Welche Säugetiere entwickeln Krebs ?

Erkenntnisse aus (globalen) Zoo-Daten

Article

Cancer risk across mammals

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Orsolya Vincze[1,2,3,4], Fernando Colchero[5,6,7], Jean-Francois Lemaître[8], Dalia A. Conde[6,7,9], Samuel Pavard[10], Margaux Bieuville[10], Araxi O. Urrutia[11,12], Beata Ujvari[13], Amy M. Boddy[14], Carlo C. Maley[15], Frédéric Thomas[1] & Mathieu Giraudeau[1,2]

Cancer is a ubiquitous disease of metazoans, predicted to disproportionately affect larger, long-lived organisms owing to their greater number of cell divisions, and thus increased probability of somatic mutations[1,2]. While elevated cancer risk with larger body size and/or longevity has been documented within species[3–5], Peto's paradox indicates the apparent lack of such an association among taxa[6]. Yet, unequivocal empirical evidence for Peto's paradox is lacking, stemming from the difficulty of estimating cancer risk in non-model species. Here we build and analyse a database on cancer-related mortality using data on adult zoo mammals (110,148 individuals, 191 species) and map age-controlled cancer mortality to the mammalian tree of life. We demonstrate the universality and high frequency of oncogenic phenomena in mammals and reveal substantial differences in cancer mortality across major mammalian orders. We show that the phylogenetic distribution of cancer mortality is associated with diet, with carnivorous mammals (especially mammal-consuming ones) facing the highest cancer-related mortality. Moreover, we provide unequivocal evidence for the body size and longevity components of Peto's paradox by showing that cancer mortality risk is largely independent of both body mass and adult life expectancy across species. These results highlight the key role of life-history evolution in shaping cancer resistance and provide major advancements in the quest for natural anticancer defences.

Complex multicellular organisms are built of millions to quadrillions of cells, ultimately all being derived from a single cell, the zygote. During the course of the organisms' lifetime and owing to various mutational processes, cell lineages tend to accumulate mutations[7,8]. While the majority of mutations are harmless, some enable cells to escape cell cycle control, to grow and proliferate uncontrollably, resulting in cancer[9,10]. Cancer is a multistage process, where a set of mutations is required for both initiation and malignant progression. Given that every cell division carries a risk of generating mutations, organisms with large bodies (composed of more cells) and extended longevities (with a longer time to accumulate mutations) should be more likely to develop cancer[1,6,11,12]. Indeed, within humans[3,11] and dogs[4], larger individuals are more likely to develop cancer than smaller ones. Similarly, increasing age is one of the most potent carcinogenic factors in species in which cancer aetiology is well studied. Yet, while current evidence suggests that large body size and extended longevity result in increased cancer risk within species, this relationship may not hold across taxa[13].

Limited data available so far indicate that vertebrates do not face clear size-dependent cancer risks despite their size and longevity varying by orders of magnitude. This poses a logical challenge, first formulated by Sir Richard Peto[6,14]. He noted that although mice have approximately 1,000 times fewer cells and >30 times shorter lifespans than humans, their risk of carcinogenesis is not markedly different (coined as Peto's paradox)[5]. Peto's paradox is an evolutionary conundrum that has puzzled the scientific community and has led to lively debate regarding the evolution of anticancer mechanisms. It is often postulated that natural selection on large size or extended longevity is inherently inseparable from the evolution of anticancer defences. Knowledge gained from investigating Peto's paradox might thus largely contribute to our knowledge on natural anticancer mechanisms that could potentially be harnessed for medical use. Further, understanding cross-species variation of cancer vulnerability is an important next step in animal health and welfare. While a few studies aimed to establish cross-species variation in cancer risk[15,16], most estimates and analyses have considerable limitations. These include small cross- or within-species sample sizes[1,6,17], lacking information on the age distribution of cancer[15–17], data heterogeneity (for example, biases due to domestication[17] or combining data from multiple taxa[17,18]) or lack of control for phylogenetic relatedness among species[17]. Moreover, the effect of longevity was generally tested using the much-debated metric

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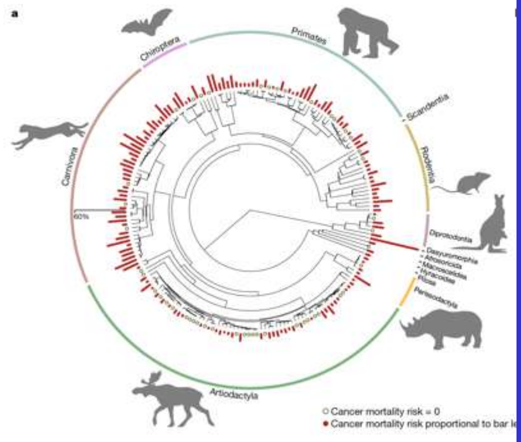

Marcus Clauss

Zürich, Biologie und Erkrankungen der Wildtiere 13.12.2022

University of Zurich[UZH]

Clinic of Zoo Animals, Exotic Pets and Wildlife

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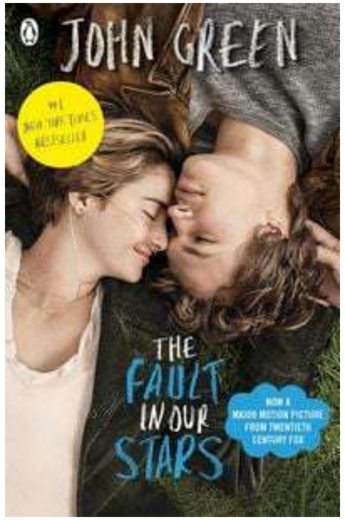

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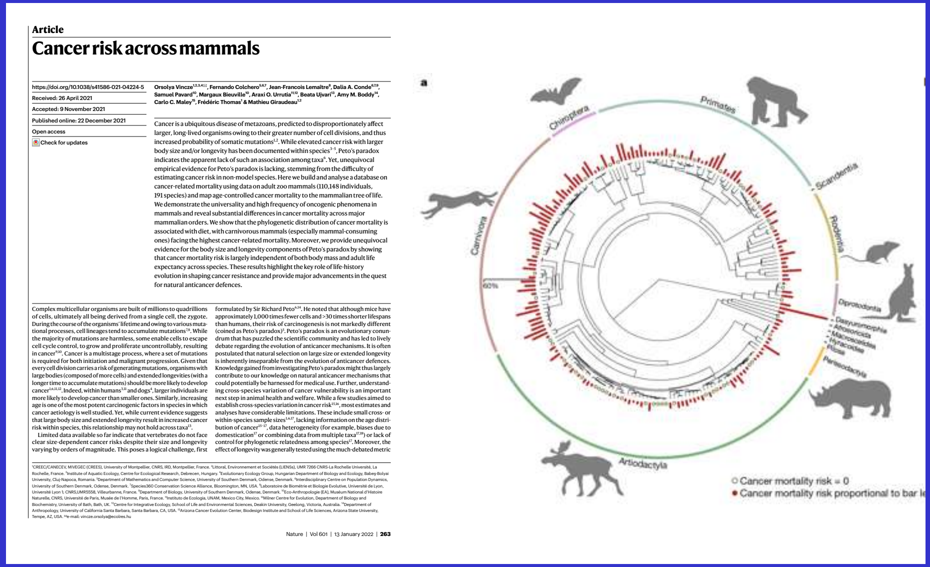
Which mammals get cancer ?

Insights from (global) zoo data



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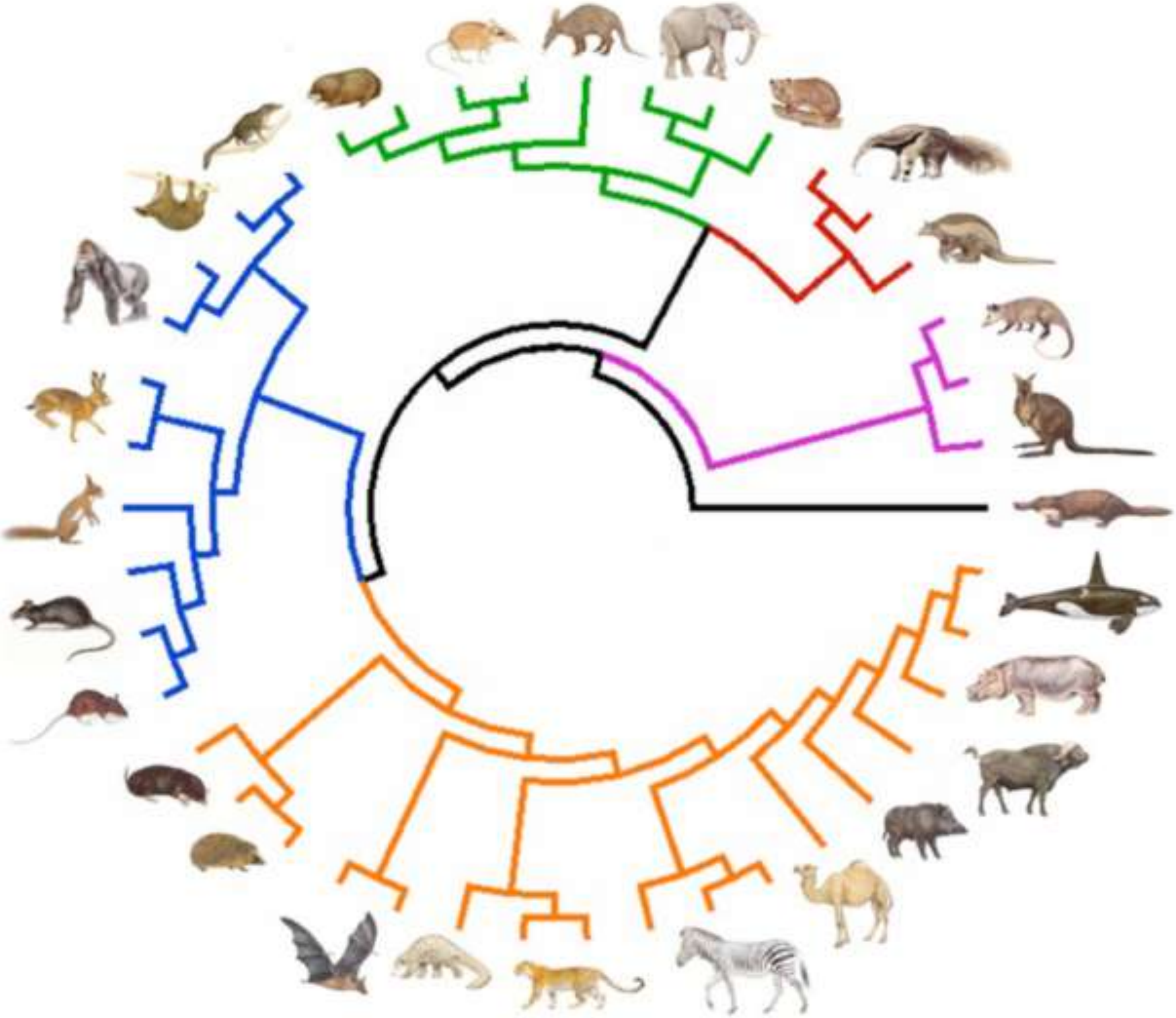
“marsupials are tumour-heaven”


DYRLÆGE
Mads F. Bertelsen
ZOO
KØBENHAVN

*“you have
to die
of
something”*

“better diets lead to more cancer”

Comparative approaches



Mechanisms of cancer resistance in long-lived mammals

NATURE REVIEWS | CANCER
VOLUME 18 | JULY 2018 | 439

Andrei Seluanov, Vadim N. Gladyshev, Jan Vijg and Vera Gorbunova

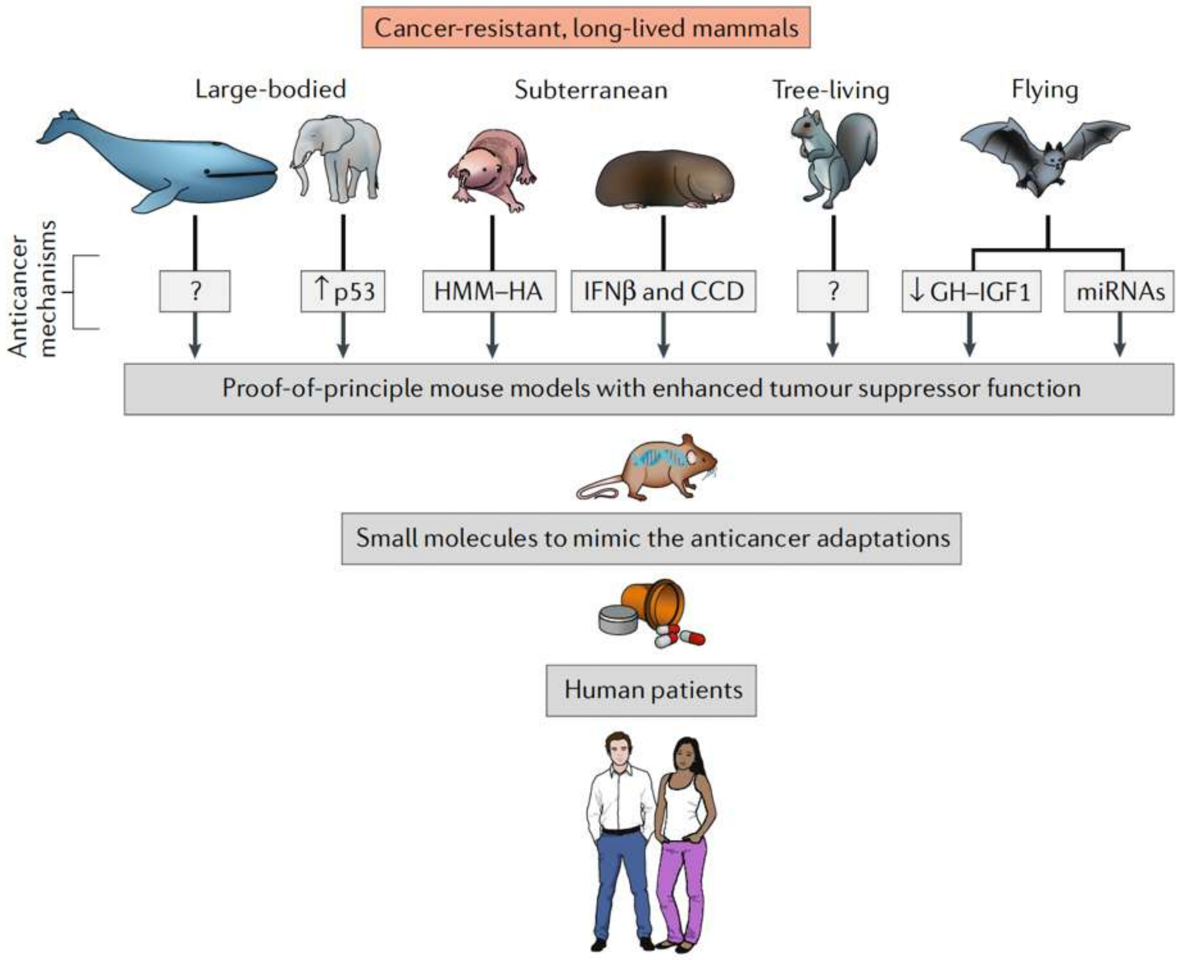


Fig. 5 | **Developing anticancer treatments based on naturally evolved cancer resistance.** Cancer

OPINION

Mechanisms of cancer resistance in long-lived mammals

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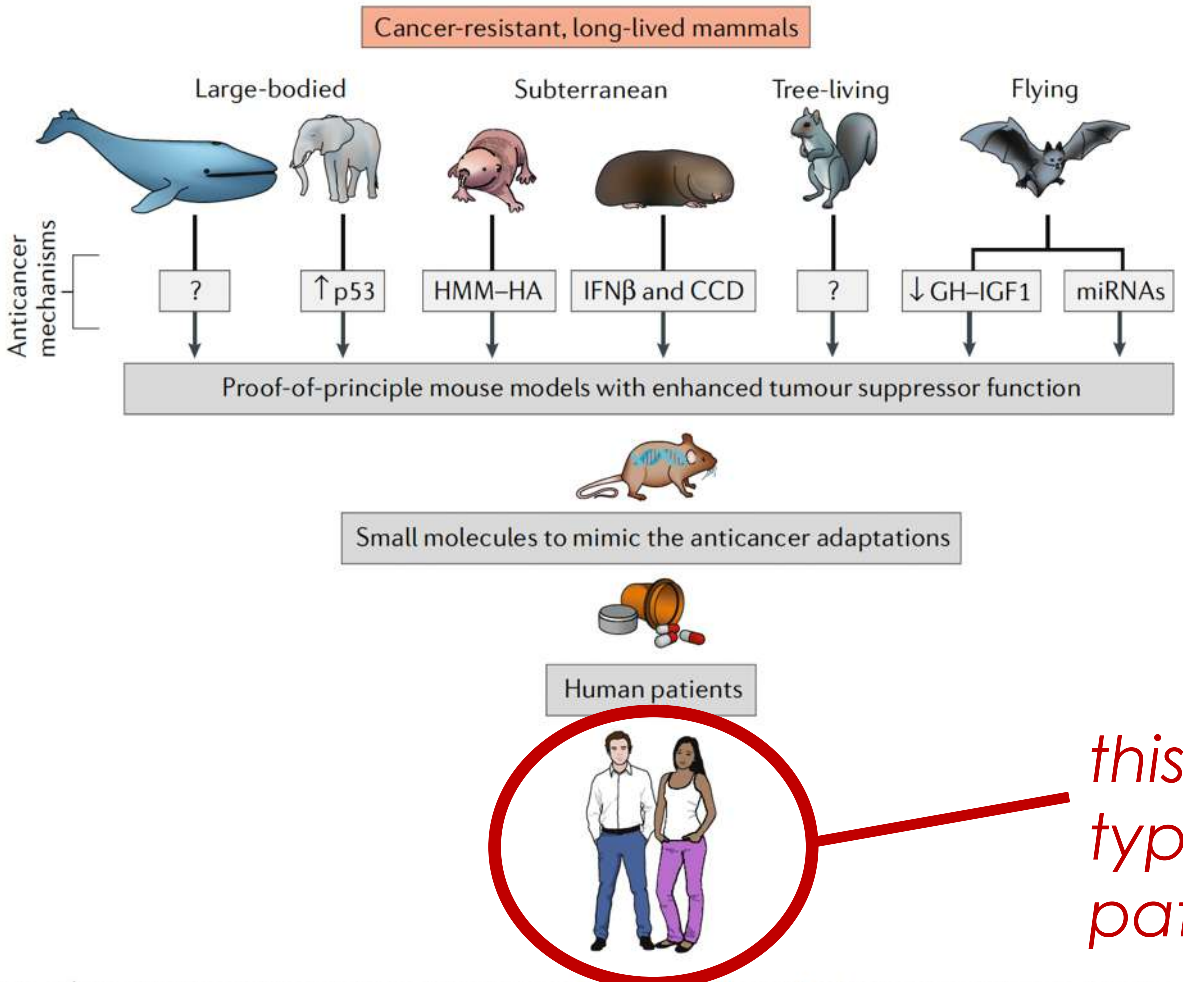
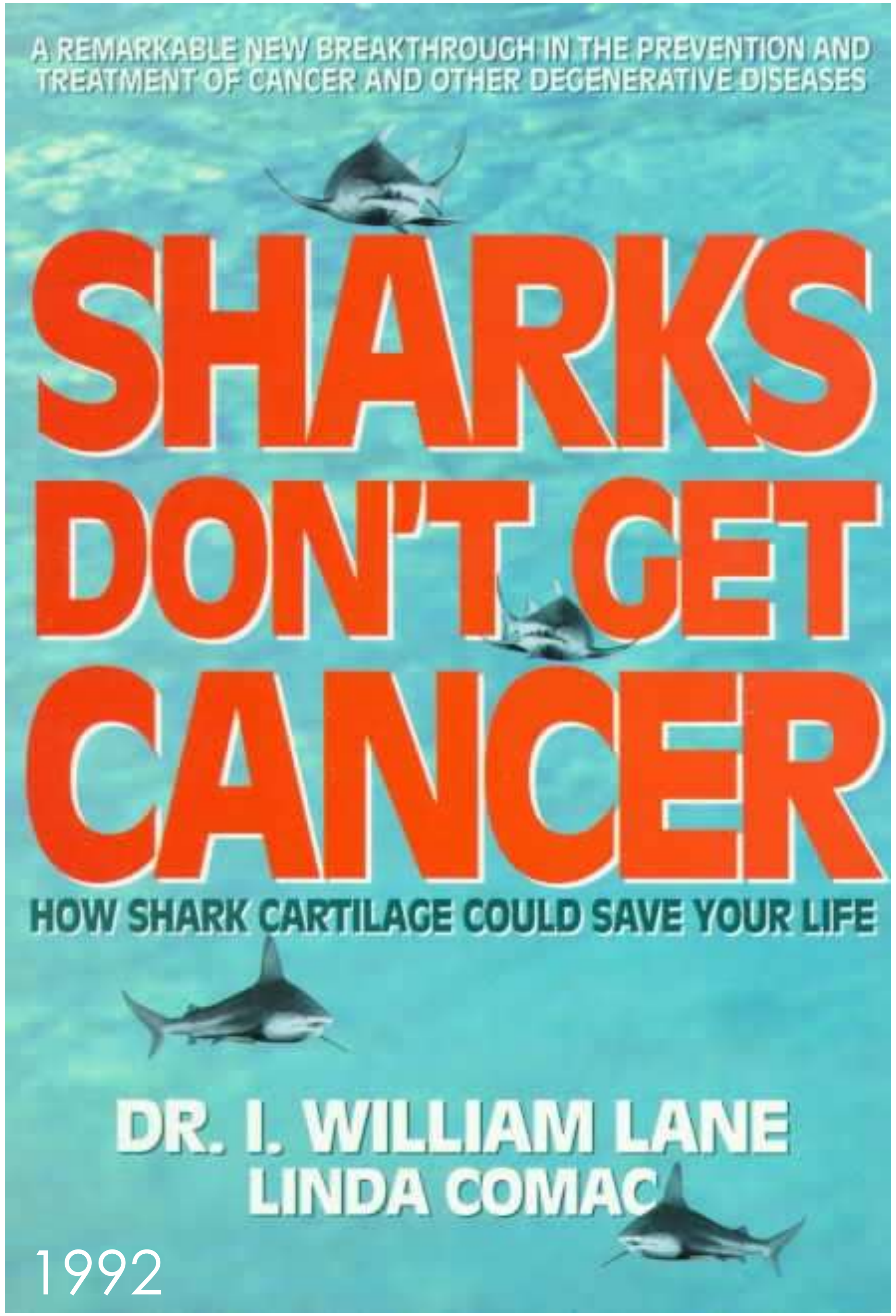


this is not what typical cancer patients look like

Fig. 5 | **Developing anticancer treatments based on naturally evolved cancer resistance.** Cancer



1992

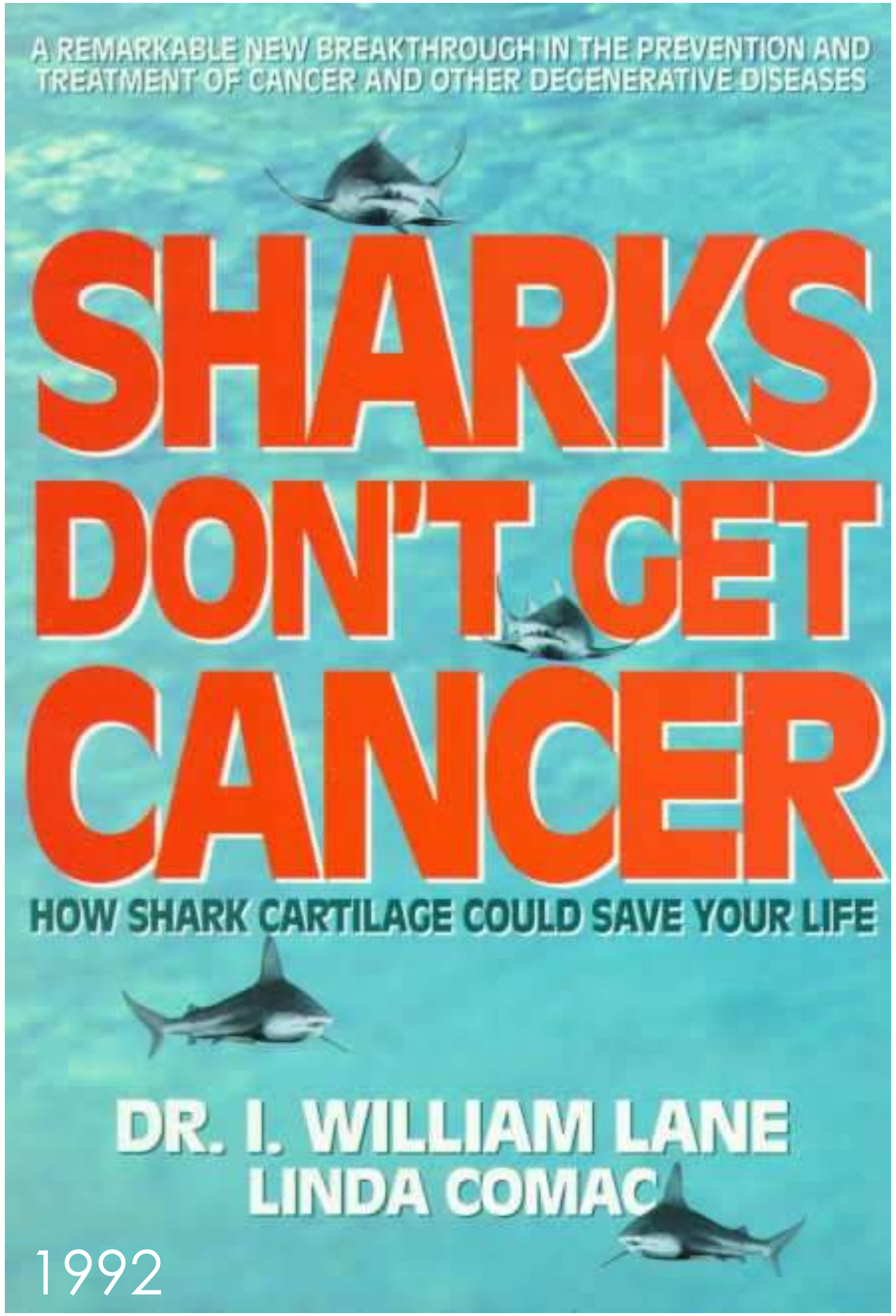
October 2001

Biol. Pharm. Bull. **24**(10) 1097—1101 (2001)

Review

Shark Cartilage as Source of Antiangiogenic Compounds: From Basic to Clinical Research

Raimundo Pajón González,*[,a] Albert Leyva,[b] and Manoel Odorico Moraes[a]

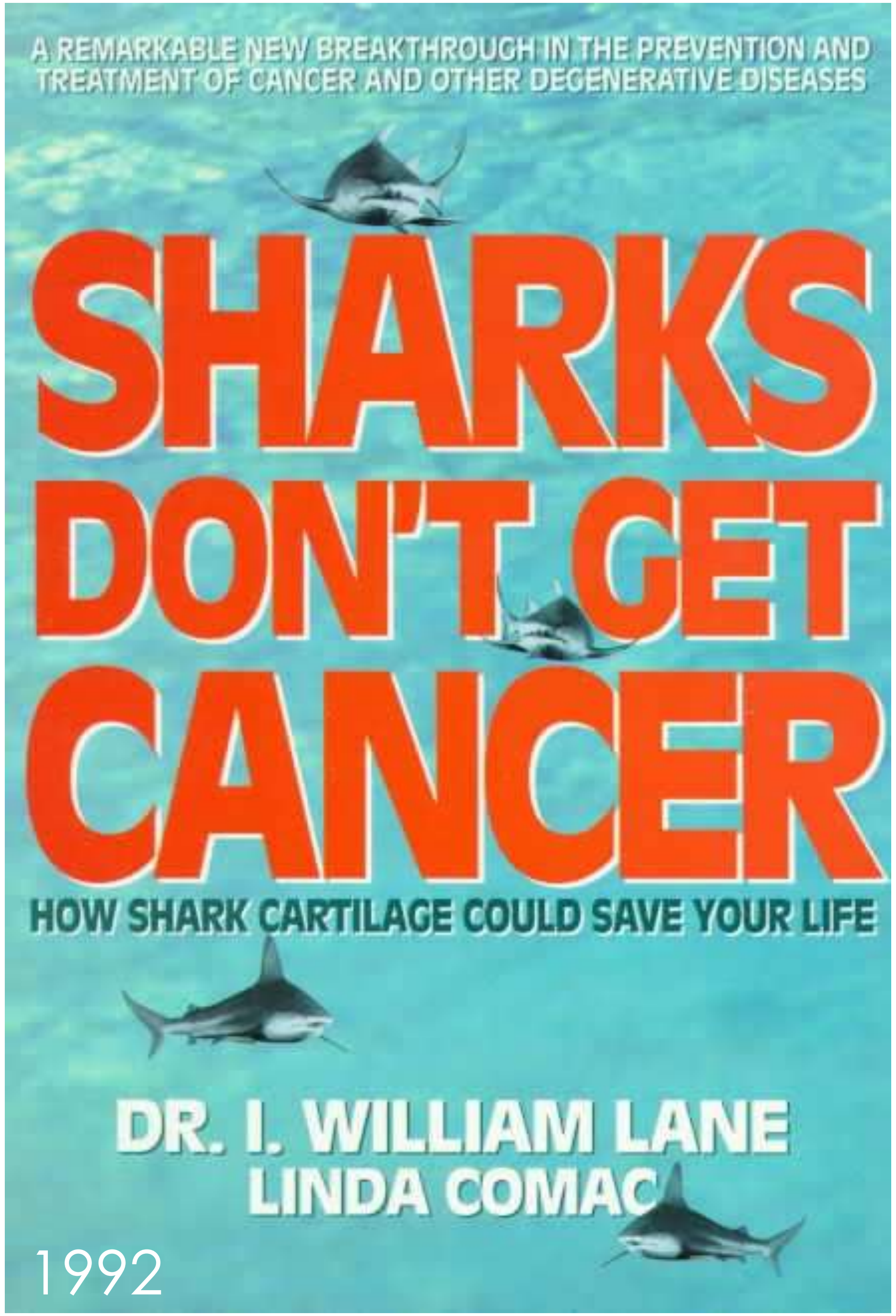


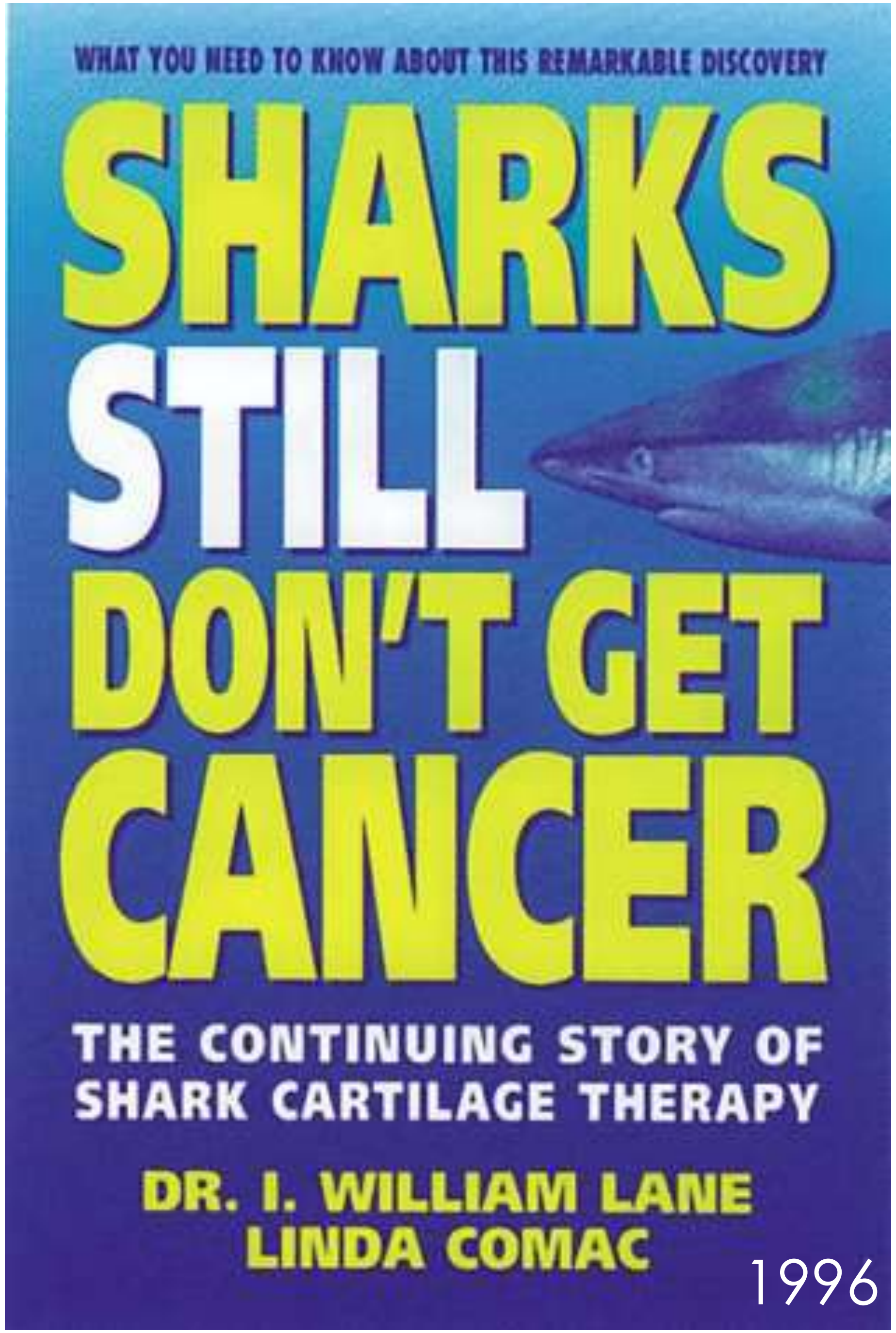
[CANCER RESEARCH 64, 8485–8491, December 1, 2004]

Review

Shark Cartilage, Cancer and the Growing Threat of Pseudoscience

Gary K. Ostrander,[1] Keith C. Cheng,[2] Jeffrey C. Wolf,[3] and Marilyn J. Wolfe[3]


A REMARKABLE NEW BREAKTHROUGH IN THE PREVENTION AND TREATMENT OF CANCER AND OTHER DEGENERATIVE DISEASES
SHARKS DON'T GET CANCER
HOW SHARK CARTILAGE COULD SAVE YOUR LIFE
DR. I. WILLIAM LANE
LINDA COMAC
1992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THE CONTINUING STORY OF SHARK CARTILAGE THERAPY
DR. I. WILLIAM LANE
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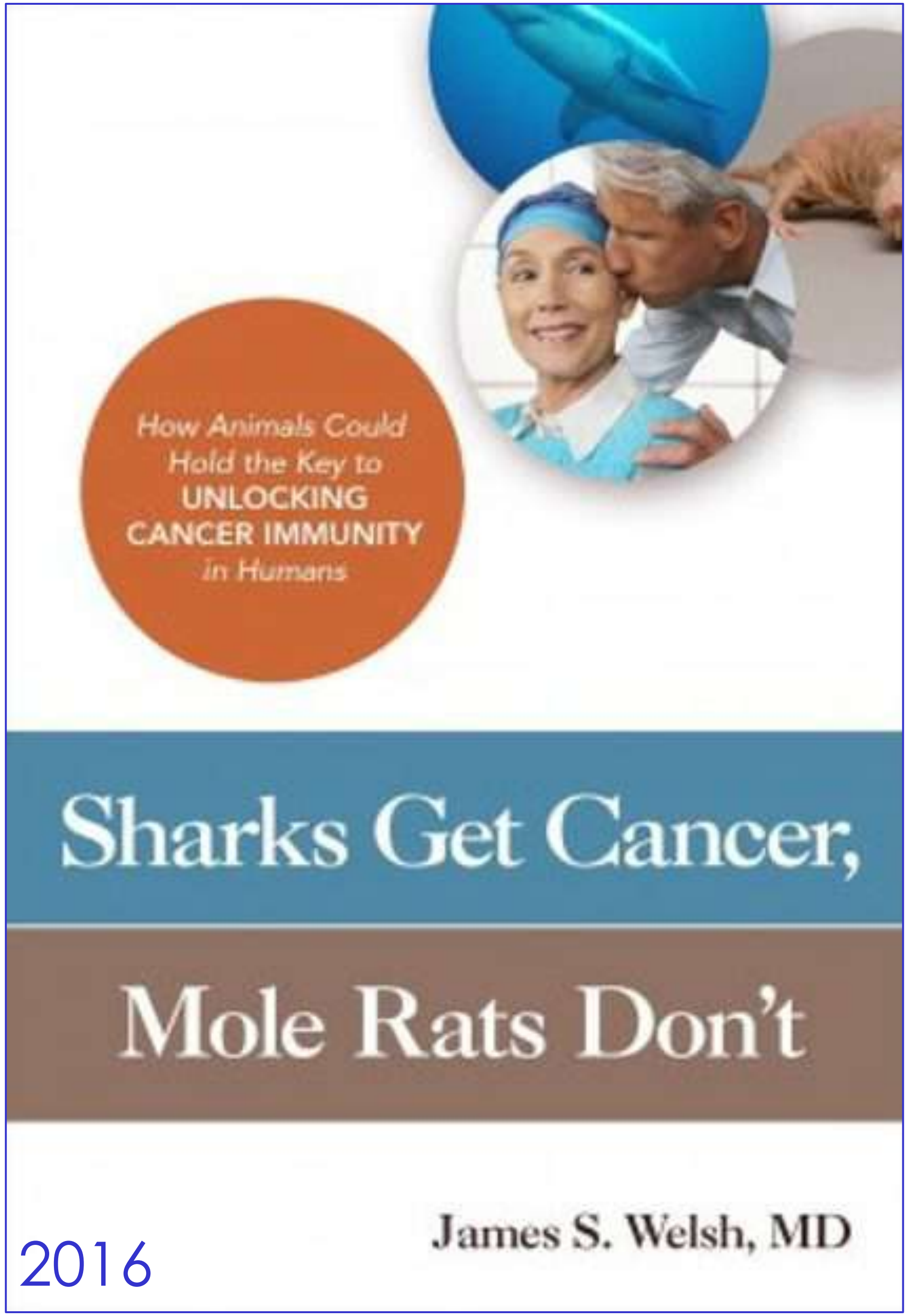
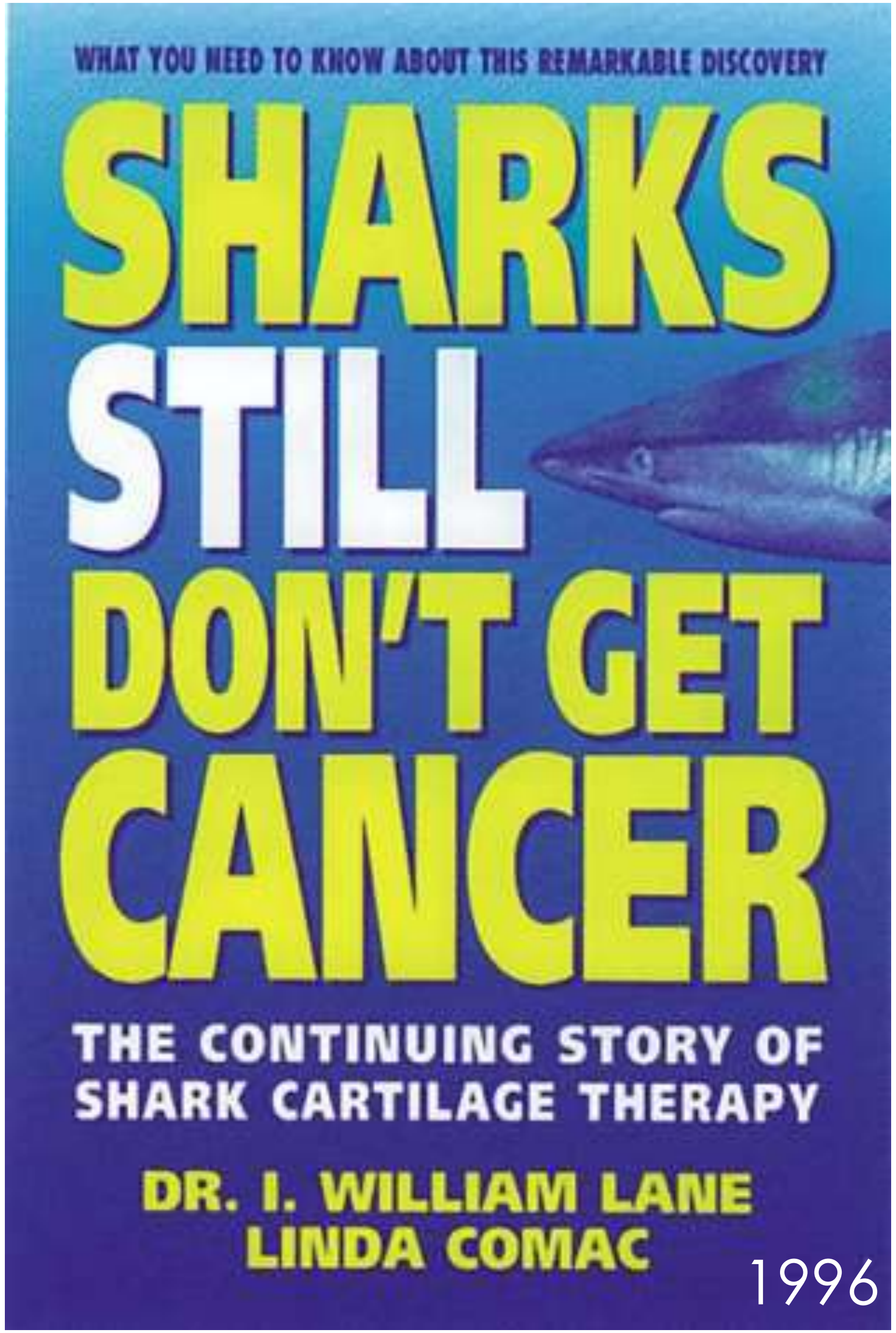
1996


How Animals Could Hold the Key to UNLOCKING CANCER IMMUNITY in Humans
Sharks Get Cancer,
Mole Rats Don't
James S. Welsh, MD

2016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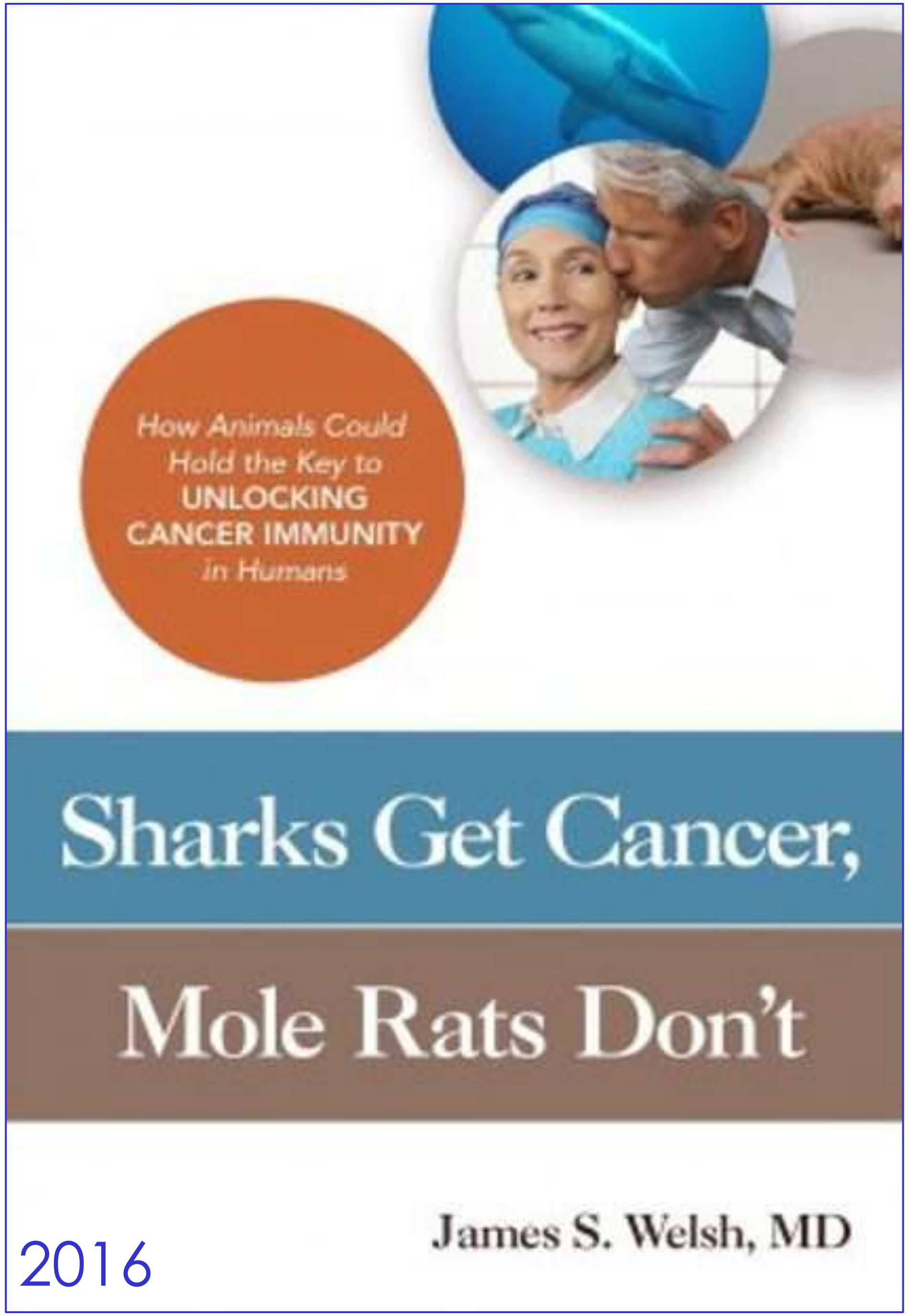
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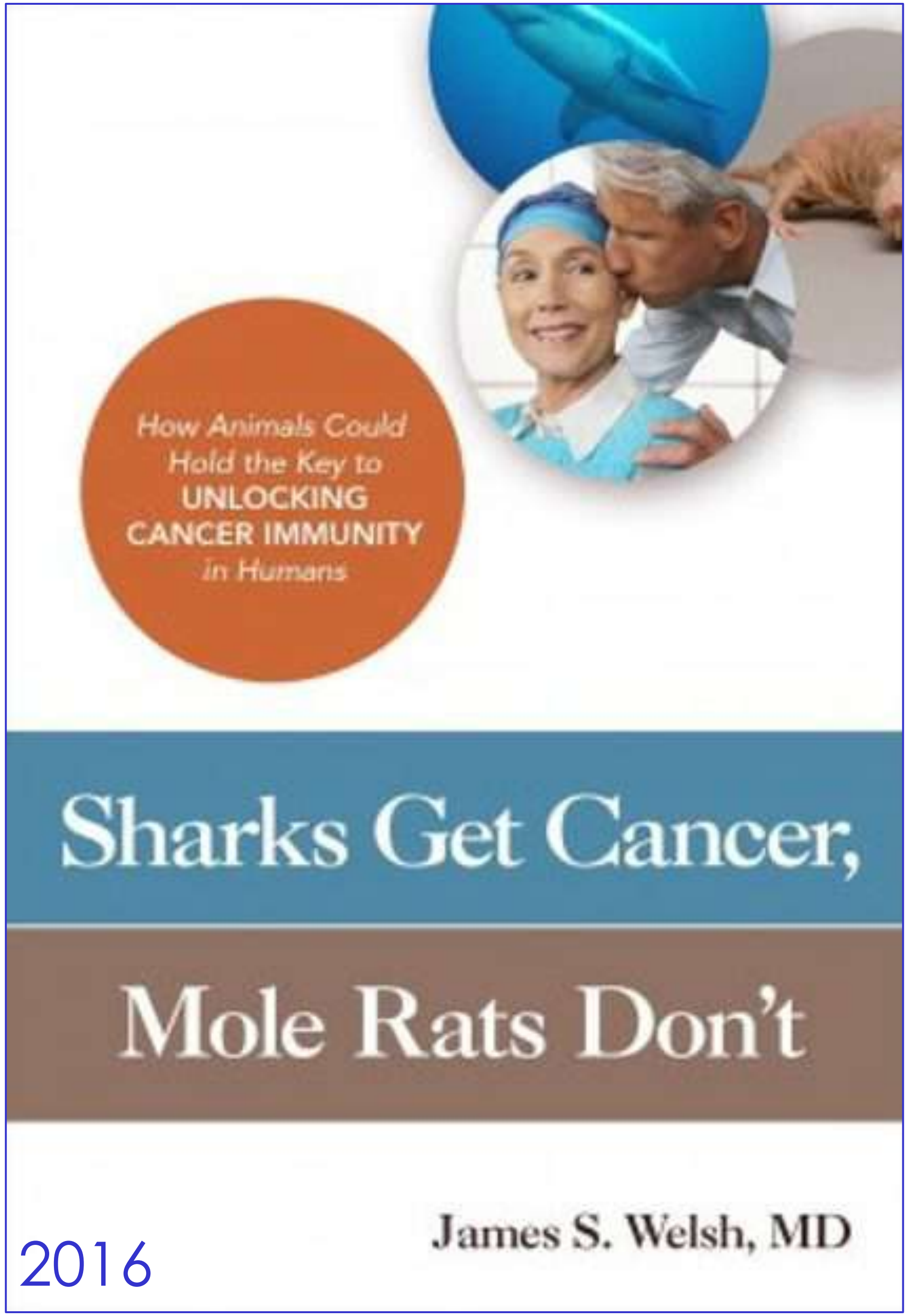


