Chapter 4

Menopause

So far we discussed aging of men and women as one. Let's now focus on one of the main differences -Menopause, a life transition that all women experience, in which menstrual cycles stop and the ovary stops ovulating.

The ovary is one of the first organ systems to fail, around age 50 (the thymus begins to degenerate in both sexes around age 20). The ovary produces most of the hormone estrogen in women which protects bone and blood vessels.

Male fertility also declines but more gradually, and male estrogen (made in men primarily from testosterone), declines together with testosterone when men reach around age 65-75 .

For most of human history, menopause was a short epilogue at the end of life. The women who survived into their 60s or beyond lived in environments that demanded constant physical activity, which maintained strong bones, strong vasculature, and low rates of metabolic disease. Menopause was uncomfortable but far less dangerous than it is today.

Modern sedentary lifestyles which weakens bone, calorie-rich diets which damage blood vessels, and long life expectancy have transformed the consequences of estrogen loss: rapid bone decline, high fracture rates, rising cardiovascular disease, and sleep and mood disturbances.

Hormone replacement has a fascinating history

When estradiol and progesterone were purified in the early 20th century, physicians recognized that replacing these hormones could prevent much of this deterioration. By the 1990s, hormone therapy was widely used, supported by observational studies showing fewer fractures and lower rates of heart disease in women who took estrogen.

The time was ripe for a randomized trial to see if hormone replacement also improve health in older women. The Women's Health Initiative (WHI) set out to test this with a massive study, the largest ever in women's health. Until then, most clinical studies were in men exclusively, and most labs tested only male mice!

But the design of the trial had an important limitation: participants were 63 years old on average, more than a decade past menopause, and many already had vascular damage. When early results showed more strokes and heart attacks in this older group, and a tiny rise in breast cancer (now known to be due to the progestin used in the study which is no longer used, estrogen itself is protective for breast cancer), the researchers stopped the trial in 2002. They held a press conference and the genie was out of the bottle.

Unfortunately, the conclusion was applied universally - even to healthy 40-50 year olds. Prescriptions collapsed, and fear overshadowed nuance. This left tens of millions of women without the opportunity for care.

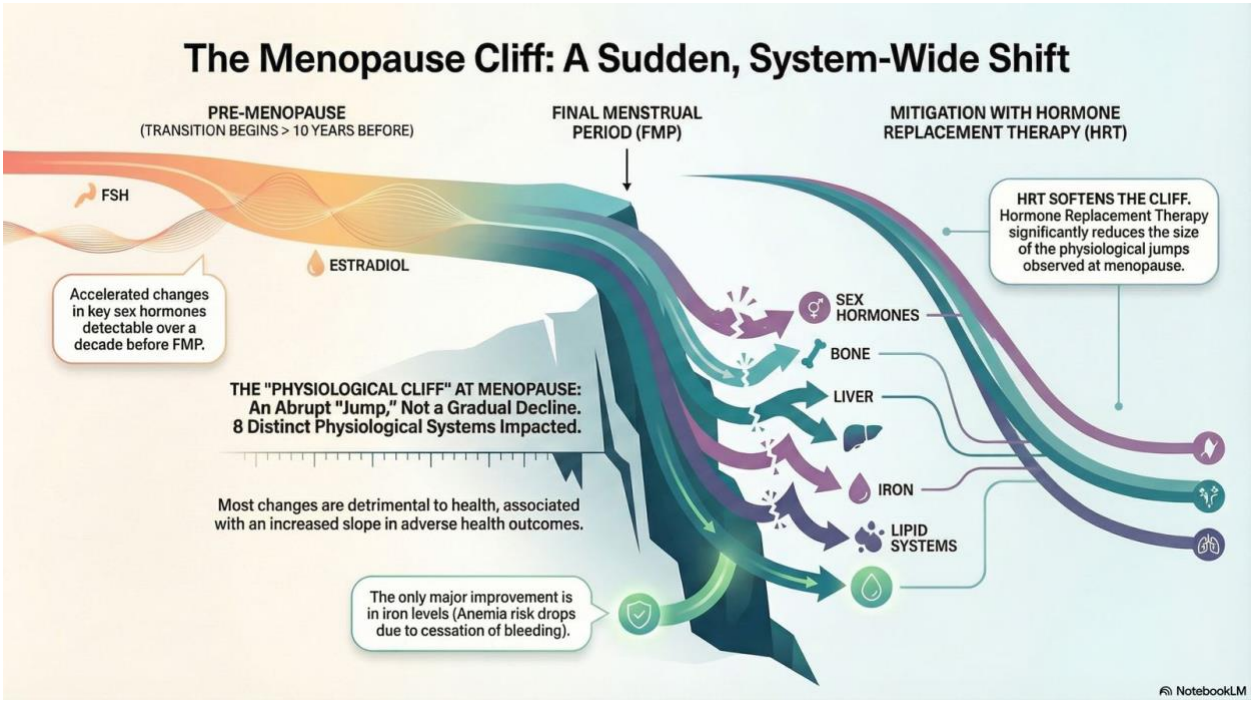
As researchers revisited the data and did more studies, the picture changed sharply. Women who begin hormone therapy within 10 years of menopause show dramatically fewer fractures, better bone density, improved metabolic profiles, and—in many studies—reduced coronary disease and lower overall mortality. The risks identified in the WHI are largely confined to women who start late, when vascular disease is already present. With modern low-dose, transdermal, and micronized formulations, HRT has regained its place as a safe and effective therapy.

