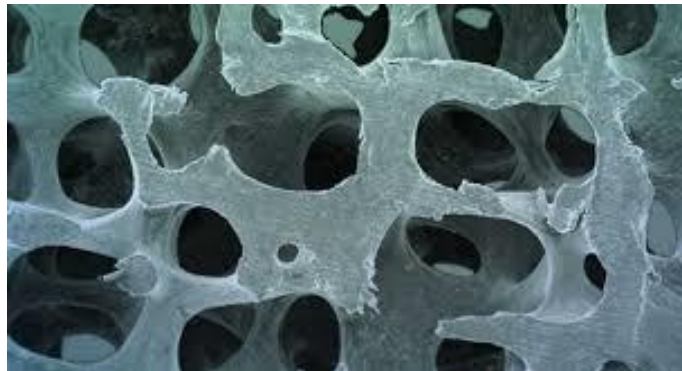
What happens in menopause?



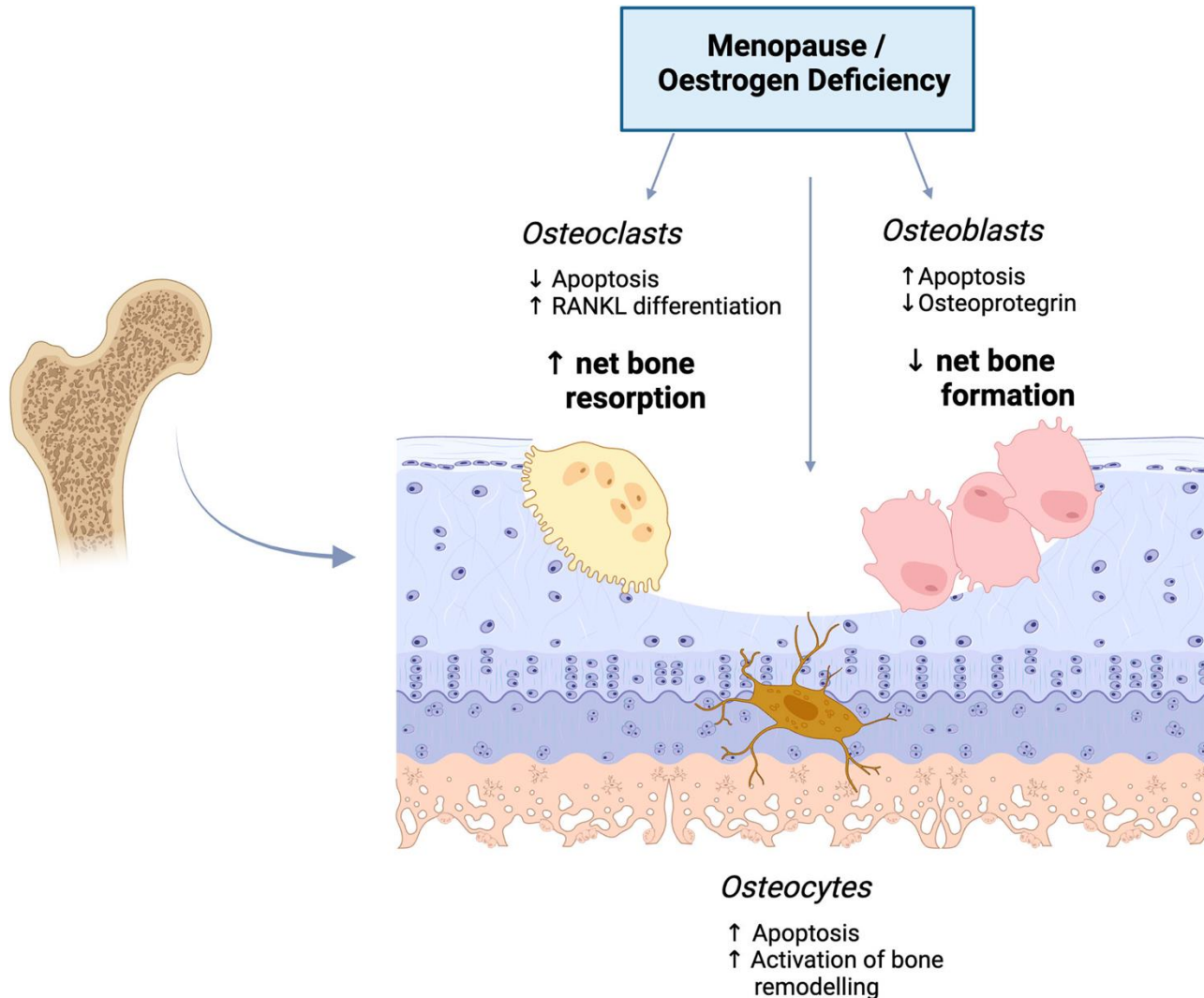
Musculoskeletal syndrome of menopause: processes and signs

<i>Process</i>	<i>Signs</i>
Inflammation	Arthralgia, joint pain, joint discomfort, frozen shoulder
Sarcopenia	Poor balance, falls, decreased muscle mass, loss of stamina, walking slowly
Decreased satellite cell proliferation	Decreased muscle mass, inability to gain muscle
Osteoporosis	Loss of height, back pain, stooped posture, low-impact fracture
Arthritis	Arthralgia, joint pain, joint stiffness

