

The musculoskeletal syndrome of menopause

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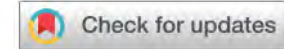
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REVIEW ARTICLE



OPEN ACCESS



The musculoskeletal syndrome of menopause

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ABSTRACT

Fifty-one percent of humans are born with ovaries. As the ovarian production of estrogen diminishes in midlife and ultimately stops, it is estimated that more than 47 million women worldwide enter the menopause transition annually. More than 70% will experience musculoskeletal symptoms and 25% will be disabled by them through the transition from perimenopause to postmenopause. This often-unrecognized collective of musculoskeletal symptoms, largely influenced by estrogen flux, includes arthralgia, loss of muscle mass, loss of bone density and progression of osteoarthritis, among others. In isolation, it can be difficult for clinicians and patients to adequately appreciate the substantial role of decreasing estrogen, anticipate the onset of related symptoms and actively treat to mitigate future detrimental processes. Thus, in this review we introduce a new term, the musculoskeletal syndrome of menopause, to describe the collective musculoskeletal signs and symptoms associated with the loss of estrogen. Given the significant effects of these processes on quality of life and the associated personal and financial costs, it is important for clinicians and the women they care for to be aware of this terminology and the constellation of musculoskeletal processes for which proper risk assessment and prophylactic management are of consequence.

ARTICLE HISTORY

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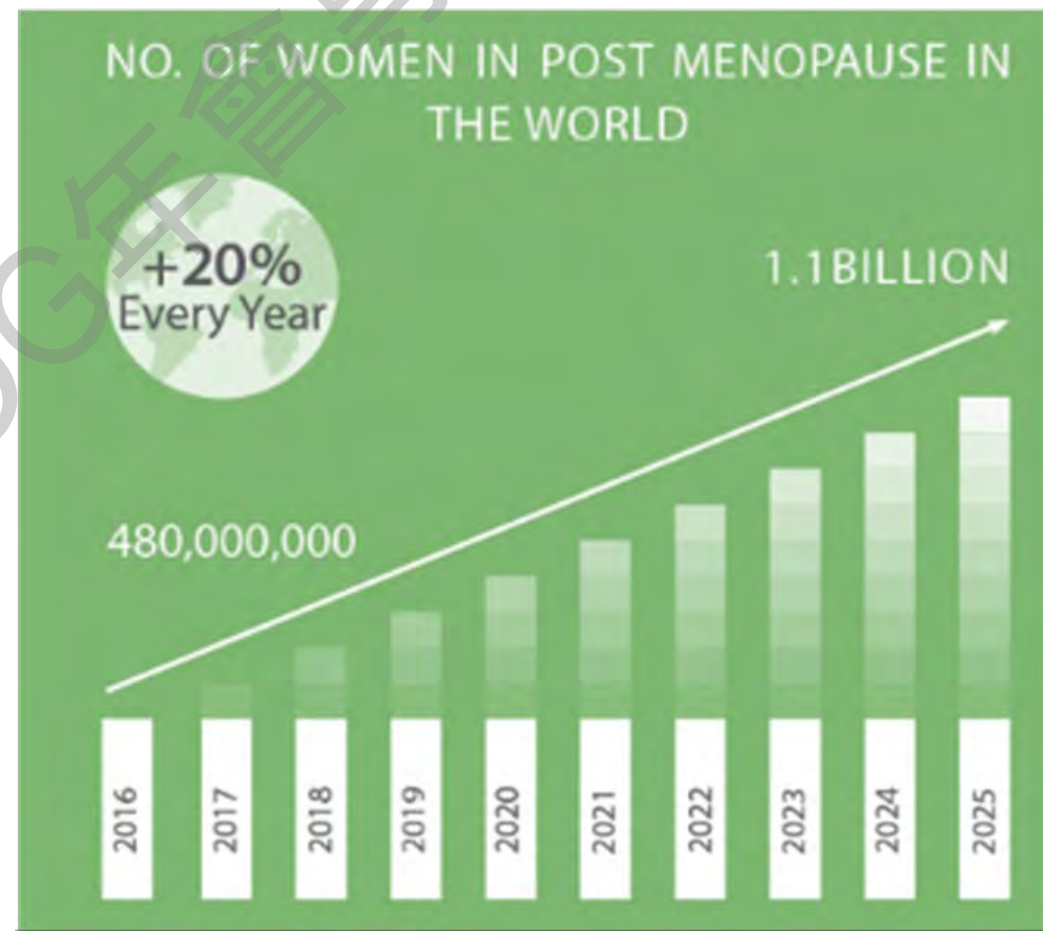
Accepted 10 July 2024

KEYWORDS

Musculoskeletal system;
menopause;
perimenopause; estrogen
deficiency

全球停經婦女人口逐年遽增

- 隨著全球人口結構的改變，已進入高齡化時代。由北美更年期協會統計全球停經婦女以每年 20% 成長增加，在2025年將會突破10億人



HEADACHES



MIND AND MOOD



Mood swings
Low mood
Anxious feelings
Irritability
Difficulty concentrating
Brain fog
Memory issues
or lapses

HOT FLASHES



MUSCLE & JOINT PAIN



Joint pain/stiffness
Long-term back pain
Muscle pain

WEIGHT CHANGES



ENERGY & SLEEP



Physical exhaustion
Mental exhaustion
Trouble sleeping

HAIR, SKIN, & NAILS



Thinning hair
Weak or brittle nails
Occasional breakouts
Itchy skin
Dry skin
Facial wrinkles
Loss of skin firmness
Dark spots