2016

THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Biological Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2017, Vol. 72, No. 1, 38–43
doi:10.1093/gerona/glw047
Advance Access publication April 29, 2016

OXFORD

Brief Report

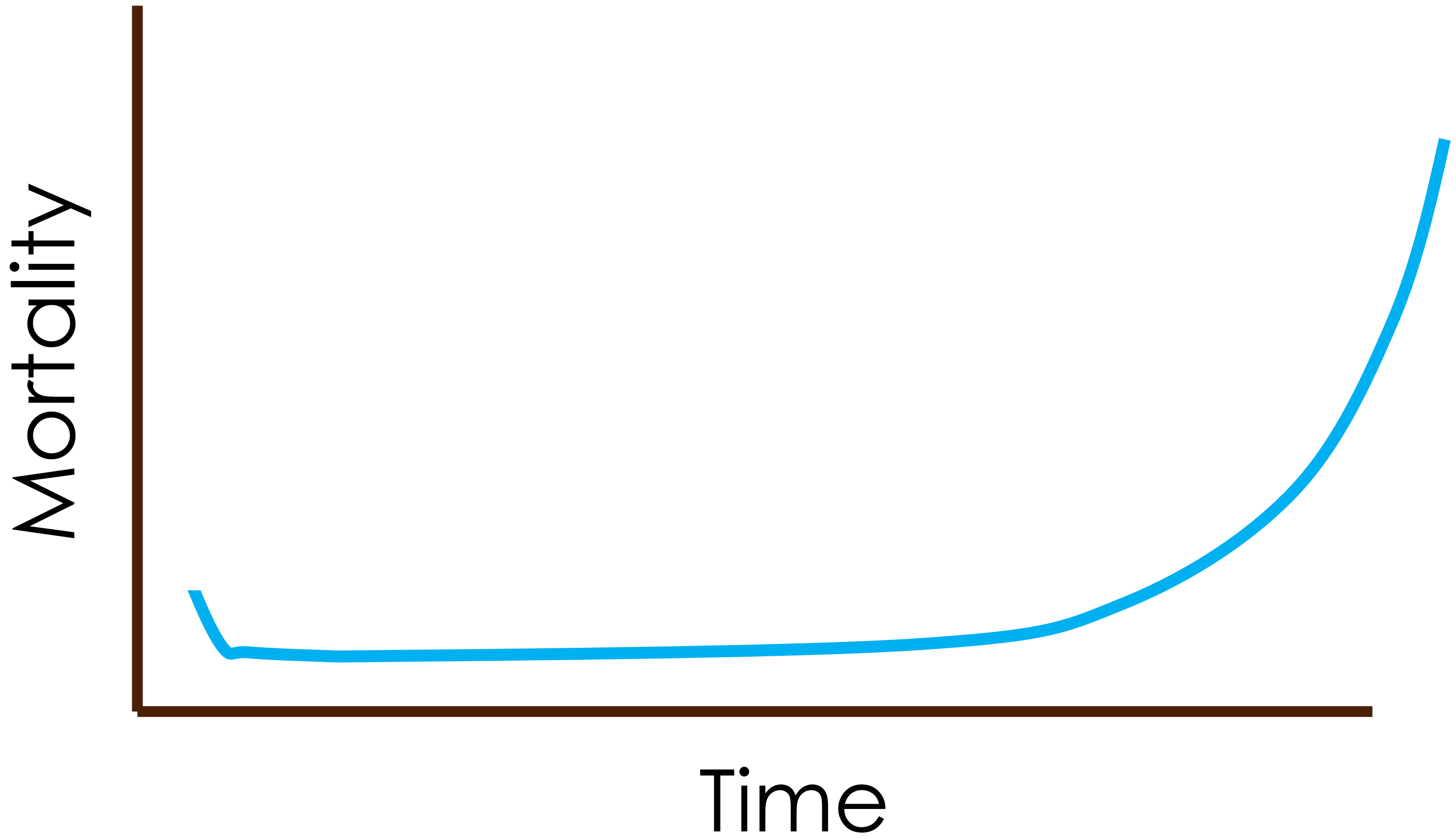
Four Cases of Spontaneous Neoplasia in the Naked Mole-Rat (*Heterocephalus glaber*), A Putative Cancer-Resistant Species

Kyle R. Taylor,[1,2] Nicholas A. Milone,[1] and Carlos E. Rodriguez[1]

Aging

We age !

We age !



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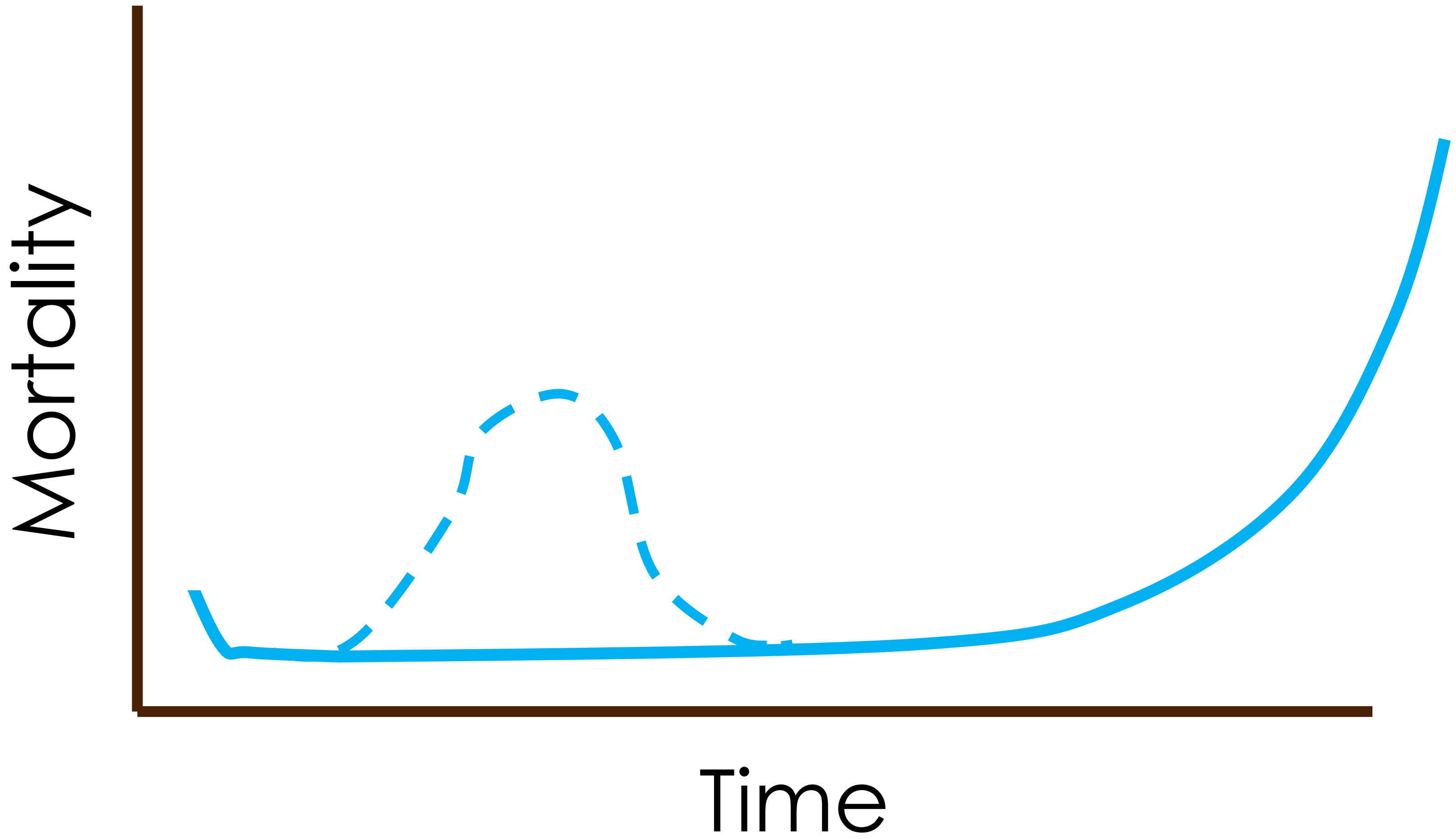

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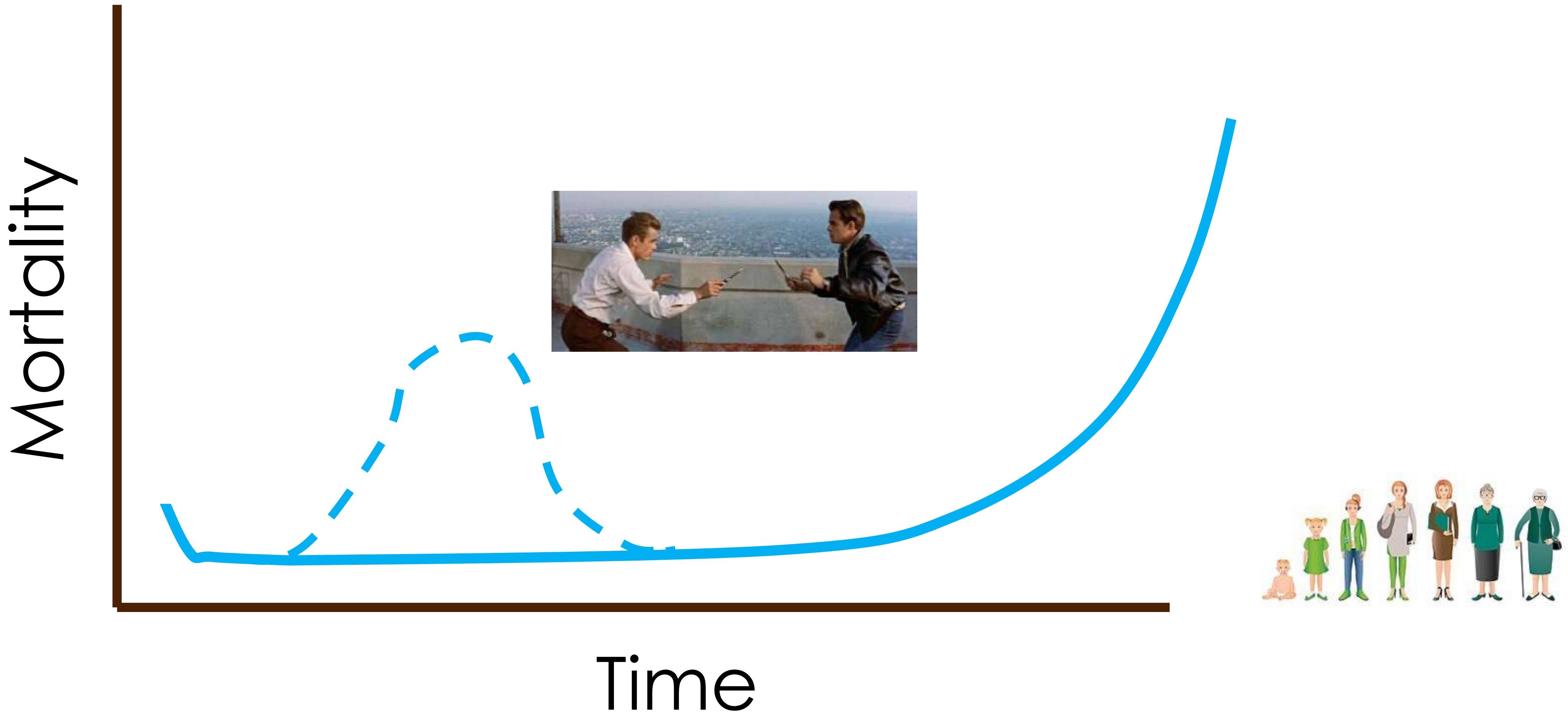

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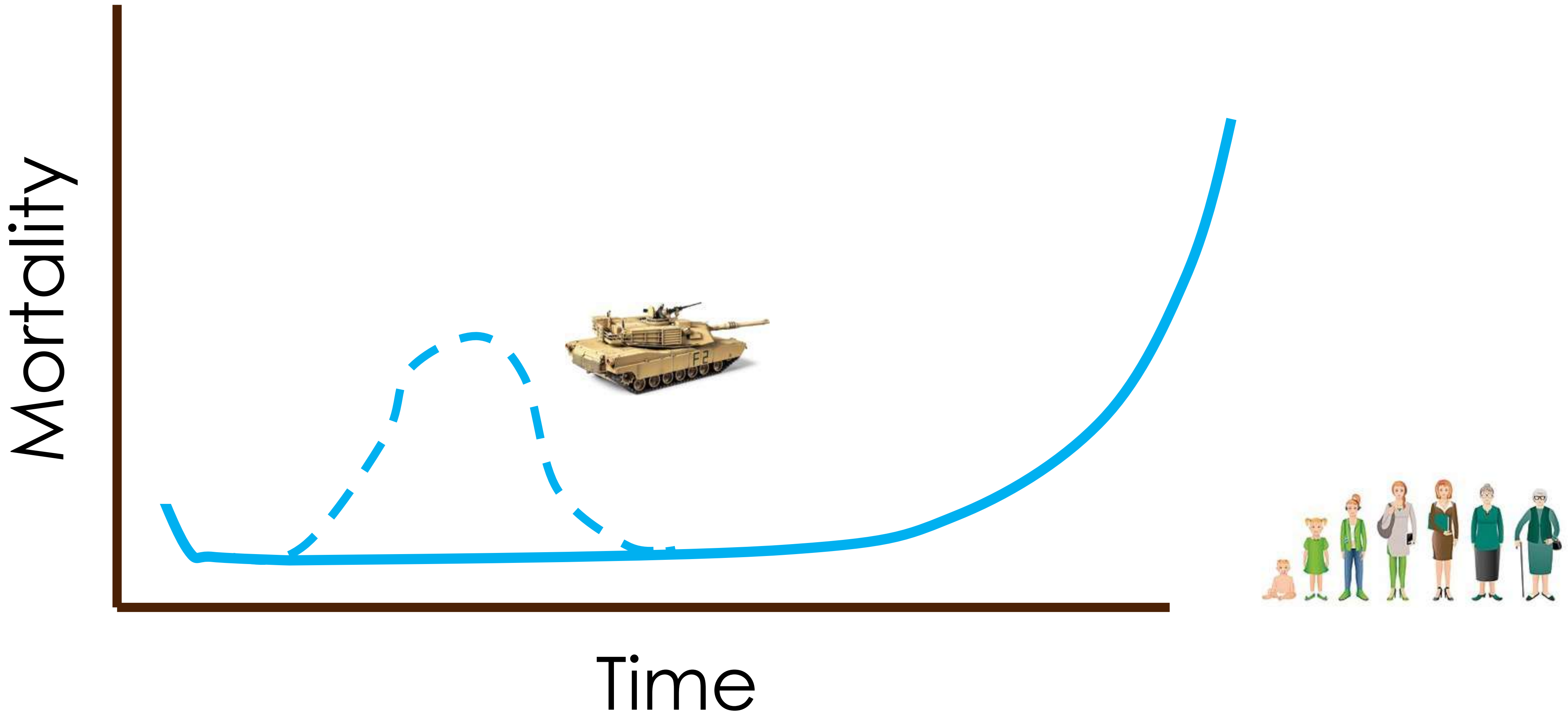
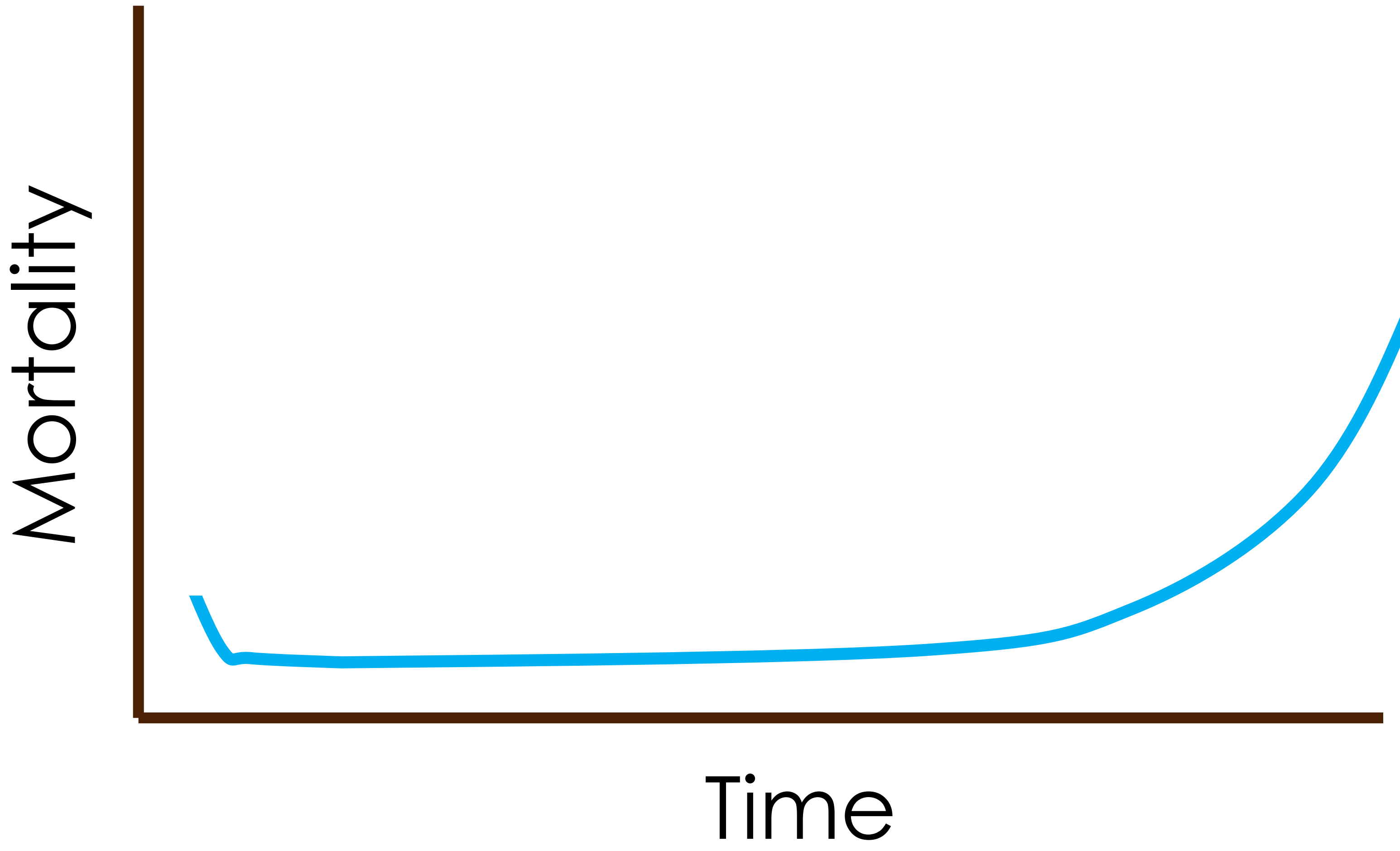


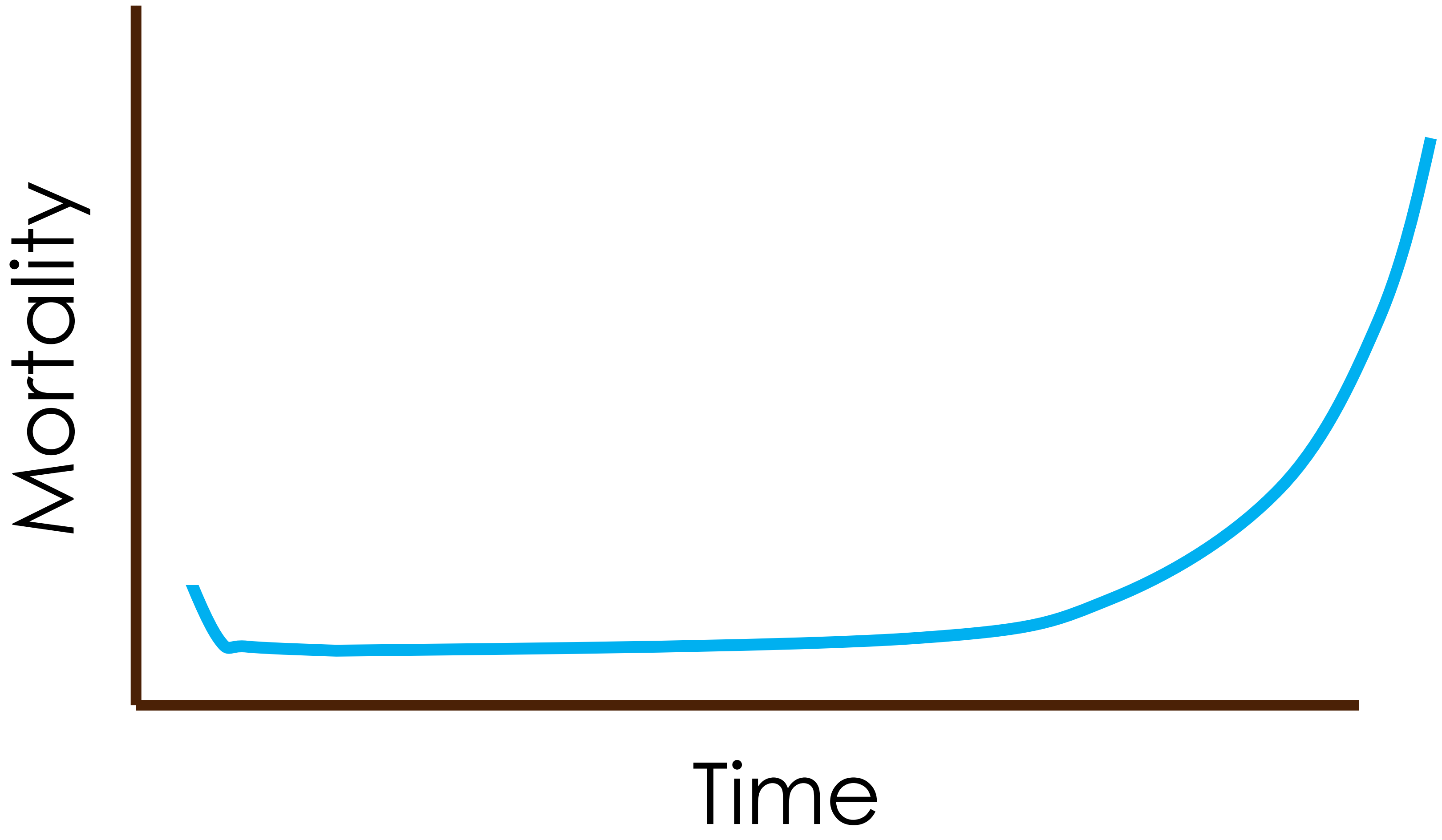
We age !

Aging = increase of mortality with time ***unrelated to extrinsic causes***



Why do we age ?

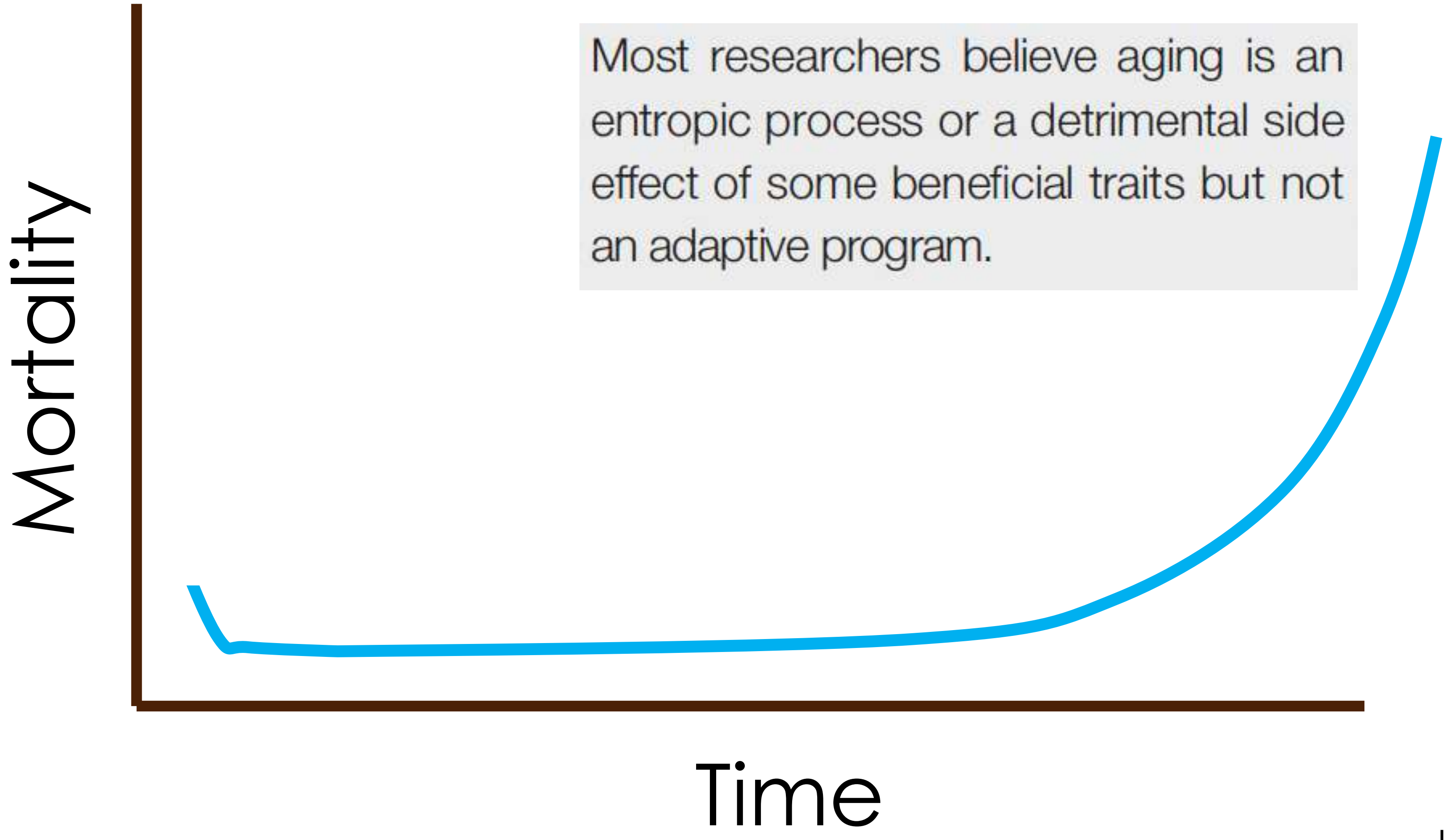
Aging = increase of mortality with time ***unrelated to extrinsic causes***



Why do we age ?

Aging = increase of mortality with time ***unrelated to extrinsic causes***

Most researchers believe aging is an entropic process or a detrimental side effect of some beneficial traits but not an adaptive program.



Lidsky & Andino (2022)

Why do we age ?

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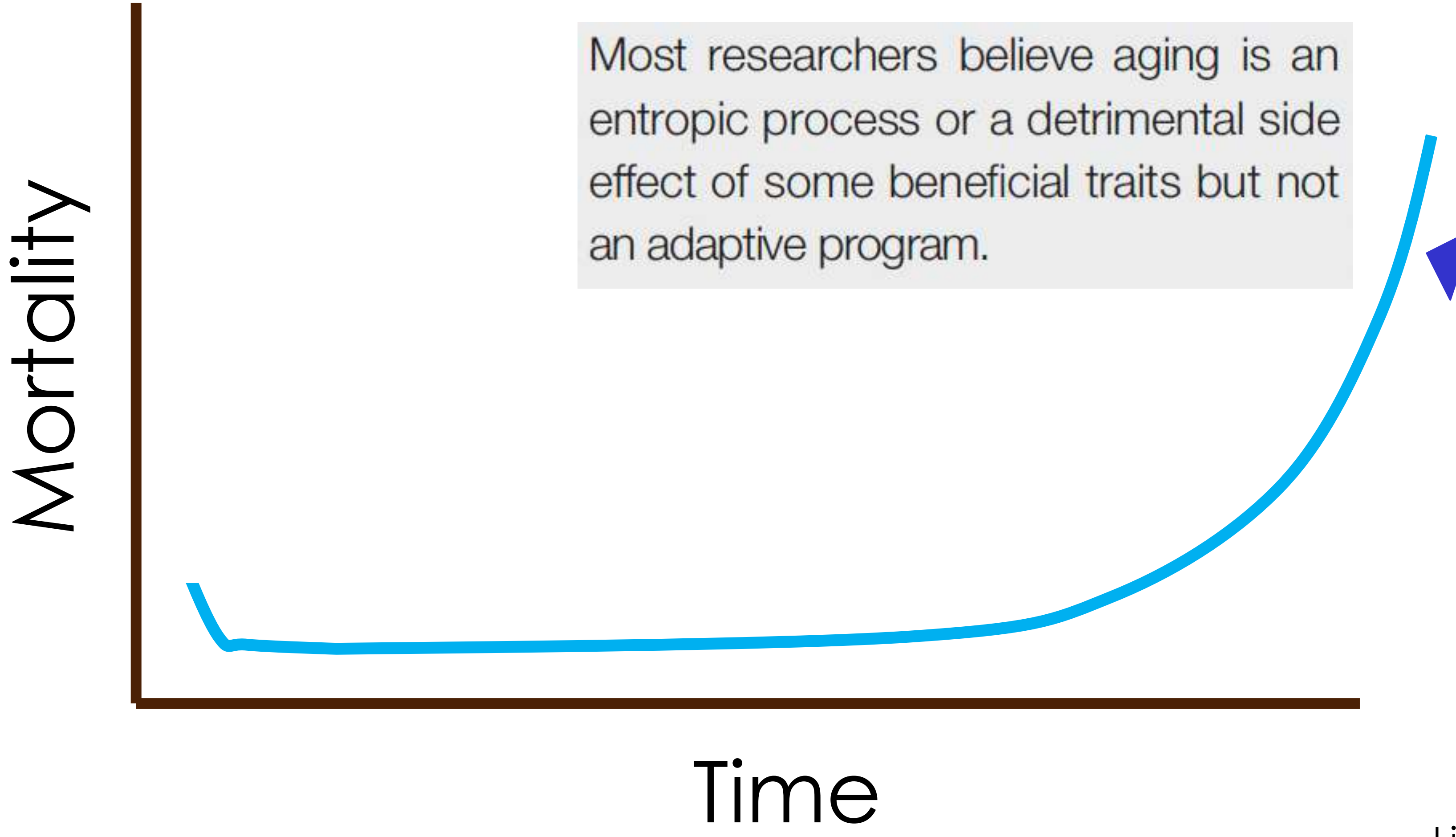

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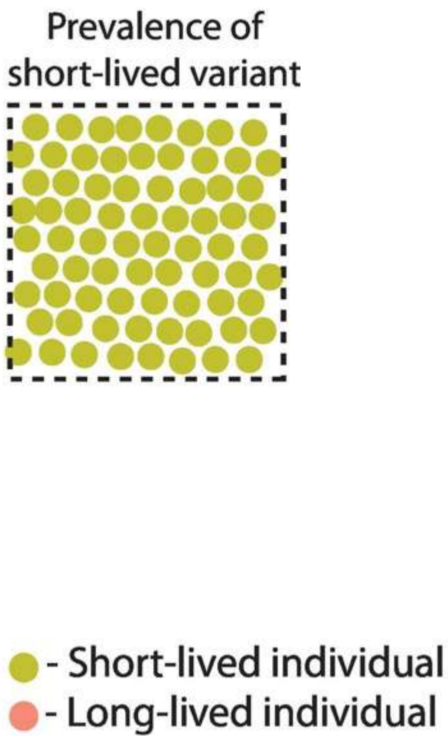
these are unpleasant accidents

Lidsky & Andino (2022)

Evolution of longevity ?



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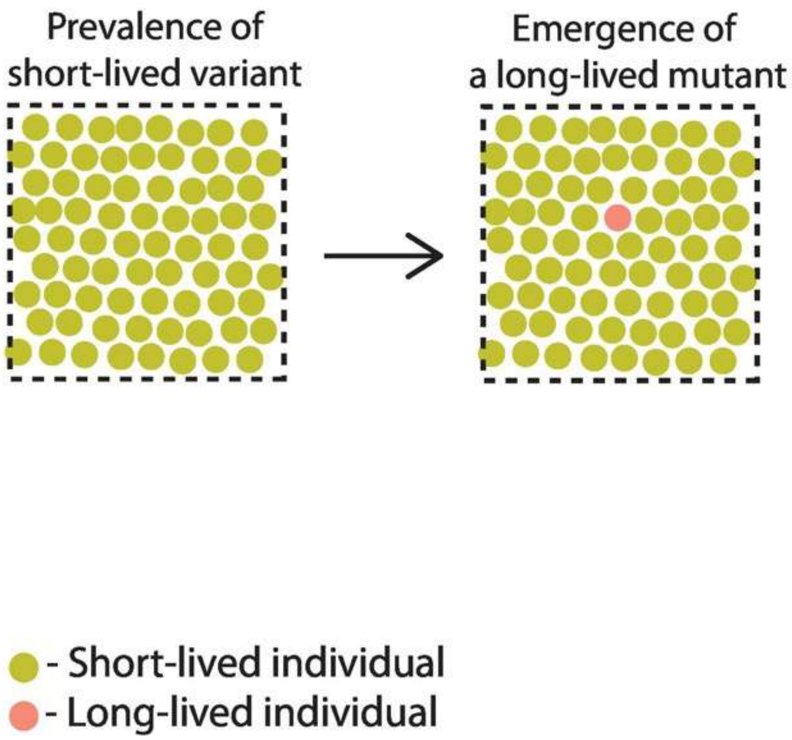

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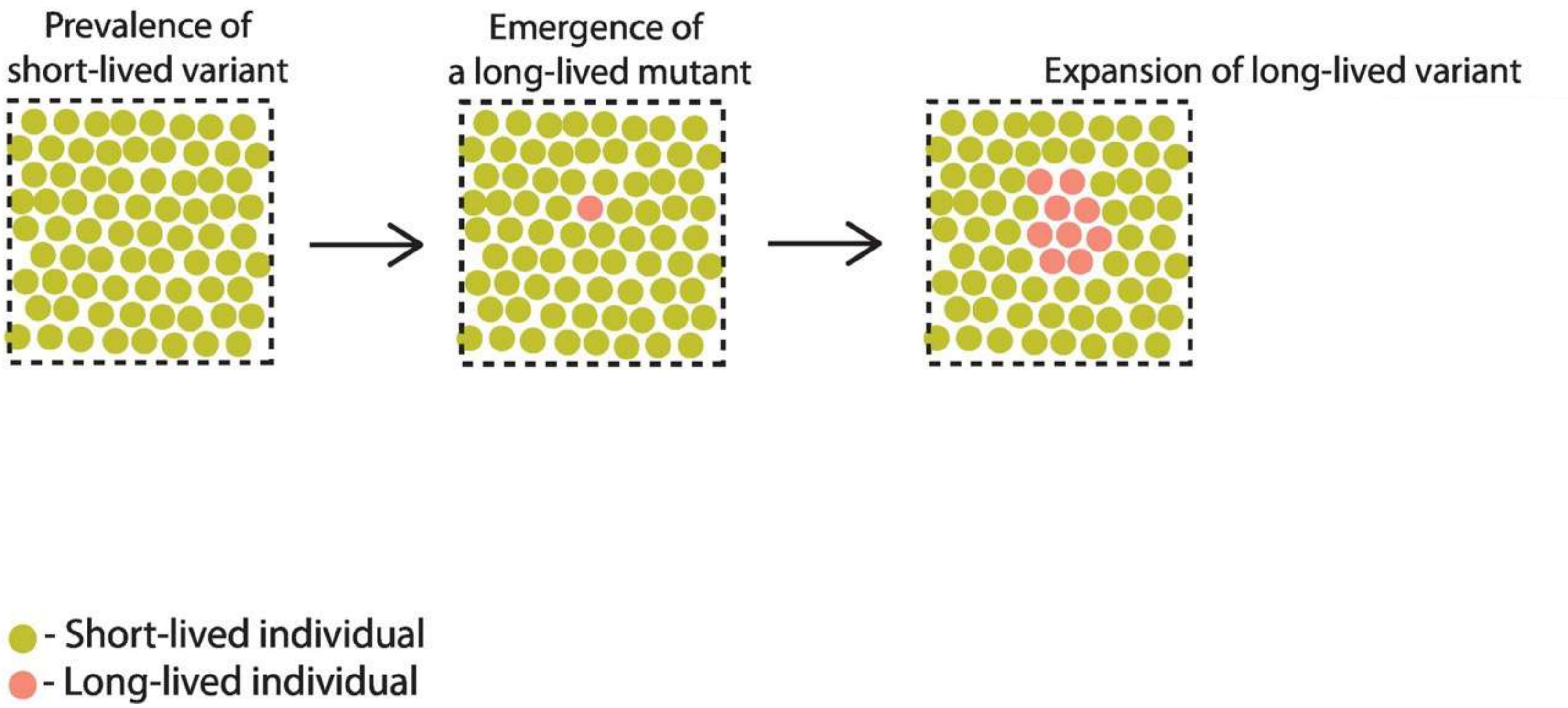

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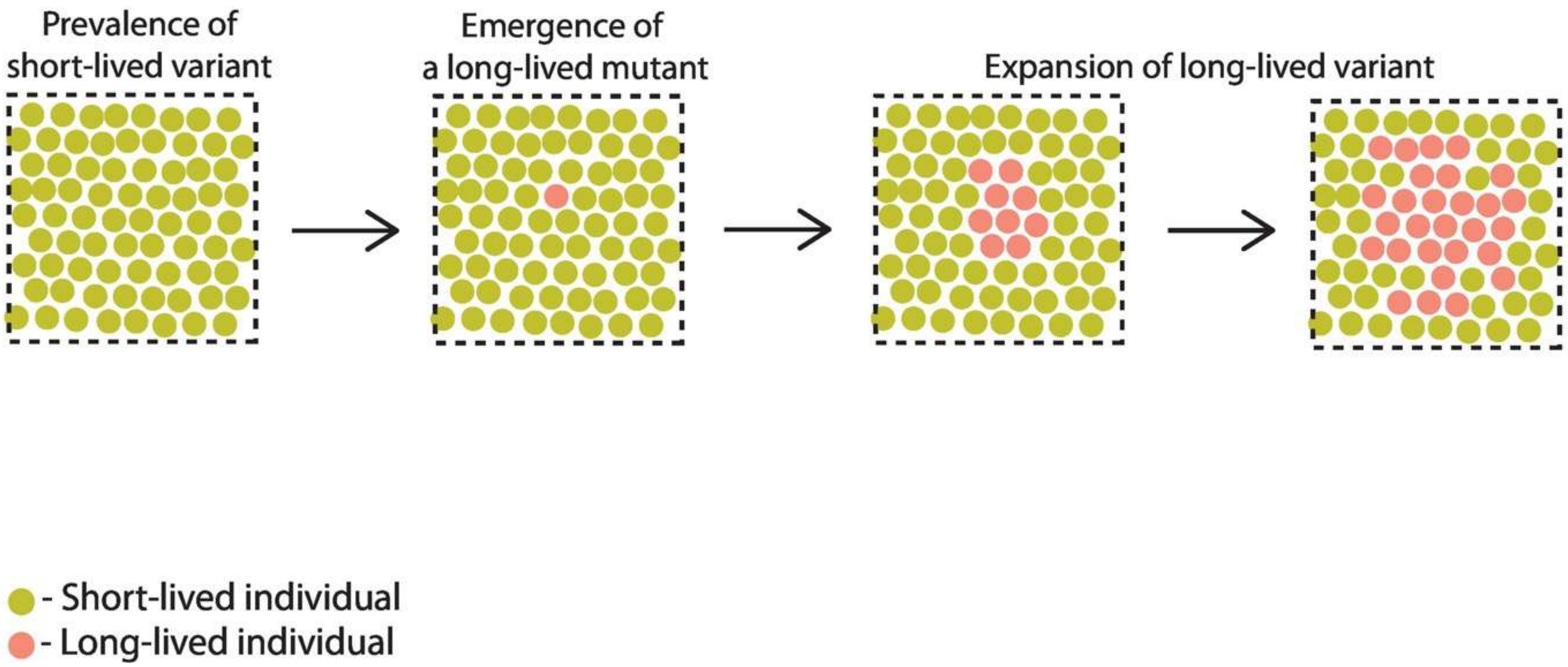

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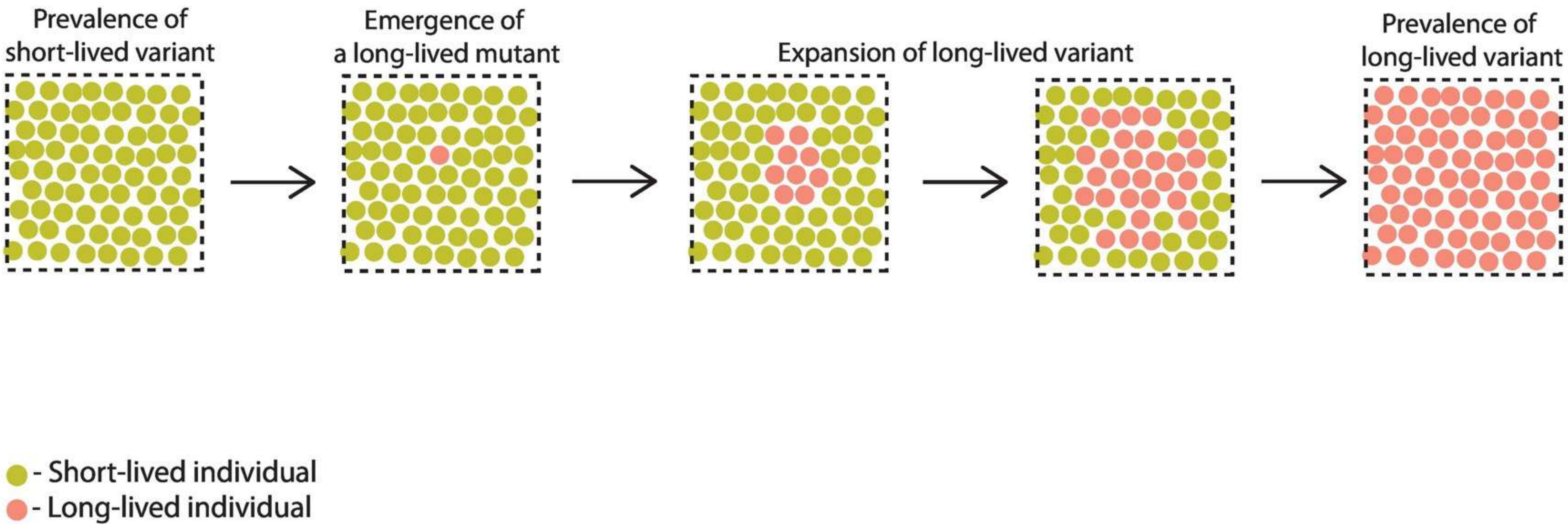
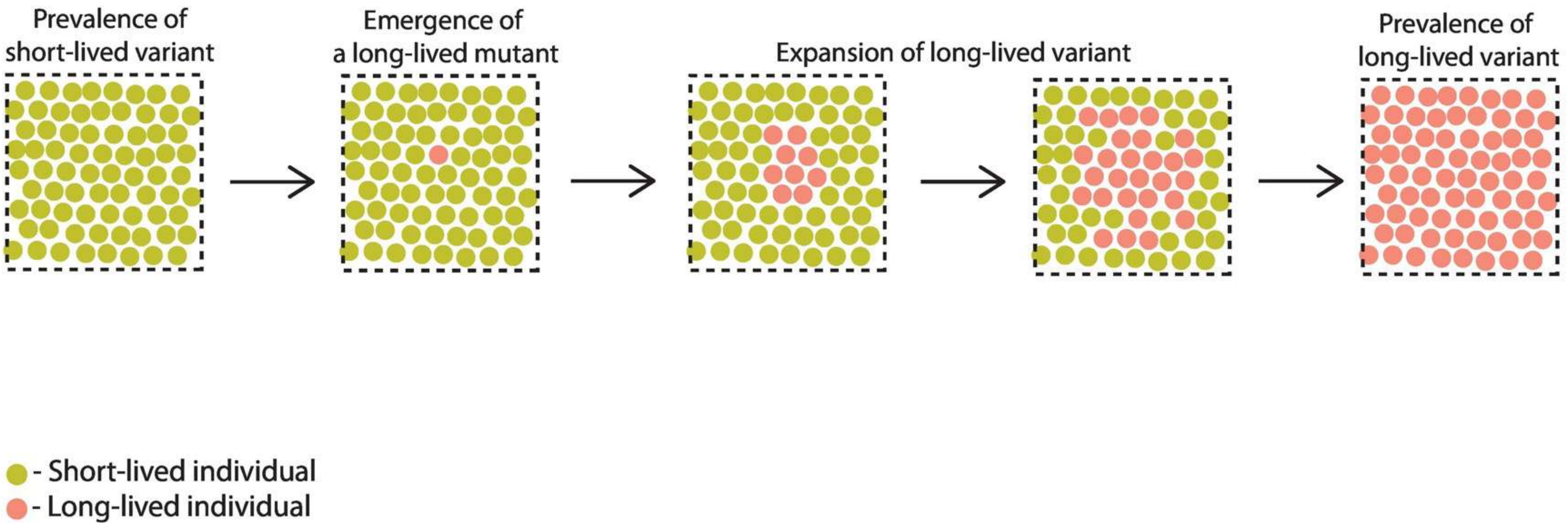


