Kidney Health In Aging and Aged Societies
JSN/ERA Symposium
Collaboration with JSDT
京都 Kyoto Japan

Altern und Niere: Facts and Fictions

Univ.-Prof. Dr. Danilo Fliser

nature reviews nephrology

September 2024

Focus: Kidney health in the ageing world

https://www.nature.com/collections/nrneph-ageing

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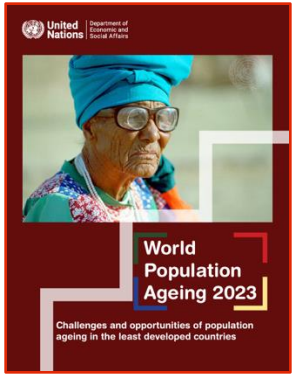
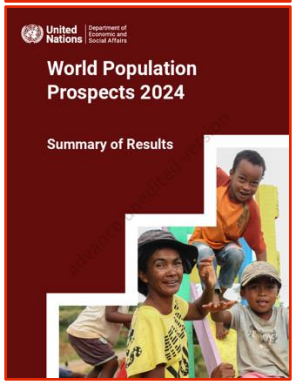
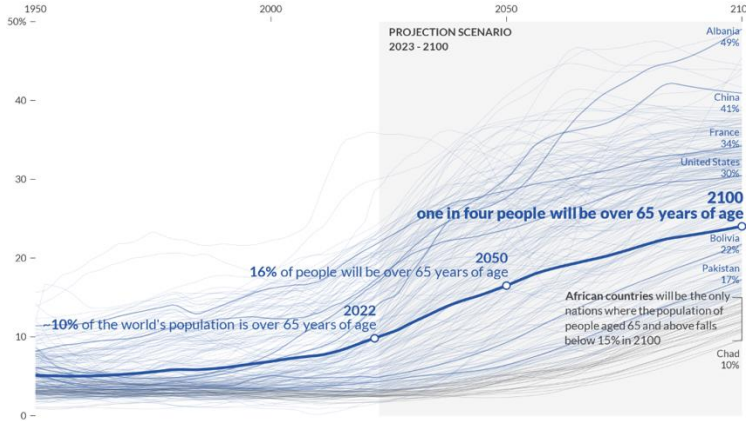
Projections on ageing





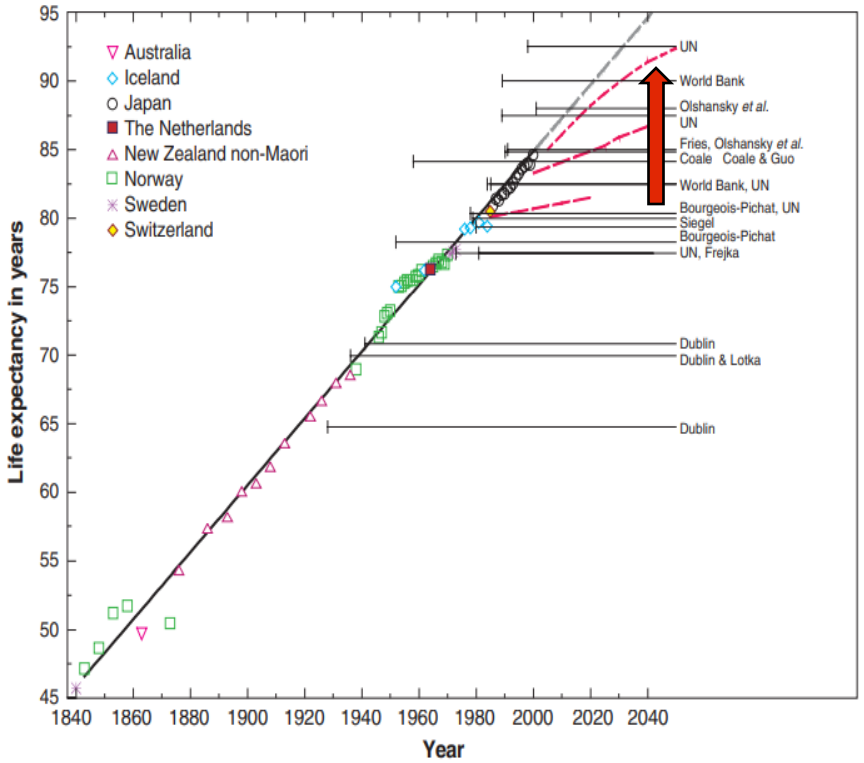
By the end of the Decade of Healthy Ageing (2030), the number of people aged >60 years will increase to 1.4 billion, by 2050 to 2.1 billion. In 2020, for the first time in history, people aged >60 years outnumbered children <5 years, by 2050 they will outnumber adolescents and young people aged 15-24 years

The pace of population ageing is accelerating



UN – *https://www.decadeofhealthyageing.org/about/join-us/collaborative*

Broken limits to life expectancy

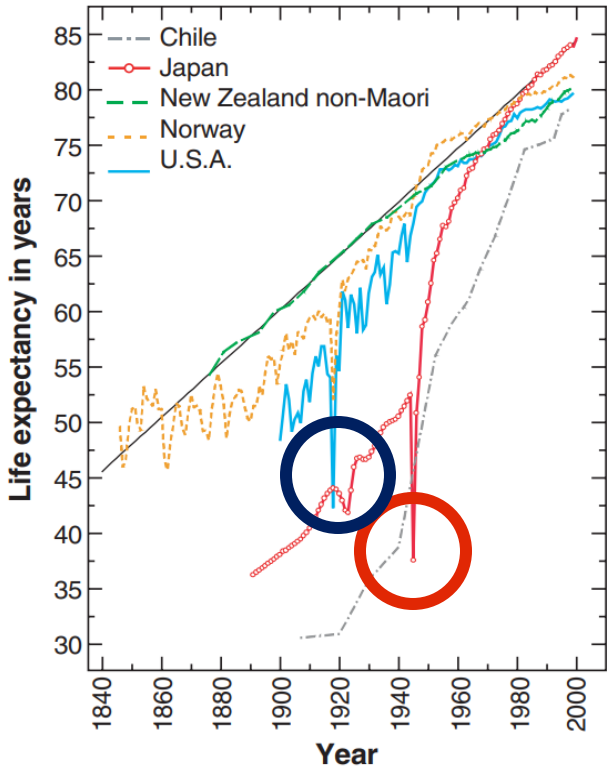


Female life expectancy from 1840 to the present:

- bold black line: linear-regression trend
- dashed gray line: extrapolated trend
- horizontal black lines: asserted ceilings on life expectancy
- short vertical line: year of publication
- dashed red lines: projections of female life expectancy in Japan published by the UN in 1986, 1999, and 2001

Oepen and Vaupel. *Science* 2002

Broken limits to life expectancy



Female life expectancy in Chile, Japan, New Zealand, Norway, and the United States compared with the trend in record life expectancy

The apparent leveling off of life expectancy in various countries is an artifact of laggards catching up and leaders falling behind. For 160 years, life expectancy has steadily increased by a quarter of a year per year, an extraordinary constancy of human achievement

Oepen and Vaupel. *Science* 2002

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Broken limits to life expectancy

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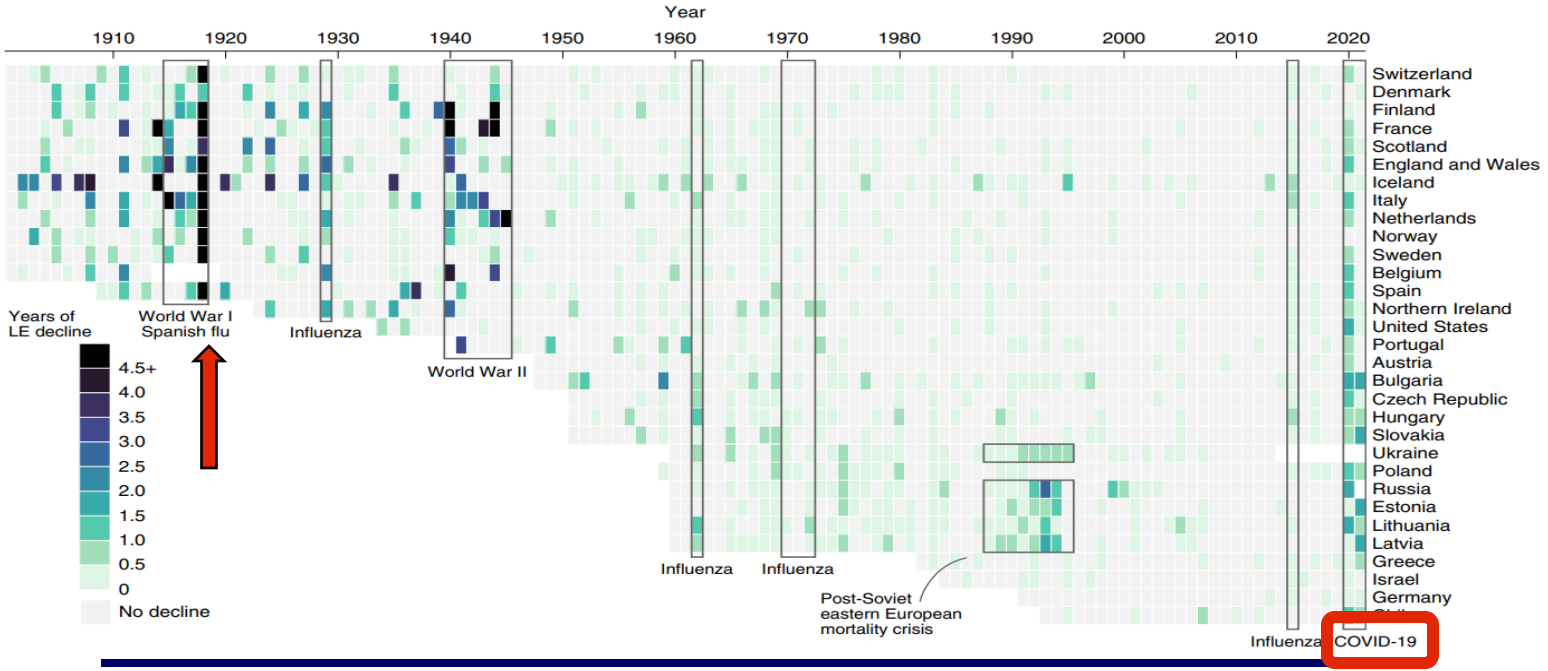
Period shocks to LE due to wars and epidemics (green vertical bands) across countries, momentarily disrupting the dominant trend of LE improvements (grey)



Schöley et al. Nat Hum Behav 2022

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Life expectancy – facts & fiction

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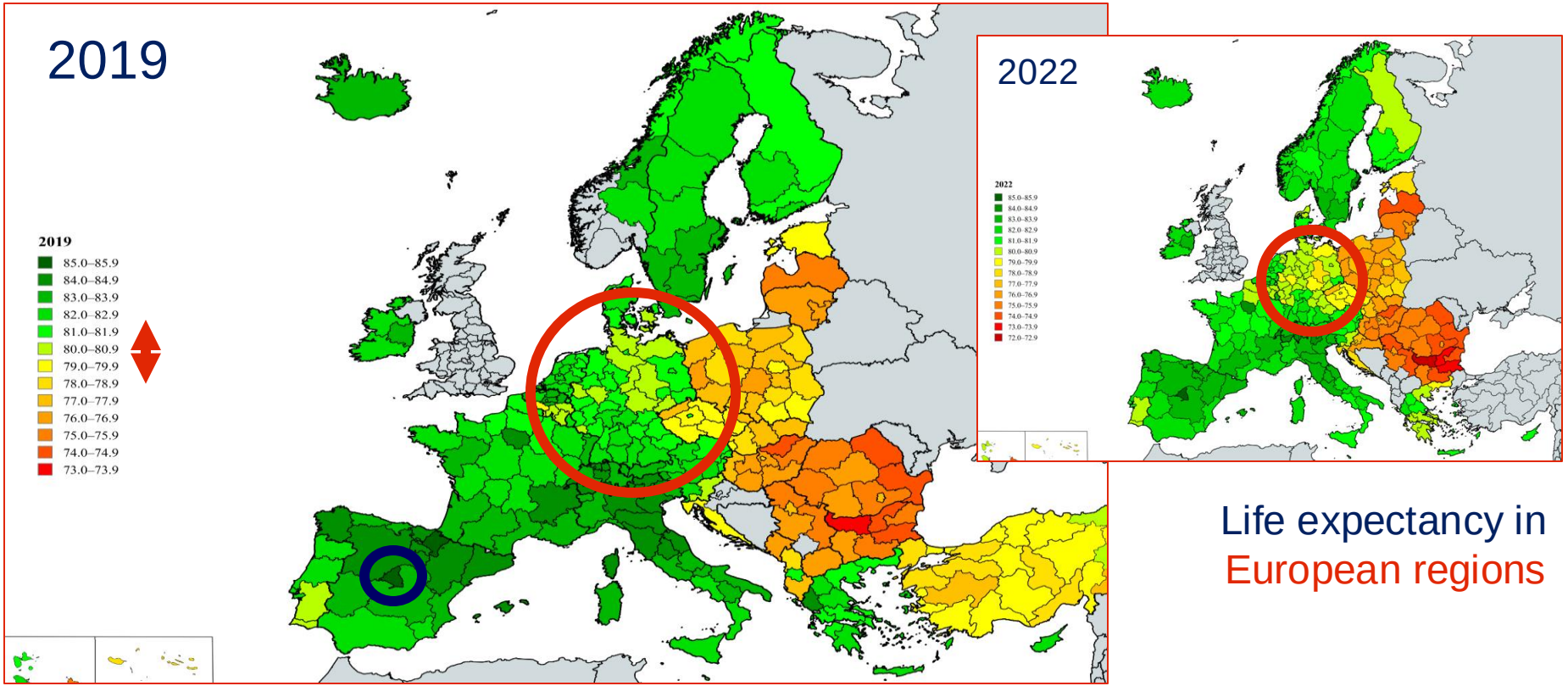

