



**Heales**  
**HEALTHY LIFE EXTENSION**  
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## REVIEW

# Nutrigerontology: why we need a new scientific discipline to develop diets and guidelines to reduce the risk of aging-related diseases

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## Summary

Many diets and nutritional advice are circulating, often based on short- or medium-term clinical trials and primary outcomes, like changes in LDL cholesterol or weight. It remains difficult to assess which dietary interventions can be effective in the long term to reduce the risk of aging-related disease and increase the (healthy) lifespan. At the same time, the scientific discipline that studies the aging process has identified some important nutrient-sensing pathways that modulate the aging process, such as the mTOR and the insulin/insulin-like growth factor signaling pathway. A thorough understanding of the aging process can help assessing the efficacy of dietary interventions aimed at reducing the risk of aging-related diseases. To come to these insights, a synthesis of biogerontological, nutritional, and medical knowledge is needed, which can be framed in a new discipline called 'nutrigerontology'.

**Key words:** aging; aging-related diseases; biogerontology; cardiovascular disease; diabetes type 2; diet; nutrient-sensing pathways; nutrition; obesity; overweight.

patterns, and diets influence the risk of aging-related diseases and (healthy) lifespan. Nutrigerontology can also be considered as a practical application of biogerontology. This article wants to clarify how biogerontological insights can be used to create dietary recommendations that can reduce the risk of various aging-related diseases that are on the rise in both developed and developing countries.

## Reduced insulin/IGF-1 and mTOR signaling increases lifespan

In the field of biogerontology, the two most well-known pathways implicated in the aging process are the insulin/insulin-like growth factor signaling pathway (IIS pathway) (Bartke *et al.*, 2013) and the mammalian or mechanistic target of rapamycin (mTOR) pathway (Johnson *et al.*, 2013). We will initially focus on these two canonical pathways to show how a better understanding of the aging process can help to develop better long-term diet recommendations. The mTOR and IIS pathways are nutrient-sensing pathways, implying that they are activated by nutrients that we eat, such as carbohydrates (which mainly activate the IIS pathway, but also the mTOR pathway) (Bartke *et al.*, 2013) and amino acids (which mainly activate the mTOR pathway, but also the IIS pathway) (Wullschleger *et al.*, 2006). The IIS pathway exerts its effects through transmembrane insulin and IGF-1 receptors, which initiate glucose uptake in the cell, and stimulate cell growth and cell prolifer-

## Ablation of insulin-producing cells prevents obesity but not premature mortality caused by a high-sugar diet in *Drosophila*

Sara Naif Al Saud, Adam C. Summerfield, Nazif Alic

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### Abstract

Ageing can be modulated by genetic as well as nutritional interventions. In female *Drosophila melanogaster*, lifespan is maximized at intermediate concentrations of sucrose as the carbohydrate source, and yeast as the protein source. Dampening the signal through the insulin/IGF signalling (IIS) pathway, by genetic ablation of median neurosecretory cells (mNSCs) that produce insulin-like peptides, extends lifespan and counteracts the detrimental effects of excess yeast. However, how IIS reduction impacts health on a high-sugar diet remains unclear. We find that, while the ablation of the mNSCs can extend lifespan and delay the age-related decline in the health of the neuromuscular system irrespective of the amount of dietary sugar, it cannot rescue the lifespan-shortening effects of excess sugar. On the other hand, ablation of mNSCs can prevent adult obesity resulting from excess sugar, and this effect appears independent from the canonical effector of IIS, *dfoxo*. Our study indicates that while treatments that reduce IIS have anti-ageing effects irrespective of dietary sugar, additional interventions may be required to achieve full benefits in humans, where excessive sugar consumption is a growing problem. At the same time, pathways regulated by IIS may be suitable targets for treatment of obesity.