Lidsky & Andino (2022)

Theories why we age



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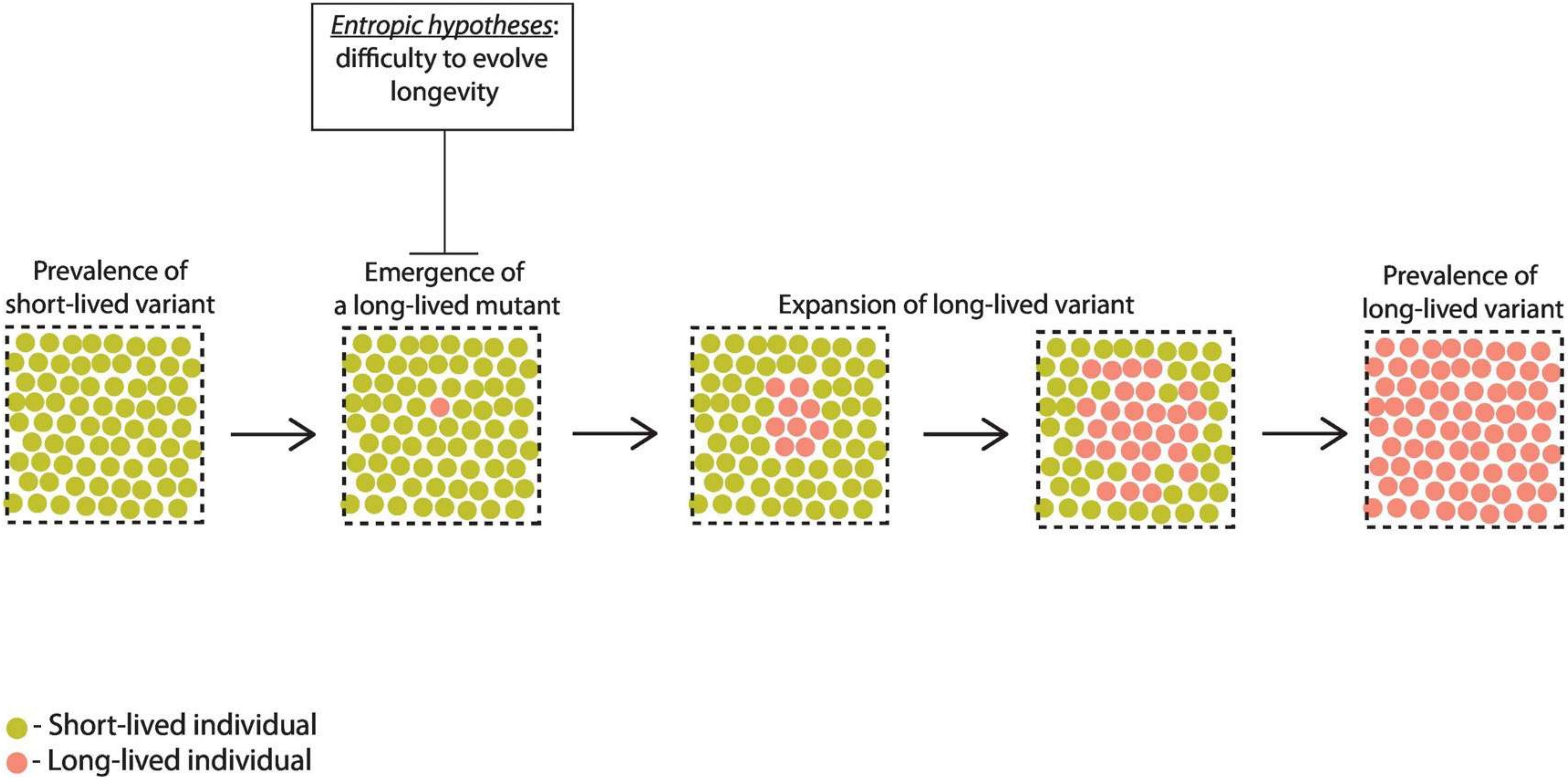

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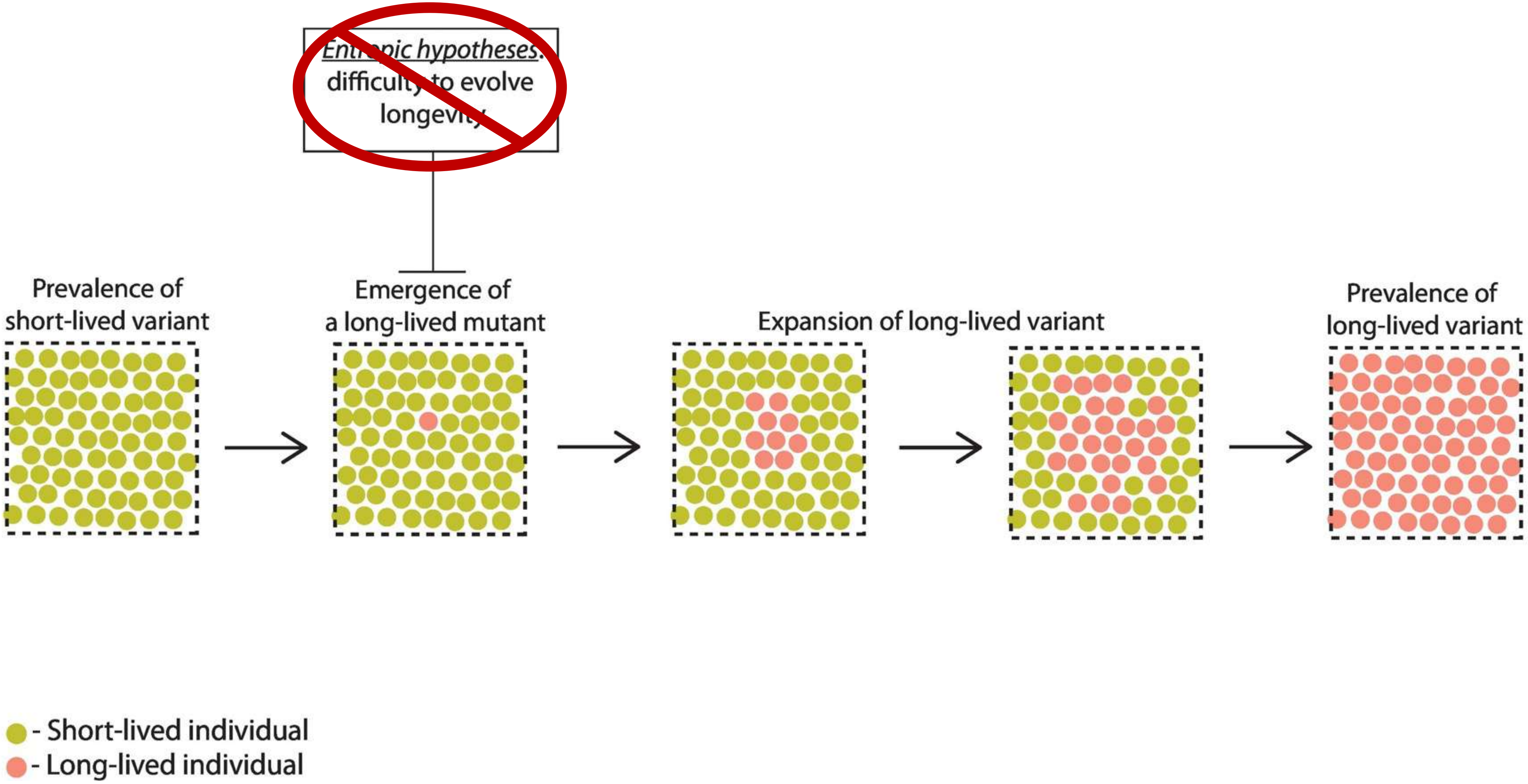

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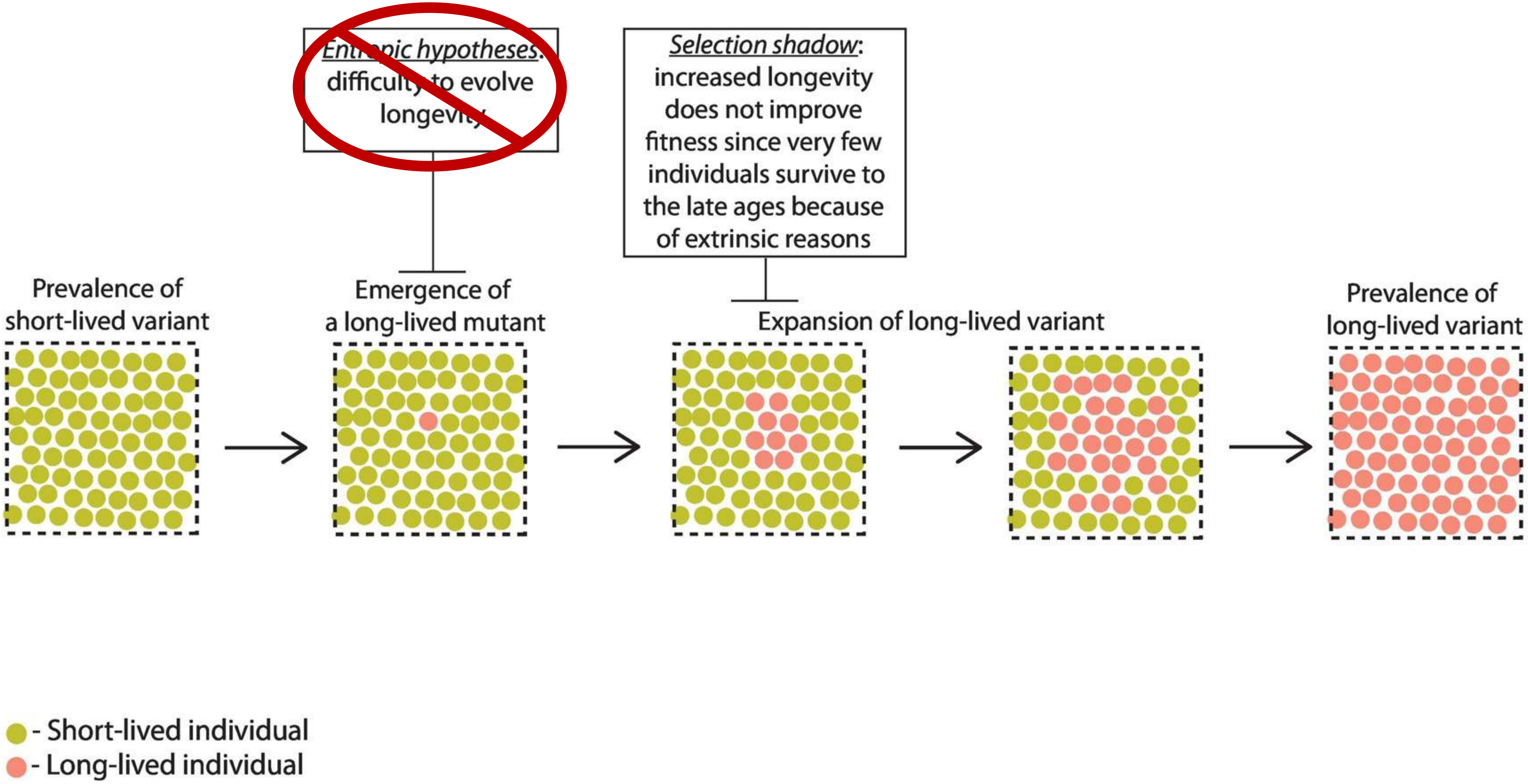
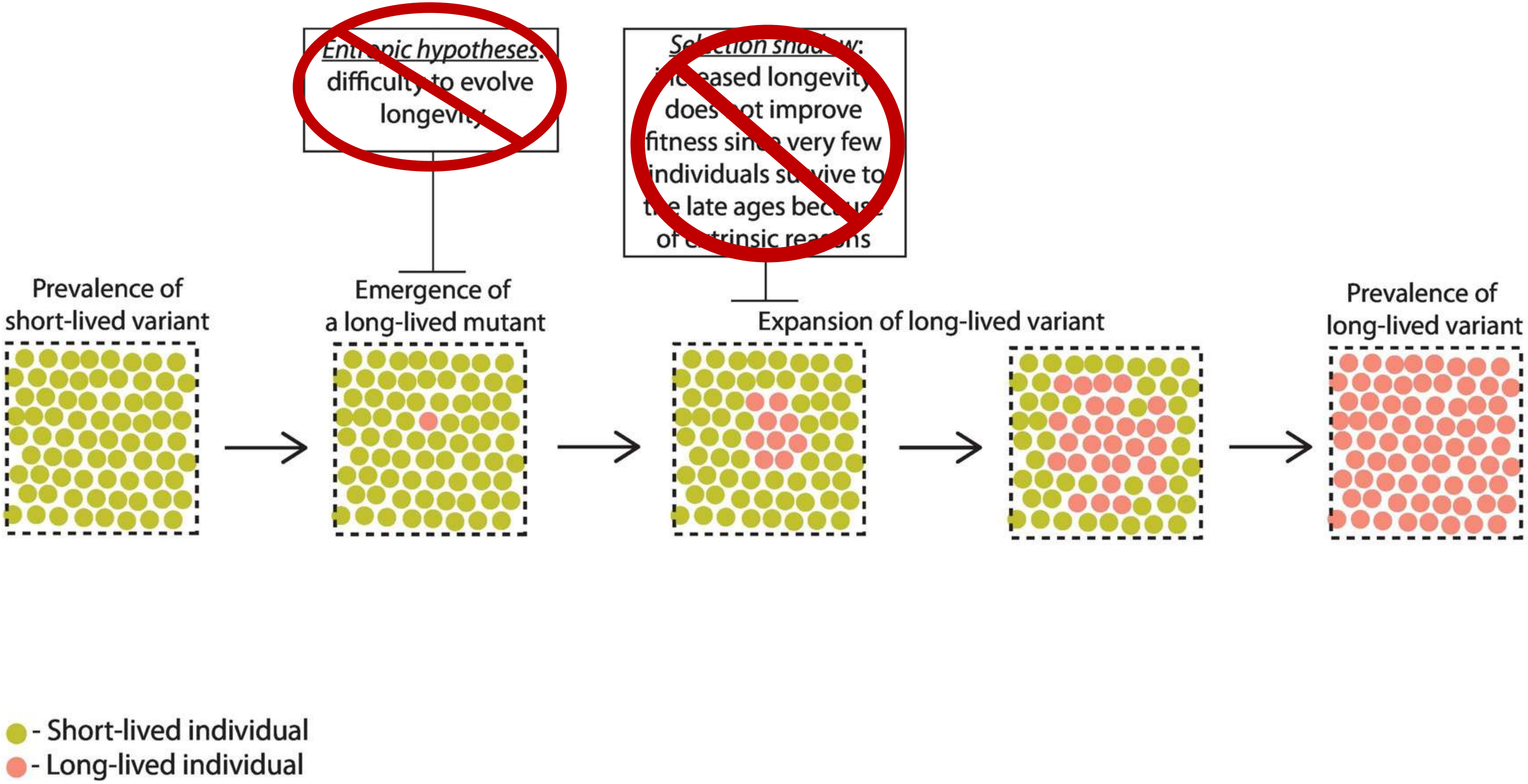


Lidsky & Andino (2022)

Michelle Aimée Oesch

Theories why we age



Lidsky & Andino (2022)

Theories why we age

Lidsky & Andino (2022)

Thinking in trade-offs

Thinking in trade-offs

energy is either invested into reproduction when young or into longevity

The trade-off fallacy

Saying that you either invest more into reproduction (live fast, produce many offspring at a time) or more into maintenance (live slower, produce less offspring at a time but over a longer period) …

The trade-off fallacy

Saying that you either invest more into reproduction (live fast, produce many offspring at a time) or more into maintenance (live slower, produce less offspring at a time but over a longer period) …

… is like saying that with a given amount of fuel, you either transport a certain load a certain distance, or a higher load a shorter distance.

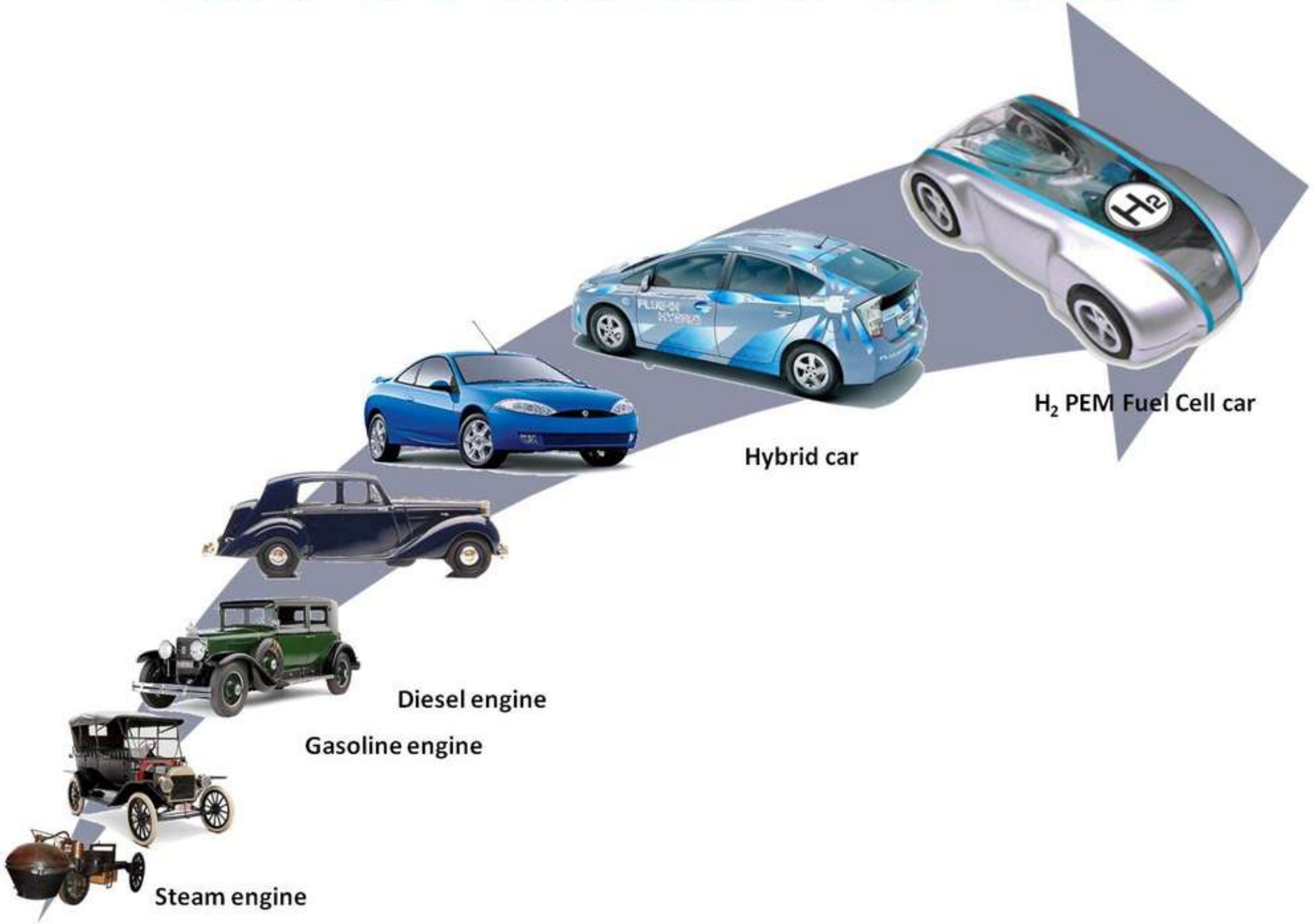
The trade-off fallacy

Saying that you either invest more into reproduction (live fast, produce many offspring at a time) or more into maintenance (live slower, produce less offspring at a time but over a longer period) …

… is like saying that with a given amount of fuel, you either transport a certain load a certain distance, or a higher load a shorter distance

ignoring the possibility that someone might develop a more efficient engine

The evolution of cars



The trade-off fallacy

Saying that you either invest more into reproduction (live fast, produce many offspring at a time) or more into maintenance (live slower, produce less offspring at a time but over a longer period) …

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… is like saying that if you want to have more meat on your chicken, you have to feed it more food for a longer period of time.

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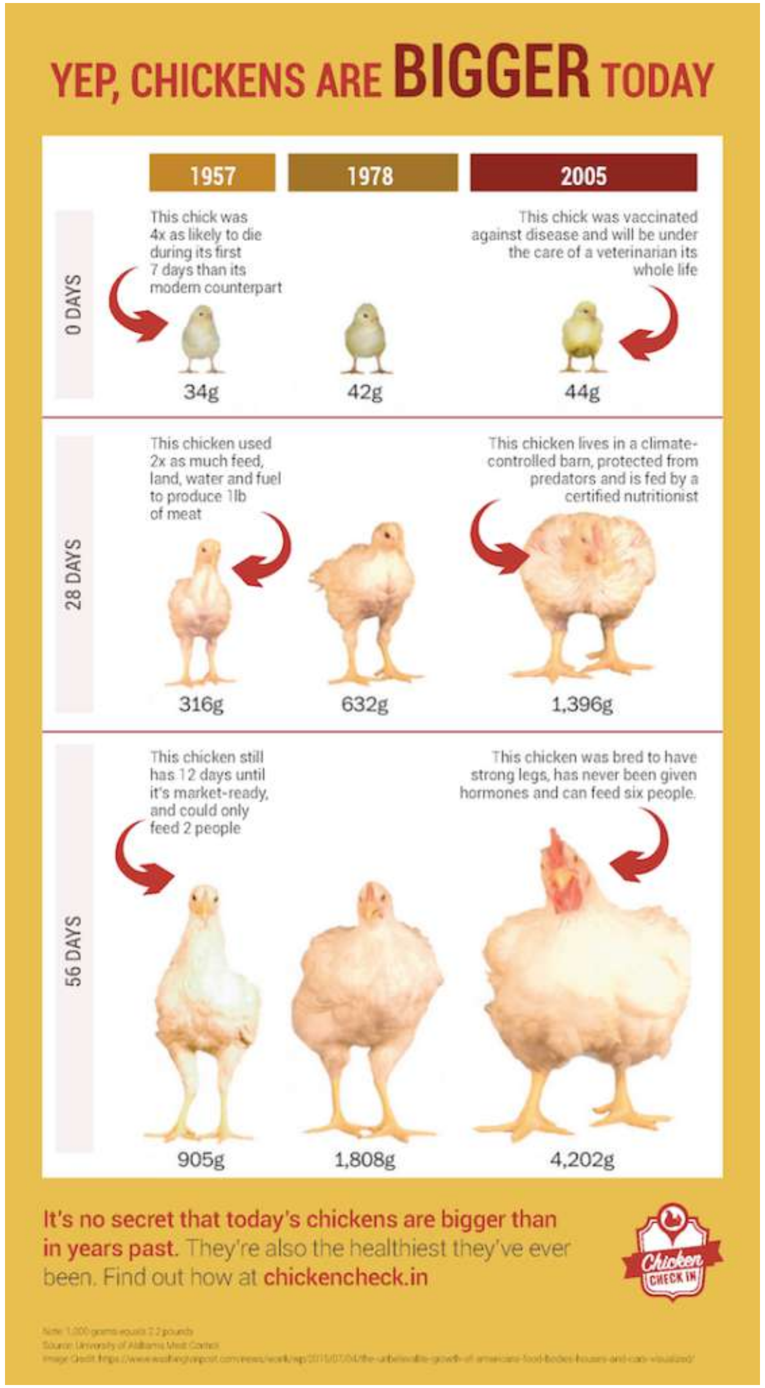
ignoring the possibility that someone might breed an animal that grows faster on less food



YEP, CHICKENS ARE BIGGER TODAY
1957
1978
2005
0 DAYS
This chick was 4x as likely to die during its first 7 days than its modern counterpart
This chick was vaccinated against disease and will be under the care of a veterinarian its whole life
34g
42g
44g
28 DAYS
This chicken used 2x as much feed, land, water and fuel to produce 1lb of meat
This chicken lives in a climate-controlled barn, protected from predators and is fed by a certified nutritionist
316g
632g
1,396g
56 DAYS
This chicken still has 12 days until it's market-ready, and could only feed 2 people
This chicken was bred to have strong legs, has never been given hormones and can feed six people.
905g
1,808g
4,202g
It's no secret that today's chickens are bigger than in years past. They're also the healthiest they've ever been. Find out how at chickencheck.in
Chicken CHECK IN

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… is ignoring the possibility that individuals (and taxa) might evolve that achieve a higher reproductive output with the same level of resources due to a higher efficiency.

High reproductive effort is associated with decreasing mortality late in life in captive ruffed lemurs

Morgane Tidière[1] | Jean-François Lemaître[1] | Guillaume Douay[2] | Mylisa Whipple[3] | Jean-Michel Gaillard[1]

Am J Primatol. 2017;**79**:e22677.

These findings indicate that individual quality rather than trade-off drives the association between reproductive success and survival pattern among individual lemurs

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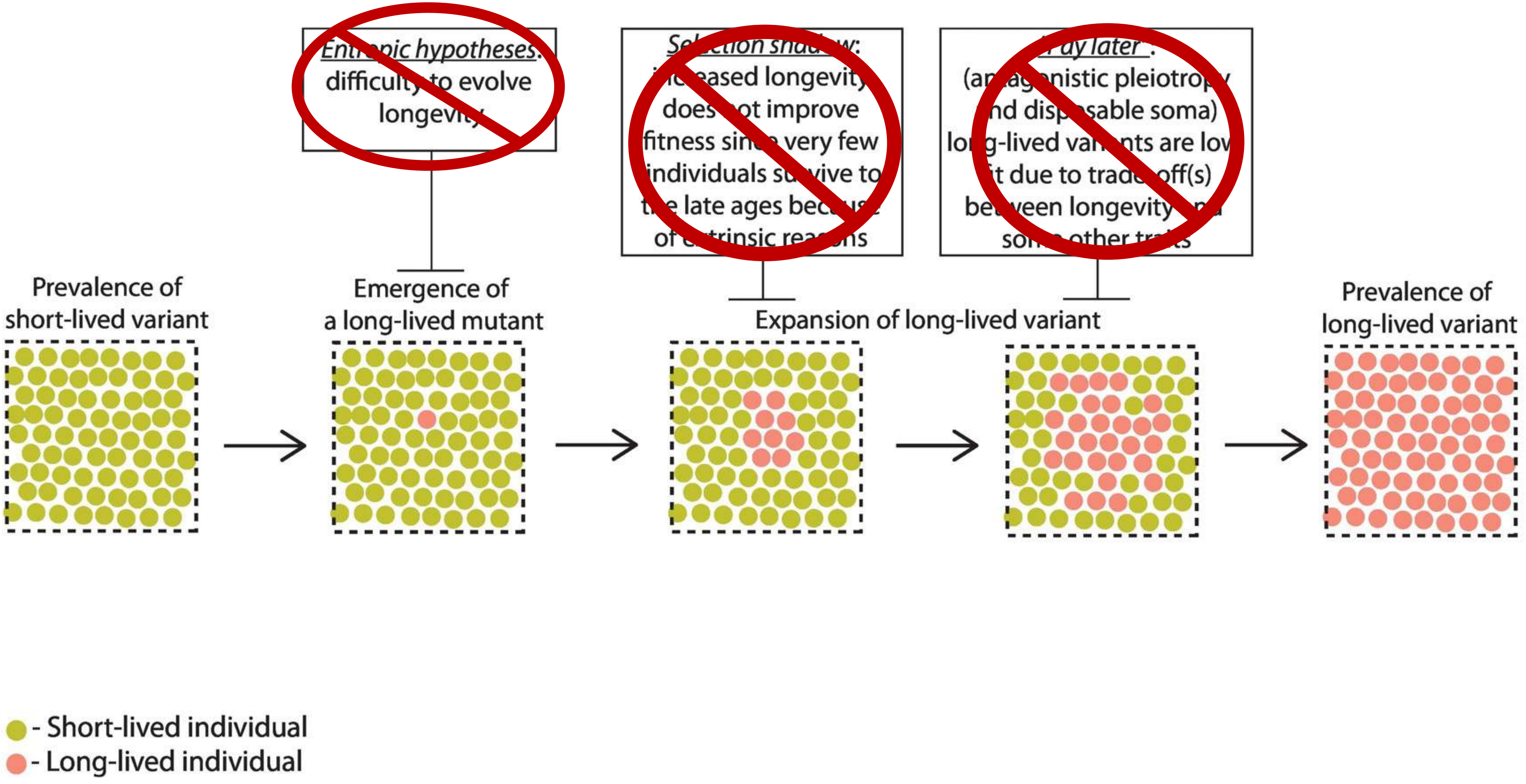
Saying that you either invest more into reproduction (live fast, produce many offspring at a time) or more into maintenance (live slower, produce less offspring at a time but over a longer period) …

*… **is like saying you do not believe that evolution can find new solutions.***

Theories why we age

Lidsky & Andino (2022)

Theories why we age



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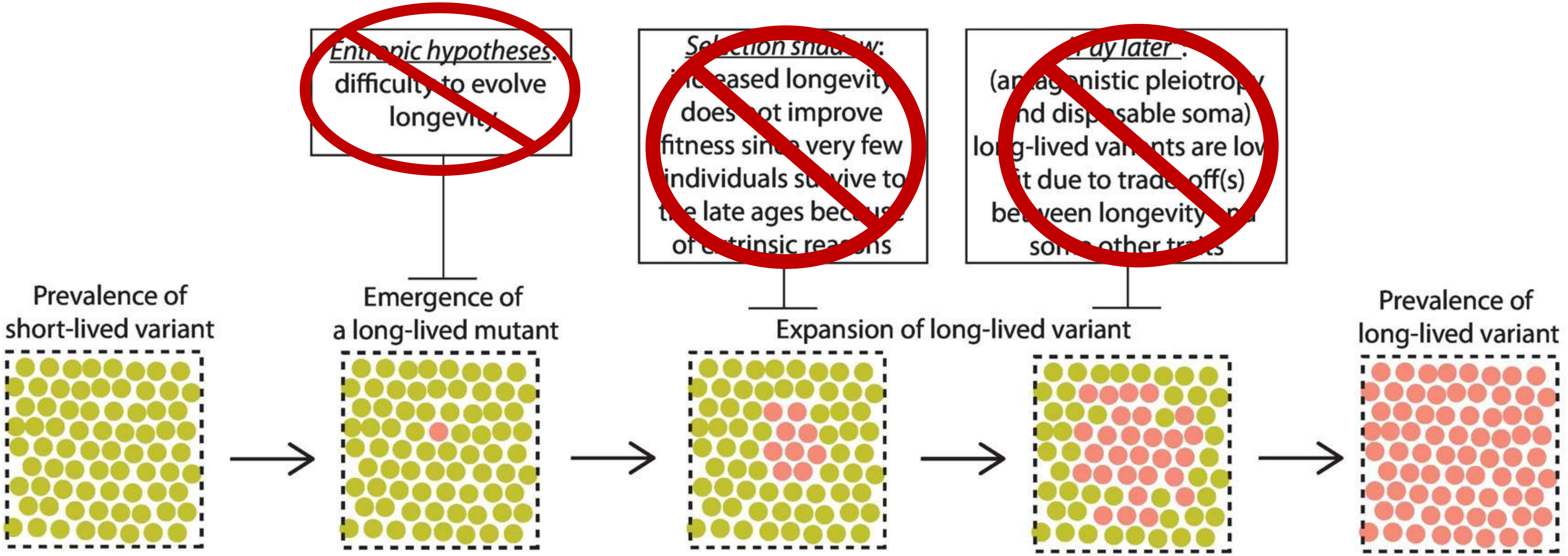

- Short-lived individual
- Long-lived individual

remember: longevity ***increases*** when energy intake is restricted

Lidsky & Andino (2022)

Could aging evolve as a pathogen control strategy?

Trends in Ecology & Evolution, December 2022, Vol. 37, No. 12

Peter V. Lidsky[1,*] and Raul Andino[1,*]

Could aging evolve as a pathogen control strategy?

Trends in Ecology & Evolution, December 2022, Vol. 37, No. 12

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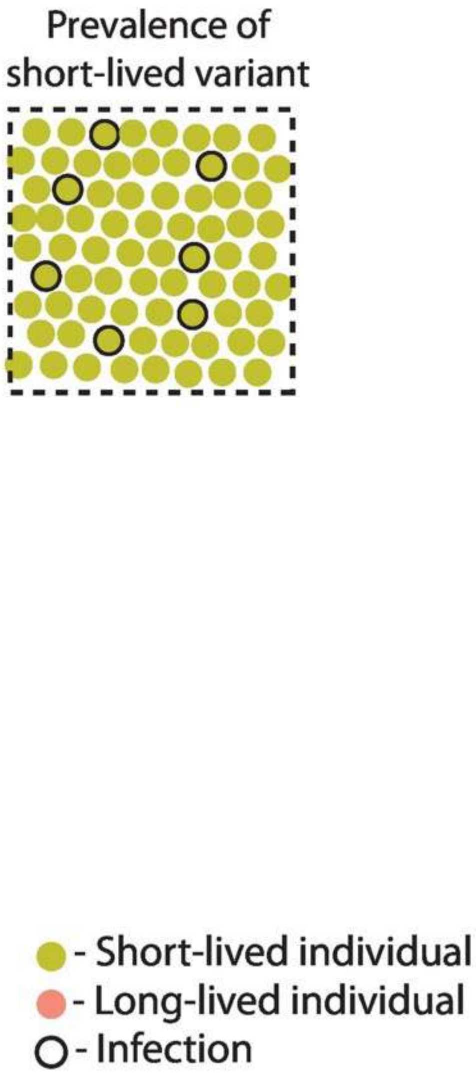
Aging might have evolved to remove older individuals who carry chronic diseases that may transmit to their younger kin. Thus, selection for shorter lifespans may benefit kin's fitness.

Theories why we age



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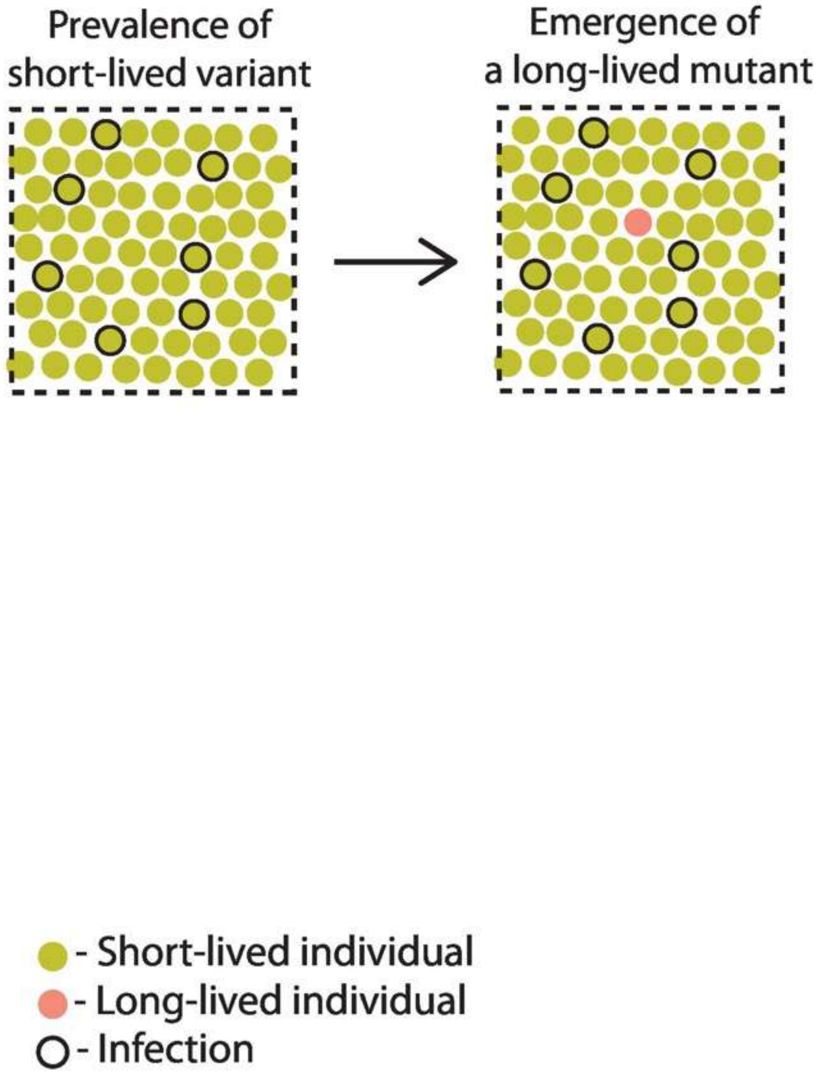

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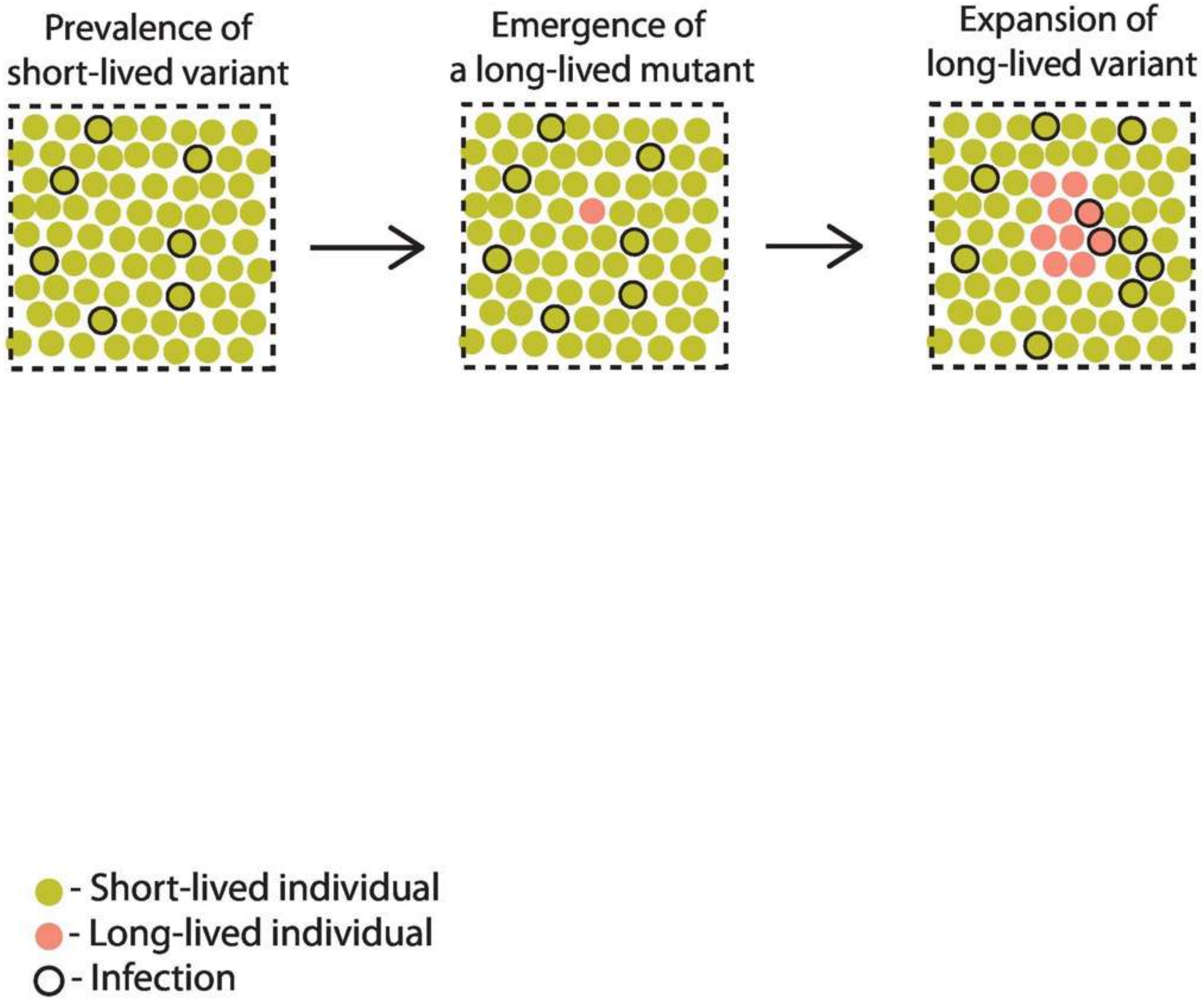

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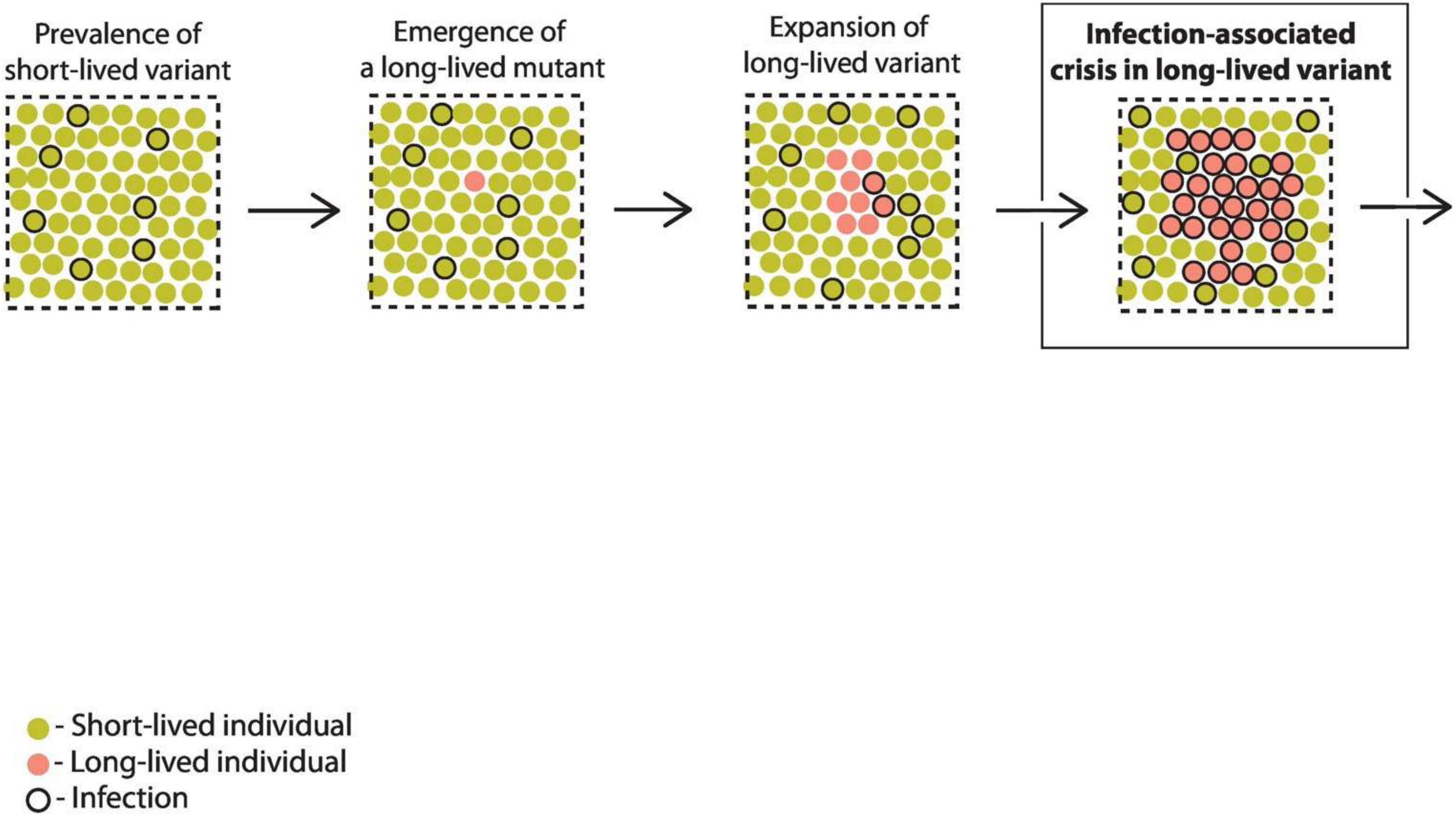

