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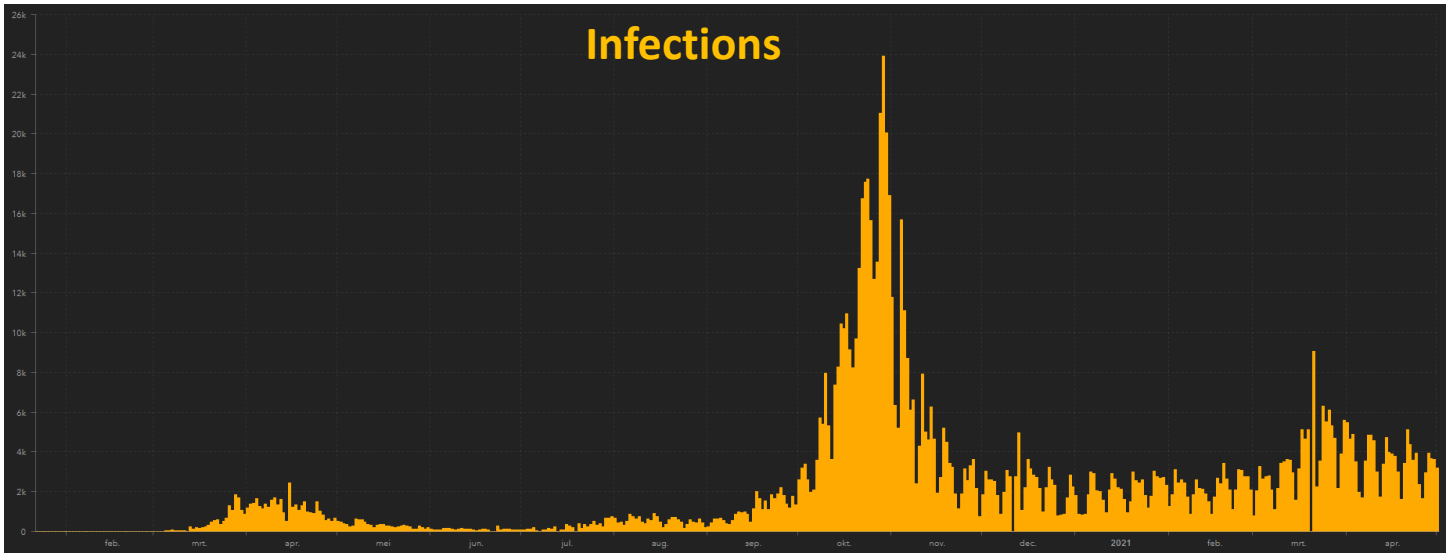
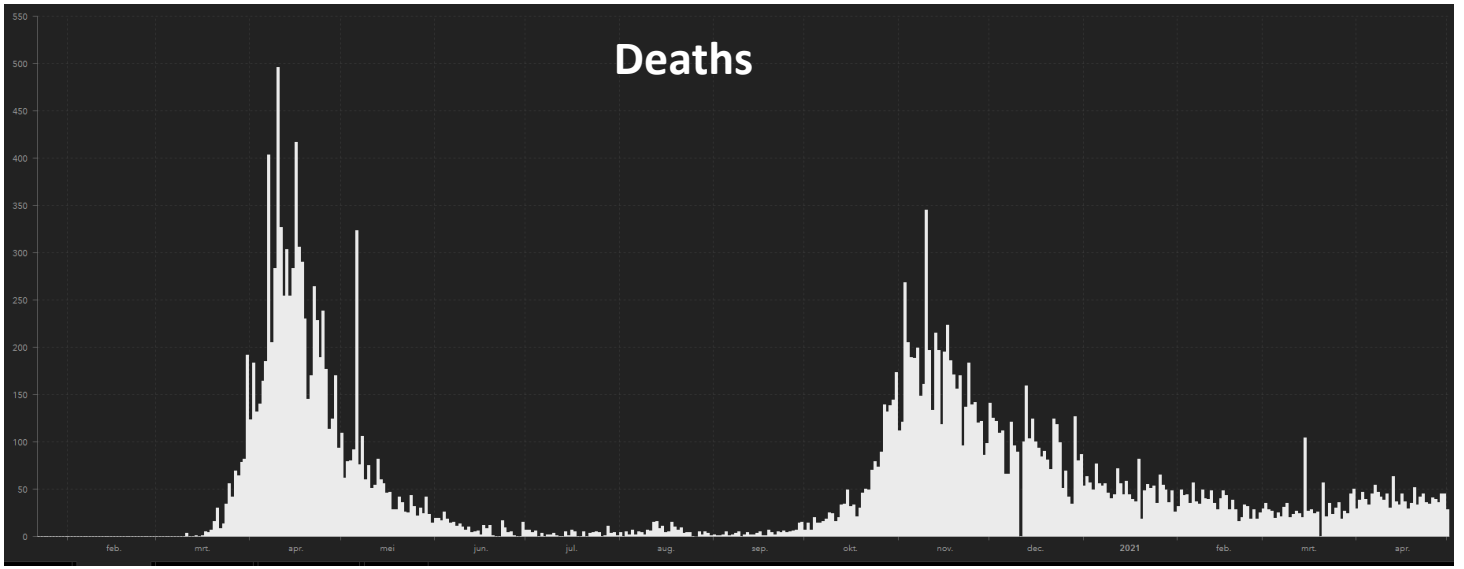
Scientific News
2nd of May 2021
Sven Bulterijs

