

Cardiac Longevity: The Timeless Heart

Jack M. Wolfson DO, FACC



NATURAL

HEART DOCTOR



Aging can be defined as the functional deterioration of physiological mechanisms which strictly depends on the passage of time. - Webster

Age is a manmade construct.

We are spiritual beings living a human experience.





**We
Are Spirits**

in the
**Material
World**

-Sting

- **10 years of medical training**
- **Senior partner in Arizona's largest cardiology group**
- **Chair of Medicine/ Director of Cardiac Rehab**
- **Phoenix Top Doc 2011**







- 
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 - **Senior partner in Arizona's largest cardiology group**
 - **Chair of Medicine/ Director of Cardiac Rehab**
 - **Phoenix Top Doc 2011**
 - **The Drs. Wolfson and Wolfson Integrative Cardiology**
 - **Top Holistic MD 2012,14-17**
 - **Dr. Axe Top 50 Functional Medicine Doctors**
 - **International Speaker**



THE PALEO CARDIOLOGIST



THE NATURAL WAY TO HEART HEALTH

JACK WOLFSON DO, FACC

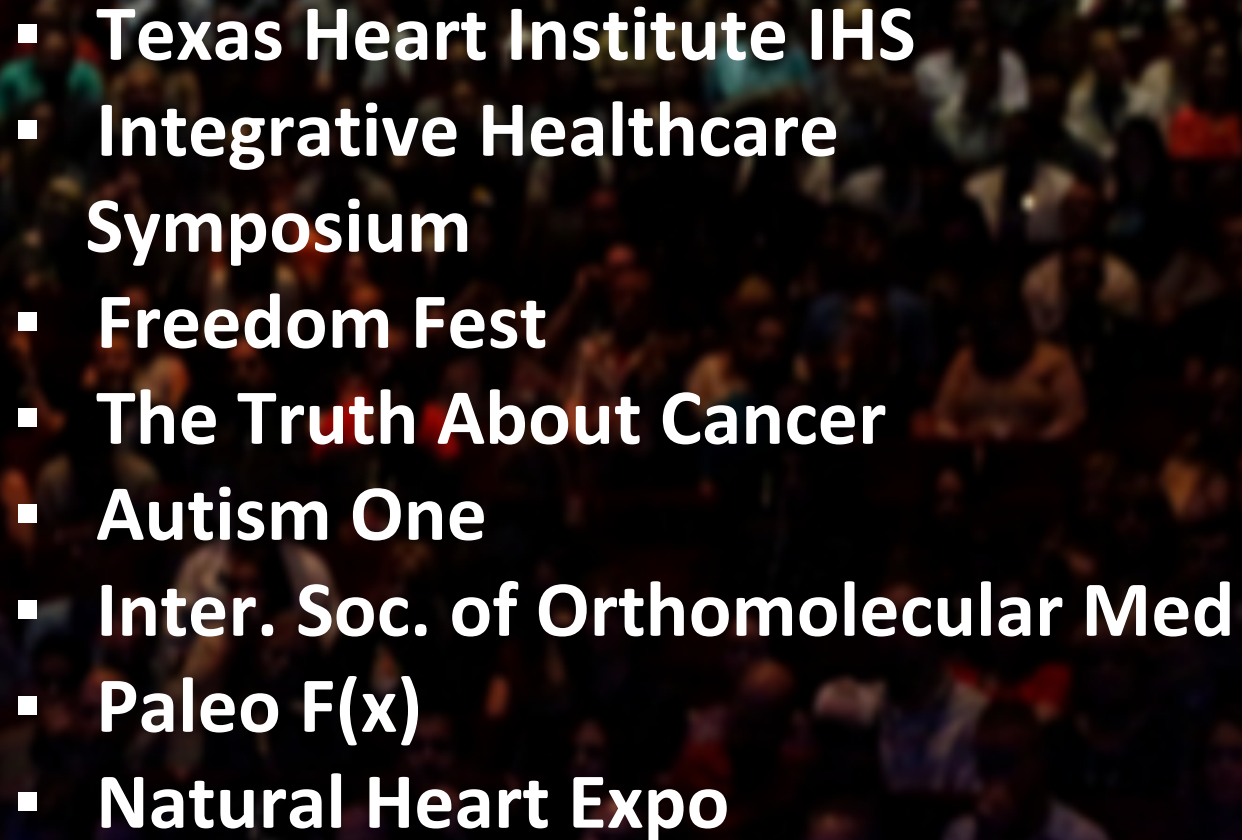
Chapter 1	Cholesterol is King
Chapter 2	LDL is Not the Boogie Man
Chapter 3	Let's Eat Paleo
Chapter 4	Nutrition: Where Did We Go Wrong?
Chapter 5	One Nation Under Prozac
Chapter 6	The Failed Promise of Big Pharma
Chapter 7	Useless Dangerous Procedures
Chapter 8	Our Toxic World
Chapter 9	Heavy Metal Madness
Chapter 10	The Body Fights Back
Chapter 11	Go to Sleep
Chapter 12	Get Off Your Butt
Chapter 13	Healthy Beverages
Chapter 14	The Wonders of Chiropractic Care
Chapter 15	Teeth are More Than a Beautiful Smile
Chapter 16	Top Twenty Supplements
Chapter 17	Top Twenty Blood Tests

Over 300 references

Personalized and Precision
Integrative
Cardiovascular
Medicine

MARK C. HOUSTON

 Wolters Kluwer

- 
- A man in a blue suit is walking on a stage, facing right. He is in profile, and his hands are slightly raised. The background is a large, dark crowd of people, mostly men in suits, seated in an auditorium. The lighting is focused on the man on stage, with the audience in shadow.
- **Texas Heart Institute IHS**
 - **Integrative Healthcare Symposium**
 - **Freedom Fest**
 - **The Truth About Cancer**
 - **Autism One**
 - **Inter. Soc. of Orthomolecular Med**
 - **Paleo F(x)**
 - **Natural Heart Expo**