DIGESTION



Bloating
Heartburn
Upset stomach
Constipation
Diarrhea
Bladder issues

INTIMACY

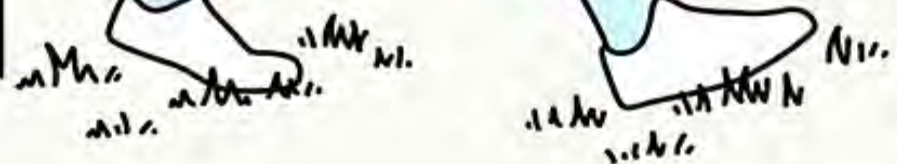


Low sex drive
Vaginal dryness
Painful sex

BONE HEALTH



More than 35 symptoms
are known to be
associated with
menopause



TOP6更年期症狀 網路聲量排行榜

1



失眠

#心理
4,261則

2



頭暈

#生理
3,595則

3



腰酸背痛

#生理
3,062則

4



煩躁

#心理
2,712則

5



盜汗

#生理
2,439則

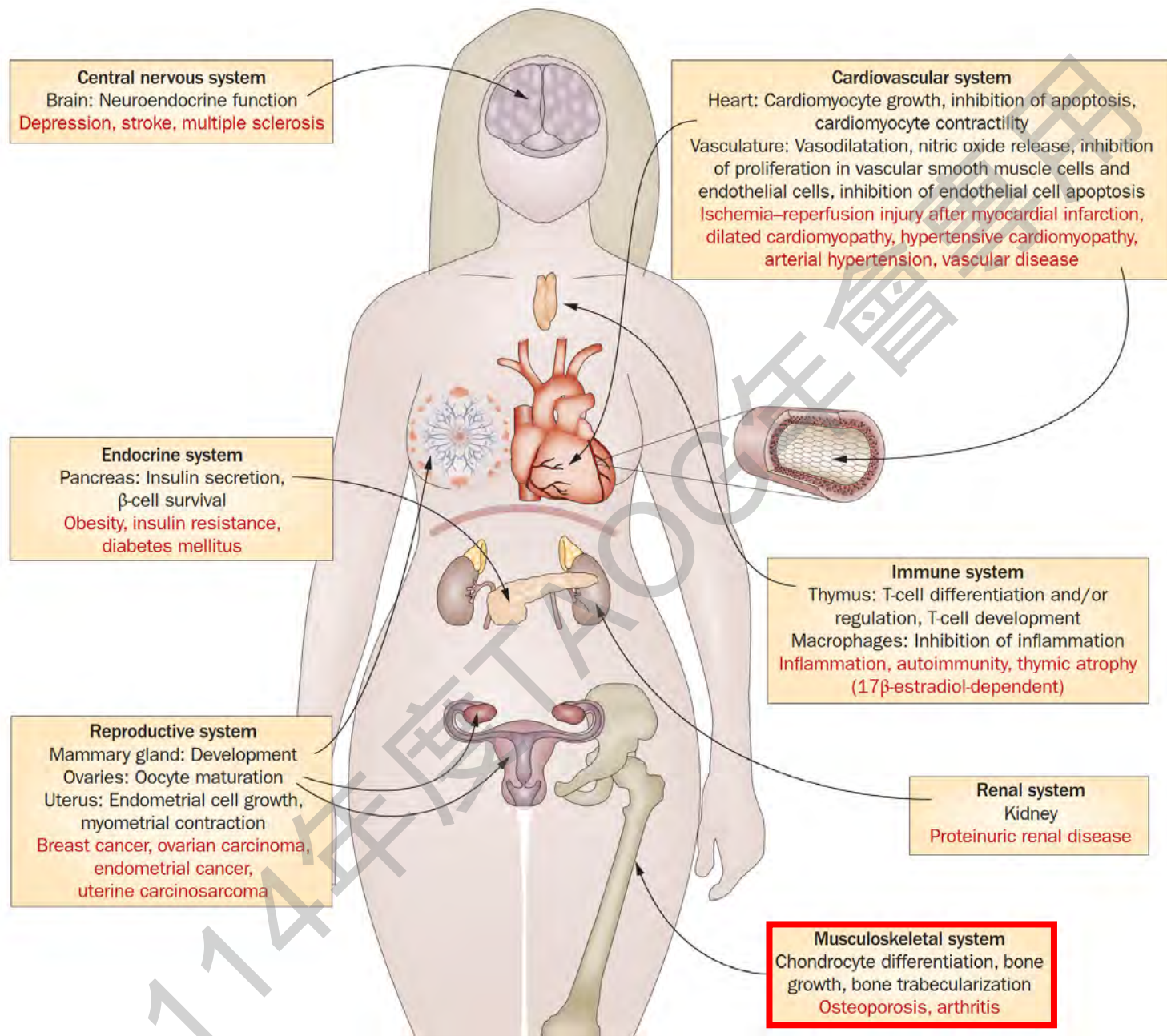
6



憂鬱

#心理
2,239則







MUSCULOSKELETAL SYNDROME OF MENOPAUSE

- Musculoskeletal pain, arthralgia, loss of lean muscle mass, loss of bone density with increased risk of resultant fracture, increased tendon and ligament injury, adhesive capsulitis and cartilage matrix fragility with the progression of osteoarthritis.
 - 70% of all midlife women will experience, 25% will experience severe symptoms and 40% will have no structural findings
-



RISK FACTORS ASSOCIATED WITH MUSCULOSKELETAL HEALTH

Modifiable risk factors	Non-modifiable risk factors
Alcohol intake Smoking Low body mass index Low calcium intake Vitamin D deficiency Insufficient physical activity Frequent falls Ergonomical, psychosocial and occupational factors	Female gender Increasing age Family history Previous fracture Race or ethnicity Prior hysterectomy Women beyond 5 years of menopause Late menarche Early menopause

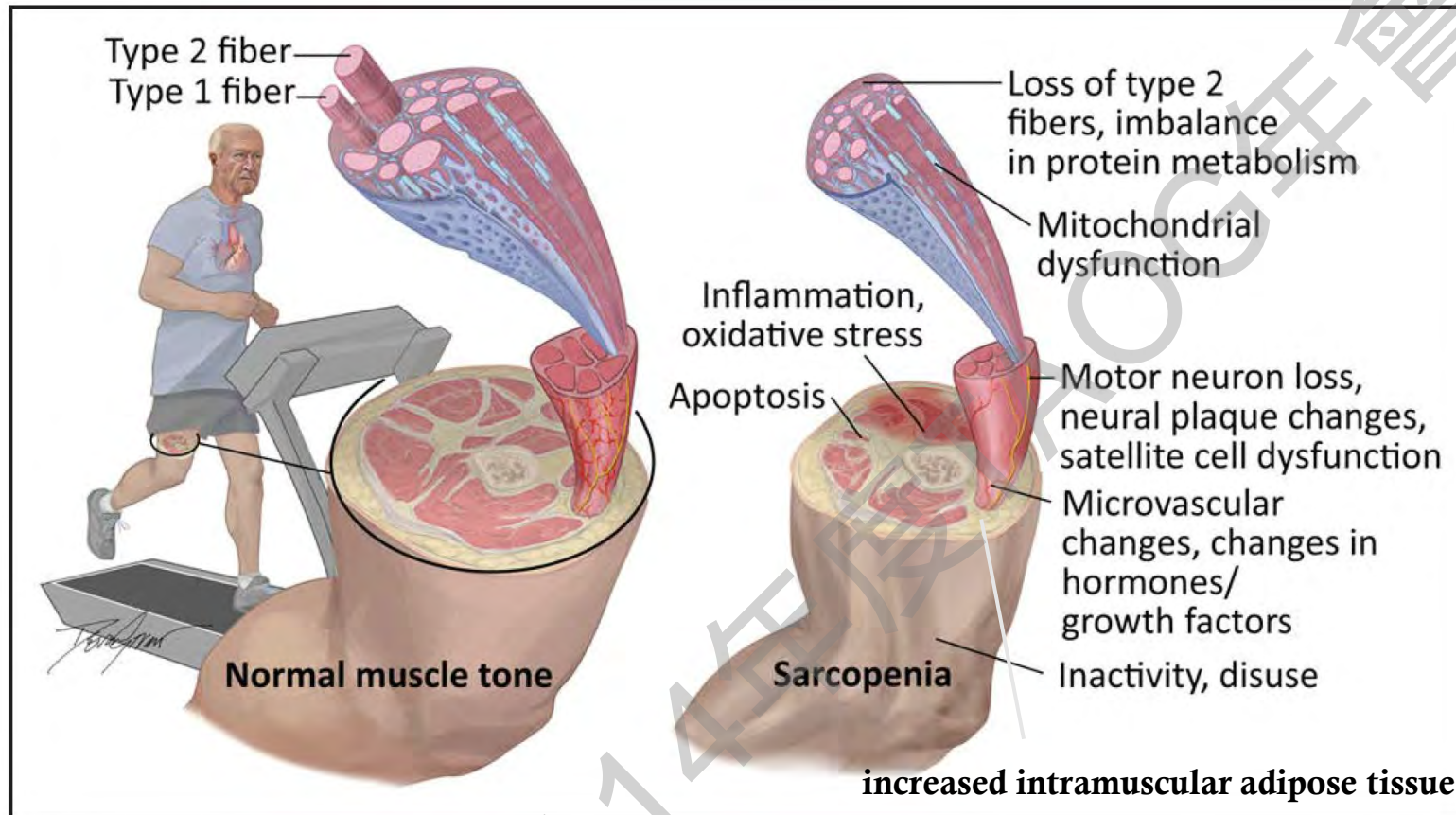
Table 1. Musculoskeletal syndrome of menopause: processes and signs.

<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

- The inflammasome is a multiprotein complex that activates caspase-1 and processes pro-inflammatory cytokines such as IL-1 β and IL-18, which modulated by estrogen receptor- β