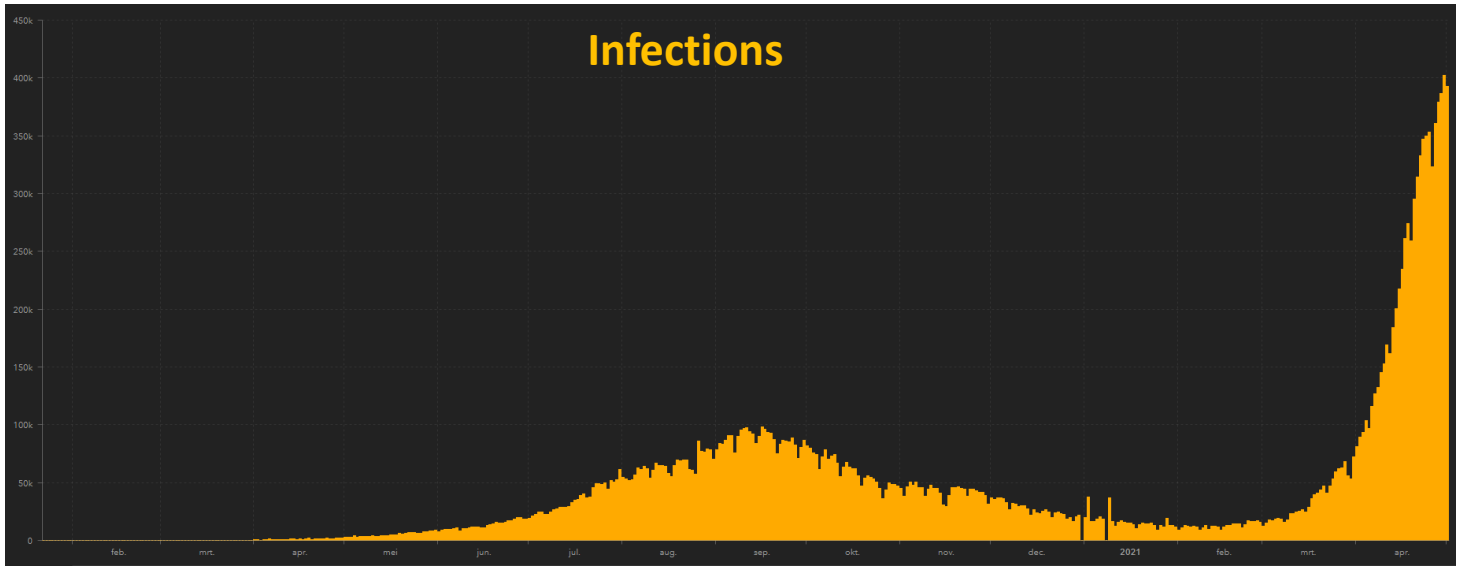
Business/Conferences/ General news

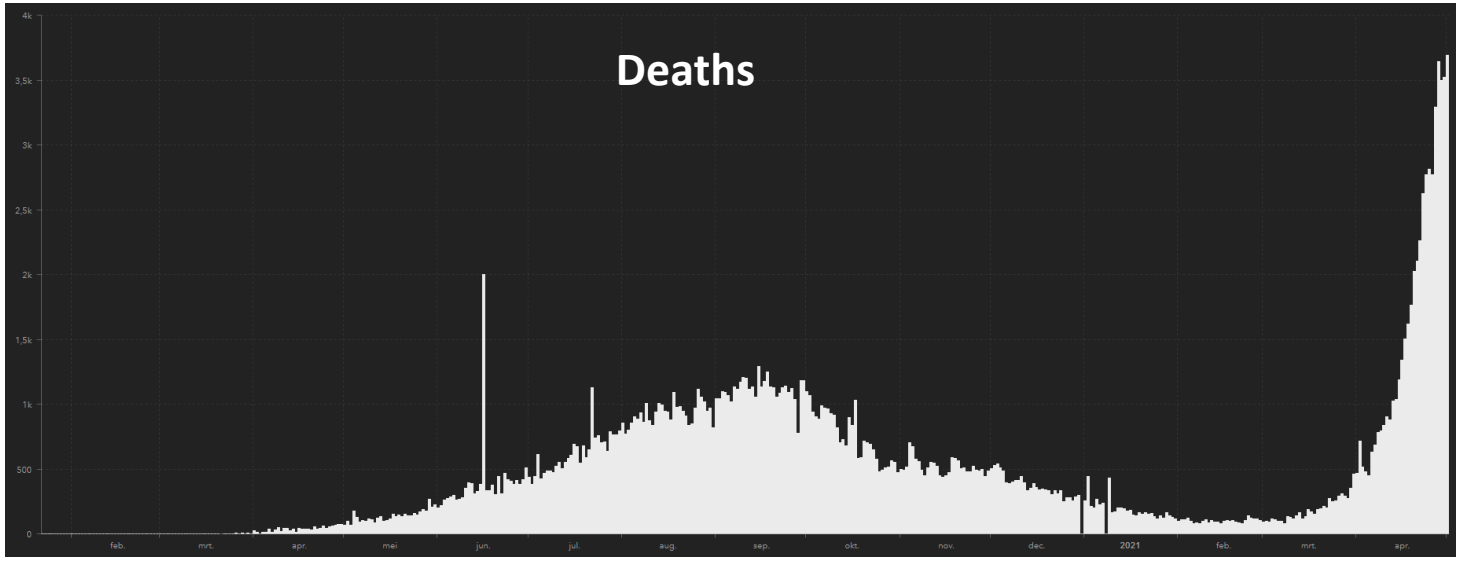
Belgium





India





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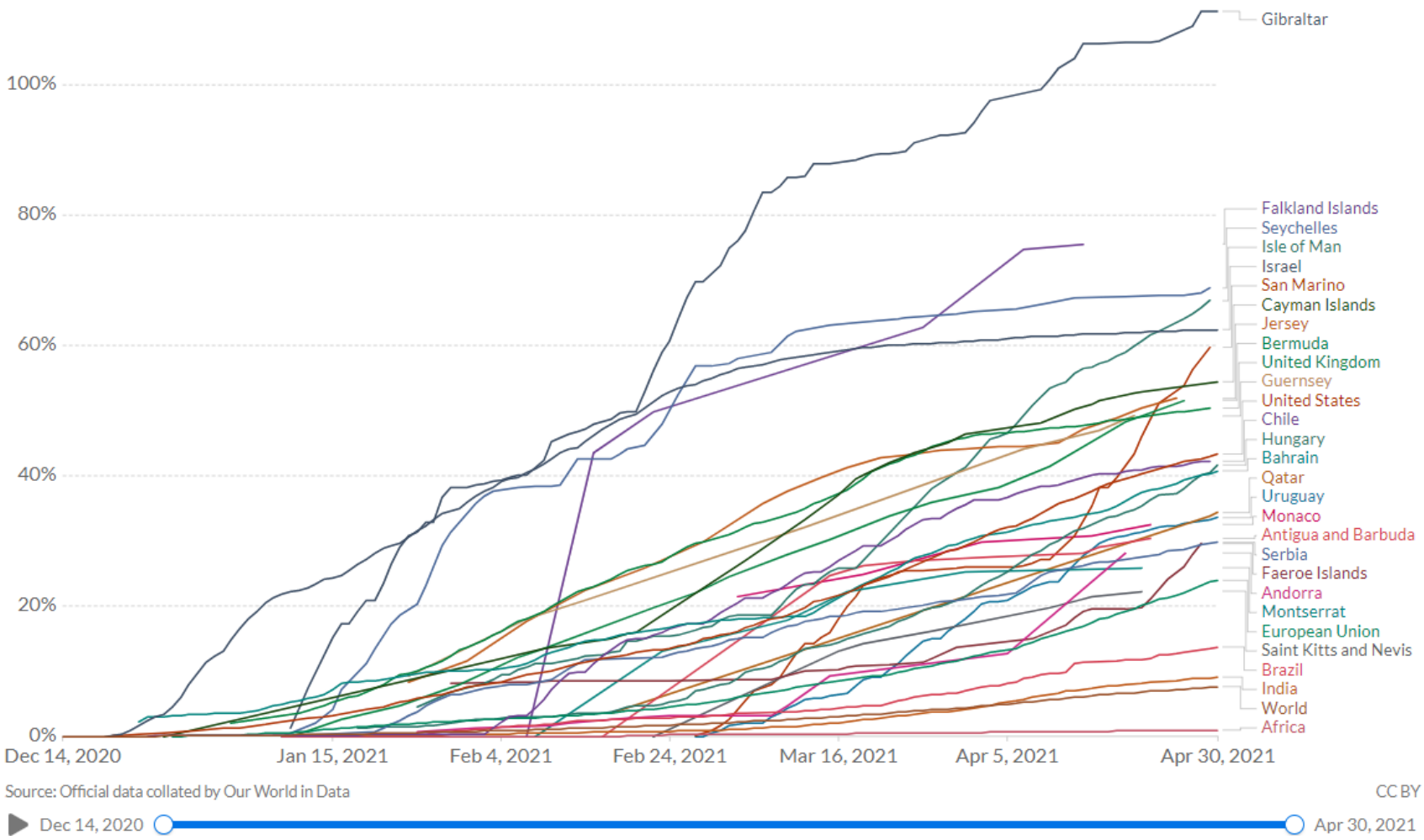
Share of people who received at least one dose of COVID-19 vaccine

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.