Life expectancy in European regions

Eurostat – European statistics

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Die Wahrheit von heute ist der Irrtum von morgen

Today's truth is tomorrow's error

今日の真実は明日の間違いになる

Jakob von Üxküll
1864-1944
Founder of the “Hamburg Institute for Environmental Research”, and forerunner of modern behavioral research

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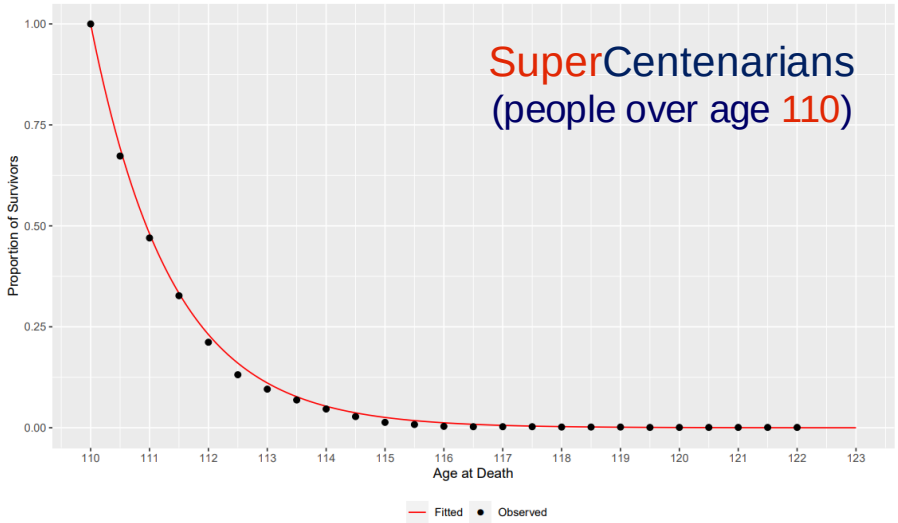
Probabilistic forecasting of maximum human lifespan by 2100 using Bayesian population projections



Based on the Bayesian analysis, there is a >99% probability that the current Maximum Reported Age at Death of 122 will be broken by 2100

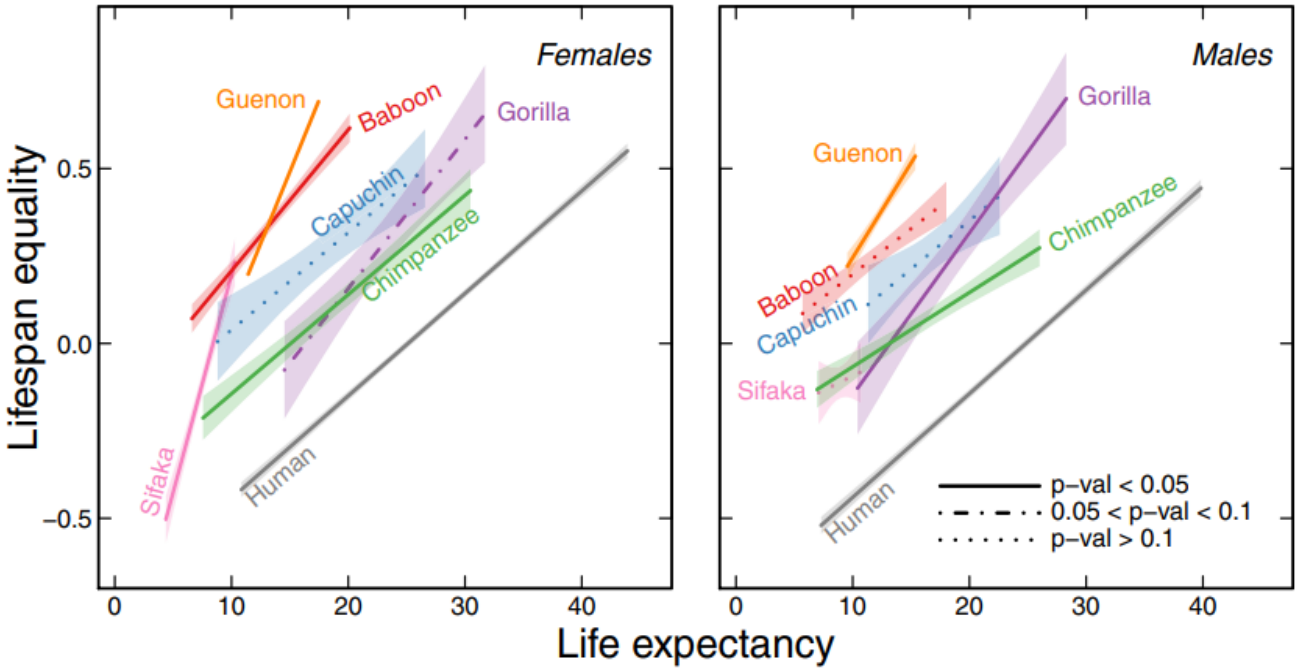
Probabilities that a person lives to at least age 126, 128, or 130 this century, are 89%, 44%, and 13%, respectively

WORLD ECONOMIC FORUM

Pearce & Raftery. *Demographic Research* 2021

Life expectancy – facts & fiction

The life expectancy-lifespan equality landscape



The ”invariant rate of ageing” hypothesis – the rate of ageing is relatively fixed within species – was tested in datasets of 7 genera of primates for both sexes

Colchero et al. Nat Comm 2021

Life expectancy – facts & fiction

In historical populations mortality improvements for infants, and improvements in age-independent mortality, were the central contributors to the decades-long trend towards longer human life expectancies and greater lifespan equality. These improvements were largely the result of environmental influences including social, economic, and public health advances

It remains to be seen if future advances in medicine can overcome the biological constraints and achieve what evolution has not

Colchero et al. Nat Comm 2021

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Add life to years

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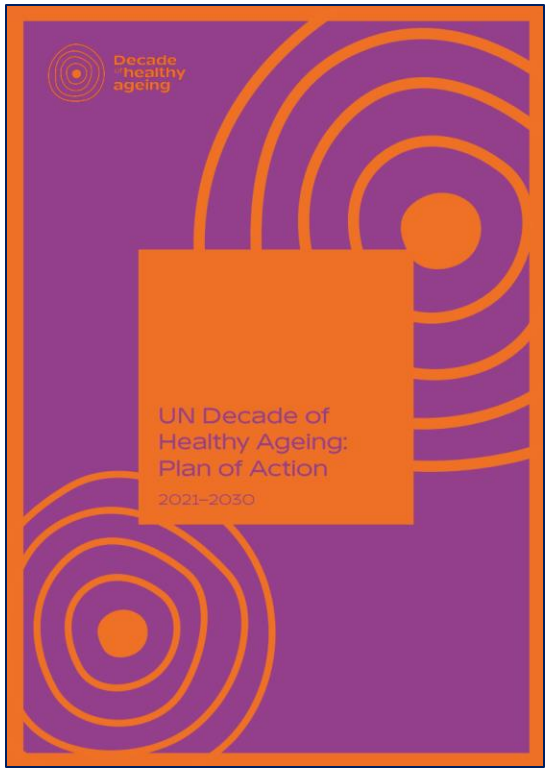
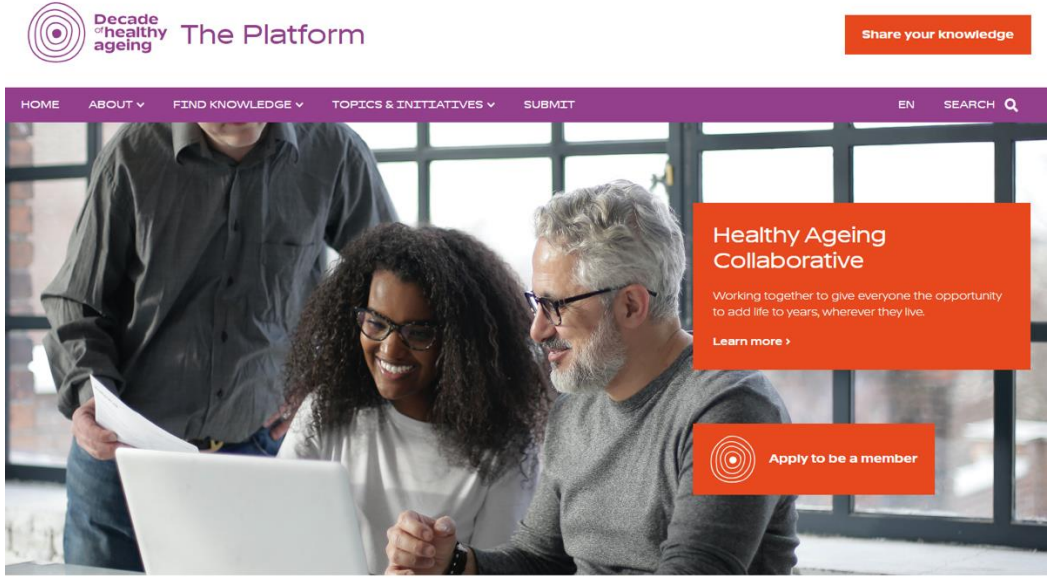


The Healthy Ageing Collaborative



The Healthy Ageing Collaborative: working together to give everyone the opportunity to add life to years, wherever they live

UN – *https://www.decadeofhealthyageing.org/about/join-us/collaborative*

Defining healthy ageing

Healthy ageing is developing and maintaining the functional ability, i.e. the intrinsic capacity of the individual, relevant environmental characteristics and the interaction between them. Healthy ageing enables older people to remain a resource to their families, communities and economies

Globally, life expectancy (LE) increased from 66.8 to 73.4 years between 2000 and 2019. Healthy life expectancy (HALE) increased from 58.3 to 63.7 years, due to declining mortality rather than reduced years lived with disability. The increase in HALE has not kept pace with the increase in life expectancy (5.4 vs. 6.6 years)

World Health Organization

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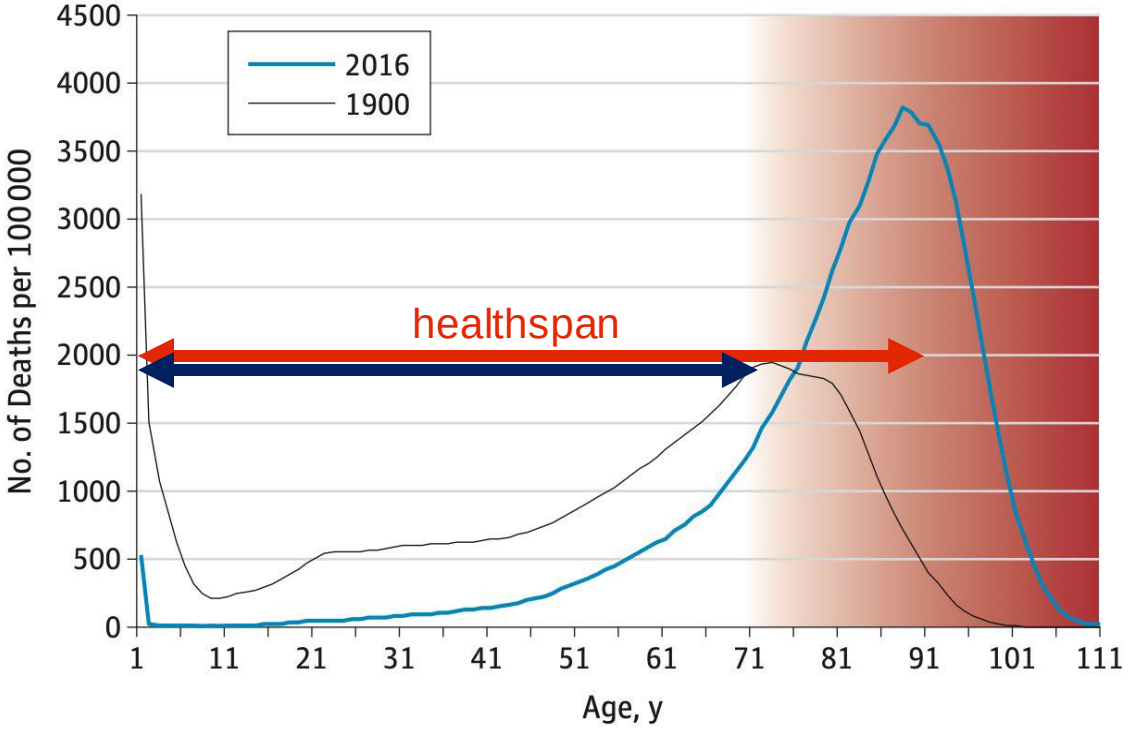
From lifespan to healthspan