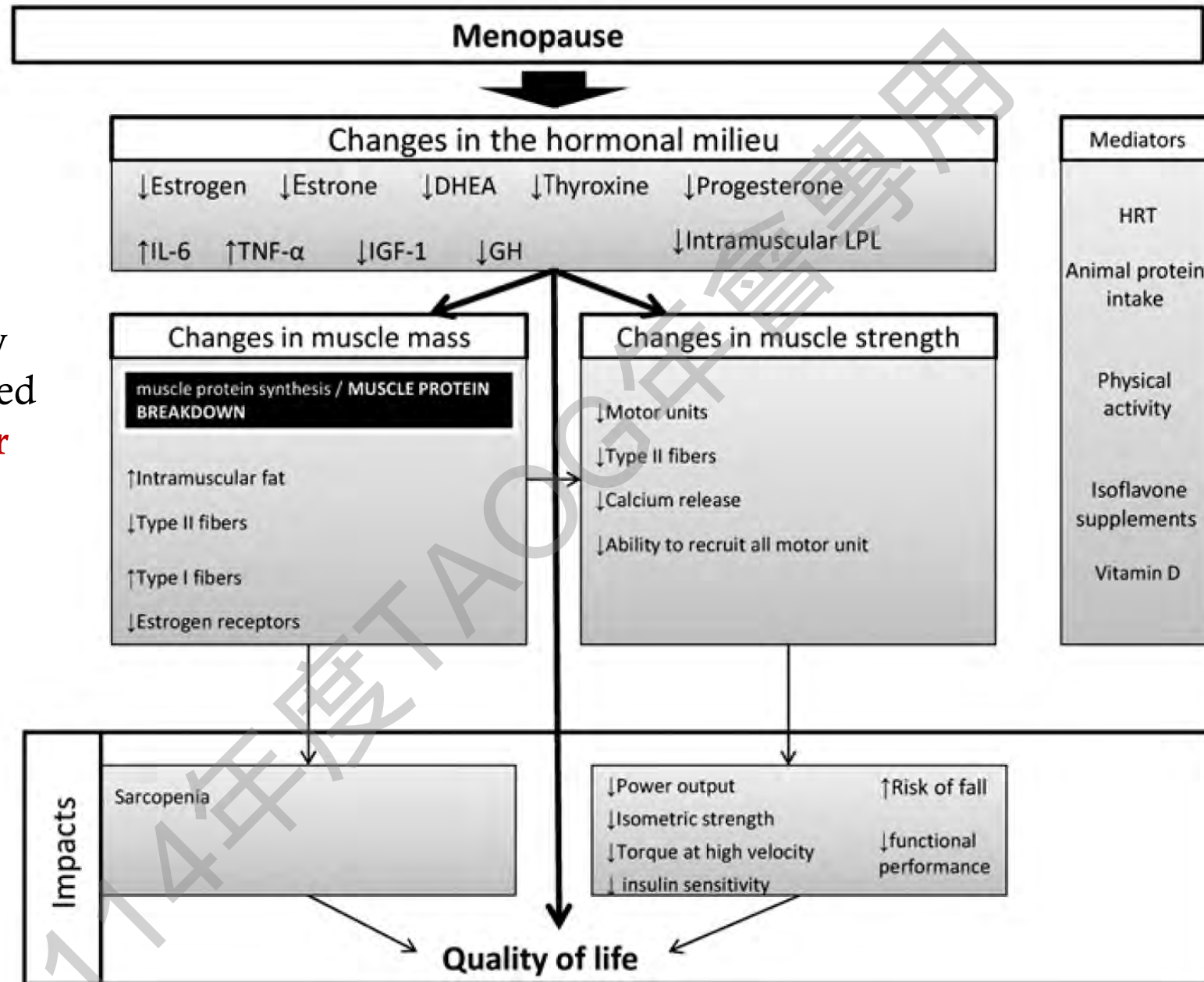
SARCOPENIA



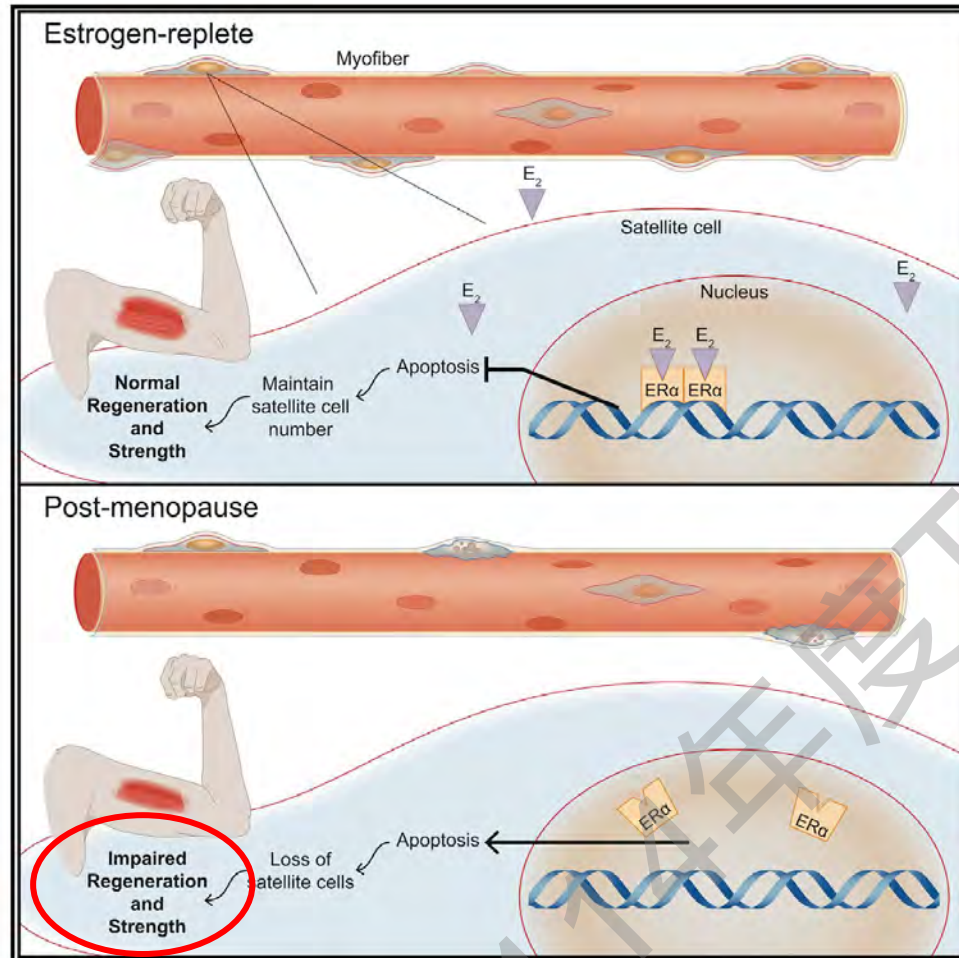
EWGSP (2019)

1. **Low muscle strength**
(sarcopenia is probable)
2. **Low muscle quantity or quality**
(sarcopenia is confirmed)
3. **Low physical performance**
(sarcopenia is severe)

A cross-sectional study by Rolland et al. showed
 A **decline of 0.6 % per year of muscle mass after menopause**



SATELLITE CELL PROLIFERATION

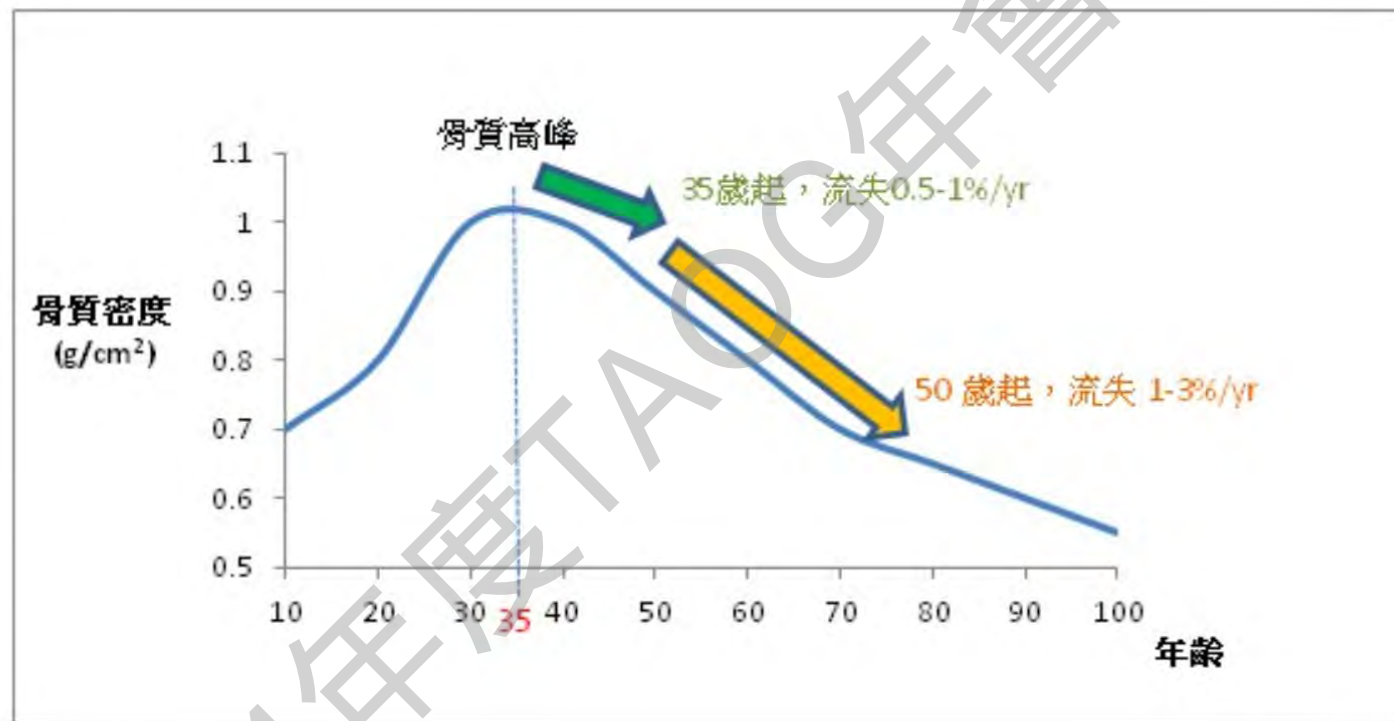


ER α is necessary for satellite cell maintenance, self-renewal, and protection from apoptosis, thereby promoting optimal muscle regeneration

Loss of estrogen in female mice and post-menopausal women leads to a decrease in skeletal muscle stem cells