Our World in Data



Source: Official data collated by Our World in Data

CC BY

Dec 14, 2020 — Apr 30, 2021

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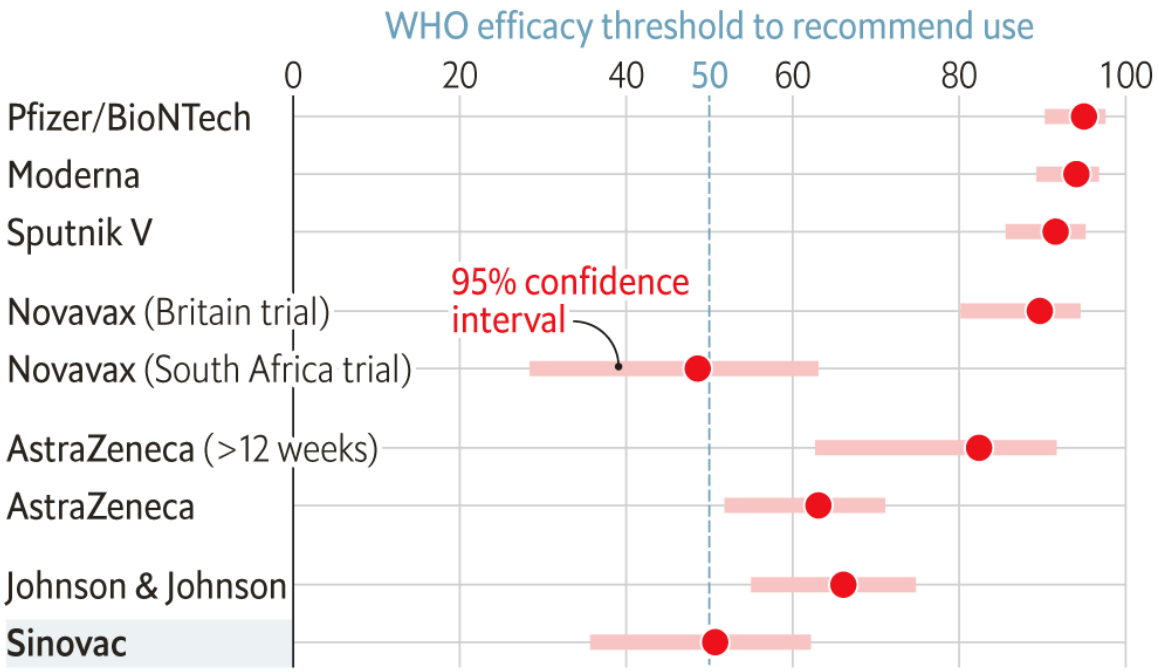
In clinical and real world trials, China's Sinovac underperforms

Covid-19 vaccine efficacy results in phase-three trials*, %



*Only trials with known confidence intervals

Source: Airfinity

The Economist

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The European Medicines Agency paved the way this week for Europe's use of a COVID-19 vaccine made by Johnson & Johnson, but questions persist about a rare clotting side effect linked to it and a similar vaccine made by AstraZeneca. ROB ENGELAAR/ANP/NEWSCOM

Do preservative and stray proteins cause rare COVID-19 vaccine side effect?

By Gretchen Vogel, Kai Kupferschmidt | Apr. 22, 2021 , 10:25 AM

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Suicide trends in the early months of the COVID-19 pandemic: an interrupted time-series analysis of preliminary data from 21 countries

Findings

We sourced data from 21 countries (16 high-income and five upper-middle-income countries), including whole-country data in ten countries and data for various areas in 11 countries). Rate ratios (RRs) and 95% CIs based on the observed versus expected numbers of suicides showed no evidence of a significant increase in risk of suicide since the pandemic began in any country or area. There was statistical evidence of a decrease in suicide compared with the expected number in 12 countries or areas: New South Wales, Australia (RR 0·81 [95% CI 0·72–0·91]); Alberta, Canada (0·80 [0·68–0·93]); British Columbia, Canada (0·76 [0·66–0·87]); Chile (0·85 [0·78–0·94]); Leipzig, Germany (0·49 [0·32–0·74]); Japan (0·94 [0·91–0·96]); New Zealand (0·79 [0·68–0·91]); South Korea (0·94 [0·92–0·97]); California, USA (0·90 [0·85–0·95]); Illinois (Cook County), USA (0·79 [0·67–0·93]); Texas (four counties), USA (0·82 [0·68–0·98]); and Ecuador (0·74 [0·67–0·82]).

Interpretation

This is the first study to examine suicides occurring in the context of the COVID-19 pandemic in multiple countries. In high-income and upper-middle-income countries, suicide numbers have remained largely unchanged or declined in the early months of the pandemic compared with the expected levels based on the pre-pandemic period. We need to remain vigilant and be poised to respond if the situation changes as the longer-term mental health and economic effects of the pandemic unfold.

The lockdown effect: A counterfactual for Sweden

Benjamin Born, Alexander M. Dietrich, Gernot J. Müller

While most countries imposed a lockdown in response to the first wave of COVID-19 infections, Sweden did not. To quantify the lockdown effect, we approximate a counterfactual lockdown scenario for Sweden through the outcome in a synthetic control unit. We find, first, that a 9-week lockdown in the first half of 2020 would have reduced infections and deaths by about 75% and 38%, respectively. Second, the lockdown effect starts to materialize with a delay of 3–4 weeks only. Third, the actual adjustment of mobility patterns in Sweden suggests there has been substantial voluntary social restraint, although the adjustment was less strong than under the lockdown scenario. Lastly, we find that a lockdown would not have caused much additional output loss.

Mask adherence and rate of COVID-19 across the United States

Charlie B. Fischer, Nedghie Adrien, Jeremiah J. Silguero, Julianne J. Hopper, Abir I. Chowdhury, Martha M. Werler

Mask wearing has been advocated by public health officials as a way to reduce the spread of COVID-19. In the United States, policies on mask wearing have varied from state to state over the course of the pandemic. Even as more and more states encourage or even mandate mask wearing, many citizens still resist the notion. Our research examines mask wearing policy and adherence in association with COVID-19 case rates. We used state-level data on mask wearing policy for the general public and on proportion of residents who stated they always wear masks in public. For all 50 states and the District of Columbia (DC), these data were abstracted by month for April – September 2020 to measure their impact on COVID-19 rates in the subsequent month (May – October 2020). Monthly COVID-19 case rates (number of cases per capita over two weeks) >200 per 100,000 residents were considered high. Fourteen of the 15 states with no mask wearing policy for the general public through September reported a high COVID-19 rate. Of the 8 states with at least 75% mask adherence, none reported a high COVID-19 rate. States with the lowest levels of mask adherence were most likely to have high COVID-19 rates in the subsequent month, independent of mask policy or demographic factors. Mean COVID-19 rates for states with at least 75% mask adherence in the preceding month was 109.26 per 100,000 compared to 249.99 per 100,000 for those with less adherence. Our analysis suggests high adherence to mask wearing could be a key factor in reducing the spread of COVID-19. This association between high mask adherence and reduced COVID-19 rates should influence policy makers and public health officials to focus on ways to improve mask adherence across the population in order to mitigate the spread of COVID-19.

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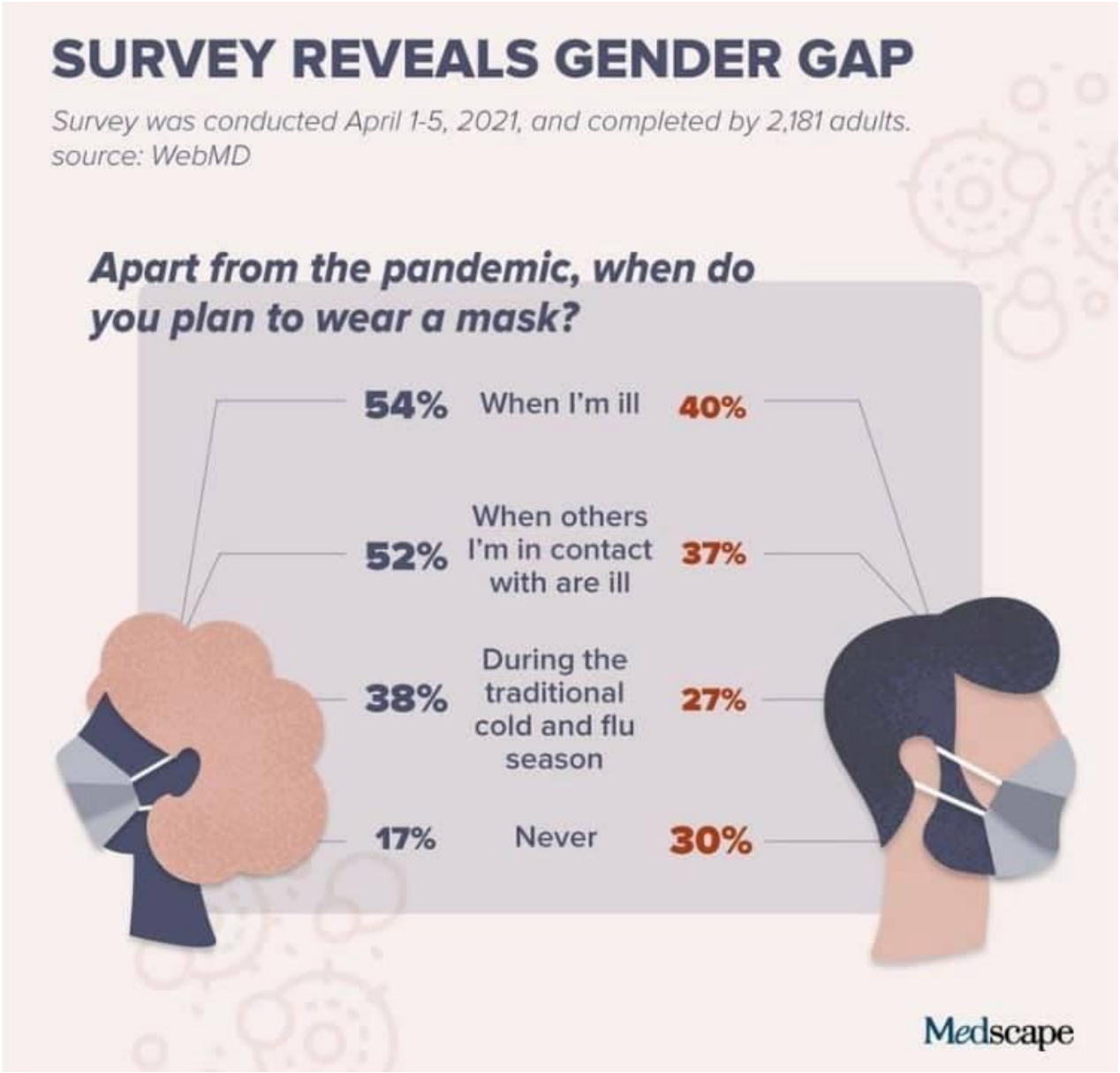