Mortality in the United States

NCHS Data Brief No. 328, November 2018

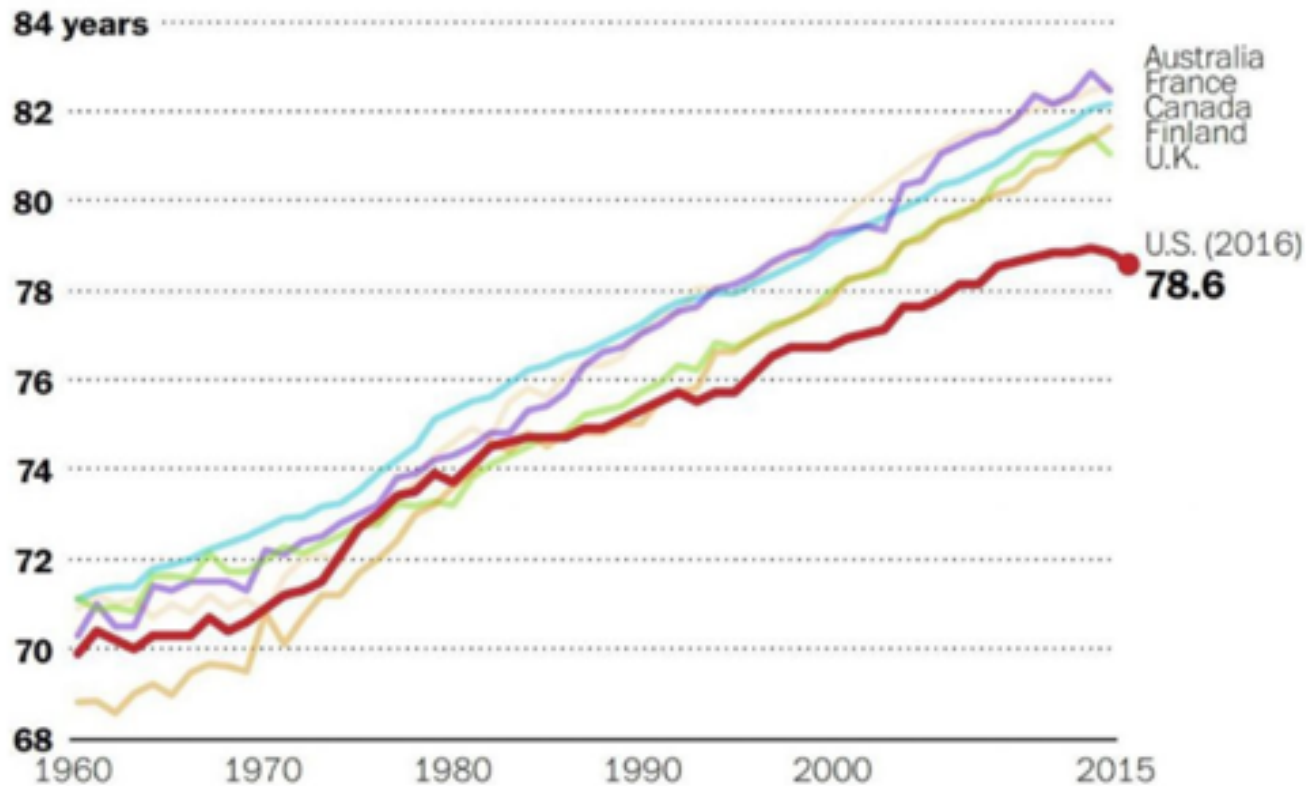
[CDC](#) > [NCHS](#) > [Publications and Information Products](#) > [Data Briefs](#)

Sherry L. Murphy, B.S., Jiaquan Xu, M.D., Kenneth D. Kochanek, M.A., and Elizabeth Arias, Ph.D.

- Life expectancy for the U.S. population declined to 78.6 years in 2017.

American exceptionalism

Life expectancy at birth, selected OECD countries



HOW THE POLYPILL WILL HELP YOU LIVE LONGER

Heart attack survivors' pill will include:

**Aspirin
75mg**
(anti blood clotting)

**Simvastatin
40mg**
(anti cholesterol)

**Atenolol
50mg**
(blood pressure lowering)

**Lisinopril
10mg**
(blood pressure lowering)

Stroke survivors' pill will include:


Aspirin 75mg
(anti blood clotting)

**Simvastatin
40mg**
(anti cholesterol)

Lisinopril 10mg
(blood pressure lowering)

Hydrochlorothiazide 12.5mg
(blood pressure lowering)





IT WILL CURE
EVERY AILMENT
KNOWN TO MAN,
THE ONLY SIDE-
EFFECT IS, YOU'LL
CHOKES TO DEATH
TRYING TO
SWALLOW IT!

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Do statin drugs save lives?

JAMA Internal Medicine

American Medical Association

Effect of Statin Treatment vs Usual Care on Primary Cardiovascular Prevention Among Older Adults