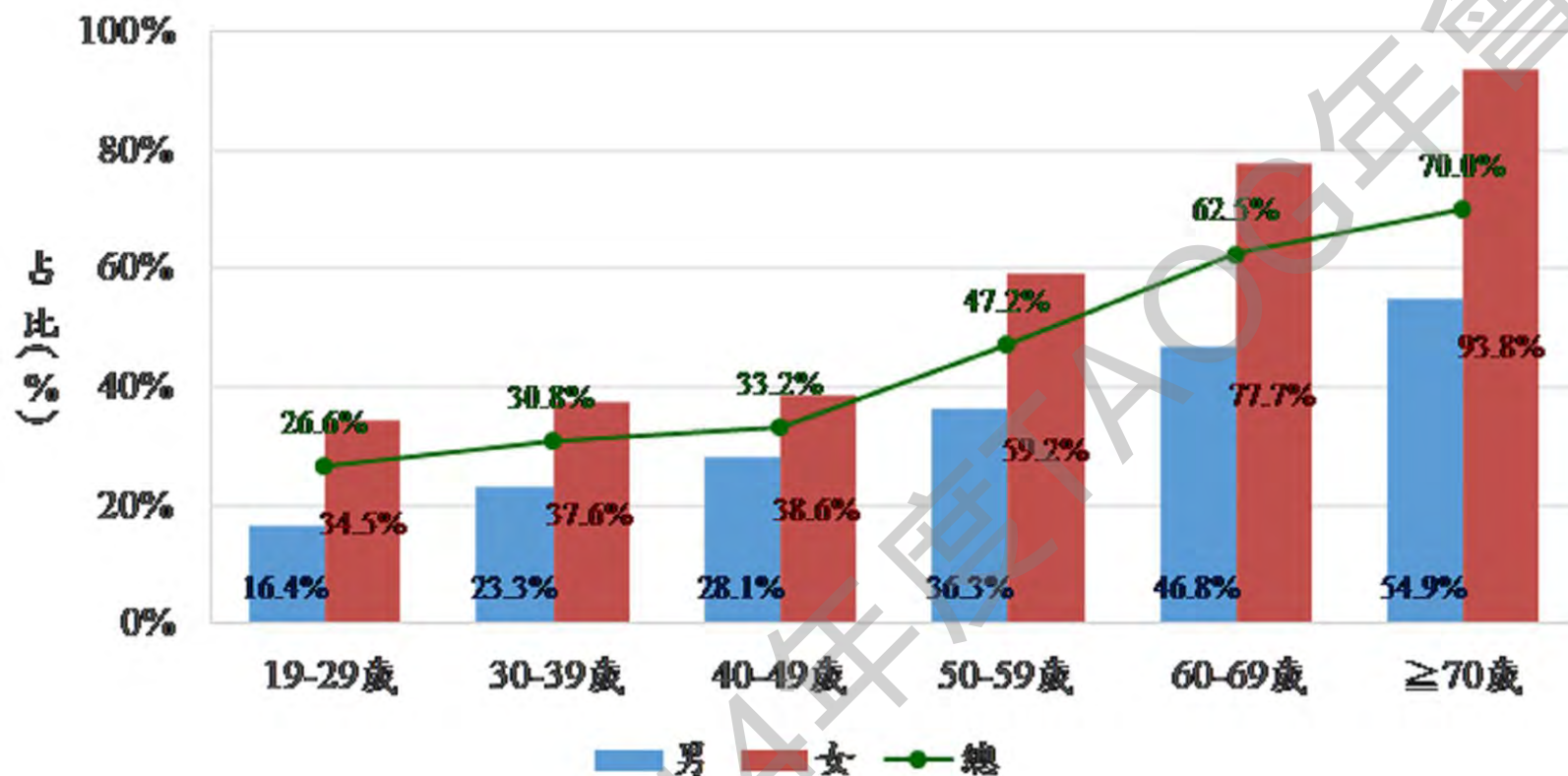
- increase frailty due to difficulty in generating muscle power and adequate regeneration

BONE DENSITY



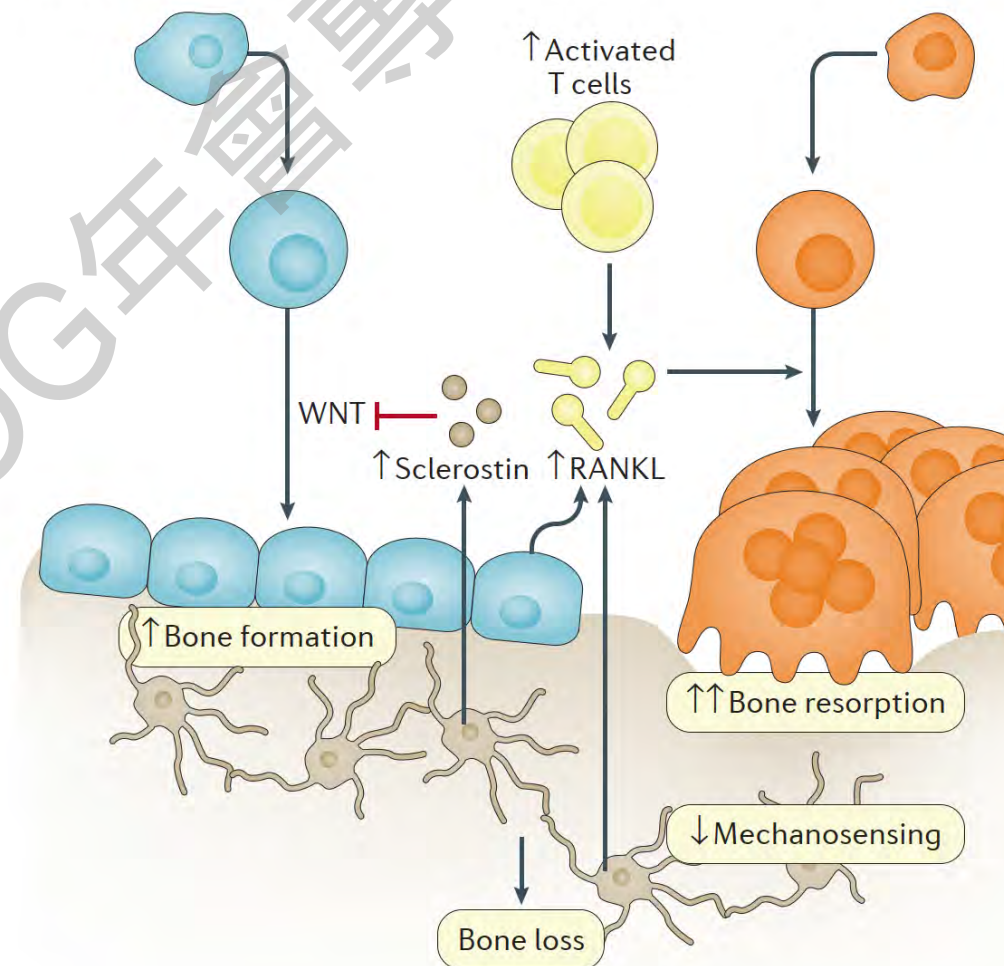
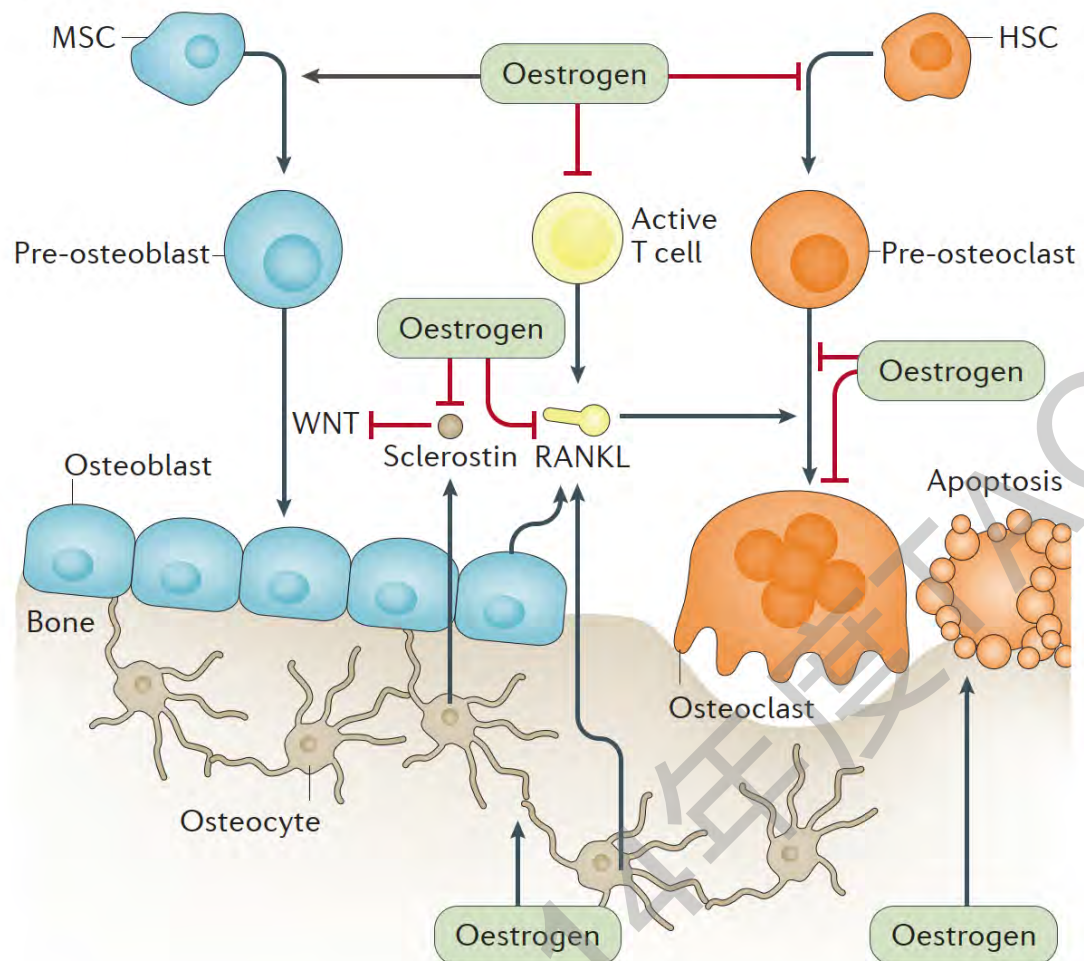
成人自 35 歲起，隨年齡增加，每年骨質流失約 0.5~1%；50 歲起流失更快，每年流失約 1~3%

OSTEOPOROSIS PREVALENCE IN TAIWAN



根據國健署所公布的2017-2020年「國民營養健康狀況變遷調查」，65歲以上民眾量測骨質密度：國人至少有一個部位骨鬆盛行率為**14.1%** (男性10.4%、**女性17.4%**)，且**隨著年紀增長而增加**。

