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HEALTHY LIFE EXTENSION SOCIETY

Scientific News
4th of April 2021
Sven Bulterijs

Business/Conferences/ General news

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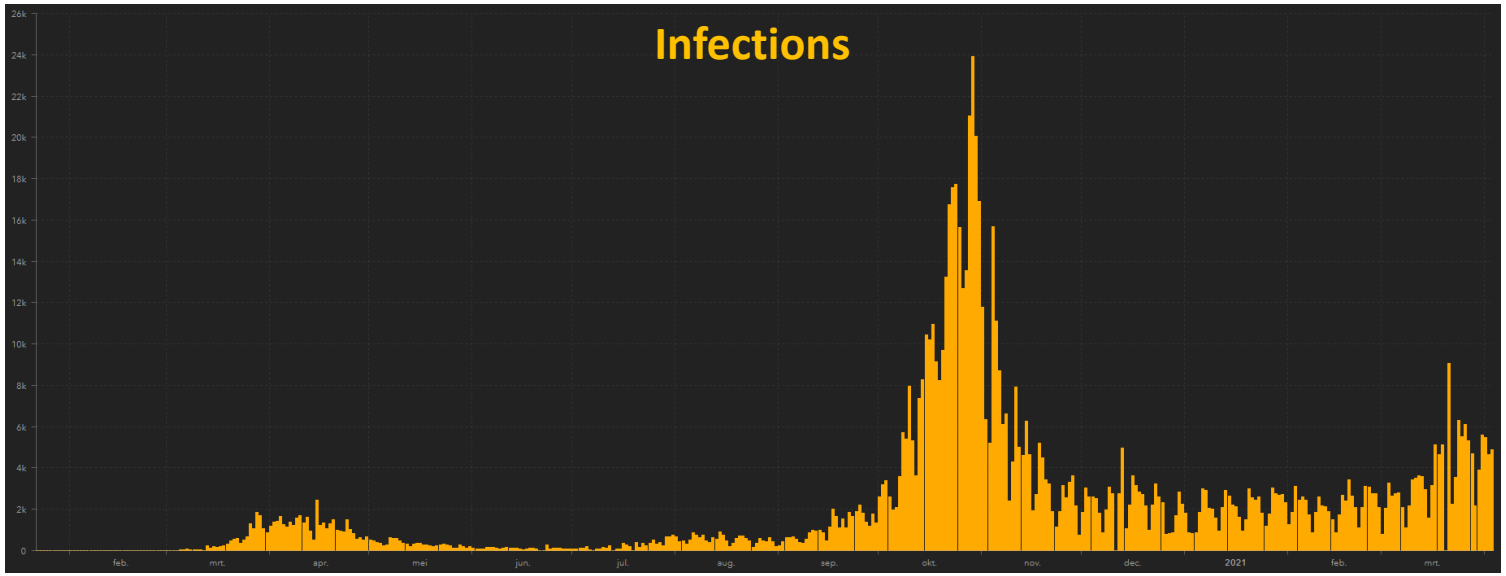
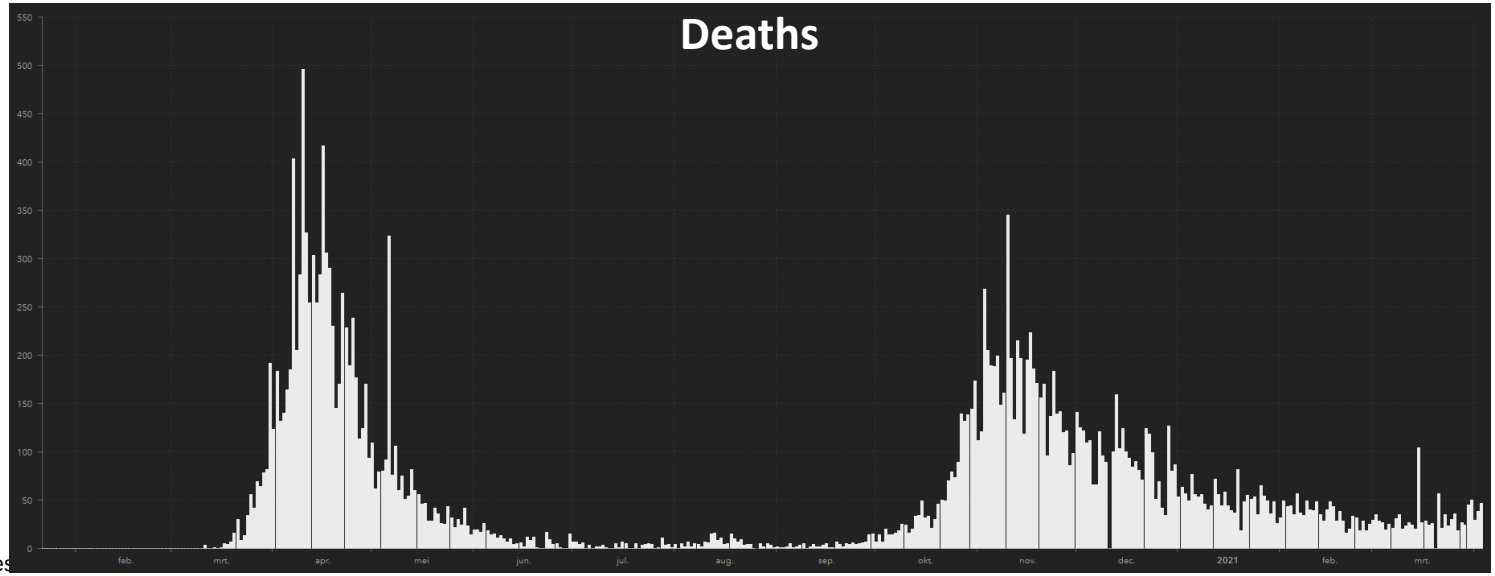
Belgium





