Dairy and Bone Health - From the Bronze Age to Balmoral

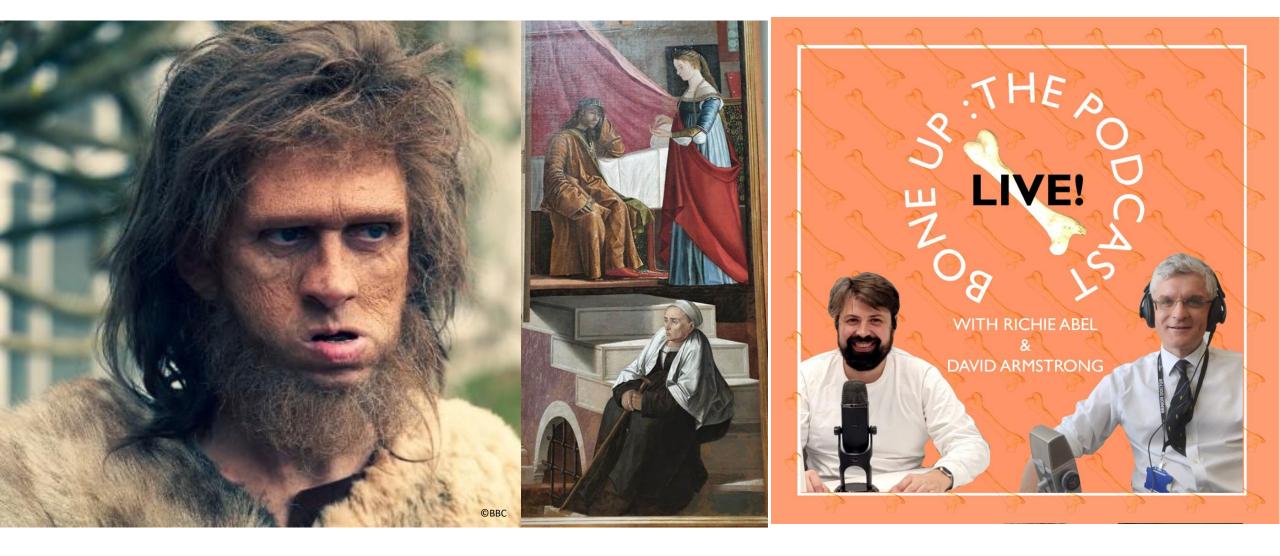
Prof David J Armstrong

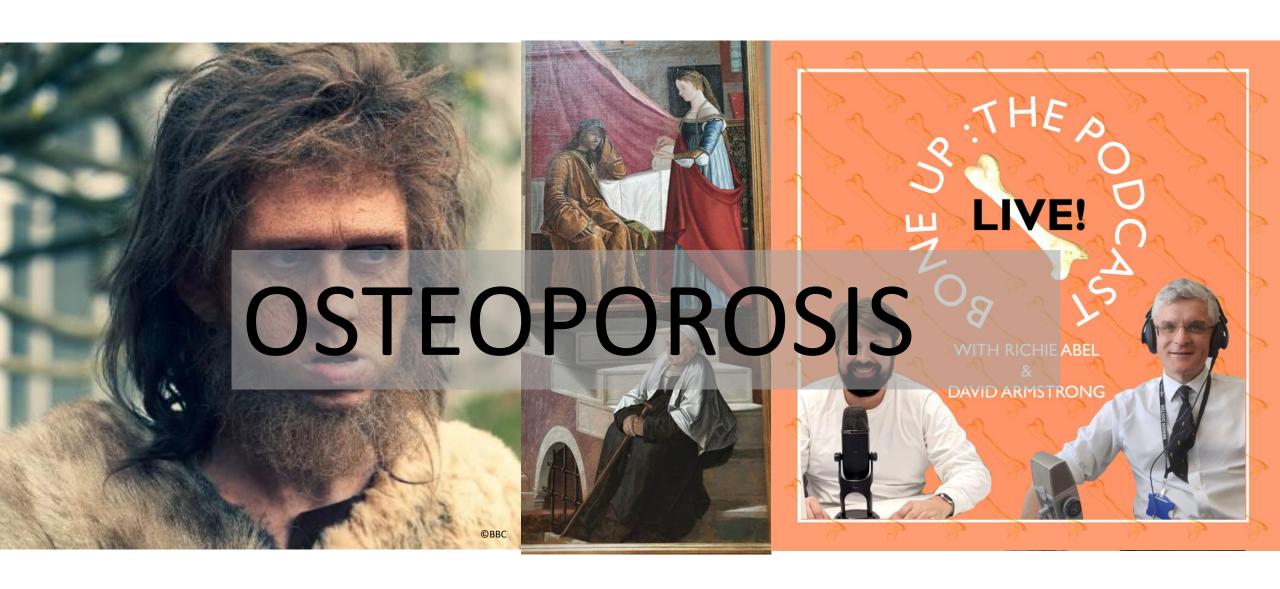
Annual DCNI Nutrition Lecture

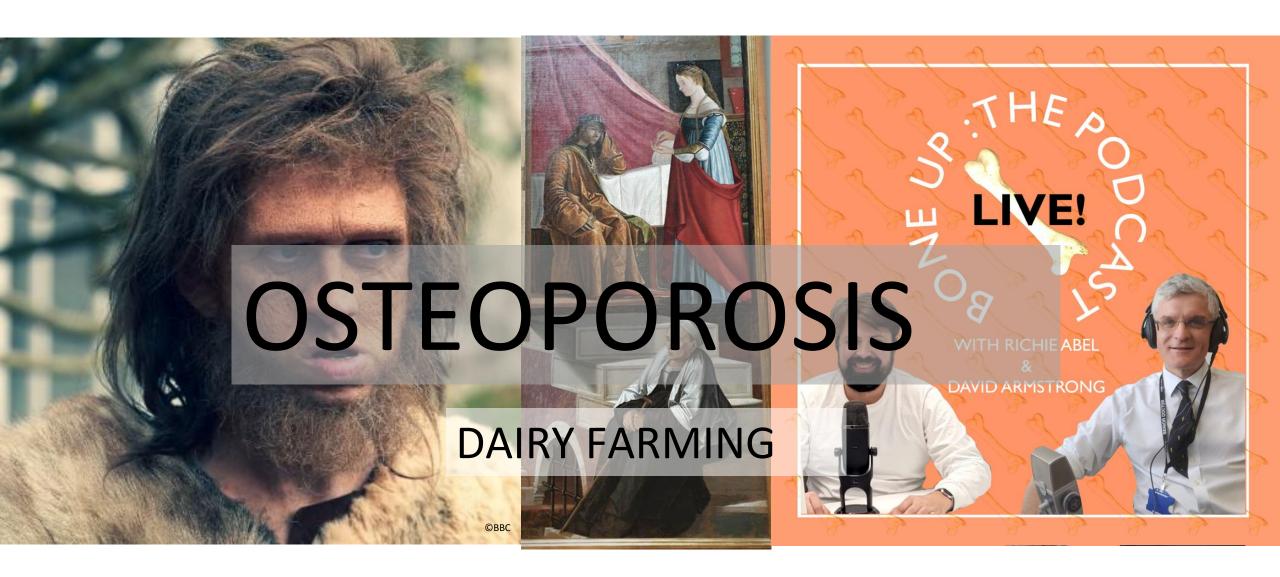
Ulster University

Disclosures

- I have received payment for giving presentations from UCB Pharma, the European Milk Forum and the Dairy Council of NI
- I am Vice Chair of the Royal Osteoporosis Society Clinical and Research Committee
- I am a member of the Expert Advisory Group for NOGG
- I am a co-opted Expert Advisor for NICE TA on HRT
- I co-host the podcast 'BoneUp' on osteoporosis





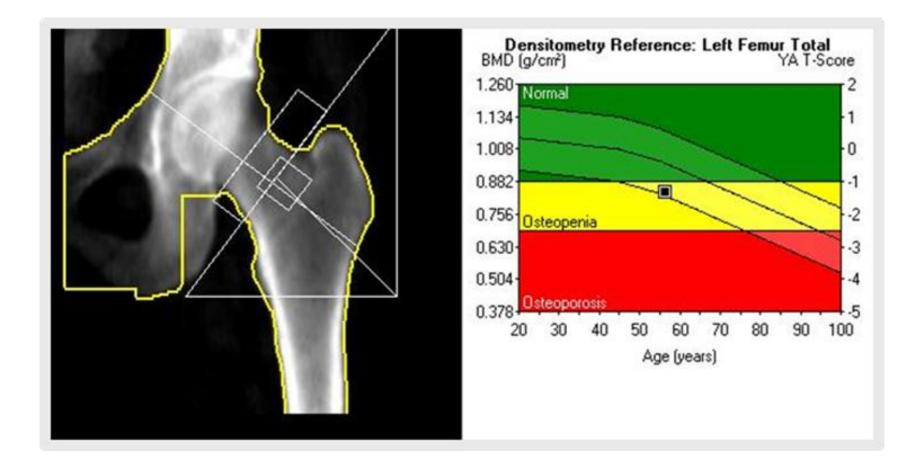


What is Osteoporosis?