65歲以上長者，則是每6人就有1人在一年內有跌倒的經驗



CARTILAGE DAMAGE AND OSTEOARTHRITIS

Figure 1 Estrogen actions on target articular tissues

Cartilage

- Increases PG production in chondrocytes
- Decreases NF- κ B, iNOS, COX-2, ROS in chondrocytes
- Regulates $[Ca^{2+}]_i$ in chondrocytes
- Decreases cartilage damage in several animal models

Subchondral bone

- Regulates bone growth and remodeling
- Regulates OB development and function
- Regulates matrix production and mineralization
- Reduces bone formation and prevalence of total marginal osteophytes in OVX monkeys
- Decreases MRI-likelihood of bone attrition in women



Muscle

- Promotes myoblasts proliferation and differentiation
- Decreases muscle cell apoptosis
- Reverses muscle contractile dysfunction in rats
- Decreases muscle atrophy and calpain levels in rats
- Enhances muscle performance and structure in women

Synovium

- Increased synovial levels of components of the IGF pathway in OVX monkeys
- Reversed autoimmune arthritis developed in mice
- Decreased rheumatoid factor, anti-double-stranded DNA, and anti-type II collagen serum levels in mice

Ligaments

- Contrasting effects on ACL mechanical properties in animal models
- High estrogen levels during the menstrual cycle have been associated with ACL ruptures in young women

Estrogen actions on target articular tissues. ACL, anterior cruciate ligament; $[Ca^{2+}]_i$, intracellular calcium concentration; COX-2, cyclooxygenase-2; IGF, insulin-like growth factor; iNOS, inducible nitric oxide synthase; MRI, magnetic resonance imaging; OB, osteoblast; OVX, ovariectomized; PG, proteoglycan.

Table 1. Prevalence of knee osteoarthritis.

Demographic subgroup	Radiographic knee OA (%)	Symptomatic knee OA (%)
Male (age in years)	31.2	10.0
60–69	27.4	7.5
70–79	33.5	12.9
≥80	40.7	12.7
Female (age in years)	42.1	13.6
60–69	35.2	10.6
70–79	44.6	15.3
≥80	55.6	18.2
BMI (kg/m²)		
<25	23.8	6.5
25–29	36.9	9.9
≥30	57.4	23.2

Although OA affects other joints similarly, the largest percentage of OA occurs in the knee; therefore prevalence data are presented for the knee by sex, age and BMI.

OA: Osteoarthritis.

Data taken from [20].

Studies in literature suggest that **women had a higher prevalence of OA**, increases dramatically around the time of menopause and experienced **more debilitating pain** than men



HRT Hormone Replacement Therapy

The effect of HRT on
musculoskeletal
syndrome of menopause

Association Between Hormone Therapy and Muscle Mass in Postmenopausal Women

A Systematic Review and Meta-analysis

JAMA Netw Open. 2019;2(8):e1910154.

Ayesha A. Javed, BSc; Alexandra J. Mayhew, MSc; Alison K. Shea, MD, PhD; Parminder Raina, PhD

Effect of hormone therapy on muscle strength in postmenopausal women: a systematic review and meta-analysis of randomized controlled trials

Menopause 27(7):p 827-835, July 2020.

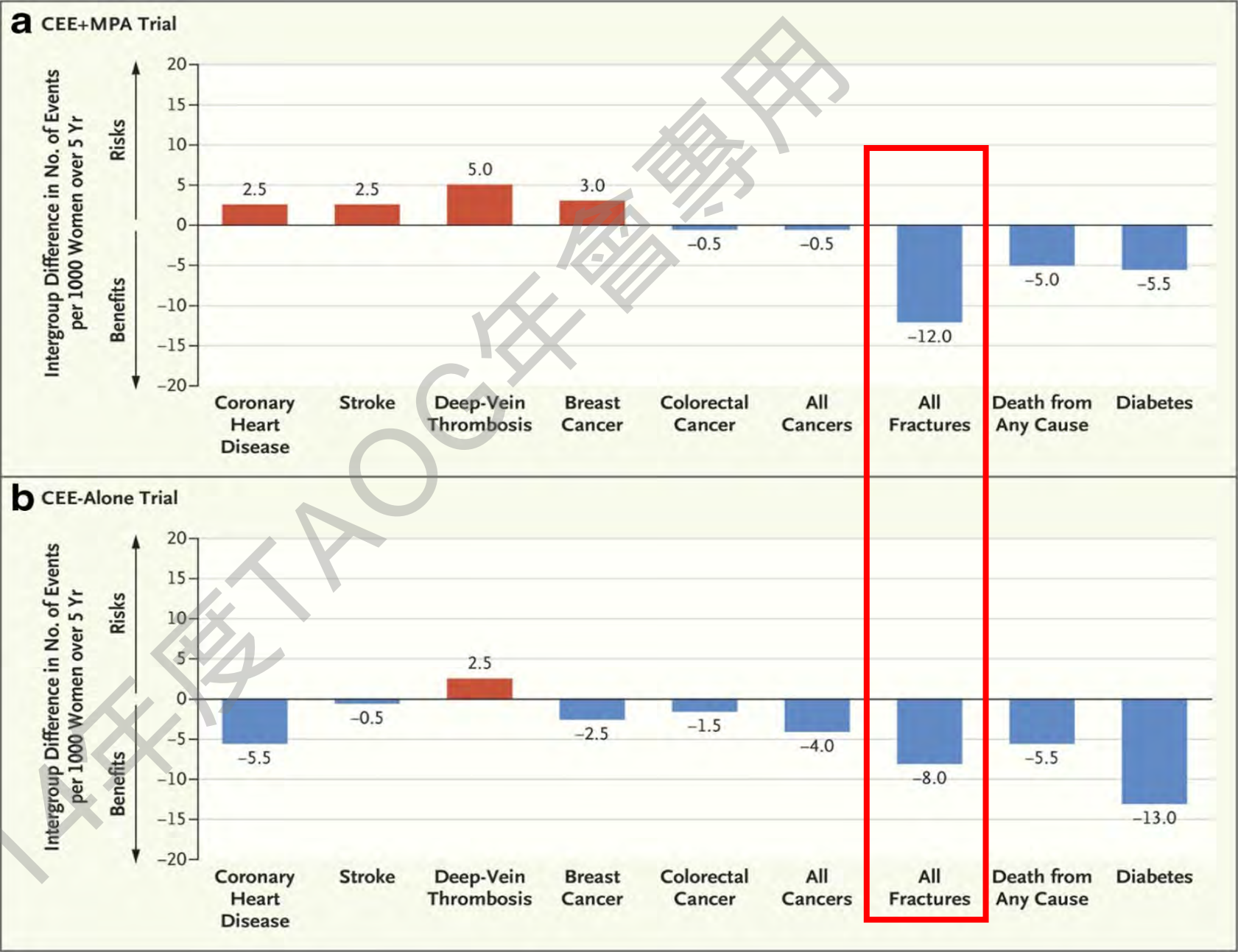
Yang Xu, BS,¹ Kai-Li Deng, BMS,¹ Tian-Fang Xing, BMS,¹ Ya-Qing Mei, BMS,¹ and Su-Mei Xiao, PhD^{1,2}

The benefits of **estrogens** in preventing loss of muscle mass and **strength** in postmenopausal women are **not confirmed** in most RCT, as reported by reviews and meta-analyses

MHT can consider as a plausible method, especially when paired with resistance training

Dieli-conwright CM et al. 1985, Pöllänen E et al. 2010

Fig. 1 Updated summary of the effects of orally administered CEE alone or combined with MPA in women ages 50–59 years during intervention phase of WHI (reused with permission from [9])