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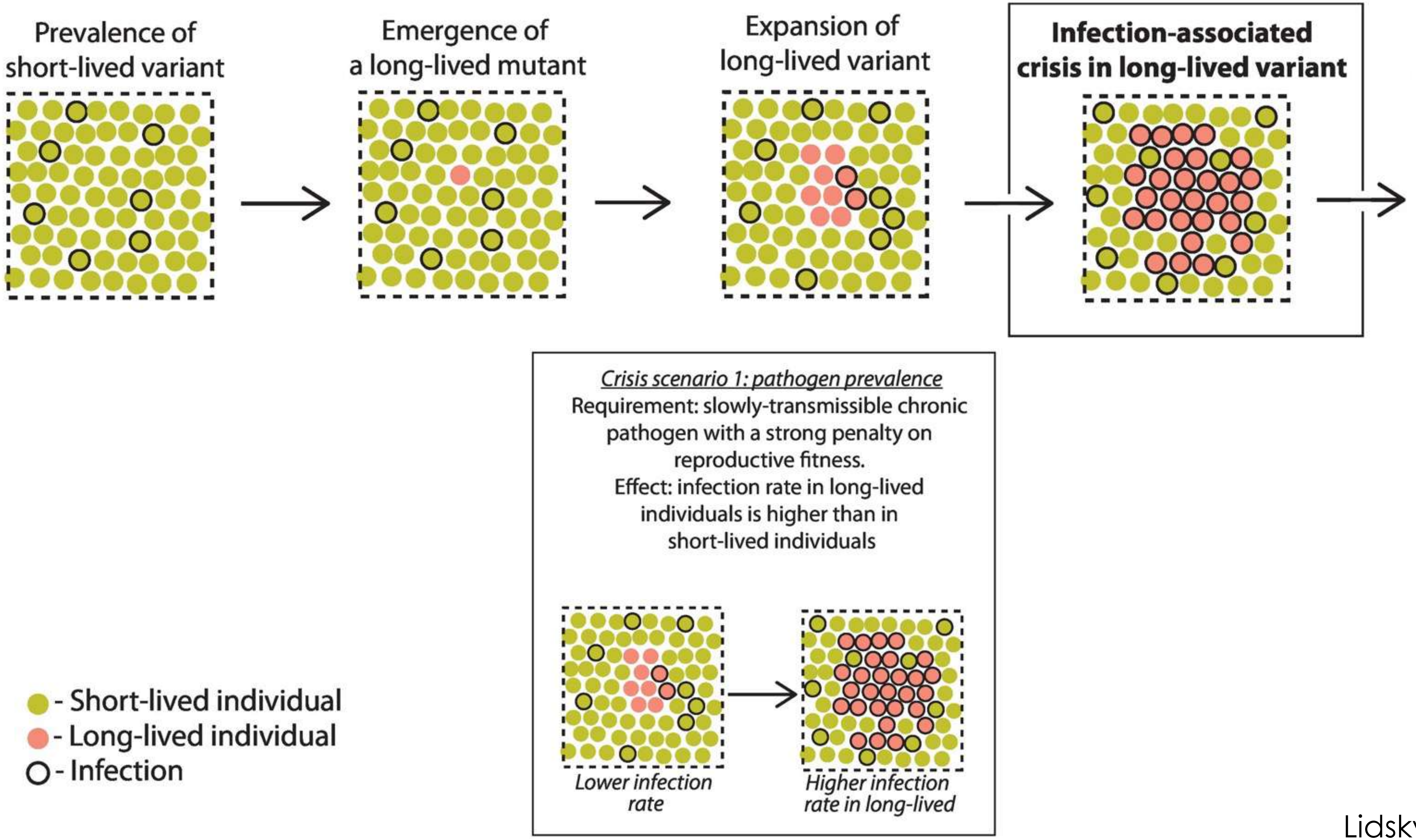

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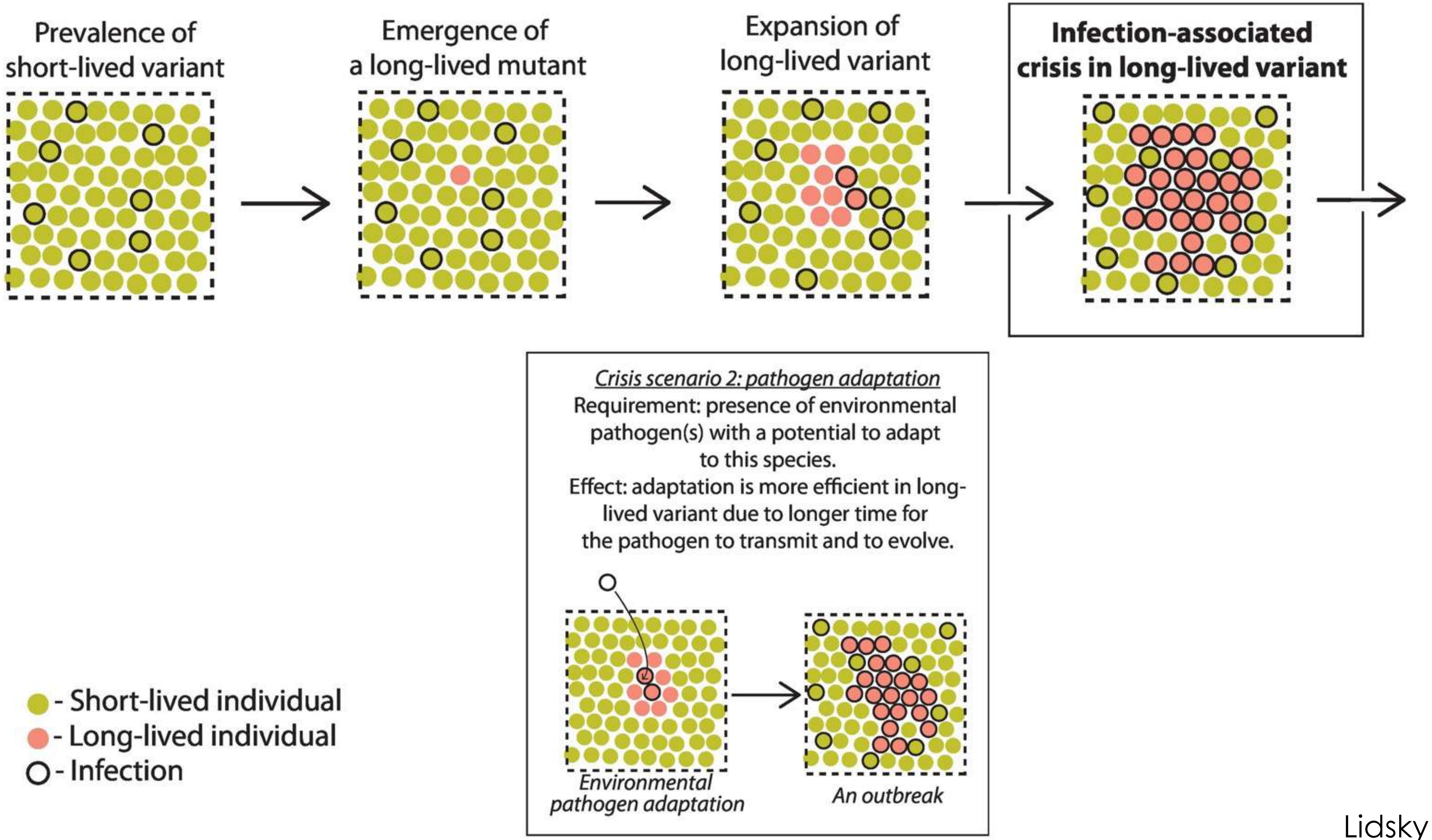

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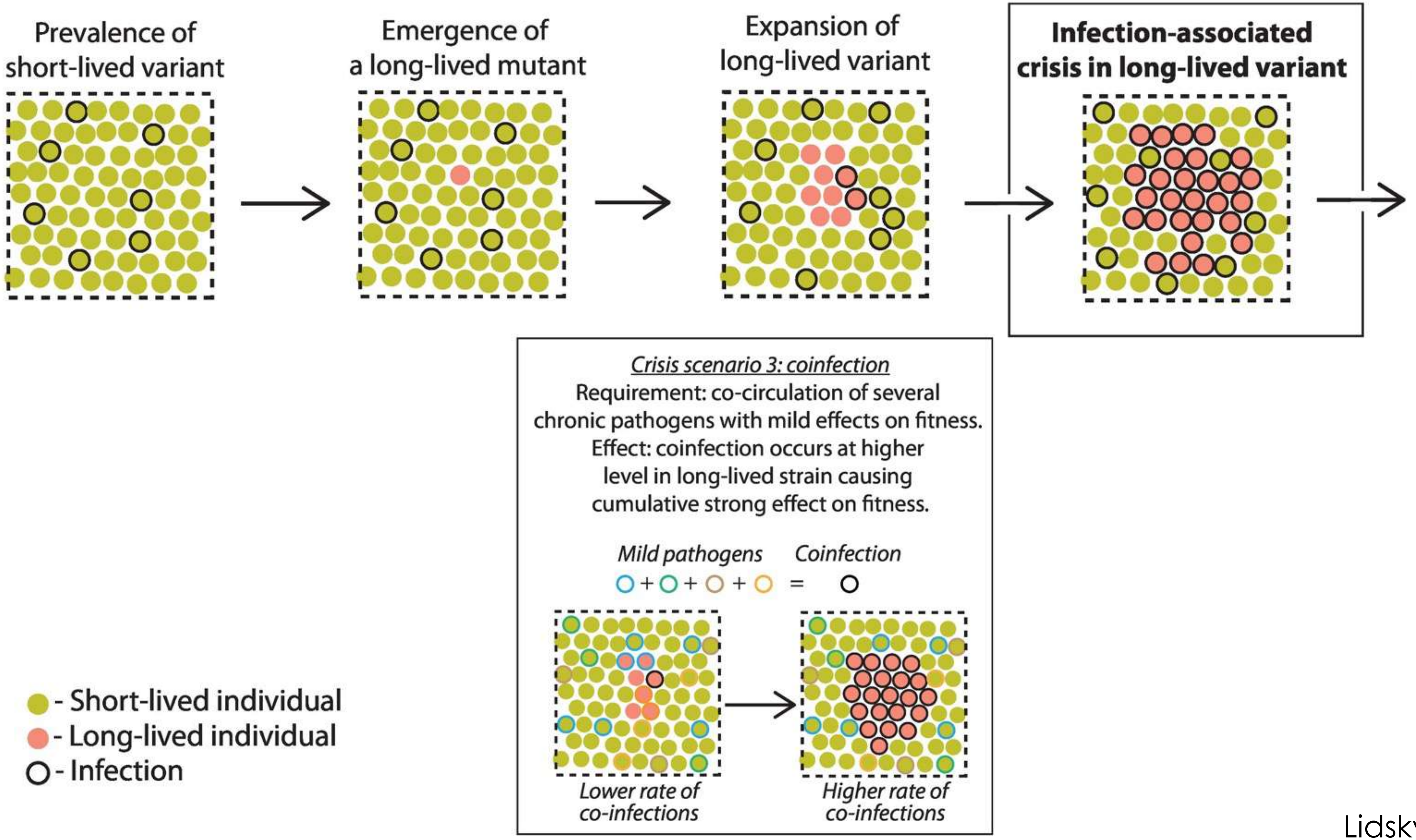

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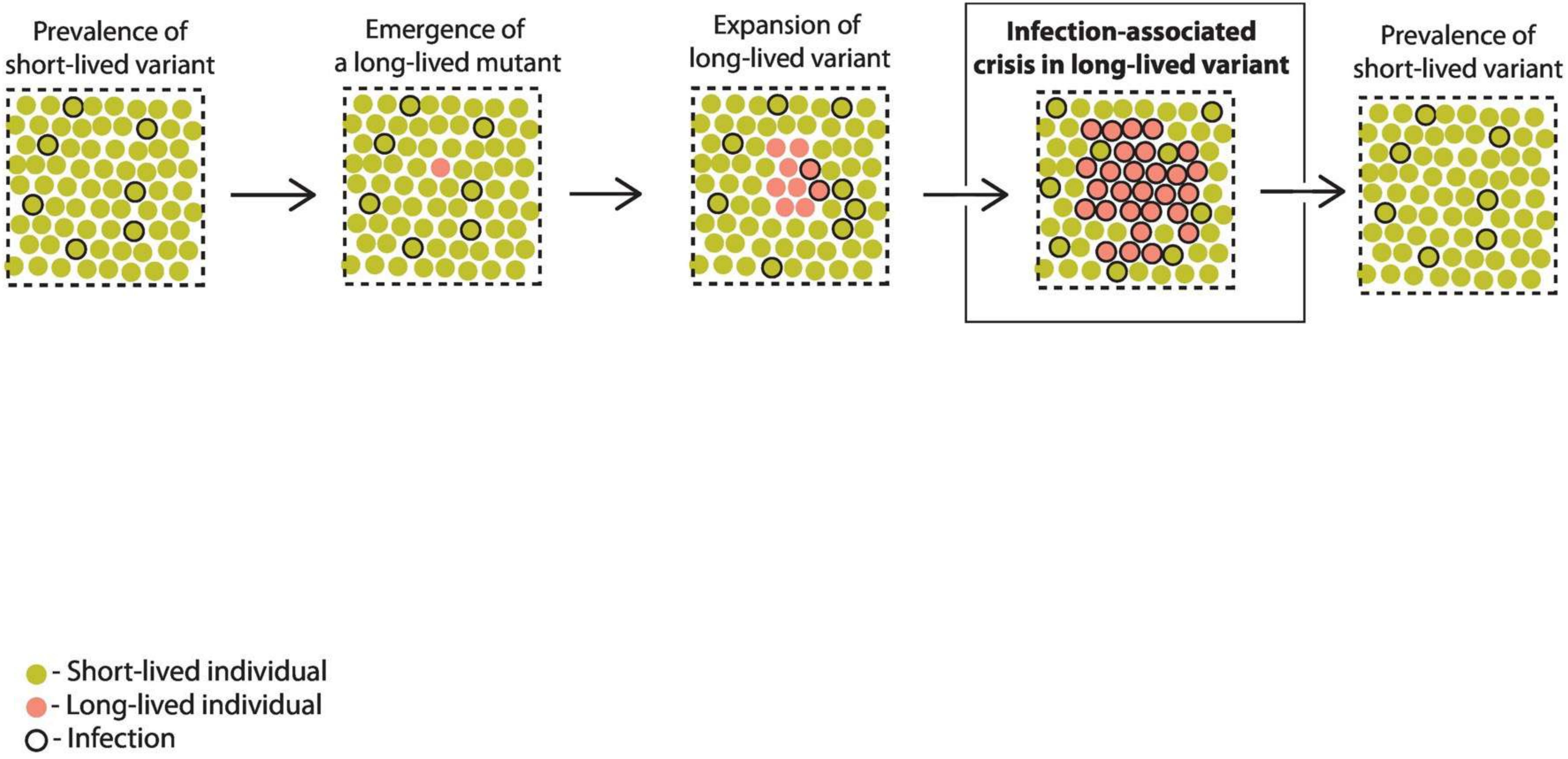

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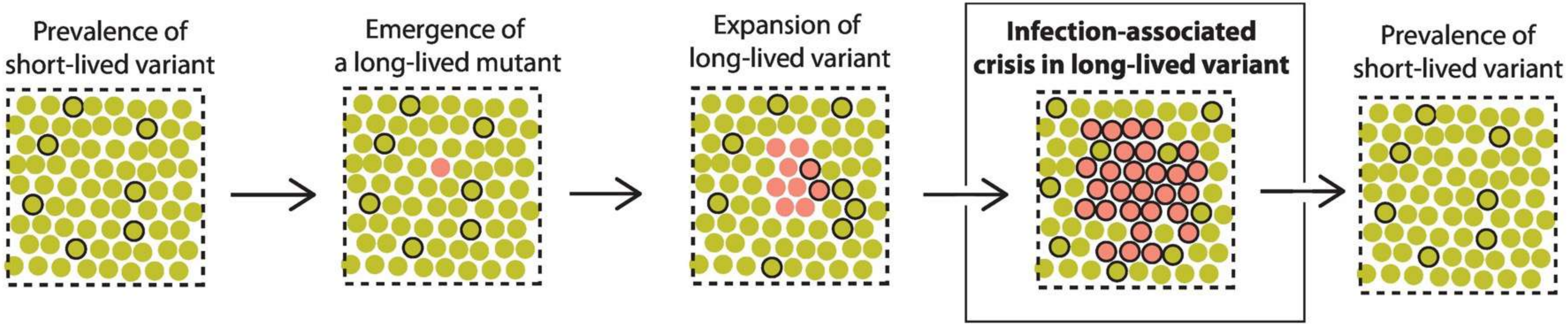
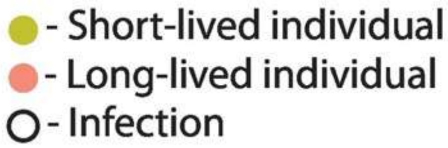


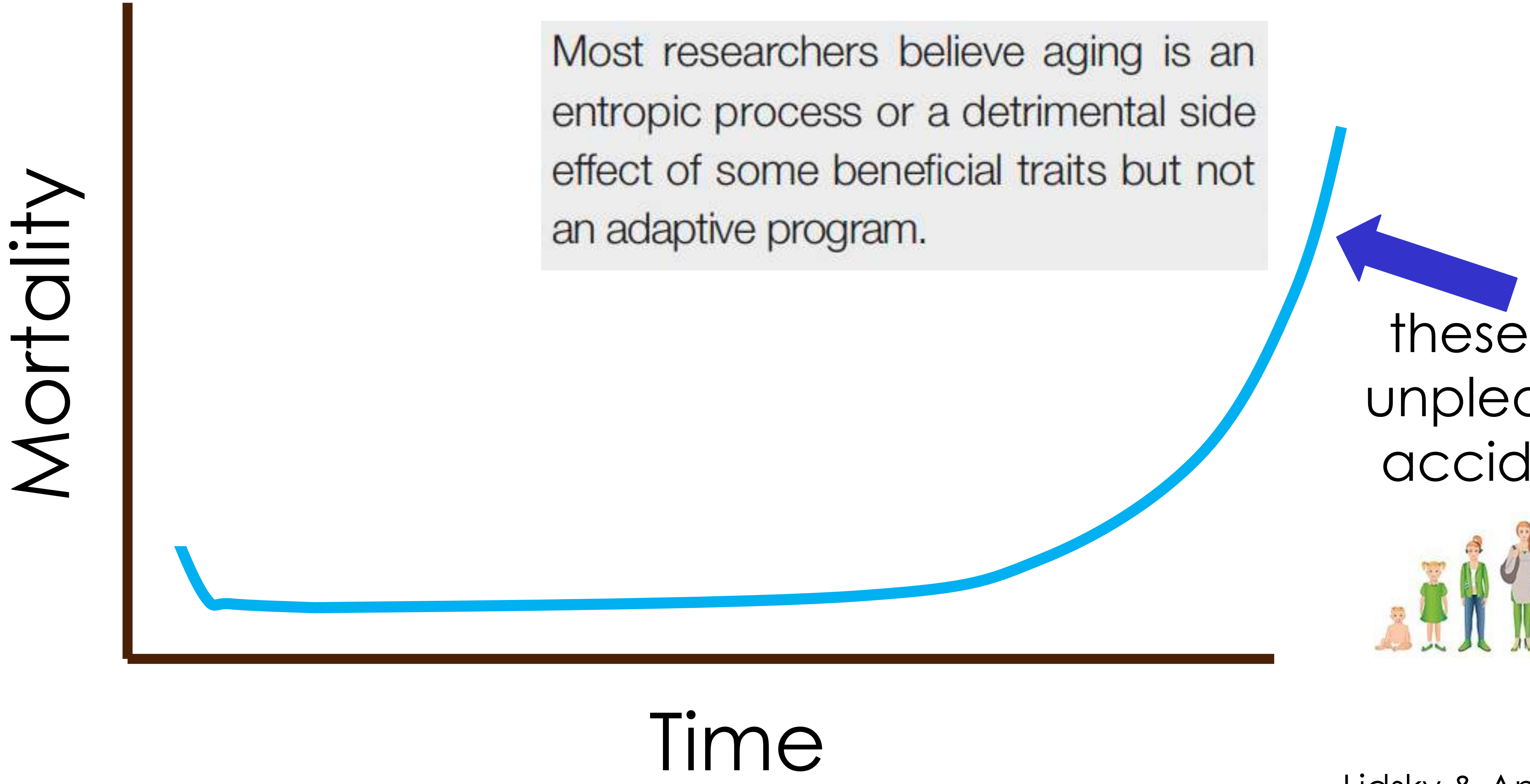
This theory explains some observations that traditional trade-off scenarios cannot explain, e.g. why longevity increases with restricted resources, or why flying birds have higher longevity (in spite of higher metabolic rates).



Lidsky & Andino (2022)

Why do we age ?

Aging = increase of mortality with time ***unrelated to extrinsic causes***



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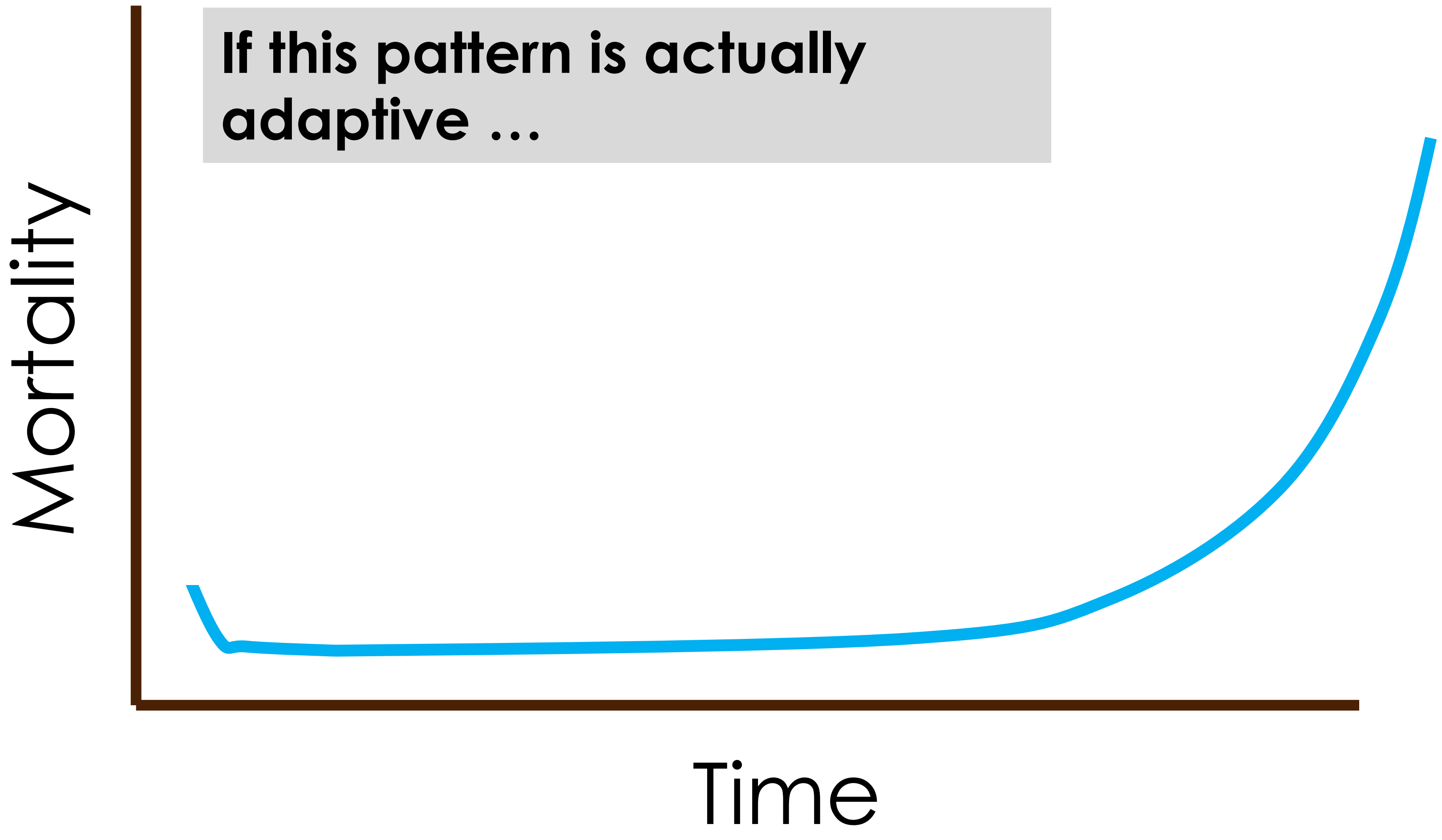

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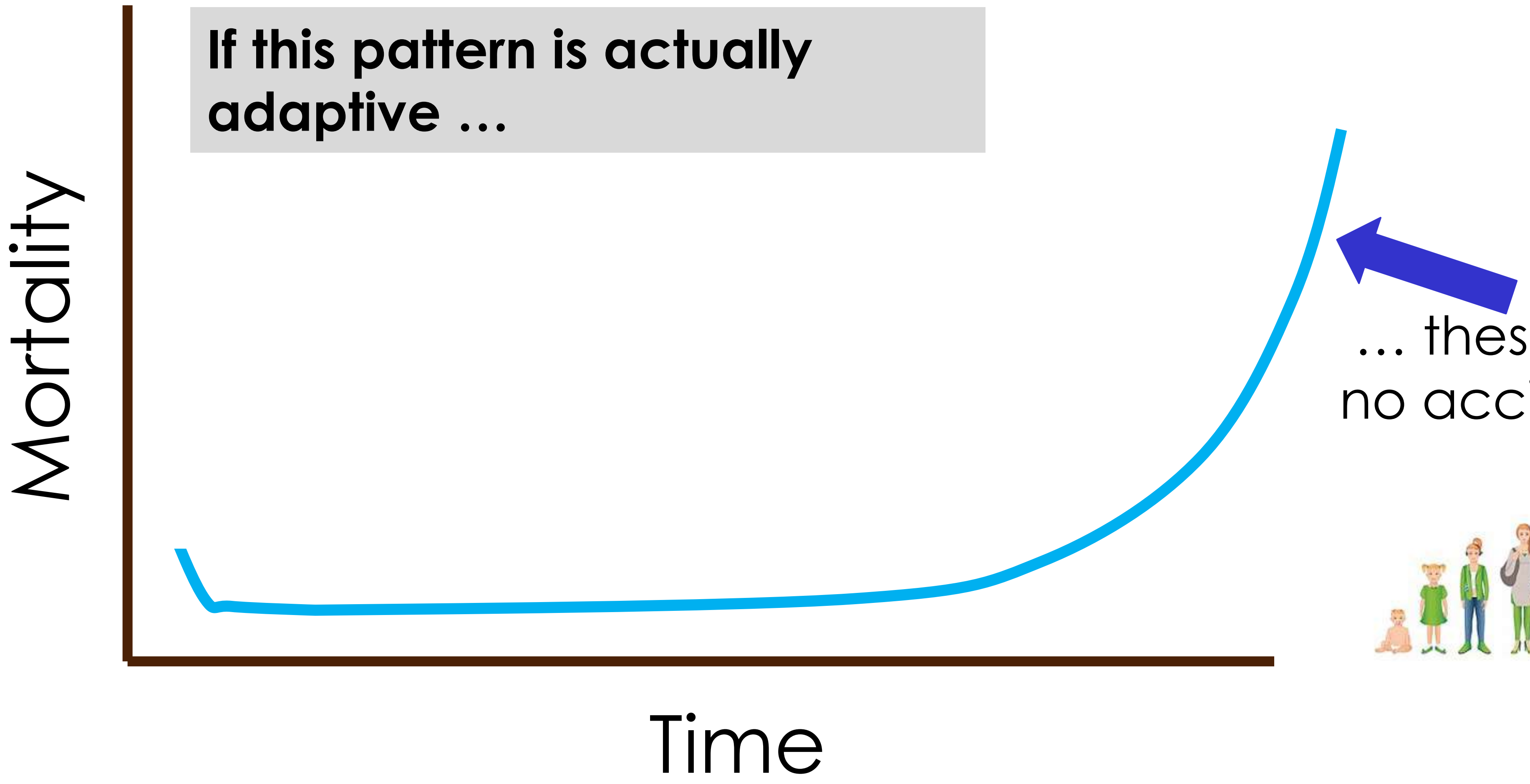

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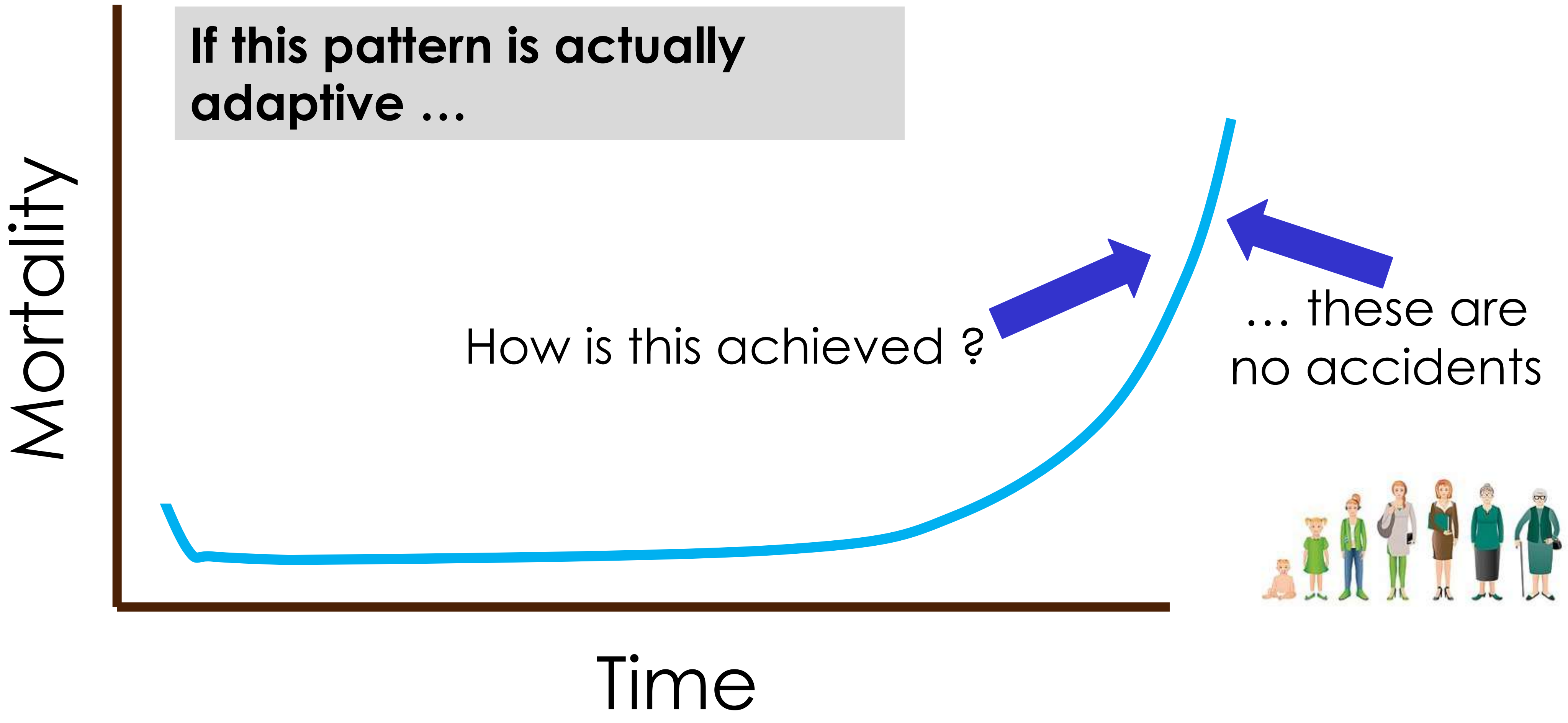

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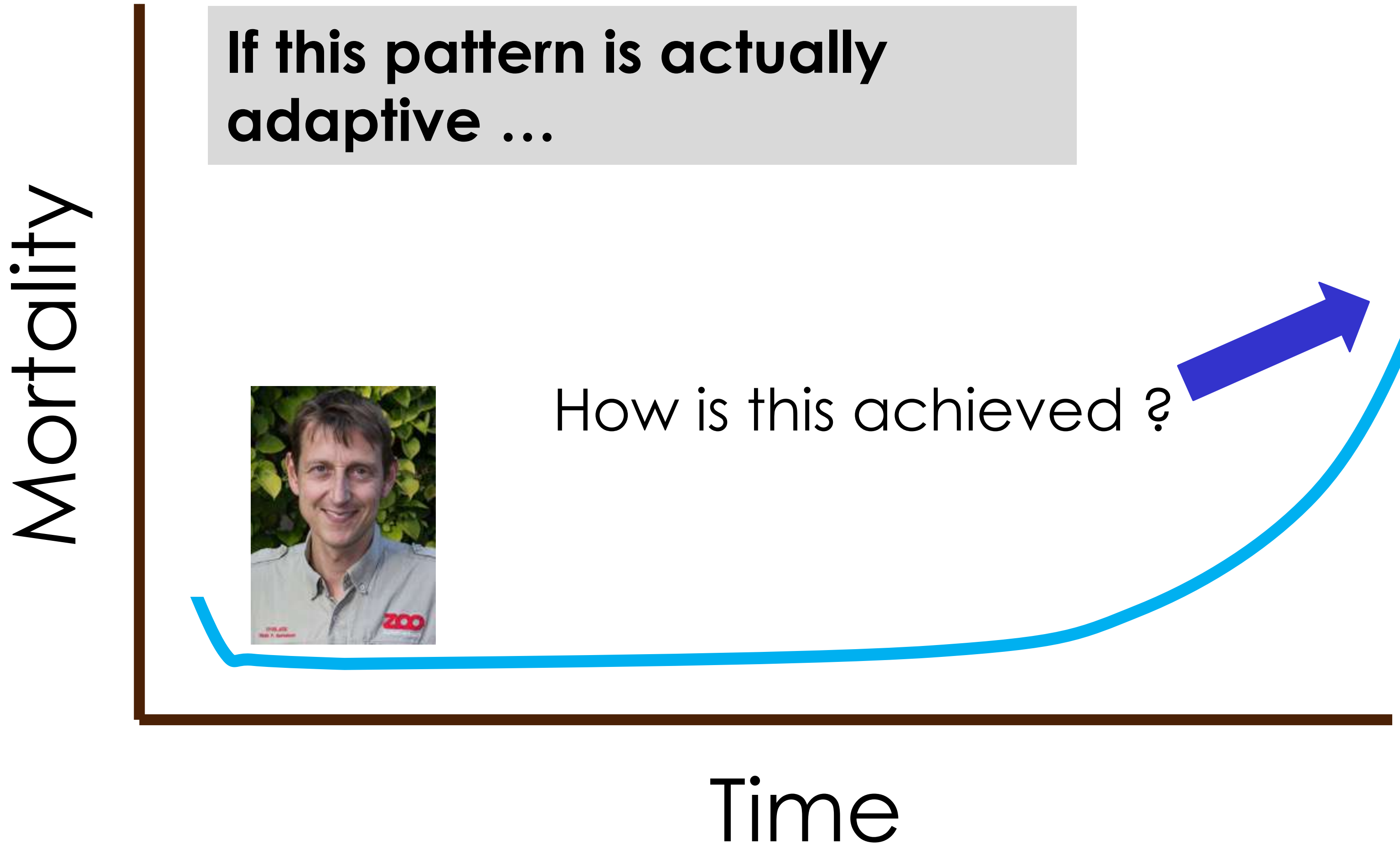

… these are no accidents

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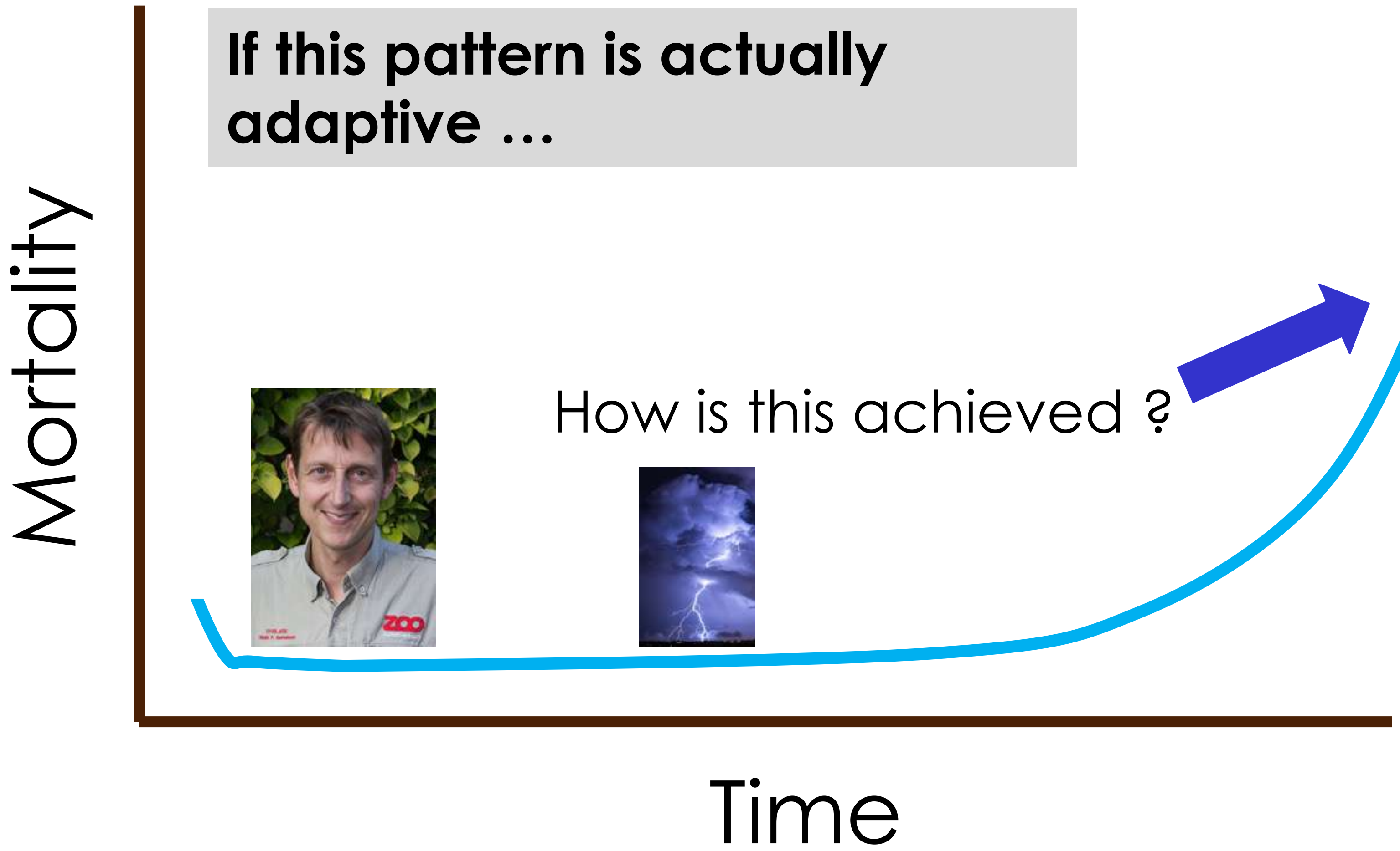

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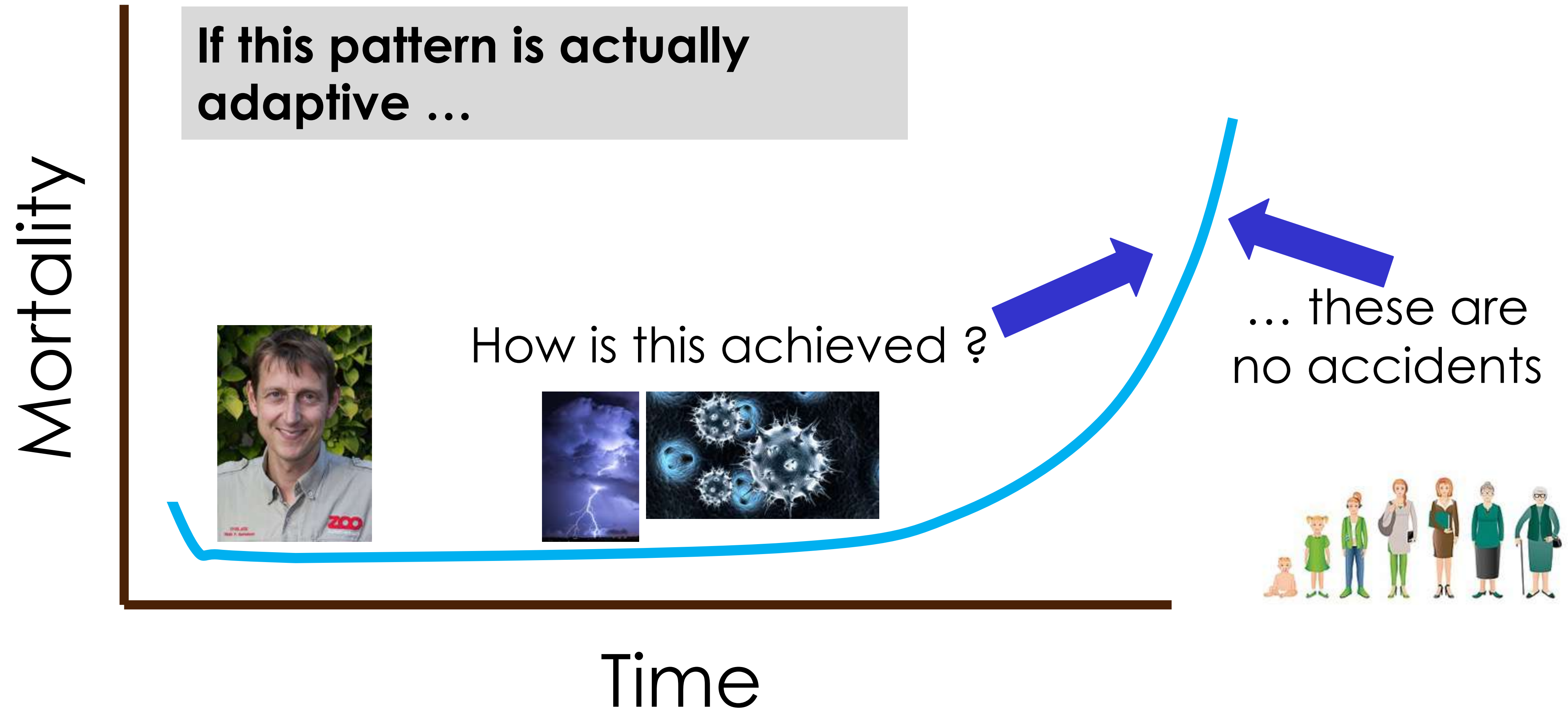

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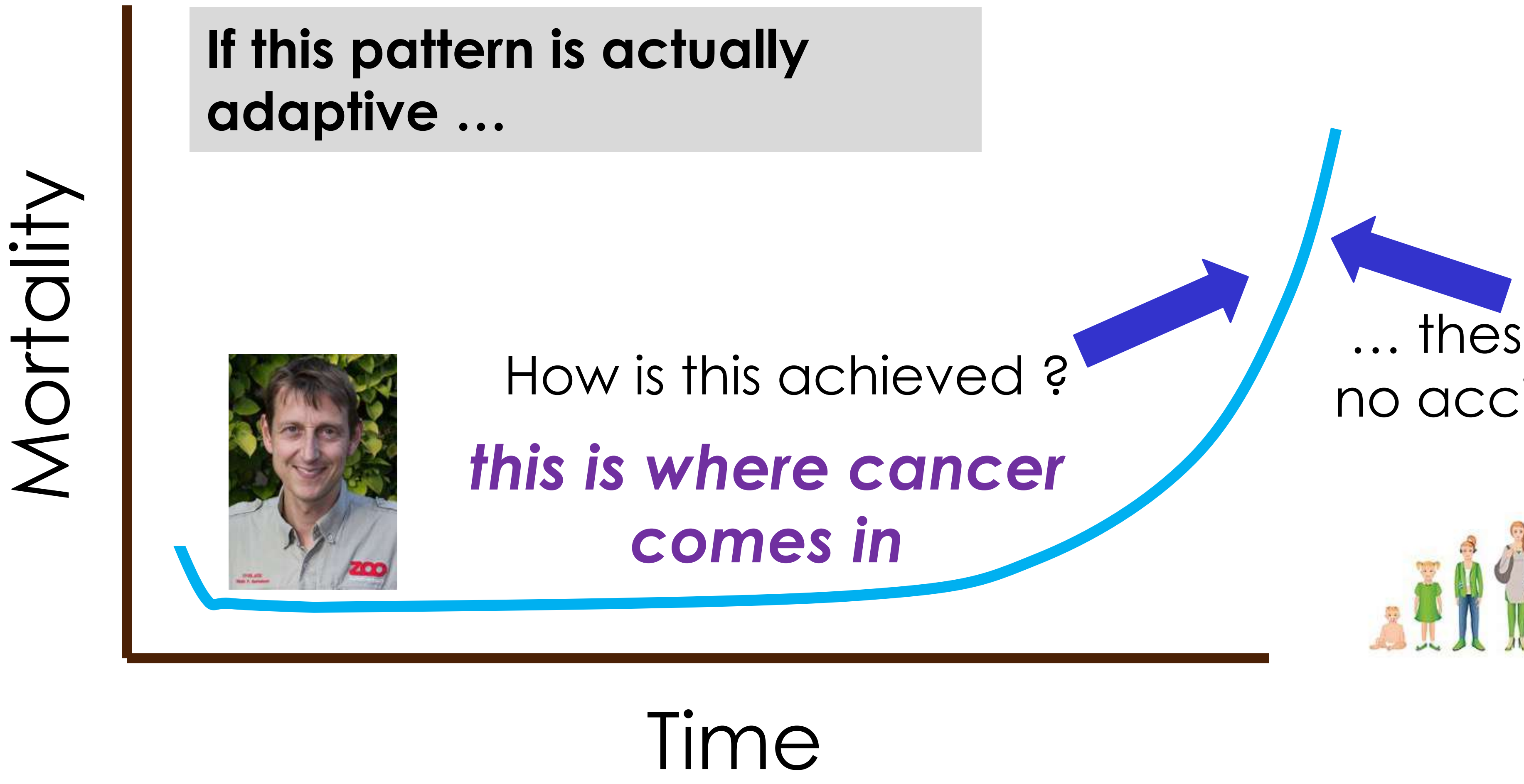

… these are no accidents

How to fine-tune aging

Cancer as a consequence of the adaptation for aging

Cancer occurs if the body does not prevent it.