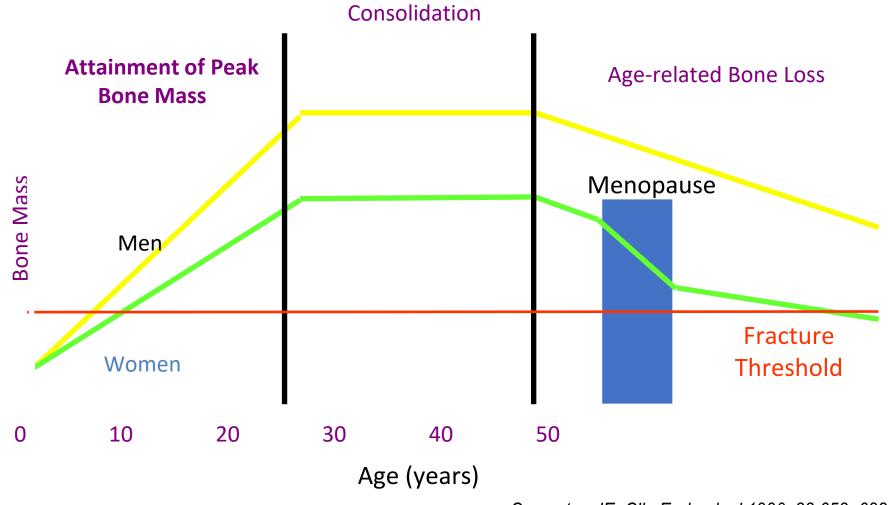
- WHO definition
- 'Disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk'
- 'You have so little bone tissue, and its quality is so poor, that even a very minor injury might cause you to break a bone'
- 'T score of <-2.5 on DEXA scan'
- '95% of healthy 25 year old females will have better bone density than you'



How do I measure up?

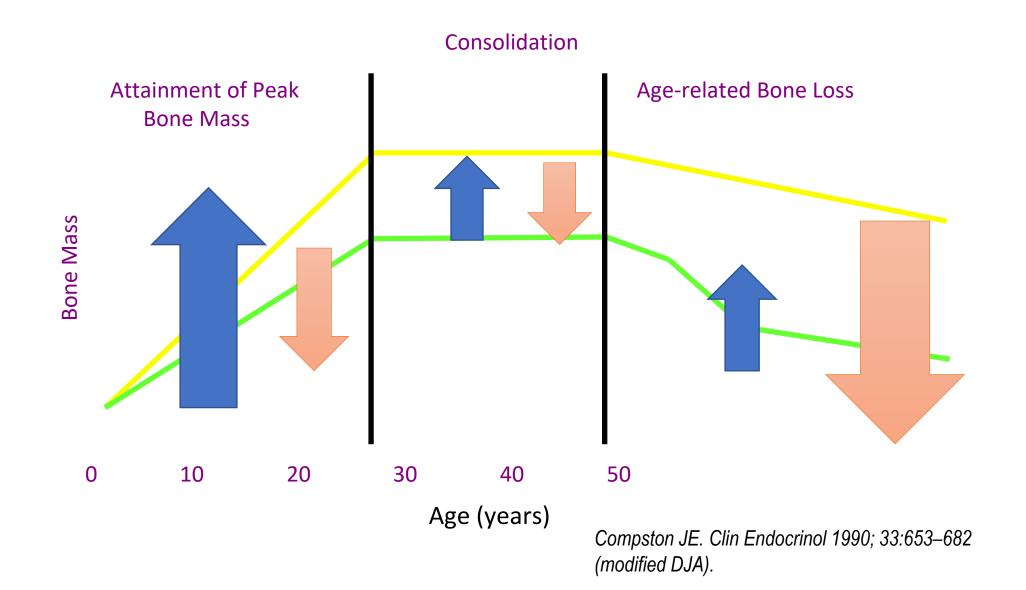


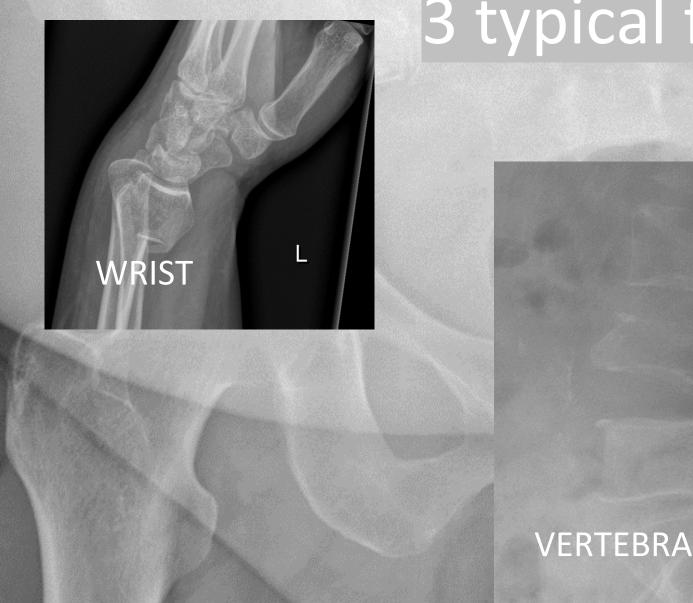
Age related changes in bone mass



Compston JE. Clin Endocrinol 1990; 33:653–682.

Age related changes in bone mass

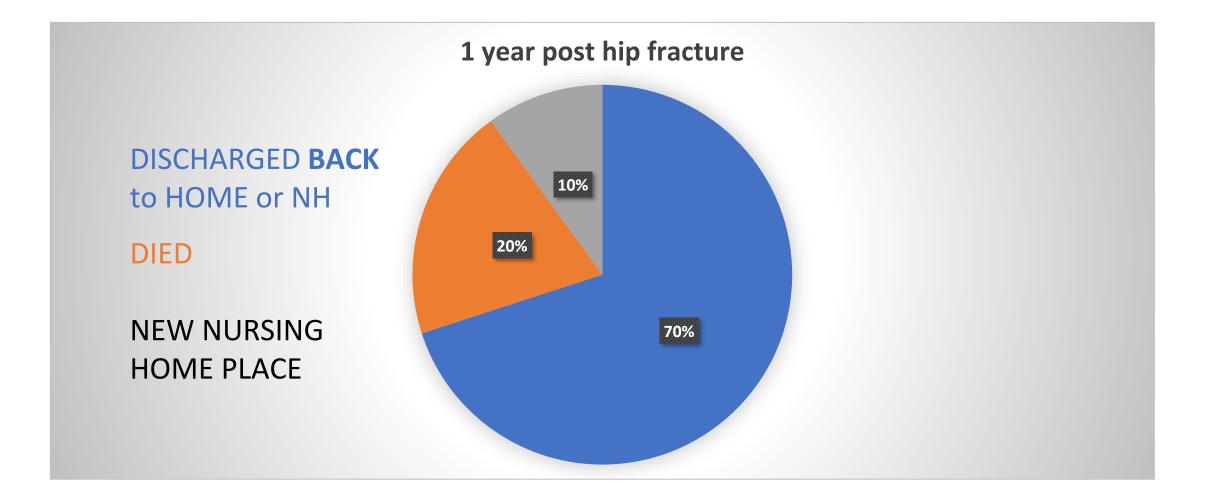




3 typical fragility fractures

HIP

Outcome from hip fracture



Hip Fracture in Northern Ireland

Over 2000 hip fractures per year

At least 200 NEW nursing home places each year

Average length of time for hip replacement = 5 days

Average length of stay after hip fracture = 10 days



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Over 2000 hip fractures per year

At least 200 NEW nursing home places each year

Average length of time for hip replacement = 5 days

Average length of stay after hip fracture = 10 days

Effective treatment of high risk patients can reduce hip fractures by 10-30%



Dr Sandra Iuliano, School of Population and Global Health, University of Melbourne, Australia



OPEN ACCESS

Check for updates

Effect of dietary sources of calcium and protein on hip fractures and falls in older adults in residential care: cluster randomised controlled trial

S Iuliano,¹ S Poon,¹ J Robbins,¹ M Bui,² X Wang,¹ L De Groot,³ M Van Loan,⁴ A Ghasem Zadeh,¹ T Nguyen,^{5,6} E Seeman¹

ABSTRACT

OBJECTIVE

To assess the antifracture efficacy and safety of a nutritional intervention in institutionalised older adults replete in vitamin D but with mean intakes of 600 mg/day calcium and <1 g/kg body weight protein/ day.

DESIGN

Two year cluster randomised controlled trial.

SETTING

60 accredited residential aged care facilities in Australia housing predominantly ambulant residents.

PARTICIPANTS

7195 permanent residents (4920 (68%) female; mean age 86.0 (SD 8.2) years).

INTERVENTION

Facilities were stratified by location and organisation, with 30 facilities randomised to provide residents with five months (P=0.02) and three months (P=0.004), respectively. Mortality was unchanged (900 v 1074; hazard ratio 1.01, 0.43 to 3.08).

CONCLUSIONS

Improving calcium and protein intakes by using dairy foods is a readily accessible intervention that reduces the risk of falls and fractures commonly occurring in aged care residents.

TRIAL REGISTRATION

Australian New Zealand Clinical Trials Registry ACTRN12613000228785.