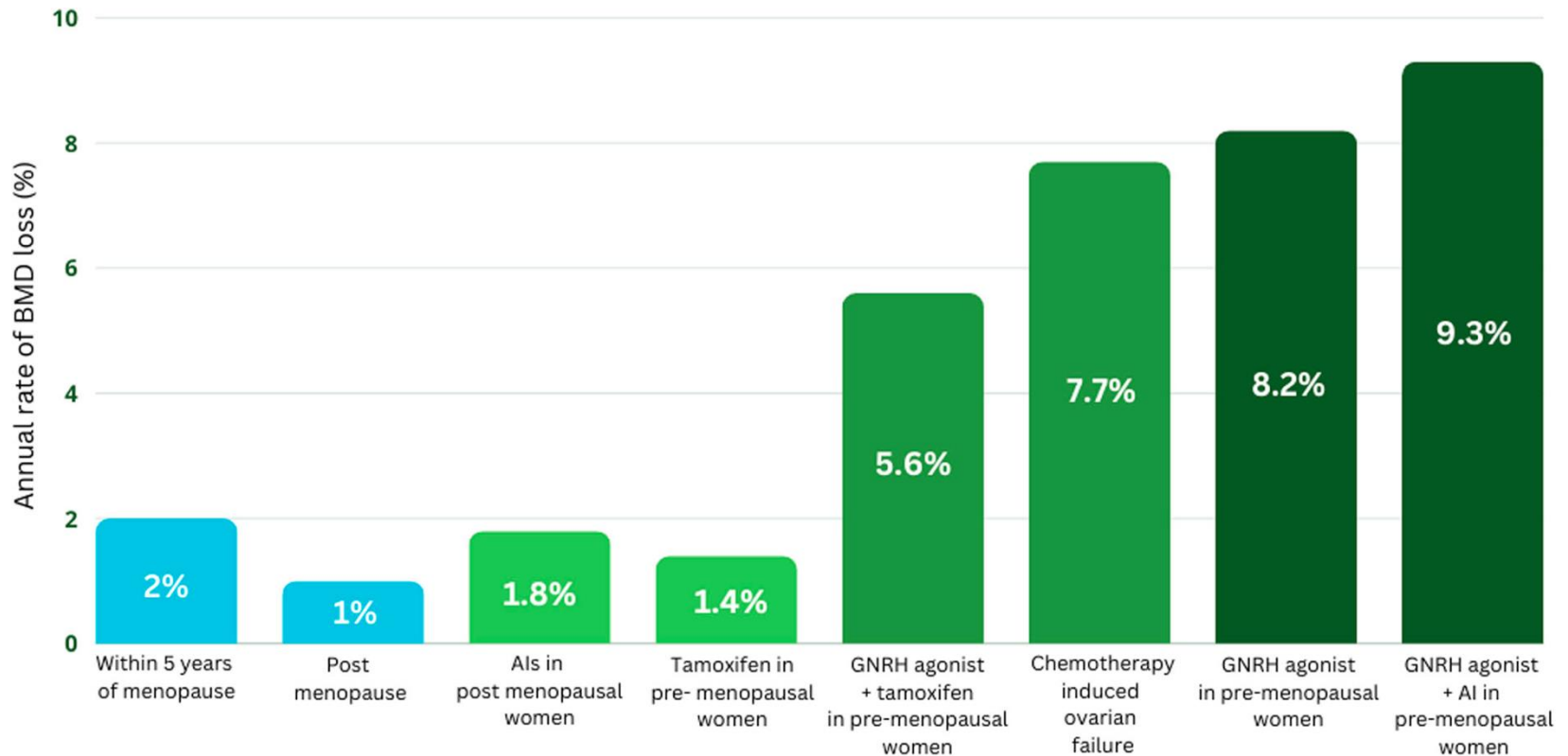
Bone



Impact of oestrogen deficiency & menopause on bone mineral density & bone turnover