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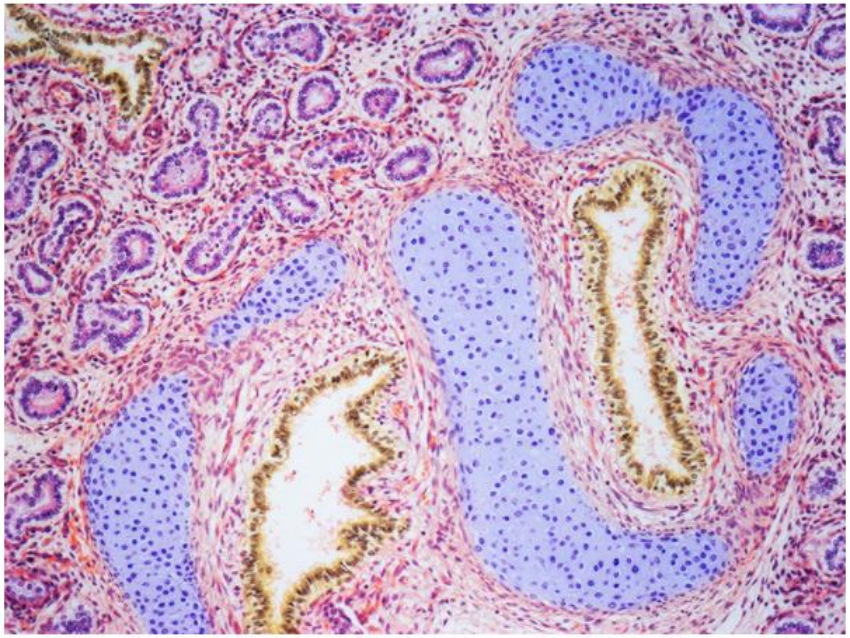
NIH reverses Trump-era restrictions on fetal-tissue research

The US National Institutes of Health will remove limits on government scientists and cancel a controversial grant-reviewing ethics panel.

Nidhi Subbaraman



Research on fetal tissue, such as the lung tissue shown here, has drawn controversy for years. Credit: Steve Gschmeissner/Science Photo Library

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Trump administration fetal-tissue research by government scientists

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Subjects

Stem cells | Politics

Developmental biology

A Ukrainian boy holds a picture of his dead grandfather, a liquidator who helped clean up radioactive debris scattered after a nuclear reactor exploded at Chernobyl in 1986. SERGEI SUPINSKY/AFP VIA GETTY IMAGES

No excess mutations in the children of Chernobyl survivors, new study finds

By Richard Stone | Apr. 22, 2021 , 2:00 PM

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Longevity investment firm announces acceleration programme

April 21, 2021

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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

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ARDD 2021

THE 8th AGING RESEARCH & DRUG DISCOVERY MEETING

31 AUGUST ——— 3 SEPTEMBER

According to the United Nations, the proportion of people aged over 65 now outnumber children younger than 5. The enormous growth in the elderly population is posing a socioeconomic challenge to societies worldwide, and necessitates new sweeping interventions for age-associated diseases. This year we have an incredibly exciting program with global thought-leaders sharing their latest insights into aging and how we target aging process ensuring everyone lives a healthier and longer life. Welcome to the 8th Aging Research and Drug Discovery Meeting.

Aging research articles

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Effect of long-term treatment with C60 fullerenes on the lifespan and health status of CBA/Ca mice

Dr. Dmytro Shytikov, Mrs. Iryna Shytikova, Mr. Deepak Rohila, Mr. Anton Kulaga, Dr. Tatiana Dubiley, and Dr. Iryna Pishel

Published Online: 13 Apr 2021 | https://doi.org/10.1089/rej.2020.2403

View article Tools Share

Abstract

Several studies claimed C60 fullerenes as a prospective geroprotector drug due to their ability to capture free radicals effectively and caused a profound interest in C60 in life extension communities. Multiple additives are already sold for human consumption despite a small body of evidence supporting the beneficial effects of fullerenes on the lifespan. In order to test the effect of C60 fullerenes on lifespan and healthspan, we administered C60 fullerenes dissolved in virgin olive oil orally to 10-12 months old CBA/Ca mice of both genders for seven months and assessed their survival. To uncover C60 and virgin olive effects, we established two control groups: mice treated with virgin olive oil (vehicle) and mice treated with drinking water. To measure healthspan, we conducted daily monitoring of health condition and lethality and monthly bodyweight measurements. We also assessed physical activity, glucose metabolism, and hematological parameters every three months. We did not observe health deterioration in the animals treated with C60 compared with the control groups. Treatment of mice with C60 fullerenes resulted in an increased lifespan of males and females compared with the olive oil-treated animals. The lifespan of C60-treated mice was similar to the mice treated with water. These results suggest that the lifespan-extending effect in C60-treated mice appears due to the protective effect of fullerenes in opposition to the negative effect of olive oil in CBA/Ca mice.

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PREPRINT

A computational solution for bolstering reliability of epigenetic clocks: Implications for clinical trials and longitudinal tracking

Epigenetic clocks are widely used aging biomarkers calculated from DNA methylation data. Unfortunately, measurements for individual CpGs can be surprisingly unreliable due to technical noise, and this may limit the utility of epigenetic clocks. We report that noise produces deviations up to 3 to 9 years between technical replicates for six major epigenetic clocks. The elimination of low-reliability CpGs does not ameliorate this issue. Here, we present a novel computational multi-step solution to address this noise, involving performing principal component analysis on the CpG-level data followed by biological age prediction using principal components as input. This method extracts shared systematic variation in DNAm while minimizing random noise from individual CpGs. Our novel principal-component versions of six clocks show agreement between most technical replicates within 0 to 1.5 years, equivalent or improved prediction of outcomes, and more stable trajectories in longitudinal studies and cell culture. This method entails only one additional step compared to traditional clocks, does not require prior knowledge of CpG reliabilities, and can improve the reliability of any existing or future epigenetic biomarker. The high reliability of principal component-based epigenetic clocks will make them particularly useful for applications in personalized medicine and clinical trials evaluating novel aging interventions.

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A cross-sectional study of functional and metabolic changes during aging through the lifespan in male mice.