The goal of aging science is to delay and compress the red zone by preventing or managing the results of chronic diseases (*such as CKD**)



data from Human Mortality Database
https://www.mortality.org/

Olschansky. JAMA 2018

** speakers note*

Ageing – facts & fiction

Senolytics – a class of drugs that selectively clear senescent cells

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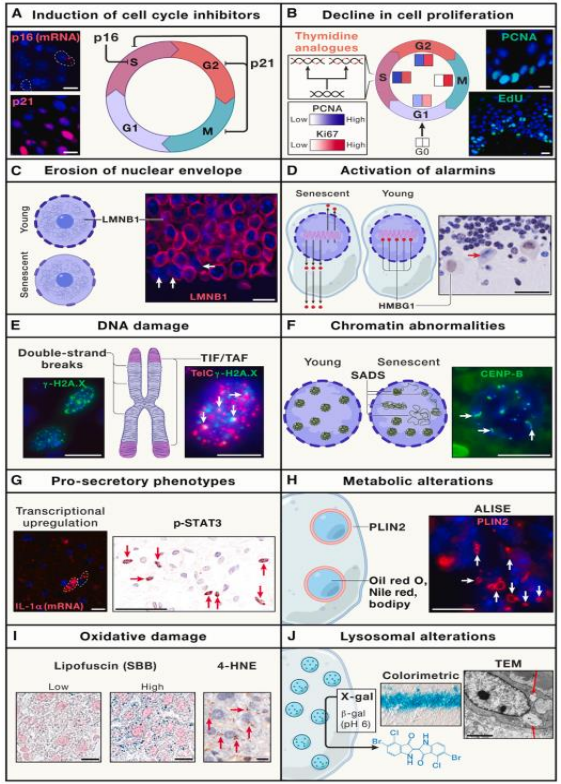
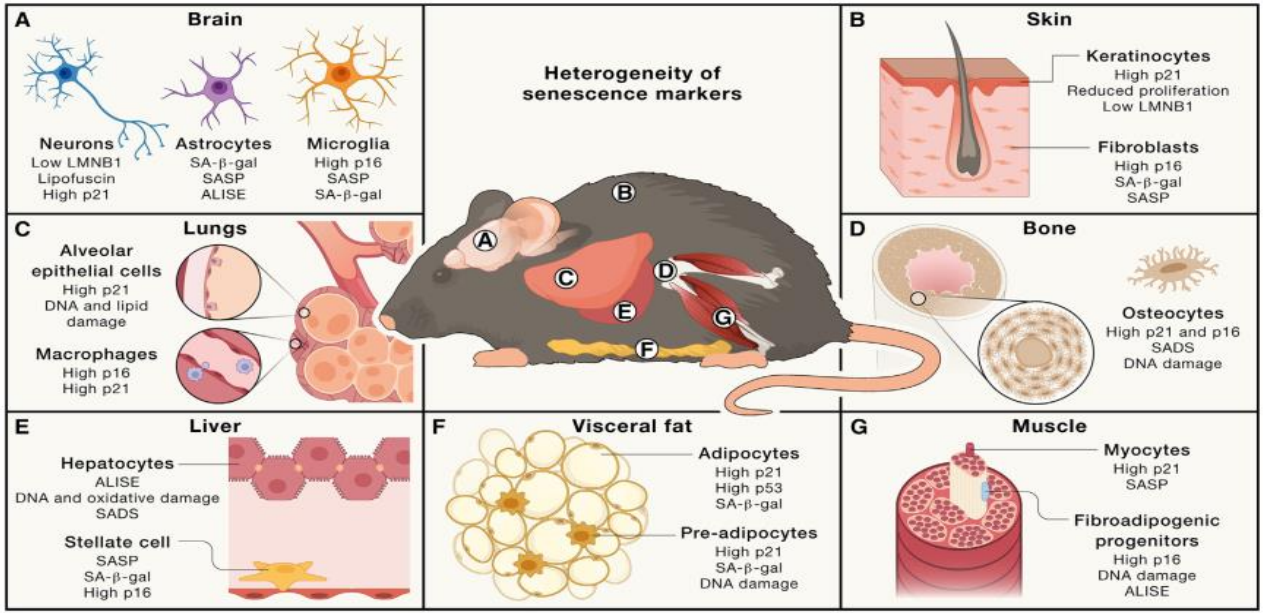


Guidelines for minimal information on cellular senescence experimentation in vivo



Ogrodnik et al. Cell 2024

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Ageing – facts & fiction

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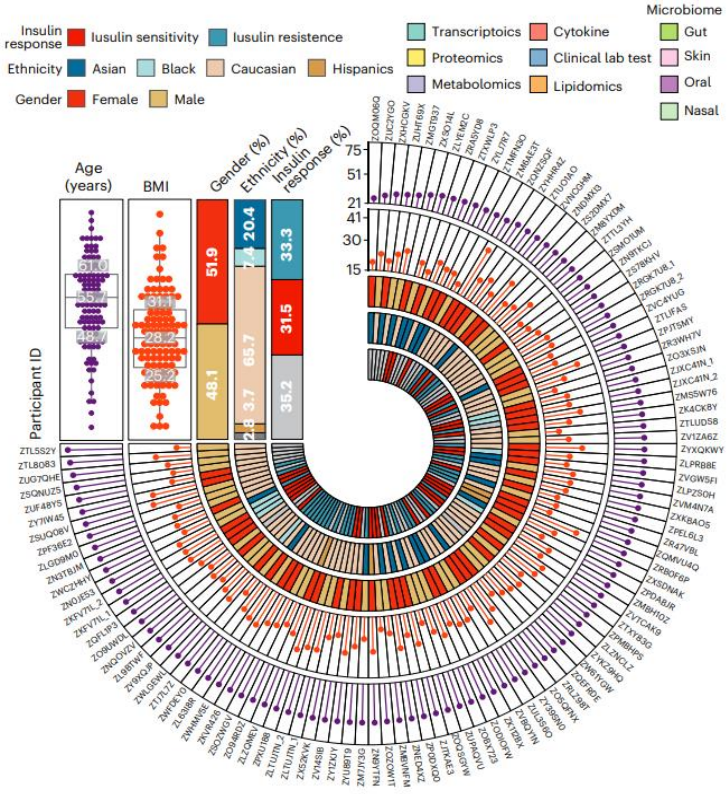

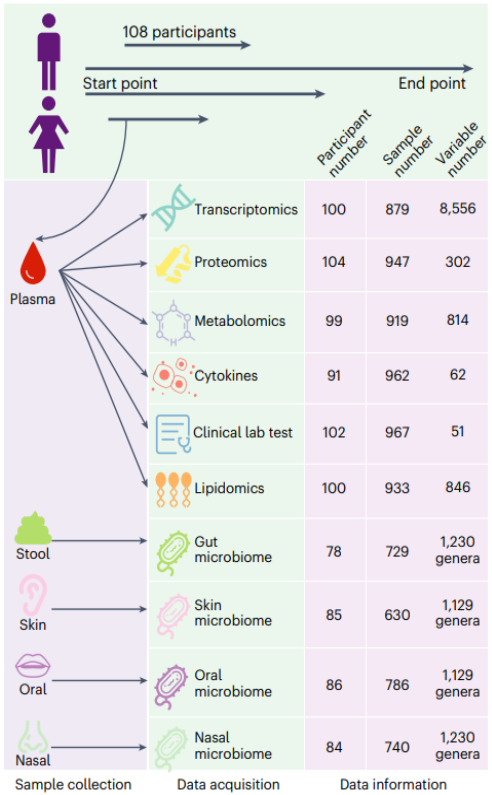

Nonlinear dynamics of multi-omics profiles during human aging

Longitudinal human cohort of 108 participants, aged between 25 and 75 years with a maximum follow-up of 6.8 years

Shen et al. Nat Aging 2024

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Ageing – facts & fiction

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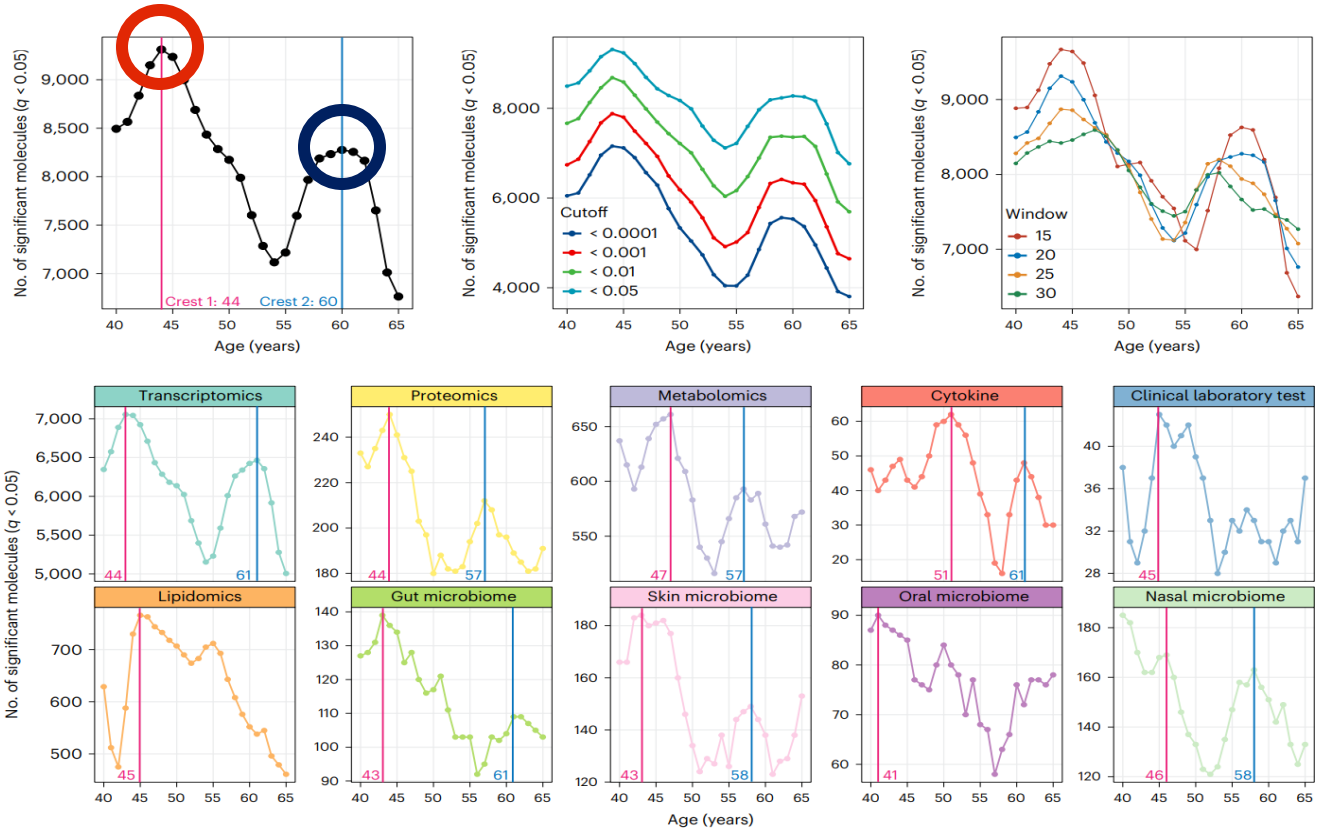

Shen et al. Nat Aging 2024

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BLUE ZONES – facts & fiction

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Buettner. National Geographic 2005

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OKINAWA diet – facts & fiction

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NATIONAL GEOGRAPHIC

Why the traditional Okinawan diet is the recipe for a long life

This plant-based, anti-inflammatory diet boosts health and promotes a longer life, all while protecting the planet.

By Stacey Colino
August 1[illegible] 2024

Women'sHealth

What is the Okinawa diet? Experts share the benefits, risks, and foods to try

The low-calorie, high-carb diet may boost longevity

BY MEGUIRE HENNES PUBLISHED: 30 AUGU[illegible] 2024

EXPRESS

The beautiful region with the world's best diet and a long life expectancy

A stunning region has the world's healthiest diet and many of its residents live to over 100 years old.