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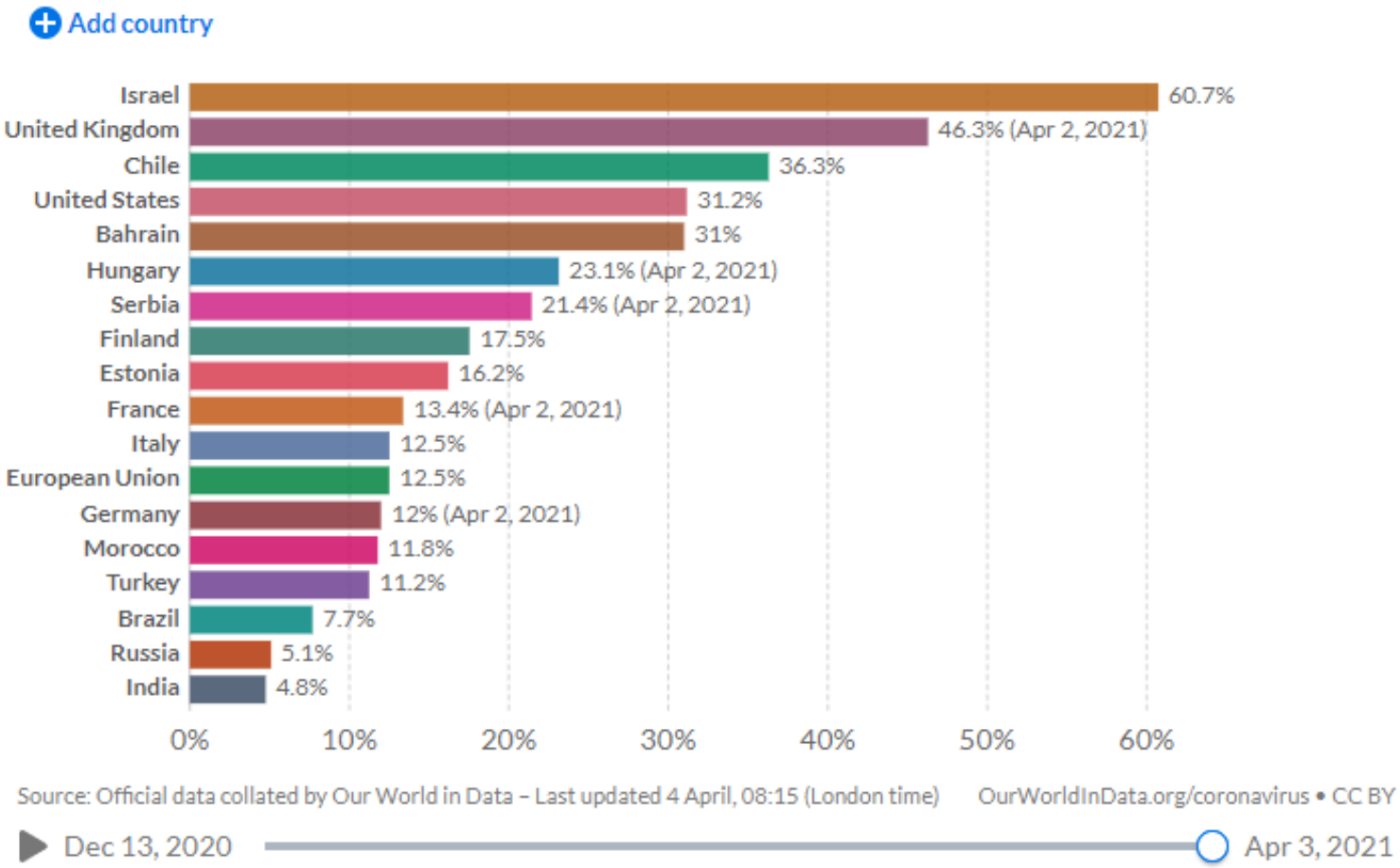
Share of people who received at least one dose of COVID-19 vaccine, Apr 3, 2021