Aging is associated with distinct phenotypical, physiological, and functional changes, leading to disease and death. The progression of aging-related traits varies widely among individuals, influenced by their environment, lifestyle, and genetics. In this study, we conducted physiologic and functional tests cross-sectionally throughout the entire lifespan of male C57BL/6N mice. In parallel, metabolomics analyses in serum, brain, liver, heart, and skeletal muscle were also performed to identify signatures associated with frailty and age-dependent functional decline. Our findings indicate that declines in gait speed as a function of age and frailty are associated with a dramatic increase in the energetic cost of physical activity and decreases in working capacity. Aging and functional decline prompt organs to rewire their metabolism and substrate selection and towards redox-related pathways, mainly in liver and heart. Collectively, the data provide a framework to further understand and characterize processes of aging at the individual organism and organ levels.

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Mouse aging cell atlas analysis reveals global and cell type-specific aging signatures

Aging is associated with complex molecular and cellular processes that are poorly understood. Here we leveraged the Tabula Muris Senis single-cell RNA-seq data set to systematically characterize gene expression changes during aging across diverse cell types in the mouse. We identified aging-dependent genes in 76 tissue-cell types from 23 tissues and characterized both shared and tissue-cell-specific aging behaviors. We found that the aging-related genes shared by multiple tissue-cell types also change their expression congruently in the same direction during aging in most tissue-cell types, suggesting a coordinated global aging behavior at the organismal level. Scoring cells based on these shared aging genes allowed us to contrast the aging status of different tissues and cell types from a transcriptomic perspective. In addition, we identified genes that exhibit age-related expression changes specific to each functional category of tissue-cell types. Altogether, our analyses provide one of the most comprehensive and systematic characterizations of the molecular signatures of aging across diverse tissue-cell types in a mammalian system.

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Common genetic associations between age-related diseases

Handan Melike Dönertaş, Daniel K. Fabian, Matías Fuentealba, Linda Partridge & Janet M. Thornton

Nature Aging **1**, 400–412(2021) | Cite this article

Abstract

Age is a common risk factor in many diseases, but the molecular basis for this relationship is elusive. In this study we identified four disease clusters from 116 diseases in UK Biobank data, defined by their age-of-onset profiles, and found that diseases with the same onset profile are genetically more similar, suggesting a common etiology. This similarity was not explained by disease categories, co-occurrences or disease cause–effect relationships. Two of the four disease clusters had an increased risk of occurrence from ages 20 and 40 years, respectively. They both showed an association with known aging-related genes, yet differed in functional enrichment and evolutionary profiles. Moreover, they both had age-related expression and methylation changes. We also tested mutation accumulation and antagonistic pleiotropy theories of aging and found support for both.

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Skeletal muscle transcriptome in healthy aging

Robert A. Tumasian III, Abhinav Harish, Gautam Kundu, Jen-Hao Yang, Ceereena Ubaida-Mohien, Marta Gonzalez-Freire, Mary Kaileh, Linda M. Zukley, Chee W. Chia, Alexey Lyashkov, William H. Wood III, Yulan Piao, Christopher Coletta, Jun Ding, Myriam Gorospe, Ranjan Sen, Supriyo De & Luigi Ferrucci

Nature Communications **12**, Article number: 2014 (2021) | Cite this article

Abstract

Age-associated changes in gene expression in skeletal muscle of healthy individuals reflect accumulation of damage and compensatory adaptations to preserve tissue integrity. To characterize these changes, RNA was extracted and sequenced from muscle biopsies collected from 53 healthy individuals (22–83 years old) of the GESTALT study of the National Institute on Aging–NIH. Expression levels of 57,205 protein-coding and non-coding RNAs were studied as a function of aging by linear and negative binomial regression models. From both models, 1134 RNAs changed significantly with age. The most differentially abundant mRNAs encoded proteins implicated in several age-related processes, including cellular senescence, insulin signaling, and myogenesis. Specific mRNA isoforms that changed significantly with age in skeletal muscle were enriched for proteins involved in oxidative phosphorylation and adipogenesis. Our study establishes a detailed framework of the global transcriptome and mRNA isoforms that govern muscle damage and homeostasis with age.

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An integrative analysis of the age-associated multi-omic landscape across cancers

Kasit Chatsirisupachai, Tom Lesluyes, Luminita Paraoan, Peter Van Loo & João Pedro de Magalhães

Nature Communications **12**, Article number: 2345 (2021) | Cite this article

Abstract

Age is the most important risk factor for cancer, as cancer incidence and mortality increase with age. However, how molecular alterations in tumours differ among patients of different age remains largely unexplored. Here, using data from The Cancer Genome Atlas, we comprehensively characterise genomic, transcriptomic and epigenetic alterations in relation to patients' age across cancer types. We show that tumours from older patients present an overall increase in genomic instability, somatic copy-number alterations (SCNAs) and somatic mutations. Age-associated SCNAs and mutations are identified in several cancer-driver genes across different cancer types. The largest age-related genomic differences are found in gliomas and endometrial cancer. We identify age-related global transcriptomic changes and demonstrate that these genes are in part regulated by age-associated DNA methylation changes. This study provides a comprehensive, multi-omics view of age-associated alterations in cancer and underscores age as an important factor to consider in cancer research and clinical practice.

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Neutrophils induce paracrine telomere dysfunction and senescence in ROS-dependent manner

Cellular senescence is characterized by an irreversible cell cycle arrest as well as a pro-inflammatory phenotype, thought to contribute to aging and age-related diseases. Neutrophils have essential roles in inflammatory responses; however, in certain contexts their abundance is associated with a number of age-related diseases, including liver disease. The relationship between neutrophils and cellular senescence is not well understood. Here, we show that telomeres in non-immune cells are highly susceptible to oxidative damage caused by neighboring neutrophils. Neutrophils cause telomere dysfunction both *in vitro* and *ex vivo* in a ROS-dependent manner. In a mouse model of acute liver injury, depletion of neutrophils reduces telomere dysfunction and senescence. Finally, we show that senescent cells mediate the recruitment of neutrophils to the aged liver and propose that this may be a mechanism by which senescence spreads to surrounding cells. Our results suggest that interventions that counteract neutrophil-induced senescence may be beneficial during aging and age-related disease.

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No evidence of physiological declines with age in an extremely long-lived fish

Derek J. Sauer, Britt J. Heidinger, Jeffrey D. Kittilson, Alec R. Lackmann & Mark E. Clark

Scientific Reports **11**, Article number: 9065 (2021) | Cite this article

Although the pace of senescence varies considerably, the physiological systems that contribute to different patterns of senescence are not well understood, especially in long-lived vertebrates. Long-lived bony fish (i.e., Class Osteichthyes) are a particularly useful model for studies of senescence because they can readily be aged and exhibit some of the longest lifespans among vertebrates. In this study we examined the potential relationship between age and multiple physiological systems including: stress levels, immune function, and telomere length in individuals ranging in age from 2 to 99 years old in bigmouth buffalo (*Ictiobus cyprinellus*), the oldest known freshwater teleost fish. Contrary to expectation, we did not find any evidence for age-related declines in these physiological systems. Instead, older fish appeared to be less stressed and had greater immunity than younger fish, suggesting age-related *improvements* rather than declines in these systems. There was no significant effect of age on telomeres, but individuals that may be more stressed had shorter telomeres. Taken together, these findings suggest that bigmouth buffalo exhibit negligible senescence in multiple physiological systems despite living for nearly a century.

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Aging alters the metabolic flux signature of the ER unfolded protein response *in vivo* in mice

Age is a risk factor for numerous diseases, including neurodegenerative diseases, cancers, and diabetes. Loss of protein homeostasis is a central hallmark of aging. Activation of the endoplasmic reticulum unfolded protein response (UPR^{ER}) includes changes in protein translation and membrane lipid synthesis. Using stable isotope labeling, a "signature" of the UPR^{ER} *in vivo* in mouse liver was developed by inducing ER stress and measuring rates of both proteome-wide translation and *de novo* lipogenesis. Several changes in protein synthesis across ontologies were noted with age, including a more dramatic suppression of translation under ER stress in aged mice as compared to young mice. Binding immunoglobulin protein (BiP) synthesis rates and mRNA levels were increased more in aged than young mice. *De novo* lipogenesis rates decreased under ER stress conditions in aged mice, including both triglyceride and phospholipid fractions. In young mice, only a significant reduction was seen in the triglyceride fraction. These data indicate that aged mice have an exaggerated response to ER stress, which may indicate that the aging renders the UPR^{ER} less effective in resolving proteotoxic stress.