Introduction

Longevity increases the proportion of older adults in the population. The accompanying increased prevalences of chronic illnesses, loss of musculoskeletal mass, frailty, and bone fragility increase the risk of falls and fractures.¹ Loss of independence increases the

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⁵Garvan Institute of Medical Research, Sydney, Australia ⁶University of Technology Sydney, Sydney, Australia

S Iuliano

BMJ 2021;375:n2364 du.au 3900-2030) http://dx.doi.org/10.1136/ bmj.n2364 s published please visit

Nutrition in Nursing Home study (Iuliano 2021)

- 7195 residents in 60 Care Homes in Australia
- 30 Care Home diets altered to increase calcium and protein intake
- Additional cheese, milk, yoghurt
- 'Even the nonnas with memory problems recognised it as food'
- Calcium per day 700mg v 1142mg
- Protein per day 58g v 69g
- 2 servings per day of dairy v 3.5 servings
- 2 year study
- Fractures, falls, all cause mortality

Outcomes

- All fractures 203 v 121 = 33% reduction
- Hip fractures 93 v 42 = 46% reduction
- Falls 2423 v 1879 = 11% reduction
- Deaths 1074 v 900 = (16% but NOT Statistically significant)
- COST = 60p per day per resident

Outcomes

- Targeted at people with higher risk of falls and fracture
- All residents included equity
- Realistic and transferable to real world practice
- Based on resident preference savoury v sweet
- Cheap
- Benefits seen in 2 years



ROMOSOZUMAB

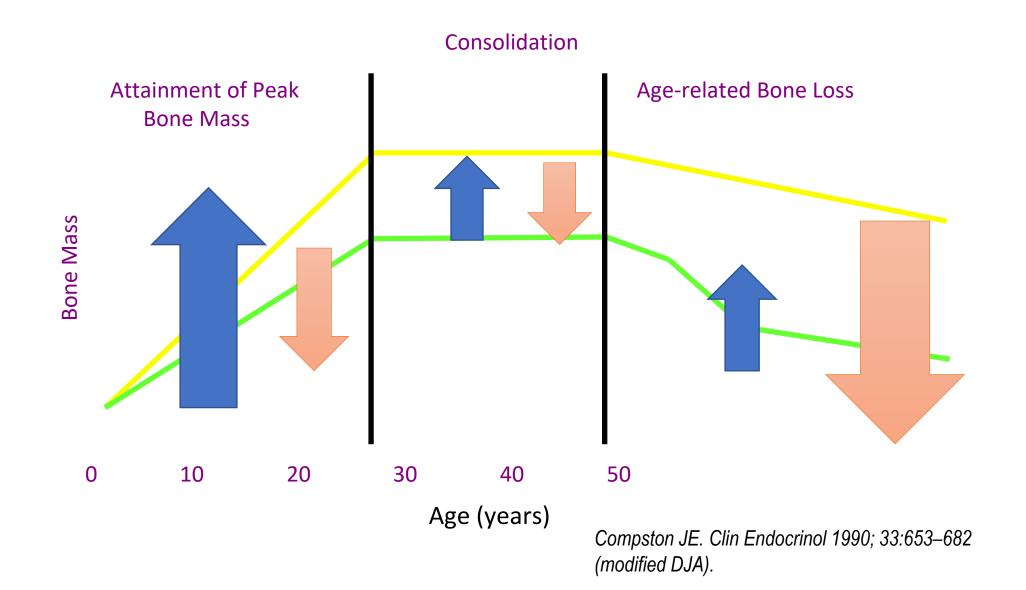
• New treatment for severe osteoporosis patients

• Very high fracture risk – 'imminent fracture'

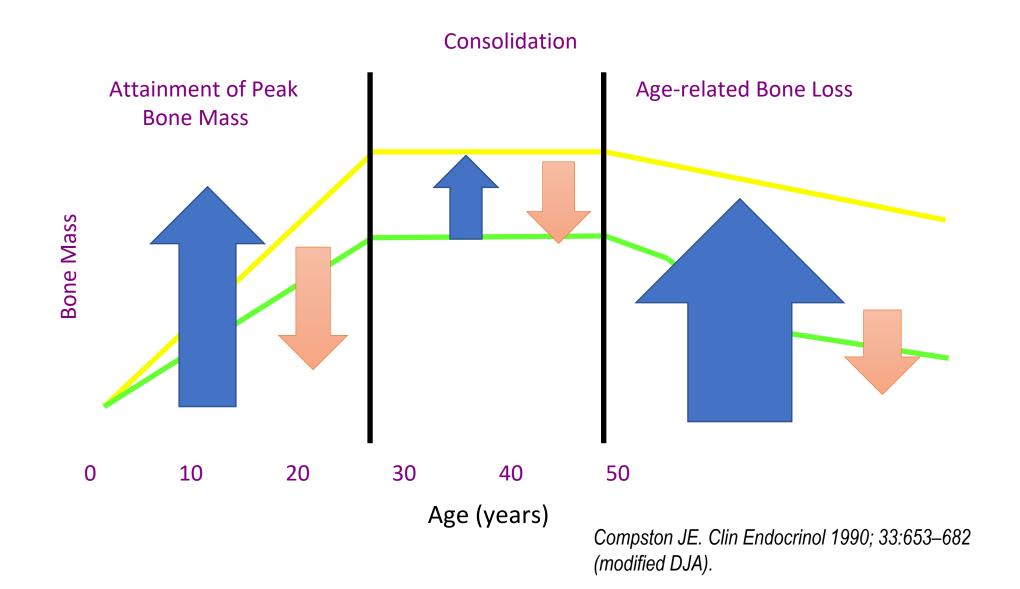
 Usually numerous previous fractures – not the same population as the Care Home residents

• Targets the sclerostin/wnt pathway – novel and unique

Age related changes in bone mass

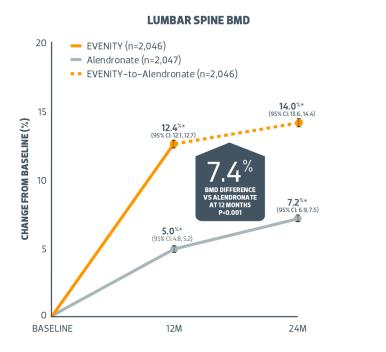


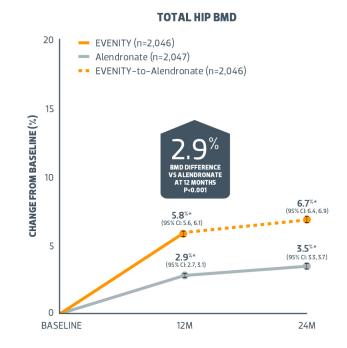
Age related changes in bone mass



ARCH trial

CHANGE FROM BASELINE THROUGH MONTH 24¹





Adapted from EVENITY SmPC.¹

*p<0.001 based on an ANCOVA model using last observation carried forward. BMD, bone mineral density.

ARCH trial (N Engl J Med 2017; 377:1417-1427)

AT PRIMARY ANALYSIS (MEDIAN 33 MONTHS)* **AT 24 MONTHS** EVENITY-to-Alendronate 13.0% 14 Alendronate INCIDENCE OF FRACTURES (%) 12 10.6% 9.7% 10 8.7% 8.0% 8 4.1% 3.2% 2.0% 2 n/N1[†] (147/1834) (74/1825) (266/2047) (198/2046) (217/2047) (178/2046) (66/2047) (41/2046) **NEW VERTEBRAL FRACTURE CLINICAL FRACTURE[‡] NON-VERTEBRAL FRACTURE HIP FRACTURE** p<0.001² p<0.001² p=0.04² p=0.02²

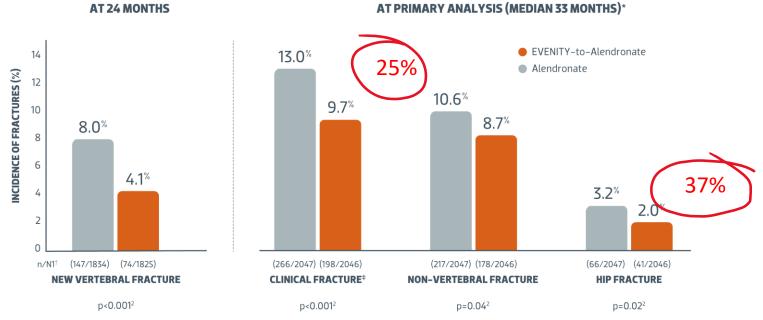
Incidence of fracture in the ARCH study¹

Adapted from EVENITY SmPC¹ and Saag KG et al. 2017.³

*Primary analysis was performed when =330 clinical fractures had occurred and every patient had completed at least 24 months of follow-up (median time: 33 months, interquartile range: 27-40). 'n/NI corresponds to number of women with fracture/number of women in analysis set. Randomised population: EVENITY n=2,046; Alendronate n=2,047. 'Clinical fractures include all symptomatic fractures including non-vertebral and painful vertebral fractures. Treatment comparisons are based on Coxy proportional-hazards model adjusted for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline. Note: All fracture types, including non-vertebral fractures, excluded severe trauma (except major osteoporotic fractures) or pathologic fractures. Severe trauma was defined as a fall from higher than the height of a stool, chair, first rung on a ladder or equivalent (>20 inches), or severe trauma other than a fall per investigator judgment. Please refer to Study Design for description of primary and secondary endpoints.

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Romosozumab

• COST = £427 per month in UK = **£35 per day!**

• IMPORTANT

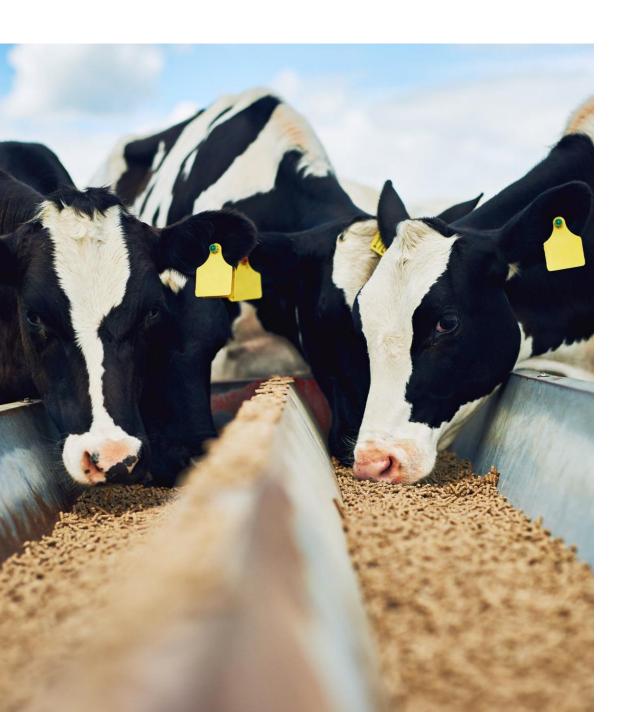
- NOT comparable populations
- Romosozumab patients would not see a 46% reduction in fracture if given cheese instead!