The scientific consensus is now clear: for healthy women near menopause, restoring ovarian hormones is one of the most powerful interventions we have to prevent fractures, preserve cardiovascular health, and support well-being.

Ovarian reserve drops with age

Female humans do not make new eggs. Eggs are formed in the ovaries of the fetus around the age of 20 weeks. The eggs begin to die, and at birth there are about 1 million left. Decline is exponential and the number drops to about 50,000 at age 35, where an inflection point occurs to an even faster decline of egg number. When the number drops below about 1000, around age 50, menopause occurs. How to slow this decline is one of the most fascinating open problems in human biology.

Menopause is a physiological cliff



As in much of women's health, research on menopause is sparse. Most of what we know is from longitudinal studies on a few thousand women sampled every two years with a handful of lab tests- such as the SWAN study. It portrays menopause as a transition over two years around the final menstrual period (FMP).

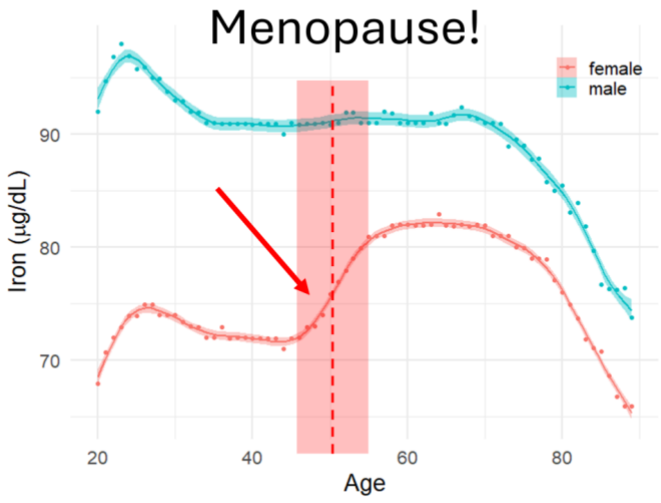
To find out how menopause affects all of the body's systems, we explored two large data sets totalling 1.3 million women. The two datasets are as different as can be. One is an organized US health and nutrition survey in which every year a few thousand people of different ages get around 100 lab tests - always different people but always the same tests - and answer hundreds of questions.

The second is a medical data set encompassing 50 million life years from Israel's largest health ensurer Clalit. It includes everyone who had a lab test. It is an all comers dataset. We removed data for a test if the person had a disease or took a drug that affected the test.

We reasoned that affects that are conserved across these two datasets would likely be true biology

When you look at the mean value of nearly any lab test versus age, you see that men show a slow and gradual change with age whereas women show a much larger change around age 40 to 60 - right around the menopause.