Our World in Data

Share of the total population that received at least one vaccine dose. This may not equal the share that are fully vaccinated if the vaccine requires two doses.



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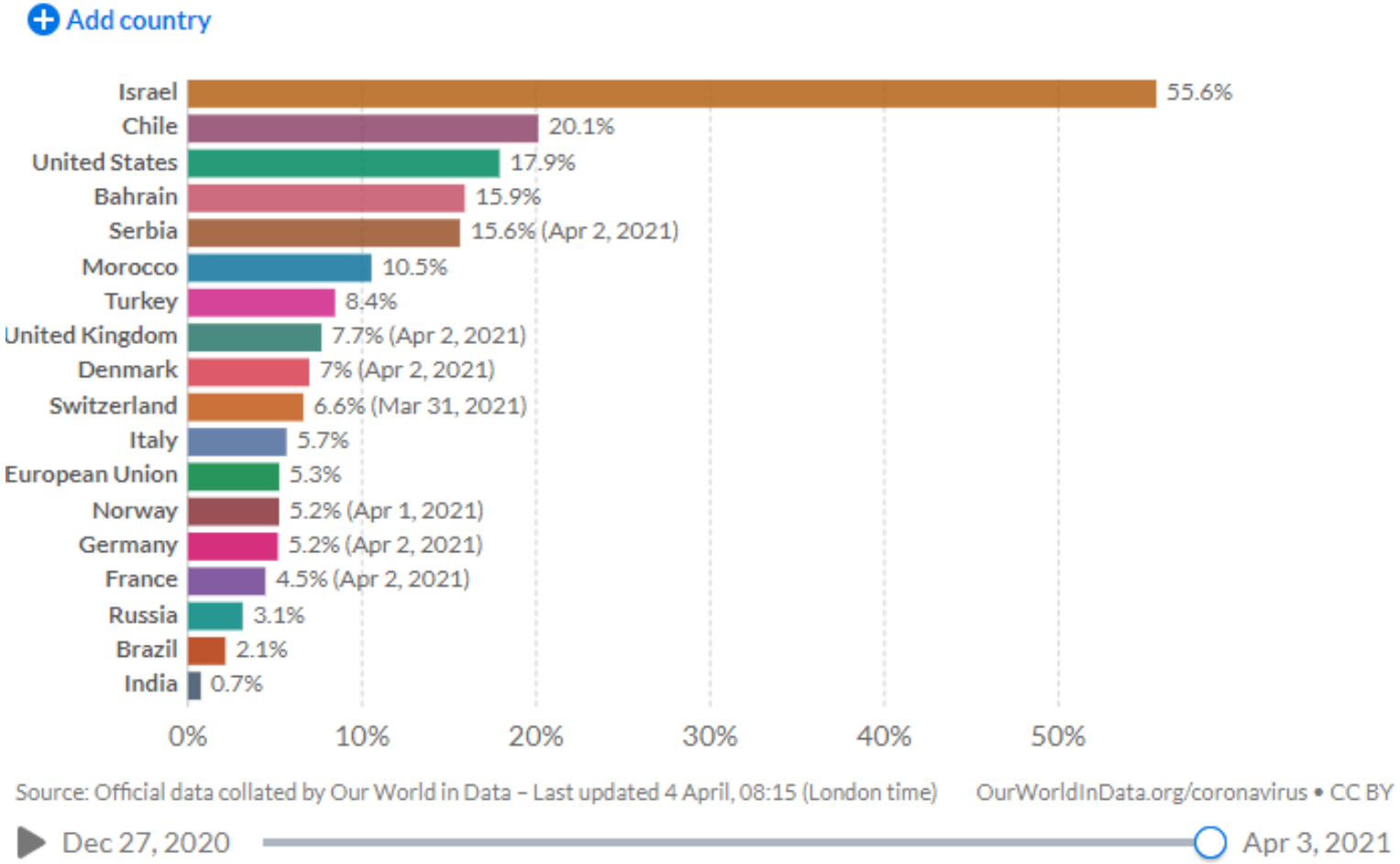
Share of the population fully vaccinated against COVID-19, Apr 3, 2021

Our World in Data

Share of the total population that have received all doses prescribed by the vaccination protocol. This data is only available for countries which report the breakdown of doses administered by first and second doses.