• NEVERTHELESS

- 50% reduction in hip fractures in 2 years is HEADLINE data
- We are used to spending £35/day/patient to achieve similar outcomes
- No form filling or waiting lists for extra dairy in nursing homes
- Preventative, equitable, important for NI population

Origins of Dairy Farming





Origins of Dairy Farming

- Evidence for farming
- Domestication of goats in Asia 8000-9000BC
- First domestication of cattle North Africa 7000BC
- Probably initially for meat
- Evidence of dairy products
- 6000-7000BC in western Anatolia (Turkey)
- 5000BC in Europe
- 4000BC in Britain and Northern Europe

How do we know when dairy farming started?

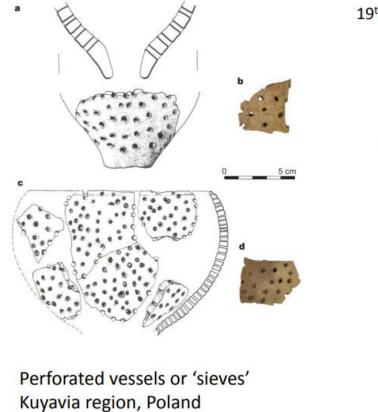
Indirect Evidence

- Direct Evidence
- CREDIT: Dr Jessica Smyth, Research Associate in Neolithic Archaeology, University of Bristol (Belfast Cheese Symposium 2016)

Indirect Evidence

- 1. Excavation of bones of **older** animals
 - young animals slaughtered for meat
 - older animals kept for milking
- 2. Vessels associated with secondary products
 - e.g. cheese strainers

Vessels for straining cheese (Poland, 5200BC)



c. 5200 BC

19th/20th century and contemporary cheese strainers

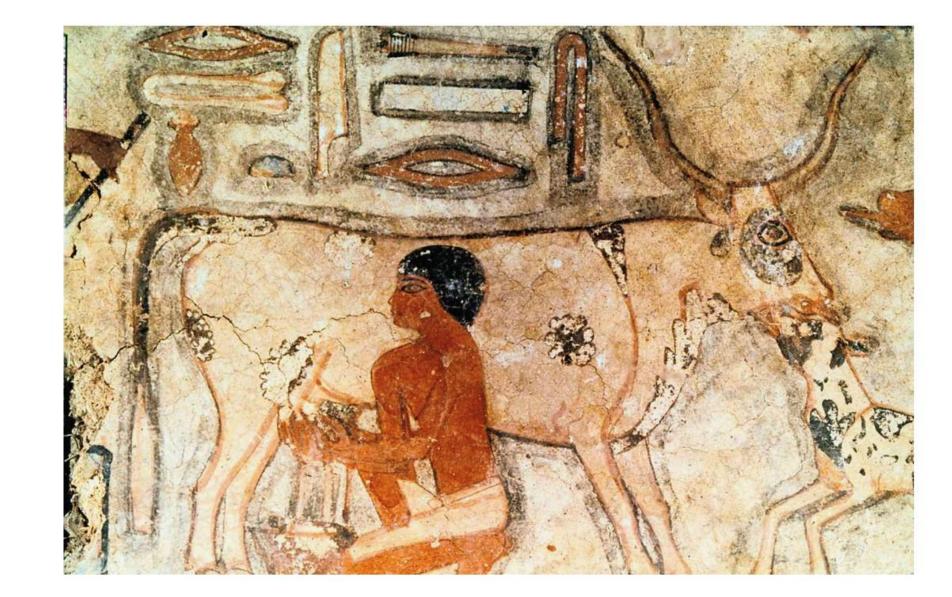


Salque et al. 2013. Earliest evidence for cheese making in the sixth millennium BC in northern Europe. Nature 493, 522-5

Indirect Evidence

- 1. Excavation of bones of **older** animals
 - young animals slaughtered for meat
 - older animals kept for milking
- 2. Vessels associated with secondary products
 - e.g. cheese strainers
- 3. Ancient art

Tomb of Methethi, Saqqara, Egypt 2350BC





Piece of a roughly 7,000-year-old sieve used to make cheese.

6,500 YEARS AGO Well-developed dairy economy established in central Europe.

7,500 YEARS AGO

Lactase persistence, the ability to drink milk in adulthood, emerges in central Europe.

8,000 YEARS AGO

Neolithic reaches the Balkans.

8,400 YEARS AGO Neolithic spreads to Greece.

11 000-10 000 YEARS AGO



Direct Evidence (1) Isotope Analysis

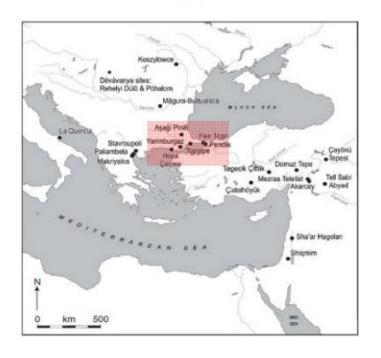
- Isotope Analysis of lipid molecules
- Lipids absorbed into pottery
- *Different lipid profiles* associated with milk and cheese than with animal fat
- Best if found in relatively acidic soil and vessel used repeatedly
- Mass spectrometry and gas chromatography
- Last 20-25 years

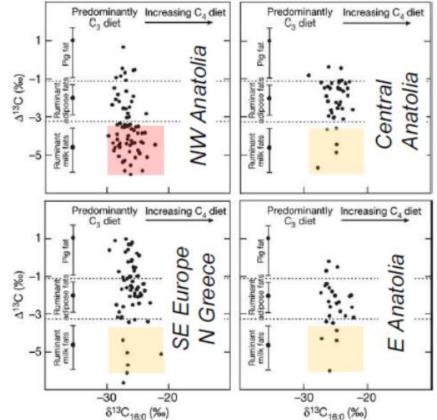
Scientific Evidence of Dairy in pots 7000BC

Milk fats present in pots from early Neolithic 7th millennium BC – northwestern Anatolia

High incidence in pots where cattle most abundant in archaeological record

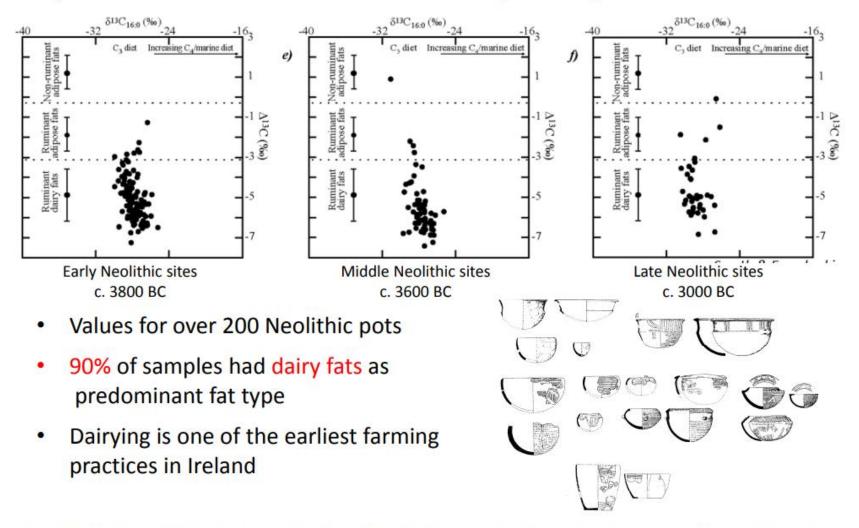
Regional variability





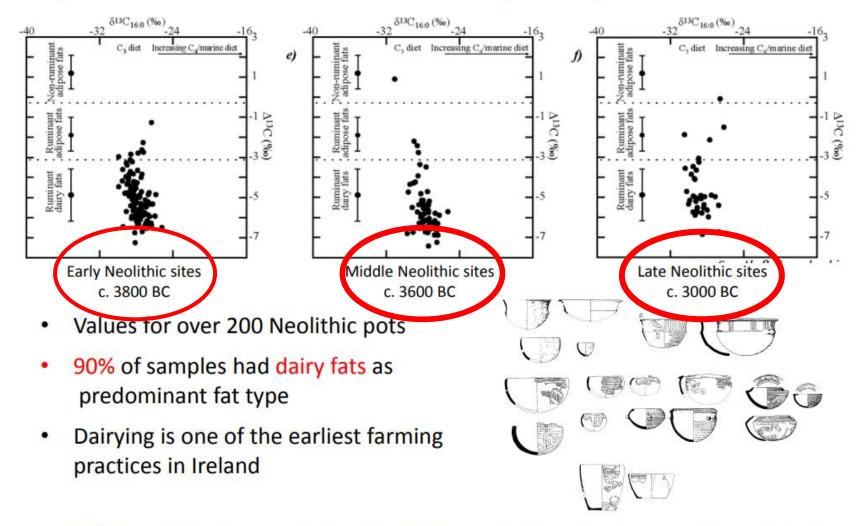
Evershed et al. 2008. Earliest date for milk use in the Near East and southeastern Europe linked to cattle herding. Nature 455, 528-31