Male and female lab values age very differently near age 50



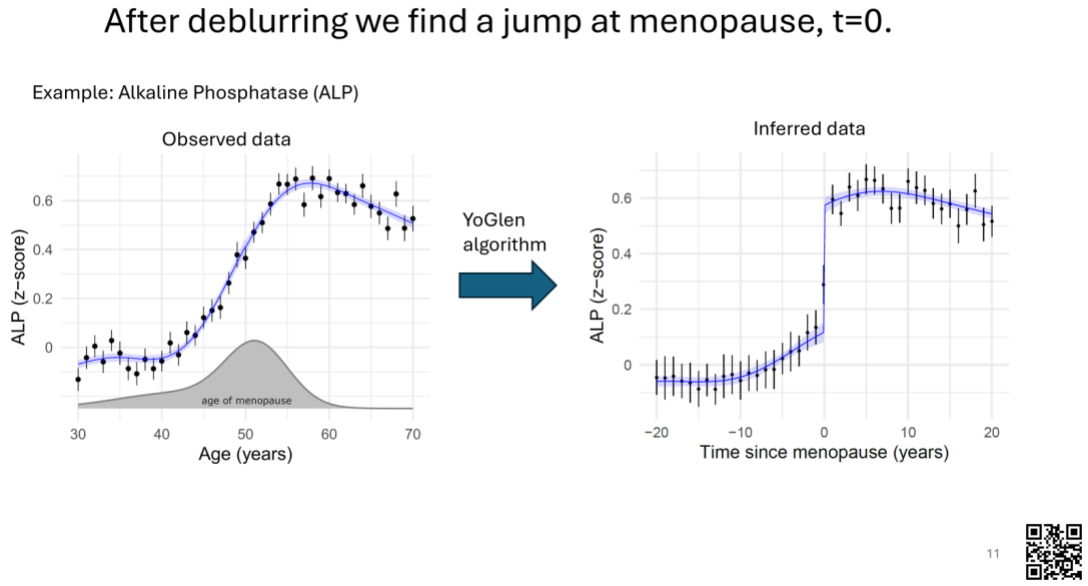
Source: Israeli electronic medical records from Mendelson-Cohen et al *Nature Medicine* 27 (2021)

But there is a problem - these large data sets were not designed to study menopause. We do not know the date of the final menstrual period for each woman. As a result, the average trace of each test is a smeared version of an individual woman's physiology because each woman

had final menstrual period at a different age. Menopause is on average around age 50 plus or minus a few years - it could be age 45 or age 53 .

we wanted to sharpen the image and resolve how lab tests change not with age but as a function of time to the final menstrual period

To do that, we borrow a method from astronomy. When you look at a star through a telescope you see a blurry image because the telescope distorts the light. but if you know how the telescope distorts a point of light-the blurring function-you can divide it out and get a sharp image. This is called deconvolution.



In our case, the blurring function is the distribution of Menopause ages, that we know accurately from menstrual diaries of hundreds of thousands of women. We could thus deconvolve the distribution of Menopause age and get a sharp picture of how each lab test changes as a function of time from Menopause.

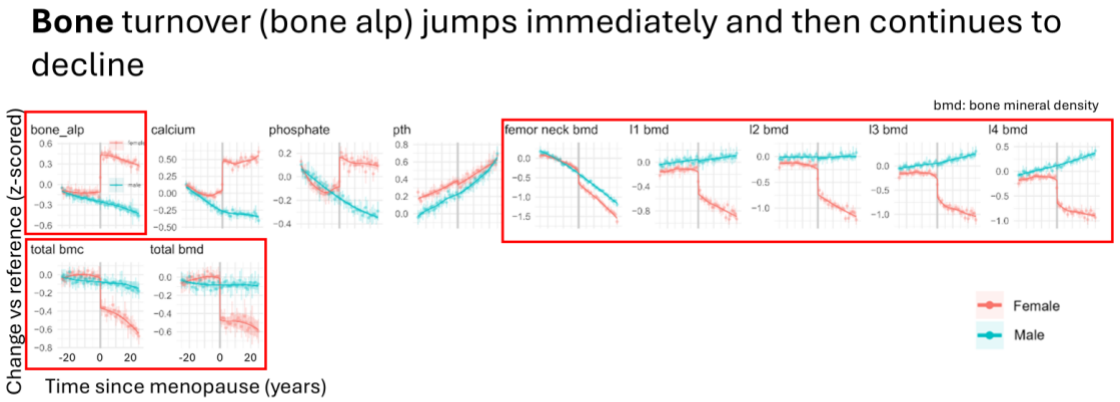
Just to be clear, we're not able to predict the age of Menopause for an individual woman. That's very hard because hormones fluctuate near menopause. Instead we compute the average physiology of all women if we knew their final mental period and aligned it at t=0.