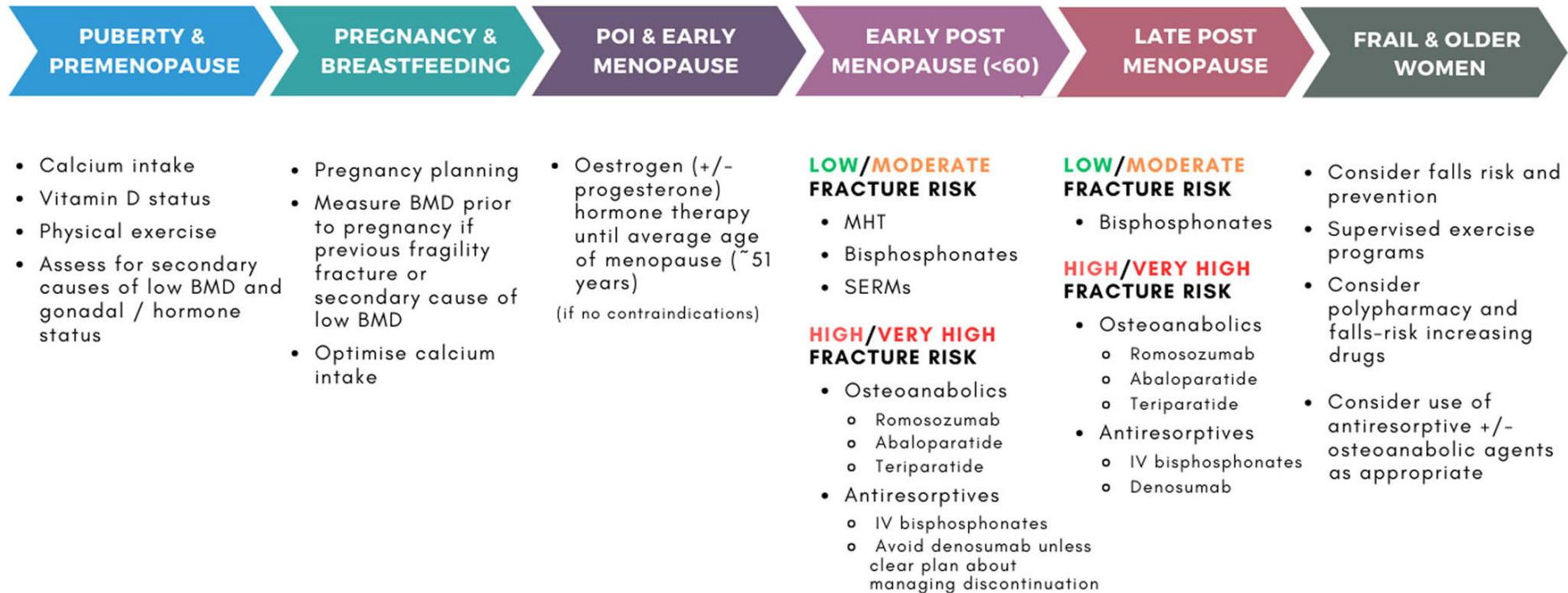


Annual lumbar spine BMD change with adjuvant endocrine breast cancer therapy



Overview of bone health across the lifespan in women

- Calcium intake - Vitamin D status - Protein - Physical exercise -



Muscle homeostasis and function

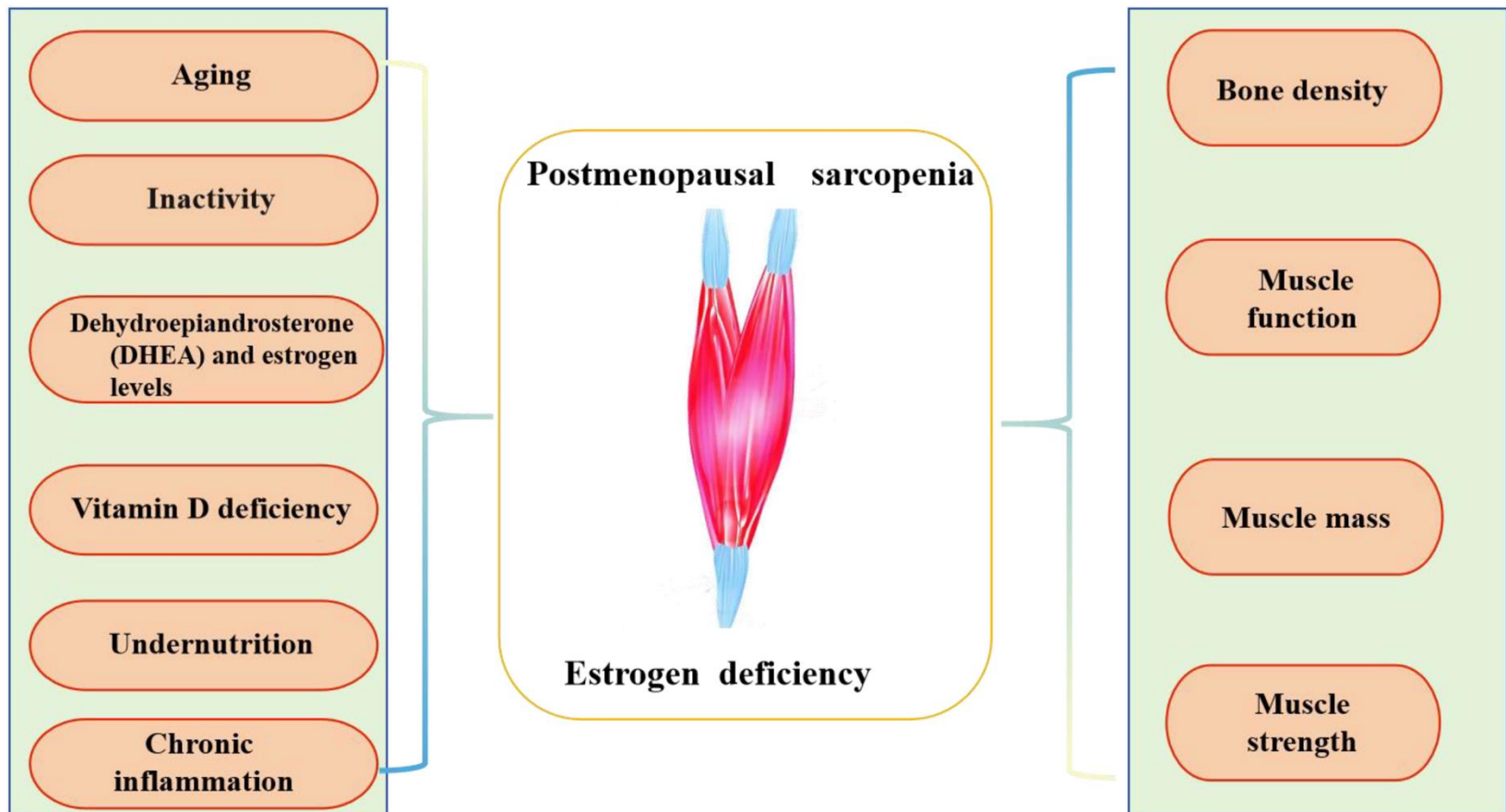


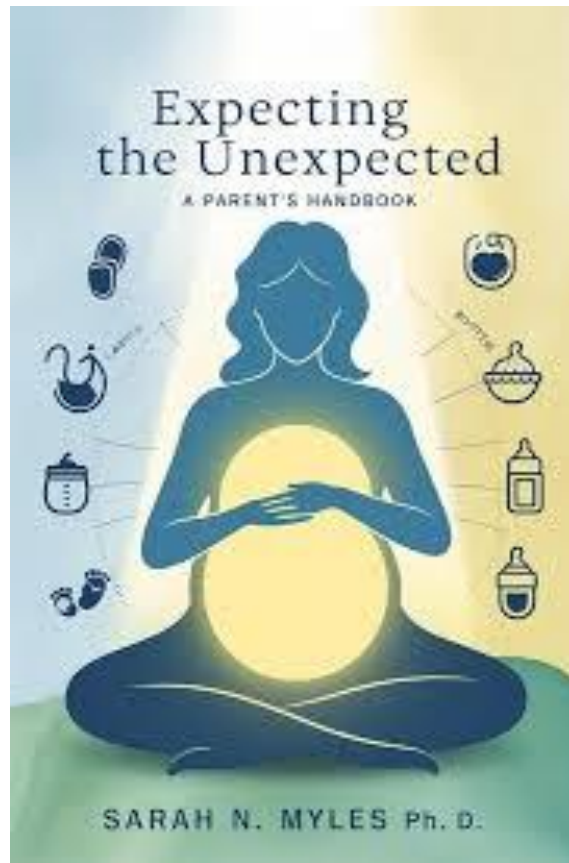
Impact of oestrogen deficiency & menopause on muscle homeostasis

Model	Delay of/timing since estrogen replacement	Outcome measure	Effect of delay or timing since estrogen replacement on outcome measure
Rat [17]	2 weeks post-OVX	Satellite cell number	Significant increases in satellite cell number following eccentric exercise
	11 weeks post-OVX		Reduced increases in satellite cell number following eccentric exercise
Human [49]	Acute replacement in EPM	Insulin sensitivity	Improved insulin sensitivity
	Acute replacement in LPM		Reduced expression of insulin sensitivity markers
Human [4]	Acute replacement in EPM	Cytosolic protein breakdown markers	Decreased FOXO3 activation Decreased MuRF1 protein expression
	Acute replacement in LPM		Increased FOXO3 activation Increased MuRF1 protein expression
Human [43]	Therapy ceased 10.6 ± 8.9 years prior to study start	MVC	Significantly higher MVC measures than participants with no prior HRT use
		RTD	HRT-associated attenuation of RTD decline due to age
		Muscle quality (MVC per unit muscle size)	History of RT use positively associated with reducing expected menopausal drop in muscle quality

HRT hormone replacement therapy, *OVX* ovariectomy, *EPM* early menopausal females (≤ 6 years past menopause), *LPM* late menopausal females (≥ 10 years past menopause), *MVC* maximum voluntary contraction, *RTD* rate of torque development

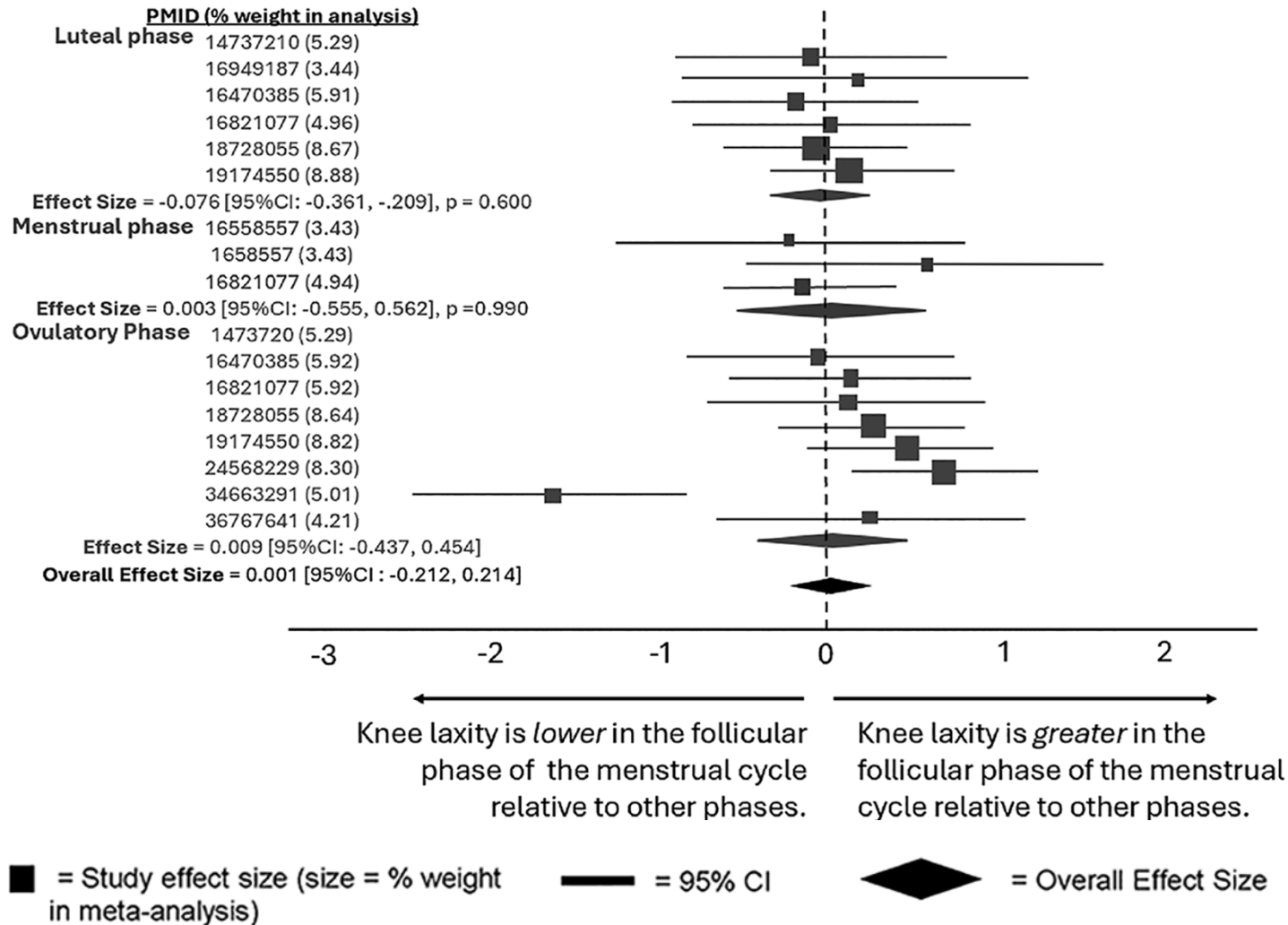
The description of postmenopausal sarcopenia