By ESTHER MARSHALL, Senior Travel Reporter
12:28, Sun, Apr 28, 2024 | UPDATED: 12:43, Sun, Apr 2[illegible] 2024

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BLUE ZONES – facts & fiction

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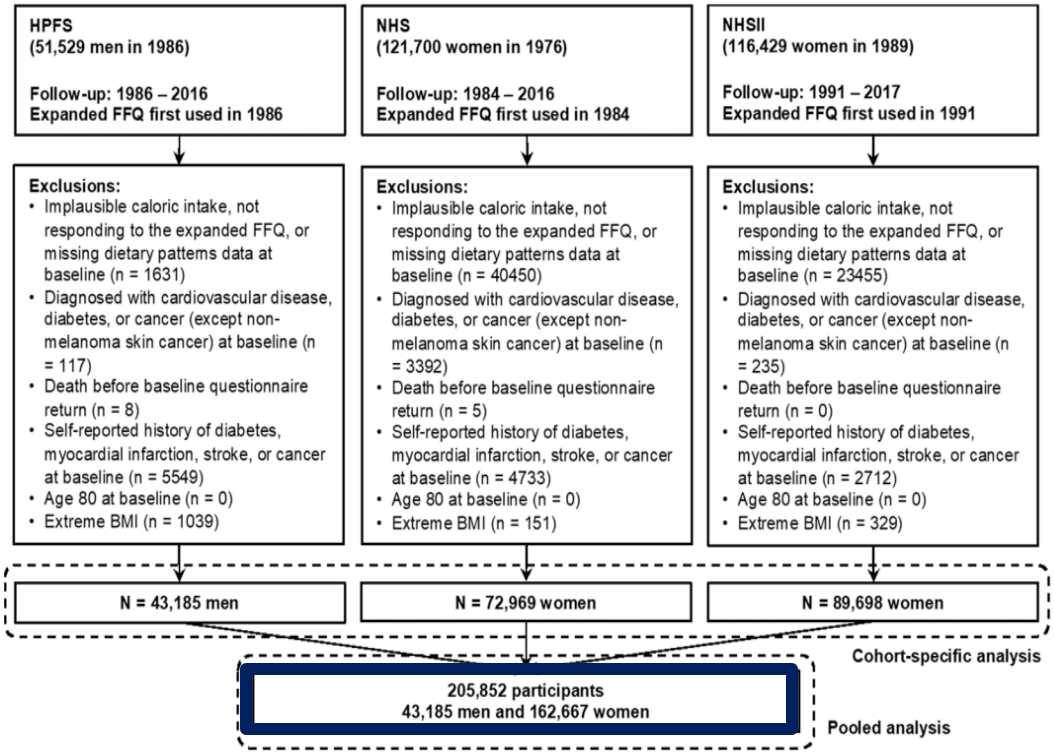
Longevity and diet in Okinawa, Japan: the past, present and future

Okinawa, Japan's poorest prefecture, previously had the highest longevity indices in the country. However, the latest life expectancy at birth for men in Okinawa is no higher than the national average

In 1990, in Okinawa, the age-adjusted death rates of the three leading causes of death were lower than their national averages. By 2000, the standard mortality ratios of heart disease and cerebrovascular disease for both sexes in Okinawa had increased, compared to their 1990 levels. Consequently, the national ranking of Okinawa prefecture for life expectancy at birth of men has dropped. By 1998, daily meat intake and fat energy ratio had surpassed 100 grams and 30%, respectively, and daily intake of pulses and green and yellow vegetables had declined to the level of the national average

Miyagi et al. Asia Pac J Pub Health 2003

Diet & longevity – facts & fiction



205,852 healthcare professionals from 3 US cohorts prospectively followed for up to 32 years; 2 diets mechanism-based and 6 based on dietary recommendations

Composite outcome of incident major CV disease, type 2 diabetes, and cancer; adherence to a healthy diet was generally associated with a lower risk of major chronic disease (HR 0.58-0.80)

Wang et al. Nat Med 2023

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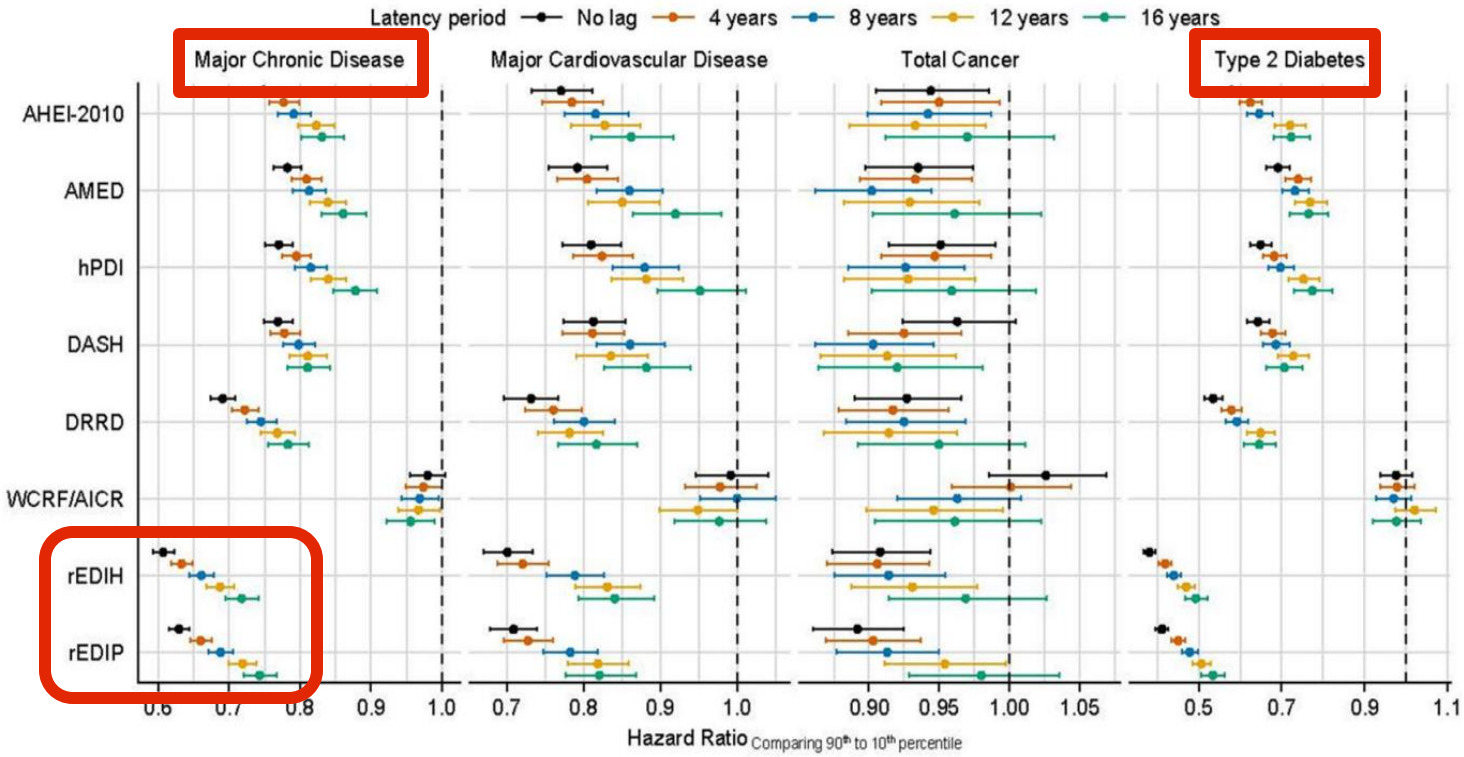
Diet & longevity – facts & fiction



Alternate MEditerranean Diet

Dietary Approaches to Stop Hypertension Diabetes Risk Reduction Diet

Wang et al. Nat Med 2023

Diet & longevity – facts & fiction

Participants with low insulinemic* (HR=0.58), low inflammatory** (HR=0.61) or diabetes risk-reducing (HR=0.70) diet had the largest risk reduction for incident major CVD, type 2 diabetes and cancer as a composite and individually. Similar findings were observed across gender and diverse ethnic groups

*reversed empirical dietary index for hyperinsulinemia (rEDIH)
**reversed empirical dietary inflammatory pattern (rEDIP)

These results suggest that dietary patterns associated with markers of hyperinsulinemia and inflammation and diabetes development may inform on future dietary guidelines for chronic disease prevention (*also CKD?*)*

Wang et al. Nat Med 2023

** speakers note*

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Diet & longevity – facts & fiction

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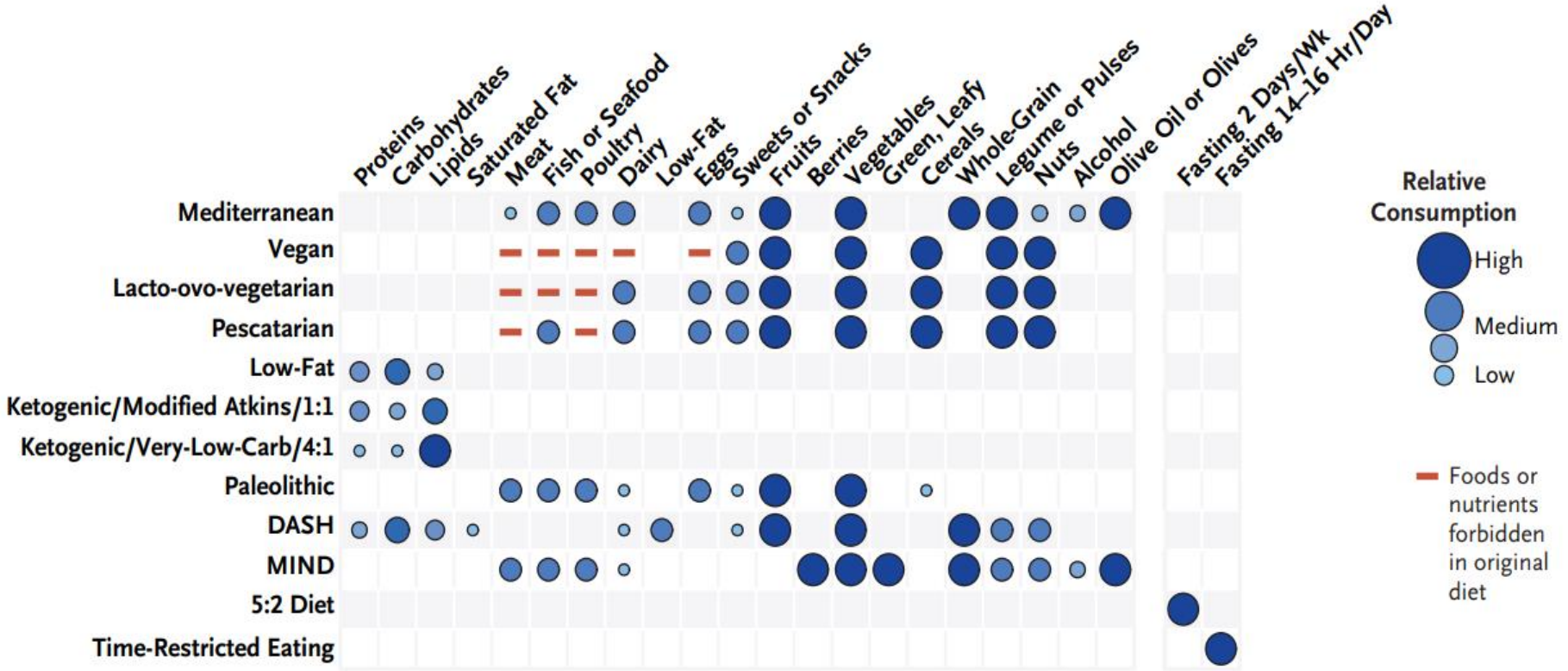

Yannakoulia & Scarmeas. N Engl J Med 2024

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Ageing and the kidneys

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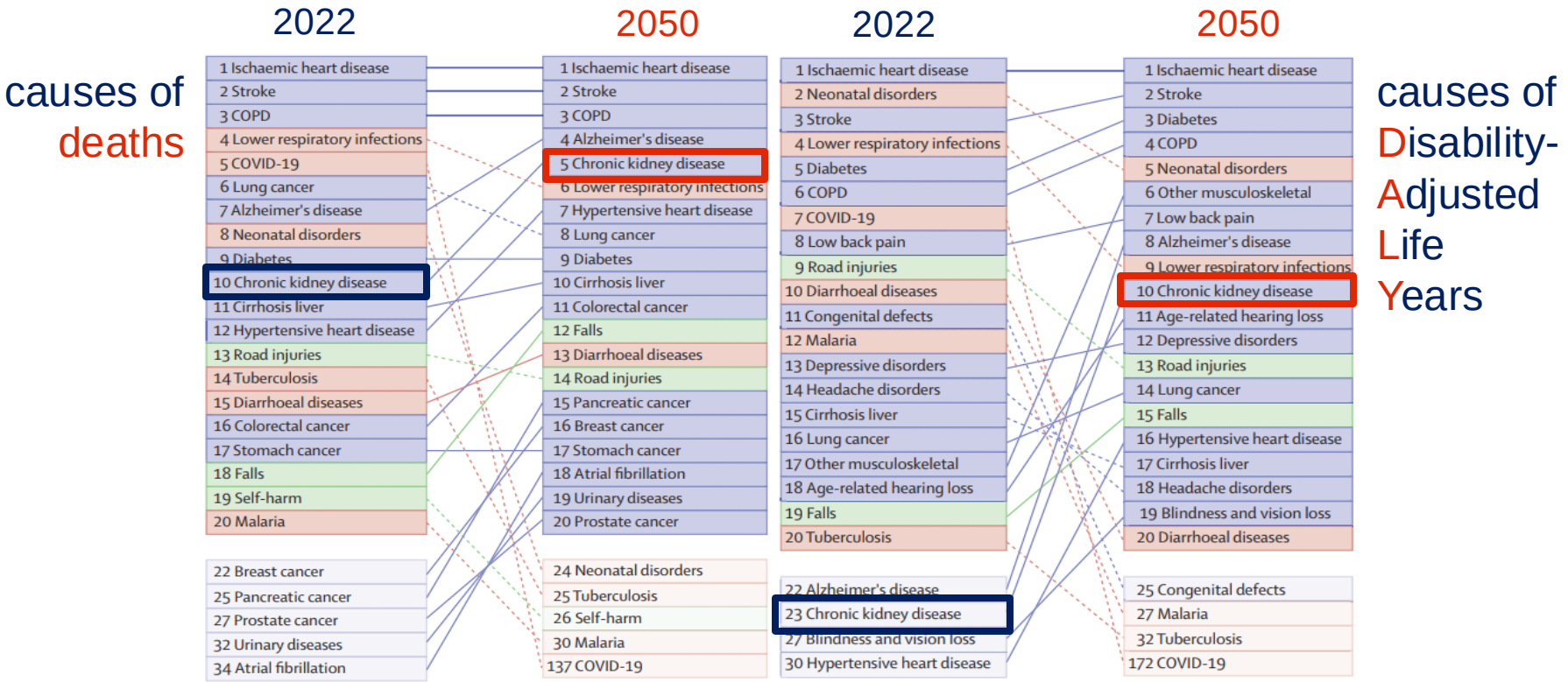