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The Effects of Muscle Cell Aging on Myogenesis

by Athanasios Moustogiannis [1,*,†], Anastassios Philippou [1,†], Orjona Taso [1,‡], Evangelos Zevolis [1], Maria Pappa [2], Antonios Chatzigeorgiou [1] and Michael Koutsilieris [1]

The process of myogenesis gradually deteriorates as the skeletal muscle ages, contributing to muscle mass loss. The aim of this study is to investigate the effect of senescence/aging on skeletal myogenesis, in vitro. A model of multiple cell divisions of C2C12 myoblasts was used to replicate cell senescence. Control and aged myoblasts were investigated during myogenesis, i.e., at days 0, 2, and 6of differentiation. SA-β-gal activity and comet assay were used as markers of aging and DNA damage. Flow cytometry was performed to characterize potential differences in cell cycle between control and aged cells. Alterations in the mRNA and/or protein expression of myogenic regulatory factors (MRFs), IGF-1 isoforms, apoptotic, atrophy, inflammatory, metabolic and aging-related factors were evaluated. Compared with the control cells, aged myoblasts exhibited G0/G1 cell cycle arrest, DNA damage, increased SA-β-gal activity, and increased expression of aging-related factors p16 and p21 during differentiation. Moreover, aged myoblasts showed a reduction in the expression of MRFs and metabolic/anabolic factors, along with an increased expression of apoptotic, atrophy and inflammatory factors. A diminished differentiation capacity characterized the aged myoblasts which, in combination with the induction of apoptotic and atrophy factors, indicated a disrupted myogenic lineage in the senescent muscle cells. View Full-Text

Dietary spermidine improves cognitive function

Decreased cognitive performance is a hallmark of brain aging, but the underlying mechanisms and potential therapeutic avenues remain poorly understood. Recent studies have revealed health-protective and lifespan-extending effects of dietary spermidine, a natural autophagy-promoting polyamine. Here, we show that dietary spermidine passes the blood-brain barrier in mice and increases hippocampal eIF5A hypusination and mitochondrial function. Spermidine feeding in aged mice affects behavior in homecage environment tasks, improves spatial learning, and increases hippocampal respiratory competence. In a *Drosophila* aging model, spermidine boosts mitochondrial respiratory capacity, an effect that requires the autophagy regulator Atg7 and the mitophagy mediators Parkin and Pink1. Neuron-specific *Pink1* knockdown abolishes spermidine-induced improvement of olfactory associative learning. This suggests that the maintenance of mitochondrial and autophagic function is essential for enhanced cognition by spermidine feeding. Finally, we show large-scale prospective data linking higher dietary spermidine intake with a reduced risk for cognitive impairment in humans.

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Analysis of longevity in Chordata identifies species with exceptional longevity among taxa and points to the evolution of longer lifespans

Animals have a considerable variation in their longevity. This fundamental life-history trait is shaped by both intrinsic and extrinsic mortality pressures, influenced by multiple parameters including ecological variables and mode-of-life traits. Here, we examined the distribution of maximum age at multiple taxonomic ranks (class, order and family) in Chordata, and identified species with exceptional longevity within various taxa. We used a curated dataset of maximum longevity of animals from AnAge database, containing a total of 2542 chordates following our filtering criteria. We determined shapes of maximum age distributions at class, order and family taxonomic ranks, and calculated skewness values for each distribution, in R programming environment. We identified species with exceptional longevity compared to other species belonging to the same taxa, based on our definition of outliers. We collected data on ecological variables and mode-of-life traits which might possibly contribute, at least in part, to the exceptional lifespans of certain chordates. We found that 23, 12 and 4 species have exceptional longevity when we grouped chordates by their class, order and family, respectively. Almost all distributions of maximum age among taxa were positively skewed (towards increased longevity), possibly showing the emergence of longer lifespans in contrast to shorter lifespans, through the course of evolution. However, potential biases in the collection of data should be taken into account. Most of the identified species in the current study have not been previously studied in the context of animal longevity. Our analyses point that certain chordates may have evolved to have longer lifespans compared to other species belonging to the same taxa, and that among taxa, outliers in terms of maximum age have always longer lifespans, not shorter. Future research is required to understand how and why increased longevity have arose in certain species.

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EX-vivo whole blood stimulation with A2E does not elicit an inflammatory cytokine response in patients with age-related macular degeneration

Age-related macular degeneration (AMD) is a highly prevalent degenerative disease and a leading cause of vision loss worldwide. Evidence for an inflammatory component in the development of AMD exists, yet the exact mechanisms remain unclear. Bisretinoid *N*-retinylidene-*N*-retinylethanolamine (A2E) in retinal pigmental epithelial (RPE) cells, and in extracellular deposits constitutes a hallmark of AMD, but its role in the pathology of AMD is elusive. Here, we tested the hypothesis that A2E is responsible for the heightened inflammatory activity in AMD. To this end, we measured ex vivo mRNA expression of the cytokines TNF-α, IL-6, and IL-10 in whole blood samples after stimulation with A2E in a clinical sample of 27 patients with neovascular AMD and 24 patients with geographic atrophy secondary to AMD. Patients' spouses (n = 30) were included as non-affected controls. After stimulation with A2E, no statistical differences were found in the median expression level of TNF-α, IL-6, IL-10 between the control group, and the neovascular AMD and the geographic atrophy group. Our findings do not support evidence for the hypothesis, that A2E per se contributes to heightened inflammatory activity in AMD.

C. elegans aging research

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Network analysis in aged *C. elegans* reveals candidate regulatory genes of ageing

Foteini Aktypi, Nikoletta Papaevgeniou, Konstantinos Voutetakis, Aristotelis Chatziioannou, Tilman Grune & Niki Chondrogianni

Biogerontology **22**, 345–367(2021) | Cite this article

Abstract

Ageing is a biological process guided by genetic and environmental factors that ultimately lead to adverse outcomes for organismal lifespan and healthspan. Determination of molecular pathways that are affected with age and increase disease susceptibility is crucial. The gene expression profile of the ideal ageing model, namely the nematode *Caenorhabditis elegans* mapped with the microarray technology initially led to the identification of age-dependent gene expression alterations that characterize the nematode's ageing process. The list of differentially expressed genes was then utilized to construct a network of molecular interactions with their first neighbors/interactors using the interactions listed in the WormBase database. The subsequent network analysis resulted in the unbiased selection of 110 candidate genes, among which well-known ageing regulators appeared. More importantly, our approach revealed candidates that have never been linked to ageing before, thus suggesting promising potential targets/ageing regulators.

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Cultivation of *Caenorhabditis elegans* on new cheap monoxenic media without peptone

Tho Son Le [1], T T Hang Nguyen [1], Bui Thi Mai Huong [1], H Gam Nguyen [1], B Hong Ha [1], Van Sang Nguyen [2], Minh Hung Nguyen [3], Huy-Hoang Nguyen [4], John Wang [5]

Affiliations + expand

PMID: 33860269 PMCID: PMC8040142 DOI: 10.21307/jofnem-2021-036

Free PMC article

Abstract

The study of species biodiversity within the *Caenorhabditis* genus of nematodes would be facilitated by the isolation of as many species as possible. So far, over 50 species have been found, usually associated with decaying vegetation or soil samples, with many from Africa, South America and Southeast Asia. Scientists based in these regions can contribute to *Caenorhabditis* sampling and their proximity would allow intensive sampling, which would be useful for understanding the natural history of these species. However, severely limited research budgets are often a constraint for these local scientists. In this study, we aimed to find a more economical, alternative growth media to rear *Caenorhabditis* and related species. We tested 25 media permutations using cheaper substitutes for the reagents found in the standard nematode growth media (NGM) and found three media combinations that performed comparably to NGM with respect to the reproduction and longevity of *C. elegans*. These new media should facilitate the isolation and characterization of *Caenorhabditis* and other free-living nematodes for the researchers in the poorer regions such as Africa, South America, and Southeast Asia where nematode diversity appears high.