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Member State	Pfizer TOTAL Q1+Q2	Pfizer TOTAL vs pro rata	Needed for 75.5% of pro rata Pfizer	Pro-rata distribution of 7 mil doses	Total vaccines + SOLIDARITY 3 mil + PRO-RATA 7 mil	Estimated % vaccinated pop. with confirmed orders en Q2	Additional doses to reach 45% target
Austria	4 688 944	91,9%	0	139 170	8 377 107	50,92%	
Belgium	6 576 261	99,3%	0	180 585	11 870 804	57,45%	
Bulgaria	1 856 945	46,6%	1151889	108 688	5 708 004	45,01%	
Croatia	1 072 500	46,1%	684009	63 450	3 428 319	45,29%	
Cyprus	500 063	98,2%	0	13 884	1 054 421	62,47%	
Czech Republic	6 153 212	100,3%	0	167 202	8 931 683	44,33%	142 940
Denmark	4 220 697	126,4%	0	91 040	7 746 253	79,88%	
Estonia	533 673	70,0%	41553	20 779	1 253 725	50,27%	
Finland	3 250 801	102,6%	0	86 389	5 783 630	58,40%	
France	39 528 523	102,7%	0	1 049 107	69 912 819	58,16%	
Germany	53 051 296	111,2%	0	1 300 333	91 450 124	61,04%	
Greece	6 030 988	98,2%	0	167 449	10 940 401	57,14%	
Hungary	4 755 428	84,9%	0	152 749	9 233 842	53,32%	
Ireland	2 881 492	101,2%	0	77 611	5 156 948	58,01%	
Italy	33 925 632	98,2%	0	941 940	61 542 164	57,14%	
Latvia	449 017	41,0%	376689	29 827	1 794 253	53,09%	
Lithuania	1 595 380	99,6%	0	43 686	2 729 803	52,29%	
Luxembourg	352 581	98,2%	0	9 789	638 798	57,08%	
Malta	435 671	147,7%	0	8 045	895 713	93,10%	
Netherlands	10 393 324	104,1%	0	272 172	19 384 479	64,59%	
Poland	21 735 644	99,9%	0	593 485	37 432 270	55,46%	
Portugal	5 769 197	97,7%	0	160 979	10 488 908	57,00%	
Romania	10 878 558	98,2%	0	302 042	19 734 047	57,14%	
Slovakia	1 759 429	56,2%	602921	85 335	4 589 274	45,59%	
Slovenia	965 598	80,3%	0	32 769	1 926 354	52,02%	
Spain	26 909 642	99,2%	0	740 016	48 606 010	57,41%	
Sweden	6 367 442	107,5%	0	161 474	11 294 518	60,75%	
TOTAL EU	**256 637 937**		**2 857 060**	**7 000 000**			
						Total	**10 000 000**

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Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study

BMJ 2021 ; 372 doi: https://doi.org/10.1136/bmj.n693 (Published 31 March 2021)
Cite this as: *BMJ* 2021;372:n693

Objective To quantify rates of organ specific dysfunction in individuals with covid-19 after discharge from hospital compared with a matched control group from the general population.

Design Retrospective cohort study.

Setting NHS hospitals in England.

Participants 47 780 individuals (mean age 65, 55% men) in hospital with covid-19 and discharged alive by 31 August 2020, exactly matched to controls from a pool of about 50 million people in England for personal and clinical characteristics from 10 years of electronic health records.

Main outcome measures Rates of hospital readmission (or any admission for controls), all cause mortality, and diagnoses of respiratory, cardiovascular, metabolic, kidney, and liver diseases until 30 September 2020. Variations in rate ratios by age, sex, and ethnicity.