GBD 2021 Forecasting Collaborators. *Lancet* 2024

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ASN – ERA – ISN

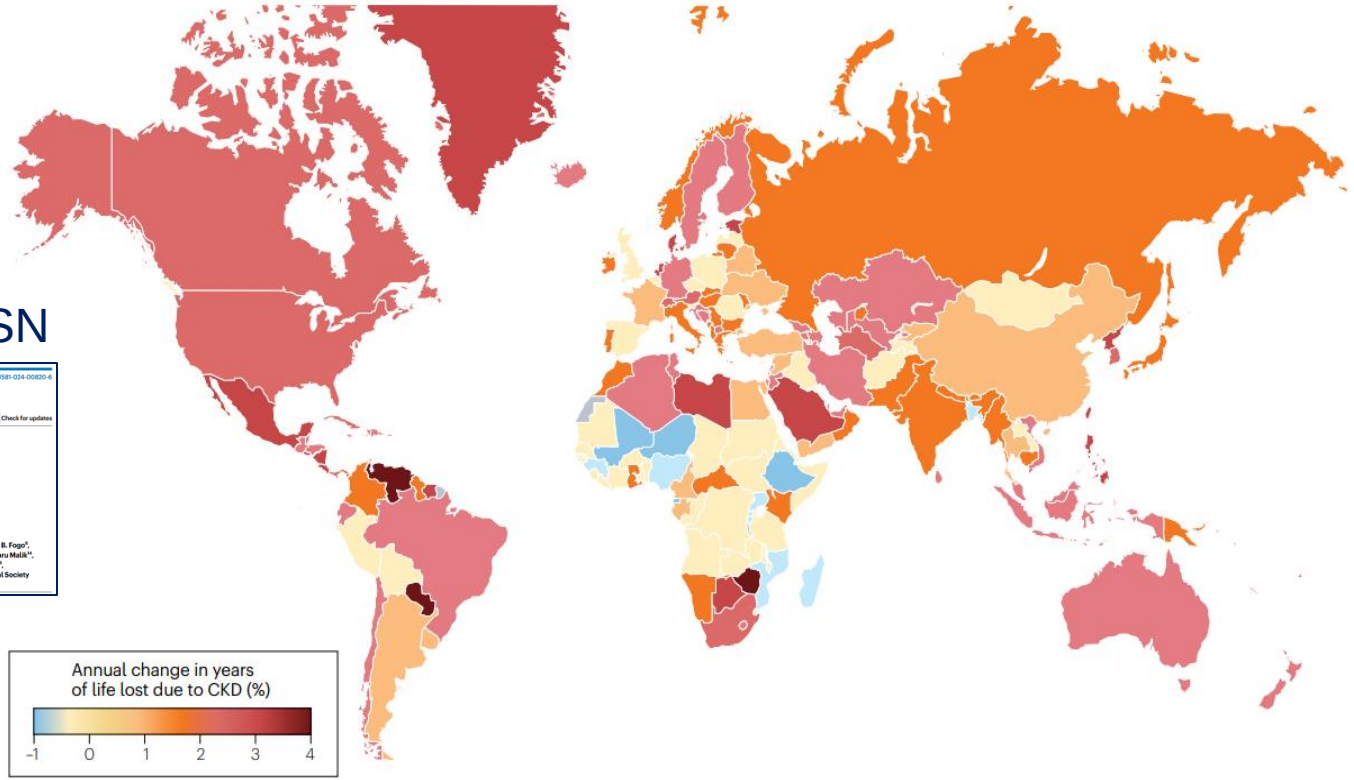
nature reviews nephrology
https://doi.org/10.1038/s41581-024-00820-6

Consensus statement

Check for updates

Chronic kidney disease and the global public health agenda: an international consensus

Anna Francis[1], Meera N. Harhay[2,3], Albert C. M. Ong[4], Sri Lekha Tummalapalli[5,6], Alberto Ortiz[7], Agnes B. Fogo[8], Danilo Fliser[9], Prabir Roy-Chaudhury[10], Monica Fontana[11], Masaomi Nangaku[12], Christoph Wanner[13], Charu Malik[14], Anne Hradsky[15], Dwomoa Adu[16], Sunita Bavanandan[17], Ana Cusumano[17], Laura Sola[18], Ifeoma Ulasi[19], Vivekanand Jha[20,21] ... ; American Society of Nephrology*, European Renal Association* & International Society of Nephrology*



Francis et al. Nat Rev Nephrol 2024

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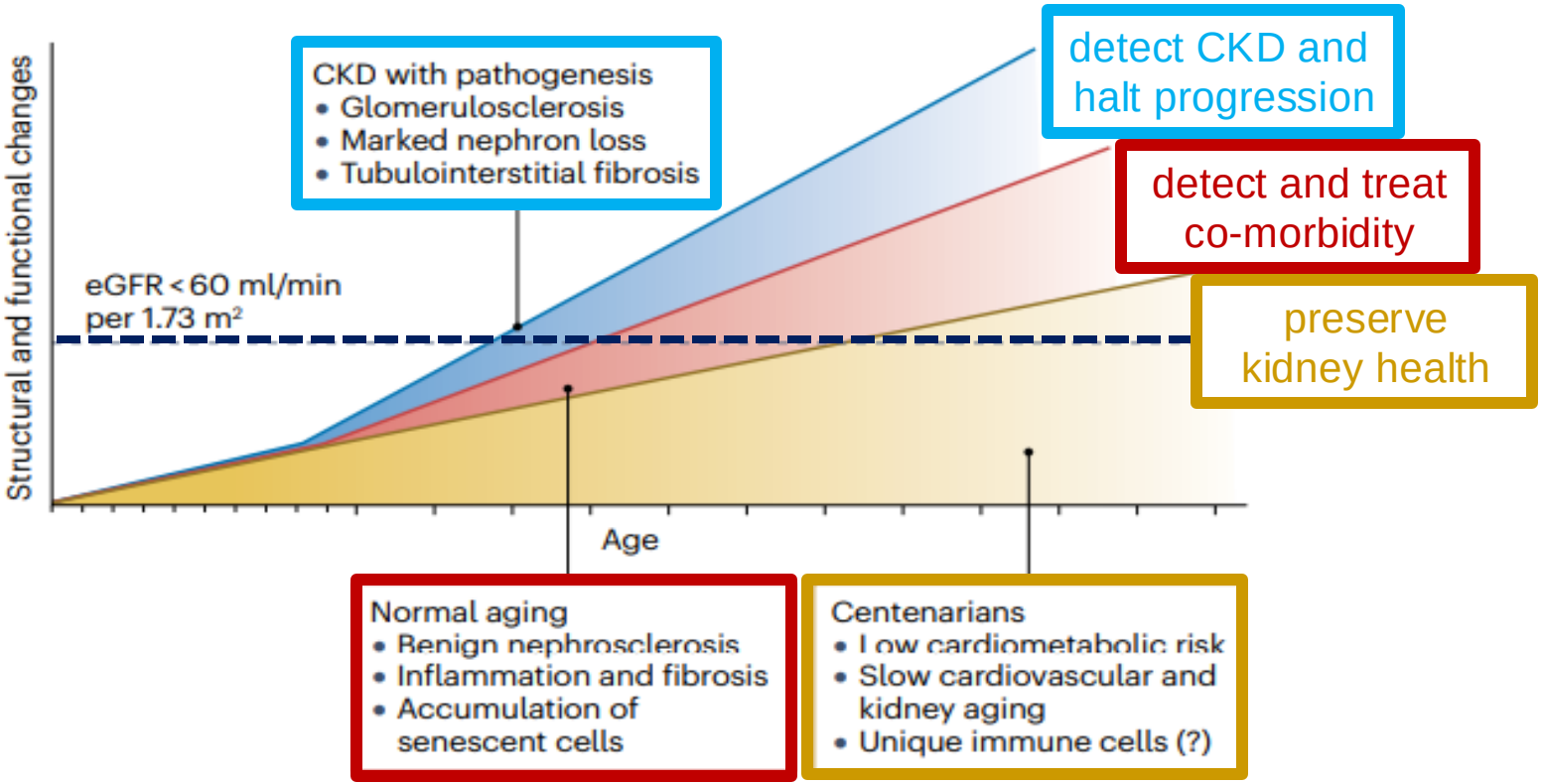
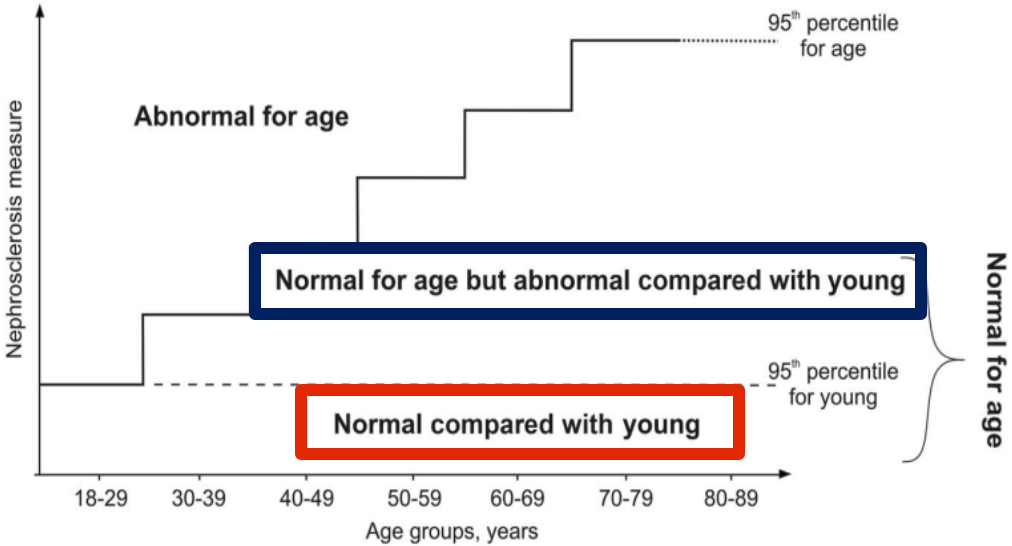


Arai & Yanagita. Nat Rev Nephrol 2024

Ageing and the kidneys

Age-based versus young-adult thresholds for nephrosclerosis on kidney biopsy and prognostic implications for CKD

3,020 living kidney donors
1,363 pts with kidney tumor
314 pts with kidney disease



Asghar et. J Am Soc Nephrol 2023

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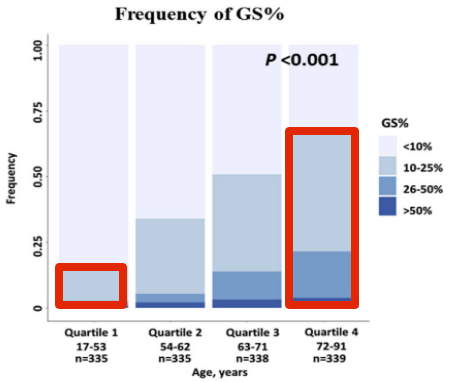
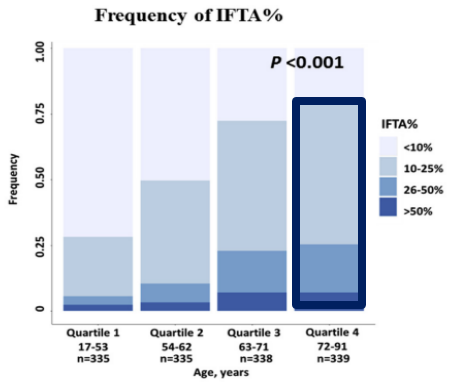
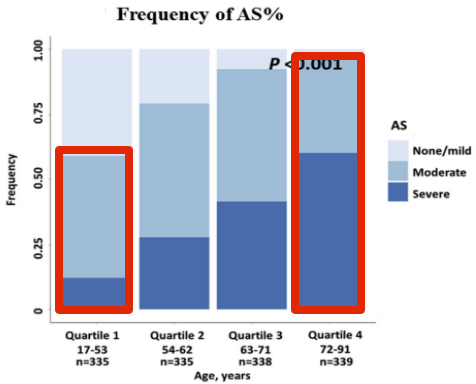
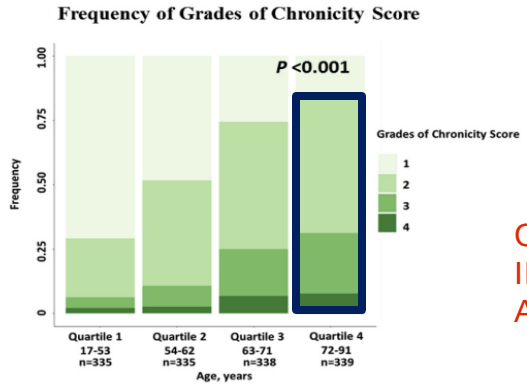
GS