Cancer as a consequence of the adaptation for aging

Cancer occurs if the body does not prevent it.

Reducing cancer prevention could be an adaptation to achieve aging.

NATURE AGING | VOL 2 | MAY 2022 | 365-366

The importance of aging in cancer research

Cancer is a disease of aging

NATURE AGING | VOL 2 | MAY 2022 | 365–366

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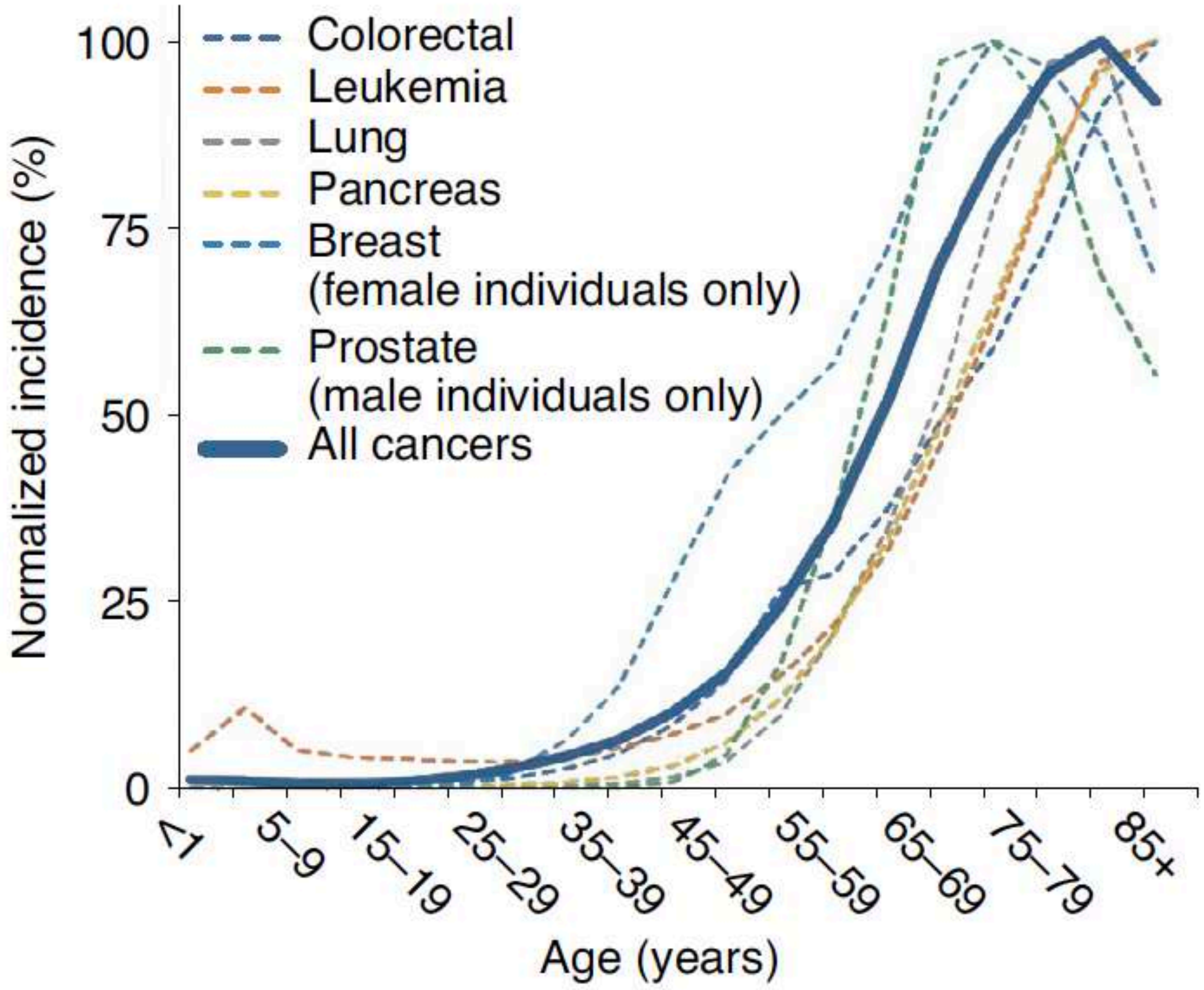

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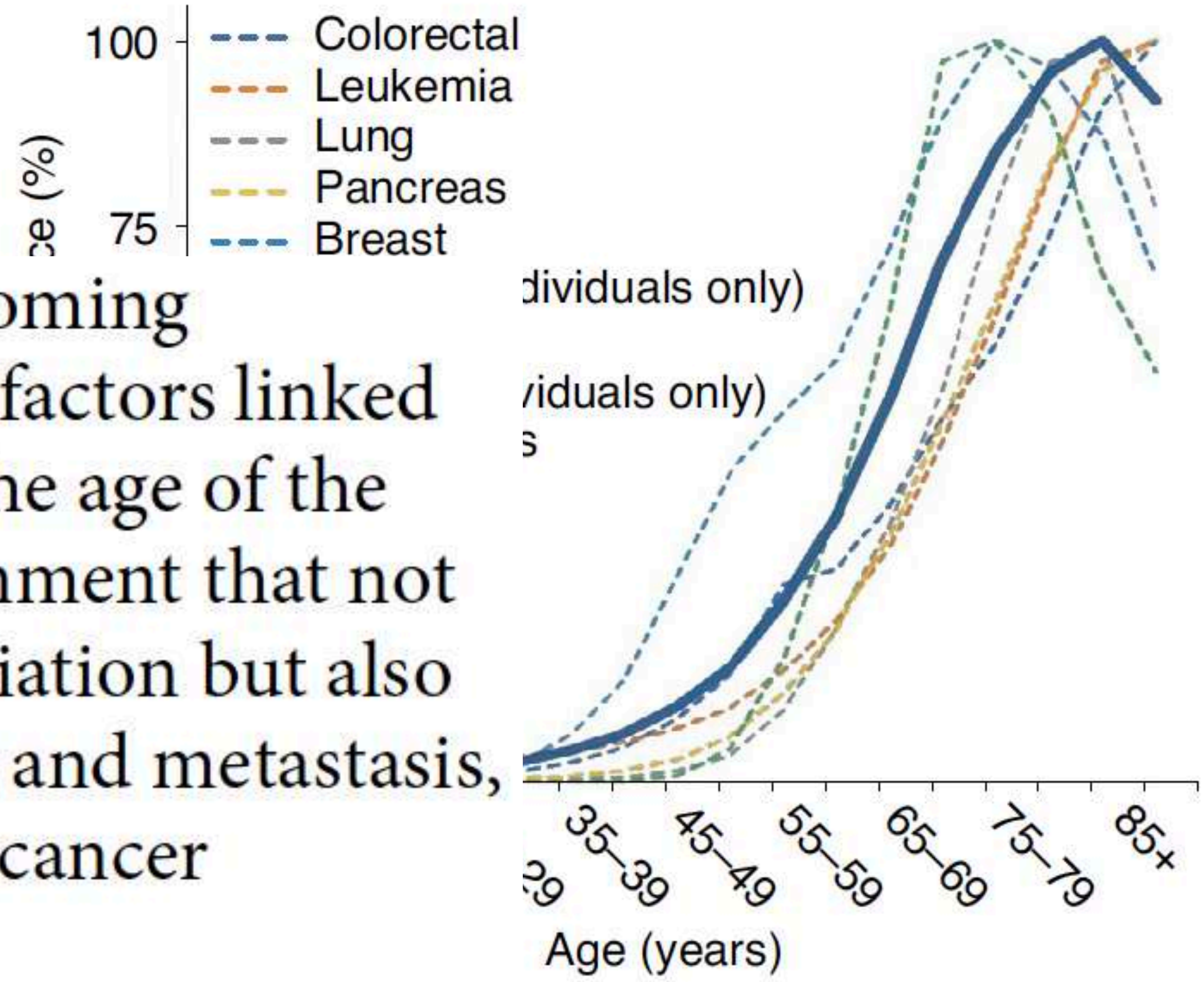


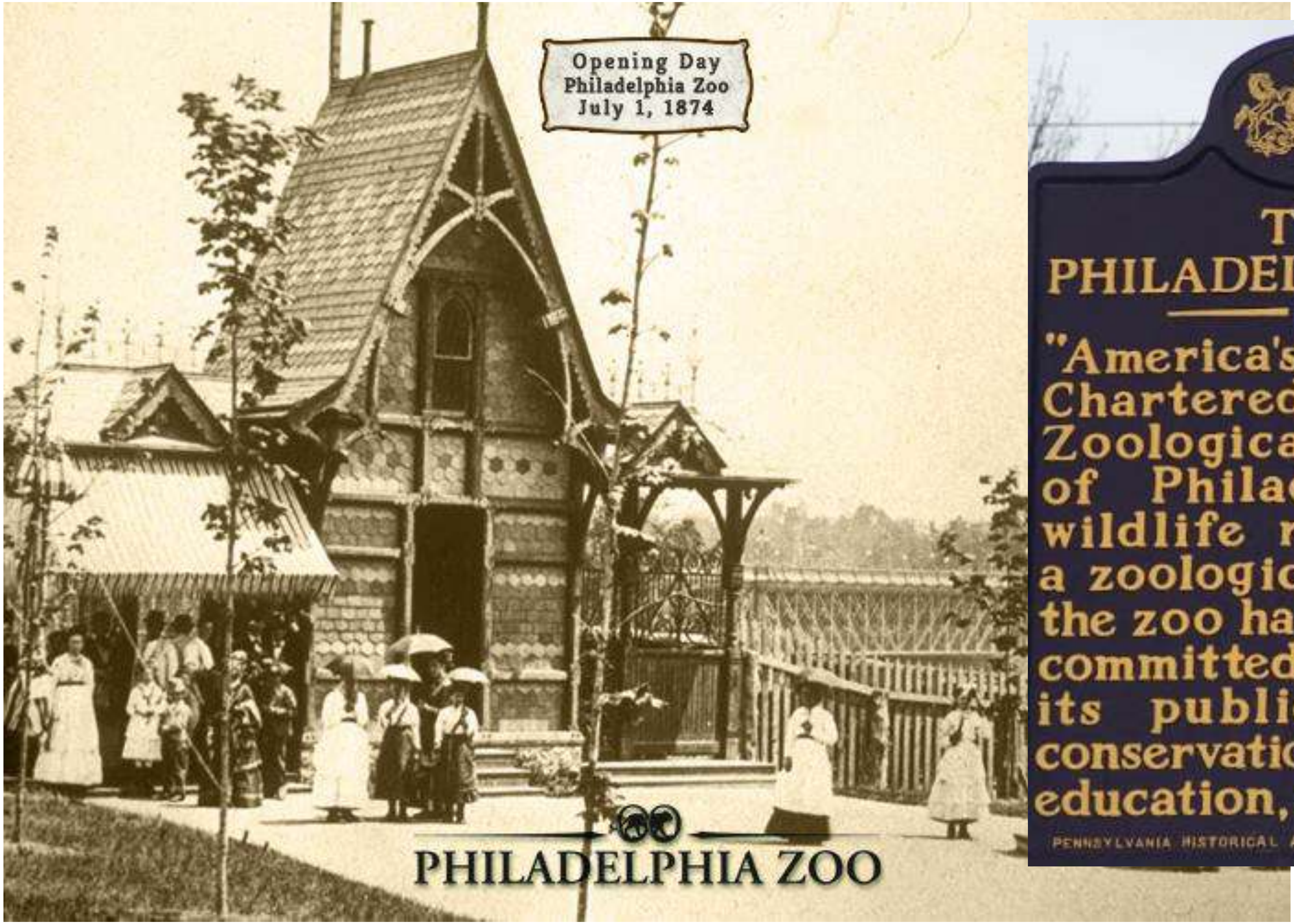
Thus, it is becoming increasingly clear that many factors linked to the biology of aging and the age of the host contribute to an environment that not only can promote tumor initiation but also influence tumor progression and metastasis, and even affect resistance to cancer treatments.

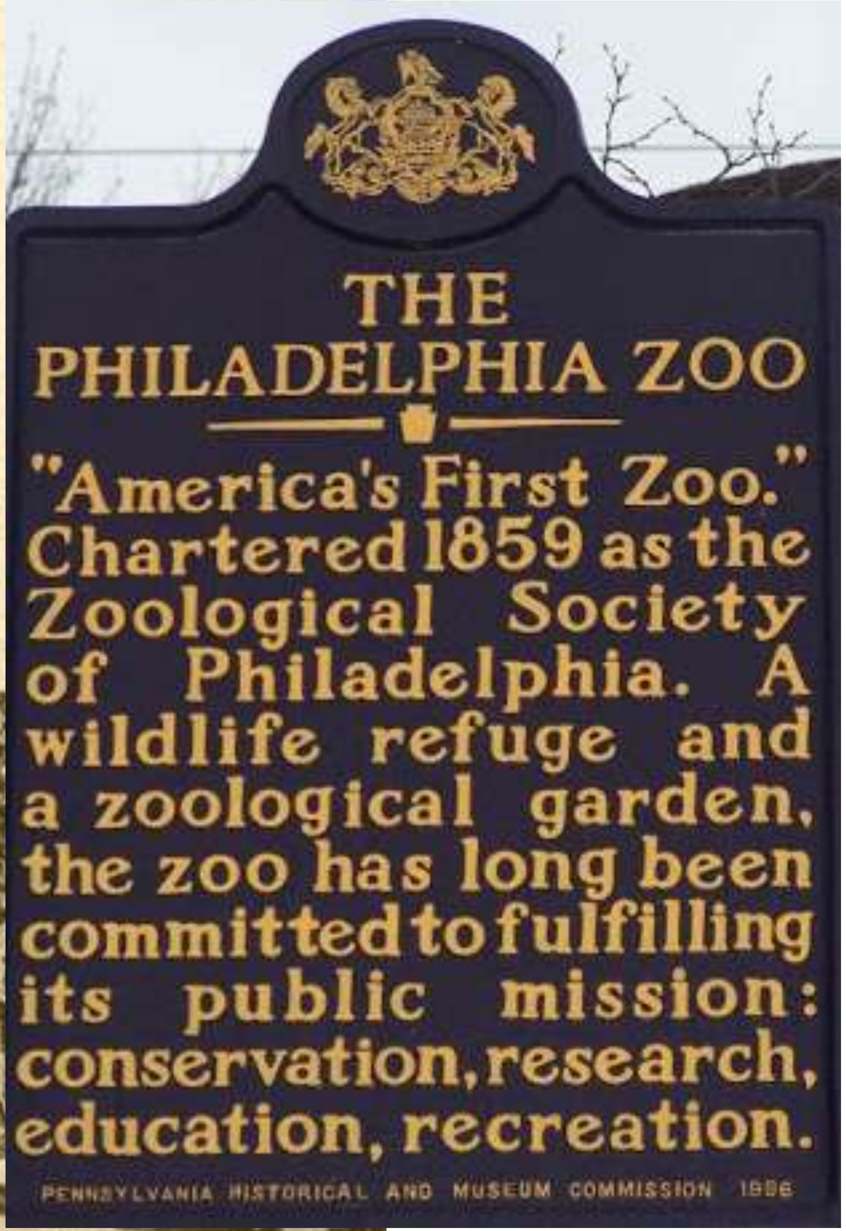
Cancer 101

Cancer 101

to get cancer, you have to get old


ZOO
PHILADELPHIA ZOO


Opening Day
Philadelphia Zoo
July 1, 1874
PHILADELPHIA ZOO


THE
PHILADELPHIA ZOO
"America's First Zoo."
Chartered 1859 as the
Zoological Society
of Philadelphia. A
wildlife refuge and
a zoological garden,
the zoo has long been
committed to fulfilling
its public mission:
conservation, research,
education, recreation.
PENNSYLVANIA HISTORICAL AND MUSEUM COMMISSION

CANCER RESEARCH

VOLUME 19 FEBRUARY 1959 NUMBER 2

Frequency and Types of Tumors in Mammals and Birds of the Philadelphia Zoological Garden

LOUISE S. LOMBARD* AND ERNEST J. WITTE†

The post mortem records of the Philadelphia Zoological Garden are continuous since 1901. Reviews of these records for each decade through 1931 have shown that the frequency and types of malignant tumors did not change appreciably during this period (7, 8, 17).

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INCIDENCE AND NATURE OF TUMORS IN CAPTIVE WILD MAMMALS AND BIRDS[1]

The American Journal of Cancer (1933)

HERBERT L. RATCLIFFE

Mammals	Maturity Period	Estimated Longevity	Average Captivity Period		Incidence
			All Animals	Tumor Bearers	
	yrs.	yrs.	yrs.	yrs.	
PRIMATES			1.5	9.2	
Cercopithecidae	2–4	10–20	1.3	10.3	1.04
Cebidae	2–4	10–20	1.6	—	—
CARNIVORA			3.6	8.7	4.32
Felidae	1–3	5–15	3.9	11.5	4.16
Canidae	1–2	5–10	3.5	7.7	5.91
Mustelidae	1	5–8	2.6	—	—
Procyonidae	1	5–8	2.5	5.2	4.00
Viverridae	1	5–8	3.7	5.5	7.55
Ursidae	2–4	10–20	6.5	13.7	6.66
ARTIODACTYLA			5.3	10.6	1.84
Bovidae	2–4	10–20	4.3	10.7	2.45
Cervidae	2–3	10–15	3.5	—	—
RODENTIA			1.9	4.3	5.57
Muridae	3 mo.–1 yr.	2–5	2.2	3.6	14.92
Sciuridae	3 mo.–1 yr.	2–6	1.5	4.2	4.50
MARSUPIALIA			2.0	3.3	2.41
Macropodidae	3	15–20	2.1	8.9	1.74
Didelphyidae	1	5–8	0.2	0.6	1.54

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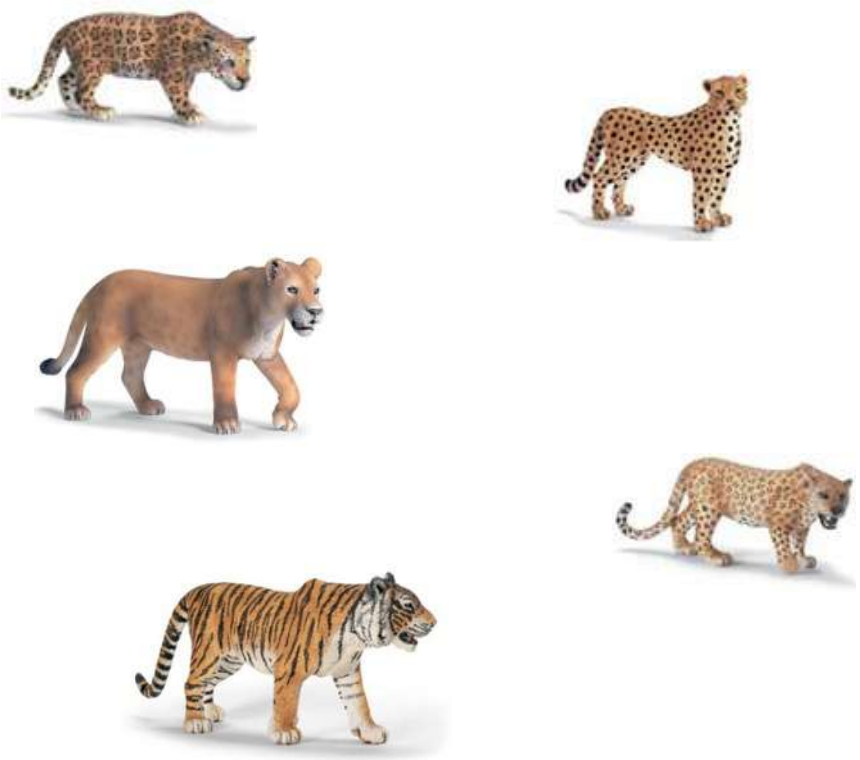
An Overview of Neoplasia in Captive Wild Felids in Southern Italy Zoos

Frontiers in Veterinary Science |
May 2022 | Volume 9 | Article 899481

Ilaria d'Aquino [1*], Giuseppe Piegari [1,2], Silvia Mariagiovanna Casciaro [1,2], Francesco Prisco [1], Guido Rosato [2], Pasquale Silvestre [3], Barbara Degli Uberti [4], Michele Capasso [5], Piero Laricchiuta [6], Orlando Paciello [1,2] and Valeria Russo [1]



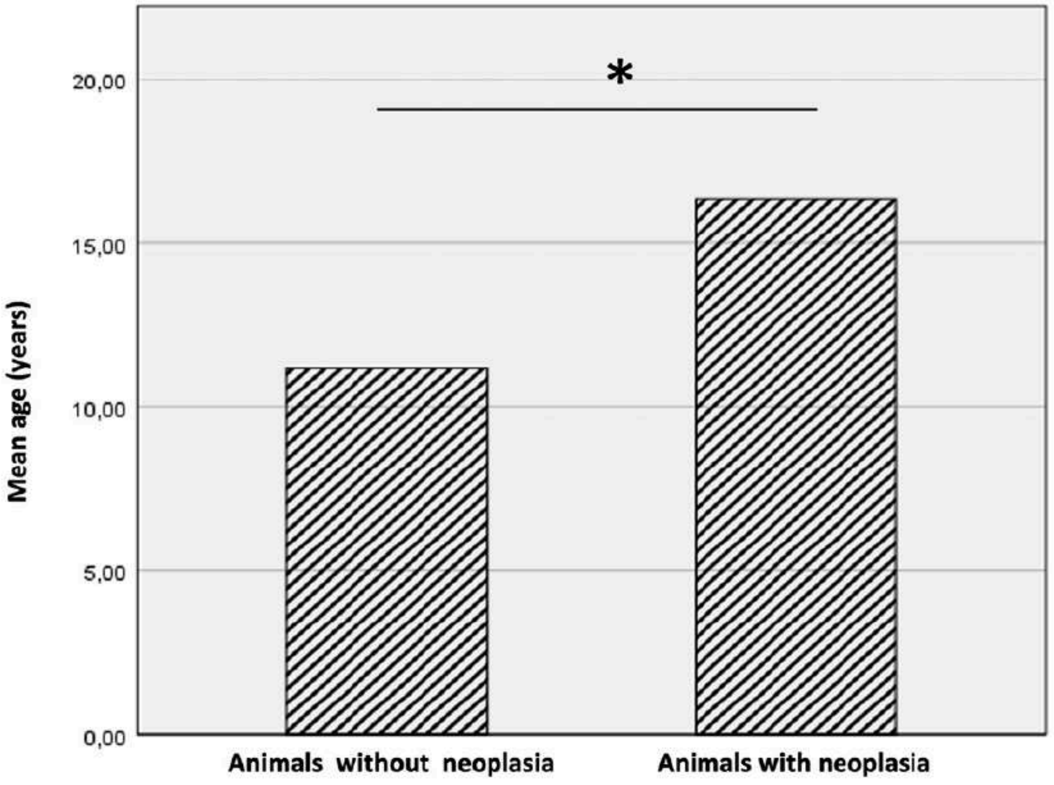


FIGURE 1 | Mean age of animals with and without neoplasia. The animals with cancer were significantly older than animals without neoplasms. The * symbol indicates the value of $P < 0.05$.

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(1) Susceptibility to tumor growth may be equal in all of the groups studied, but unequal adaptability to captive conditions may not allow equal opportunity for tumor development; or (2) the differences in tumor incidence found in this series may be expressions of natural resistance or susceptibility to neoplasia.

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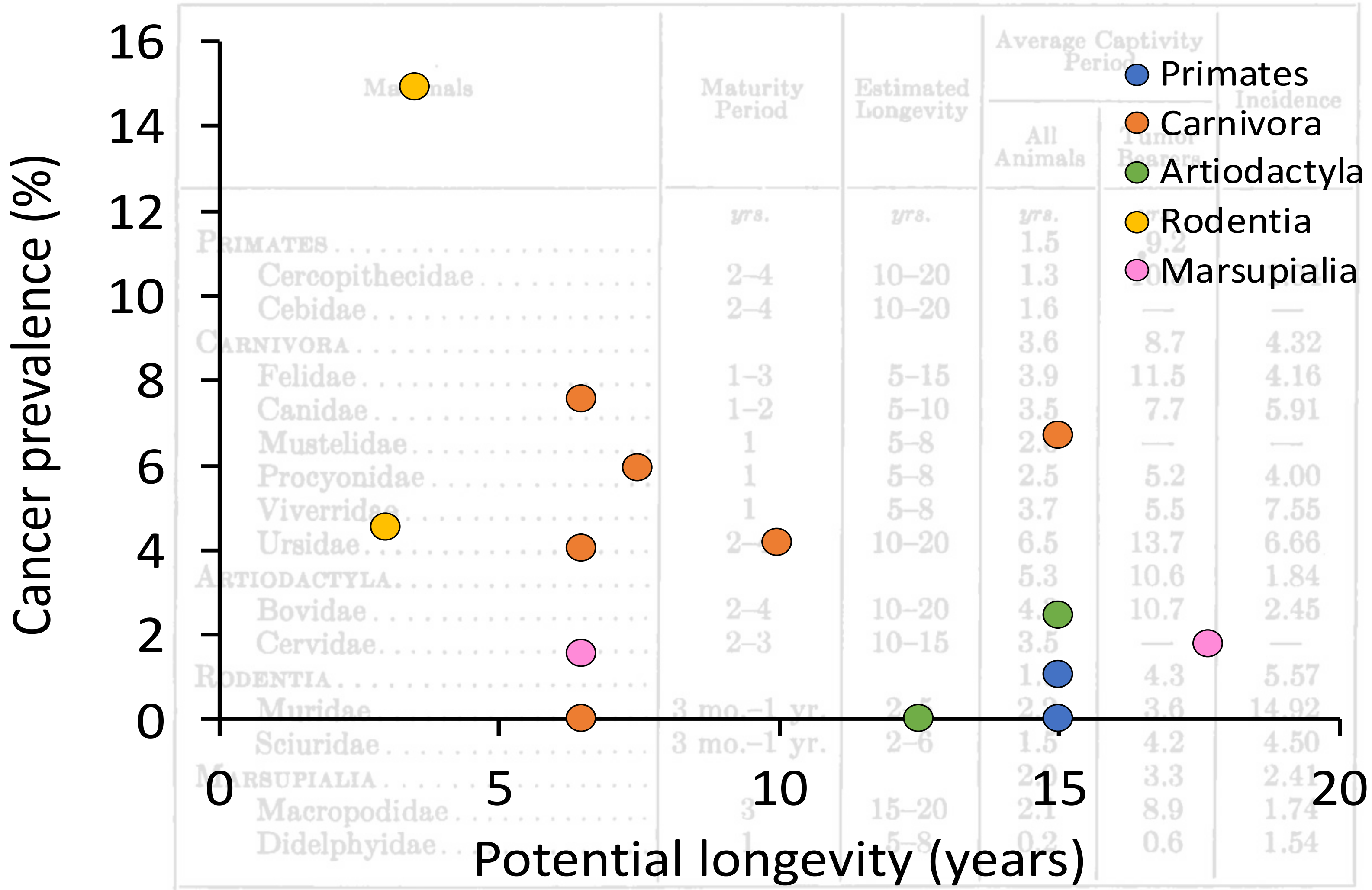

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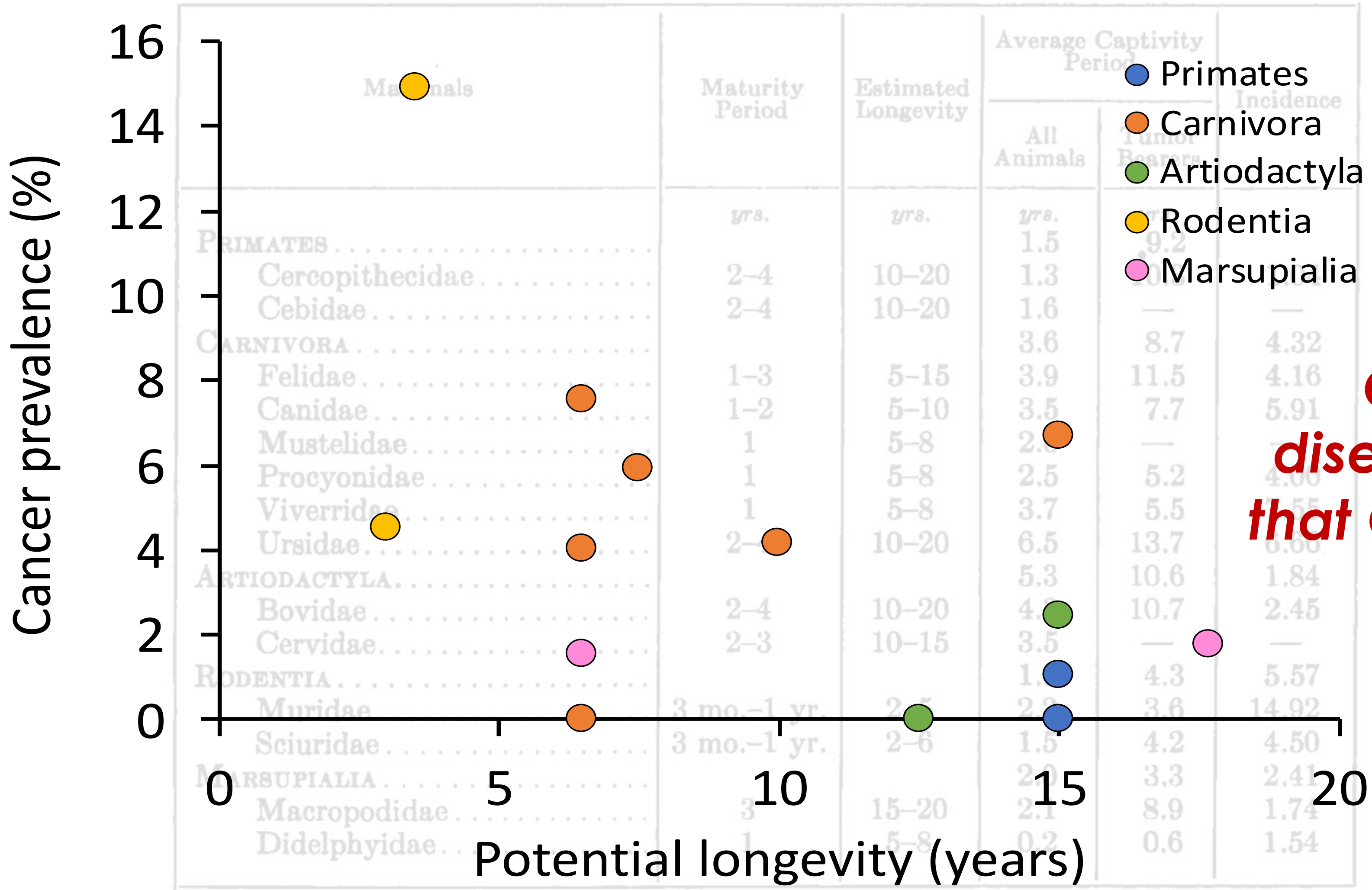

Cancer is not a disease of animals that CAN live many years.

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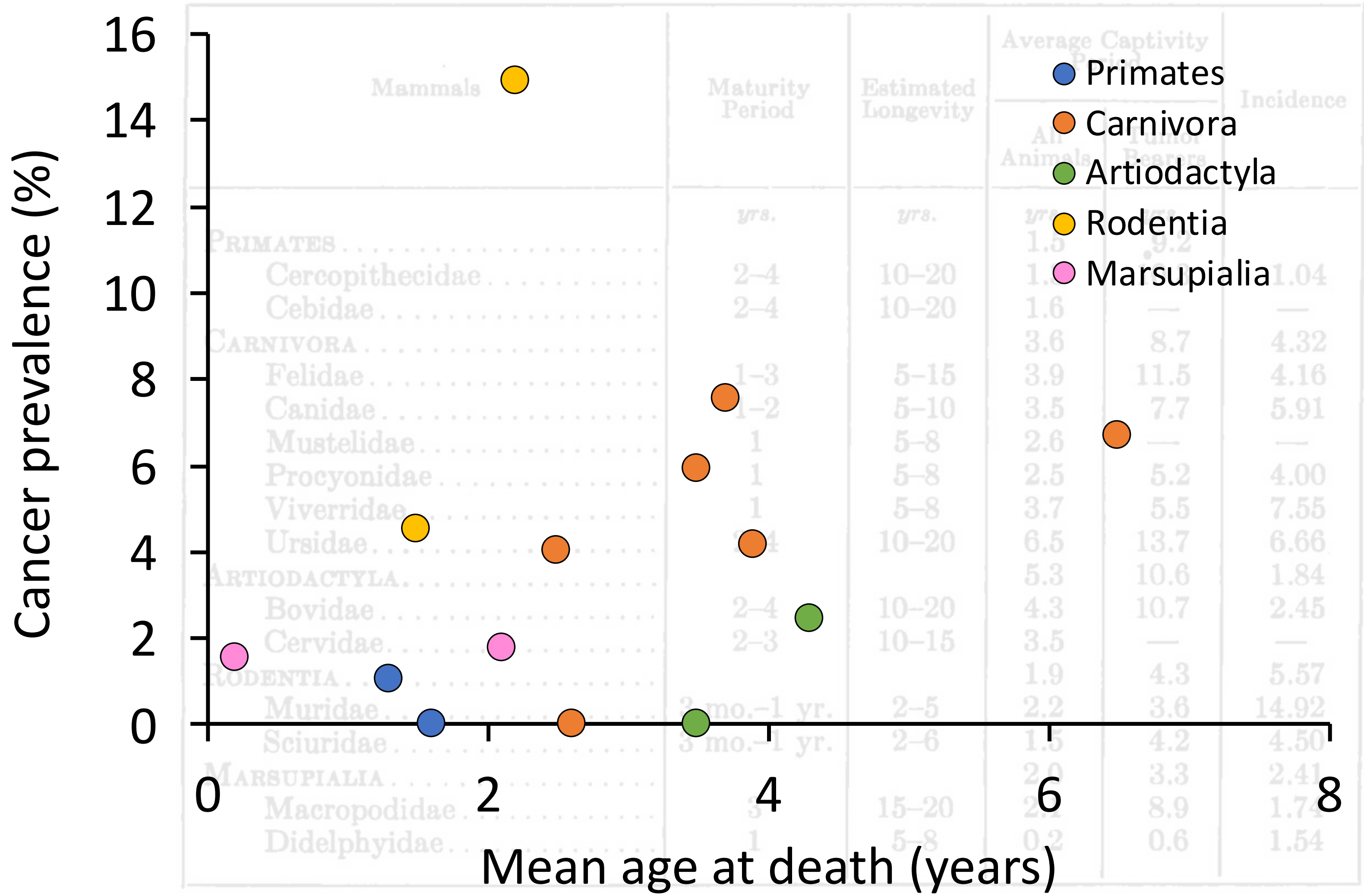
The American Journal of Cancer (1933)



INCIDENCE AND NATURE OF TUMORS IN CAPTIVE WILD MAMMALS AND BIRDS[1]

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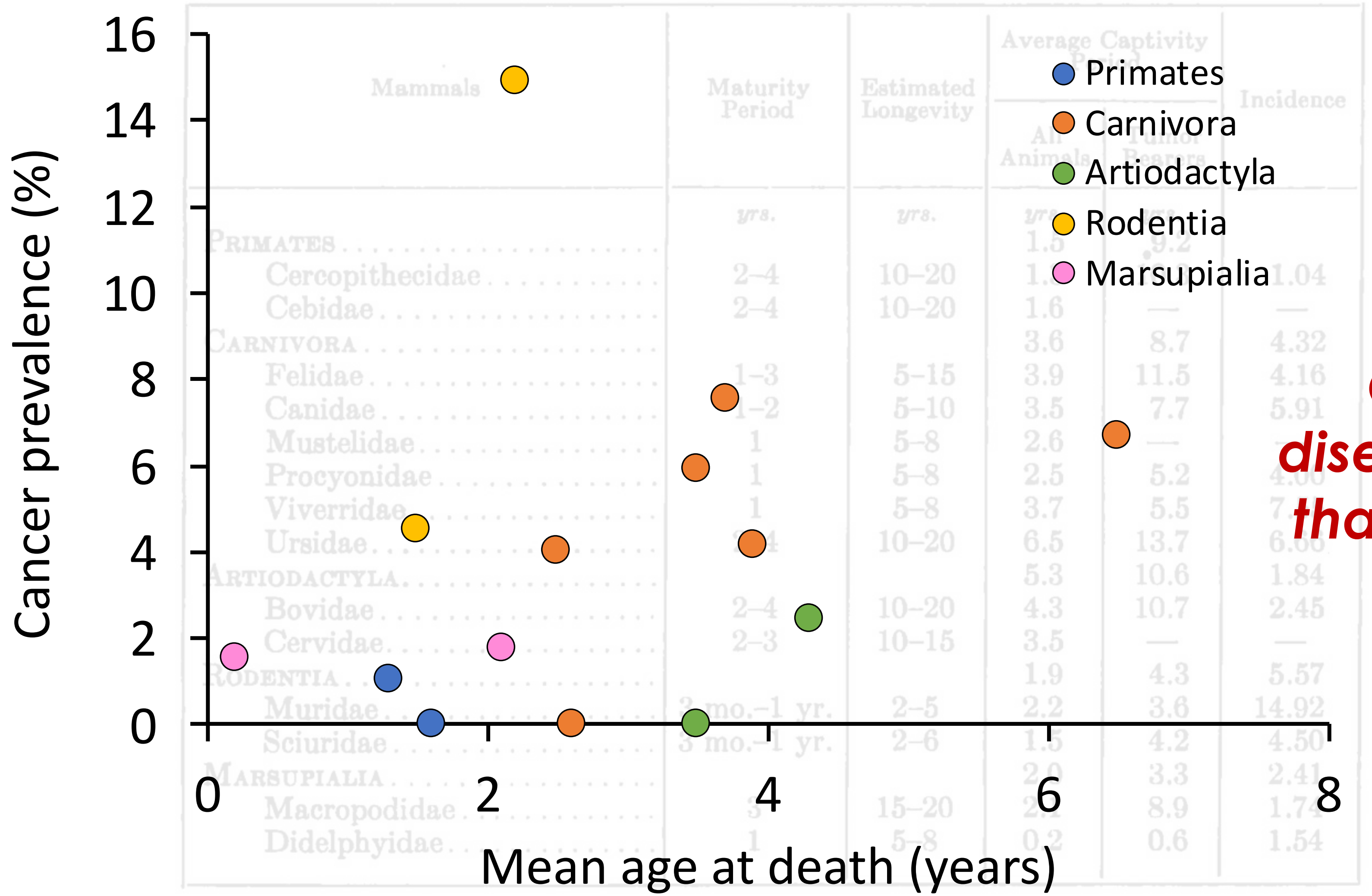

Cancer is not a disease of animals that DO live many years.

INCIDENCE AND NATURE OF TUMORS IN CAPTIVE WILD MAMMALS AND BIRDS[1]

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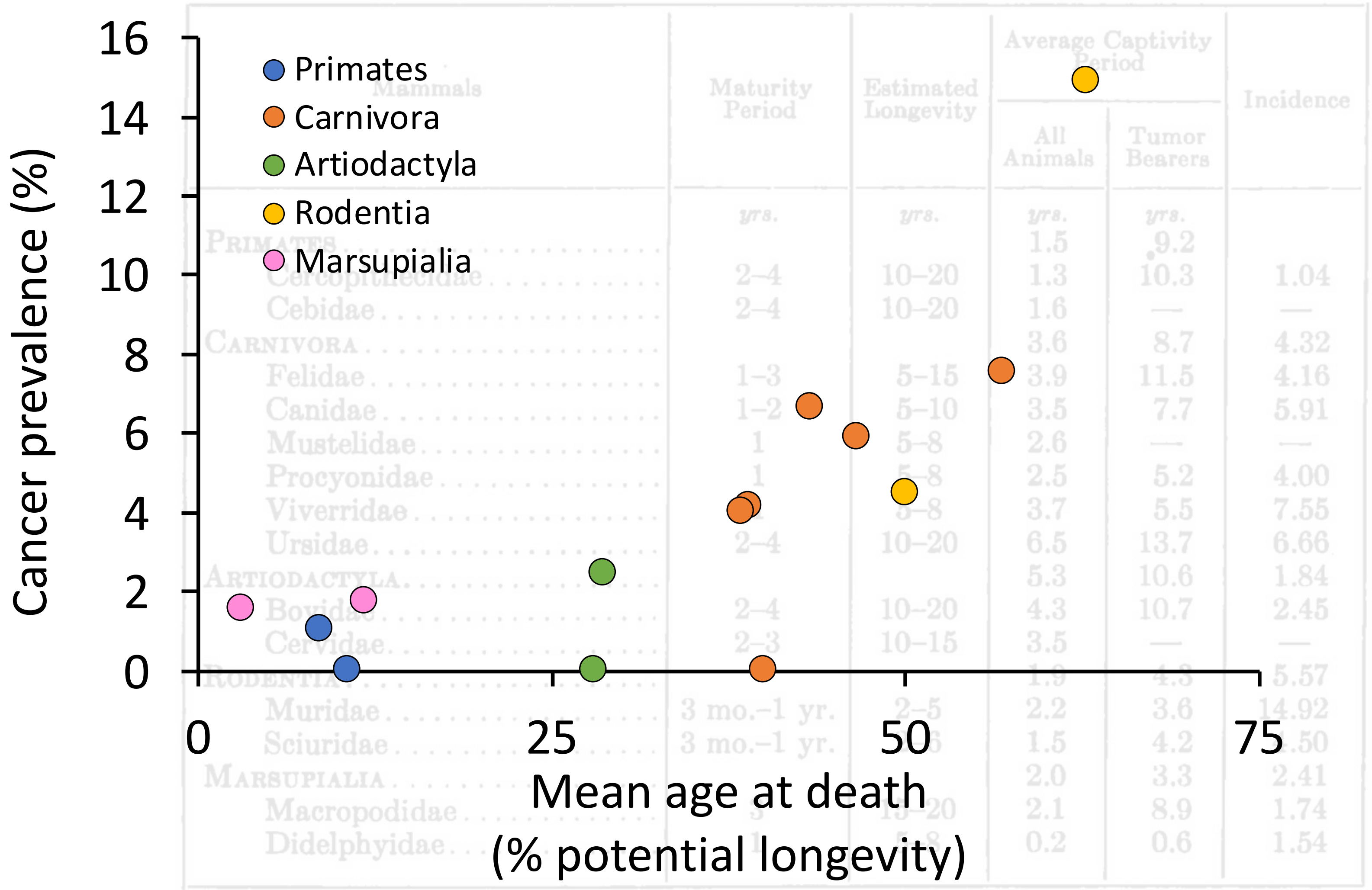

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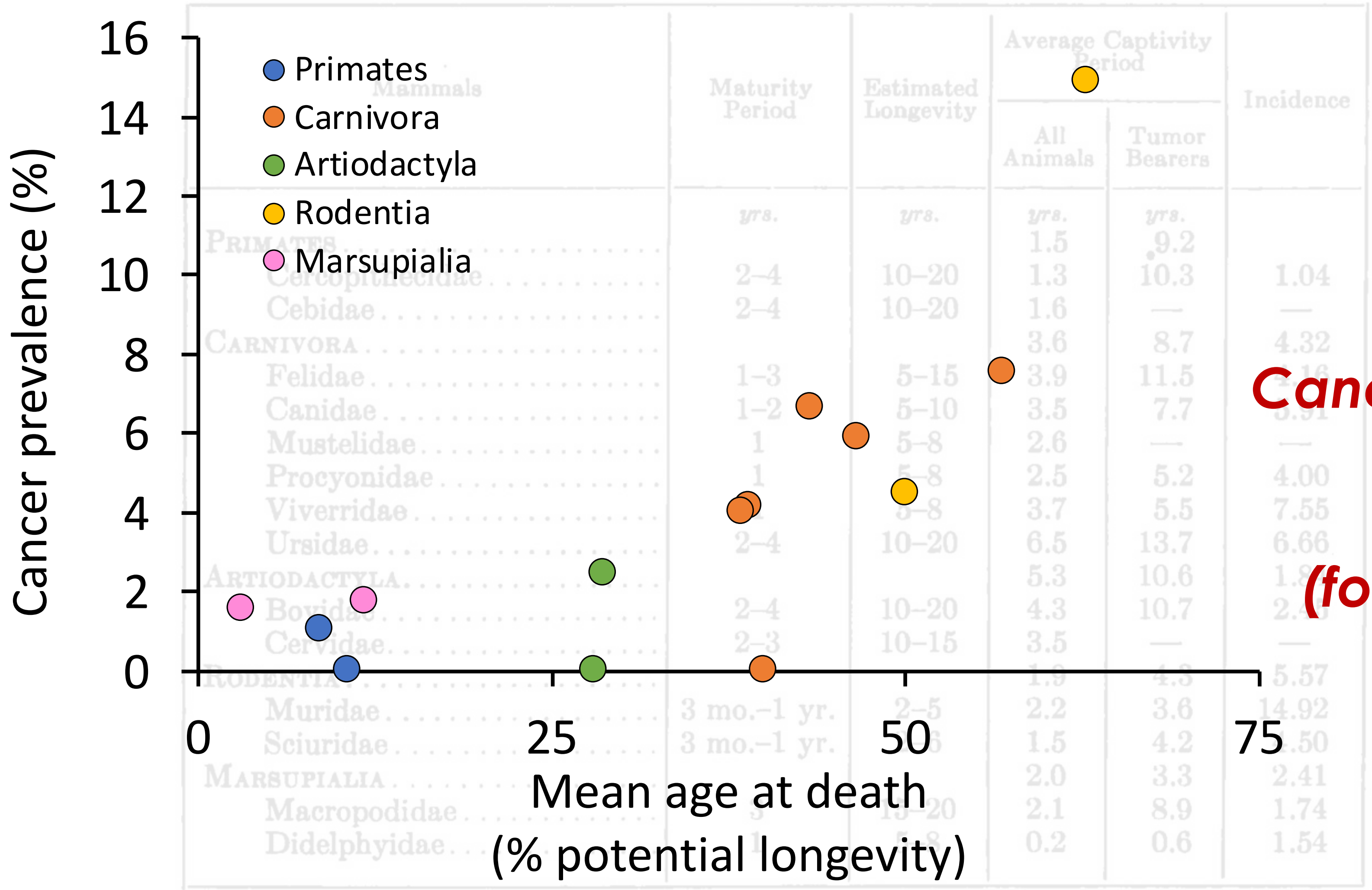


Cancer is a disease of animals that ARE OLD (for their species).