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### KEYWORDS

ageing, *Drosophila melanogaster*, high-sugar diet, obesity, insulin/IGF-like signalling

# Enhanced Longevity by Ibuprofen, Conserved in Multiple Species, Occurs in Yeast through Inhibition of Tryptophan Import

Chong He, Scott K. Tsuchiyama, Quynh T. Nguyen, Ekaterina N. Plyusnina, Samuel R. Terrill, Sarah Sahibzada, Bhumil Patel, Alena R. Faulkner, Mikhail V. Shaposhnikov, Ruilin Tian, Mitsuhiro Tsuchiya, Matt Kaeberlein, Alexey A. Moskalev, Brian K. Kennedy , Michael Polymenis 

The common non-steroidal anti-inflammatory drug ibuprofen has been associated with a reduced risk of some age-related pathologies. However, a general pro-longevity role for ibuprofen and its mechanistic basis remains unclear. Here we show that ibuprofen increased the lifespan of *Saccharomyces cerevisiae*, *Caenorhabditis elegans* and *Drosophila melanogaster*, indicative of conserved eukaryotic longevity effects. Studies in yeast indicate that ibuprofen destabilizes the Tat2p permease and inhibits tryptophan uptake. Loss of Tat2p increased replicative lifespan (RLS), but ibuprofen did not increase RLS when Tat2p was stabilized or in an already long-lived strain background impaired for aromatic amino acid uptake. Concomitant with lifespan extension, ibuprofen moderately reduced cell size at birth, leading to a delay in the G1 phase of the cell cycle. Similar changes in cell cycle progression were evident in a large dataset of replicatively long-lived yeast deletion strains. These results point to fundamental cell cycle signatures linked with longevity, implicate aromatic amino acid import in aging and identify a largely safe drug that extends lifespan across different kingdoms of life.

[Neurochem Res.](#) 2014 Dec 10. [Epub ahead of print]

## **Intracerebroventricular Metformin Decreases Body Weight But Has Pro-oxidant Effects and Decreases Survival.**

[Portela LV<sup>1</sup>](#), [Gnoatto J](#), [Wigner Brochier A](#), [Haas CB](#), [de Assis AM](#), [de Carvalho AK](#), [Hansel G](#), [Rigon Zimmer E](#), [Osés JP](#), [Muller AP](#).

### **⊕ Author information**

#### **Abstract**

Metformin (Met), which is an insulin-sensitizer, decreases insulin resistance and fasting insulin levels. The precise molecular target of Met is unknown; however, several reports have shown an inhibitory effect on mitochondrial complex I of the electron transport chain (ETC), which is a related site for reactive oxygen species production. In addition to peripheral effects, Met is capable of crossing the blood-brain barrier, thus regulating the central mechanism involved in appetite control. The present study explores the effects of intracerebroventricular (i.c.v.) infusion of Met on ROS production on brain, insulin sensitivity and metabolic and oxidative stress outcomes in CF1 mice. Metformin (Met 50 and 100 µg) was injected i.c.v. in mice daily for 7 days; the brain mitochondrial H<sub>2</sub>O<sub>2</sub> production, food intake, body weight and fat pads were evaluated. The basal production of H<sub>2</sub>O<sub>2</sub> of isolated mitochondria from the hippocampus and hypothalamus was significantly increased by Met (100 µg). There was increased peripheral sensitivity to insulin (Met 100 µg) and glucose tolerance tests (Met 50 and 100 µg). Moreover, Met decreased food intake, body weight, body temperature, fat pads and survival rates. Additionally, Met (1, 4 or 10 mM) decreased mitochondrial viability and increased the production of H<sub>2</sub>O<sub>2</sub> in neuronal cell cultures. In summary, our data indicate that a high dose of Met injected directly into the brain has remarkable neurotoxic effects, as evidenced by hypothermia, hypoglycemia, disrupted mitochondrial ETC flux and decreased survival rate.

[Am J Respir Crit Care Med](#). 2014 Dec 18. [Epub ahead of print]

## **Survival of Stage IV Lung Cancer Patients with Diabetes Treated with Metformin.**

[Lin JJ<sup>1</sup>](#), [Gallagher EJ](#), [Sigel K](#), [Mhango G](#), [Galsky MD](#), [Smith CB](#), [LeRoith D](#), [Wisnivesky JP](#).