Hormone Replacement Therapy and Prevention of Nonvertebral Fractures

A Meta-analysis of Randomized Trials *JAMA. 2001;285(22):2891-2897.*

Figure 1. Relative Risk Plot of Trials Pooled by Random Effects Model

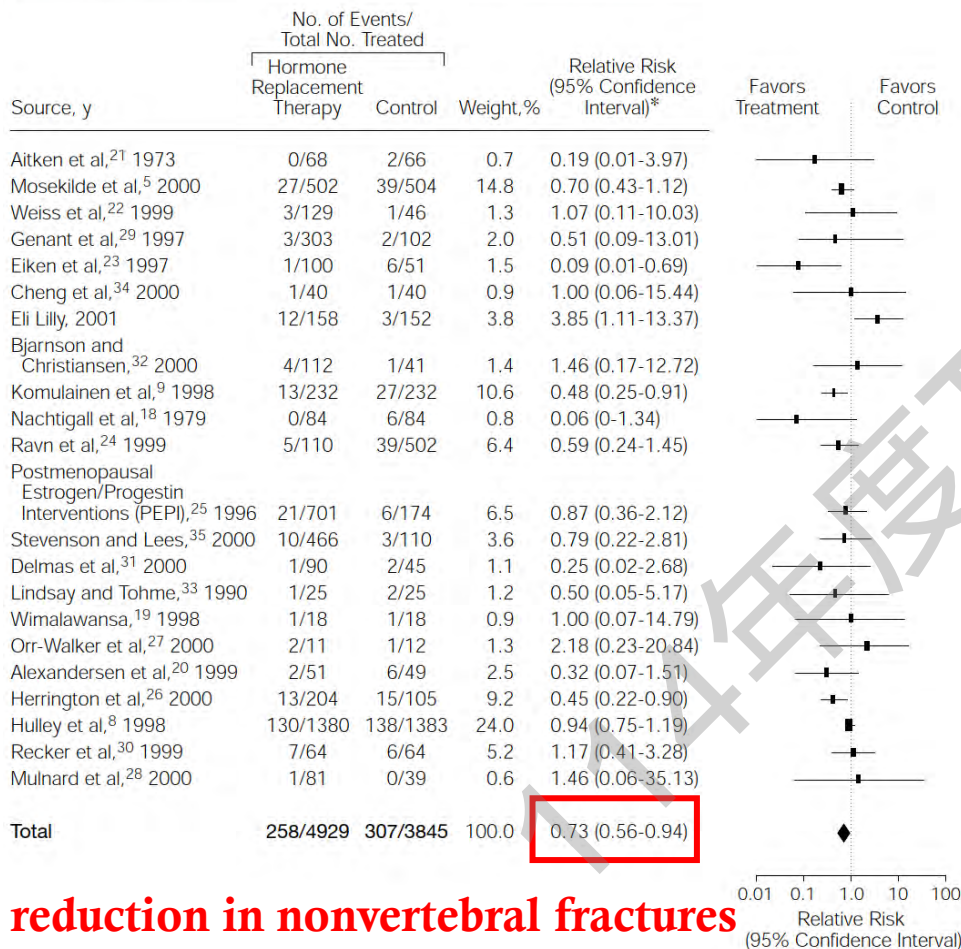


Table 3. Sensitivity and Subgroup Analyses of the Effects of Hormone Replacement Therapy Using Different Inclusion and Exclusion Criteria

Comparison on Fracture Effects	No. of Trials	Estimate of Effect by Random Effects Model (95% Confidence Interval)	P Value
All trials	22	0.73 (0.56-0.94)	.02
Women <60 y	14	0.67 (0.46-0.98)	.03
Women ≥60 y	8	0.88 (0.71-1.08)	.22
All placebo-controlled trials	18	0.74 (0.55-1.00)	.05
Women <60 y	12	0.70 (0.44-1.10)	.12
Women ≥60 y	6	0.79 (0.53-1.19)	.26
All trials with hip or wrist fractures	14	0.60 (0.40-0.91)	.02
Women <60 y	8	0.45 (0.26-0.79)	.005
Women ≥60 y	6	0.88 (0.47-1.59)	.63
All trials with published fracture data*	14	0.64 (0.47-0.86)	.003
All unpublished trials of fracture data	8	1.09 (0.65-1.81)	.74

*Refers to studies in which the fracture data are, or will soon be, in the public domain.

This effect was greater among women randomized to HRT who had a mean age younger than 60 years

27% reduction in nonvertebral fractures

V. Meta-Analysis of the Efficacy of Hormone Replacement Therapy in Treating and Preventing Osteoporosis in Postmenopausal Women

Endocrine Reviews, August 2002, 23(4):529 –539

TABLE 2. RR of fracture after treatment with HRT

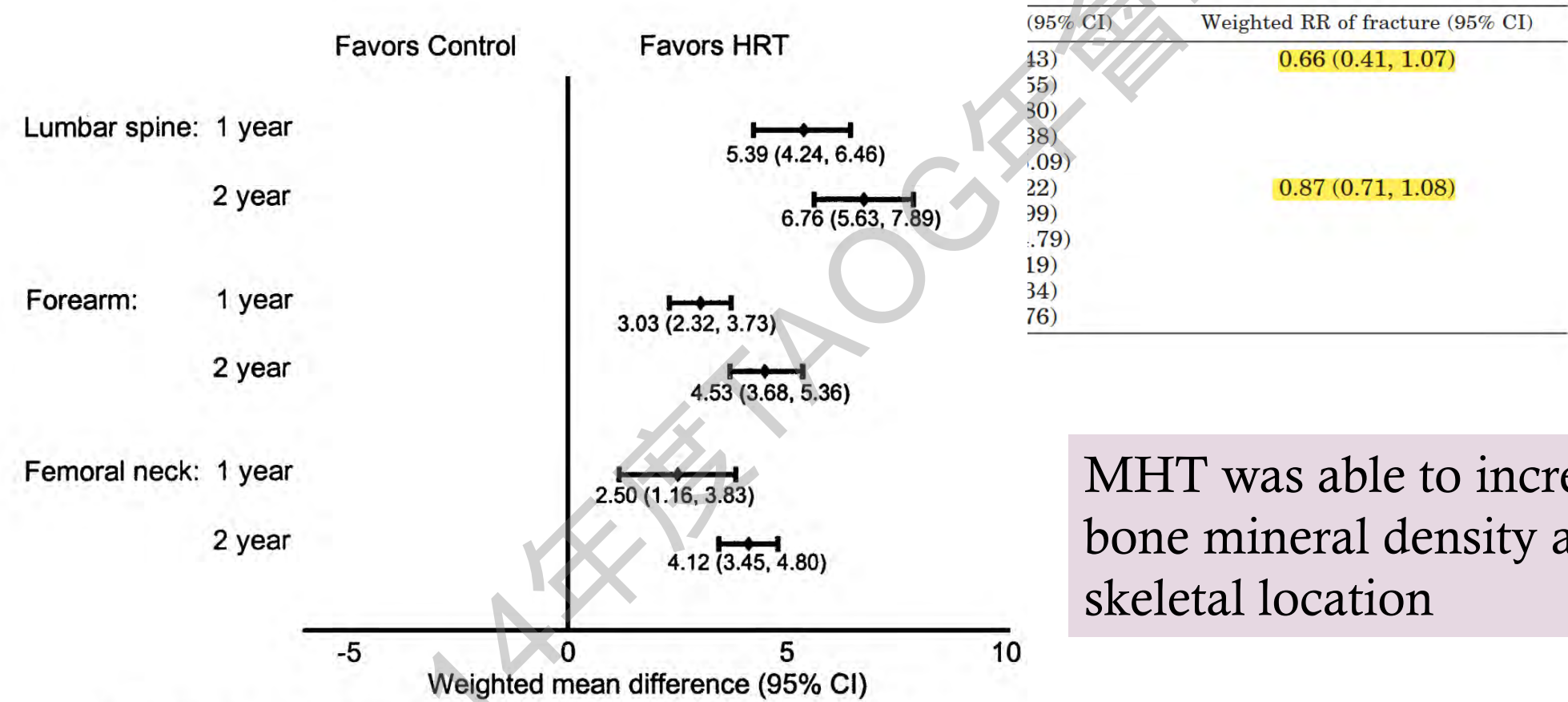


FIG. 3. Weighted mean difference in percent change in bone density after treatment with HRT.

MHT was able to increase bone mineral density at all skeletal location

- The subject of MHT in the prevention and treatment of **osteoarthritis** in postmenopausal women is **controversial**

TABLE 1 | Overview of the influence of HT on OA/CVD outcomes.

Type of HT	Mechanism of HT	OA risk/outcome
Estrogen* (17β-estradiol and 17β-estradiol)	Estrogen receptors in joint tissues (66)	No clear association (73)
<div>Oral CEE</div>	Mixture of estrogen compounds, antagonistically bind to estrogen receptors (76)	Modest reduction in joint pain, lower rates of arthroplasty (14, 77)
Oral Progesterone** (progestin) Estrogen-progestogen combination treatment	Stabilizes endometrial lining (79)	Aids in bone remodeling (80) No significant effect compared to placebo (82), may reduce severity of OA (83)
<div>Tibolone SERM</div>	Selective tissue estrogenic activity (85) Selective tissue estrogenic activity without stimulating breast or endothelium tissue (85, 89)	Decreases bone loss (86, 87) Decreases bone loss maintains bone mineral density (Bazedoxifene, Raloxifene) (86, 87)