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PREPRINT

Lipid droplets modulate proteostasis, SQST-1/SQSTM1 dynamics, and lifespan in *C. elegans*

The ability of organisms to live long depends largely on the maintenance of proteome stability via proteostatic mechanisms including translational regulation, protein chaperoning and degradation machineries. In several long-lived *Caenorhabditis elegans* strains, such as insulin/IGF-1 receptor *daf-2* mutants, enhanced proteostatic mechanisms are accompanied by elevated intestinal lipid stores, but the role of lipid droplets in longevity has remained obscure. Here, while determining the regulatory network of the selective autophagy receptor SQST-1/SQSTM1, we unexpectedly uncovered a novel role for lipid droplets in proteostasis and longevity. Using an unbiased genome-wide RNAi screening approach, we identified several SQST-1 modulators, including proteins found on lipid droplets and those prone to aggregate with age. SQST-1 accumulated on lipid droplets when autophagy was inhibited, suggesting that lipid droplets may serve a role in facilitating selective autophagy. Expansion of intestinal lipid droplets by silencing the conserved cytosolic triacylglycerol lipase gene *atgl-1/ATGL* enhanced autophagy, and extended lifespan in an HSF-1/HSF1-dependent and CDC-48/VCP-dependent manner. Silencing *atgl-1* mitigated the age-related accumulation of SQST-1 and reduced overall ubiquitination of proteins. Reducing *atgl-1* also improved proteostasis in a nematode model of Alzheimer's disease. Subcellular analyses revealed that lipid droplets unexpectedly harbor more ubiquitinated proteins than the cytosol. Accordingly, low lipid droplet levels exacerbated the proteostatic collapse when autophagy or proteasome function was compromised. Altogether, our study uncovers a key role for lipid droplets in *C. elegans* as a proteostatic mediator that reduces protein ubiquitination, facilitates autophagy, and promotes longevity.

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Trimethylamine modulates dauer formation, neurodegeneration, and lifespan through *tyra-3/daf-11* signaling in *Caenorhabditis elegans*

In the nematode *Caenorhabditis elegans*, signals derived from bacteria in the diet, the animal's major nutrient source, can modulate both behavior and healthspan. Here we describe a dual role for trimethylamine (TMA), a human gut flora metabolite, which acts as a nutrient signal and a neurotoxin. TMA and its associated metabolites are produced by the human gut microbiome and have been suggested to serve as risk biomarkers for diabetes and cardiovascular diseases. We demonstrate that the tyramine receptor TYRA-3, a conserved G protein-coupled receptor (GPCR), is required to sense TMA and mediate its responses. TMA activates guanylyl cyclase DAF-11 signaling through TYRA-3 in amphid neurons (ASK) and ciliated neurons (BAG) to mediate food-sensing behavior. Bacterial mutants deficient in TMA production enhance dauer formation, extend lifespan, and are less preferred as a food source. Increased levels of TMA lead to neural damage in models of Parkinson's disease and shorten lifespan. Our results reveal conserved signaling pathways modulated by TMA in *C. elegans* that are likely to be relevant for its effects in mammalian systems.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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Programs, Hyperfunction, and Damage: Why Definitions and Logic Matter So Much in Biogerontology

Aubrey D.N.J. de Grey

Response to the Thought-Provoking Critique of Hyperfunction Theory by Aubrey de Grey

Mikhail V. Blagosklonny

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Senescence in tissue samples of humans with age-related diseases: A systematic review

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Background

Higher numbers of senescent cells have been implicated in age-related disease pathologies. However, whether different diseases have different senescent phenotypes is unknown. Here we provide a systematic overview of the current available evidence of senescent cells in age-related diseases pathologies in humans and the markers currently used to detect senescence levels in humans.

Methods

PubMed, Web of Science and EMBASE were systematically searched from inception to the 29th of September 2019, using keywords related to 'senescence', 'age-related diseases' and 'biopsies'.

Results

In total 12,590 articles were retrieved of which 103 articles were included in this review. The role of senescence in age-related disease has been assessed in 9 different human organ system and 27 different age-related diseases of which heart (27/103) and the respiratory systems (18/103) are the most investigated. Overall, 27 different markers of senescence have been used to determine cellular senescence and the cell cycle regulator $p16^{ink4a}$ is most often used (23/27 age-related pathologies).

Conclusion

This review demonstrates that a higher expression of senescence markers are observed within disease pathologies. However, not all markers to detect senescence have been assessed in all tissue types.

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An energetics perspective on geroscience: mitochondrial protonmotive force and aging

Brandon J. Berry & Matt Kaeberlein

Mitochondria are organelles that provide energy to cells through ATP production. Mitochondrial dysfunction has long been postulated to mediate cellular declines that drive biological aging. Many well-characterized hallmarks of aging may involve underlying energetic defects that stem from loss of mitochondrial function with age. Why and how mitochondrial function declines with age is an open question and one that has been difficult to answer. Mitochondria are powered by an electrochemical gradient across the inner mitochondrial membrane known as the protonmotive force (PMF). This gradient decreases with age in several experimental models. However, it is unclear if a diminished PMF is a cause or a consequence of aging. Herein, we briefly review and define mitochondrial function, we summarize how PMF changes with age in several models, and we highlight recent studies that implicate PMF in aging biology. We also identify barriers that must be addressed for the field to progress. Emerging technology permits more precise in vivo study of mitochondria that will allow better understanding of cause and effect in metabolic models of aging. Once cause and effect can be discerned more precisely, energetics approaches to combat aging may be developed to prevent or reverse functional decline.

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Lipid metabolism and lipid signals in aging and longevity

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Lipids play crucial roles in regulating aging and longevity. In the past few decades, a series of genetic pathways have been discovered to regulate lifespan in model organisms. Interestingly, many of these regulatory pathways are linked to lipid metabolism and lipid signaling. Lipid metabolic enzymes undergo significant changes during aging and are regulated by different longevity pathways. Lipids also actively modulate lifespan and health span as signaling molecules. In this review, we summarize recent insights into the roles of lipid metabolism and lipid signaling in aging and discuss lipid-related interventions in promoting longevity.

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Lipids: biomarkers of healthy aging

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Abstract

Life expectancy, and longevity have been increasing in recent years. However, this is, in most cases, accompanied by age-related diseases. Thus, it became essential to better understand the mechanisms inherent to aging, and to establish biomarkers that characterize this physiological process. Among all biomolecules, lipids appear to be a good target for the study of these biomarkers. In fact, some lipids have already been associated with age-related diseases. With the development of analytical techniques such as Mass Spectrometry, and Nuclear Magnetic Resonance, Lipidomics has been increasingly used to study pathological, and physiological states of an organism. Thus, the study of serum, and plasma lipidome in centenarians, and elderly individuals without age-related diseases can be a useful tool for the identification of aging biomarkers, and to understand physiological aging, and longevity. This review focus on the importance of lipids as biomarkers of aging, and summarize the changes in the lipidome that have been associated with aging, and longevity.

Keywords: Aging; Biomarkers of aging; Lipidomics; Lipids; Longevity.