The ALLHAT-LLT Randomized Clinical Trial

Benjamin H. Han, MD, MPH, David Sutin, MD, [...], and

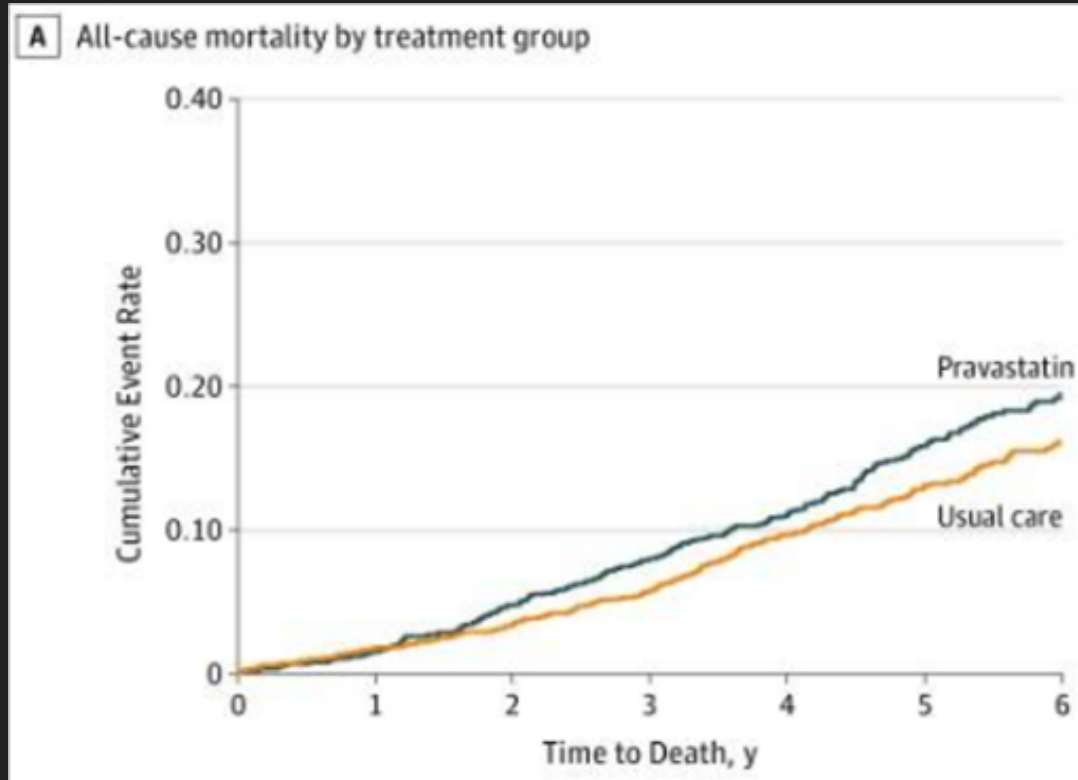
Caroline S. Blaum, MD

3000 people- 65 and older

Statin drug vs. placebo

6 years

Do statin drugs save lives?





The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

October 18, 2018

N Engl J Med 2018; 379:1519-1528

Effect of Aspirin on All-Cause Mortality in the Healthy Elderly

John J. McNeil, M.B., B.S., Ph.D., Mark R. Nelson, M.B., B.S., Ph.D., Robyn L. Woods, Ph.D., Jessica E. Lockery, M.B., B.S., Rory Wolfe, Ph.D., Christopher M. Reid, Ph.D., M.P.H., Brenda Kirpach, C.C.R.A., Raj C. Shah, M.D., Diane G. Ives, M.P.H., Elsdon Storey, M.B., B.S., D.Phil., Joanne Ryan, Ph.D., Andrew M. Tonkin, M.B., B.S., M.D., [et al.](#), for the ASPREE Investigator Group^{*}

Table 1. Mortality According to the Underlying Cause of Death.*

Cause of Death	Overall (N = 19,114)	Aspirin (N = 9525)	Placebo (N = 9589)
	<i>no. of deaths</i>	<i>no. of deaths (%)</i>	
Any	1052	558 (5.9)	494 (5.2)
Cancer†	522	295 (3.1)	227 (2.3)
Cardiovascular disease, including ischemic stroke‡	203	91 (1.0)	112 (1.2)
Major hemorrhage, including hemorrhagic stroke§	53	28 (0.3)	25 (0.3)

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Low vitamin D leads to 71% higher risk of being dead

Am J Clin Nutr. 2013 Apr;97(4):782-93. doi: 10.3945/ajcn.112.047712. Epub 2013 Feb 27.

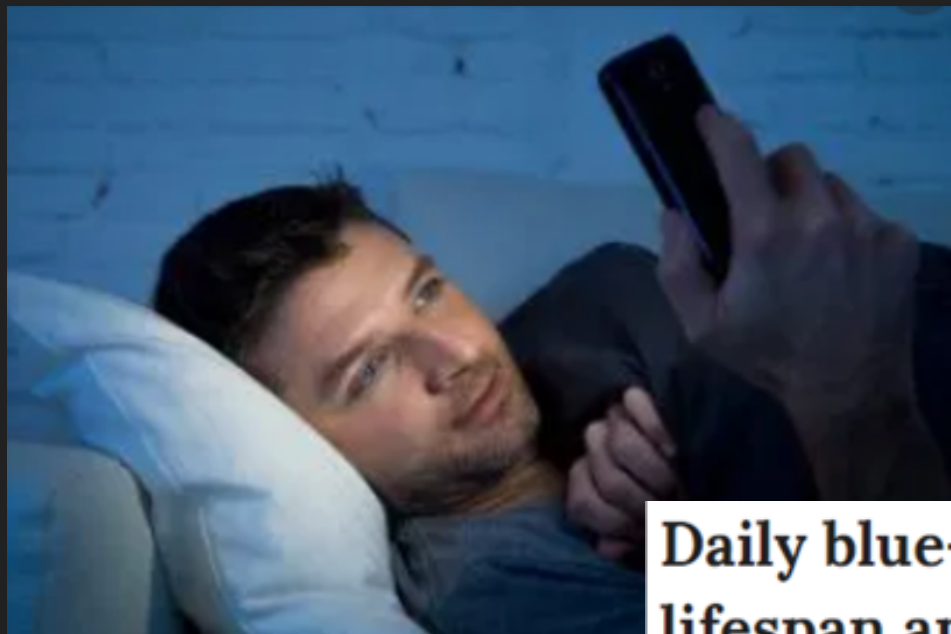
Strong associations of 25-hydroxyvitamin D concentrations with all-cause, cardiovascular, cancer, and respiratory disease mortality in a large cohort study.

Schöttker B¹, Haug U, Schomburg L, Köhrle J, Perna L, Müller H, Holleczer B, Brenner H.

Abstract

DESIGN: Concentrations of 25(OH)D were measured in n = 9578 baseline and n = 5469 5-y follow-up participants of the ESTHER study, which is a German population-based cohort aged 50-74 y at baseline. Deaths were recorded during 9.5 y of follow-up (median). Restricted cubic splines were used to assess dose-response relations, and Cox regression with time-dependent variables was used to estimate hazard ratios.