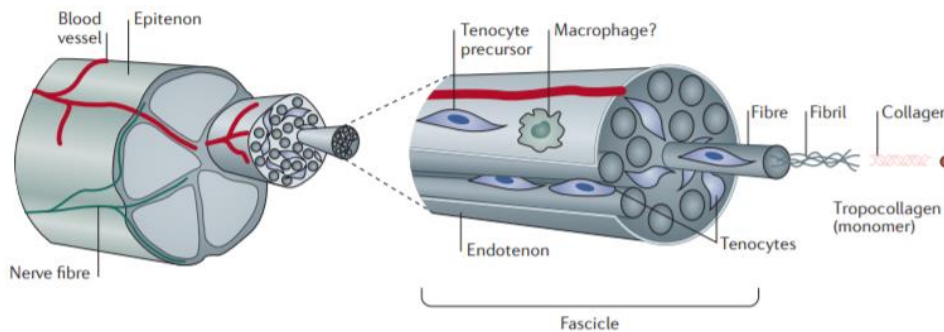


Effect of Sex Hormones on Joint Ligament Properties?

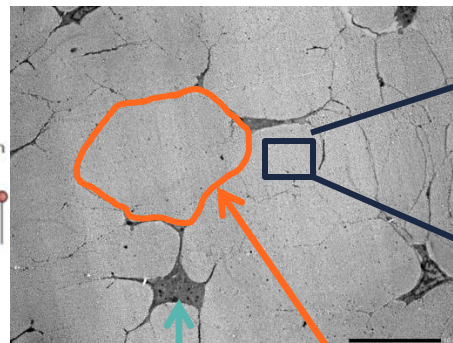
Effect of the menstrual cycle on knee laxity



Fibroblasts are gatekeepers of tendon & ligament homeostasis



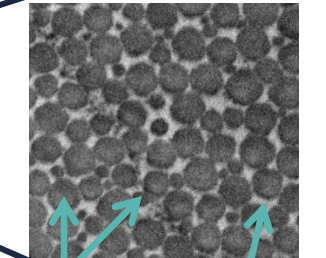
Electron microscopy:
Mouse Achilles tendon, 1000x



Tenocyte
(Tendon
fibroblast)