Lipid residues from Irish Neolithic pottery



Smyth & Evershed. 2015. Milking the megafauna: the role of organic residue analysis in understanding early farming practice. *Environmental Archaeology*

Lipid residues from Irish Neolithic pottery



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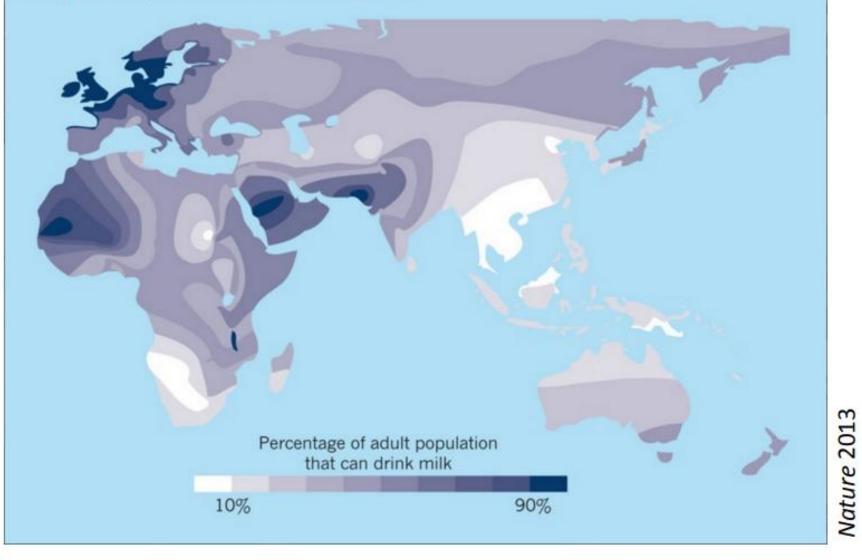


Direct Evidence (2) Lactase Persistence

- Lactose = sugar in milk (and other dairy)
- Lactase = enzyme which breaks this down
- Lactase usually disappears from humans after early childhood
- In some populations lactase persists enabling adults to drink milk
- Lactase persistence 'surrogate marker for milk drinkers'

LACTASE HOTSPOTS

Only one-third of people produce the lactase enzyme during adulthood, which enables them to drink milk.



Lactase Persistence in Europe

Lactase persistence (LP) evolved after development of dairy Yoghurt and cheese – lower levels of lactose due to processing Is there evolutionary advantage in being able to drink milk?



Lactase Growth Hypothesis (LGH)

- Is there evolutionary advantage to being able to consume milk?
- Suggests that development of lactase persistence
- 1. increases dietary energy
- 2. alters the energy biology of human growth (eg IGF-1)
- 3. fuels regional differences in body size?

Did drinking milk make us heavier and taller?

- Long-term trends in human body size track regional variation in subsistence transitions and growth acceleration linked to dairying
- Jay T. Stock et al. Proc Natl Acad Sci U S A. 2023 Jan 24; 120(4): e2209482119
- 3507 skeletons from 366 sites across the globe



Long-term trends in human body size track regional variation in subsistence transitions and growth acceleration linked to dairying

Jay T. Stock^{a,1}, Emma Pomeroy^b, Christopher B. Ruff^c, Marielle Brown^b, Matthew A. Gasperetti^b, Fa-Jun Li^d, Lisa Maher^e, Caroline Malone^f, Veena Mushrif-Tripathy^g, Eóin Parkinson^f, Michael Rivera^h, Yun Ysi Siew^b, Sofija Stefanovicⁱ, Simon Stoddart^b, Gunita Zariŋa^j, and Jonathan C. K. Wells^k

Edited by Clark Spencer Larsen, The Ohio State University, Columbus, OH; received June 28, 2022; accepted October 13, 2022

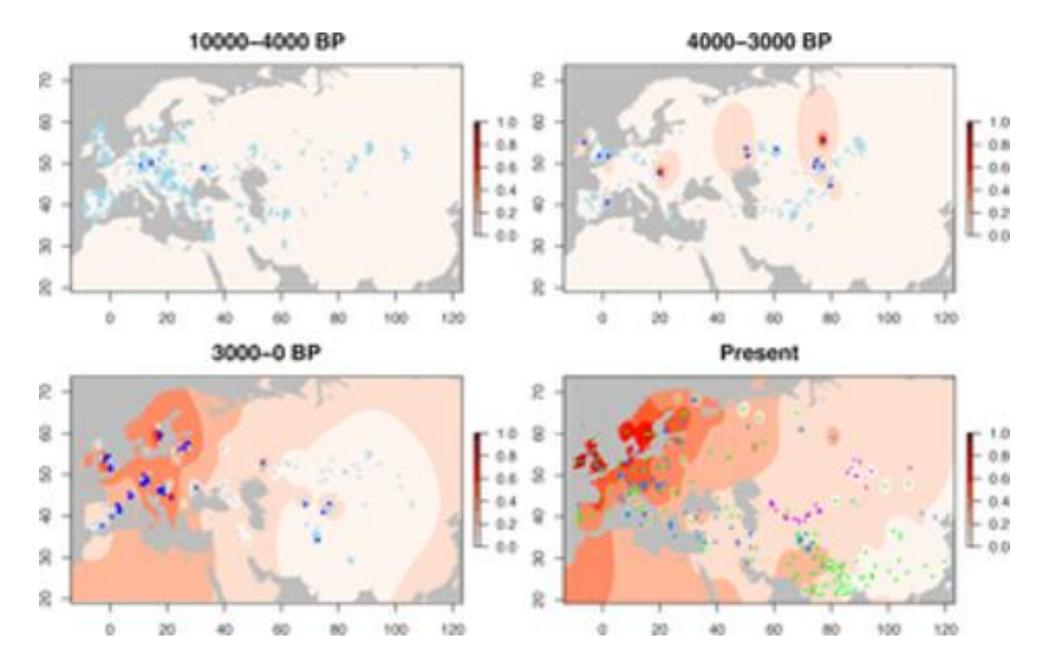
Evidence for a reduction in stature between Mesolithic foragers and Neolithic farmers has been interpreted as reflective of declines in health, however, our current understanding of this trend fails to account for the complexity of cultural and dietary transitions or the possible causes of phenotypic change. The agricultural transition was extended in primary centers of domestication and abrupt in regions characterized by demic diffusion. In regions such as Northern Europe where foreign domesticates were difficult to establish, there is strong evidence for natural selection for lactase persistence in relation to dairying. We employ broad-scale analyses of diachronic variation in stature and body mass in the Levant, Europe, the Nile Valley, South Asia, and China, to test three hypotheses about the timing of subsistence shifts and human body size, that: 1) the adoption of agriculture led to a decrease in stature, 2) there were different trajectories in regions of in situ domestication or cultural diffusion of agriculture; and 3) increases in stature and body mass are observed in regions with evidence for selection for lactase persistence. Our results demonstrate that 1) decreases in stature preceded the origins of agriculture in some regions; 2) the Levant and China, regions of in situ domestication of species and an extended period of mixed foraging and agricultural subsistence, had stable stature and body mass over time; and 3) stature and body mass increases in Central and Northern Europe coincide with the timing of selective sweeps for lactase persistence, providing support for the "Lactase Growth Hypothesis."

Significance

The transition from **foraging** to herding and farming influenced human health, but the impact of regional differences in trajectories of cultural change on human biology are poorly resolved. We investigate longterm trends in human stature and body mass of 3,507 skeletons from 366 archaeological sites in seven regions with varying trajectories of Holocene subsistence change. We observe declines in body size that preceded the transition to

Findings

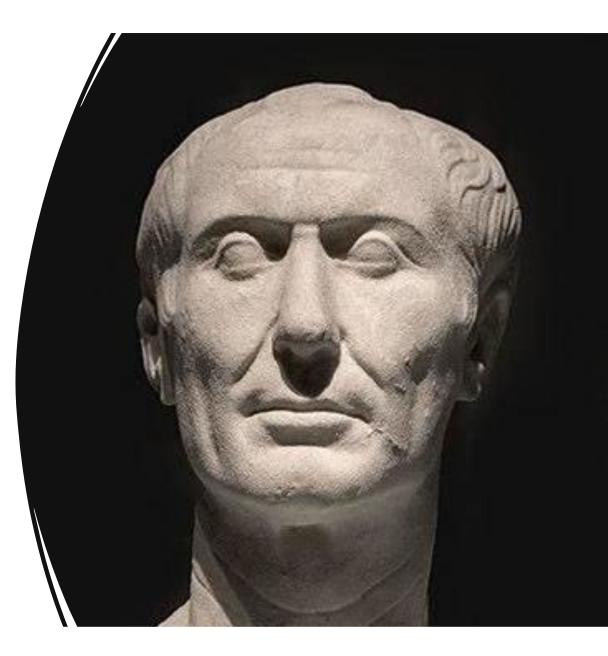
- 'Holocene statures and body mass remained relatively stable in primary regions of domestication;
- however, in areas such as Central and Northern Europe where nonnative crops were difficult to establish,
- increases in stature and body mass coincide with the timing of selective sweeps for lactase persistence'
- Increase in skeletal size corelated with persistence of lactase gene
- Areas where crops from Anatolia unable to grow, farmers turned to milk



Why and when was lactase persistence selected for? Insights from Central Asian herders and ancient DNA. journals.plos.org

Milk drinking and Barbarianism

- Milk = barbarianism
- Olive Oil v Butter
- Cheese (and yoghurt) contains much less lactose
- Easily consumed by those without lactase
- Cheese widely consumed in Classical Greece and Rome
- Caesar ate cheese for breakfast
- Milk for plebians, farmers's children and Barbarians