RESULTS: During follow-up, 1083 study participants died; of those, 350 individuals died of cardiovascular diseases, 433 individuals died of cancer, and 55 individuals died of respiratory diseases. The overall mortality [HR (95% CI)] of subjects with vitamin D deficiency [25(OH)D concentrations <30 nmol/L] or vitamin D insufficiency [25(OH)D concentrations from 30 to 50 nmol/L] was significantly increased [1.71 (1.43, 2.03) and 1.17 (1.02, 1.35), respectively] compared with that of subjects with sufficient 25(OH)D concentrations (>50 nmol/L). Vitamin D deficiency was also associated with increased cardiovascular mortality [1.39 (95% CI: 1.02, 1.89)], cancer mortality [1.42 (95% CI: 1.08, 1.88)] and respiratory disease mortality [2.50 (95% CI: 1.12, 5.56)]. The association of 25(OH)D concentrations with all-cause mortality proved to be a nonlinear inverse association with risk that started to increase at 25(OH)D concentrations <75 nmol/L.



Daily blue-light exposure shortens lifespan and causes brain neurodegeneration in *Drosophila*

Trevor R. Nash, Eileen S. Chow, Alexander D. Law, Samuel D. Fu, Elzbieta Fuszara, Aleksandra Biliska, Piotr Bebas, Doris Kretzschmar & Jadwiga M. Giebultowicz 

npj Aging and Mechanisms of Disease **5**, Article number: 8 (2019) | [Cite this article](#)

High air pollution lowers life expectancy



Sci. Total Environ. 2014 Jul 15;487:57-64. doi: 10.1016/j.scototenv.2014.03.142. Epub 2014 Apr 23.

A study of air pollutants influencing life expectancy and longevity from spatial perspective in China.

Wang L¹, BinogunWei², Li Y³, Li H², Zhang F⁴, Rosenberg M⁵, Yang L², Huang J², Kraff T⁶, Wang W².

Author information

Abstract

Life expectancy and longevity are influenced by air pollutants and socioeconomic status, but the extend and significance are still unclear. Better understanding how the spatial differences of life expectancy and longevity are affected by air pollutants is needed for generating public health and environmental strategies since the whole of China is now threatened by deteriorated air quality. 85 major city regions were chosen as research areas. Geographically Weighted Regression (GWR) and Stepwise Regression (SR) were used to find the spatial correlations between health indicators and air pollutants, adjusted by per capita GDP(1). The results were, regions with higher life expectancy were mainly located in the east area and areas with good air quality, a regional difference of 10 $\mu\text{g}/\text{m}^3$ in ambient air SO_2 (2) could cause adjusted 0.28 year's difference in life expectancy, a regional difference of 10 $\mu\text{g}/\text{m}^3$ in ambient air PM_{10} (3) could lead to a longevity ratio difference of 2.23, and per capita GDP was positively associating with life expectancy but not longevity ratio, with a regional difference of 10,000 RMB(4) associating with adjusted 0.49 year's difference in life expectancy. This research also showed the evidences that there exist spatially differences for ambient air PM_{10} and SO_2 influencing life expectancy and longevity in China, and this influences were clearer in south China.

Prenatal Air Pollution and Newborns' Predisposition to Accelerated Biological Aging.

Martens DS¹, Cox B¹, Janssen BG¹, Clemente DBP^{1,2,3}, Gasparini A^{4,5}, Vanpoucke C⁶, Lefebvre W⁷, Roels HA^{1,8}, Plusquin M¹, Nawrot TS^{1,9}.

CONCLUSIONS AND RELEVANCE: Mothers who were exposed to higher levels of PM2.5 gave birth to newborns with shorter telomere length. The observed telomere loss in newborns by prenatal air pollution exposure indicates less buffer for postnatal influences of factors