Results Over a mean follow-up of 140 days, nearly a third of individuals who were discharged from hospital after acute covid-19 were readmitted (14 060 of 47 780) and more than 1 in 10 (5875) died after discharge, with these events occurring at rates four and eight times greater, respectively, than in the matched control group. Rates of respiratory disease (P<0.001), diabetes (P<0.001), and cardiovascular disease (P<0.001) were also significantly raised in patients with covid-19, with 770 (95% confidence interval 758 to 783), 127 (122 to 132), and 126 (121 to 131) diagnoses per 1000 person years, respectively. Rate ratios were greater for individuals aged less than 70 than for those aged 70 or older, and in ethnic minority groups compared with the white population, with the largest differences seen for respiratory disease (10.5 (95% confidence interval 9.7 to 11.4) for age less than 70 years *v* 4.6 (4.3 to 4.8) for age ≥70, and 11.4 (9.8 to 13.3) for non-white *v* 5.2 (5.0 to 5.5) for white individuals).

Conclusions Individuals discharged from hospital after covid-19 had increased rates of multiorgan dysfunction compared with the expected risk in the general population. The increase in risk was not confined to the elderly and was not uniform across ethnicities. The diagnosis, treatment, and prevention of post-covid syndrome requires integrated rather than organ or disease specific approaches, and urgent research is needed to establish the risk factors.

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Eli Lilly COVID-19 antibody combo aces study, cutting hospitalizations and deaths by a whopping 87%

by Eric Sagonowsky | Mar 10, 2021 7:38am

Eli Lilly's antibody combo posted impressive new data.

Eli Lilly's COVID-19 antibody combo already boasts an FDA authorization for patients at a high risk of developing severe disease, but now the company has even stronger data backing the duo.

In trial data released Wednesday, the company said its bamlanivimab-etesevimab duo slashed the risk of hospitalization and death by a whopping 87% versus placebo. Investigators tested a combination of 700 mg of bamlanivimab and 1400 mg of etesevimab in a trial comprising 769 patients total.

Studie Planbureau

Corona zindert nog tien jaar na in woonzorgcentra: rusthuisbevolking pas in 2031 weer op peil

Vandaag om 03:00 door Tom Le Bacq

(FOTO: JOREN DE WEERDT)

De coronacrisis heeft zo hard toegeslagen in de woonzorgcentra dat de gevolgen nog jaren voelbaar zullen zijn. Volgens een nieuwe studie van het Planbureau zal de populatie pas binnen tien jaar weer op het niveau zijn van nu. Minister Wouter Beke wil nieuwe woon-zorgcentra en uitbreidingen nu "maximaal uitstellen".

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Taking gene therapy to the masses with innovations in diabetes, Alzheimer's and more

by Arlene Weintraub | Mar 30, 2021 7:00am

Could gene therapy make these tools a relic in the treatment of diabetes? (Pixabay / stevepb)

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Science of Aging: A Physiological & Translational Perspective

The American Physiological Society (APS), Alliance for Aging Research (AAR), and InsideScientific are pleased to announce a joint webinar series covering fundamental principles, late-breaking research and novel discoveries in the field of aging science.

Topics

Musculoskeletal Composition, Strength and Sarcopenia

Aging research articles

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17-a-estradiol late in life extends lifespan in aging UM-HET3 male mice; nicotinamide riboside and three other drugs do not affect lifespan in either sex

In genetically heterogeneous mice produced by the CByB6F1 x C3D2F1 cross, the "non-feminizing" estrogen, 17-α-estradiol (17aE2), extended median male lifespan by 19% ($p < 0.0001$, log-rank test) and 11% ($p = 0.007$) when fed at 14.4 ppm starting at 16 and 20 months, respectively. 90th percentile lifespans were extended 7% ($p = 0.004$, Wang–Allison test) and 5% ($p = 0.17$). Body weights were reduced about 20% after starting the 17aE2 diets. Four other interventions were tested in males and females: nicotinamide riboside, candesartan cilexetil, geranylgeranylacetone, and MIF098. Despite some data suggesting that nicotinamide riboside would be effective, neither it nor the other three increased lifespans significantly at the doses tested. The 17aE2 results confirm and extend our original reports, with very similar results when started at 16 months compared with mice started at 10 months of age in a prior study. The consistently large lifespan benefit in males, even when treatment is started late in life, may provide information on sex-specific aspects of aging.