Diseases of Dasyurid Marsupials

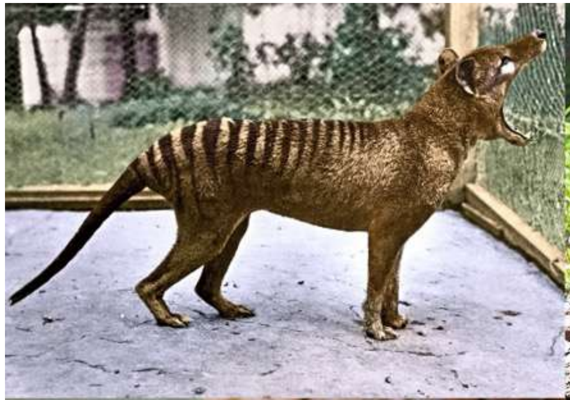
1993

David L. Obendorf

Tumors are particularly prevalent in captive dasyurids (Barker et al., 1963; Attwood and Woolley, 1973).

Dasyurids

Thylacine



Tasmanian devil

Quoll

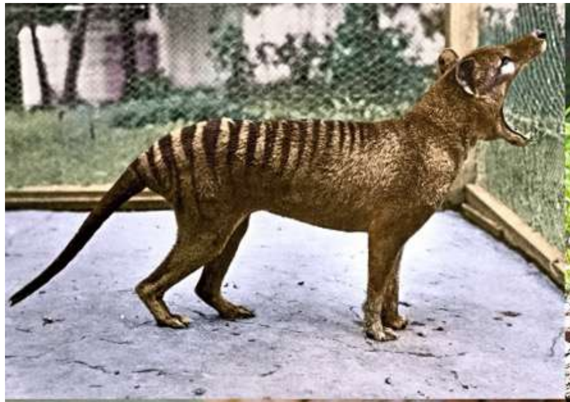
Numbat

Antechinus

Dunnart

Dasyurids

Thylacine



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Eastern quolls and Tasmanian devils rarely live longer than two and four years respectively in the wild (Godsell, 1982; Green, 1967). Life expectancy in captivity can be twice as long as in the wild but a variety of degenerative diseases occur in older animals.

Cancer 101

to get cancer, you have to get old

Cancer 202

to get cancer, you have to get old

Cancer 202

to get cancer, you have to get old
(and to get old, you must not die of other stuff)

INCIDENCE AND NATURE OF TUMORS IN CAPTIVE WILD MAMMALS AND BIRDS[1]

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The American Journal of Cancer (1933)

INCIDENCE AND NATURE OF TUMORS IN CAPTIVE WILD MAMMALS AND BIRDS[1]

HERBERT L. RATCLIFFE

The American Journal of Cancer (1933)

DIETS FOR ZOOLOGICAL GARDENS: AIDS TO CONSERVATION AND DISEASE CONTROL

by Herbert L. Ratcliffe

THE INTERNATIONAL

ZOO YEARBOOK

VOLUME VI

Edited by
Caroline Jarvis

Assisted by
Ruth Biegler

Yearbook Advisory Committee

Professor E. J. W. Barrington, DSC
Professor F. Bourlière, MD, LSC
William G. Conway
The Earl of Cranbrook, MA, TREAS. LS
Francis C. Fraser, CBE, DSC
R. E. Glover, DSC, FRCVS
Sir Allen Lane, MA, LLD
W. Lane-Petter, MA, MB, BCHIR
W. K. Van den bergh

CURAE GENUS OMNE ANIMANTIUM

published by
THE ZOOLOGICAL SOCIETY OF LONDON
1966

DIETS FOR ZOOLOGICAL GARDENS: AIDS TO CONSERVATION AND DISEASE CONTROL

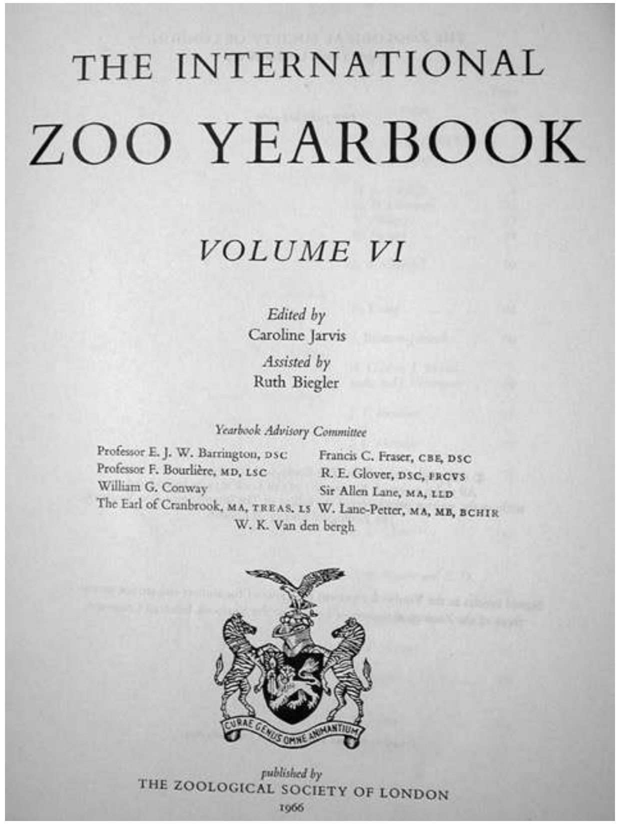
by Herbert L. Ratcliffe

Director, Penrose Research Laboratory, Zoological Society of Philadelphia, and Professor of Comparative Pathology, University of Pennsylvania, U S A

FEEDING WILD ANIMALS IN ZOOLOGICAL GARDENS

by Hans Wackernagel

Scientific Assistant, Basle Zoological Garden, Switzerland



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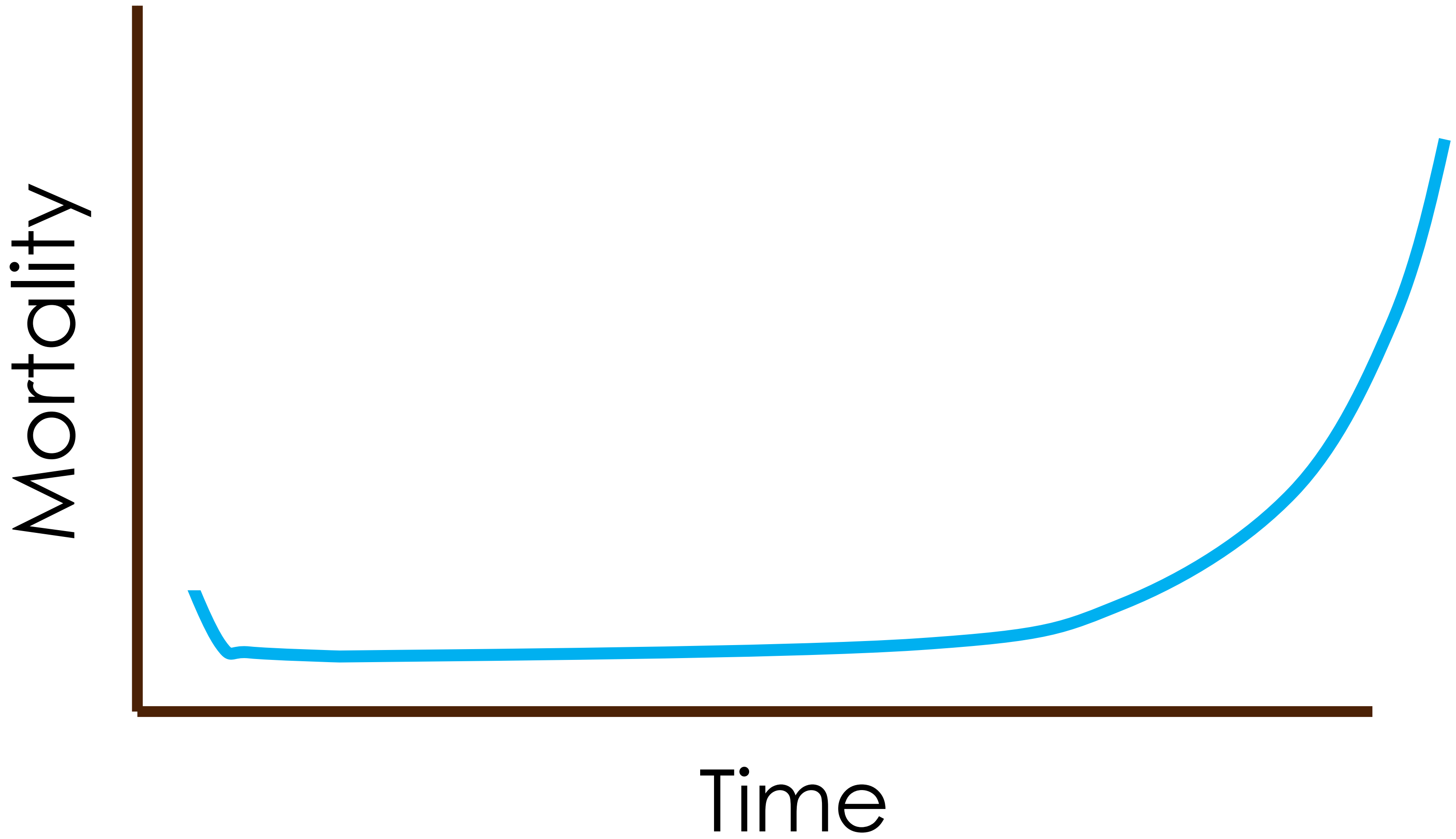
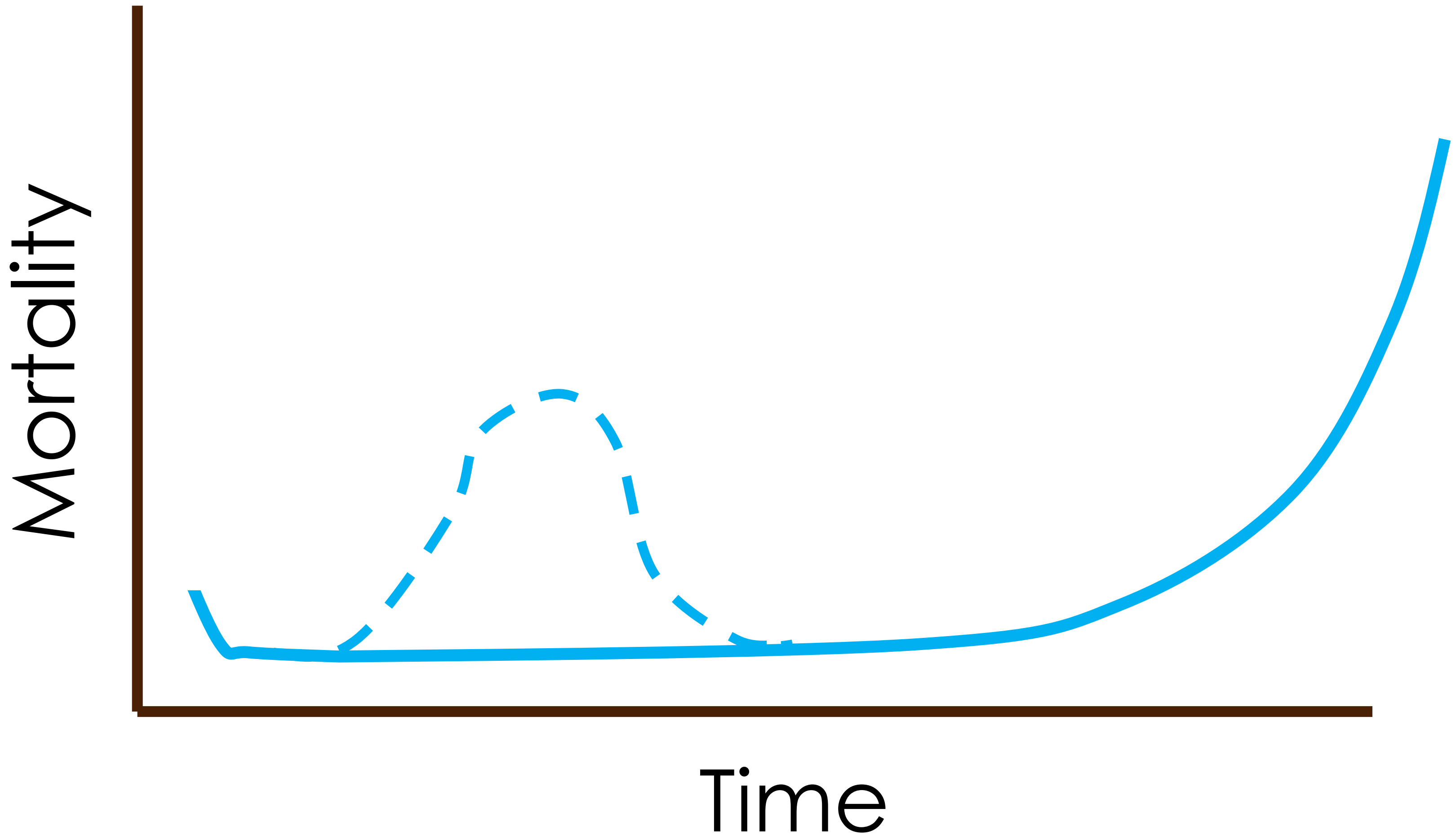
Patterns of mortality

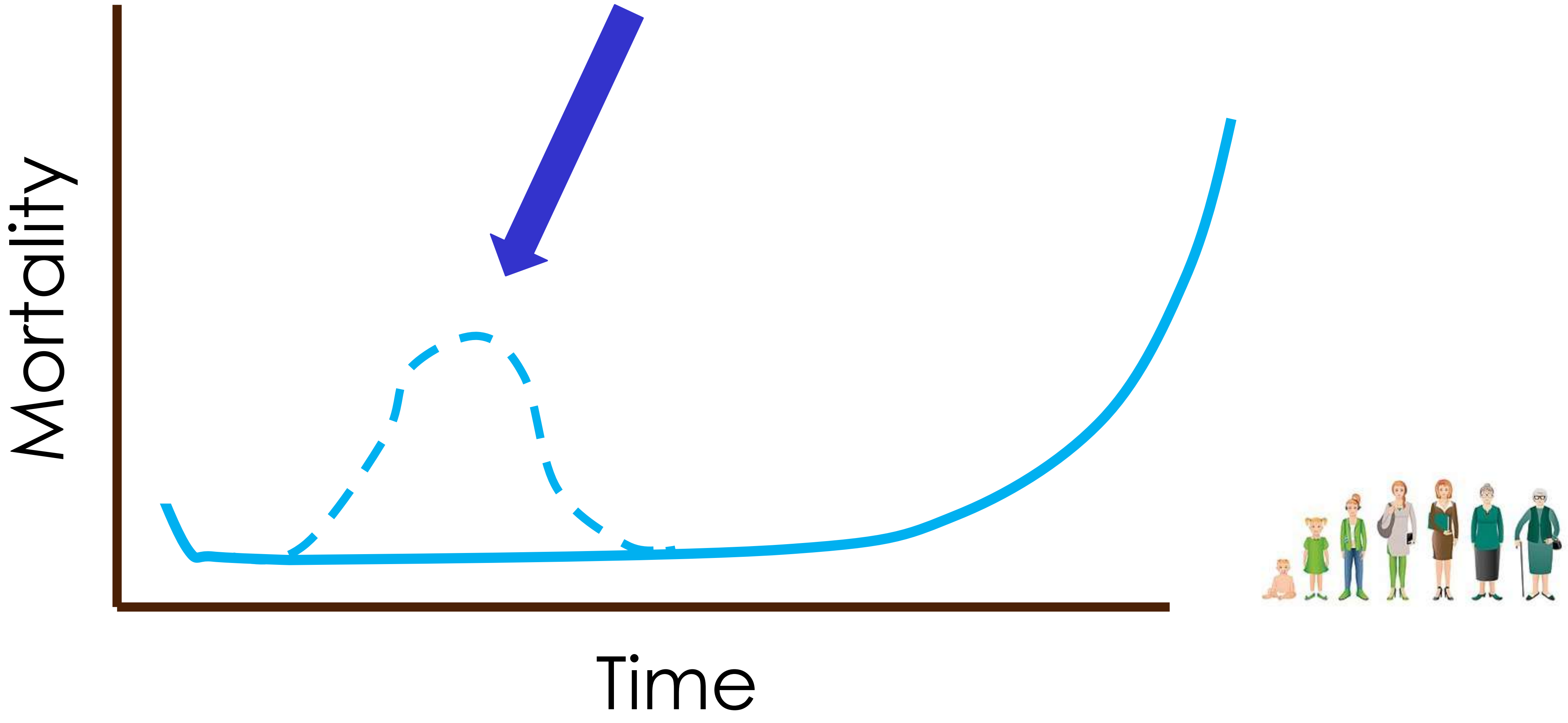


Patterns of mortality



Patterns of mortality

if there is more mortality due to ***extrinsic causes***



Patterns of mortality

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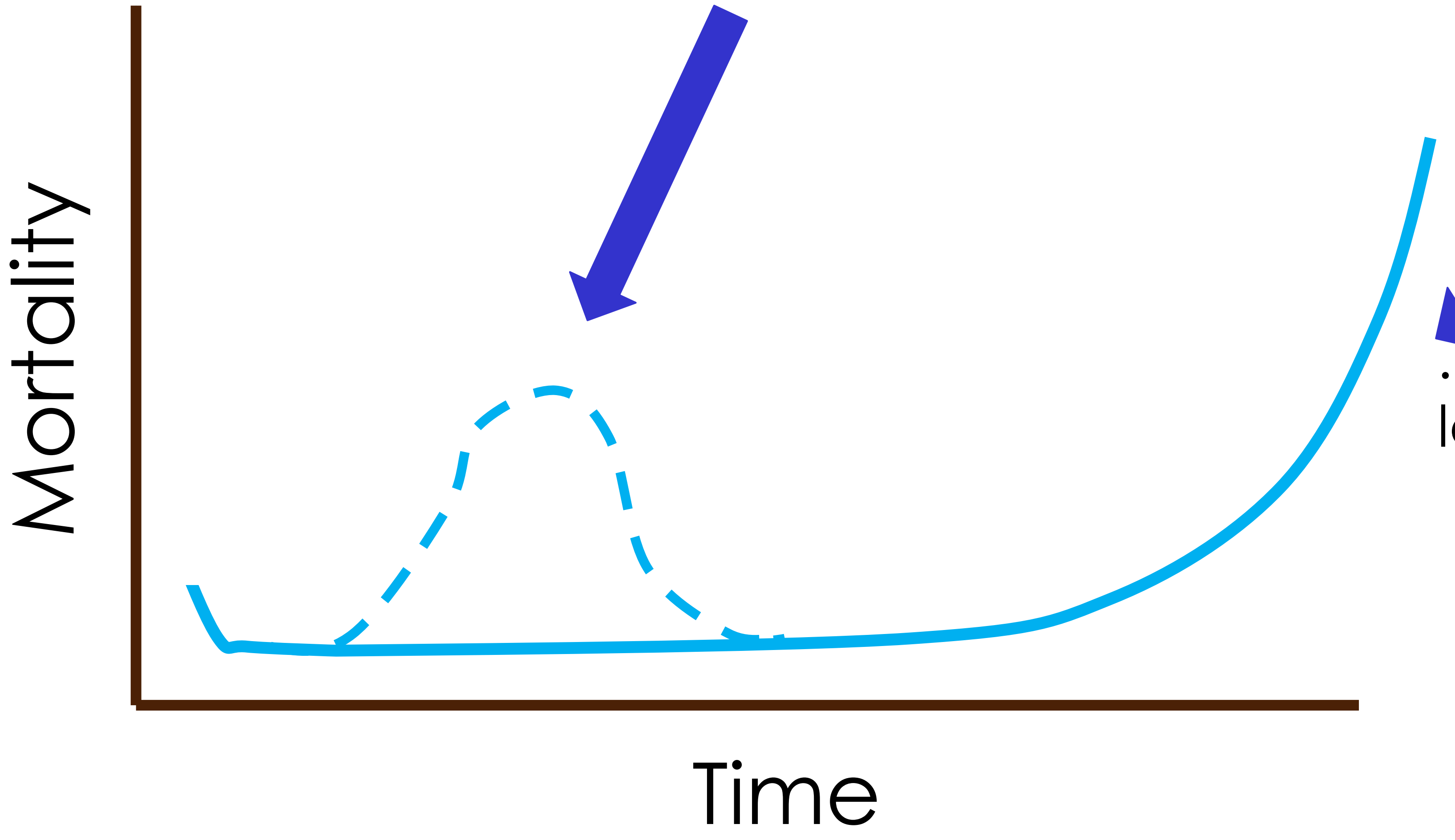
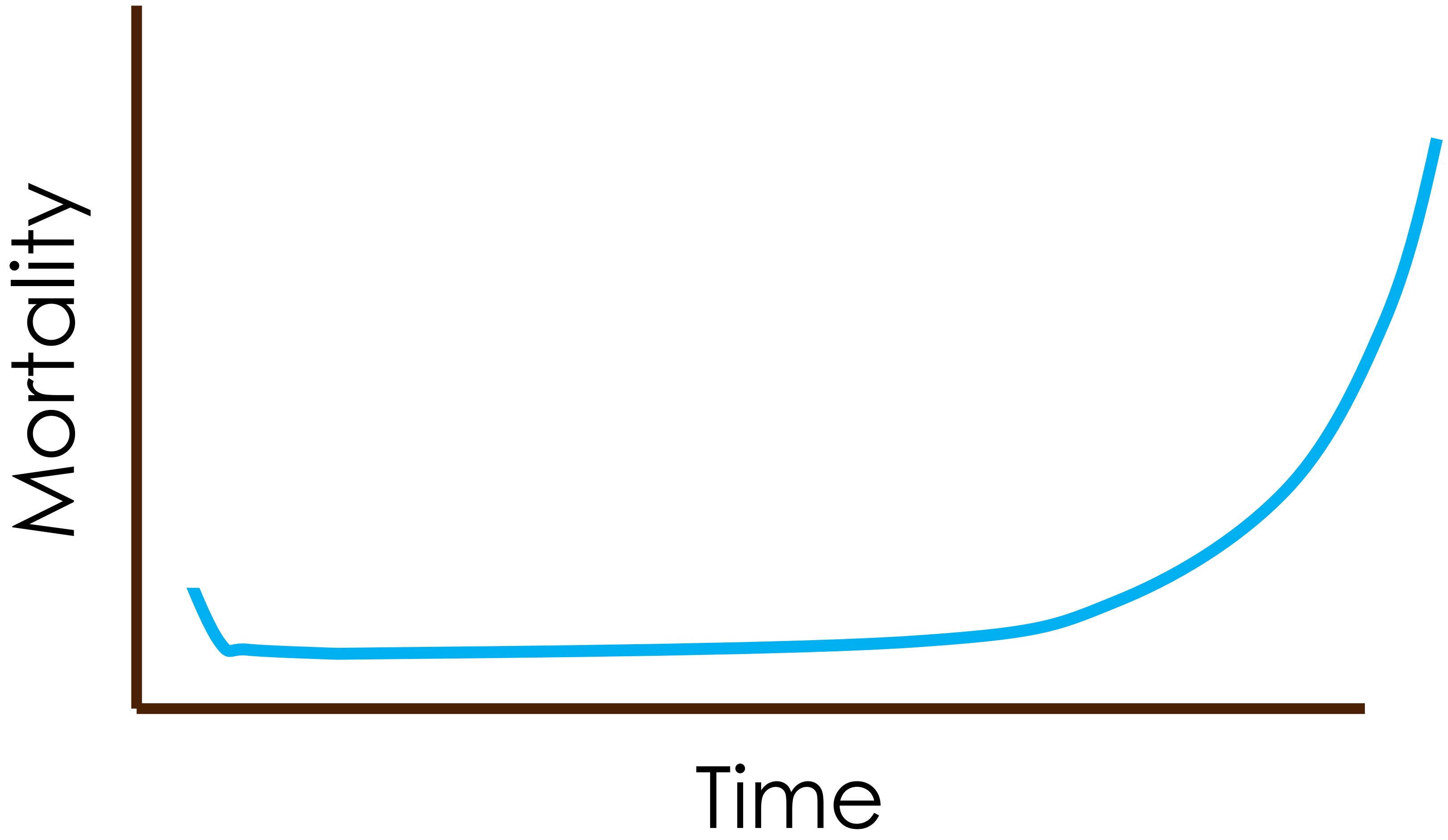


Patterns of mortality

if there are less ***extrinsic causes***



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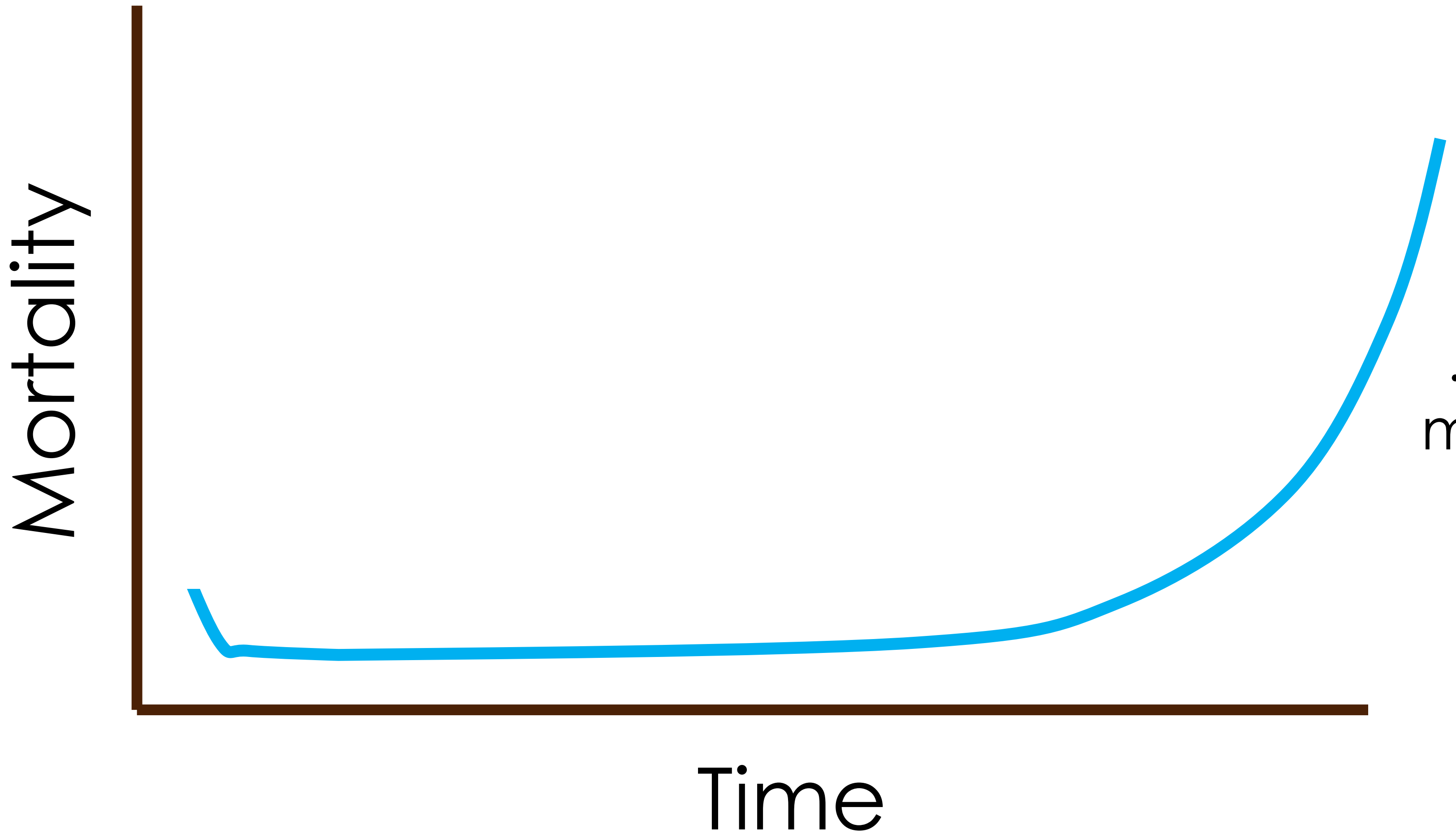
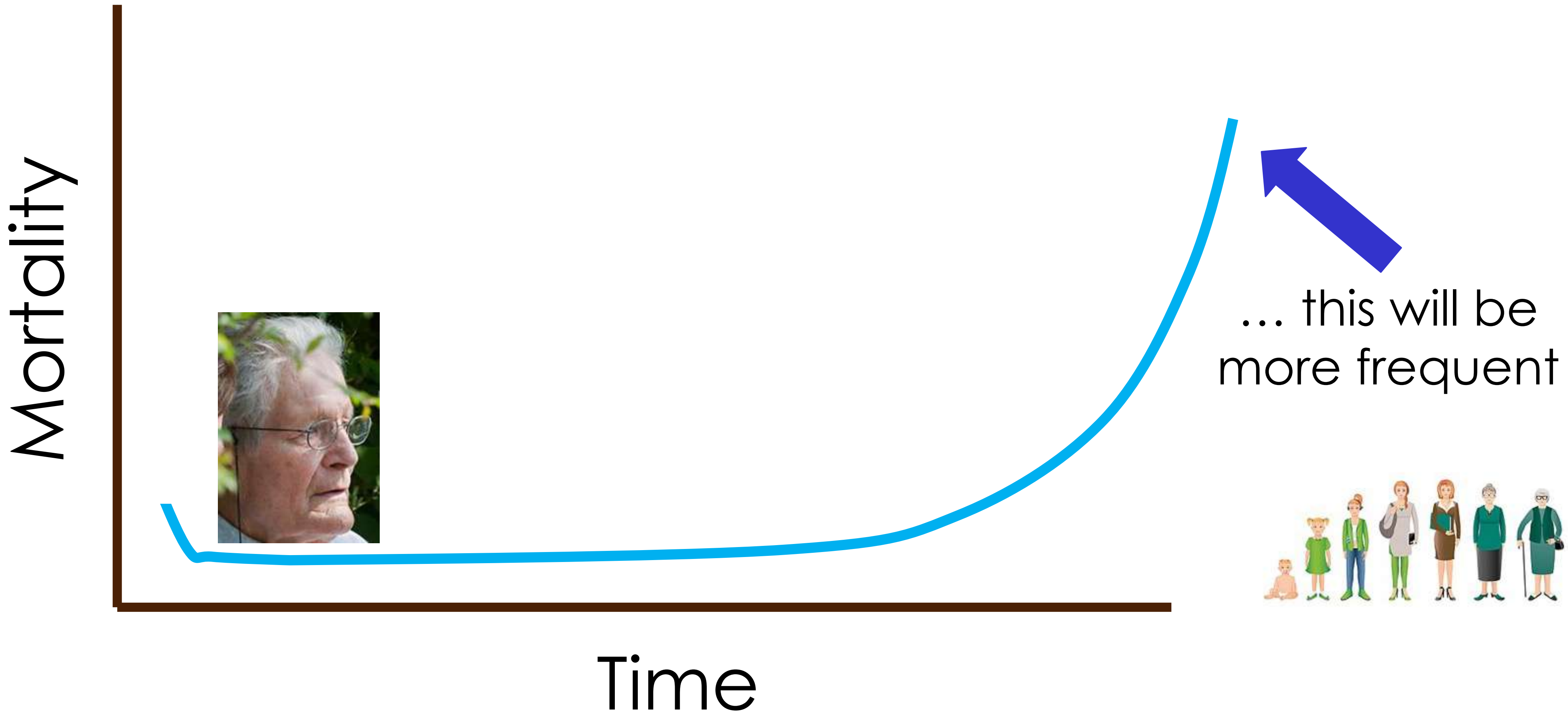


… this will be more frequent

Patterns of mortality

if there are less ***extrinsic causes***



CANCER RESEARCH

VOLUME 19 FEBRUARY 1959 NUMBER 2

Frequency and Types of Tumors in Mammals and Birds of the Philadelphia Zoological Garden

LOUISE S. LOMBARD* AND ERNEST J. WITTE†

During 1935 the traditional and often inadequate diets then common to zoological gardens were replaced in the Philadelphia Zoological Garden by controlled diets (19, 20).

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Cancer prevalence in zoo mammals

Philadelphia Zoo
1901-1932

2.6 %

Ratcliffe (1933)

Cancer prevalence in zoo mammals

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2.6 %

Philadelphia Zoo
1935-1955

4.6 %

Ratcliffe (1933)

Lombard & Witte (1959)

Cancer prevalence in zoo mammals

Philadelphia Zoo
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4.6 %

Ntl. Zoological Park
Washington DC
1975-1977

10.4 %

Ratcliffe (1933)

Lombard & Witte (1959)

Montali (1980)

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1901-1932

2.6 %

Philadelphia Zoo
1935-1955

4.6 %

Ntl. Zoological Park
Washington DC
1975-1977

10.4 %

Sand Diego Zoo
1964-2015

12.5 %

Ratcliffe (1933)

Lombard & Witte (1959)

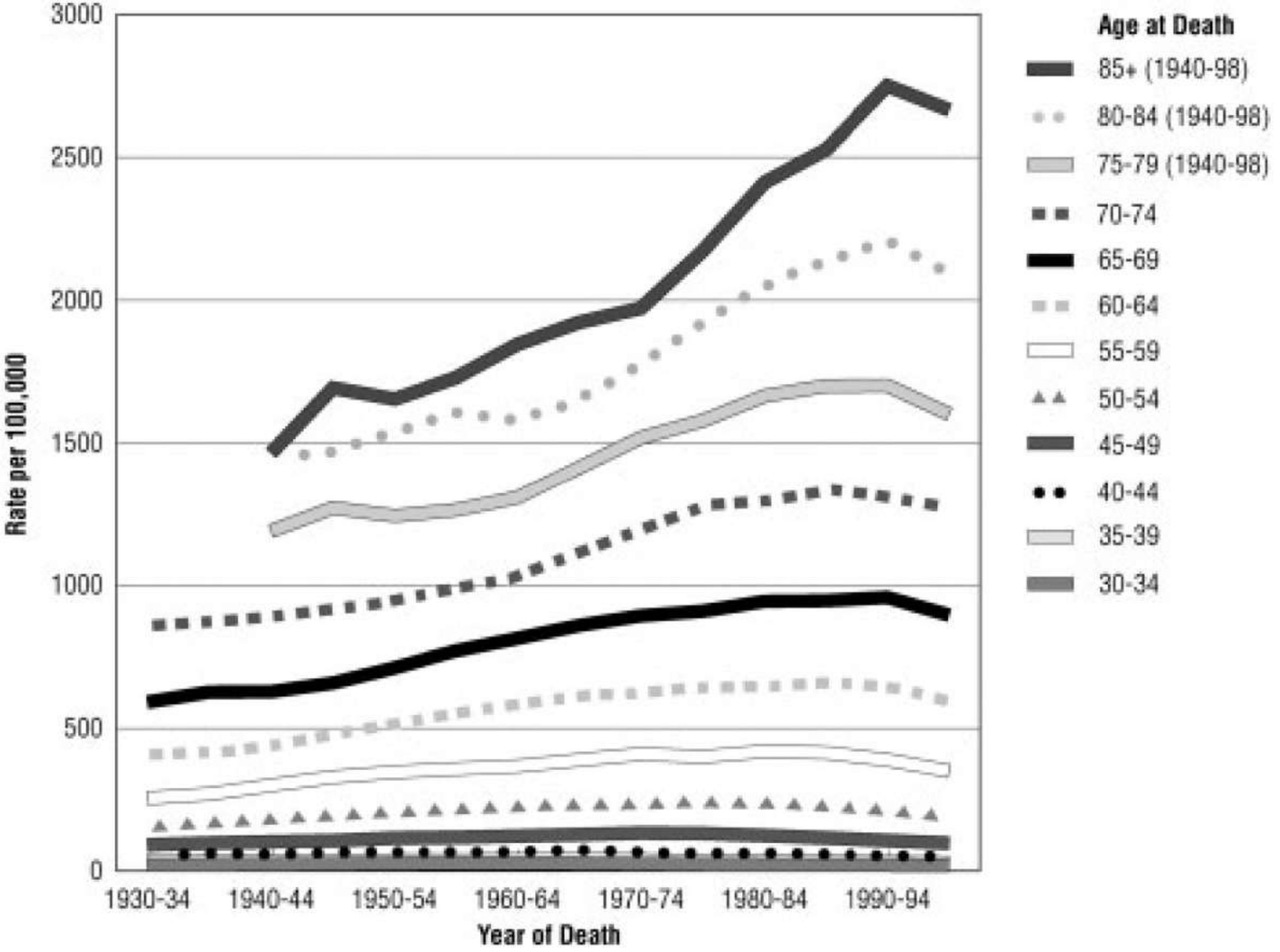
Montali (1980)

Boddy et al. (2020)

Long-Term Trends in Cancer Mortality in the United States, 1930–1998

Cancer 2003;97(11 Suppl):3133–3275.

Phyllis A. Wingo, Ph.D., M.S.[1]
Cheryll J. Cardinez, M.S.P.H.[1]
Sarah H. Landis, M.P.H.[1]
Robert T. Greenlee, Ph.D., M.P.H.[1]
Lynn A. G. Ries, M.S.[2]
Robert N. Anderson, Ph.D.[3]
Michael J. Thun, M.D., M.S.[1]



Peto's "paradox"

The eminent biologist Richard Peto, now at the University of Oxford, pointed out in the 1970s that large-bodied animals ought to be at great statistical risk for cancer – but that does not happen in reality.

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A man has 1000 times as many cells as a mouse (although the ratio of our epithelial *stem*-cell numbers is not known), and we usually live at least 30 times as long as mice. Exposure of two *similar* organisms to risk of carcinoma, one for 30 times as long as the other, would give perhaps 30^4 or 30^6 (i.e., a million or a billion) times the risk of carcinoma induction per epithelial cell. However, it seems that, in the wild, the probabilities of carcinoma induction in mice and in men are not vastly different. Are our stem cells really, then, a billion or a trillion times more "cancer-proof" than murine stem cells?

Preliminary Communication

JAMA. 2015;314(17):1850-1860

Potential Mechanisms for Cancer Resistance in Elephants and Comparative Cellular Response to DNA Damage in Humans

Lisa M. Abegglen, PhD; Aleah F. Caulin, PhD; Ashley Chan, BS; Kristy Lee, PhD; Rosann Robinson, BS; Michael S. Campbell, PhD; Wendy K. Kiso, PhD; Dennis L. Schmitt, DVM, PhD; Peter J. Waddell, PhD; Srividya Bhaskara, PhD; Shane T. Jensen, PhD; Carlo C. Maley, PhD; Joshua D. Schiffman, MD

Data from the Elephant Encyclopedia[14] were analyzed on the cause of death in captive African (*Loxodonta africana*) and Asian (*Elephas maximus*) elephants to estimate age incidence and overall lifetime cancer risk.

Preliminary Communication

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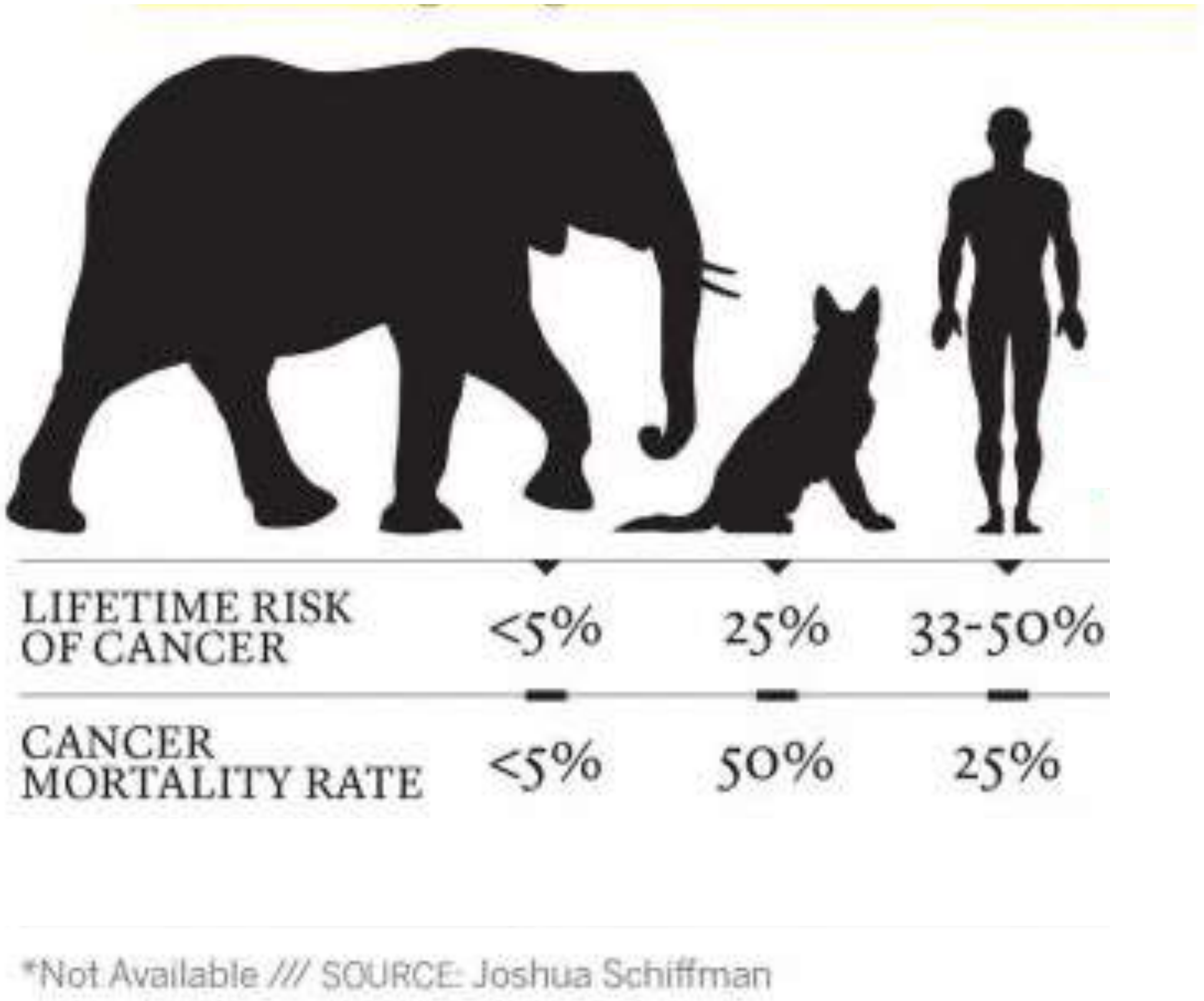
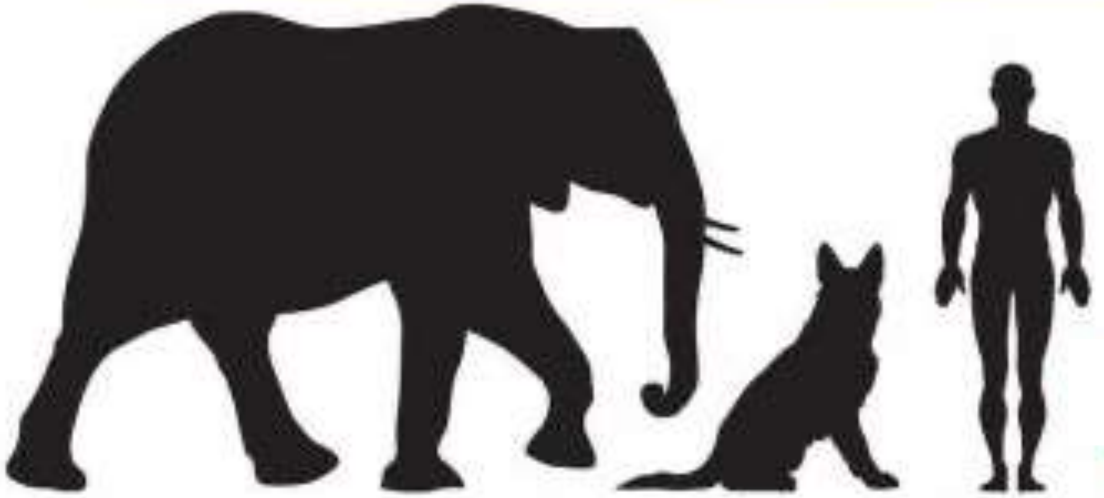
Among 644 annotated elephant deaths from the Elephant Encyclopedia database, the lifetime cancer incidence was 3.11% (95% CI, 1.74%-4.47%) (**Table 1**). To obtain a more conservative estimate, an inferred cancer incidence was calculated for cases that lacked adequate details for the cause of death, leading to an estimated elephant cancer mortality rate of 4.81% (95% CI, 3.14%-6.49%).


LIFETIME RISK OF CANCER
<5%
25%
33-50%
CANCER MORTALITY RATE
<5%
50%
25%
*Not Available /// SOURCE: Joshua Schiffman

MAGIC GENE IN A BOTTLE

A tumor suppressor gene, TP53 is the police officer of the cellular world. If a cell with faulty DNA is replicating, it can arrest the process and allow it to move forward only once the DNA is fixed. Or it can shoot to kill, getting rid of the cell with bad DNA.