### **+ Author information**

#### **Abstract**

**Rational:** Prior studies have shown an anticancer effect of metformin in patients with breast and colorectal cancer. It is unclear, however, whether metformin has a mortality benefit in lung cancer. **Objectives:** To compare overall survival of diabetic patients with stage IV non-small cell lung cancer (NSCLC) taking metformin versus those not on metformin. **Methods:** Using data from the Surveillance, Epidemiology and End Results registry linked to Medicare claims, we identified 750 diabetic patients 65-80 years of age diagnosed with stage IV NSCLC between 2007 and 2009. We used propensity score methods to assess the association of metformin use with overall survival while controlling for potential confounders. **Measurements and Main Results:** Overall, 61% of patients were on metformin at time of lung cancer diagnosis. Median survival in the metformin group was five months, compared to three months in patients not treated with metformin ( $p < 0.001$ ). Propensity score analyses showed that metformin use was associated with a statistically significant improvement in survival (hazard ratio: 0.80, 95% confidence interval 0.71 to 0.89), after controlling for sociodemographics, diabetes severity, other diabetes medications, cancer characteristics, and treatment. **Conclusions:** Metformin is associated with improved survival among diabetic patients with stage IV NSCLC suggesting a potential anticancer effect. Further research should evaluate plausible biological mechanisms as well as test the effect of metformin in prospective clinical trials.

# Dauer-independent insulin/IGF-1-signalling implicates collagen remodelling in longevity

Collin Y. Ewald, Jess N. Landis, Jess Porter Abate, Coleen T. Murphy & T. Keith Blackwell


Interventions that delay ageing mobilize mechanisms that protect and repair cellular components<sup>1, 2, 3</sup>, but it is unknown how these interventions might slow the functional decline of extracellular matrices<sup>4, 5</sup>, which are also damaged during ageing<sup>6, 7</sup>. Reduced insulin/IGF-1 signalling (rIIS) extends lifespan across the evolutionary spectrum, and in juvenile *Caenorhabditis elegans* also allows the transcription factor DAF-16/FOXO to induce development into dauer, a diapause that withstands harsh conditions<sup>1, 2</sup>. It has been suggested that rIIS delays *C. elegans* ageing through activation of dauer-related processes during adulthood<sup>2, 8, 9</sup>, but some rIIS conditions confer robust lifespan extension unaccompanied by any dauer-like traits<sup>1, 10, 11</sup>. Here we show that rIIS can promote *C. elegans* longevity through a program that is genetically distinct from the dauer pathway, and requires the Nrf (NF-E2-related factor) orthologue SKN-1 acting in parallel to DAF-16. SKN-1 is inhibited by IIS and has been broadly implicated in longevity<sup>12, 13, 14</sup>, but is rendered dispensable for rIIS lifespan extension by even mild activity of dauer-related processes. When IIS is decreased under conditions that do not induce dauer traits, SKN-1 most prominently increases expression of collagens and other extracellular matrix genes. Diverse genetic, nutritional, and pharmacological pro-longevity interventions delay an age-related decline in collagen expression. These collagens mediate adulthood extracellular matrix remodelling, and are needed for ageing to be delayed by interventions that do not involve dauer traits. By genetically delineating a dauer-independent rIIS ageing pathway, our results show that IIS controls a broad set of protective mechanisms during *C. elegans* adulthood, and may facilitate elucidation of processes of general importance for longevity. The importance of collagen production in diverse anti-ageing interventions implies that extracellular matrix remodelling is a generally essential signature of longevity assurance, and that agents promoting extracellular matrix youthfulness may have systemic benefit.





REPORT

## Lysosomal signaling molecules regulate longevity in *Caenorhabditis elegans*

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ABSTRACT

EDITOR'S SUMMARY

Lysosomes are crucial cellular organelles for human health that function in digestion and recycling of extracellular and intracellular macromolecules. We describe a signaling role for lysosomes that affects aging. In the worm *Caenorhabditis elegans*, the lysosomal acid lipase LIPL-4 triggered nuclear translocation of a lysosomal lipid chaperone LBP-8, which promoted longevity by activating the nuclear hormone receptors NHR-49 and NHR-80. We used high-throughput metabolomic analysis to identify several lipids in which abundance was increased in worms constitutively overexpressing LIPL-4. Among them, oleoylethanolamide directly bound to LBP-8 and NHR-80 proteins, activated transcription of target genes of NHR-49 and NHR-80, and promoted longevity in *C. elegans*. These findings reveal a lysosome-to-nucleus signaling pathway that promotes longevity and suggest a function of lysosomes as signaling organelles in metazoans.