Collagen
fibre

5000X



Collagen fibrils
Proteoglycan-
water matrix

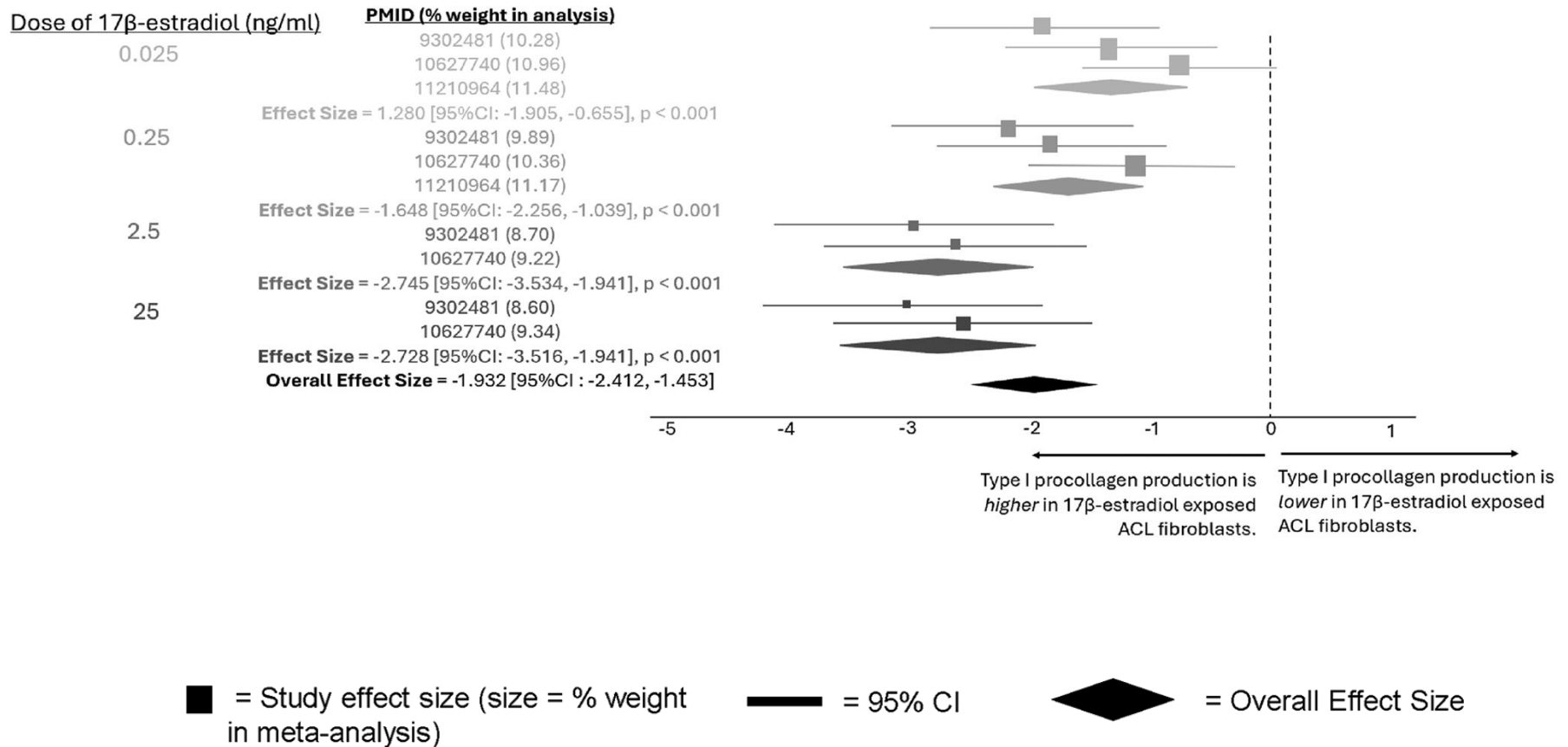


Eric Gracey

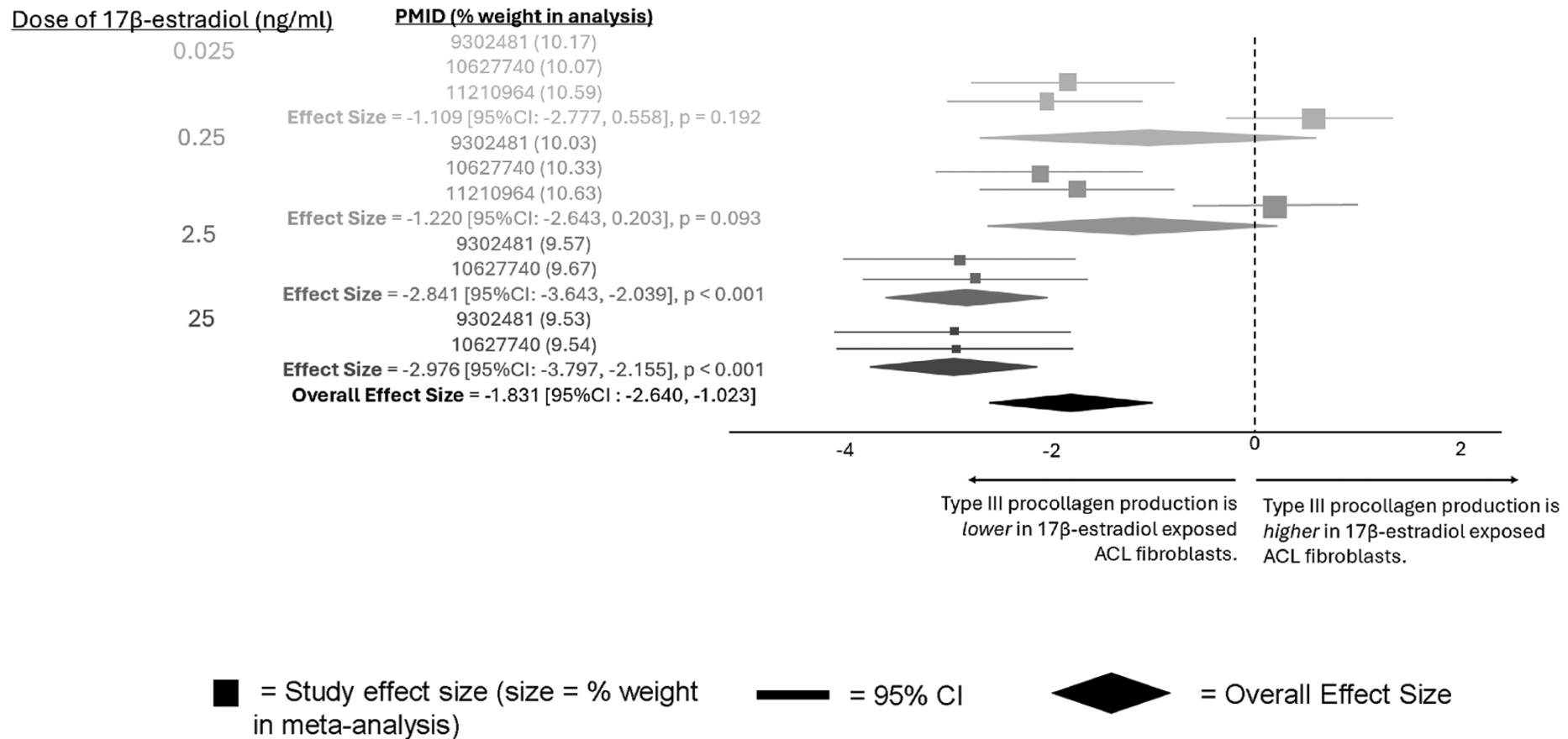


Guillaume Planckaert

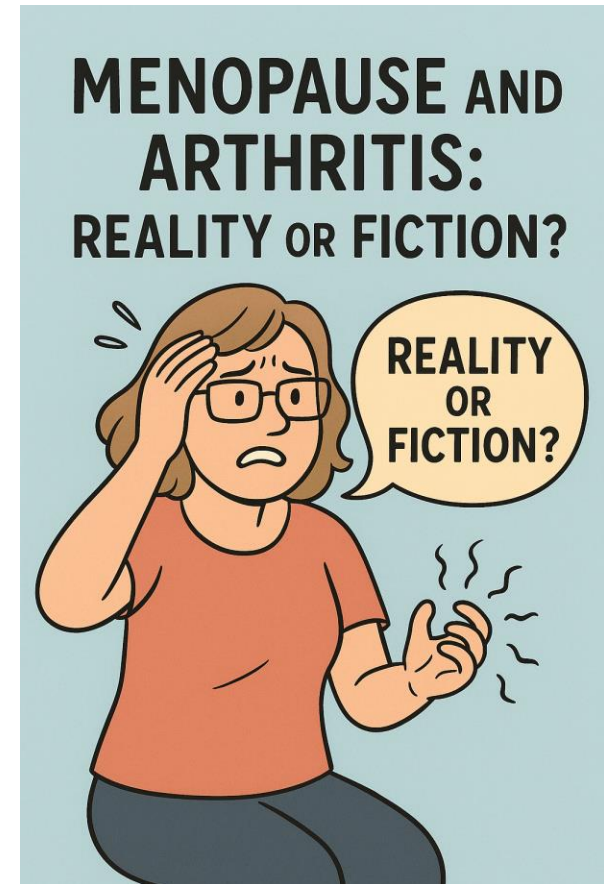
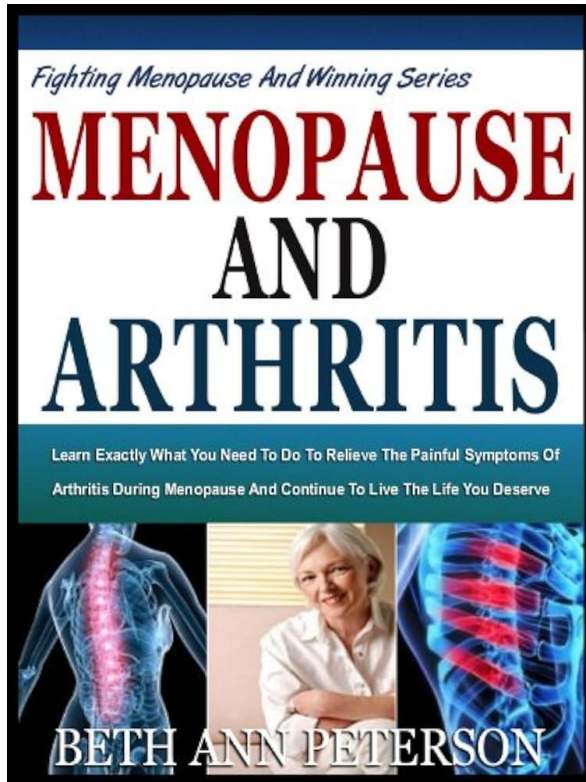
The impact of the 17 β -estradiol type I procollagen production in ACL fibroblasts