What we discovered took our breath away. About half of the test showed a jump at the final menstrual period which we term a physiological cliff. every system changes and most of the changes are the direction of elevated disease risk, similar to the changes that occur at old age. And the changes are long lasting. It's like a step change.

The changes are large -about a standard deviation of the lab values in a healthy young population. A standard deviation is a lot — it is roughly the difference between young and old, the difference between sick and healthy.

The cliff sizes were almost identical in the two datasets - a 90% correlation between the jump magnitudes. When we applied the same algorithm to the male lab tests, we found no cliffs. All this adds confidence that the results are a real jump.

The cliff is especially steep in bone density, which drops at Menopause. when bone loss occurs in an adult nothing will return it. This bone is gone. exercise can strengthen muscles but not the bone and calcium can't do it either.



Low bone density-osteoporosis-has the deadly consequence of bone fractures. A woman in her 70s that suffers a hip fracture has a 30% chance to die within a year . even if she survives, her life has changed with less activity and more isolation causing a spiral of illness. Therefore preventing bone loss is a huge medical and societal need.

Other systems that show a cliff include liver damage tests and blood cholesterol measurements. In other words metabolism shifts for the worse. Salt in the blood rises, technically known as osmolality. This is due to oestrogen's effect on the thirst hormone ADH. Lead- a toxin- rises in the blood, because it is normally stored in bone, and is released at menopause when bone melts away.

The only silver lining is improved iron and red blood cell tests. They improve at menopause because menstrual bleeding stops. in fact bleeding is often extra strong before the final menstrual period and indeed you see a drop for the worse in iron test in the years before menopause. then at the final menstrual period a sudden improvement, followed by a gradual decline over decades due to aging, as in men.

Incidence of bone and heart disease begin to climb with the final menstrual period

Up to now we considered lab tests, which are what clinicians care about as a signal that something is wrong, a warning that a disease can occur in the future. If you have high blood pressure you get blood pressure medication to prevent a heart attack 20 years later , and the same with high ldl cholesterol where you are prescribed statins to prevent heart attack and stroke. Therefore the cliff is an invitation for prevention

To see the impact of the increased risk, we looked at clinical outcomes. Their incidence starts to rise at the final menstrual period: the largest rise is in osteoporosis. Whereas men in their 70s have less than 5% incidence, Women have a whopping 25%.

A Similar rise occurred in heart attacks, the leading cause of death for both men and women. men have more heart attacks to begin with, but after menopause women begin to catch up.

Liver disease incidence shows a jump at the final menstrual period . This makes sense given the jump in liver damage tests.

The only clinical outcome that improves is anemia due to the stop of bleeding at Menopause