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PREPRINT

DNA methylation clocks show slower progression of aging in naked mole-rat queens

Steve Horvath, Amin Haghani, Nicholas Macoretta, Julia Ablaeva, Joseph A. Zoller, Caesar Z. Li, Joshua Zhang, Masaki Takasugi, Yang Zhao, Elena Rydkina, Zhihui Zhang, Stephan Emmrich, Ken Raj, Andrei Seluanov, Chris G. Faulkes, Vera Gorbunova

Naked mole-rats (NMRs) live an exceptionally long life, appear not to exhibit age-related decline in physiological capacity, and are seemingly resistant to age-related diseases. However, it has been unknown whether NMRs also evade aging according to a primary hallmark of aging: epigenetic changes. To address this question, we generated DNA methylation profiles from 329 tissues from animals of known age, at loci that are highly conserved between mammalian species, using a custom Infinium array (HorvathMammalMethylChip40). We observed strong aging effects on NMR DNA methylation, from which we developed seven highly accurate age estimators (epigenetic clocks) for several tissues (pan-tissue, blood, kidney clock, liver clock, skin clock) and two dual species (human-NMR) clocks. By identifying age-related cytosine methylation that are shared between NMR and humans, but not with the mouse, we identified genes and cellular pathways that impinge on developmental and metabolic processes that are potentially involved in NMR and human longevity. The NMR epigenetic clocks revealed that breeding NMR queens age more slowly than non-breeders, a feature that is also observed in some eusocial insects. CpGs associated with queen status were located near developmental genes and those that are regulated by the *LHX3* transcription factor that controls pituitary development. In summary, our study demonstrates that despite a phenotype of reduced senescence, the NMR ages epigenetically through developmental and metabolic processes, and that NMR queens age more slowly than non-breeders.

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PREPRINT

Epigenetic clock and methylation studies in dogs

DNA methylation profiles have been used to develop biomarkers of aging known as epigenetic clocks, which predict chronological age with remarkable accuracy and show promise for inferring health status as an indicator of biological age. Epigenetic clocks were first built to monitor human aging but the principles underpinning them appear to be evolutionarily conserved, as they have now been successfully developed for over 120 mammalian species. Here we describe reliable and highly accurate epigenetic clocks shown to apply to 51 domestic dog breeds. The methylation profiles were generated using a custom array with DNA sequences that are conserved across all mammalian species (HorvathMammalMethylChip40). Canine epigenetic clocks were constructed to estimate age and also predict mortality risk by estimating average time-to-death. We also present two highly accurate human-dog dual species epigenetic clocks (R=0.97), which may facilitate the ready translation from canine to human use (or vice versa) of anti-aging treatments being developed for longevity and preventive medicine. Finally, epigenome-wide association studies herein reveal individual methylation sites that may underlie the inverse relationship between breed weight and lifespan. Overall, we describe robust biomarkers to measure aging and potentially health status in canines.

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DNA methylation predicts age and provides insight into exceptional longevity of bats

Gerald S. Wilkinson, Danielle M. Adams, [...] Steve Horvath

Exceptionally long-lived species, including many bats, rarely show overt signs of aging, making it difficult to determine why species differ in lifespan. Here, we use DNA methylation (DNAm) profiles from 712 known-age bats, representing 26 species, to identify epigenetic changes associated with age and longevity. We demonstrate that DNAm accurately predicts chronological age. Across species, longevity is negatively associated with the rate of DNAm change at age-associated sites. Furthermore, analysis of several bat genomes reveals that hypermethylated age- and longevity-associated sites are disproportionately located in promoter regions of key transcription factors (TF) and enriched for histone and chromatin features associated with transcriptional regulation. Predicted TF binding site motifs and enrichment analyses indicate that age-related methylation change is influenced by developmental processes, while longevity-related DNAm change is associated with innate immunity or tumorigenesis genes, suggesting that bat longevity results from augmented immune response and cancer suppression.

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Short and dysfunctional telomeres sensitize the kidneys to develop fibrosis

Sarita Saraswati, Paula Martínez, Osvaldo Graña-Castro & Maria A. Blasco

Accumulation of short telomeres is a hallmark of aging. Mutations in telomerase or telomere-binding proteins lead to telomere shortening or dysfunction and are at the origin of human pathologies known as 'telomere syndromes', which are characterized by loss of the regenerative capacity of tissues and fibrotic pathologies. Here, we generated two mouse models of kidney fibrosis, either by combining telomerase deficiency to induce telomere shortening and a low dose of folic acid, or by conditionally deleting *Trf1*, a component of the shelterin telomere protective complex, from the kidneys. We find that short telomeres sensitize the kidneys to develop fibrosis in response to folic acid and exacerbate the epithelial-to-mesenchymal transition (EMT) program. *Trf1* deletion in kidneys led to fibrosis and EMT activation. Our findings suggest that telomere shortening or dysfunction may contribute to pathological, age-associated renal fibrosis by influencing the EMT program.