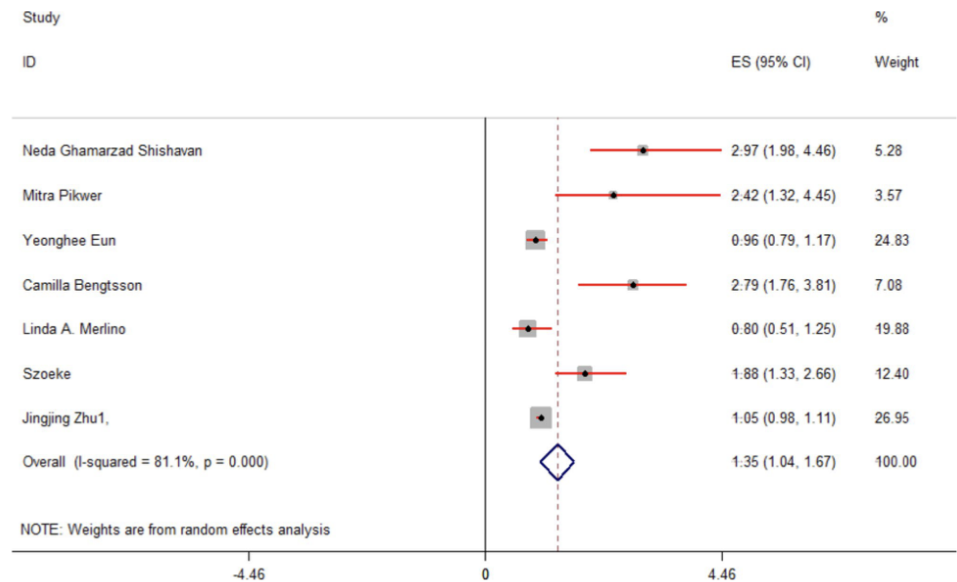
The impact of the 17 β -estradiol type III procollagen production in ACL fibroblasts



Arthritis and menopause?



Rheumatoid arthritis incidence in post-menopausal versus premenopausal women



Namavari N, Jokar M, Ghodsian A, Jahromi HK, Rahmanian V. Menopausal state and rheumatoid arthritis: a systematic review and meta-analysis. BMC Rheumatol. 2024 Sep 30;8(1):48. doi: 10.1186/s41927-024-00418-2. PMID: 39350181; PMCID: PMC11441135.

Erosive hand osteoarthritis (OA): a prevalent and distinct disease



a severe form of hand OA

Occurs mostly in postmenopausal women

radiological hallmark of EHOA is central erosion of the joint

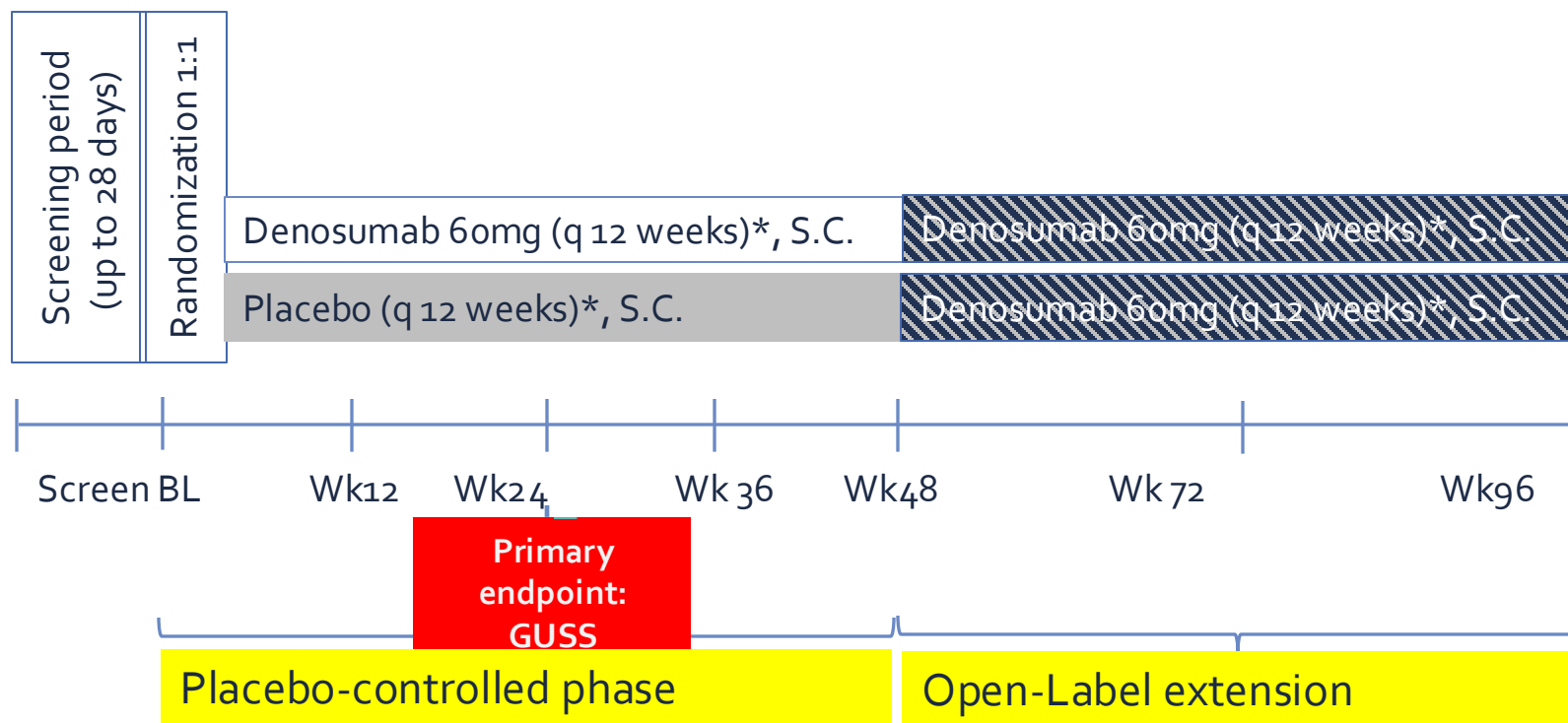
characterized by the presence of signs of inflammation, which correlates with symptoms & appearance of bone erosions.