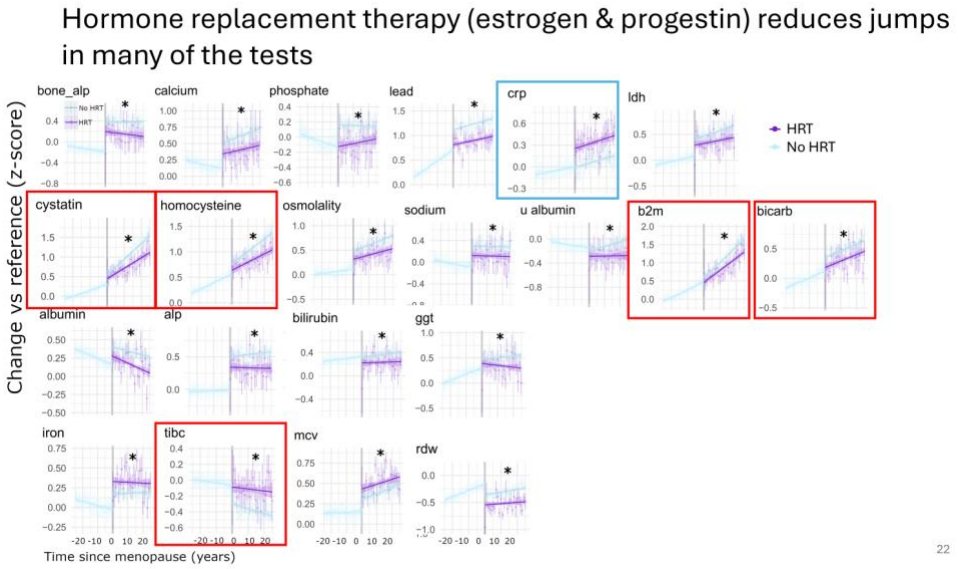
Hormone replacement therapy reduces the cliff

We wanted to ask what hormone replacement therapy does. But here we faced another challenge. After 2002 the use of hormone replacement therapy in our data dropped from about 30% of the women to less than 4% . the US study even stopped asking about hormone replacement therapy after 2012.

there was enough data in those 4% . However, since it's such a small fraction of the population one may worry that they are somehow different- maybe in their social economic status, education symptom severity, or some other factor.

Therefore, we sought to compare the hormone replacement therapy users to another 4% of women that are as similar as possible in their demographics and biology, but did not take hormone replacement therapy.

This comparison reveals that hormone replacement therapy reduces the cliff dramatically. In many of the lab tests women now seem to age as gradually as men. The iron benefits still remain since estrogen replacement does not restore menstrual cycles.



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Changes begin more than a decade before menopause

The high resolution of our sharpened trajectories reveal how early physiological dysregulation begins. The sex hormones begin to drop more than a decade before menopause and with them the most sensitive lab tests such as bone and liver tests .

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This expands the window of pre-menopause beyond the few years of peri-menopause you find in textbooks, to the late 30s or early 40s of a woman's life.

The second mountain

In this book, I like to touch on the meaning of aging for our life. Since both men and women show a turn for the worse around age 50 in their heath, one may speculate that Menopause evolved to protect women from having to deliver a child at age 70, which would be deadly. It preserves these wise and experienced individuals that can increase the fitness of their kin. Studies in both human beings and other mammals such as elephants and whales show that the presence of old females increases the health of their family members.

Both men and women around age 50 have already climbed the first mountain - establishing relationships, family and career. The menopause symptoms are like a wake up call - reproductive function has ended and we enter a valley from which we need to define our second mountain.

Biology gives us a clue about what that second mountain might involve. As we saw, physical functions like muscle strength and lung capacity decline, as does cognitive processing speed and memory. One of the only things that improves with age is wisdom with its components of emotional regulation, decision-making based on experience and crystallized knowledge of the world.

So the second mountain is a purpose that benefits circles larger than the self. Generativity versus dissipation is the life task at hand, according to Erickson. Climbing the second mountain we are powered by our interpersonal aplomb, experience and self knowledge. That's why I'm inspired by research on menopause to reflect on my own second mountain.

Appendix

The indispensable Gnoma theory

Currently most discussions on evolution of aging are influenced by the disposable soma theory. After reproduction ends the body- the soma- is dispensable. That theory is based on a long tradition that aging is in the shadow of selection - a theory of neutral evolution at old age. Any mutation that benefits the young at the expense of the old is selected.

But if there is even a small selective advantage/disadvantage to be old it would dominate any neutral effects. Indeed there is evidence that elders raise the fitness of their kin.

Across humans and several long-lived mammals, there is strong empirical evidence that older females significantly increase the fitness of their kin through survival benefits, knowledge transmission, and social support.