AS





1,347 subjects aged 17-91 who underwent nephrectomy for any indication

The prevalence of advanced changes was higher in the oldest group of patients, but a subset had excellent kidney function and limited histologic changes

GS – glomerulosclerosis
IFTA – interstistial fibrosis/tubular atrophy
AS – arterial sclerosis/arteriosclerosis

Li et. Am J Kidney Dis 2020

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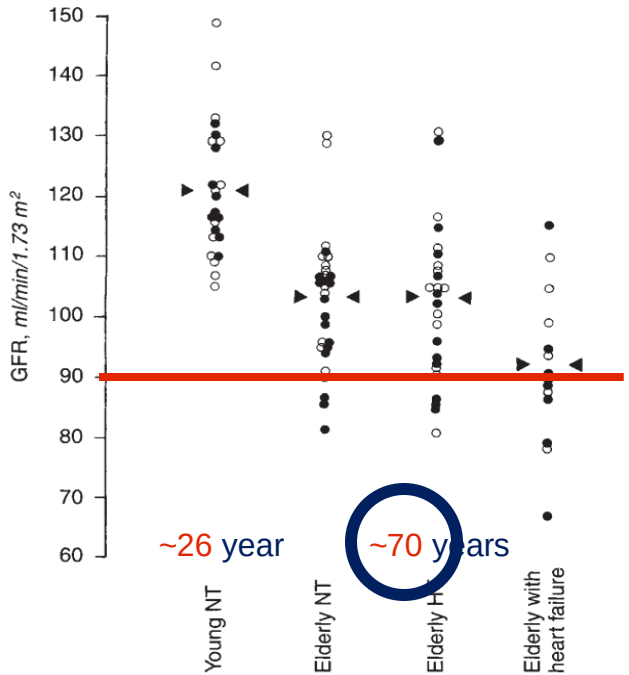
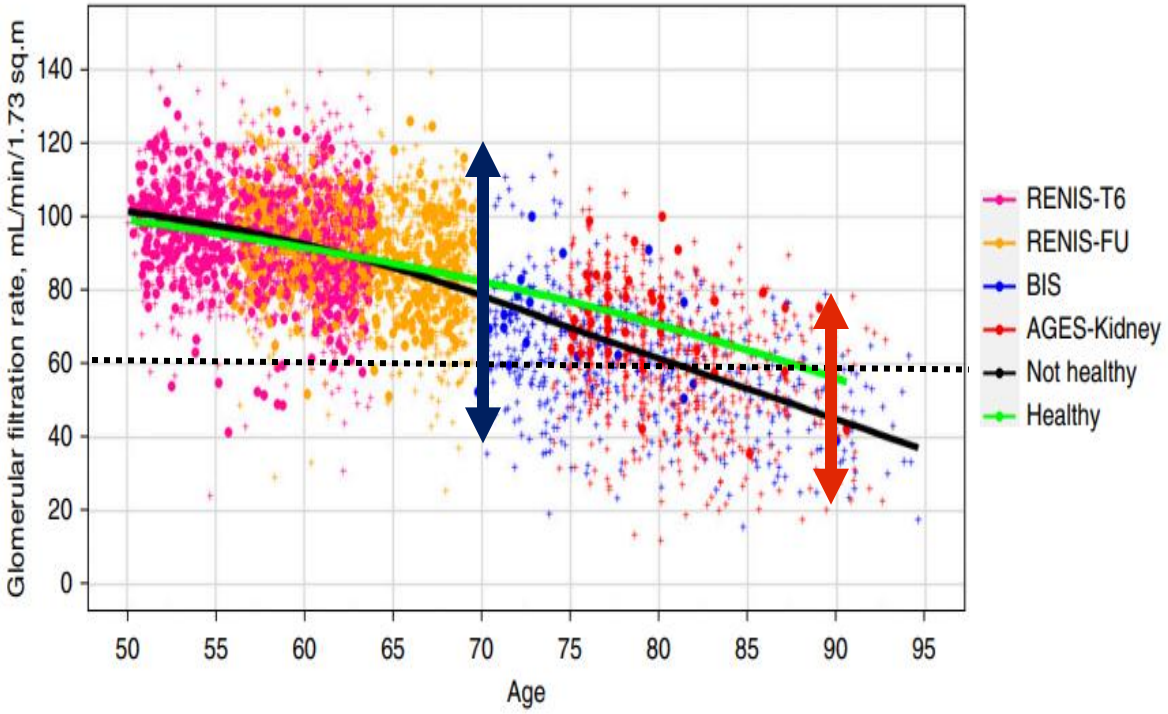
Glomerular Filtration Rate
(inulin clearance)



- male
- female

Fliser et al. Kidney Int 1997

Ageing and the kidneys



Association between mGFR, age, and health in persons aged 50-97 years (iohexol clearance measurements in 3 European population-based cohorts)

Healthy person were defined as having no major chronic disease or risk factors for CKD and all others as unhealthy

Eriksen et al. J Am Soc Nephrol 2020

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Age, Gene, Environment Susceptibility – Reykjavik Study

Cross-sectional analysis of a sub-study of a prospective cohort

mGFR (plasma clearance of iohexol) and UACR in 805 individuals

	Reykjavik Study (midlife)	AGES-II-Reykjavik (late life)	*P*
Age (y)[a]	51 [47-55]	80 [77-83]	<0.001
Male sex[a]	355 (44.1)	355 (44.1)	
mGFR (mL/min/1.73 m^2)[a]	—	62.4 ± 16.5	
Creatinine (mg/dL)	0.9 ± 0.2	1.0 ± 0.4	<0.001
eGFR (mL/min/1.73 m^2)	85.5 ± 12.5	65.7 ± 17.0	<0.001
Urinary ACR (mg/g)	—	8.0 [5.4-16.5]	
Diabetes	12 (1.6)	90 (11.8)	<0.001
Smoking			<0.001
Never	318 (41.7)	291 (39.1)	
Past	216 (28.4)	411 (55.2)	
Current	228 (29.9)	43 (5.8)	
Obesity	76 (10.0)	170 (22.3)	<0.001
Hyperlipidemia	358 (47.0)	476 (62.5)	<0.001
Cardiovascular disease	6 (0.8)	227 (29.8)	<0.001
Hypertension	197 (25.9)	684 (89.9)	<0.001
No CVD or vascular disease risk factors	118 (15.5)	11 (1.4)	<0.001
Systolic blood pressure (mm Hg)	129.4 ± 15.2	142.5 ± 20.3	<0.001
Diastolic blood pressure (mm Hg)	82.3 ± 9.1	69.6 ± 10.7	<0.001
On treatment for hypertension	115 (15.1)	564 (74.0)	<0.001
RAS blockers	—	308 (40.4)	
Other medications	—	256 (33.6)	
None	—	198 (26.0)	

Inker et al. Am J Kidney Dis 2015

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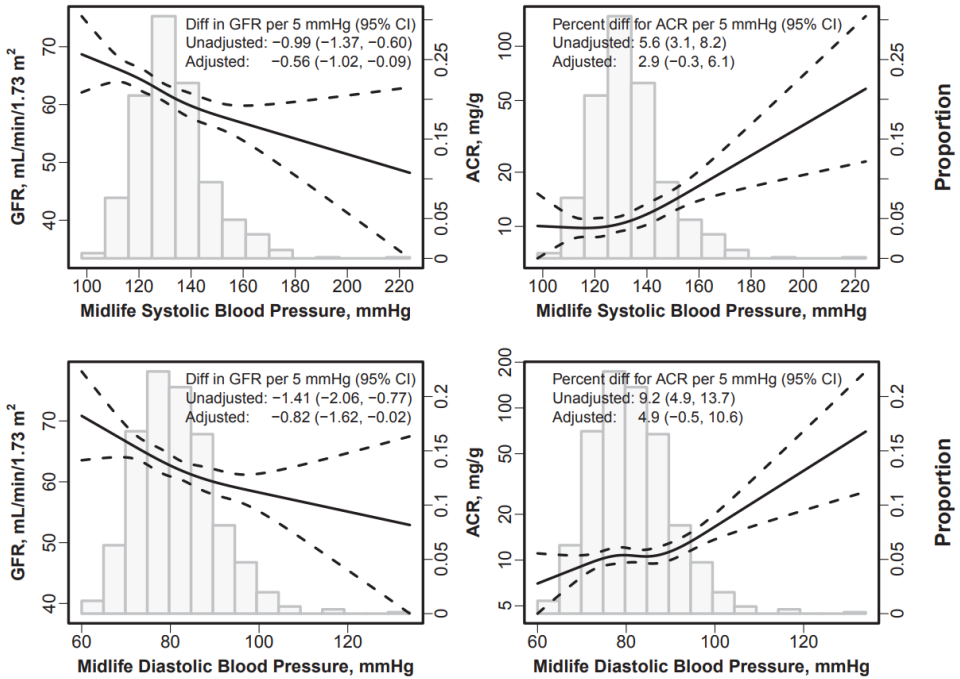
Age, Gene, Environment Susceptibility – Reykjavik Study



Factors other than advanced age may account for the high CKD prevalence in the elderly

Midlife factors such as (uncontrolled*) hypertension are potential contributing factors to late-life kidney dysfunction

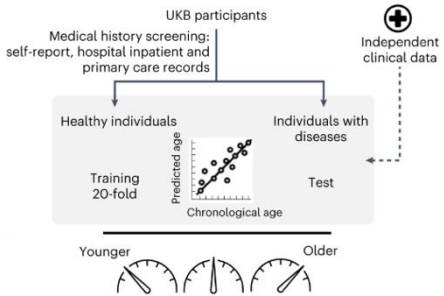
Inker et al. Am J Kidney Dis 2015

** speakers note*

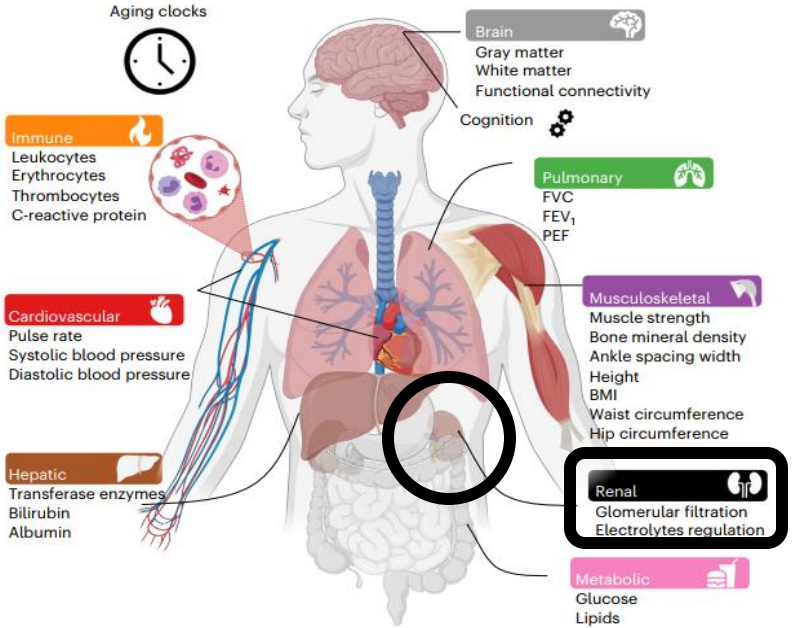
Kidney Health In Aging and Aged Societies
JSN/ERA Symposium
Collaboration with JSDT