High clinical burden & unmet need

**Aim: To study the effect and tolerability of denosumab,
a RANKL-inhibitor in erosive hand OA**



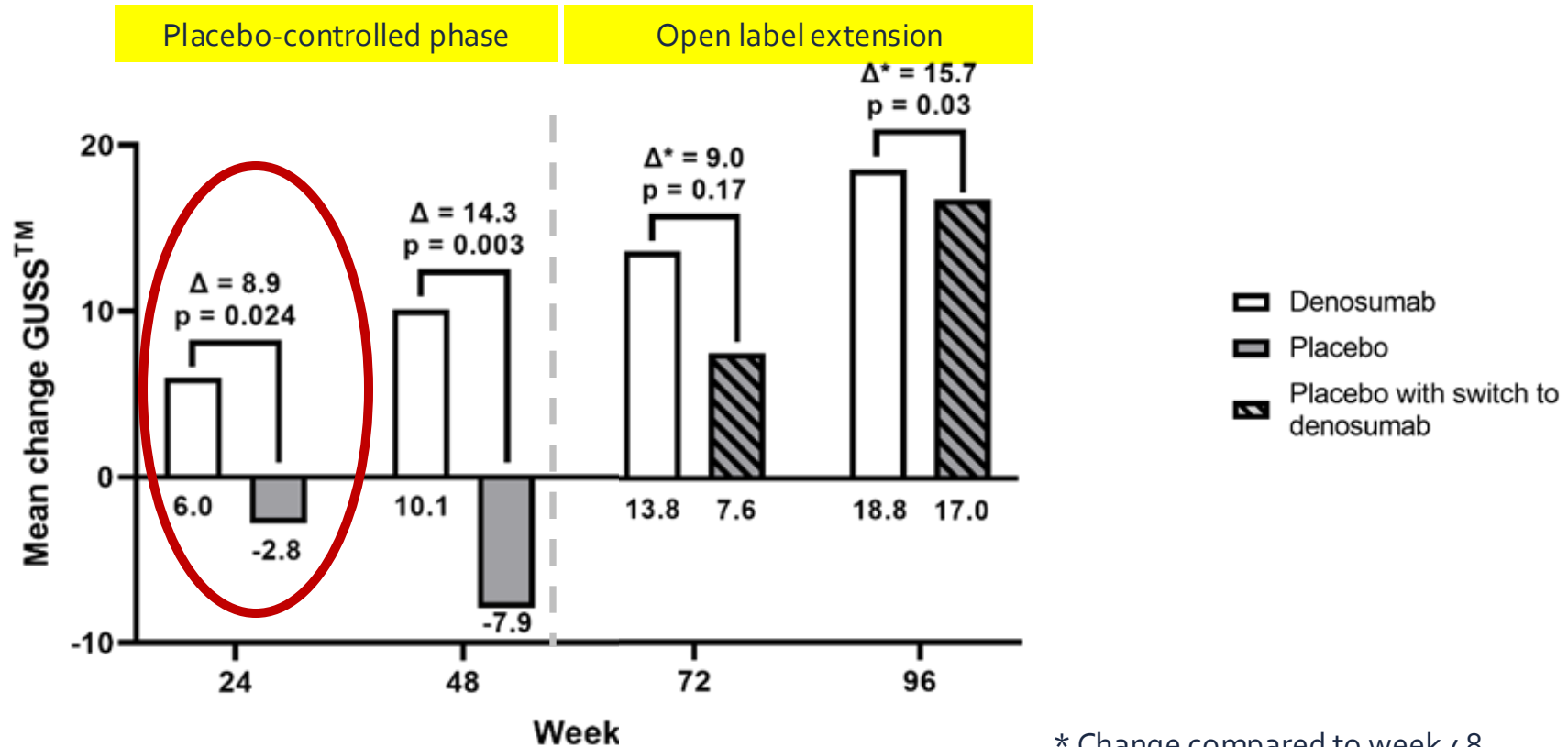
Methods: study design



* Supplemented with daily intake of calcium (1000mg) and vitamin D₃ (880IU)