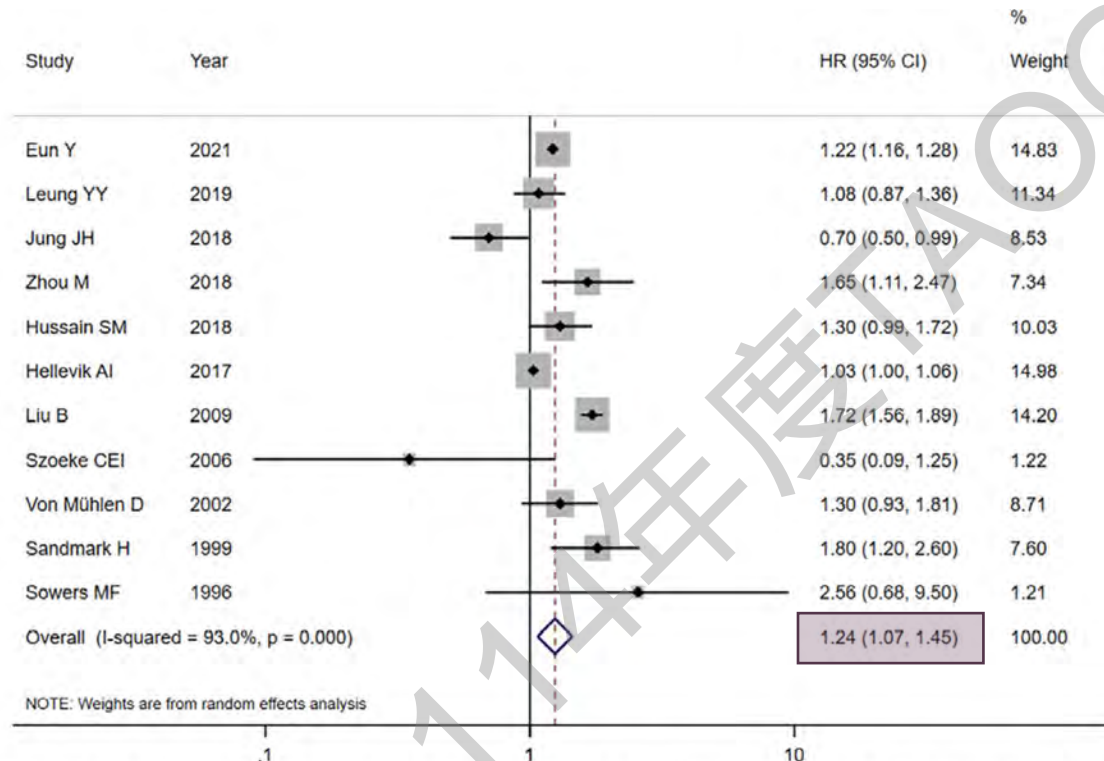
Association of hormone replacement therapy and the risk of knee osteoarthritis

A meta-analysis

Medicine 2022;101:51(e32466).

Wen-Yuan Hou, MD^{a,b}, Cai-Yu Zhu, MD^{a,b}, Yi-Fan Gu, PhD^a, Lei Zhu, MD^a, Zheng-Xin Zhou, MD^{a,*} 

There existed 13 pieces of research, containing **1 case-control research**, **4 cross-sectional pieces of research**, as well as **8 cohort pieces of research**, involving 2573,164 participants.



- HRT was related to a raised risk of knee OA (HR = **1.24**, 95% CI 1.07–1.45)
- HRT user statistically significant raised risk of knee joint replacement (HR = **1.30**, 95% CI 1.09–1.54)

No randomized, prospective, controlled trial was designed to specifically assess the impact of hormone replacement therapy on symptomatic or structural progression of OA

Figure 2. The pooled results of the relationship between HRT use and risk of knee OA. CI = confidence interval, HR = hazard ratio, HRT = hormone replacement therapy, OA = osteoarthritis.



Nutrition and Exercise

Table I Involvement of Different Macronutrients and Dietary Recommendations in Bone Health

Macronutrient	Role in Bone Health	Dietary Recommendation
Saturated Fatty Acids	Promote the formation of complexes with calcium, leading to its elimination through faeces, and apoptosis of osteoblasts ^{1,26}	Limit the consumption of ultra-processed foods
Polyunsaturated Fatty Acids	Modulate the activity of osteoclasts and osteoblasts; control inflammatory processes ^{27,28}	Ensure proper consumption of foods rich in omega-3 fatty acids, such as walnuts or fatty fish
Carbohydrates	Hyperglycemia increases inflammation, oxidative stress, bone resorption due to acidosis, and urinary calcium excretion ²⁹	Recommend foods with a high glycemic index and rich in fiber, such as fruits, vegetables, and whole grains
Proteins	Provide necessary amino acids for bone remodelling and enhance calcium absorption in the intestine ^{1,30}	Increase protein intake above 0.8 g/kg of body weight per day if there are no contraindications





TABLE 1 Studies of VD in osteoporosis and muscle loss.

Vitamin D	Methods	Results	Ref
VD ₃	36,282 postmenopausal women receive 1000 mg carbonate with 400 IU of VD ₃ daily or placebo for 7 years of follow-up	Calcium plus VD improved hip BMD ^a in postmenopausal women but did not significantly reduce hip fractures	Jackson et al. (2006)
VD ₃	160 women were into the VD group (1000 IU of VD ₃ /day, n = 80) or placebo group (n = 80) for 9 months	In young postmenopausal women with VD deficiency, supplementation with 1000 IU of VD ₃ alone may reduce bone turnover (s-CTX ^b , P1NP ^c) markers	Nahas-Neto et al. (2018)
Calcitriol (活性D3)	70 post-menopausal women were into two groups: 40 patients received calcitriol (0.5 microg/day) and calcium; and 30 patients received calcium alone for 6 months	Calcitriol treatment increased BMD and reduced serum IL-1 and TNF-alpha concentrations	Inanir et al. (2004)
Cholecalciferol and calcitriol (D3)	485 postmenopausal women were divided three group, which were treated with calcium (600 mg/d) alone, calcium and cholecalciferol (800 IU/d) or calcium and calcitriol (0.25 µg/d)	Supplementation with calcitriol and calcium modifies the bone turnover marker (β-CTX, P1NP) levels, supplementation with cholecalciferol and calcium prevents aging-mediated deterioration in quality of life	Gao et al. (2015)
Calcitriol	141 postmenopausal women were into two groups: 75 participants received calcitriol 0.5 µg/day and 66 participants received a placebo for 12 weeks	Calcitriol reduces serum PTH ^d , creatinine, uric acid and improves left hand grip strength	Cheng et al. (2018)
Calcifediol (25-hydroxyvitamin D3)	113 post-menopausal women received calcifediol (20 µg, 4 oral drops/day) for a 6-month period for 6 months	Calcifediol improves serum levels of 25(OH)D and muscle function and reduces the average number of falls in postmenopausal women	Iolascon et al. (2017)
1alpha hydroxyVD ₃	92 osteoporotic women were into four groups: 1alpha hydroxyVD ₃ , (0.75 microg/day, n = 29), VK ₂ (n = 22), VD ₃ plus vitamin VK ₂ (n = 21), and calcium (n = 20)	Combined administration of VD ₃ and VK ₂ helps to increase BMD in the lumbar spine of postmenopausal women	Iwamoto et al. (2000)
VD ₃	160 postmenopausal women were into two groups: VD group, (1,000 IU/day, n = 80) and placebo group (n = 80) for 9 months	VD supplementation alone can reduce the incidence of falls and improve postural balance in postmenopausal women	Cangussu et al. (2016)

Impact of **magnesium** on bone health in older adults: A systematic review and meta-analysis

Bone. 2022;154:116233.

Inge Groenendijk^{a,*}, Marieke van Delft^a, Pieter Versloot^a, Luc J.C. van Loon^b, Lisette C.P.G. M. de Groot^a

- Magnesium is an enzymes cofactor for the **synthesis of bone matrix** and **stimulating osteoblast proliferation**. Magnesium deficiency can promote inflammation and oxidative stress, alter PTH secretion, and reduce 25-hydroxyvitamin D levels.

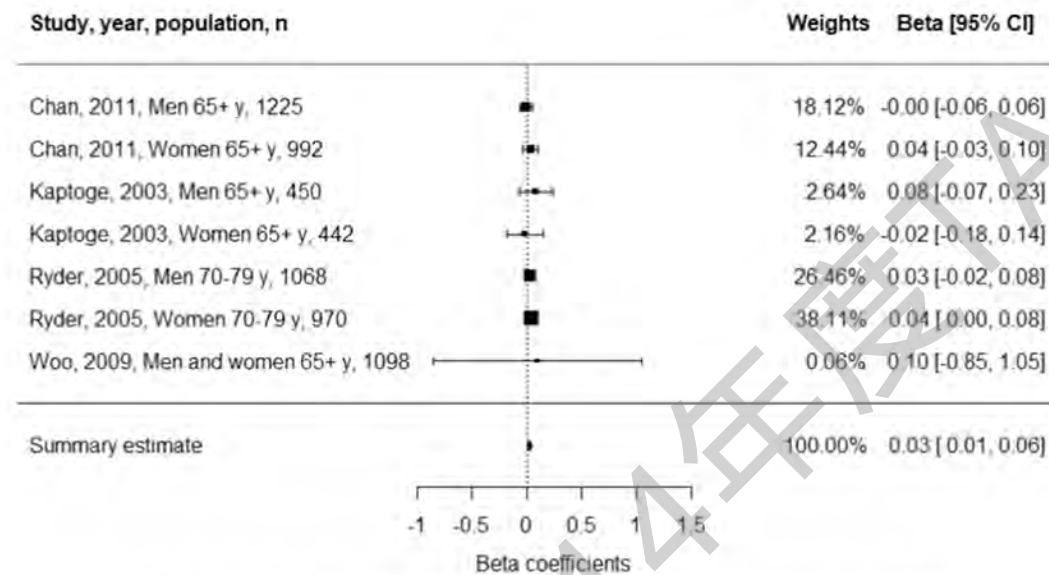


Fig. 2. Forest plot illustrating the impact of dietary magnesium intake on hip BMD.