Nutrition

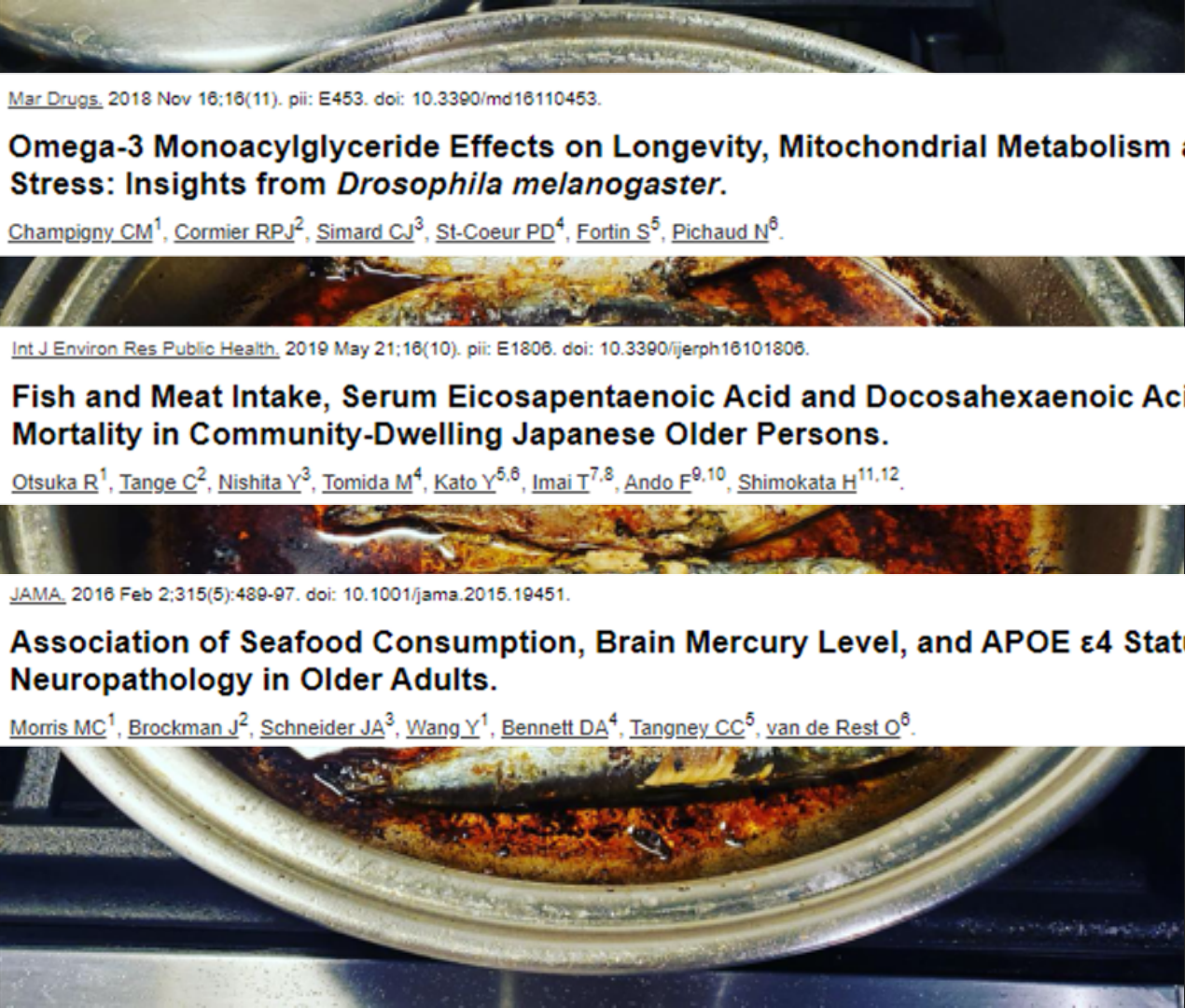




Fruit flies live
15% longer
with fish oil

High DHA
27% lower
mortality

Seafood eaters
have lower
dementia risk



[Mar Drugs](#). 2018 Nov 16;16(11). pii: E453. doi: 10.3390/md16110453.

Omega-3 Monoacylglyceride Effects on Longevity, Mitochondrial Metabolism and Oxidative Stress: Insights from *Drosophila melanogaster*.

[Champigny CM](#)¹, [Cormier RPJ](#)², [Simard CJ](#)³, [St-Coeur PD](#)⁴, [Fortin S](#)⁵, [Pichaud N](#)⁶.

[Int J Environ Res Public Health](#). 2019 May 21;16(10). pii: E1806. doi: 10.3390/ijerph16101806.

Fish and Meat Intake, Serum Eicosapentaenoic Acid and Docosahexaenoic Acid Levels, and Mortality in Community-Dwelling Japanese Older Persons.

[Otsuka R](#)¹, [Tange C](#)², [Nishita Y](#)³, [Tomida M](#)⁴, [Kato Y](#)^{5,6}, [Imai T](#)^{7,8}, [Ando F](#)^{9,10}, [Shimokata H](#)^{11,12}.

[JAMA](#). 2016 Feb 2;315(5):489-97. doi: 10.1001/jama.2015.19451.

Association of Seafood Consumption, Brain Mercury Level, and APOE ϵ 4 Status With Brain Neuropathology in Older Adults.

[Morris MC](#)¹, [Brockman J](#)², [Schneider JA](#)³, [Wang Y](#)¹, [Bennett DA](#)⁴, [Tangney CC](#)⁵, [van de Rest O](#)⁶.



CARNIVORE
Challenge
with Team TDW

Sugar linked to 350% higher risk of cognitive decline



Clin Interv Aging. 2019 Jul 22;14:1331-1342. doi: 10.2147/CIA.S211534. eCollection 2019.

Habitual sugar intake and cognitive impairment among multi-ethnic Malaysian older adults.

Chong CP¹, Shahar S¹, Haron H¹, Din NC².

<https://www.ncbi.nlm.nih.gov/pubmed/31413554>



Fasting-induced anti-aging molecule keeps blood vessels young

New research has found that fasting triggers a molecule that can delay the aging of our arteries. The findings could help prevent age-related chronic diseases such as cancer, cardiovascular disease, and Alzheimer's.

Organic Coffee Crafted for Health

Drinking healthier coffee is one of the easiest things you can do to improve your wellness, performance and longevity.

Eur J Epidemiol. 2019 Aug;34(8):731-752. doi: 10.1007/s10654-019-00524-3. Epub 2019 May 4.

Coffee consumption and all-cause and cause-specific mortality: a meta-analysis by potential modifiers.

Kim Y¹, Je Y², Giovannucci E³.

Coffee consumption has been associated with decreased mortality in previous studies. As aging, obesity, and lifestyle factors affect the risk of mortality, the association between coffee and mortality needs to be examined in various subpopulations by characteristics of subjects. To quantitatively assess this association, we conducted an updated meta-analysis including stratified analyses by potential modifiers. We searched in the PubMed and Web of Science databases through March 8, 2019, and conducted meta-analysis including linear and non-linear dose-response analyses. We identified 40 studies including 3,852,651 subjects and 450,256 all-cause and cause-specific deaths. Non-linear inverse associations between coffee consumption and mortality from all-causes, cardiovascular disease (CVD), and cancers were found. The lowest relative risk (RR) was at intakes of 3.5 cups/day for all-cause mortality (RR = 0.85, 95% CI 0.82-0.89), 2.5 cups/day for CVD mortality (RR = 0.83, 95% CI 0.80-0.87), and 2 cups/day for cancer mortality (RR = 0.96, 95% CI 0.94-0.99), while additional intakes were not associated with further lower mortality. An inverse association between coffee consumption and all-cause mortality was maintained





Advanced Laboratory Testing

1. Apolipoprotein B, Apolipoprotein A and Triglycerides
2. Lp(a)
3. Hs-crp, PLA-2, ox-LDL, and myeloperoxidase (MPO)
4. Homocysteine
5. 25 - hydroxy vitamin D
6. Uric acid
7. CBC with iron and ferritin
8. Full thyroid panel including anti-thyroglobulin and anti-TPO
9. Sex hormone panel
10. Insulin, fasting glucose, and Hgb A1C