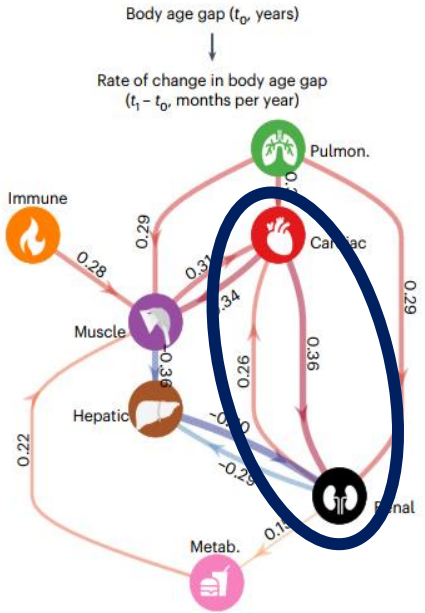
Ageing and the kidneys

Heterogeneous aging across multiple organ systems and prediction of chronic disease and mortality



multi-organ aging network



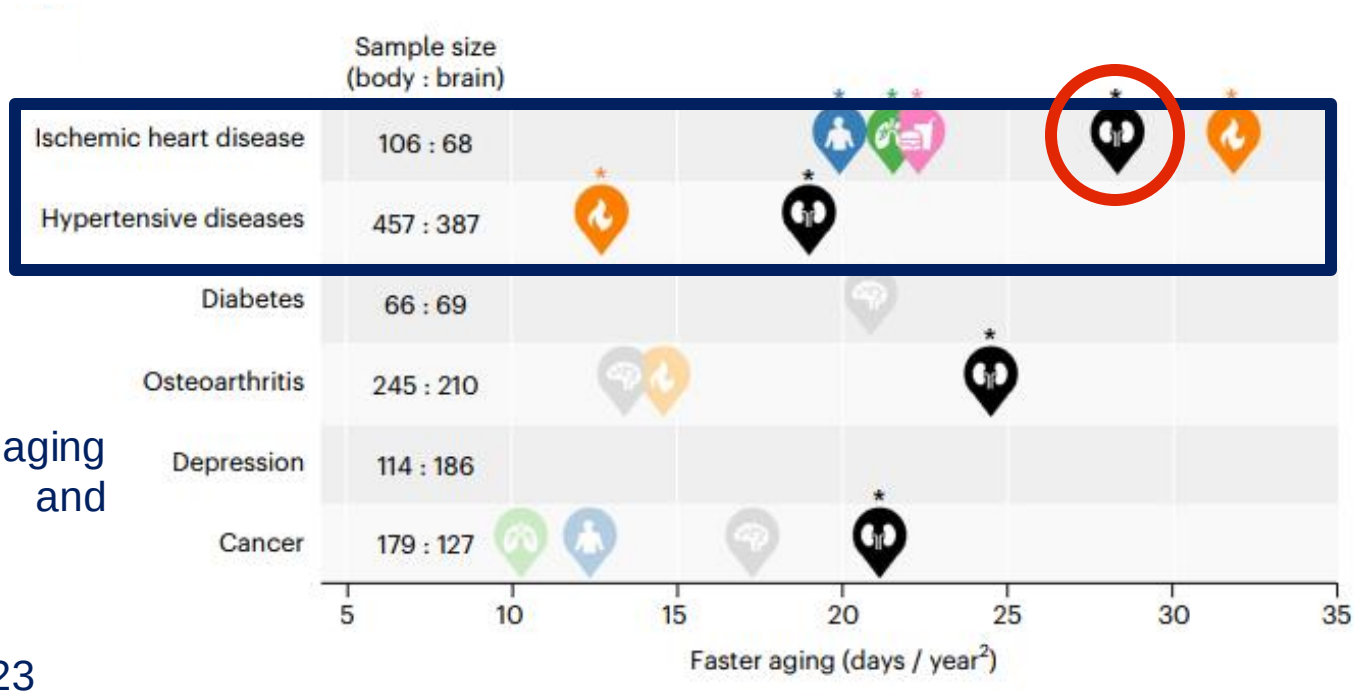


n = 143,423

Tian et al. Nat Med 2023

Ageing and the kidneys

Heterogeneous aging across multiple organ systems and prediction of chronic disease and mortality



Associations between aging and disease effects and progression (age gap)

n = 143,423

Tian et al. Nat Med 2023

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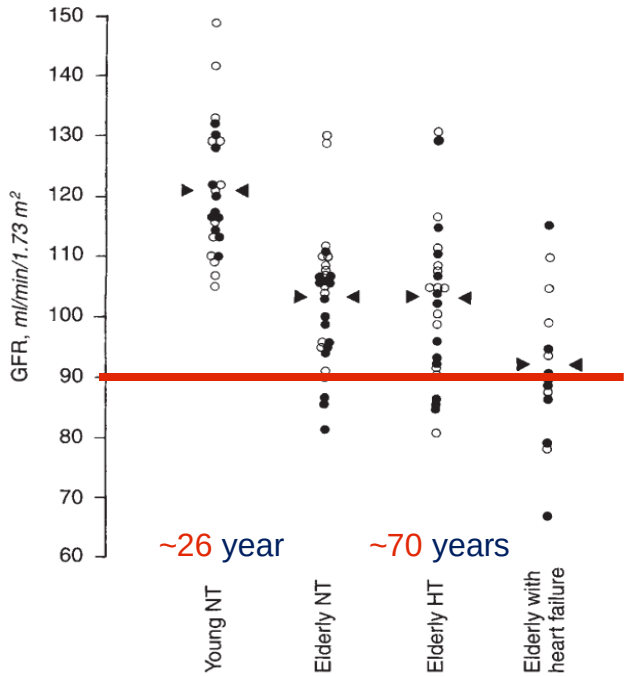
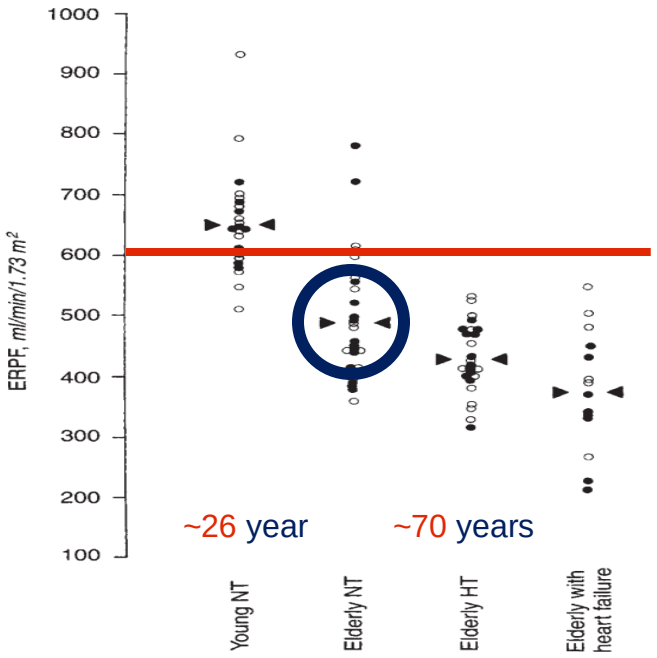
Glomerular Filtration Rate
(inulin clearance)



Efective Renal Plasma Flow
(PAH-clearance)



○ male
● female

Fliser et al. Kidney Int 1997

Ageing and the kidneys

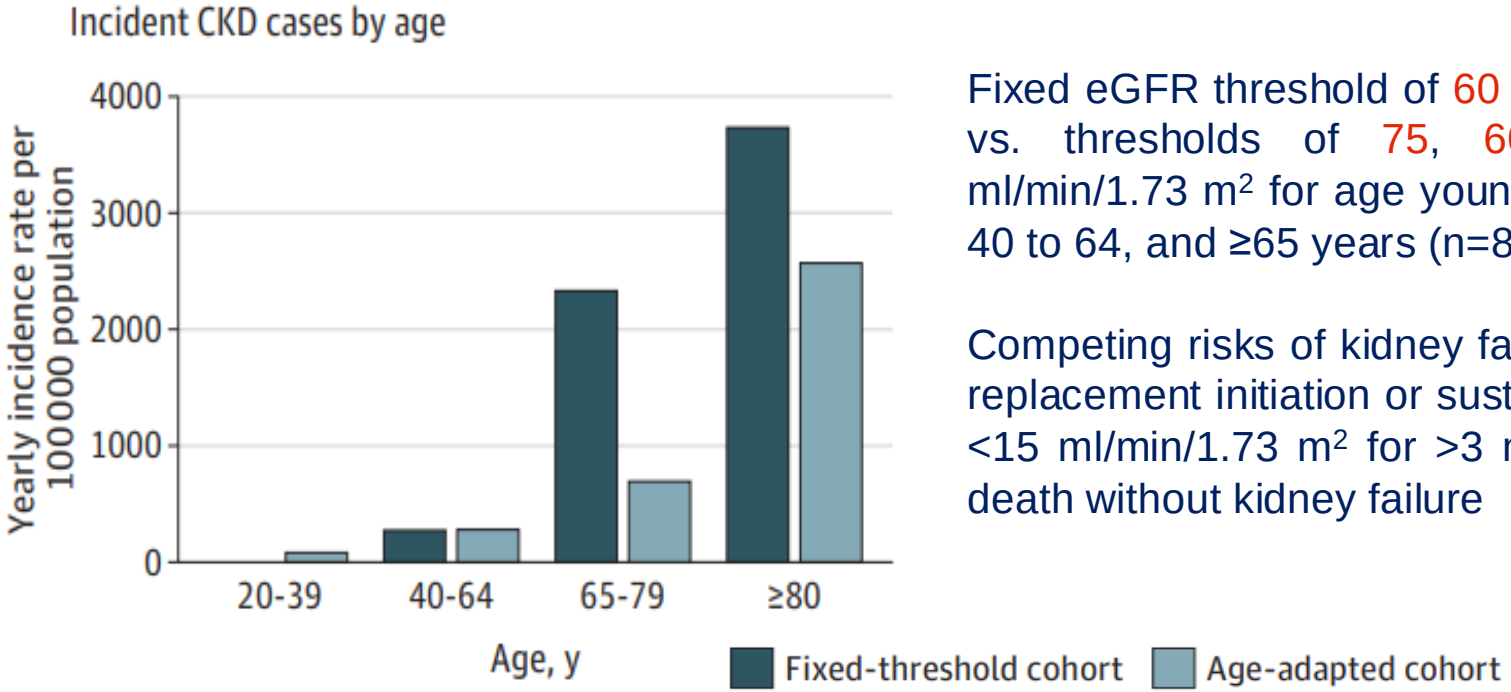
	Young healthy (N = 24)	Elderly healthy (N = 29)	Elderly hypertensive (N = 25)	Elderly with heart failure (N = 14)
P_{Na} *mmol/liter*	140 ± 1[a]	140 ± 2[a]	139 ± 2[a]	139 ± 2[a]
P_{Cl} *mmol/liter*	102 ± 3[a]	102 ± 3[a]	101 ± 3[a]	101 ± 4[a]
P_{K} *mmol/liter*	3.9 ± 0.3[a]	4.0 ± 0.3[a]	4.0 ± 0.3[a]	4.2 ± 0.4[a]
FE_{Na} %	0.8 ± 0.2[a]	0.9 ± 0.3[a]	0.9 ± 0.3[a]	1.1 ± 0.5[a]
C_{Li} *ml/min*	27 ± 12	14 ± 7[a]	15 ± 7[a]	12 ± 5[a]
FPR_{Na} %	77 ± 9	87 ± 6[a]	86 ± 7[a]	87 ± 5[a]
FDR_{Na} %	96 ± 2	92 ± 6[a]	93 ± 5[a]	89 ± 7[a]
PRA *ng AI/ml/hr*	0.75 ± 0.36	0.46 ± 0.46[a]	0.35 ± 0.27[a]	0.39 ± 0.20[a]

	Young healthy (N = 24)	Elderly healthy (N = 29)	Elderly hypertensive (N = 25)	Elderly with heart failure (N = 14)
P_{Ca} *mmol/liter*	2.31 ± 0.14[a]	2.30 ± 0.09[a]	2.32 ± 0.10[a]	2.39 ± 0.08
P_{P} *mmol/liter*	1.18 ± 0.13	1.08 ± 0.15[a]	0.98 ± 0.12[b]	1.02 ± 0.18[ab]
PTH *pmol/liter*	2.8 ± 1.1	4.4 ± 1.4[a]	5.0 ± 1.4[a]	6.6 ± 4.2[a]
25-(OH)D_3 *nmol/liter*	112 ± 52	75 ± 31[a]	77 ± 35[a]	65 ± 32[a]
Calcitriol *pg/ml*	57 ± 13[a]	53 ± 9[ab]	50 ± 11[b]	44 ± 12
U_{Ca} *mmol/24 hr*	4.6 ± 2.0[a]	4.3 ± 2.2[a]	3.6 ± 2.1[a]	3.3 ± 2.4[a]
U_{P} *mmol/24 hr*	28 ± 8[a]	25 ± 9[a]	24 ± 7[a]	26 ± 8[a]
U_{Py} *µg/g creatinine*	177 ± 34	253 ± 70[a]	243 ± 54[a]	253 ± 60[a]
U_{DPy} *µg/g creatinine*	35 ± 8	47 ± 14[a]	45 ± 16[a]	47 ± 18[a]

Fliser et al. Kidney Int 1997

Ageing and the kidneys

Accounting for age in the definition of CKD



Fixed eGFR threshold of 60 (n=127,132) vs. thresholds of 75, 60, and 45 ml/min/1.73 m^2 for age younger than 40, 40 to 64, and ≥65 years (n=81,209)

Competing risks of kidney failure (kidney replacement initiation or sustained eGFR <15 ml/min/1.73 m^2 for >3 months) and death without kidney failure