# Insights into the Evolution of Longevity from the Bowhead Whale Genome

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## SUMMARY

The bowhead whale (*Balaena mysticetus*) is estimated to live over 200 years and is possibly the longest-living mammal. These animals should possess protective molecular adaptations relevant to age-related diseases, particularly cancer. Here, we report the sequencing and comparative analysis of the bowhead whale genome and two transcriptomes from different populations. Our analysis identifies genes under positive selection and bowhead-specific mutations in genes linked to cancer and aging. In addition, we identify gene gain and loss involving genes associated with DNA repair, cell-cycle regulation, cancer, and aging. Our results expand our understanding of the evolution of mammalian longevity and suggest possible players involved in adaptive genetic changes conferring cancer resistance. We also found potentially relevant changes in genes related to additional processes,

including thermoregulation, sensory perception, dietary adaptations, and immune response. Our data are made available online (<http://www.bowhead-whale.org>) to facilitate research in this long-lived species.

## INTRODUCTION

The lifespan of some animals, including quahogs, tortoises, and certain whale species, is far greater than that of humans (Austad, 2010; Finch, 1990). It is remarkable that a warm-blooded species such as the bowhead whale (*Balaena mysticetus*) has not only been estimated to live over 200 years (estimated age of one specimen 211 SE 35 years), suggesting it is the longest-lived mammal, but also exhibits very low disease incidence until an advanced age compared to humans (George et al., 1999; Philo et al., 1993). As in humans, the evolution of longevity in whales was accompanied by low fecundity and longer developmental time (Tacutu et al., 2013), as predicted by evolutionary theory. The cellular, molecular, and genetic mechanisms underlying longevity and resistance to age-related diseases in bowhead

# Transient delivery of modified mRNA encoding TERT rapidly extends telomeres in human cells



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Telomere extension has been proposed as a means to improve cell culture and tissue engineering and to treat disease. However, telomere extension by nonviral, nonintegrating methods remains inefficient. Here we report that delivery of modified mRNA encoding TERT to human fibroblasts and myoblasts increases telomerase activity transiently (24–48 h) and rapidly extends telomeres, after which telomeres resume shortening. Three successive transfections over a 4 d period extended telomeres up to 0.9 kb in a cell type-specific manner in fibroblasts and myoblasts and conferred an additional  $28 \pm 1.5$  and  $3.4 \pm 0.4$  population doublings (PD), respectively. Proliferative capacity increased in a dose-dependent manner. The second and third transfections had less effect on proliferative capacity than the first, revealing a refractory period. However, the refractory period was transient as a later fourth transfection increased fibroblast proliferative capacity by an additional  $15.2 \pm 1.1$  PD, similar to the first transfection. Overall, these treatments led to an increase in absolute cell number of more than  $10^{12}$ -fold. Notably, unlike immortalized cells, all treated cell populations eventually stopped increasing in number and expressed senescence markers to the same extent as untreated cells. This rapid method of extending telomeres and increasing cell proliferative capacity without risk of insertional mutagenesis should have broad utility in disease modeling, drug screening, and regenerative medicine.—Ramunas, J., Yakubov, E., Brady, J. J., Corbel, S. Y., Holbrook, C., Brandt, M., Stein, J., Santiago, J. G., Cooke, J. P., Blau, H. M. Transient delivery of modified mRNA encoding TERT rapidly extends telomeres in human cells.

# Mice deficient in Rbm38, a target of the p53 family, are susceptible to accelerated aging and spontaneous tumors

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RNA-binding motif protein 38 (Rbm38), also called RNPC1 [RNA-binding region (RNP1, RRM) containing 1], is a target of the p53 family and modulates p53 expression via mRNA translation. To investigate the biological function of Rbm38 in vivo, we generated an *Rbm38*-null mouse model. We showed that mice deficient in *Rbm38* exhibit signs of accelerated aging and are prone to hematopoietic defects and spontaneous tumors. To determine the biological significance of the p53-Rbm38 loop, we showed that *Rbm38* deficiency enhances accumulation of p53 induced by ionizing radiation (IR) and sensitizes mice to IR-induced lethality in a p53-dependent manner. Most importantly, *Rbm38* deficiency markedly decreases the tumor penetrance in mice heterozygous for *p53* via enhanced p53 expression. Interestingly, we found that *Rbm38* deficiency shortens the life span of, and promotes lymphomagenesis in, mice deficient in *p53*. These results provide genetic evidence that Rbm38 is necessary for normal hematopoiesis and for suppressing accelerated aging and tumorigenesis. Thus, the p53-Rbm38 axis might be explored for extending longevity and for tumor suppression.