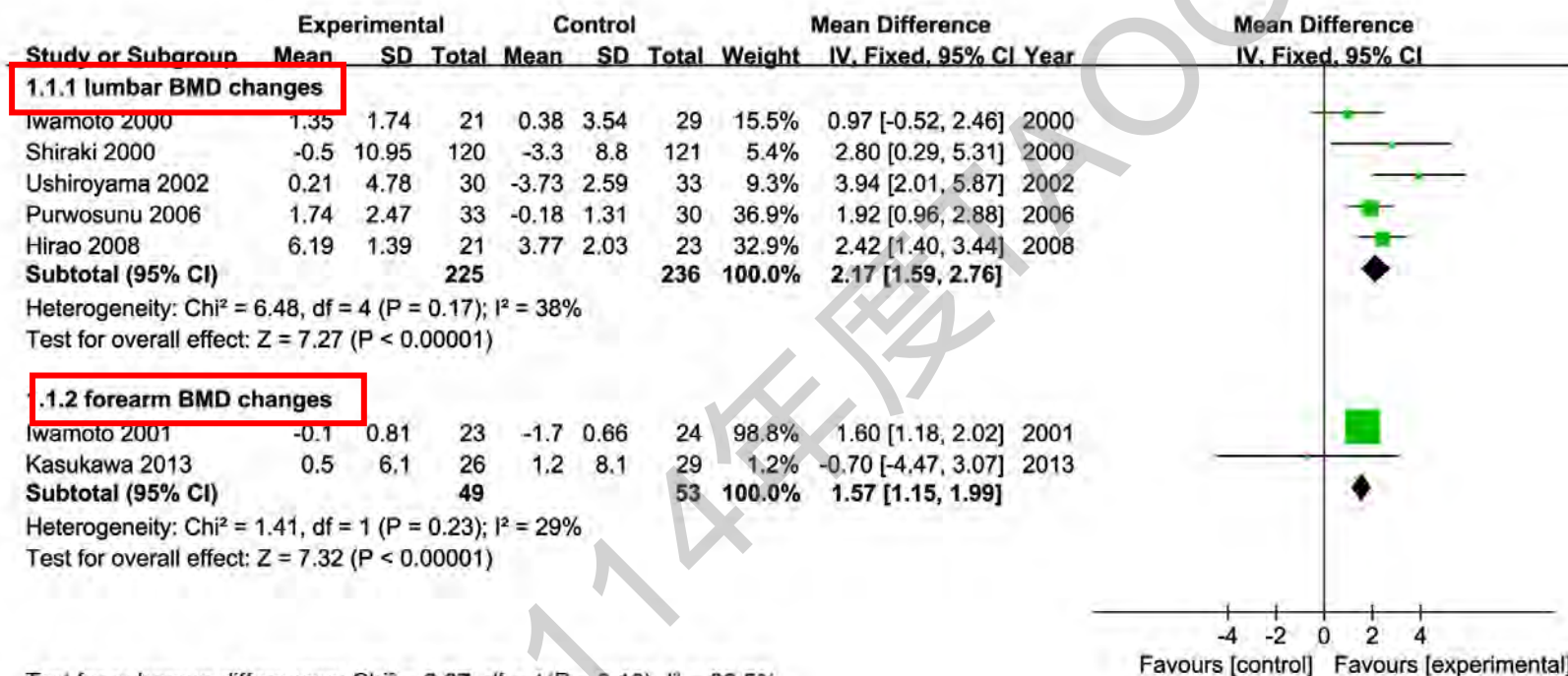
Higher magnesium intake may support an increase in hip and femoral neck BMD

Efficacy and safety of vitamin K2 for postmenopausal women with osteoporosis at a long-term follow-up: meta-analysis and systematic review

Journal of Bone and Mineral Metabolism (2022) 40:763–772

Ming Zhou¹ · Shiliang Han² · Wenpeng Zhang¹ · Dan Wu³ 

- Vitamin K is necessary for the gamma-carboxylation of osteocalcin, a protein synthesized and secreted by osteoblasts essential for the formation of hydroxyapatite crystals



No difference in the incidence of fractures between the two groups with obvious heterogeneity (RR = 0.99, 95% CI [0.87–1.13], $p = 0.9$, $I^2 = 67\%$).

BENEFITS OF EXERCISE BEYOND MENOPAUSE

- Exercise **increases the cardiorespiratory function**. If done regularly, it reduces the metabolic risks associated with declining estrogen. It **increases HDL, reduces LDL, triglycerides and fibrinogen**. There is an additional benefit of a **reduced risk of high blood pressure, heart attacks, and strokes**.
- Exercise can help create a calorie deficit and **minimize midlife weight gain**.
- It **increases the bone mass**. Strength training and impact activities (like walking or running) can help to offset the decline of bone mineral density and **prevent osteoporosis**.
- It also **reduces low back pain**.
- It is proven to help **reduce stress and improve the mood**
- It may help to **reduce hot flashes**, thereby minimizing the “Domino effect.”

Progressive resistance strength training for improving physical function in older adults (Review)

Liu CJ, Latham NK. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD002759.

漸進式阻力肌力訓練 (progressive resistance training, PRT) 是一種鍛鍊，接受訓練者以對抗某種阻力的方式，鍛鍊自己的肌肉。所施用的阻力強度，會隨著受訓者的肌力增強逐漸增加。漸進式阻力肌力訓練通常1週進行2至3次，利用運動訓練器械、自由重體或彈力帶，進行中度至高強度的訓練。


來自121項隨機對照試驗 (randomised controlled trial) (6,700 名受試者) 的證據顯示，以對抗某種力量或阻力的方式鍛鍊肌肉的老年人，會變得比較強壯。他們執行簡單活動的能力獲得改善，例如走路、爬樓梯，從椅子上站起來的速度也較快。諸如從椅子上站起來或爬樓梯等活動的改善幅度，通常大於步行速度。此外，訓練肌力的鍛鍊也能改善老年人的體能，包括比較複雜的日常活動，例如洗澡或準備餐點。PRT也能減輕骨關節炎 (osteoarthritis) 患者的疼痛。由於證據不夠充分，因此無法評論PRT的風險或長期療效。

- Menopause friendly exercise prescription: The exercise program for postmenopausal women should include, **endurance exercise (aerobic), strength exercise, and balance exercise**

- 5個建議步驟如下:

- 步驟1. 暖身和拉筋: 減少受傷風險
- 步驟2. 有氧運動: 提升心肺功能
- 步驟3. 阻力與肌力訓練: 保持肌肉力量和提升骨質密度
- 步驟4. 平衡訓練: 如太極，能幫助預防跌倒
- 步驟5. 緩和與伸展: 讓肌肉有更好的恢復和功能發揮





How to approach women with musculoskeletal syndrome of menopause

55歲女性，已停經，除了更年期血管收縮症狀外，也提到有肩膀僵硬、關節疼痛，且最近自覺體力及肌耐力變差，身高變矮

Consider musculoskeletal syndrome of menopause

- Risk factors assessment
- Sarcopenia evaluation
- DXA exam
- Vit. D or Mg deficiency

Management

- Dietary and exercise modifications
- Vitamin supplementation
- MHT if no contraindication

Table 2. Causes of arthralgia in menopausal women.

Cause	Features
Primary/idiopathic (peri-menopausal)	Timing (and presence) of other estrogen deficiency symptoms (absence of identifiable secondary causes)
Secondary causes	
Endocrine <ul style="list-style-type: none">• Hypothyroidism• Hyperparathyroidism (primary or secondary)• Vitamin D deficiency• Anaemia	Fatigue; weight gain; hyporeflexia; proximal myopathy Abdominal pains; high calcium Fatigue; proximal myopathy Fatigue; shortness of breath
Drug related <ul style="list-style-type: none">• Statins and other lipid-lowering drugs• Aromatase inhibitors• Selective estrogen receptor modulators• Bisphosphonates (particularly intravenous)• Thiazide diuretics	Relevant temporal history Response, if appropriate, to drug holiday/cessation (aromatase inhibitors should not be stopped without oncology guidance)
Metabolic <ul style="list-style-type: none">• Liver disease• Renal disease	Appropriate history, or abnormality on blood testing
Rheumatic <ul style="list-style-type: none">• Connective tissue disease (lupus^a, scleroderma, Sjogrens^a)• Sarcoidosis^a• Vasculitis• Hyperuricaemia• Hypermobility	Rashes, oral ulcers, other clinical features of the disease Other blood test abnormalities, e.g. antinuclear antibody (ANA) or anti-neutrophil cytoplasmic antibodies (ANCA) positivity, raised serum angiotensin converting enzyme (ACE), raised serum urate Evidence of hypermobility on examination
Infection <ul style="list-style-type: none">• Parvovirus^a• Hepatitis B^a/C^a/HIV^a• Ross River virus^a• Brucellosis^a• Whipple's disease^a• Lyme disease^a	Relevant rash, viral symptoms Relevant travel or other risk history History of insect bite
Malignancy <ul style="list-style-type: none">• Disseminated bony malignancy• Paraneoplastic syndrome	Red flags, e.g. weight loss, bone pain, fever Other clinical features of malignancy

^aMay be associated with arthralgia or a frank arthritis.



61歲「健力阿嬤」李彩薇，2022年代表台灣參加在杜拜舉辦的亞洲經典健力錦標賽，在蹲舉、臥舉、硬舉項目，拿下60歲以上組69公斤級3項冠軍及總合冠軍，更打破亞洲紀錄，成為新亞洲紀錄的保持者