Micronutrient testing

Micronutrient	Plasma			WBC		
	Current	Previous	Ref	Current	Previous	Ref
Vitamin A	74.86 (mcg/dL)		32.96-82.27	0.21 (pg/MM WBC)		0.21-21.08
Vitamin B1	304.99 (nmol/L)		164.73-397.23	0.47 (pg/MM WBC)		0.34-3.77
Vitamin B2	38.91 (mcg/L)		23.41-358.56	0.45 (pg/MM WBC)		0.07-4.23
Vitamin B3	8.25 (ng/mL)		5.05-84.36	8.01 (pg/MM WBC)		0.99-14.76
Vitamin B5	64.03 (mcg/L)		23.23-269.15	0.07 (pg/MM WBC)		0.02-0.39
Vitamin B6	1.94 ↑ (ng/mL)		0.46-1.76	0.010 (pg/MM WBC)		0.003-0.040
Vitamin B12	>2000 (pg/mL)		>211			
Vitamin C	0.71 (mg/dL)		0.34-0.71	41.06 ↑ (pg/MM WBC)		0.55-28.77
Vitamin D3	1.77 (ng/mL)		0.74-2.46	10.74 (pg/MM WBC)		7.68-84.76
Vitamin E	20.8 (ng/L)		7.6-24.6	10.45 ↓ (pg/MM WBC)		11.34-116.04
Vitamin K1	3.05 ↑ (ng/mL)		0.22-2.50	0.004 (pg/MM WBC)		0.003-1.440
Vitamin K2	0.18 (ng/mL)		>0.08	0.004 ↓ (pg/MM WBC)		0.005-5.152
Folate						

Vitamins

Ultimate Longevity Tests

Wheat Zoomer- Leaky gut

Gut Zoomer

Neural Zoomer

Toxic Metals

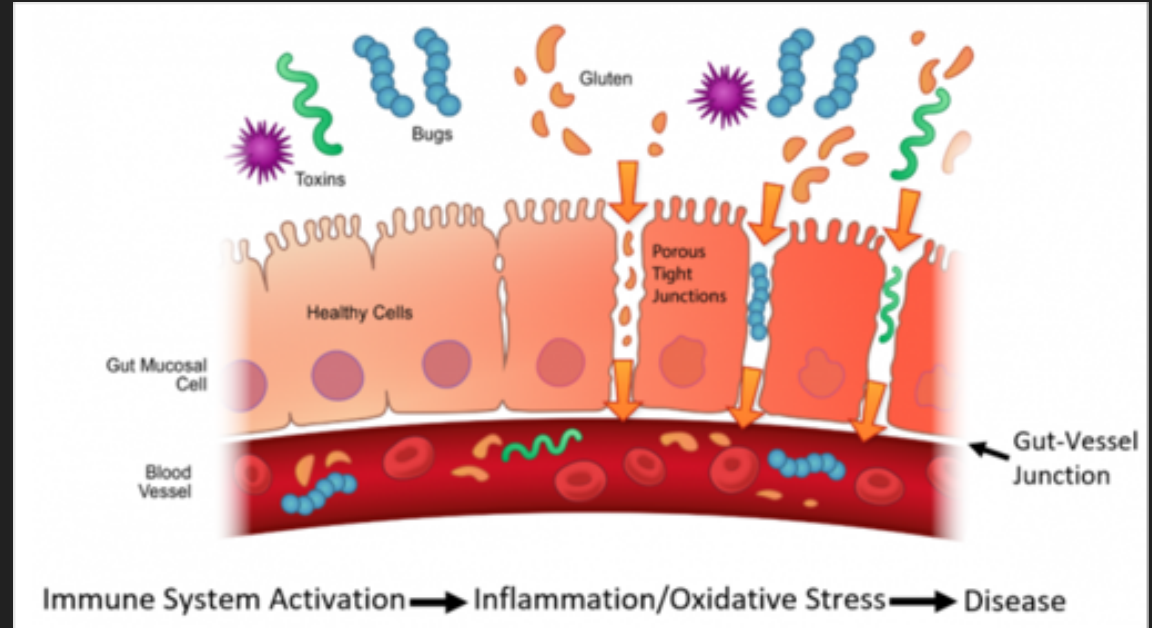
Mold mycotoxins

Environmental toxins

CV analysis

Micronutrient

Genetic testing



Gut microbiome

[Nutr Healthy Aging](#). 2018 Jun 15;4(4):267-285. doi: 10.3233/NHA-170030.

Gut microbiome and aging: Physiological and mechanistic insights.

[Nagpal R](#)¹, [Mainali R](#)¹, [Ahmadi S](#)^{1,2}, [Wang S](#)¹, [Singh R](#)¹, [Kavanagh K](#)³, [Kitzman DW](#)⁴, [Kushugulova A](#)⁵, [Marotta F](#)⁶, [Yadav H](#)¹.

[Nutr Res](#). 2009 Apr;29(4):281-9. doi: 10.1016/j.nutres.2009.03.010.

Oral administration of live Bifidobacterium substrains isolated from healthy centenarians enhanced immune function in BALB/c mice.

[Yang HY](#)¹, [Liu SL](#), [Ibrahim SA](#), [Zhao L](#), [Jiang JL](#), [Sun WF](#), [Ren FZ](#).

[Front Genet](#). 2020 Jan 15;10:1329. doi: 10.3389/fgene.2019.01329. eCollection 2019.

The Epigenetic Connection Between the Gut Microbiome in Obesity and Diabetes.

[Sharma M](#)¹, [Li Y](#)^{2,3,4}, [Stoll ML](#)⁵, [Tollefsbol TO](#)^{1,3,4,6,7}.