# Glutamatergic regulation prevents hippocampal-dependent age-related cognitive decline through dendritic spine clustering

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John H. Morrison<sup>b,c,d,1</sup>

The dementia of Alzheimer's disease (AD) results primarily from degeneration of neurons that furnish glutamatergic corticocortical connections that subserve cognition. Although neuron death is minimal in the absence of AD, age-related cognitive decline does occur in animals as well as humans, and it decreases quality of life for elderly people. Age-related cognitive decline has been linked to synapse loss and/or alterations of synaptic proteins that impair function in regions such as the hippocampus and prefrontal cortex. These synaptic alterations are likely reversible, such that maintenance of synaptic health in the face of aging is a critically important therapeutic goal. Here, we show that riluzole can protect against some of the synaptic alterations in hippocampus that are linked to age-related memory loss in rats. Riluzole increases glutamate uptake through glial transporters and is thought to decrease glutamate spillover to extrasynaptic NMDA receptors while increasing synaptic glutamatergic activity. Treated aged rats were protected against age-related cognitive decline displayed in nontreated aged animals. Memory performance correlated with density of thin spines on apical dendrites in CA1, although not with mushroom spines. Furthermore, riluzole-treated rats had an increase in clustering of thin spines that correlated with memory performance and was specific to the apical, but not the basilar, dendrites of CA1. Clustering of synaptic inputs is thought to allow nonlinear summation of synaptic strength. These findings further elucidate neuroplastic changes in glutamatergic circuits with aging and advance therapeutic development to prevent and treat age-related cognitive decline.



# Methionine restriction restores a younger metabolic phenotype in adult mice with alterations in fibroblast growth factor 21

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## Summary

**Methionine restriction (MR) decreases body weight and adiposity and improves glucose homeostasis in rodents. Similar to caloric restriction, MR extends lifespan, but is accompanied by increased food intake and energy expenditure. Most studies have examined MR in young animals; therefore, the aim of this study was to investigate the ability of MR to reverse age-induced obesity and insulin resistance in adult animals. Male C57BL/6J mice aged 2 and 12 months old were fed MR (0.172% methionine) or control diet (0.86% methionine) for 8 weeks or 48 h. Food intake and whole-body physiology were assessed and serum/tissues analyzed biochemically. Methionine restriction in 12-month-old mice completely reversed age-induced alterations in body weight, adiposity, physical activity, and glucose tolerance to the levels measured in healthy 2-month-old control-fed mice. This was despite a significant increase in food intake in 12-month-old MR-fed mice. Methionine restriction decreased hepatic lipogenic gene expression and caused a remodeling of lipid metabolism in white adipose tissue, alongside increased insulin-induced phosphorylation of the insulin receptor (IR) and Akt in peripheral tissues. Mice restricted of methionine exhibited increased circulating and hepatic gene expression levels of FGF21, phosphorylation of eIF2 $\alpha$ , and expression of ATF4, with a concomitant decrease in IRE1 $\alpha$  phosphorylation. Short-term 48-h MR treatment increased hepatic FGF21 expression/secretion and insulin signaling and improved whole-body glucose homeostasis without affecting body weight. Our findings suggest that MR feeding can reverse the negative effects of aging on body mass, adiposity, and insulin resistance through an FGF21 mechanism. These findings implicate MR dietary intervention as a viable therapy for age-induced metabolic syndrome in adult humans.**

**Key words:** activating transcription factor 4; aging; fibroblast growth factor 21; lipid; metabolism; unfolded protein response.

## Introduction

Aging is characterized by increased adiposity (Huffman & Barzilai, 2009) and insulin resistance (Selman & Withers, 2011), which may play a role in regulating lifespan (Huffman & Barzilai, 2009; Selman & Withers, 2011) due to their association with further metabolic complications, including type 2 diabetes, cardiovascular disease and cancer (Biddinger, 2006). Removal of visceral fat is enough to increase mean and maximum lifespan in rodents (Muzumdar *et al.*, 2008). Visceral fat removal also improves insulin sensitivity in rats (Barzilai *et al.*, 1999) and enhanced insulin sensitivity is a characteristic of many long-lived mouse models (Selman & Withers, 2011).