Tacitus (56-120AD)

 'The Germanic tribes eat a very plain diet; wild fruit, fresh meat and milk'

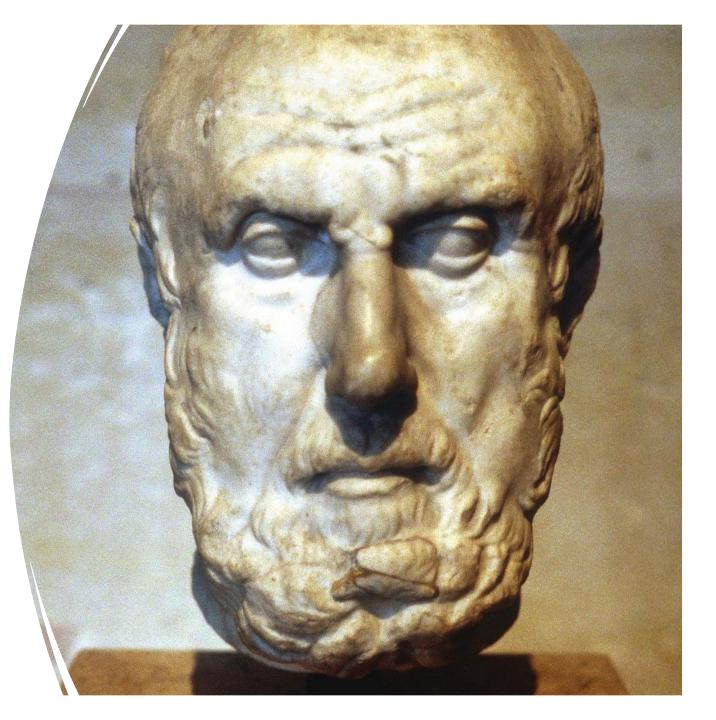


Apicius 1st century AD – 'The Art of Cooking' **Chapter VII** 'polyteles' – dishes made almost entirely from curdled milk



'Let food be thy medicine'

- Hippocrates of Kos
- C 460BC



Galen 129-216AD

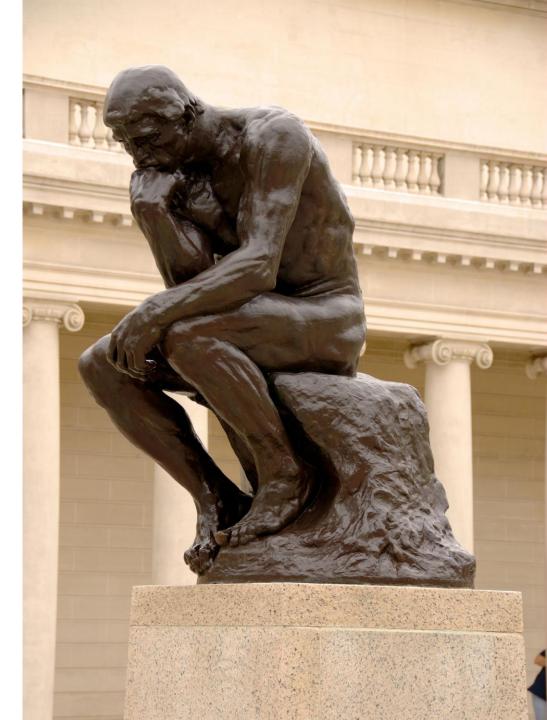
• Four humours

- Often cooked for his patients
- Cooling effects of milk on fever
- Advocate of milk as a laxative
- Dairy produce (and meat) useful for producing blood



Dairy consumption and developing civilisation

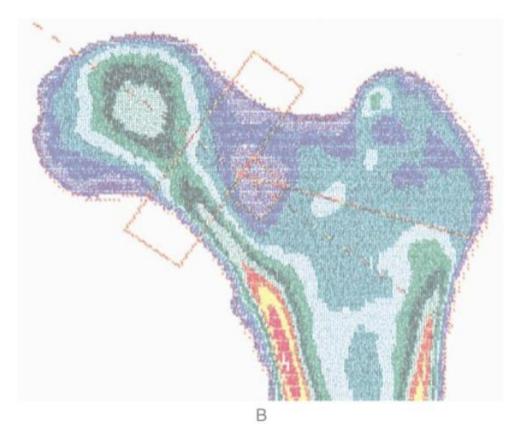
- Bigger skeleton, stronger bones more protein and calcium
- Increased fertility rate? lactation & pregnancy
- Mobility portable source of food early cheese
- Move north and west colder, fewer cereal crops
- Antibodies and infectious diseases?
- More leisure time to think??



Brief history of osteoporosis

- Identified in Egyptian mummies (2000BC) generally older females
- Identified in many Bronze age skeletons across Europe
- Present in (small number) of >45yr old women v younger subjects
- Evidence for survival after major fractures

45 year old woman buried around 2000BC in Unterhautzental, Austria





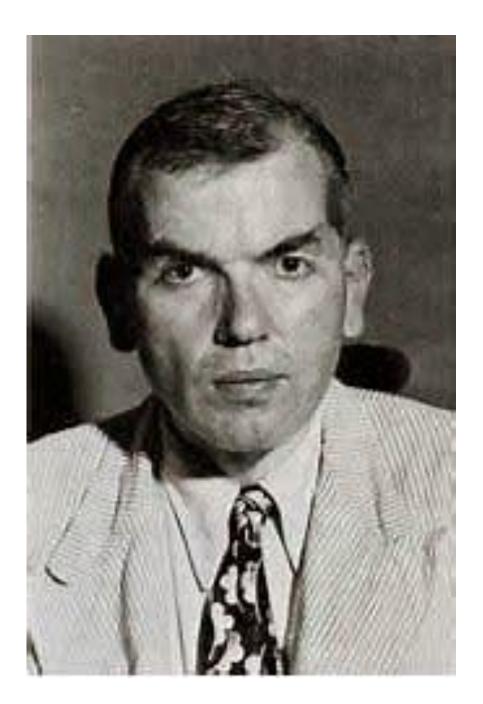


Arrival of the English Ambassadors at the Court of the King of Brittany Scenes in the Life of St Ursula Vittore Carpaccio 1495



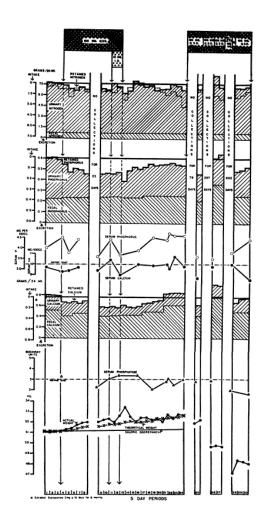
Timeline of Osteoporosis

- Dr Jean Lobstein (1835) first used the word to describe bone (The patient had Osteogenesis Imperfecta!)
- Sir Astley Cooper (1768-1841) recognised reduced bone density related to the risk of fracture
- Dr Fuller Albright (1900-1969) falling oestrogen associated with bone loss, and replacing oestrogen associated with bone gain



Dr Fuller Albright 1900-1969

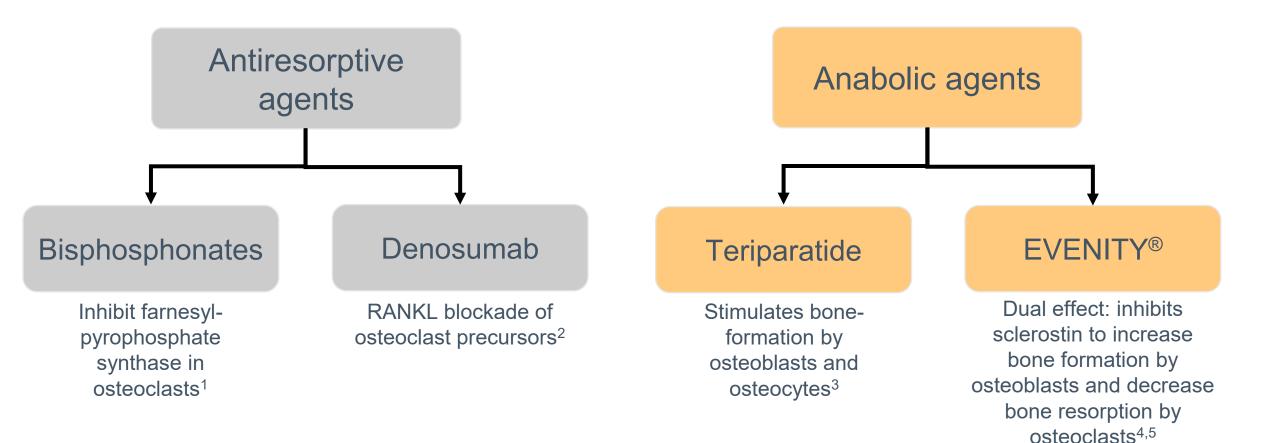
Reifenstein EC, Albright F. The metabolic effects of steroid hormones in osteoporosis. J Clin Invest. 1947;26:24-56



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- Herbert Fleisch (1933-2007) 1960s developed bisphosphonates
- Also 1960s basic bone densitometry measurement