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β-catenin-promoted cholesterol metabolism protects against cellular senescence in naked mole-rat cells

Woei-Yaw Chee, Yuriko Kurahashi, Junhyeong Kim, Kyoko Miura, Daisuke Okuzaki, Tohru Ishitani, Kentaro Kajiwara, Shigeyuki Nada, Hideyuki Okano & Masato Okada

The naked mole-rat (NMR; *Heterocephalus glaber*) exhibits cancer resistance and an exceptionally long lifespan of approximately 30 years, but the mechanism(s) underlying increased longevity in NMRs remains unclear. In the present study, we report unique mechanisms underlying cholesterol metabolism in NMR cells, which may be responsible for their anti-senescent properties. NMR fibroblasts expressed β-catenin abundantly; this high expression was linked to increased accumulation of cholesterol-enriched lipid droplets. Ablation of β-catenin or inhibition of cholesterol synthesis abolished lipid droplet formation and induced senescence-like phenotypes accompanied by increased oxidative stress. β-catenin ablation downregulated apolipoprotein F and the LXR/RXR pathway, which are involved in cholesterol transport and biogenesis. Apolipoprotein F ablation also suppressed lipid droplet accumulation and promoted cellular senescence, indicating that apolipoprotein F mediates β-catenin signaling in NMR cells. Thus, we suggest that β-catenin in NMRs functions to offset senescence by regulating cholesterol metabolism, which may contribute to increased longevity in NMRs.

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Mesenchymal stem cell-derived extracellular vesicles reduce senescence and extend health span in mouse models of aging

Aging drives progressive loss of the ability of tissues to recover from stress, partly through loss of somatic stem cell function and increased senescent burden. We demonstrate that bone marrow-derived mesenchymal stem cells (BM-MSCs) rapidly senescence and become dysfunctional in culture. Injection of BM-MSCs from young mice prolonged life span and health span, and conditioned media (CM) from young BM-MSCs rescued the function of aged stem cells and senescent fibroblasts. Extracellular vesicles (EVs) from young BM-MSC CM extended life span of *Ercc1*$^{-/-}$ mice similarly to injection of young BM-MSCs. Finally, treatment with EVs from MSCs generated from human ES cells reduced senescence in culture and *in vivo*, and improved health span. Thus, MSC EVs represent an effective and safe approach for conferring the therapeutic effects of adult stem cells, avoiding the risks of tumor development and donor cell rejection. These results demonstrate that MSC-derived EVs are highly effective senotherapeutics, slowing the progression of aging, and diseases driven by cellular senescence.

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PREPRINT

IDENTIFICATION OF BIOCHEMICAL AND MOLECULAR MARKERS OF EARLY AGING IN CHILDHOOD CANCER SURVIVORS

Purpose: Survival rates of Childhood Cancer Patients have improved tremendously over the past four decades. However, cancer treatments are associated with an increased risk of developing an anticipated onset of chronic diseases typical of aging. Thus, we aimed to identify molecular/metabolic cellular alterations responsible for early aging in Childhood Cancer Survivors (CCS). Patients and Methods: Biochemical, proteomic and molecular biology analyses were conducted on mononuclear cells (MNCs) isolated from peripheral blood of 196 CCS, comparing the results with those obtained on MNCs of 154 healthy subjects. Results: Data demonstrate that CCS-MNCs show: i) inefficient oxidative phosphorylation associated with low energy status and a metabolic switch to lactate fermentation compared with age-matched normal controls; ii) increment of lipid peroxidation due to an unbalance among the oxidative stress production and the activation of the antioxidant defenses; (iii) significantly lower expression of genes and proteins involved in mitochondrial biogenesis and metabolism regulation, such as CLUH, PGC1-alpha;, and SIRT6 in CCS, not observed in the age-matched healthy or elderly subjects. The application of a mathematical model based on biochemical parameters predicts that CCS have a biological age significantly increased by decades compared to the chronological age. Overall, the results show that the impact of chemo/chemoradiotherapy on mitochondria efficiency in 196 CCS was rather homogeneous, irrespective of cancer type, treatment protocols, and time elapsed from the end of the curative period. Conclusions: Our study identifies some biochemical and molecular alterations possibly contributing to the pathophysiology of anticipated aging and metabolic deficiency described in CCS. These results may be useful in identifying approaches to restore the mitochondrial function, slowing down the aging and the associated pathological conditions in CCS.