Thus I'd like to propose a theory of the **Indispensable Gnoma,** the benefit of experience of the elders. Gnoma comes from the Greek word for knowledge and means opinion, judgment, intention, inner thought, resolve.

Old females elevate the survival of their family and tribe. Historical demographic records from Finland, Quebec, and Africa show that the presence of a living maternal grandmother raises child survival by 10–20%, accelerates daughters' reproduction, and increases total lifetime reproductive success. Hunter-gatherer data reveal that postmenopausal women contribute a substantial portion of calories for weaned children and buffer families during food scarcity.

In non-human species, post-reproductive killer whales and pilot whales dramatically increase offspring survival—older females guide group foraging, and losing a post-reproductive mother can increase adult male mortality 3–8 fold. Elephants led by older matriarchs have higher calf survival, better predator responses, and improved drought navigation. Primates show similar effects through social buffering and conflict mediation.

Together, these lines of evidence converge on a single conclusion: old females are not disposable but evolutionarily indispensable, enhancing kin survival, stability, and long-term reproductive success.

But if that were all, only benefit, elders would be selected to function indefinitely. There would be no selection for declining function, rise in mortality- in short, for aging. One plausible cost of being old - advocated by Barral, Lindsky, and others- , is the accumulated exposure to pathogens in the elders (due to being around for a long time) that can infect kin.

Here is a model designed to show that in principle such cost and benefit balance can lead to evolutionary selection of linearly declining function, and thus aging. It's just a proof of concept- has assumptions tailored for that conclusion- so it is just to demonstrate possibilities, not a final word.

Simple evolutionary optimization model for linearly declining function with age

Consider individuals beyond the reproductive age R.

Let F(a) denote their physical/immune function at age a> R.

Each living elder contributes benefit to kin (e.g., childcare, knowledge, foraging) but also harm via a chronic infection whose probability increases linearly with elder age due to cumulative exposure.

Both benefit and harm are proportional to shared activity, which is proportional to physiologic action.

Per-unit-time inclusive fitness at age a\ge R:

Fitness(a)=(b-c a) F(a) - 0.5 lambda F(a)^2

Optimum

F(a)=(b-c a)/lambda

Linear decline with age, Reaches zero at t=b/c

$$\Phi(a,F(a))=\big[b - c(a-R)\big]F(a)\,\ell(a) \;-\; \frac{\lambda}{2}F(a)^2\,\ell(a)$$

- b>0: benefit per unit function
- c>0: viral harm coefficient rising linearly with elder age
- $\lambda>0$: energetic/maintenance cost of sustaining function
- $\ell(a)$: survival probability to age a (any mortality model: constant, Gompertz, etc.)

Linear cost of function lambda0 F(a) gets absorbed in benefit b. This this is a Taylor expansion.

Total elder-phase fitness:

$$W[F(\cdot)] = \int_R^\infty \Phi(a,F(a))\,da$$

Because the integrand depends on F(a) locally, we maximize at each age a.

Optimal age-dependent function

Setting $\partial\Phi/\partial F = 0$ yields:

$$\boxed{F^*(a) = \max\left\{0,\;\frac{b - c(a-R)}{\lambda}\right\}}$$

This is a strictly linear decline in optimal physical/immune function with age:

- Function starts at

  $$F^*(R)=\frac{b}{\lambda}$$

- Declines with slope

  $$\frac{dF^*}{da} = -\frac{c}{\lambda}$$

- Reaches zero (no selection to maintain function) at

  $$\boxed{a = R + \frac{b}{c}}$$

Importantly, the survival curve \ell(a) does not affect the shape of F^*(a) as long as \ell(a)>0; it only weights the magnitude of fitness effects.

Interpretation

- Elders provide net benefits early in elderhood (b > c(a-R)).
- Later, accumulated viral harm outweighs benefits.
- Quadratic maintenance costs penalize high function.
- The optimal compromise is a linearly declining function across age, matching the empirical pattern of many physiological systems (aerobic capacity, strength, immune competence).