LIFETIME RISK OF CANCER	<5%	25%	33-50%
CANCER MORTALITY RATE	<5%	50%	25%
TP53 GENE	40	2	2

*Not Available /// SOURCE: Joshua Schiffman

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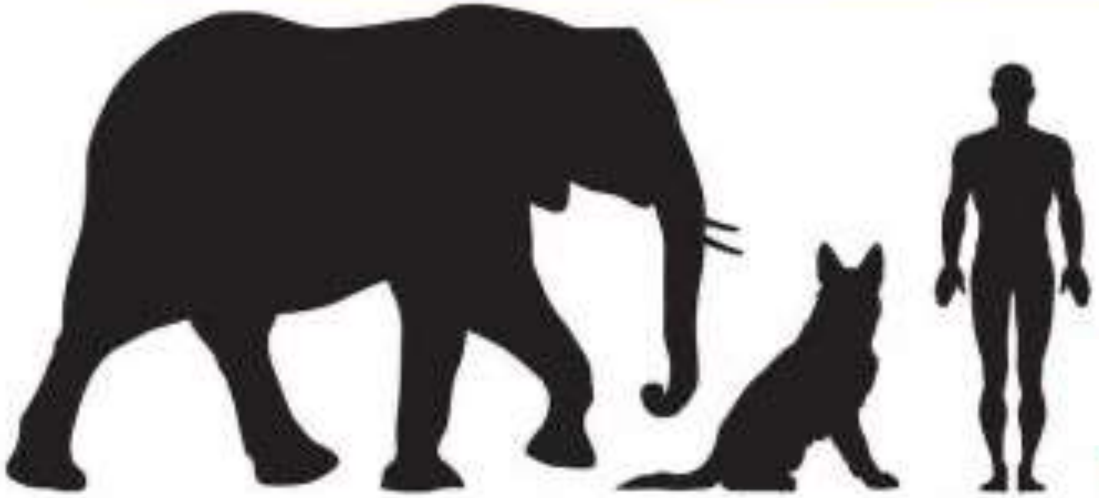

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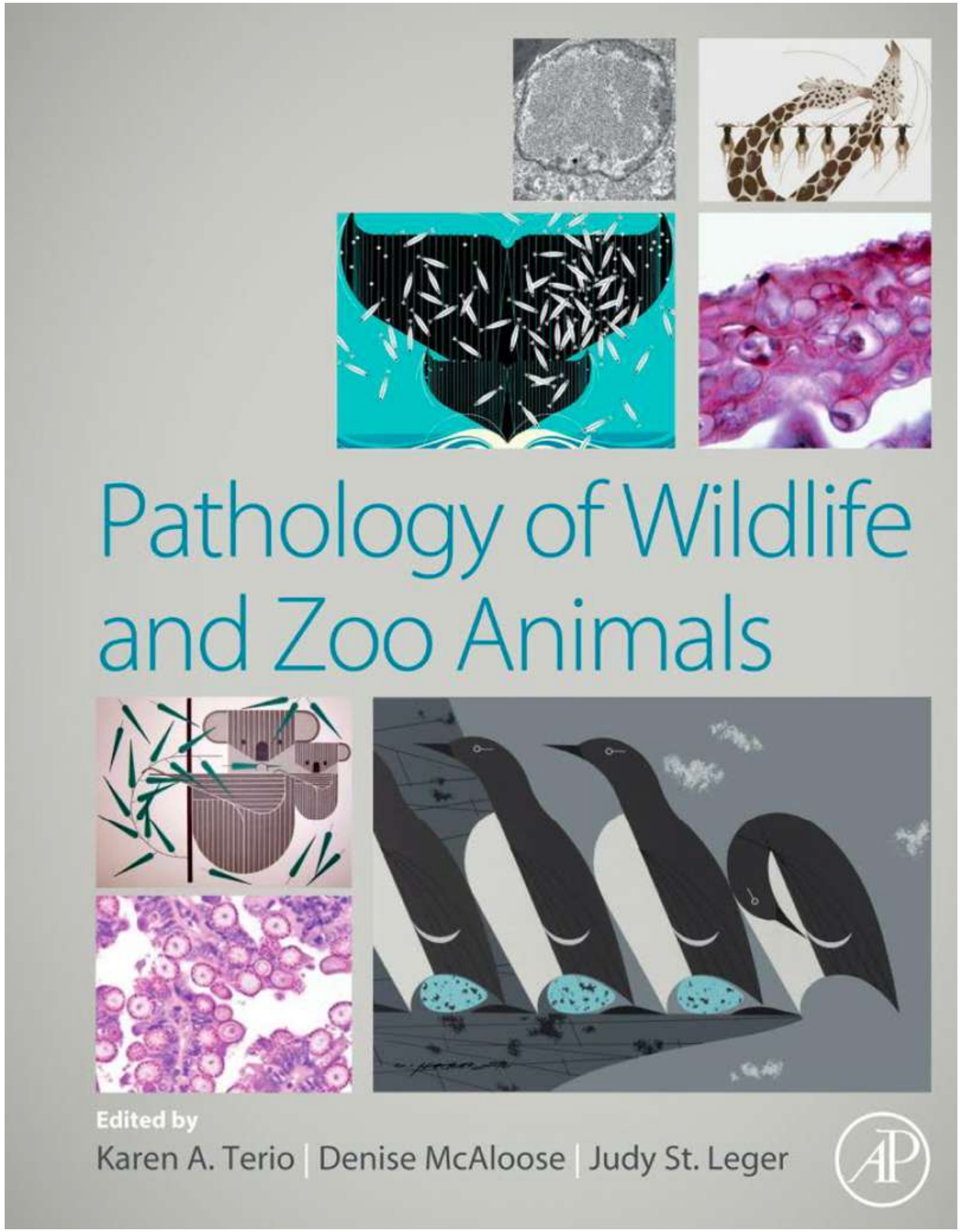

Proboscidae

Jennifer A. Landolfi* and Scott P. Terrell**

Neoplastic

Analyses of archival postmortem data from one large zoo-based veterinary pathology program revealed estimated lifetime prevalence for malignancies of 33.3%; with inclusion of benign neoplastic lesions, prevalence was 66.7%. These data negate the assertion that rates of neoplasia in elephants significantly differ from rates in other zoo mammals (Pessier et al., 2016).

Lifetime cancer prevalence and life history traits in mammals

Evolution, Medicine, and Public Health [2020] pp. 187–195

Amy M. Boddy,[1,*] Lisa M. Abegglen,[2] Allan P. Pessier,[3] Athena Aktipis,[4,5]
Joshua D. Schiffman,[2] Carlo C. Maley [5] and Carmel Witte[6]

We report higher cancer prevalence in elephants than previously reported [2]. Previous estimates were derived from the Elephant Encyclopedia Database ($n = 644$ elephants) [2]. While this database is an important resource for the elephant community, we are not confident that all of the data were medically curated.

Veterinary Pathology
2021, Vol. 58(6) 1131-1141

DOI: 10.1177/03009858211031843
journals.sagepub.com/home/vet

Reproductive tract neoplasia in adult female Asian elephants (*Elephas maximus*)

Jennifer A. Landolfi[1], Patricia M. Gaffney[2], Rita McManamon[3], Nicole L. Gottdenker[3], Angela E. Ellis[3], Raquel R. Rech[3], Sushan Han[4], Linda J. Lowenstine[5], Dalen Agnew[6], Michael M. Garner[7], Denise McAloose[8], Charlotte Hollinger[8], Judy St. Leger[9], Scott P. Terrell[10], Mary Duncan[11], and Allan P. Pessier[2,12]

This study is an archival review of reproductive tract neoplasia in 80 adult female Asian elephant mortalities in managed care facilities in the United States from 1988 to 2019. Neoplasms occurred in 64/80 (80%) of cases.

Cancer prevalence in zoo elephants

Preliminary Communication

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Lisa M. Abegglen, PhD; Aleah F. Caulin, PhD; Ashley Chan, BS; Kristy Lee, PhD; Rosann Robinson, BS; Michael S. Campbell, PhD; Wendy K. Kiso, PhD; Dennis L. Schmitt, DVM, PhD; Peter J. Waddell, PhD; Srividya Bhaskara, PhD; Shane T. Jensen, PhD; Carlo C. Maley, PhD; Joshua D. Schiffman, MD

Abbeglen et al.
(2015)
4.8 %

INCIDENCE AND NATURE OF TUMORS IN CAPTIVE WILD MAMMALS AND BIRDS [1]

HERBERT L. RATCLIFFE

Ratcliffe
(1933)
25 %

Landolfi & Terrell
(2018)
67 %

Lifetime cancer prevalence and life history traits in mammals

Amy M. Boddy,[1,*] Lisa M. Abegglen,[2] Allan P. Pessier,[3] Athena Aktipis,[4,5] Joshua D. Schiffman,[2] Carlo C. Maley [5] and Carmel Witte[6]

Boddy et al.
(2020)
47 %

Nondomestic, Exotic, Wild and Zoo Animals–Original Article

Veterinary Pathology
2021, Vol. 58(6) 1131-1141
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DOI: 10.1177/03009858211031843
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Landolfi et al.
(2021)
80 %

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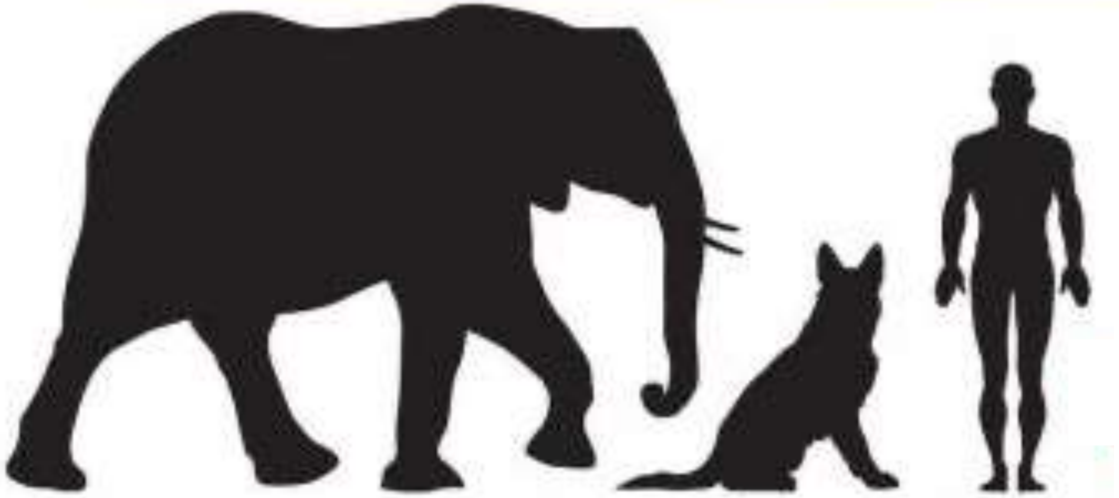

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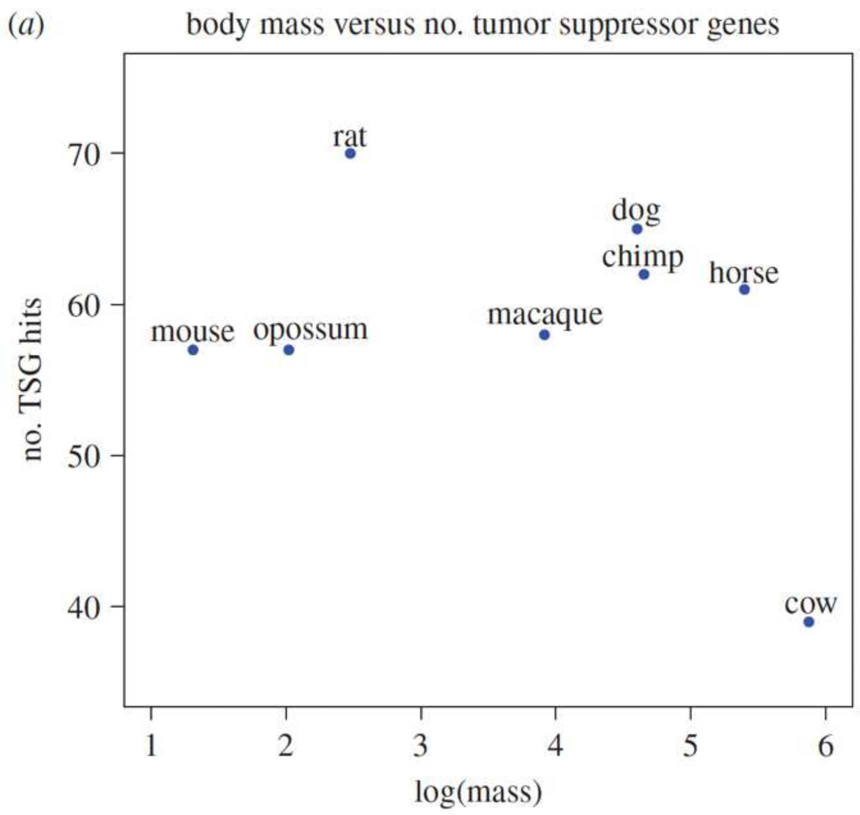
CANCER MORTALITY RATE	<5%	50%	25%
TP53 GENE	40	2	2

*Not Available /// SOURCE: Joshua Schiffman

Solutions to Peto's paradox revealed by mathematical modelling and cross-species cancer gene analysis

2015 Phil. Trans. R. Soc. B **370**: 20140222.

Aleah F. Caulin[1], Trevor A. Graham[3], Li-San Wang[2] and Carlo C. Maley[4,5]



Peto's "paradox"

Peto's "paradox"

Is it a paradox ?

Peto‘s “paradox”

Is it a paradox ?

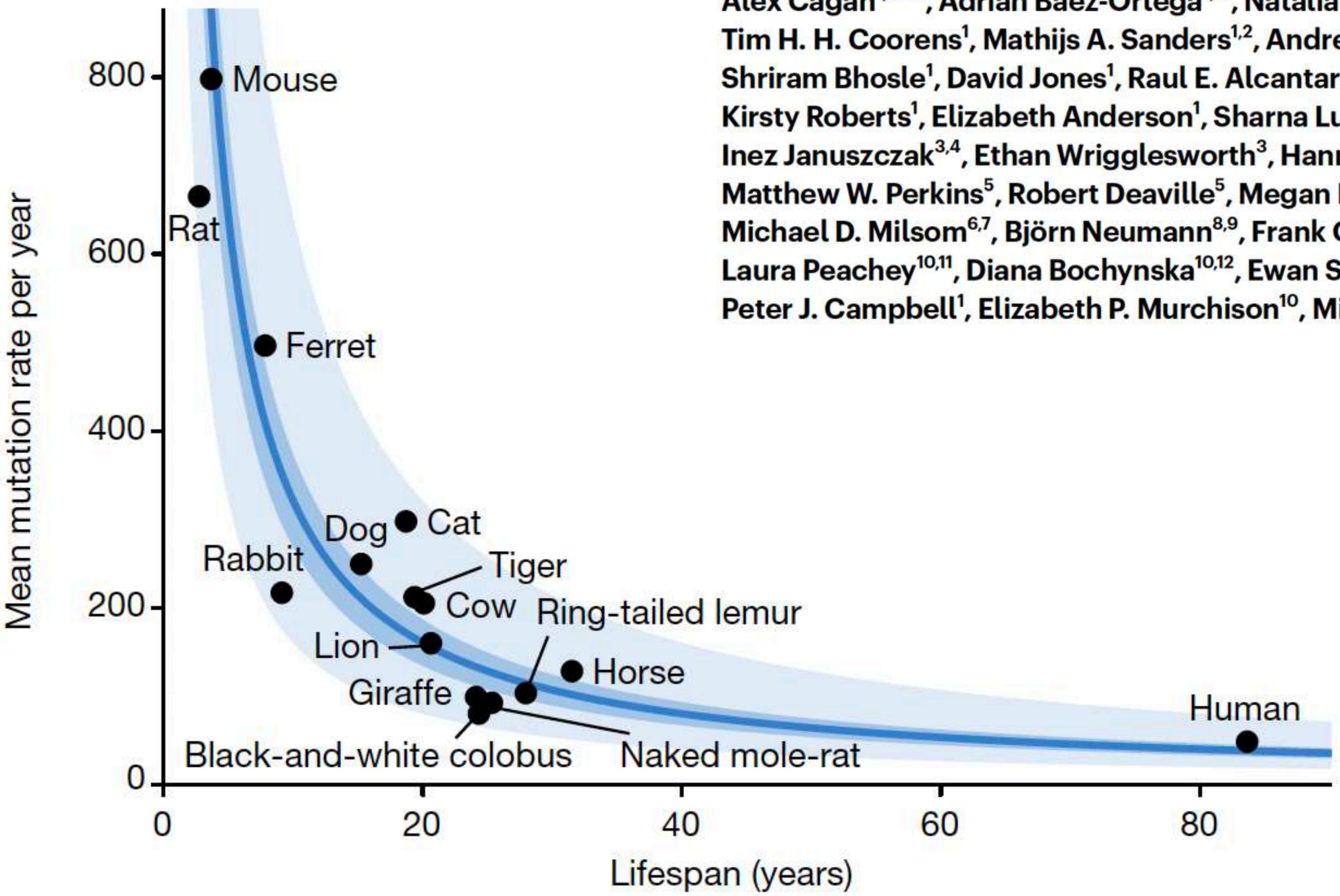
The cells of an elephant do not have the same metabolism as that of a mouse – why should they have the same mutation rate?

Somatic mutation rates scale with lifespan across mammals

Nature | Vol 604 | 21 April 2022 | 517

Alex Cagan[1,15]✉, Adrian Baez-Ortega[1,15], Natalia Brzozowska[1], Federico Abascal[1], Tim H. H. Coorens[1], Mathijs A. Sanders[1,2], Andrew R. J. Lawson[1], Luke M. R. Harvey[1], Shriram Bhosle[1], David Jones[1], Raul E. Alcantara[1], Timothy M. Butler[1], Yvette Hooks[1], Kirsty Roberts[1], Elizabeth Anderson[1], Sharna Lunn[1], Edmund Flach[3], Simon Spiro[3], Inez Januszczak[3,4], Ethan Wrigglesworth[3], Hannah Jenkins[3], Tilly Dallas[3], Nic Masters[3], Matthew W. Perkins[5], Robert Deaville[5], Megan Druce[6,7], Ruzhica Bogeska[6,7], Michael D. Milsom[6,7], Björn Neumann[8,9], Frank Gorman[10], Fernando Constantino-Casas[10], Laura Peachey[10,11], Diana Bochynska[10,12], Ewan St. John Smith[13], Moritz Gerstung[14], Peter J. Campbell[1], Elizabeth P. Murchison[10], Michael R. Stratton[1] & Iñigo Martincorena[1]✉

c



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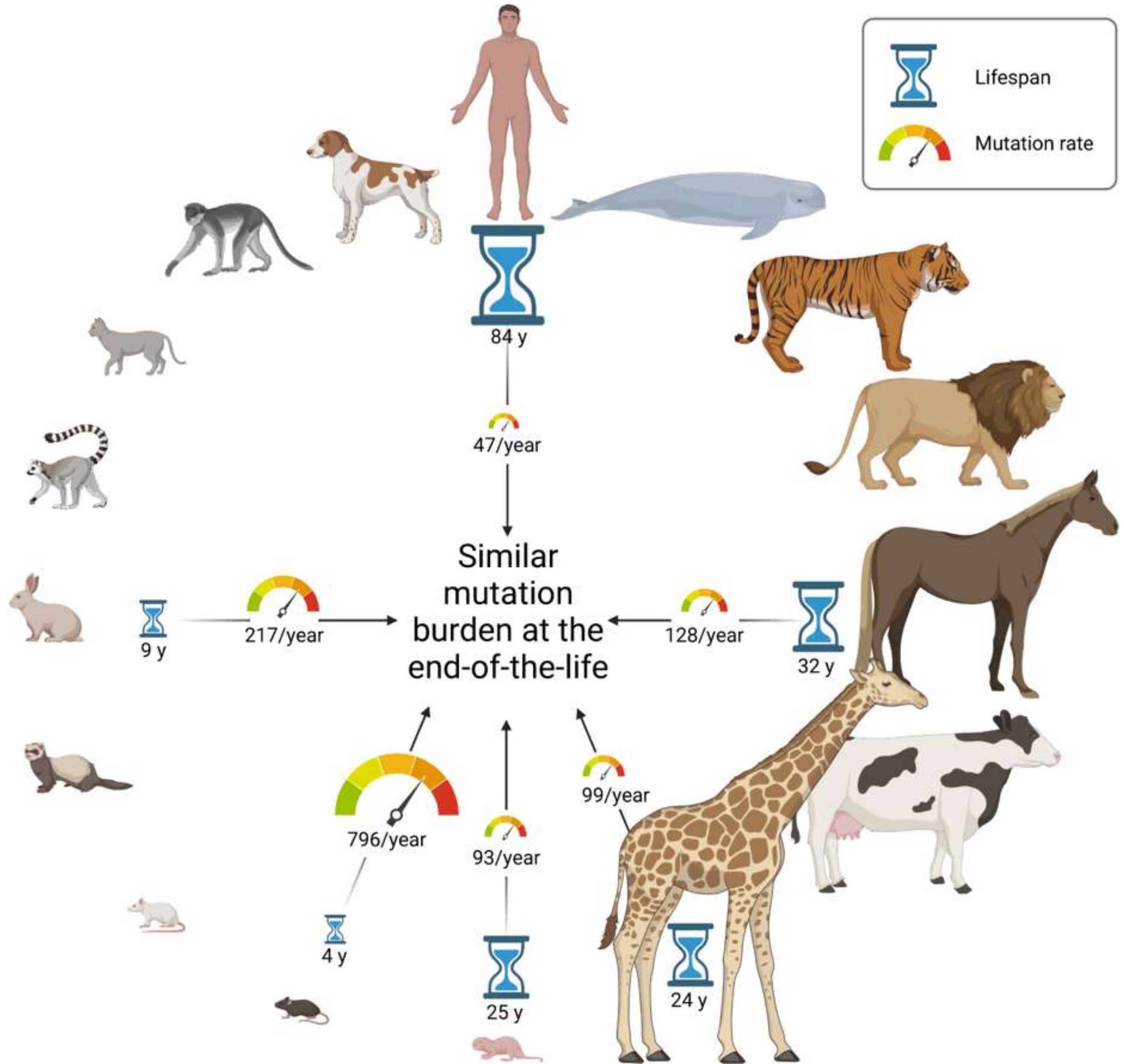
Nature | Vol 604 | 21 April 2022 | 517



recent evaluations with zoo data

Lifetime cancer prevalence and life history traits in mammals

Evolution, Medicine, and Public Health [2020] pp. 187–195

Amy M. Boddy,[1,*] Lisa M. Abegglen,[2] Allan P. Pessier,[3] Athena Aktipis,[4,5]
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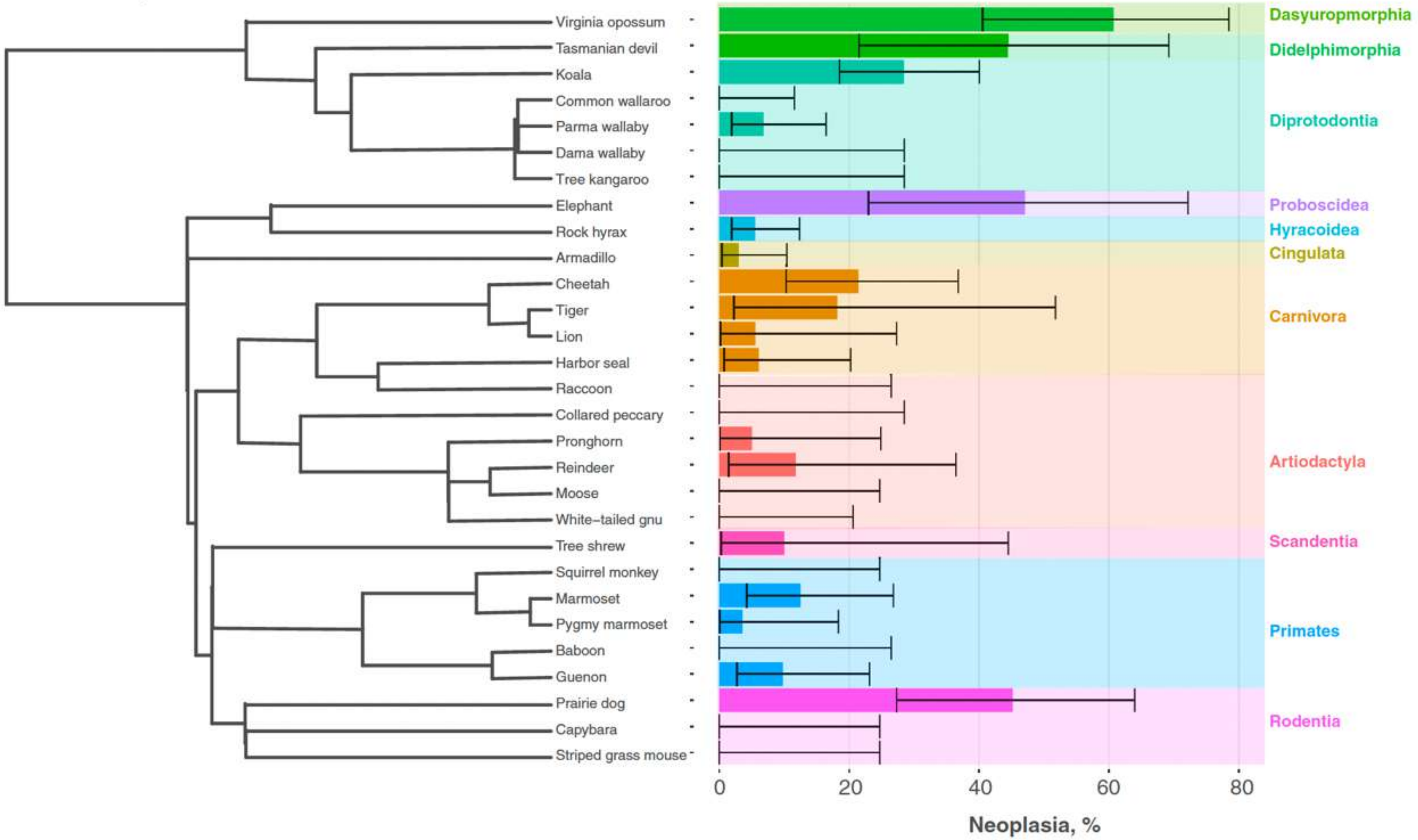

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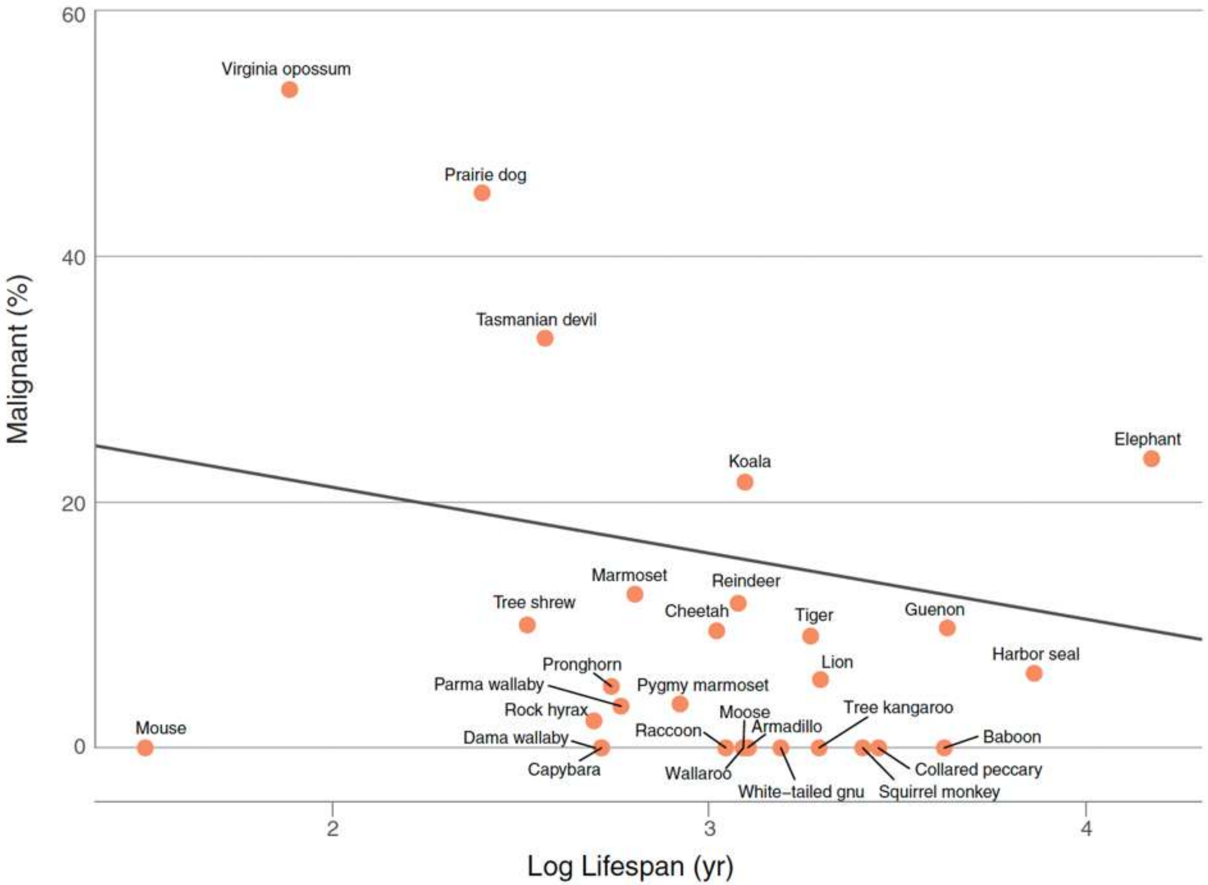

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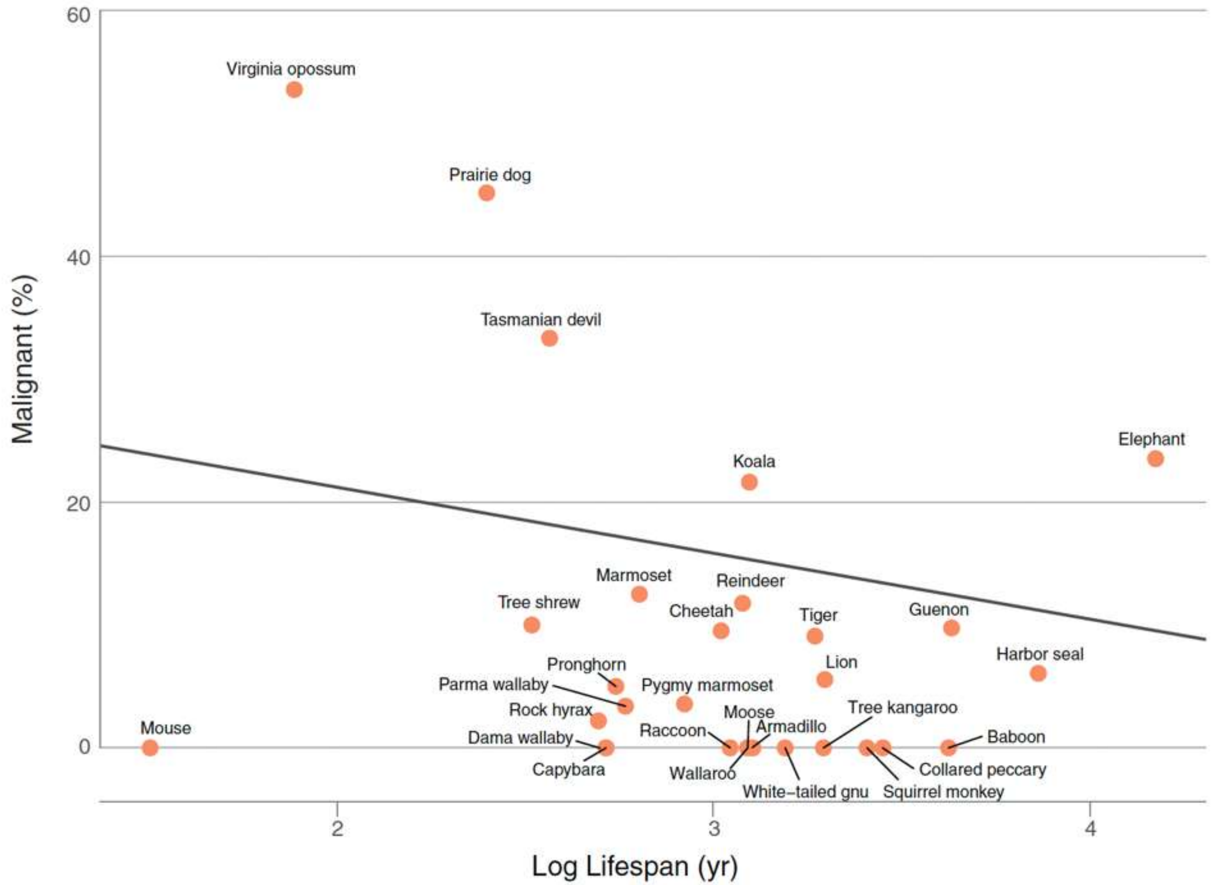
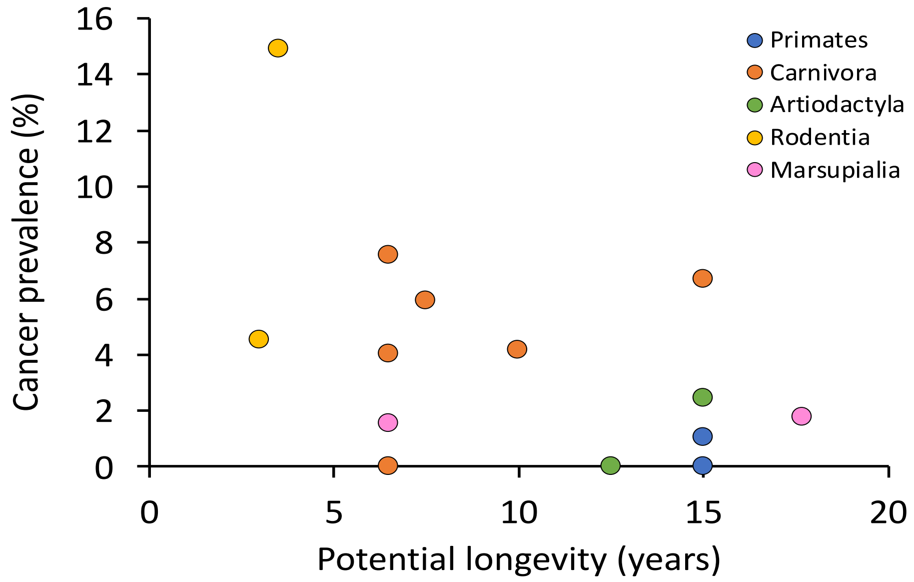


Cancer is not a disease of animals that CAN live many years.



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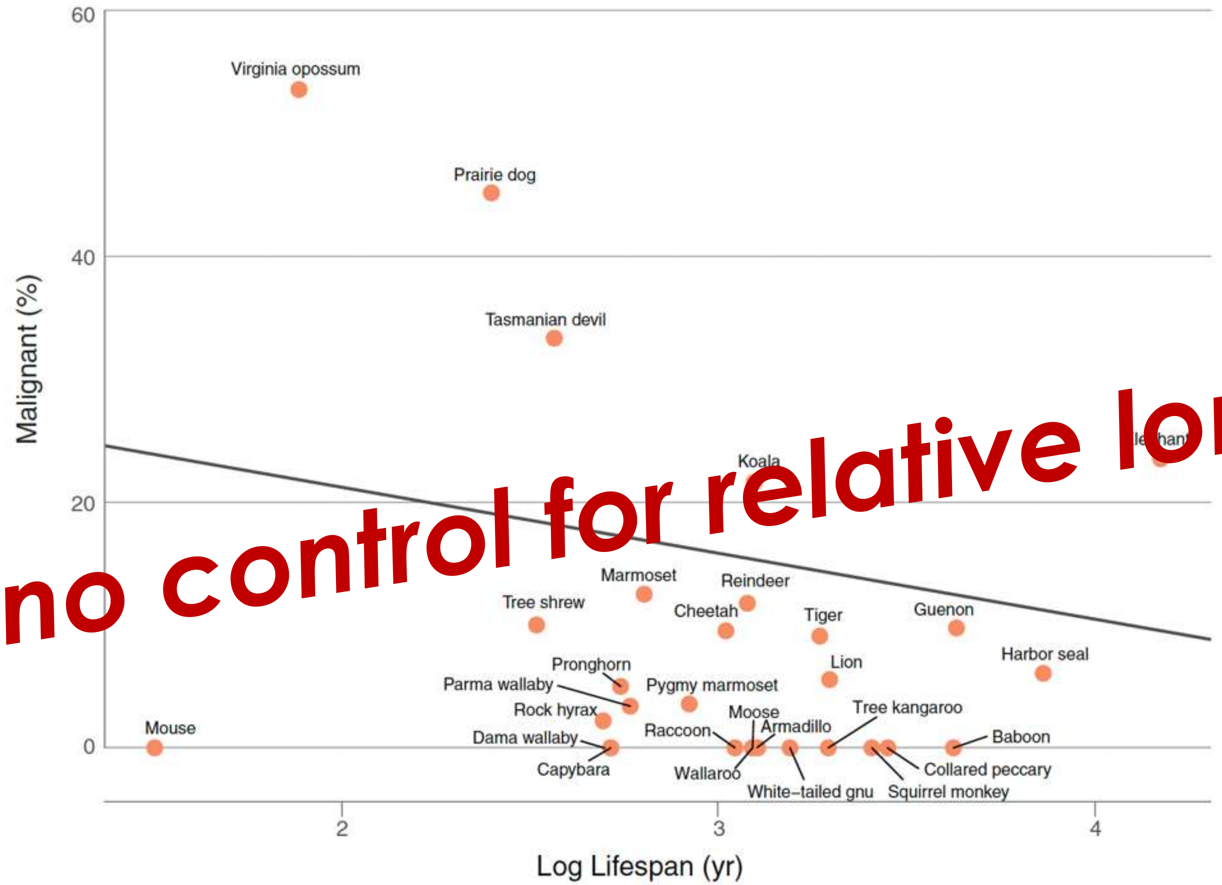
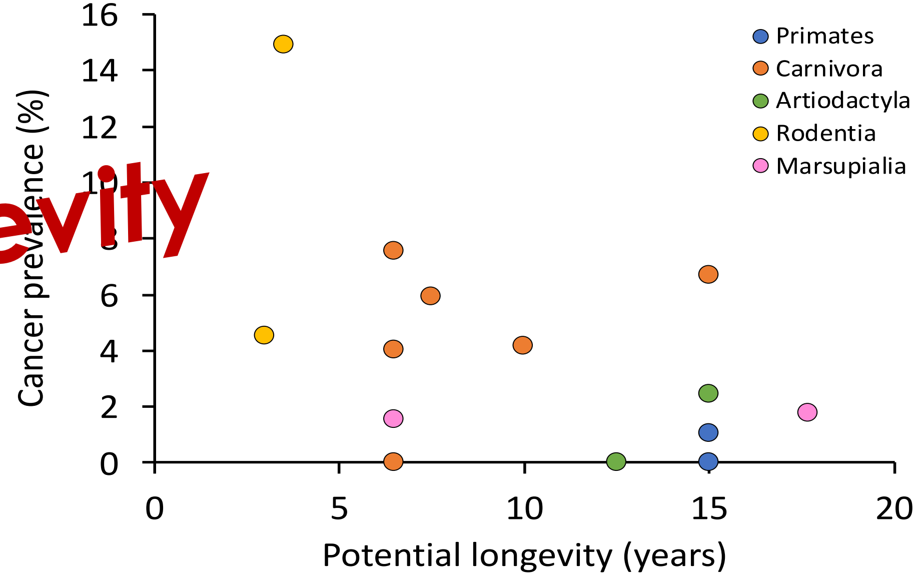


no control for relative longevity



Current Nutrition Reports (2022) 11:508–525
https://doi.org/10.1007/s13668-022-00420-5

CANCER (RA MURPHY, SECTION EDITOR)

Diet, Microbes, and Cancer Across the Tree of Life: a Systematic Review

Stefania E. Kapsetaki[1,2] · Gissel Marquez Alcaraz[1,2] · Carlo C. Maley[1,2] · Corrie M. Whisner[3,4] · Athena Aktipis[1,5]

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Check for updates

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Carnivorous Diets May Be Associated with Cancer-Inducing Microbes

Comparative oncology studies show that within mammals, the order Carnivora has higher benign or malignant tumour prevalence than other primarily herbivorous mammalian orders [3, 131]. Also, our group has been investigating the cancer prevalence of species at different trophic levels, including carnivores, herbivores, insectivores, and others. Our preliminary results across vertebrate species show that lower trophic levels (such as herbivores) have lower cancer prevalence than higher trophic levels (such as secondary carnivores) (Kapsetaki et al. in prep).

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CANCER RESEARCH

VOLUME 19 | FEBRUARY 1959 | NUMBER 2

Frequency and Types of Tumors in Mammals and Birds of the Philadelphia Zoological Garden

LOUISE S. LOMBARD* AND ERNEST J. WITTE†

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no control for relative longevity

ISIS
International Species Information System

SPECIES 360
Global information serving conservation.

EAZA

Standards for the Accommodation and Care of Animals in Zoos and Aquaria

EUROPEAN ASSOCIATION OF ZOOS AND AQUARIA

EAZA

Approved by EAZA Annual
General Meeting
2 October 2020

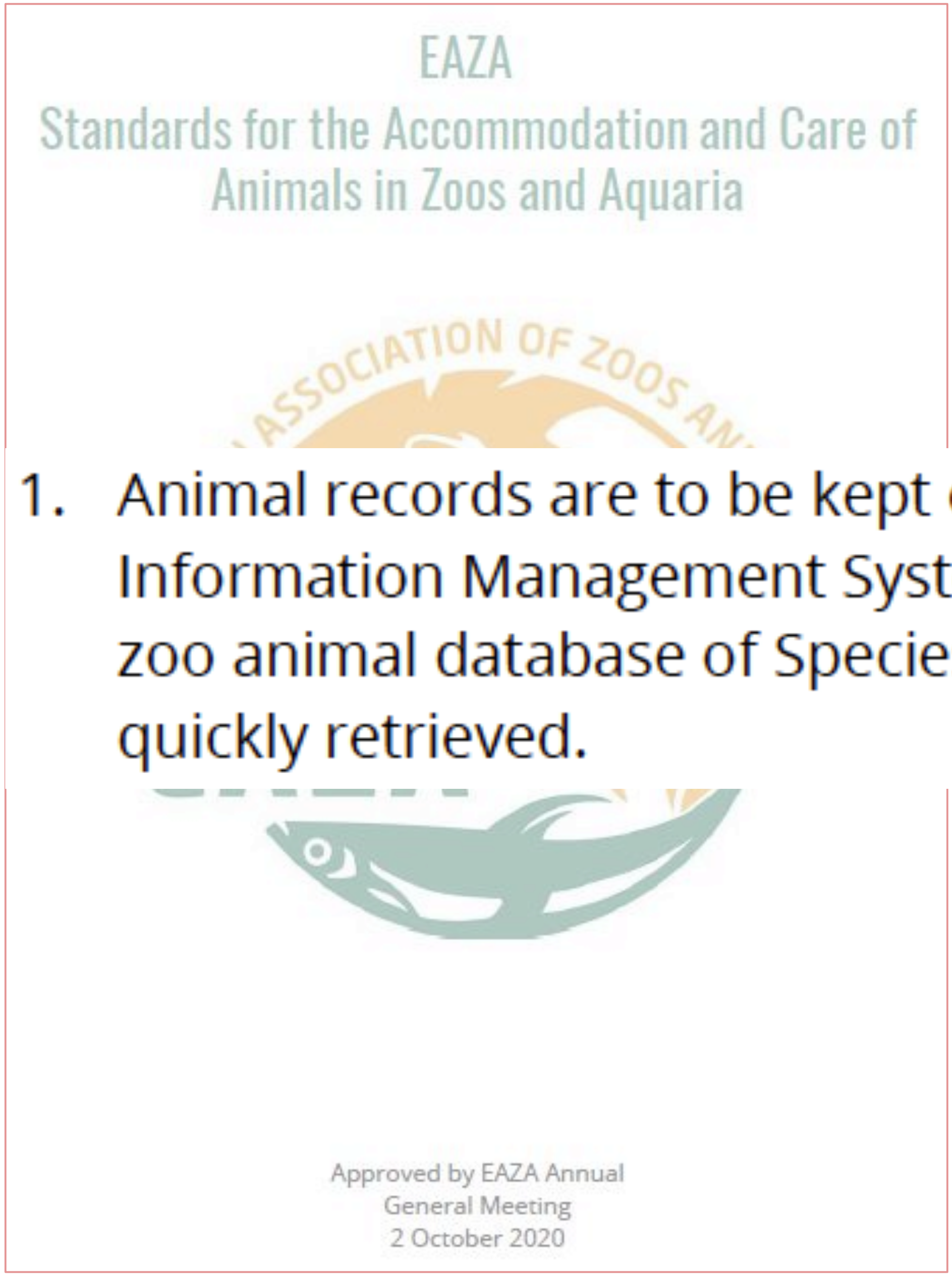
EAZA

Standards for the Accommodation and Care of Animals in Zoos and Aquaria

Approved by EAZA Annual General Meeting
2 October 2020

5.2 Stock records

1. Animal records are to be kept on a computer system using the Zoological Information Management System (ZIMS), and to be included on the global zoo animal database of Species360, by means of which information can be quickly retrieved.
2. Alternatively, records may be kept by means of an established and globally recognised and accepted record system, that is easily able to share data with ZIMS and that is and maintained in relation to all individually recognised animals and groups of animals. If a Member wishes to use an alternative record system, it shall request prior approval of the Council. The Council shall decide in its absolute discretion.
3. Where animals are disposed of or die, the records to be kept in the appropriate recording system as described in Article 95.
4. The records should provide the following information:
    a. the correct identification and scientific name;
    b. the origin (i.e. whether wild or captive born, including identification of parents, where known, and previous location/s, if any);
    c. the dates of entry into, and disposal from, the collection and to whom;
    d. the date, or estimated date, of birth;
    e. the sex of the animals (where known);
    f. any distinctive markings, including tattoo or freeze brands etc.;
    g. clinical data, including details of and dates when drugs, injections, and any other forms of treatment were given, and details of the health of the animal;
    h. the date of death and the result of any post-mortem examination;
    i. the reason, where an escape has taken place, or damage or injury has been caused to, or by, an animal to persons or property, for such escape, damage or injury and a summary of remedial measures taken to prevent recurrence of such incidents.



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EAZA Membership and Accreditation Manual

EUROPEAN ASSOCIATION OF ZOOS AND AQUARIA

EAZA

ACCREDITED MEMBER

You learn a lot about the natural world if you keep your animals in an intelligent way.