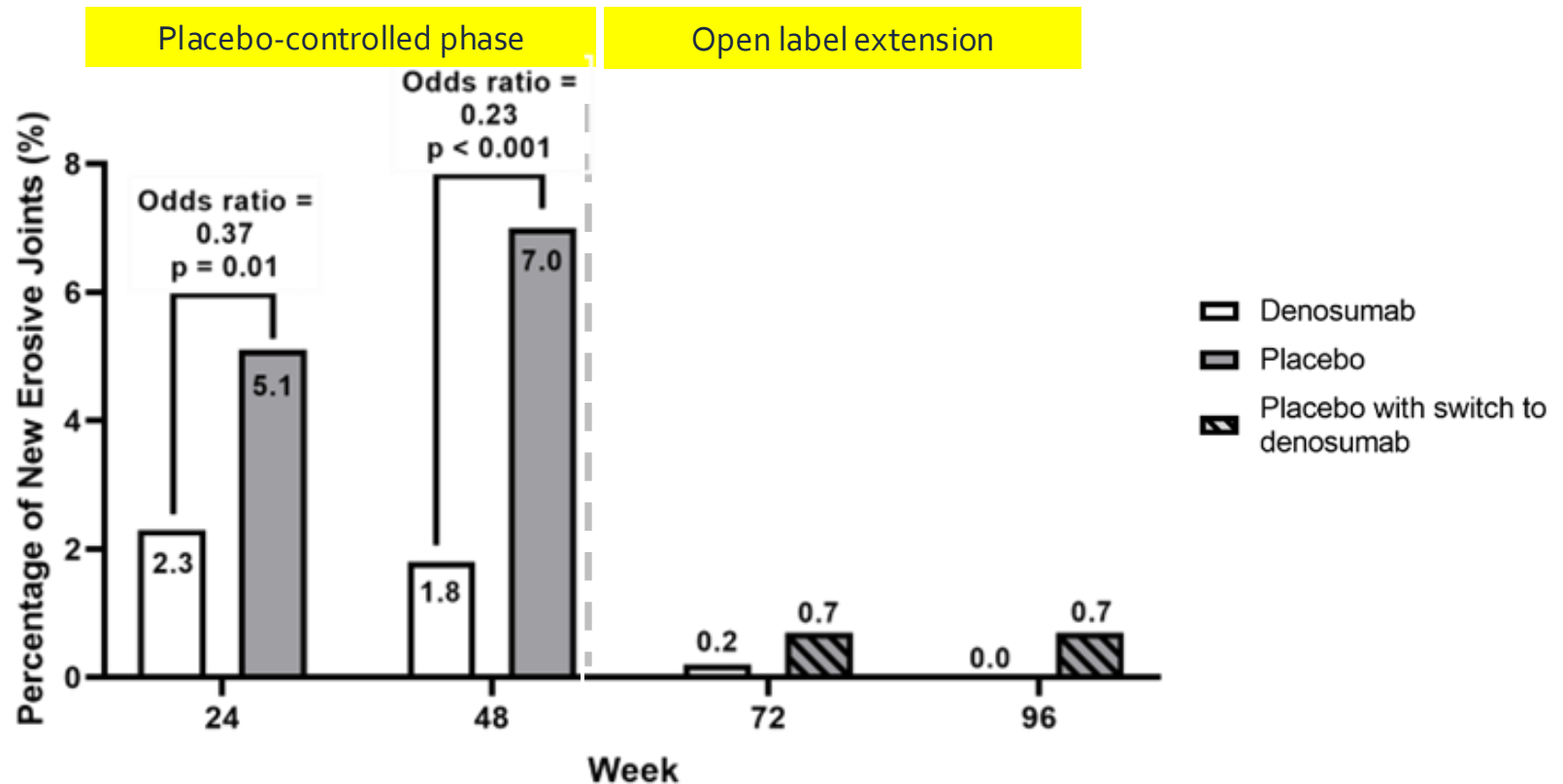
Results: primary endpoint

Mean change GUSS™ at week 24

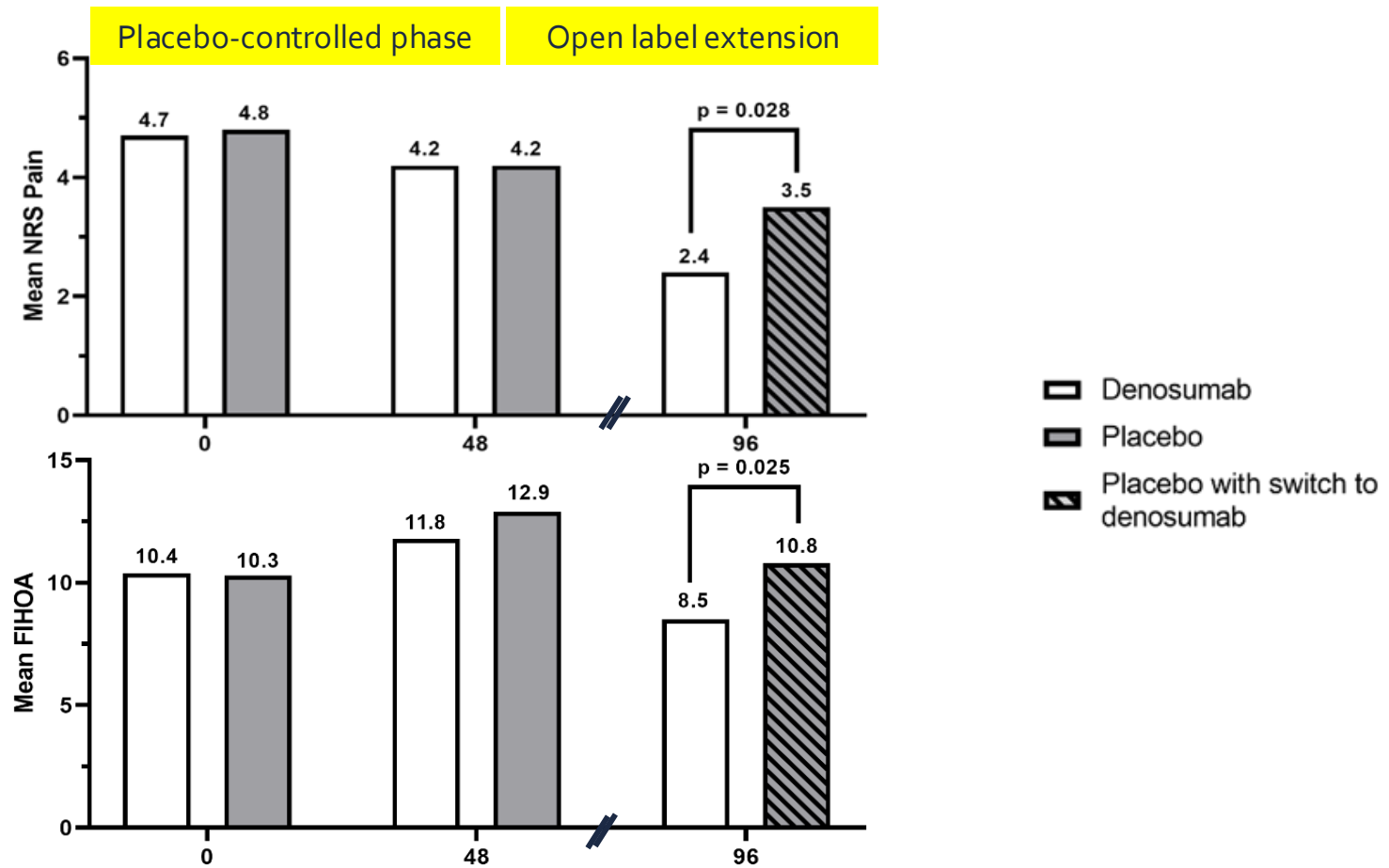


Results: secondary endpoint

New erosive joints at week 48



Results: exploratory endpoints



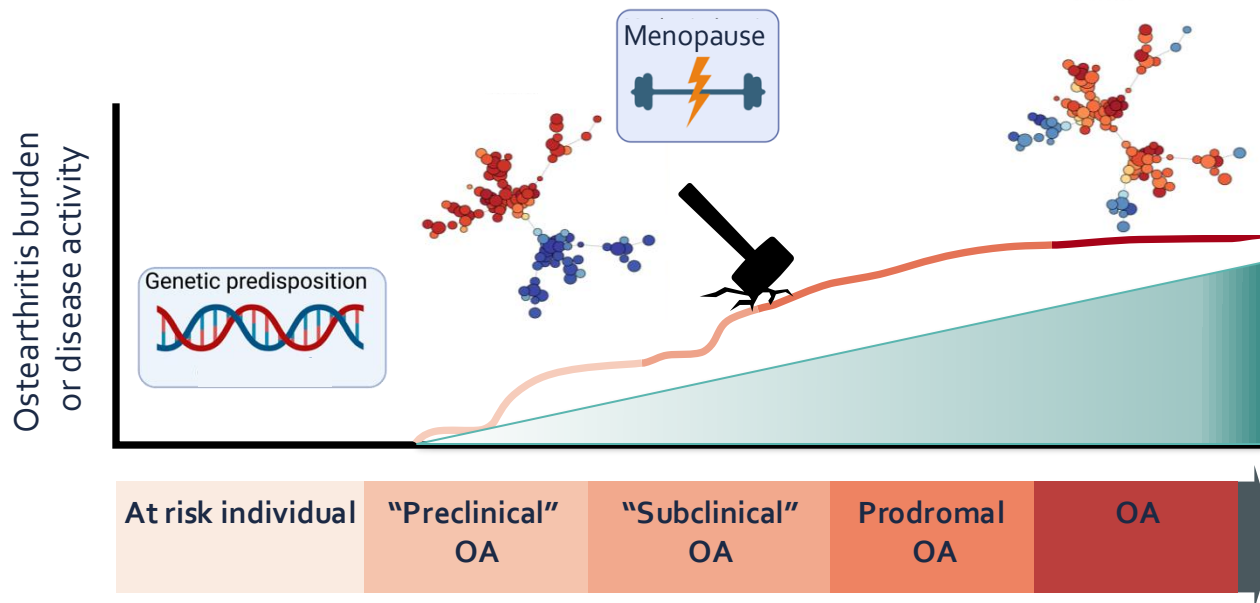


Conclusion

First proof of concept of successful structure modification in erosive hand OA by denosumab, a RANKL inhibitor

Osteoclast inhibition is a suitable strategy to target erosive progression in hand OA

Menopause may act as a second hit in roadmap to hand OA



Take home messages part 3

Sex hormones have a profound and pleiotropic effect on the musculoskeletal system

Estrogen loss linked to a myriad of symptoms in joints, muscle and ligaments

Menopause may act as “second hit” in at risk individuals to trigger some rheumatic diseases