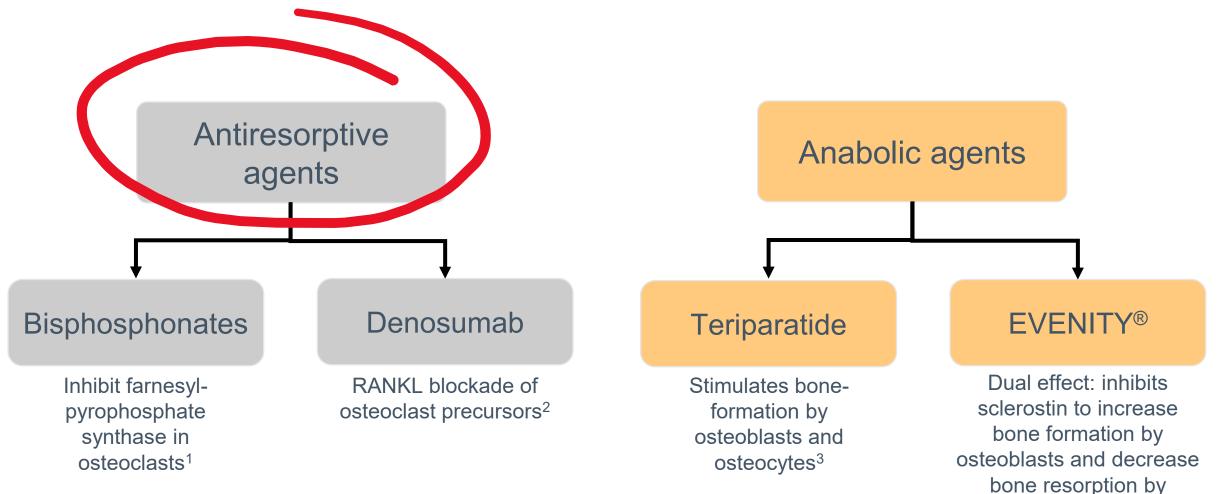
MODERN TREATMENT OPTIONS



RANKL, receptor activator of nuclear factor kappa-B ligand.

1. Rogers MJ, et al. Bone 2011;49:34–41; 2. Ming J, et al. Front Oncol 2020;10:1283; 3. Canalis E, et al. N Engl J Med 2007; 357:905–16; 4. Baron R, Gori F. Curr Opin Pharmacol 2018;40:134–41; 5. EVENITY[®]. Summary of Product Characteristics. Available at: www.medicines.org.uk/emc/product/10956 (accessed August 2021).

Common therapeutic options for patients with osteoporosis at high risk of fracture

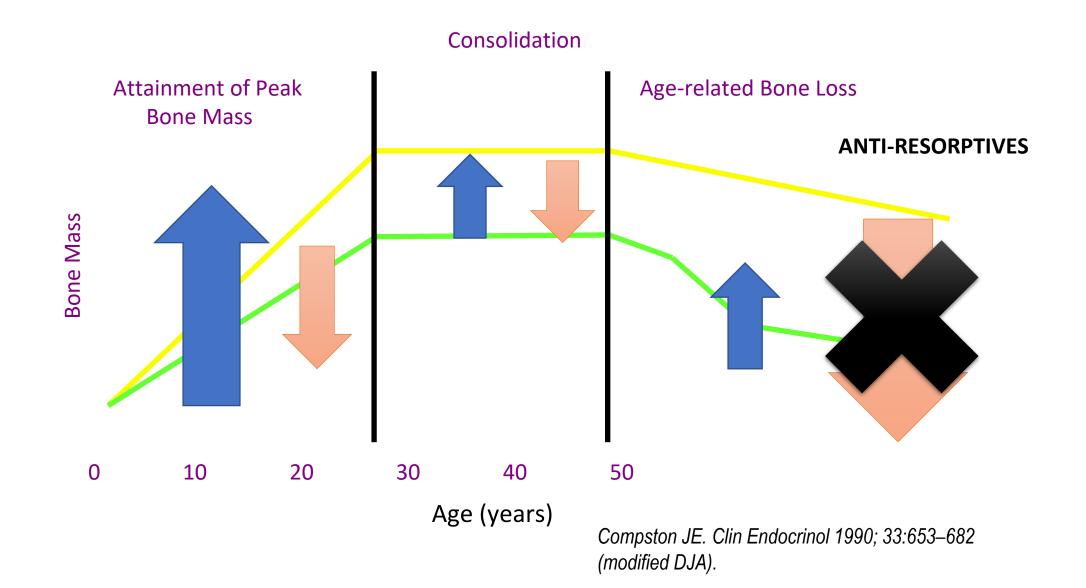


osteoclasts^{4,5}

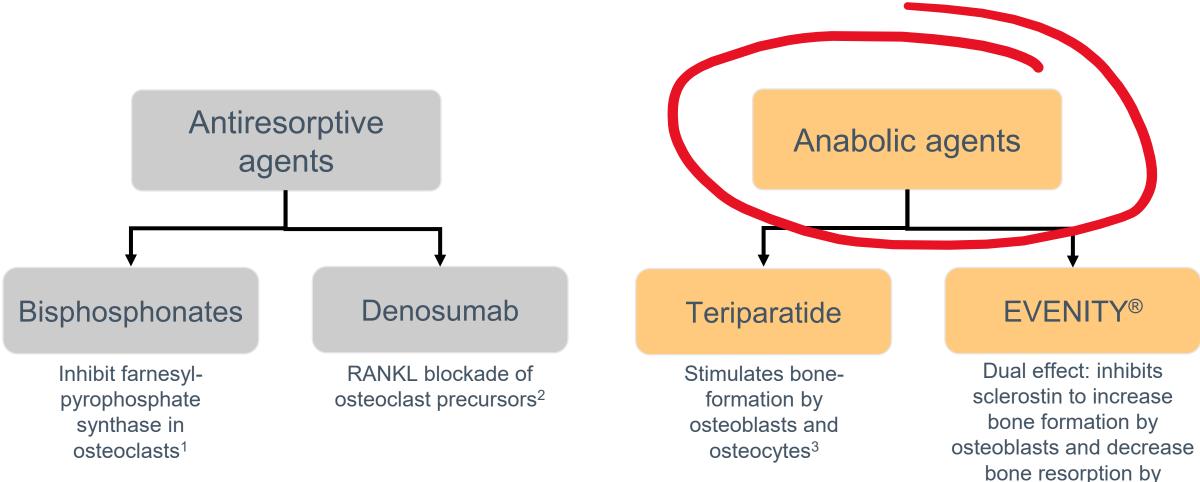
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Age related changes in bone mass



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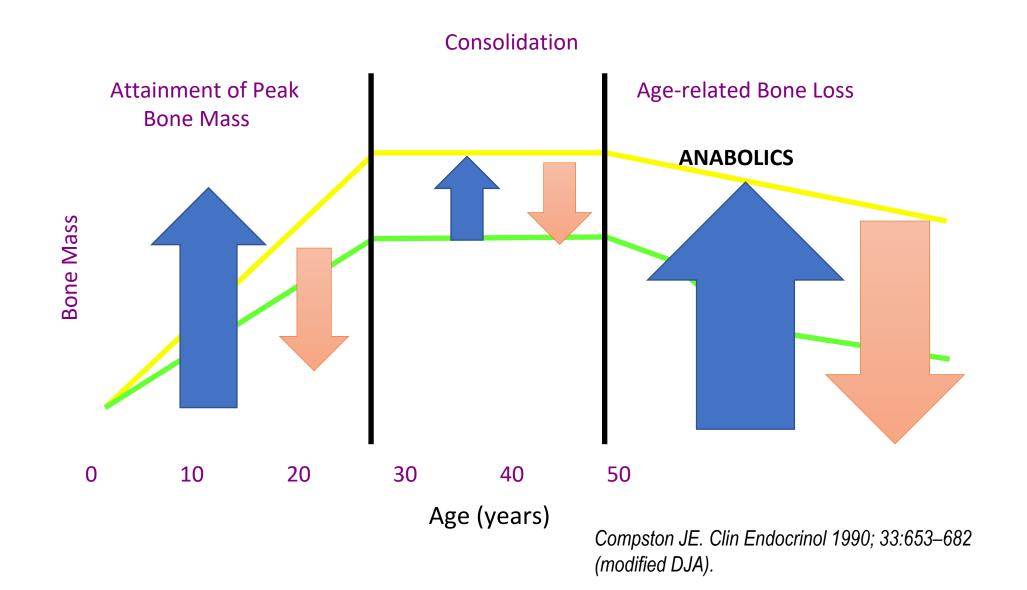


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Age related changes in bone mass



MODERN OSTEOPOROSIS MANAGEMENT

- Lots of good news!
- Ample nutritious food
- Targeted exercise regimes to improve BMD
- Exciting targeted drugs
- 'We have the Bricks and we have the Builders'



The anti-food movement

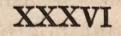


IDENTITY



Expressing yourself through food...

- Choosing food on ethical or health grounds
- From the Ancient word
- (Vegetarian Society UK founded 1843)
- Dairy part of 'Boom food' concept



A MEDITATION ON MILK

I did not realise until last week what a dangerous thing milk was.

I met a lady who was in a state of extreme indignation because a rather advanced doctor had accused her of drinking milk with as severe an air as though he had caught her drinking whisky.

"But it makes me feel better," she protested.

"Of course, it makes you *feel* better," he replied, with a contemptuous sneer; "that is the reason why a man drinks whisky-and-soda. Don't you realise that milk is a powerful stimulant—a far too powerful stimulant for a human being? It is so strong that a calf fed on it grows to its full height in three years. The human being isn't intended to grow at that rate. To drink milk is simply to intoxicate yourself with 'boom-food."

And he put her on to barley-water. ... I had

Robert Lynd 1879-1949

'Meditation on Milk (1922)'

What's wrong with dairy?

- 1. Bad for the planet?
- 2. Bad for animal welfare?
- 3. Bad for your health?