- David Attenborough, *2016*

European Association of Zoos and Aquaria
Amsterdam
Version 4
Approved by the EAZA Annual General Meeting on 22 April 2021

EAZA Membership and Accreditation Manual

EUROPEAN ASSOCIATION OF ZOOS AND AQUARIA

EAZA

ACCREDITED MEMBER

EAZA Members are required to meet obligations regarding, e.g.:

- Participation in EAZA Ex situ Programmes (EEPs) for population management
- Animal records (Species360 membership)

Cancer risk across mammals

Orsolya Vincze[1,2,3,4] ✉, Fernando Colchero[5,6,7], Jean-Francois Lemaître[8], Dalia A. Conde[6,7,9], Samuel Pavard[10], Margaux Bieuville[10], Araxi O. Urrutia[11,12], Beata Ujvari[13], Amy M. Boddy[14], Carlo C. Maley[15], Frédéric Thomas[1] & Mathieu Giraudeau[1,2]

Nature | Vol 601 | 13 January 2022 | **263**

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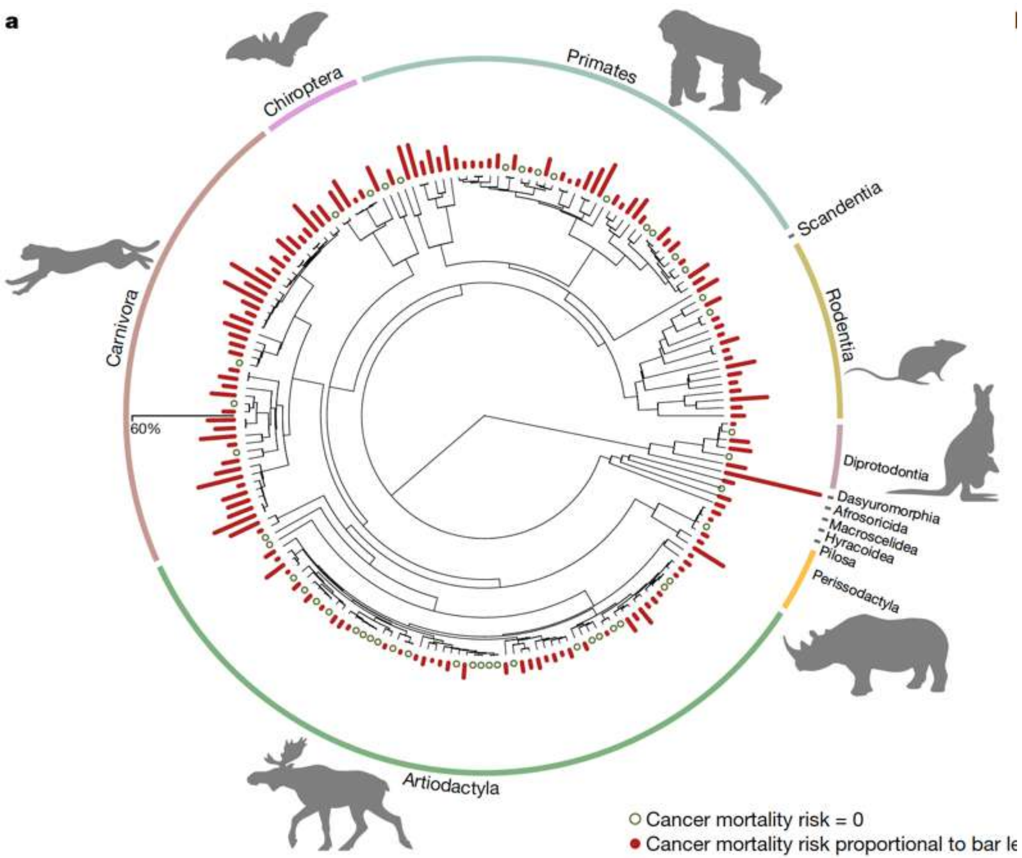

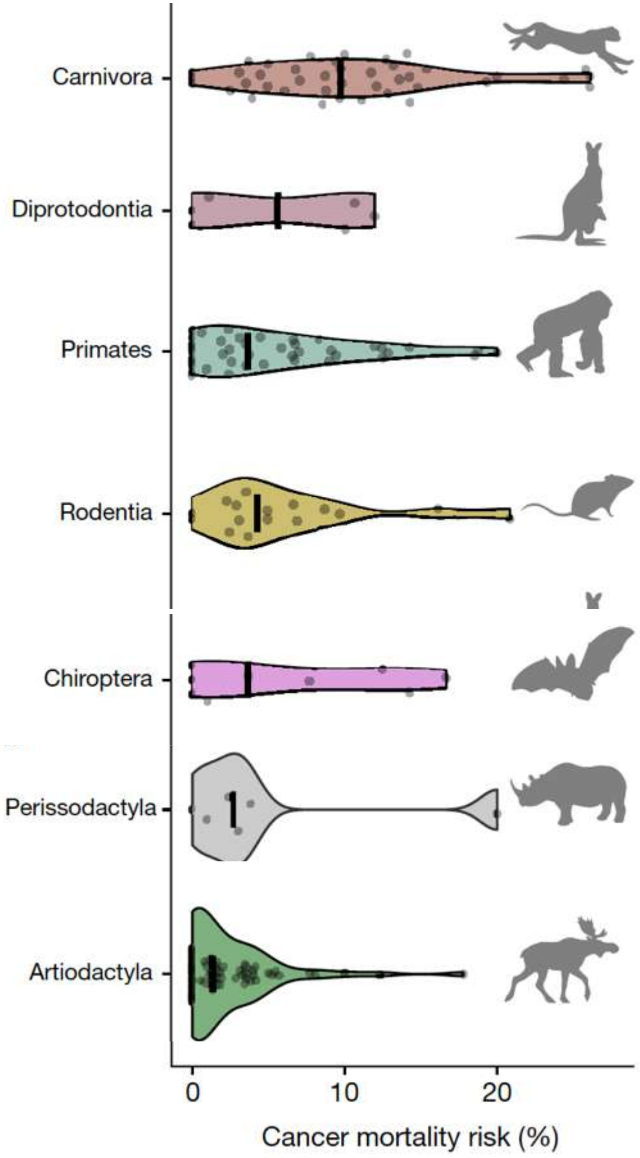

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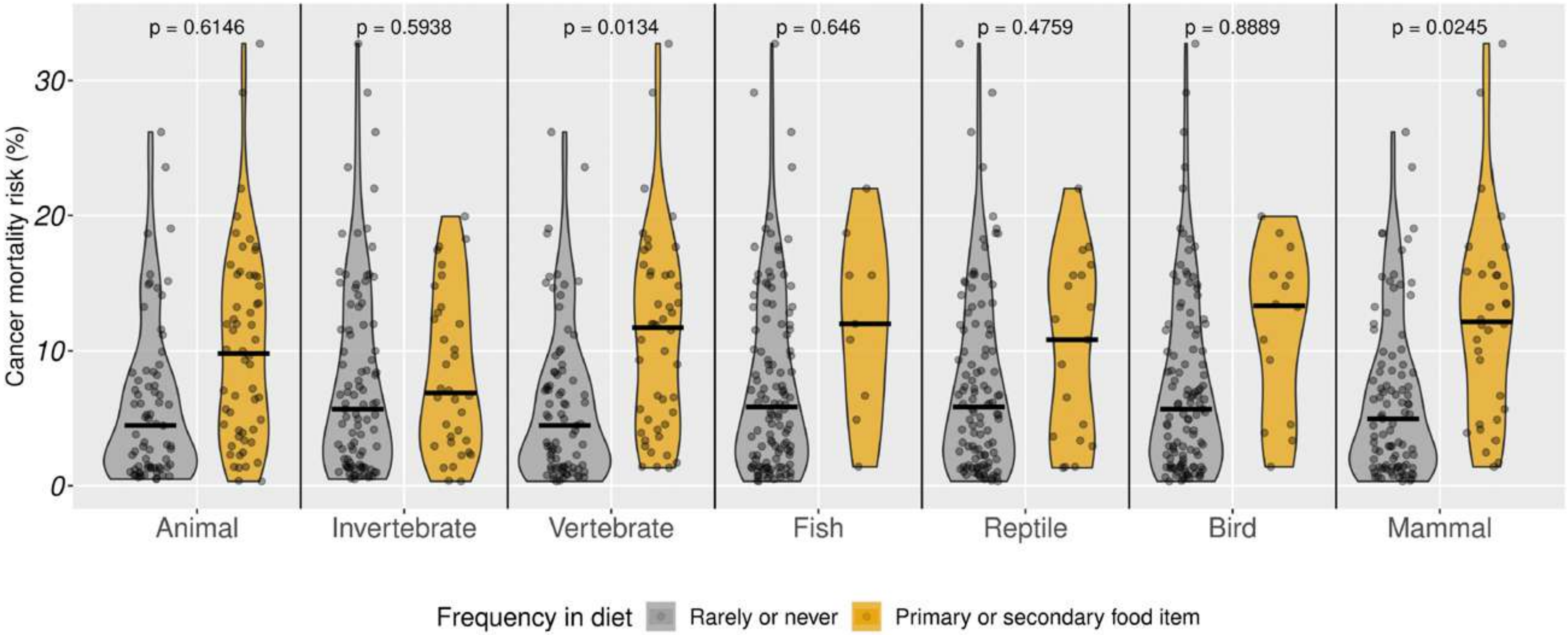

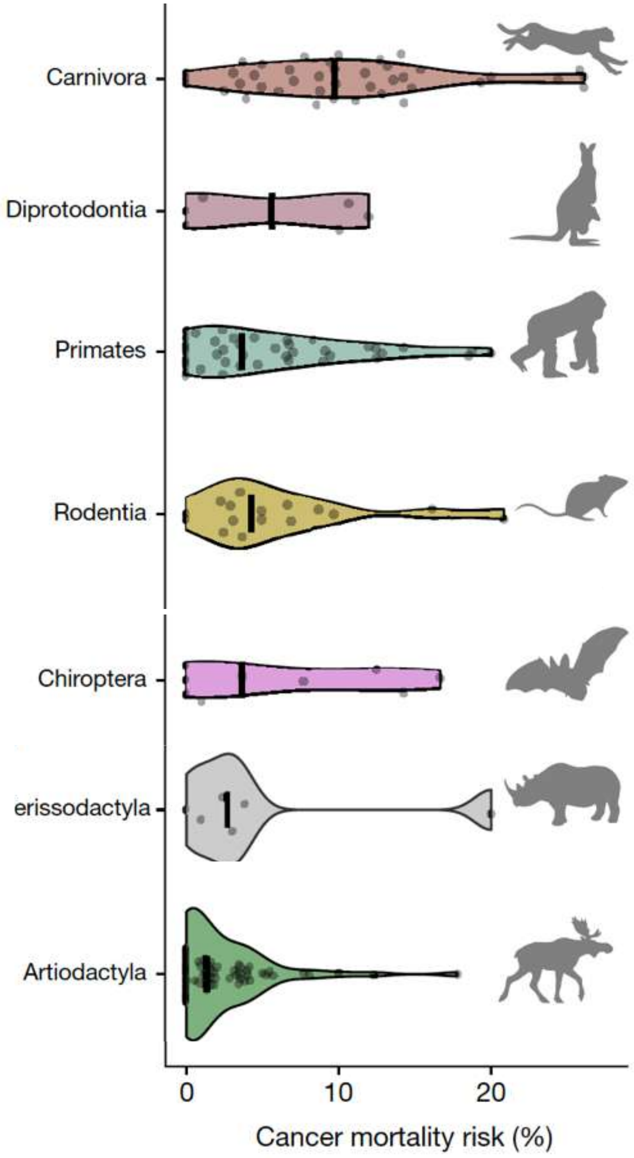

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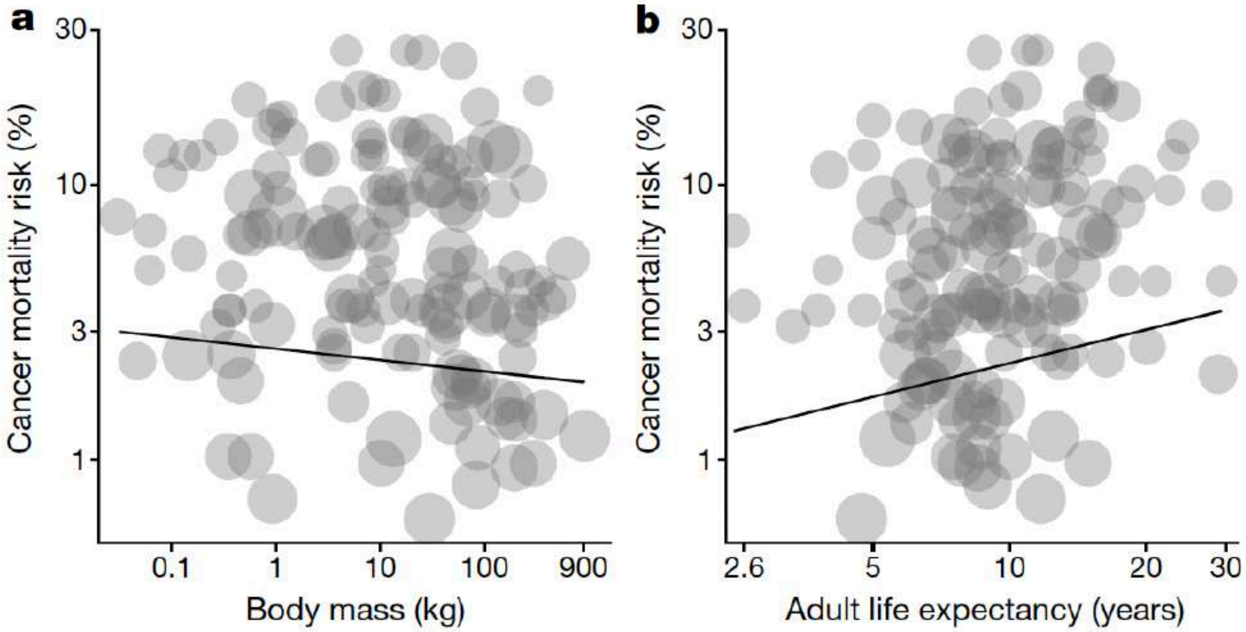

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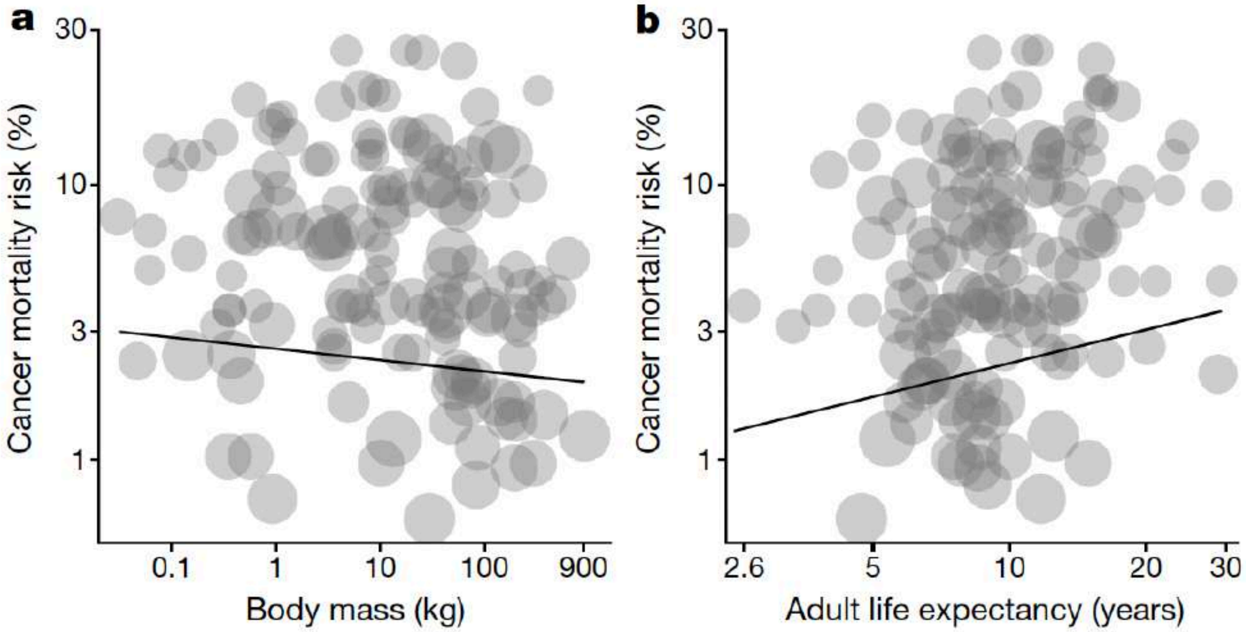

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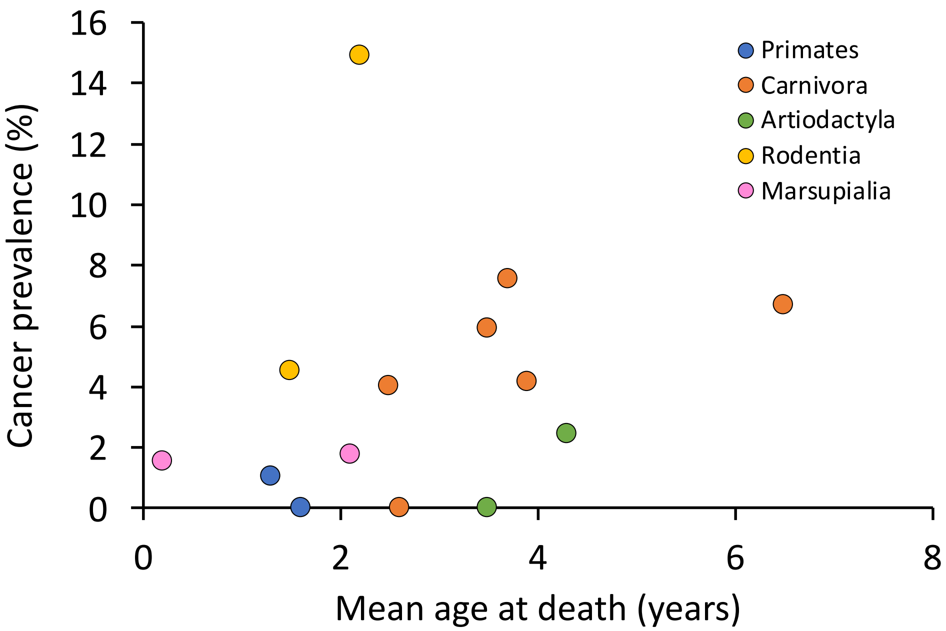

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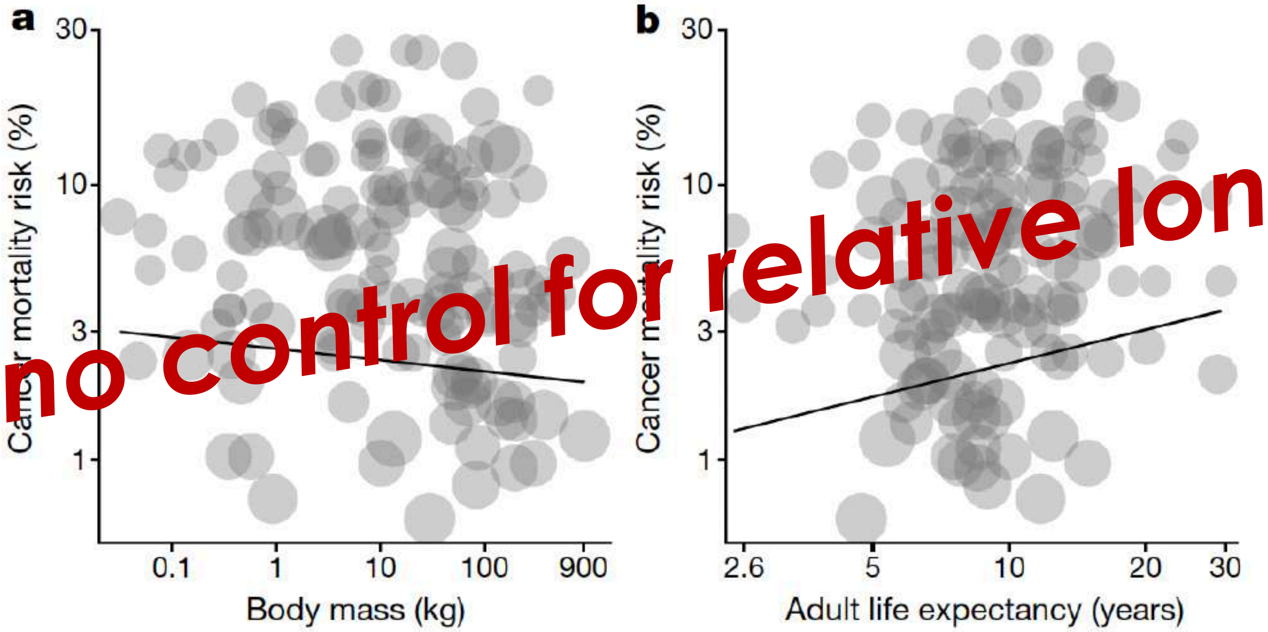

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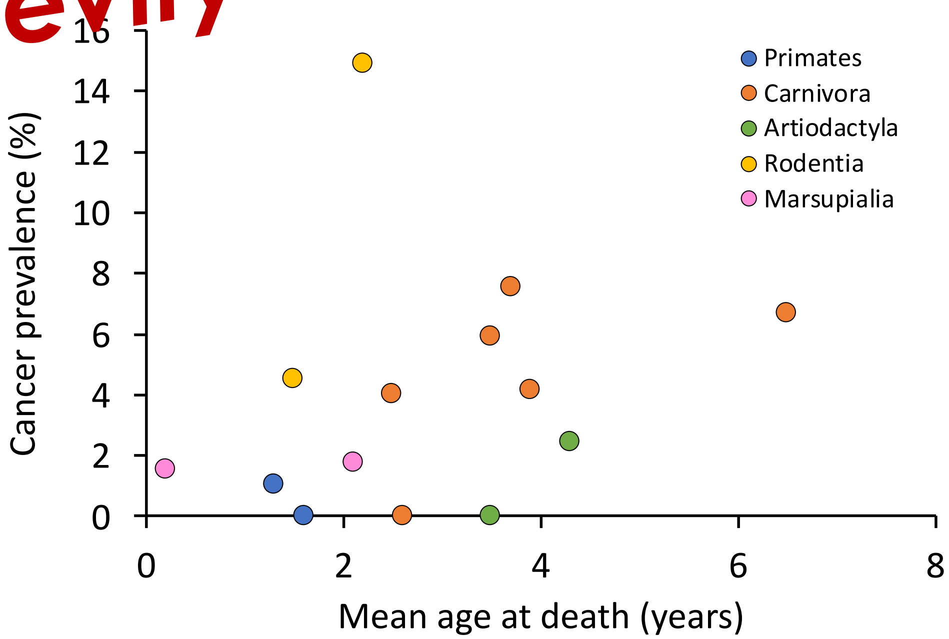

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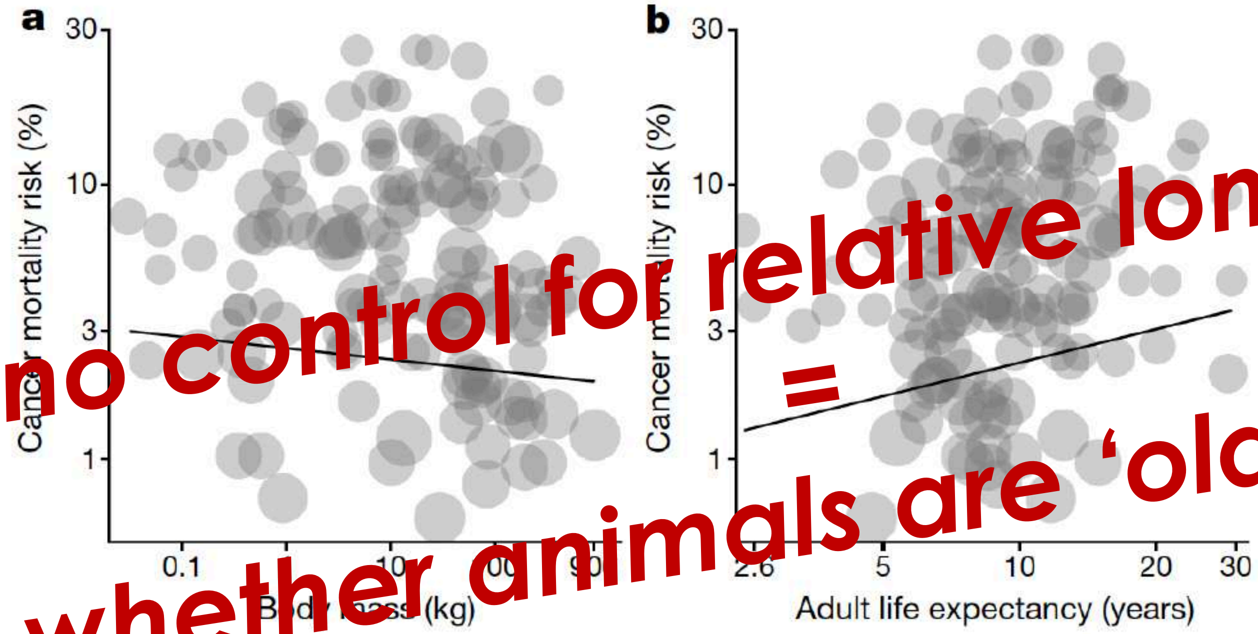

no control for relative longevity = whether animals are 'old' or not

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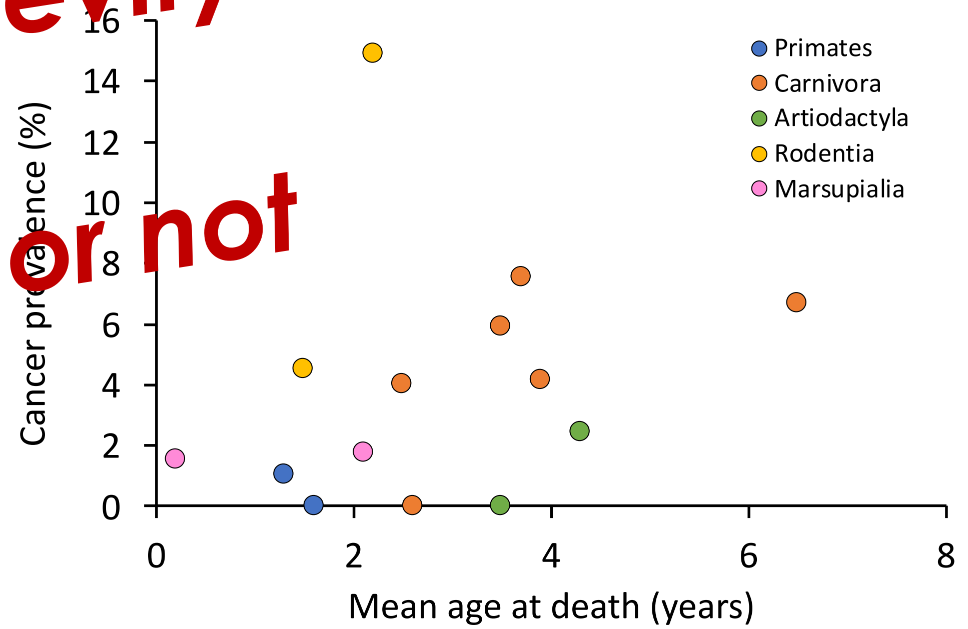

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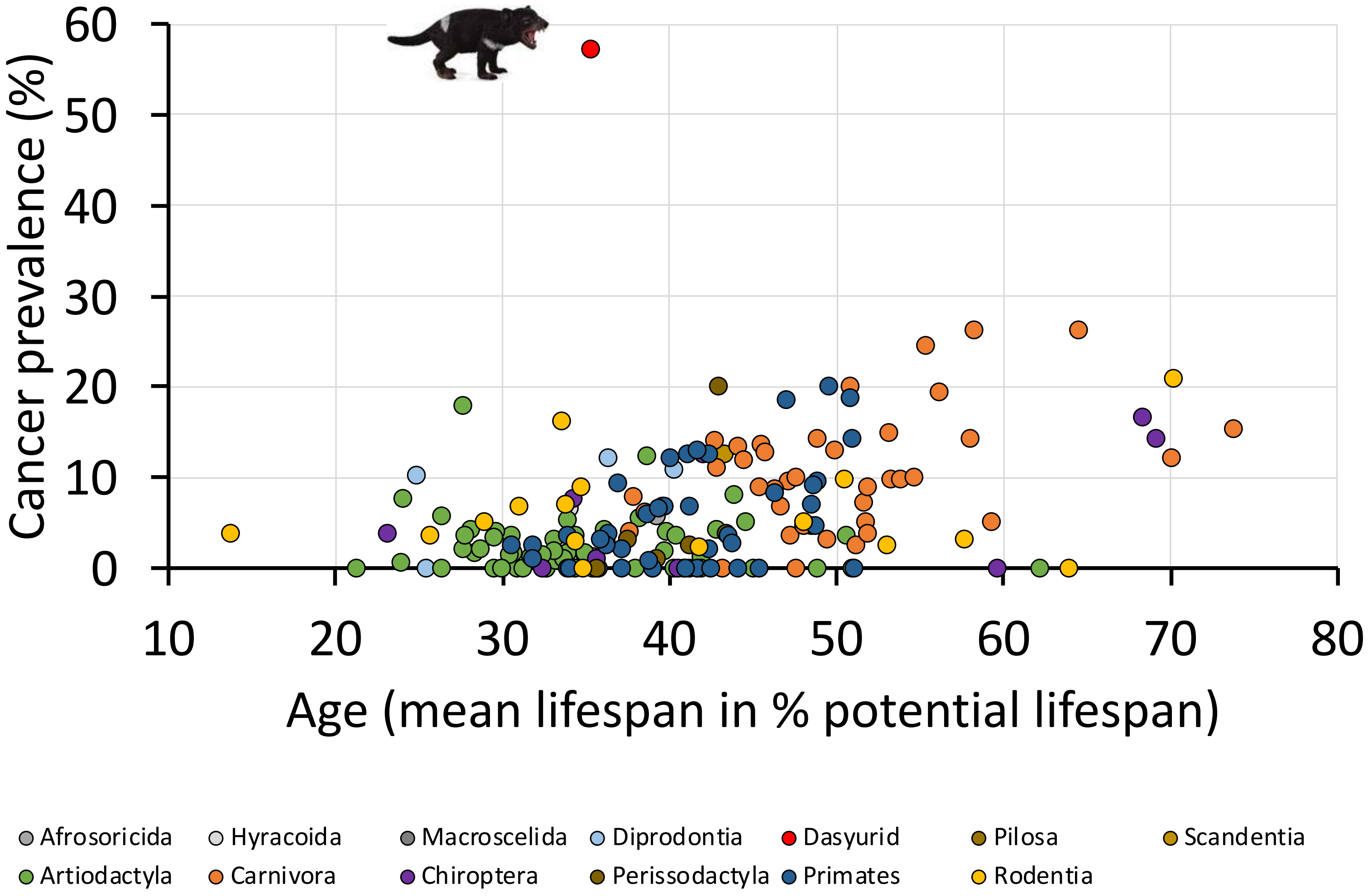
Nature | Vol 601 | 13



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model presented in
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using longevity data
from the AnAge
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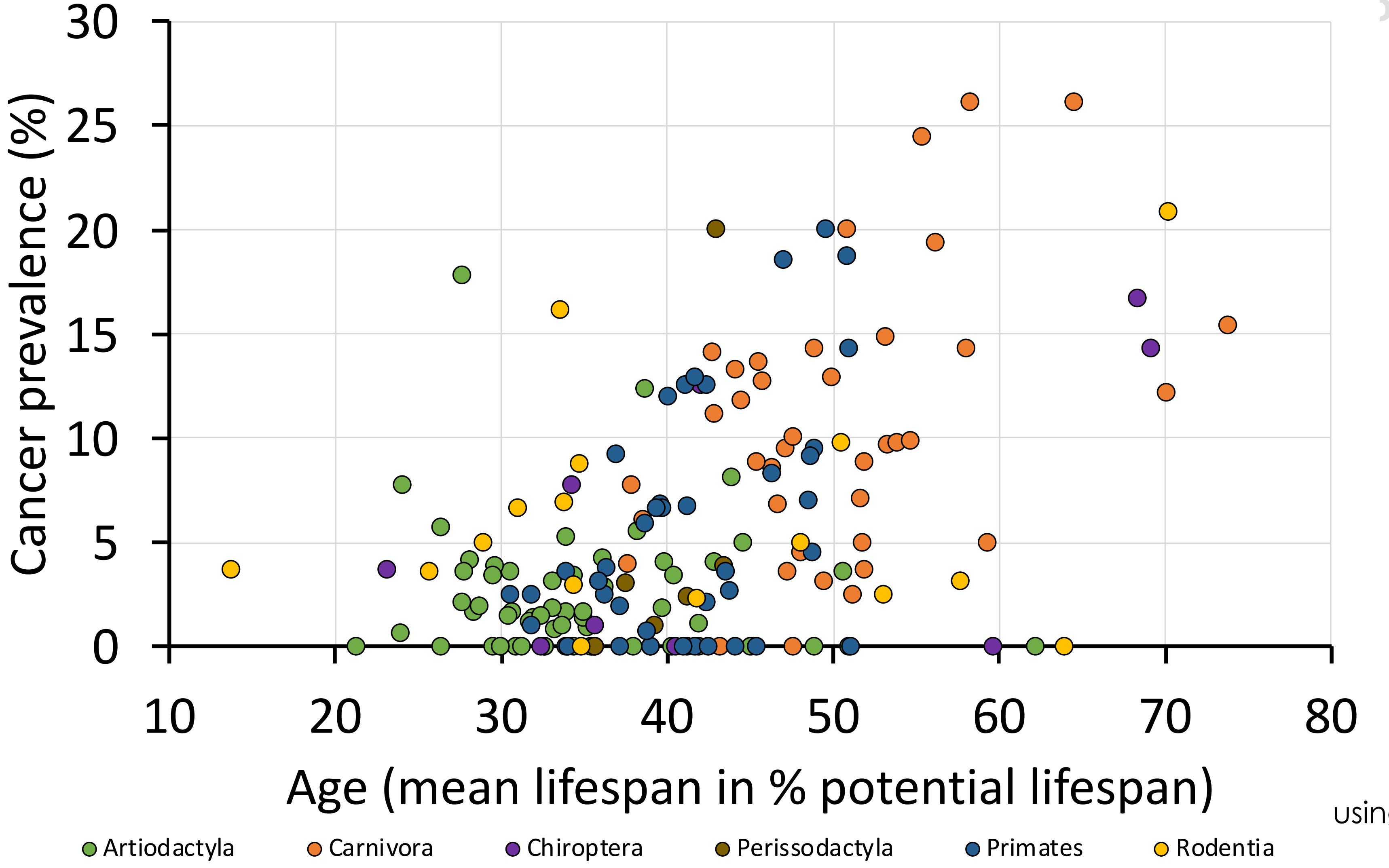

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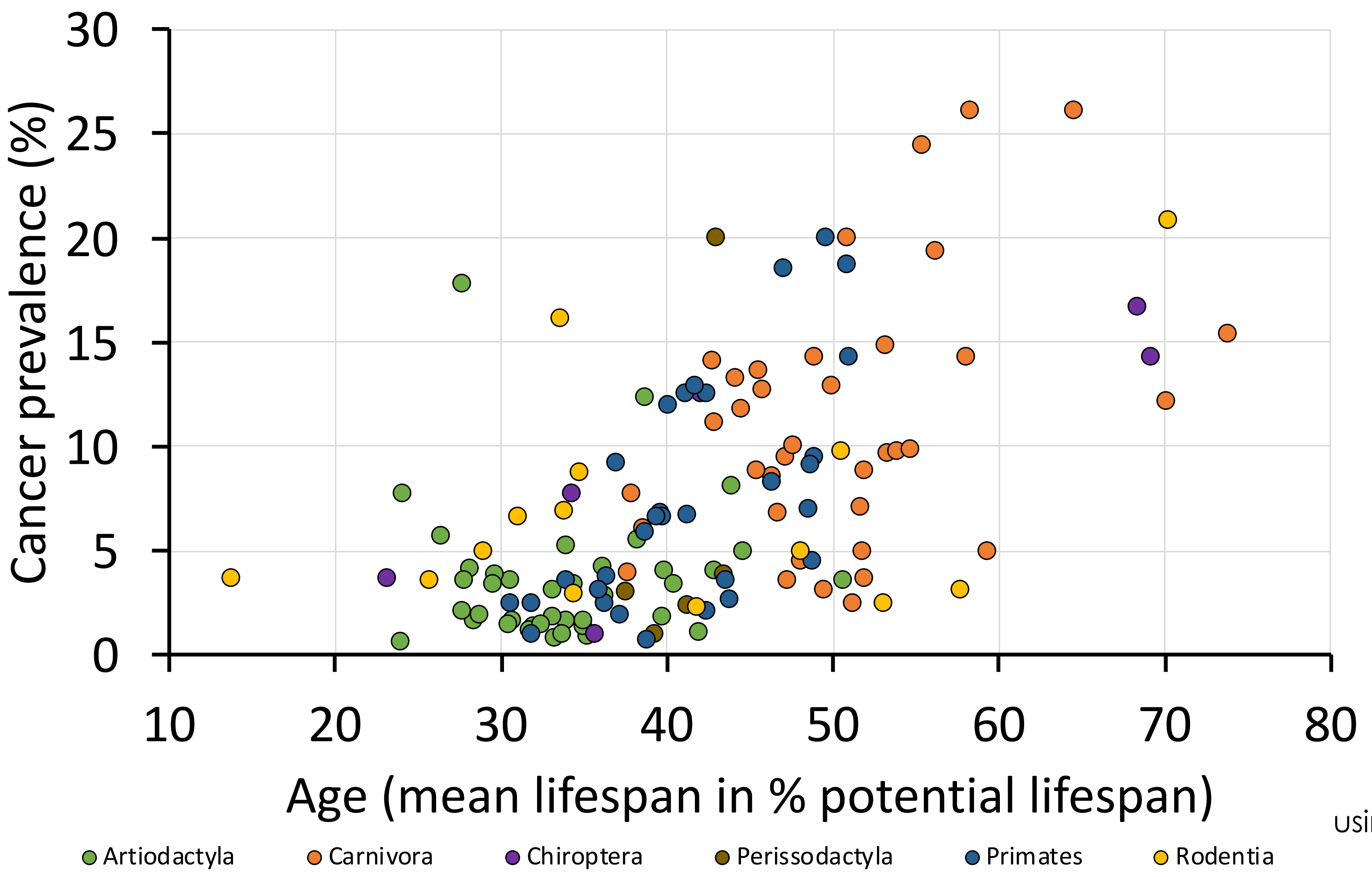

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Our study indicates that death due to oncogenic phenomena is frequent and taxonomically widespread in mammals. In some species more than 20–40% of the managed adult population die of cancer-related pathologies. This estimate is staggering, especially knowing that cancer incidences estimated here are conservative (Methods). This observation urges the extensive exploration of cancer in wildlife, especially in the context of recent environmental perturbations[38], as serious threats to animal welfare[29].

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good zoo husbandry (i.e., higher welfare) should lead to more, not less, cancer

Which mammals develop cancer ?

Which mammals develop cancer ?

Those that are kept so that they get old enough.

Summary: cancer (mostly) …

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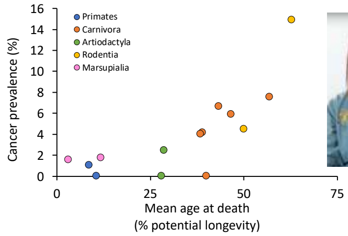
… is a disease of old age.

(old age cannot be counted in years, but in % of potential longevity)



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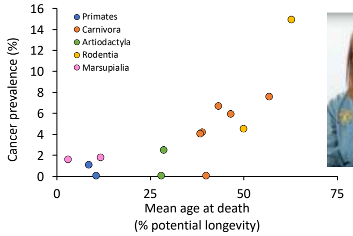

… becomes more prevalent if mortality due to bad husbandry is reduced.

(a high cancer prevalence therefore might well be a sign of good husbandry)

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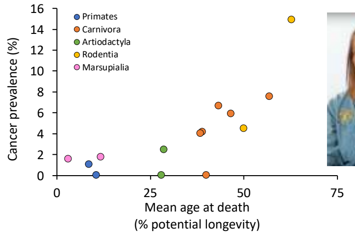

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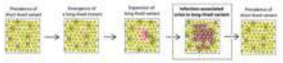
… does not attack the organism but is ***permitted by*** the organism as part of an adaptation for aging.

(cancer is not your friend, but it may be the friend of your offspring)



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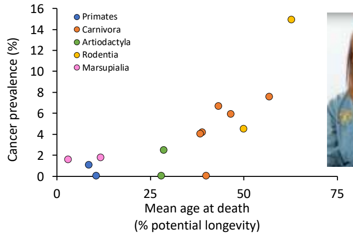

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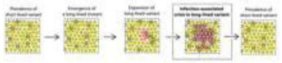

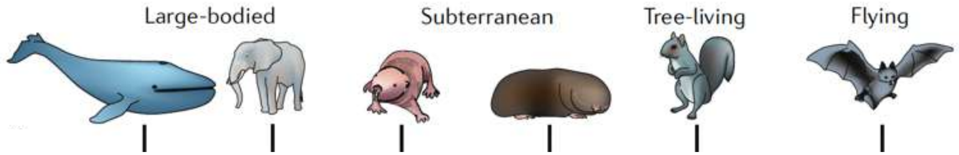

Because current comparative evaluations do not account for aging, we cannot conclude with certainty which species are particularly susceptible to cancer.

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Detailed Status Information

Manuscript #	2022-12-19728
Current Revision #	0
Submission Date	10th December 22
Current Stage	Manuscript received
Title	Zoo cancer prevalence may not indicate intrinsic cancer risk but rather husbandry success
Manuscript Type	Matters Arising
Corresponding Author	Marcus Clauss (University of Zurich)
Contributing Author	Dennis Müller
Authorship	Yes
Abstract	ARISING FROM Vincze, O., Colchero, F., Lemaître, JF. et al. Cancer risk across mammals. Nature 601, 263–267 (2022). https://doi.org/10.1038/s41586-021-04224-5 In the tradition of evaluating cancer prevalence across zoo animal taxa to explore which biological characteristics make animals particularly susceptible or resistant to cancer, as done by Vincze et al.1, one must not overlook that whether a taxon lives long enough to develop cancer will depend distinctively on how easily it is managed in zoos.
Subject Terms	Biological sciences/Cancer/Cancer epidemiology Biological sciences/Zoology/Animal physiology
Show Author Information	Allow Referees to see Author information.
Competing interests policy	There is **NO** Competing Interest.
Applicable Funding Source	No Applicable Funding
Previous Interactions	None of the above

Stage	Start Date
Manuscript received	10th December 22
Manuscript under submission	10th December 22

BRIEF COMMUNICATIONS ARISING

Zoo cancer prevalence may not indicate intrinsic cancer risk but rather husbandry success

ARISING FROM Vincze, O., Colchero, F., Lemaître, JF. *et al.* Cancer risk across mammals. *Nature* **601**, 263–267 (2022). https://doi.org/10.1038/s41586-021-04224-5

In the tradition of evaluating cancer prevalence across zoo animal taxa to explore which biological characteristics make animals particularly susceptible or resistant to cancer, as done by Vincze et al.[1], one must not overlook that whether a taxon lives long enough to develop cancer will depend distinctively on how easily it is managed in zoos.

Comparative pathologist Herbert L. Ratcliffe revolutionized zoo animal nutrition.[2] In doing so, he increased cancer prevalence in mammals at the Philadelphia Zoo from 2.6% between 1901-1932[3] to 4.6% after the diet transformation in 1935.[4] Better diets lead to more cancer? Of course. The prevalence of all causes of death must add up to 100% - you have to die of something. You take away husbandry-related deaths like malnutrition, and the prevalence of other causes must increase. Cancer is (not only, but mainly) an old-age phenomenon. If cancer prevalence is high among zoo animals, this is not '*staggering'* or indication of a '*threat to animal welfare'*,[1] but rather a sign zoos are doing something right: keeping animals alive long enough for cancer to develop.
For an individual animal taxon, this might mean that cancer prevalence in zoos does not necessarily indicate a specific susceptibility or intrinsic '*cancer risk'*,[1] but how successful the husbandry of the taxon actually is. Taxa differ in how successfully they are kept in zoos.[e.g.5] In one of the first comparative cancer evaluations,[3] Ratcliffe himself demonstrated this already: those species that attained, at Philadelphia zoo at the time, a higher proportion of their potential lifespan had more cancer. Plotting his tabulated data – crude as it is – makes the point: There is no clear pattern of cancer prevalence with a taxon's potential lifespan (Fig. 1A; a concept used repeatedly in the comparative cancer literature[e.g.6] that might even suggest a decrease in cancer prevalence in animals with a high potential lifespan), or with a taxon's mean absolute lifespan actually achieved at the zoo (Fig. 1B; the concept used in the recent comparative cancer study by Vincze et al.[1]). However, there is a clear relationship with the mean *relative* lifespan (the mean age attained at the zoo in % of the taxon's potential lifespan; Fig. 1C): taxa that get *relatively* older have more cancer.[3] Rather than indicating a specific cancer risk for carnivores,[1] the comparative zoo cancer literature might inadvertently give testimony that carnivores fare particularly well in zoos[7] and their husbandry has been continuously improving.[8] Without accounting for this fact, any evaluation of zoo-derived data cannot indicate intrinsic taxon-specific cancer risks with certainty but might only indicate which taxa are kept particularly successfully.

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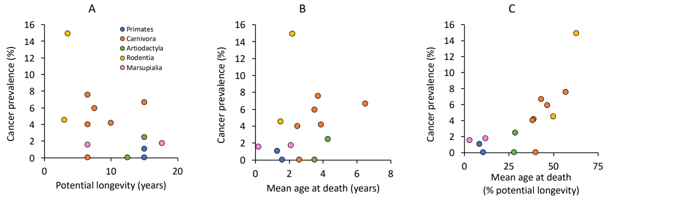

Fig. 1 | The relationship of cancer prevalence to a taxon's potential absolute longevity (A), mean actual absolute lifespan (B), and its mean relative lifespan (C). Note that the data do not indicate taxon-specific cancer susceptibility but that those taxa that achieved a relatively higher proportion of their longevity at this particular zoo had a higher cancer prevalence. Data from Ratcliffe[3].

thank you for your attention