Liu et al. JAMA Internal Med 2021

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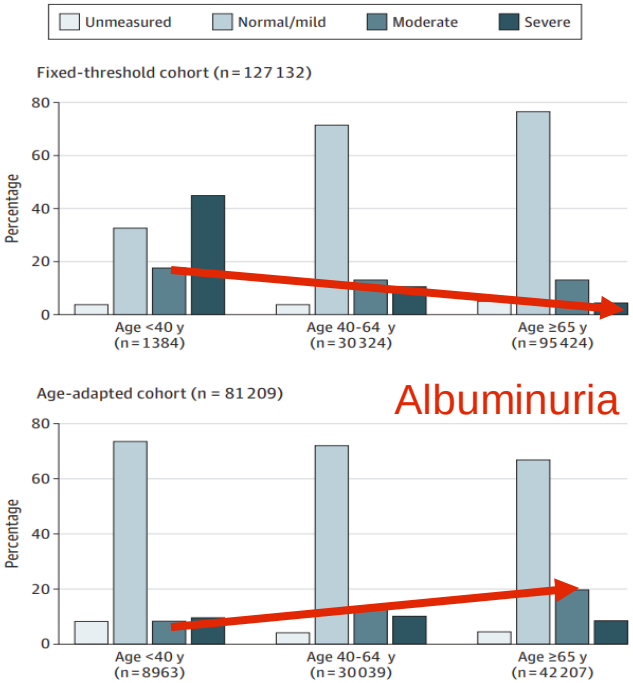

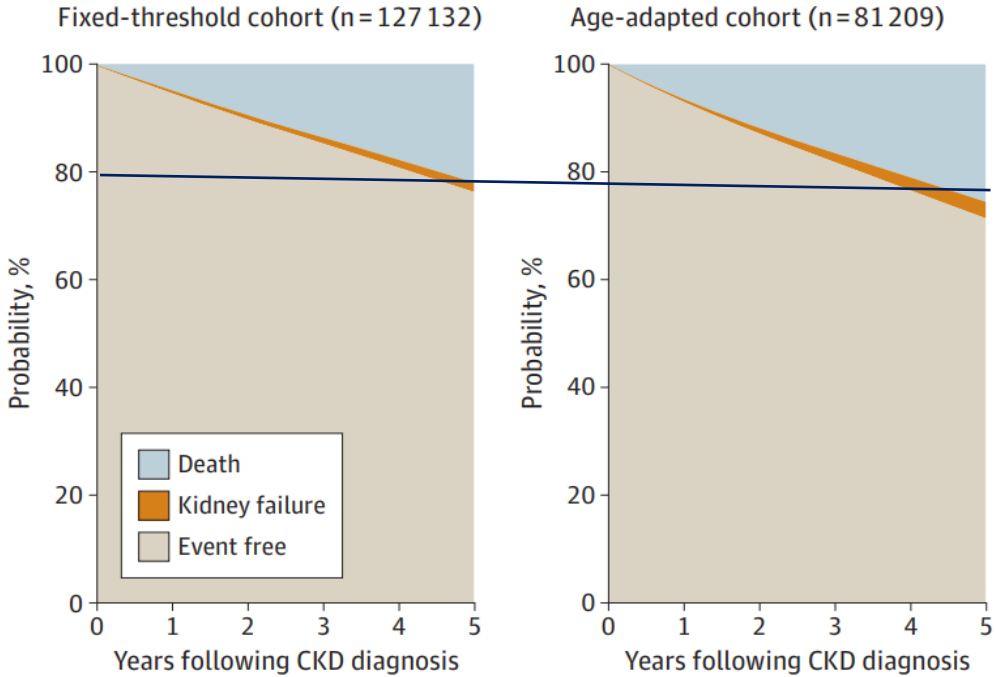

Liu et al. JAMA Internal Med 2021

Ageing and the kidneys

Accounting for age in the definition of CKD

Current eGFR criteria for CKD that do not account for the age-related eGFR decline may result in overestimation of the CKD burden in an aging population

The excess incidence of CKD with current eGFR criteria is largely explained by elderly people who have an eGFR of 45 to 59 ml/min/1.73 m^2 and normal/mild albuminuria. Their risks of kidney failure and death are similar in magnitude to people of the same age who do not have CKD. An eGFR of 45-59 ml/min/1.73 m^2 without albuminuria may not have implications for kidney health

Liu et al. JAMA Internal Med 2021

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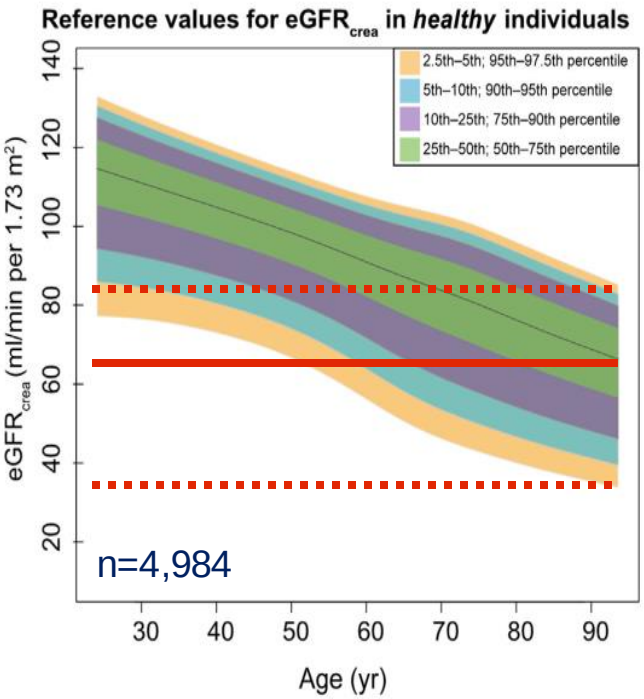

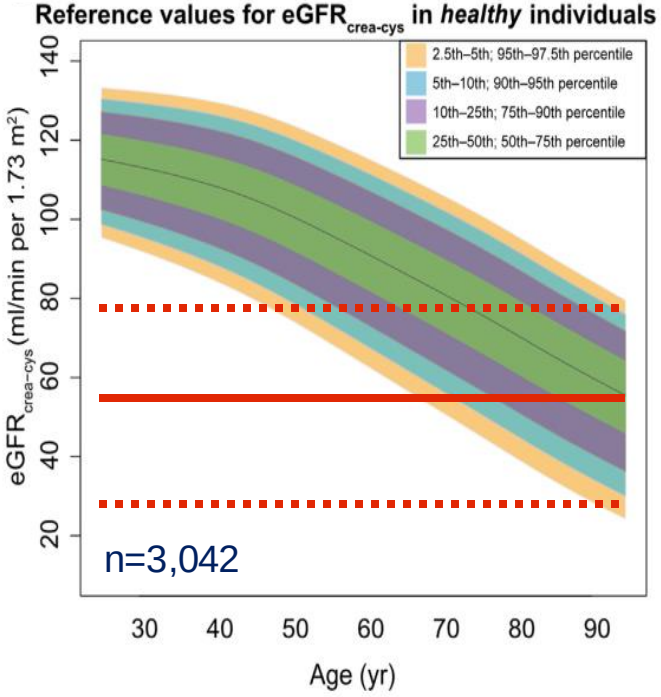

KORA 3
KORA 4
AugUR
DIACORE

n=12,000
25-95 years

Herold et al. Kidney Int 2024

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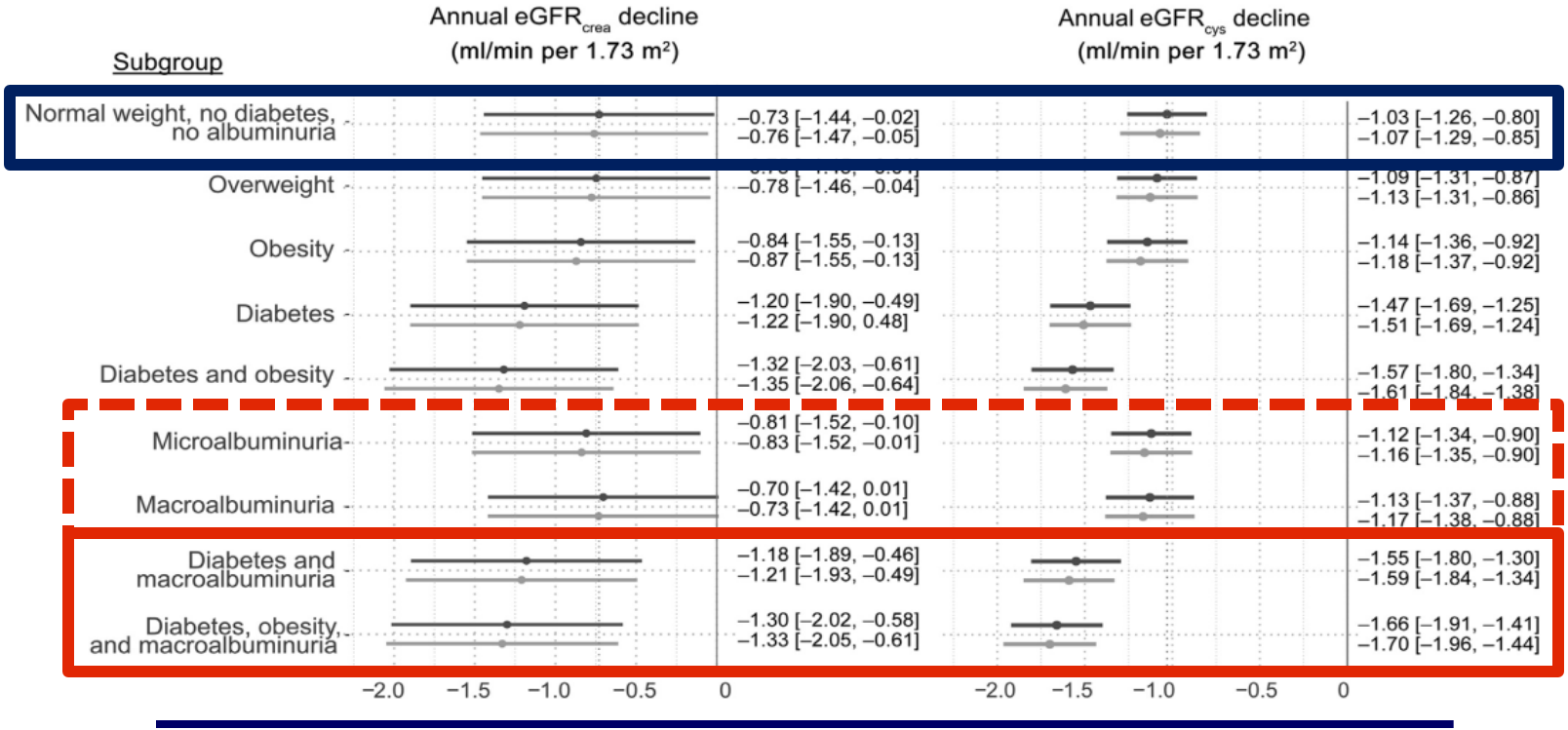

Herold et al. Kidney Int 2024

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Ageing and the kidneys

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	uDKK3/Cr **0 <30** pg/mg (n=1,147)	uDKK3/Cr **≥30 to <400** pg/mg (n=132)	uDKK3/Cr **≥400 pg/mg** (n=37)	P
Age (years)	63.6 ± 4.0	63.8 ± 4.1	64.0 ± 3.9	0.68
Women (n, %)	621 (54%)	35 (27%)	10 (27%)	<0.001
BMI (kg/m²)	27.2 (4.1)	27.1 (3.8)	27.4 (4.0)	0.89
Systolic BP (mmHg)	**130** (17)	**132** (17)	**139** (16)	0.005
Diastolic BP (mmHg)	**82** (9)	**83** (10)	**87** (10)	0.002
Antihypertensives (n, %)	360 (31%)	42 (32%)	13 (35%)	0.88
Current smoker (n, %)	147 (13%)	24 (18%)	6 (16%)	0.20
Use of NSAIDs (n, %)	69 (6%)	7 (5%)	1 (3%)	0.67
HbA1c (%)	5.6 (0.4)	5.6 (0.3)	5.6 (0.3)	0.94
Diabetes mellitus (n, %)	24 (2%)	2 (2%)	1 (3%)	0.87
CVD (n, %)	51 (4%)	10 (8%)	3 (8%)	0.19
UACr (mg/mmol)	0.34 [0.10 to 0.58]	0.33 [0.10 to 0.65]	0.36 [0.10 to 0.57]	0.41
GFR (ml/min/1.73 m²)	**89.0** [14.4]	**90.0** [14.5]	**89.2** [15.6]	0.75
Annual GFR change (ml/min/1.73 m²/year)	**-1.26 (0.60)**	**-1.68 (1.82)**	**-2.22 (2.87)**	**0.001**
uDKK3/Cr (pg/mg)	**0**	**129 [80 to 248]**	**763 [523 to 1,255]**	**0.001**

RENIS study (n=1,316)
Tromsø/Norway

Association between urinary DKK3 and age-associated decline in mGFR in persons aged 50-97 years assessed with iohexol clearance

Healthy person were defined as having no major chronic disease or risk factors for CKD and all others as unhealthy

Norvik et al. JSN/ERA 2024

Ageing and the kidneys

Nephrol Dial Transplant (2005) 20: 482–485
doi:10.1093/ndt/gfh710

Ren sanus in corpore sano: the myth of the inexorable decline of renal function with senescence

Danilo Fliser

Hannover Medical School, Hannover, Germany

Fliser et al. Nephrol Dial Transplant 2005

Julia "Hurricane" Hawkins
108 years old
2017 world record for women 100 or older:
100 meters in 39.62 seconds

„Age is an issue of mind over matter.
If you don´t mind, it doesn´t matter.“

Mark Twain