Methionine restriction (MR) is a dietary technique, with the only manipulation of the diet being a reduction in the essential amino acid methionine (from 0.86% of the diet to 0.172%). Methionine restriction has been shown previously to extend lifespan (Orentreich *et al.*, 1993; Richie *et al.*, 1994), dramatically decrease body weight and adiposity, and improve insulin sensitivity relative to animals on a control diet (Hasek *et al.*, 2010; Plaisance *et al.*, 2010; Ables *et al.*, 2012). Methionine restriction has, therefore, been proposed to mimic effects of caloric restriction (CR) (Masoro, 2005); however, in contrast to CR, animals on MR diet are fed *ad libitum* and actually consume more food than control-fed animals (Hasek *et al.*, 2010; Plaisance *et al.*, 2010). This loss in body mass despite an increase in energy intake is thought to be accomplished through creating a vast metabolic inefficiency, which leads to increased energy expenditure, through uncoupling protein 1 (UCP1) nonshivering thermogenesis in adipose tissue (Hasek *et al.*, 2010). In young animals, MR stunts growth and development, including reducing total length, serum insulin-like growth factor 1 (IGF-1), and growth hormone signaling (Ables *et al.*, 2012). Fibroblast growth factor (FGF) 21 is another regulator of growth that is released from the liver in response to fasting through a PPAR $\alpha$  mechanism (Badman *et al.*, 2007). FGF21 transgenic mice also show decreased circulating levels of IGF-1 and are smaller than wild type mice (Bassik

# Added Sugar Intake and Cardiovascular Diseases Mortality Among US Adults

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**Importance** Epidemiologic studies have suggested that higher intake of added sugar is associated with cardiovascular disease (CVD) risk factors. Few prospective studies have examined the association of added sugar intake with CVD mortality.

**Objective** To examine time trends of added sugar consumption as percentage of daily calories in the United States and investigate the association of this consumption with CVD mortality.

**Design, Setting, and Participants** National Health and Nutrition Examination Survey (NHANES, 1988-1994 [III], 1999-2004, and 2005-2010 [n = 31 147]) for the time trend analysis and NHANES III Linked Mortality cohort (1988-2006 [n = 11 733]), a prospective cohort of a nationally representative sample of US adults for the association study.

**Main Outcomes and Measures** Cardiovascular disease mortality.

**Results** Among US adults, the adjusted mean percentage of daily calories from added sugar increased from 15.7% (95% CI, 15.0%-16.4%) in 1988-1994 to 16.8% (16.0%-17.7%;  $P = .02$ ) in 1999-2004 and decreased to 14.9% (14.2%-15.5%;  $P < .001$ ) in 2005-2010. Most adults consumed 10% or more of calories from added sugar (71.4%) and approximately 10% consumed 25% or more in 2005-2010. During a median follow-up period of 14.6 years, we documented 831 CVD deaths during 163 039 person-years. Age-, sex-, and race/ethnicity-adjusted hazard ratios (HRs) of CVD mortality across quintiles of the percentage of daily calories consumed from added sugar were 1.00 (reference), 1.09 (95% CI, 1.05-1.13), 1.23 (1.12-1.34), 1.49 (1.24-1.78), and 2.43 (1.63-3.62;  $P < .001$ ), respectively. After additional adjustment for sociodemographic, behavioral, and clinical characteristics, HRs were 1.00 (reference), 1.07 (1.02-1.12), 1.18 (1.06-1.31), 1.38 (1.11-1.70), and 2.03 (1.26-3.27;  $P = .004$ ), respectively. Adjusted HRs were 1.30 (95% CI, 1.09-1.55) and 2.75 (1.40-5.42;  $P = .004$ ), respectively, comparing participants who consumed 10.0% to 24.9% or 25.0% or more calories from added sugar with those who consumed less than 10.0% of calories from added sugar. These findings were largely consistent across age group, sex, race/ethnicity (except among non-Hispanic blacks), educational attainment, physical activity, health eating index, and body mass index.

**Conclusions and Relevance** Most US adults consume more added sugar than is recommended for a healthy diet. We observed a significant relationship between added sugar consumption and increased risk for CVD mortality.

# Reviews/Editorials/Commentaries

## Ageing research: Blood to blood

By splicing animals together, scientists have shown that young blood rejuvenates old tissues. Now, they are testing whether it works for humans.