Reasons to avoid dairy, doctor

- 1. Causes cancer
- 2. Causes heart disease
- 3. Doesn't help prevent fractures
- 4. Actively causes fractures



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'Give up dairy to beat cancer': Leading scientist given just months to live changes her diet and is still alive nearly 20 years later

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'I went straight back to my oncologist - who prescribed a small daily dose of the oestrogen-suppressor drug letrozole, which I continue to take,' she added.

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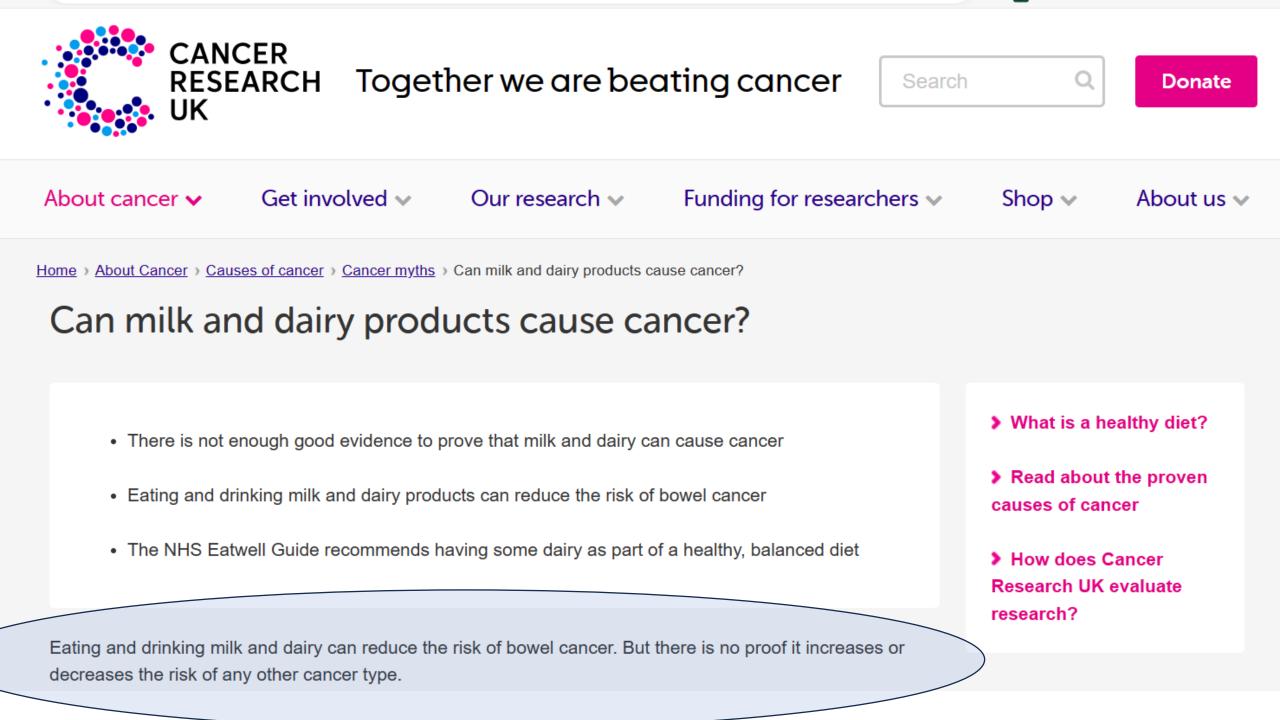
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'Give up dairy to beat cancer': Leading scientist given just months to live changes her diet and is still alive nearly 20 years later



Dairy Produce and breast cancer

- Wu Y et al. Dairy foods, calcium, and risk of breast cancer overall and for subtypes defined by estrogen receptor status: a pooled analysis of 21 cohort studies. Am J Clin Nutr. 2021;114(2):450-461.
- doi: 10.1093/ajcn/nqab097.
- Pooled data of >1,000,000 women, 37,861 cases breast cancer
- "...no clear association was observed between the consumption of specific dairy foods, dietary (from foods only) calcium, and total (from foods and supplements) calcium, and risk of overall breast cancer..."
- 10% (yoghurt) and 15% (cottage cheese) reduction in ER –ve breast tumours

Dairy and other cancers

Prostate Cancer

- Epidemiological evidence that populations with high intake of dairy produce may have higher rates of prostate cancer
- Little experimental evidence on pathophysiology IGF? Oestrogens?
- Sargsyan A, Dubasi HB. Milk Consumption and Prostate Cancer: A Systematic Review. World J Mens Health. 2021 Jul;39(3):419-428

Colon Cancer

- Convincing epidemiological evidence that high dairy consumption related to reduce risk of colon cancer
- Aune D, Lau R, Chan DSM, Vieira R, Greenwood DC, Kampman E, Norat T. Dairy products and colorectal cancer risk: a systematic review and meta-analysis of cohort studies. Ann Oncol. 2012 Jan;23(1):37-45

Does Dairy Produce cause heart disease?

- Rice BH. Dairy and Cardiovascular Disease: A Review of Recent Observational Research. Curr Nutr Rep. 2014;3(2):130-138.
- No rise in cardiovascular disease with dairy consumption
- Dairy consumption was associated with better quality diet in general
- Soedamah-Muthu SS et al. Consumption of dairy products and associations with incident diabetes, CHD and mortality in the Whitehall II study. Br J Nutr. 2013;109(4):718-26
- Fermented dairy products was inversely associated with overall mortality
- 30% reduced risk in middle and higher tertiles

Dairy and Heart Disease

- Bhupathi V, Mazariegos M, Cruz Rodriguez JB, Deoker A. Dairy Intake and Risk of Cardiovascular Disease. Curr Cardiol Rep. 2020;22(3):11
- 'Due to their complex biochemistry, dairy consumption is a rather heterogeneous exposure'
- 'Randomized clinical trials and large prospective studies on lipid-related cardiometabolic disease risk factors are consistent with results from most meta-analyses of prospective cohort studies,...'
- '...which suggest null or inverse relationship between CVD risk and mortality with dairy consumption'
- 'current evidence suggests that dairy products are neutral or positive effect on human cardiovascular diseases.'



Does Dairy cause osteoporosis?

- Acid-Ash hypothesis
- Milk is acidic
- Acid food intake leads to increase acidity of blood
- Calcium is lost from bones in attempt to 'neutralise' acid
- Osteoporosis results

Does Dairy cause osteoporosis?

- Fenton TR, Tough SC, Lyon AW, Eliasziw M, Hanley DA. Causal assessment of dietary acid load and bone disease: a systematic review & meta-analysis applying Hill's epidemiologic criteria for causality. Nutr J. 2011;10:41.
- 'A causal association between dietary acid load and osteoporotic bone disease is not supported by evidence and there is no evidence that an alkaline diet is protective of bone health'

Poor science

- Milk pH 6.7
- Stomach acid pH 2.0
- No intervention studies provided direct evidence of osteoporosis progression (fragility fractures, or bone strength as measured using biopsy).
- Quoted prospective cohort studies were not controlled regarding important osteoporosis risk factors eg weight loss, family history, baseline bone mineral density etc
- No study revealed a **biologic mechanism** functioning at physiological pH.
- **Randomized studies** did not provide evidence for an adverse role of phosphate, milk etc in osteoporosis

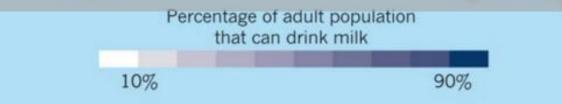
Milk is a cheap and effective method of achieving good calcium and protein intake in high risk groups



LACTASE HOTSPOTS

Only one-third of people produce the lactase enzyme during adulthood, which enables them to drink milk.

The spread of dairy farming and milk intake associated with spread of human civilisation north and west and increase in skeletal size



Nature 2013

Osteoporosis is a common and under-recognised condition associated with high risk of fracture, and has a major impact on health spending in NI

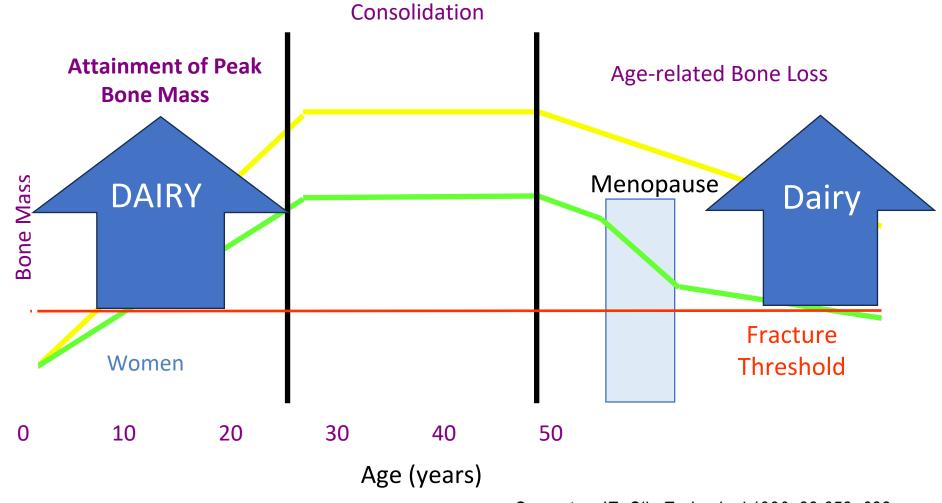
Dairy is a safe way of increasing peak bone density in young people, reducing fractures in older people in care, and supporting a vital local industry



EIKON

n A'

PREVENTATIVE MEDICINE – PEAK BONE MASS



Compston JE. Clin Endocrinol 1990; 33:653–682.



Milk – preventative medicine from the Bronze Age to Balmoral!



BoneUp – the Podcast all about bones