C. elegans aging research

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Health and longevity studies in *C. elegans*: the "healthy worm database" reveals strengths, weaknesses and gaps of test compound-based studies

Nadine Saul ✉, Steffen Möller, Francesca Cirulli, Alessandra Berry, Walter Luyten & Georg Fuellen

Several biogerontology databases exist that focus on genetic or gene expression data linked to health as well as survival, subsequent to compound treatments or genetic manipulations in animal models. However, none of these has yet collected experimental results of compound-related health changes. Since quality of life is often regarded as more valuable than length of life, we aim to fill this gap with the "Healthy Worm Database" (http://healthy-worm-database.eu). Literature describing health-related compound studies in the aging model *Caenorhabditis elegans* was screened, and data for 440 compounds collected. The database considers 189 publications describing 89 different phenotypes measured in 2995 different conditions. Besides enabling a targeted search for promising compounds for further investigations, this database also offers insights into the research field of studies on healthy aging based on a frequently used model organism. Some weaknesses of *C. elegans*-based aging studies, like underrepresented phenotypes, especially concerning cognitive functions, as well as the convenience-based use of young worms as the starting point for compound treatment or phenotype measurement are discussed. In conclusion, the database provides an anchor for the search for compounds affecting health, with a link to public databases, and it further highlights some potential shortcomings in current aging research.

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PREPRINT

ANALYSIS OF CHD-7 DEFECTIVE DAUER NEMATODES IMPLICATES COLLAGEN MISREGULATION IN CHARGE SYNDROME FEATURES

CHARGE syndrome is a complex developmental disorder caused by mutations in the chromodomain helicase DNA-binding protein7 (CHD7) and characterized by retarded growth and malformations in the heart and nervous system. However, despite the public health relevance of this disorder, relevant targets of CHD7 that relate to disease pathology are still poorly understood. Here we report that *chd-7*, the nematode ortholog of CHD7, is required for dauer morphogenesis, lifespan determination, and stress response. Genetic epistasis placed *chd-7* in the TGF-β pathway. Consistent with our discoveries, we found *chd-7* to be allelic to *scd-3*, a previously identified dauer suppressor from the TGF-β pathway. Interestingly, DAF-12 transcriptionally upregulated *chd-7*, which is necessary to repress *daf-9* for execution of the dauer program. Transcriptomic analysis comparing *chd-7*–defective and normal dauers showed enrichment of collagen genes, consistent with a conserved role for the TGF-β pathway in expression of the extracellular matrix. To validate a conserved function for *chd-7* in vertebrates, we used *Xenopus laevis* embryos, an established model to study craniofacial development. Morpholino mediated knockdown of Chd7 led to embryonic lethality, a reduction in *col2a1* mRNA levels and craniofacial defects in tadpoles. Both lethality and malformations were partially rescued in Chd7-depleted embryos by over-expression of *col2a1*. We suggest that pathogenic features of CHARGE syndrome caused by Chd7 mutations, such as craniofacial malformations, result from the reduction of collagen levels. These studies establish *C. elegans* as an amenable animal model to study the etiology of the developmental defects associated with pathogenic Chd7.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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Cellular aging beyond cellular senescence: Markers of senescence prior to cell cycle arrest *in vitro* and *in vivo*

Mikolaj Ogrodnik

The field of research on cellular senescence experienced a rapid expansion from being primarily focused on *in vitro* aspects of aging to the vast territories of animal and clinical research. Cellular senescence is defined by a set of markers, many of which are present and accumulate in a gradual manner prior to senescence induction or are found outside of the context of cellular senescence. These markers are now used to measure the impact of cellular senescence on aging and disease as well as outcomes of anti-senescence interventions, many of which are at the stage of clinical trials. It is thus of primary importance to discuss their specificity as well as their role in the establishment of senescence. Here, the presence and role of senescence markers are described in cells prior to cell cycle arrest, especially in the context of replicative aging and *in vivo* conditions. Specifically, this review article seeks to describe the process of "cellular aging": the progression of internal changes occurring in primary cells leading to the induction of cellular senescence and culminating in cell death. Phenotypic changes associated with aging prior to senescence induction will be characterized, as well as their effect on the induction of cell senescence and the final fate of cells reviewed. Using published datasets on assessments of senescence markers *in vivo*, it will be described how disparities between quantifications can be explained by the concept of cellular aging. Finally, throughout the article the applicational value of broadening cellular senescence paradigm will be discussed.