**Megan Scudellari**

21 January 2015



PDF



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Illustration by Gary Neill





## Rapamycin and Ageing: When, for How Long, and How Much?

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The mechanistic target of rapamycin (mTOR) is a nutrient and growth factor responsive kinase that modulates lifespan in species from yeast to mice (Johnson et al., 2013b). mTOR exists in two complexes within cells, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) (Laplante and Sabatini, 2012). Abundant evidence suggests that mTORC1 is the primary mTOR complex involved in regulating longevity: mutations that reduce the activity of mTORC1 have been shown to extend lifespan in yeast (Kaeberlein et al., 2005; Powers et al., 2006), nematode worms (Vellai et al., 2003; Jia et al., 2004), fruit flies (Kapahi et al., 2004), and mice (Lamming et al., 2012), as has deletion of the mTORC1 substrate ribosomal S6 kinase (Fabrizio et al., 2001, 2004; Kapahi et al., 2004; Pan et al., 2007; Selman et al., 2009). Consistent with these genetic data, treatment with the mTORC1 inhibitor rapamycin has also been found to increase lifespan in yeast (Powers et al., 2006; Medvedik et al., 2007), worms (Robida-Stubbs et al., 2012), fruit flies (Bjedov et al., 2010), and mice (Harrison et al., 2009).

mTORC1 inhibition is sufficient to extend lifespan in each of these species, has led to the general consensus that inhibition of mTORC1 plays a direct role in promoting longevity and healthspan in response to DR (Kapahi et al., 2010; Kaeberlein, 2013a).

As of early 2014, at least seven independent studies have reported lifespan extension from rapamycin in wild type mice (Table 1), with most studies using a dietary formulation where rapamycin is encapsulated for enteric release (Nadon et al., 2008). The first report, published in 2009, demonstrated that UMHET3 mice fed a diet containing encapsulated rapamycin at 14 ppm (~2.24 mg/kg/day) beginning at 600 days of age is sufficient to increase lifespan in both male and female animals (Harrison et al., 2009). Subsequent reports where rapamycin feeding was initiated in young adulthood showed a similar magnitude of lifespan extension in UMHET3 mice (Miller et al., 2011). Rapamycin feeding has also been shown to extend lifespan in C57BL/6J mice when initiated at mixed ages (Neff et al., 2013) or as late as 19 months of age in

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## **Circulating elastin peptides, role in vascular pathology.**

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### **+ Author information**

#### **Abstract**

The atherosclerotic process starts with the degradation of elastic fibers. Their presence was demonstrated in the circulation as well as several of their biological properties elucidated. We described years ago a procedure to obtain large elastin peptides by organo-alkaline hydrolysis,  $\kappa$ -elastin. This method enabled also the preparation of specific antibodies used to determine elastin peptides, as well as anti-elastin antibodies in body fluids and tissue extracts. Elastin peptides were determined in a large number of human blood samples. Studies were carried out to explore their pharmacological properties. Similar recent studies by other laboratories confirmed our findings and arose new interest in circulating elastin peptides for their biological activities. This recent trend justified the publication of a review of the biological and pathological activities of elastin peptides demonstrated during our previous studies, subject of this article.

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## **The role of collagen crosslinks in ageing and diabetes - the good, the bad, and the ugly.**

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### **Abstract**

The non-enzymatic reaction of proteins with glucose (glycation) is a topic of rapidly growing importance in human health and medicine. There is increasing evidence that this reaction plays a central role in ageing and disease of connective tissues. Of particular interest are changes in type-I collagens, long-lived proteins that form the mechanical backbone of connective tissues in nearly every human organ. Despite considerable correlative evidence relating extracellular matrix (ECM) glycation to disease, little is known of how ECM modification by glucose impacts matrix mechanics and damage, cell-matrix interactions, and matrix turnover during aging. More daunting is to understand how these factors interact to cumulatively affect local repair of matrix damage, progression of tissue disease, or systemic health and longevity. This focused review will summarize what is currently known regarding collagen glycation as a potential driver of connective tissue disease. We concentrate attention on tendon as an affected connective tissue with large clinical relevance, and as a tissue that can serve as a useful model tissue for investigation into glycation as a potentially critical player in tissue fibrosis related to ageing and diabetes.