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The changing landscape of atherosclerosis

Peter Libby

Emerging evidence has spurred a considerable evolution of concepts relating to atherosclerosis, and has called into question many previous notions. Here I review this evidence, and discuss its implications for understanding of atherosclerosis. The risk of developing atherosclerosis is no longer concentrated in Western countries, and it is instead involved in the majority of deaths worldwide. Atherosclerosis now affects younger people, and more women and individuals from a diverse range of ethnic backgrounds, than was formerly the case. The risk factor profile has shifted as levels of low-density lipoprotein (LDL) cholesterol, blood pressure and smoking have decreased. Recent research has challenged the protective effects of high-density lipoprotein, and now focuses on triglyceride-rich lipoproteins in addition to low-density lipoprotein as causal in atherosclerosis. Non-traditional drivers of atherosclerosis—such as disturbed sleep, physical inactivity, the microbiome, air pollution and environmental stress—have also gained attention. Inflammatory pathways and leukocytes link traditional and emerging risk factors alike to the altered behaviour of arterial wall cells. Probing the pathogenesis of atherosclerosis has highlighted the role of the bone marrow: somatic mutations in stem cells can cause clonal haematopoiesis, which represents a previously unrecognized but common and potent age-related contributor to the risk of developing cardiovascular disease. Characterizations of the mechanisms that underpin thrombotic complications of atherosclerosis have evolved beyond the 'vulnerable plaque' concept. These advances in our understanding of the biology of atherosclerosis have opened avenues to therapeutic interventions that promise to improve the prevention and treatment of now-ubiquitous atherosclerotic diseases.

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Pathophysiology of Atherosclerotic Plaque Development-Contemporary Experience and New Directions in Research

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Abstract

Atherosclerotic plaque is the pathophysiological basis of important and life-threatening diseases such as myocardial infarction. Although key aspects of the process of atherosclerotic plaque development and progression such as local inflammation, LDL oxidation, macrophage activation, and necrotic core formation have already been discovered, many molecular mechanisms affecting this process are still to be revealed. This minireview aims to describe the current directions in research on atherogenesis and to summarize selected studies published in recent years—in particular, studies on novel cellular pathways, epigenetic regulations, the influence of hemodynamic parameters, as well as tissue and microorganism (microbiome) influence on atherosclerotic plaque development. Finally, some new and interesting ideas are proposed (immune cellular heterogeneity, non-coding RNAs, and immunometabolism) which will hopefully bring new discoveries in this area of investigation. View Full-Text

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The central role of DNA damage in the ageing process

Björn Schumacher ✉, Joris Pothof, Jan Vijg & Jan H. J. Hoeijmakers

Ageing is a complex, multifaceted process leading to widespread functional decline that affects every organ and tissue, but it remains unknown whether ageing has a unifying causal mechanism or is grounded in multiple sources. Phenotypically, the ageing process is associated with a wide variety of features at the molecular, cellular and physiological level—for example, genomic and epigenomic alterations, loss of proteostasis, declining overall cellular and subcellular function and deregulation of signalling systems. However, the relative importance, mechanistic interrelationships and hierarchical order of these features of ageing have not been clarified. Here we synthesize accumulating evidence that DNA damage affects most, if not all, aspects of the ageing phenotype, making it a potentially unifying cause of ageing. Targeting DNA damage and its mechanistic links with the ageing phenotype will provide a logical rationale for developing unified interventions to counteract age-related dysfunction and disease.

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Sarcopenia – Molecular mechanisms and open questions

Sarcopenia represents a muscle-wasting syndrome characterized by progressive and generalized degenerative loss of skeletal muscle mass, quality, and strength occurring during normal aging. Sarcopenia patients are mainly suffering from the loss in muscle strength and are faced with mobility disorders reducing their quality of life and are, therefore, at higher risk for morbidity (falls, bone fracture, metabolic diseases) and mortality.

Several molecular mechanisms have been described as causes for sarcopenia that refer to very different levels of muscle physiology. These mechanisms cover e. g. function of hormones (e. g. IGF-1 and Insulin), muscle fiber composition and neuromuscular drive, myo-satellite cell potential to differentiate and proliferate, inflammatory pathways as well as intracellular mechanisms in the processes of proteostasis and mitochondrial function.

In this review, we describe sarcopenia as a muscle-wasting syndrome distinct from other atrophic diseases and summarize the current view on molecular causes of sarcopenia development as well as open questions provoking further research efforts for establishing efficient lifestyle and therapeutic interventions.

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On the Role of Normal Aging Processes in the Onset and Pathogenesis of Diseases Associated with the Abnormal Accumulation of Protein Aggregates

Nikolay S Ilyinsky [1], Semen V Nesterov [2 3], Elizaveta I Shestoperova [2], Alexander V Fonin [2 4], Vladimir N Uversky [2 5], Valentin I Gordeliy [2 6 7]

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Abstract

Aging is a prime systemic cause of various age-related diseases, in particular, proteinopathies. In fact, most diseases associated with protein misfolding are sporadic, and their incidence increases with aging. This review examines the process of protein aggregate formation, the toxicity of such aggregates, the organization of cellular systems involved in proteostasis, and the impact of protein aggregates on important cellular processes leading to proteinopathies. We also analyze how manifestations of aging (mitochondrial dysfunction, dysfunction of signaling systems, changes in the genome and epigenome) facilitate pathogenesis of various proteinopathies either directly, by increasing the propensity of key proteins for aggregation, or indirectly, through dysregulation of stress responses. Such analysis might help in outlining approaches for treating proteinopathies and extending healthy longevity.

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No Time to Age: Uncoupling Aging from Chronological Time

by Dana Larocca [1,*], Jieun Lee [2], Michael D. West [2], Ivan Labat [2] and Hal Sternberg [2]

Multicellular life evolved from simple unicellular organisms that could replicate indefinitely, being essentially ageless. At this point, life split into two fundamentally different cell types: the immortal germline representing an unbroken lineage of cell division with no intrinsic endpoint and the mortal soma, which ages and dies. In this review, we describe the germline as clock-free and the soma as clock-bound and discuss aging with respect to three DNA-based cellular clocks (telomeric, DNA methylation, and transposable element). The ticking of these clocks corresponds to the stepwise progressive limitation of growth and regeneration of somatic cells that we term somatic restriction. Somatic restriction acts in opposition to strategies that ensure continued germline replication and regeneration. We thus consider the plasticity of aging as a process not fixed to the pace of chronological time but one that can speed up or slow down depending on the rate of intrinsic cellular clocks. We further describe how germline factor reprogramming might be used to slow the rate of aging and potentially reverse it by causing the clocks to tick backward. Therefore, reprogramming may eventually lead to therapeutic strategies to treat degenerative diseases by altering aging itself, the one condition common to us all. View Full-Text

OTHER RESEARCH & REVIEWS

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Genome-wide programmable transcriptional memory by CRISPR-based epigenome editing

A general approach for heritably altering gene expression has the potential to enable many discovery and therapeutic efforts. Here, we present CRISPRoff—a programmable epigenetic memory writer consisting of a single dead Cas9 fusion protein that establishes DNA methylation and repressive histone modifications. Transient CRISPRoff expression initiates highly specific DNA methylation and gene repression that is maintained through cell division and differentiation of stem cells to neurons. Pairing CRISPRoff with genome-wide screens and analysis of chromatin marks establishes rules for heritable gene silencing. We identify single guide RNAs (sgRNAs) capable of silencing the large majority of genes including those lacking canonical CpG islands (CGIs) and reveal a wide targeting window extending beyond annotated CGIs. The broad ability of CRISPRoff to initiate heritable gene silencing even outside of CGIs expands the canonical model of methylation-based silencing and enables diverse applications including genome-wide screens, multiplexed cell engineering, enhancer silencing, and mechanistic exploration of epigenetic inheritance.

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Small-Molecule Inhibitors of Reactive Oxygen Species Production

Elisa Sassetti, Mads H. Clausen*, and Luca Laraia*

Reactive oxygen species (ROS) are involved in physiological cellular processes including differentiation, proliferation, and apoptosis by acting as signaling molecules or regulators of transcription factors. The maintenance of appropriate cellular ROS levels is termed redox homeostasis, a balance between their production and neutralization. High concentrations of ROS may contribute to severe pathological events including cancer, neurodegenerative, and cardiovascular diseases. In recent years, approaches to target the sources of ROS production directly in order to develop tool compounds or potential therapeutics have been explored. Herein, we briefly outline the major sources of cellular ROS production and comprehensively review the targeting of these by small-molecule inhibitors. We critically assess the value of ROS inhibitors with different mechanisms-of-action, including their potency, mode-of-action, known off-target effects, and clinical or preclinical status, while suggesting future avenues of research in the field.