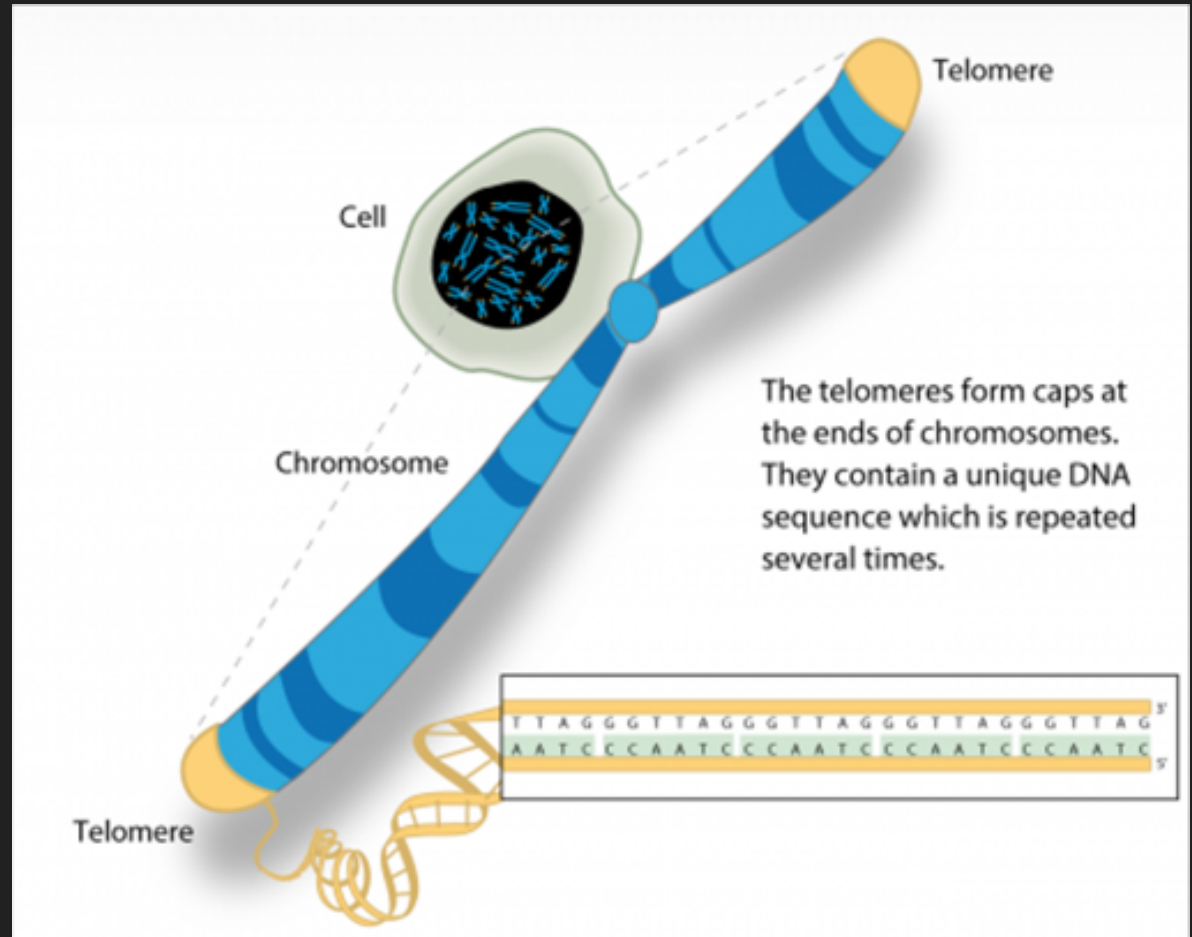
The Gut Zoomer report provides you with actionable recommendations that include potential risks for:

- Intestinal permeability (SCFA producing bacteria and tight junction integrity)
- Intestinal disorders (IBS and IBD related bacteria)
- Small Intestinal Bacterial Overgrowth (SIBO)- related bacteria
- Cardiovascular health (inflammation influencing and TMAO-related bacteria)
- Autoimmune health (celiac, Crohn's, rheumatoid arthritis, etc)
- Neurological health (MS, Parkinson's, and more)
- Liver diseases (cirrhosis, hepatitis, cholangitis, and more)
- Metabolic health (Obesity, diabetes, etc)
- Nutrition (Vitamin production, oxalate metabolism)
- Microbiome and hormone connections (Beta-glucuronidase and Beta-glucosidase)
- 67 pathogenic bacteria
- 24 Intestinal parasites
- 8 viruses
- 5 Fungal or yeast species
- 5 worm species

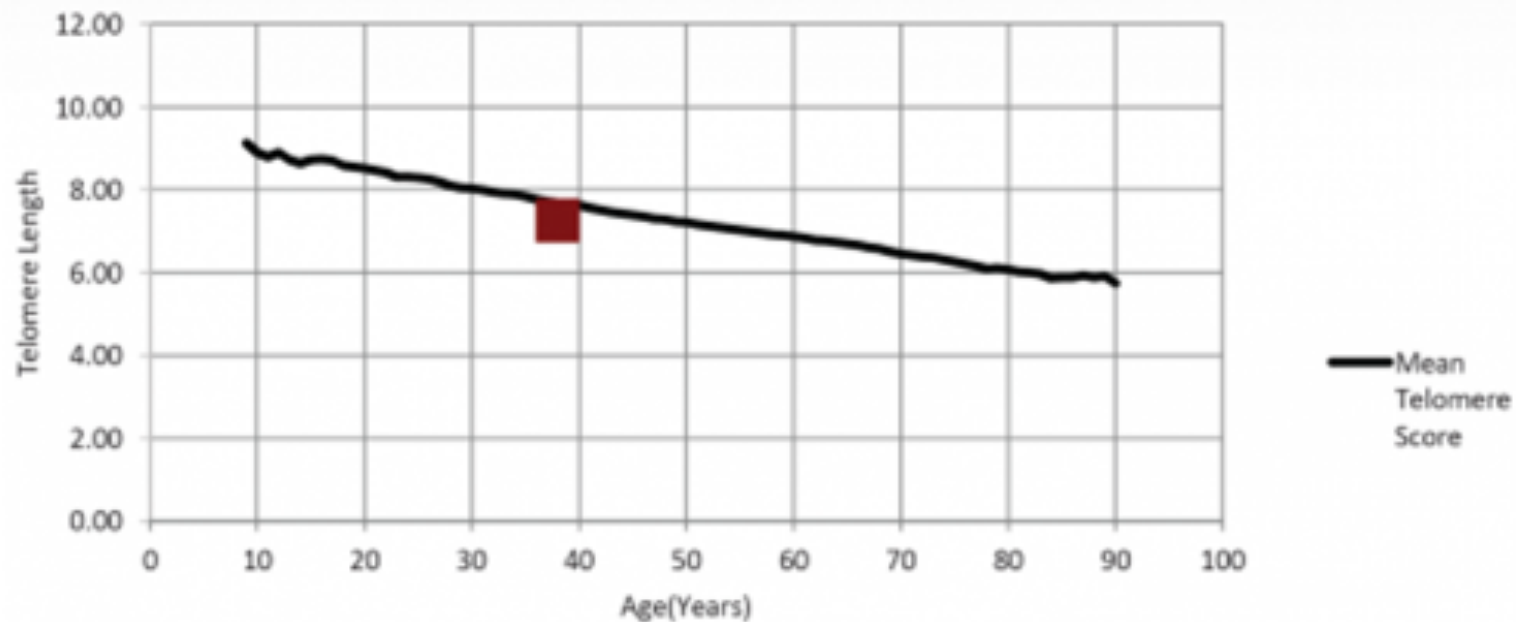
and newly added additional markers of functional digestive status:

- Calprotectin
- Pancreatic elastase 1
- Bile acids
- Cholic acid
- Chenodeoxycholic acid
- Deoxycholic acid
- Lithocholic acid
- Acetic acid
- Butyric acid
- Propionic acid
- Valeric acid
- Total SCFAs
- β -glucuronidase

How old are you?



Telomere Test Results



Sirtuins, AMPK, FOXO, mTOR

Oxid Med Cell Longev. 2017;2017:1750308. doi: 10.1155/2017/1750308. Epub 2017 Nov 8.

Regulation of Sirtuin-Mediated Protein Deacetylation by Cardioprotective Phytochemicals.

Treviño-Saldaña N¹, García-Rivas G^{1,2}.

Abstract

Modulation of posttranslational modifications (PTMs), such as protein acetylation, is considered a novel therapeutic strategy to combat the development and progression of cardiovascular diseases. Protein hyperacetylation is associated with the development of numerous cardiovascular diseases, including atherosclerosis, hypertension, cardiac hypertrophy, and heart failure. In addition, decreased expression and activity of the deacetylases Sirt1, Sirt3, and Sirt6 have been linked to the development and progression of cardiac dysfunction. Several phytochemicals exert cardioprotective effects by regulating protein acetylation levels. These effects are mainly exerted via activation of Sirt1 and Sirt3 and inhibition of acetyltransferases. Numerous studies support a cardioprotective role for sirtuin activators (e.g., resveratrol), as well as other emerging modulators of protein acetylation, including curcumin, honokiol, oroxilyn A, quercetin, epigallocatechin-3-gallate, bakuchiol, tyrosol, and berberine. Studies also point to a cardioprotective role for various nonaromatic molecules, such as docosahexaenoic acid, alpha-lipoic acid, sulforaphane, and caffeic acid ethanamide. Here, we review the vast evidence from the bench to the clinical setting for the potential cardioprotective roles of various phytochemicals in the modulation of sirtuin-mediated deacetylation.

AMPK activation--protean potential for boosting healthspan.

McCarty ME¹.

 Author information

Abstract

AMP-activated kinase (AMPK) is activated when the cellular (AMP+ADP)/ATP ratio rises; it therefore serves as a detector of cellular "fuel deficiency." AMPK activation is suspected to mediate some of the health-protective effects of long-term calorie restriction. Several drugs and nutraceuticals which slightly and safely impede the efficiency of mitochondrial ATP generation--most notably metformin and berberine--can be employed as clinical AMPK activators and, hence, may have potential as calorie restriction mimetics for extending healthspan. Indeed, current evidence indicates that AMPK activators may reduce risk for atherosclerosis, heart attack, and stroke; help to prevent ventricular hypertrophy and manage congestive failure; ameliorate metabolic syndrome, reduce risk for type 2 diabetes, and aid glycemic control in diabetics; reduce risk for weight gain; decrease risk for a number of common cancers while improving prognosis in cancer therapy; decrease risk for dementia and possibly other neurodegenerative disorders; help to preserve the proper structure of bone and cartilage; and possibly aid in the prevention and control of autoimmunity. While metformin and berberine appear to have the greatest utility as clinical AMPK activators--as reflected by their efficacy in diabetes management--regular ingestion of vinegar, as well as moderate alcohol consumption, may also achieve a modest degree of health-protective AMPK activation. The activation of AMPK achievable with any of these measures may be potentiated by clinical doses of the drug salicylate, which can bind to AMPK and activate it allosterically.

Curcumin supplementation increases survival and lifespan in *Drosophila* under heat stress conditions.

Chen Y¹, Liu X¹, Jiang C¹, Liu L², Ordovas JM^{3,4}, Lai CQ⁵, Shen L¹.

Author information

Abstract

Harsh climate induces physiological stress thus compromising organismal survival. Our previous studies demonstrated that curcumin (CUR) supplementation increased survival of turtle under heat stress (HS). Here, we span this work to investigate the survival and lifespan of HS *Drosophila* fed a diet supplemented with CUR. For this purpose, female and male flies were fed basal diet (N) and CUR diet (0.2 mg/g), and exposed to three conditions: 25°C and 29°C continuously, and 34 °C for 2 h at days 1, 4, and 7, then kept at 25 °C. Lifespan analysis showed that, compared to N-25 °C flies, the mean lifespans of N-29 °C and N-34 °C flies were decreased significantly by 8.5-15.7% in males, and 3.7-7.9% in females. Conversely, in the CUR-supplemented diet, mean lifespans of C-29 °C and C-34 °C flies were significantly extended by 8.7-16.4% in males, and by 8.9-12.8% in females, compared to that of temperature-matched flies fed basal diets. The MDA levels of C-34 °C flies were significantly lower than those of N-34 °C flies, indicating CUR reduced oxidative stress caused by HS. Furthermore, CUR palliated the increased oxidative stress caused by HS, by increasing the expression of SOD1, CAT, and PHGPx and decreasing the expression of Hsp70 and Hsp83. Our results indicated that CUR supplementation increases the survival rate of *Drosophila* by enhancing thermal tolerance.



Supplement Facts

Serving Size: 2 capsules

Servings Per Container: 30

	Amount Per Serving
Berberine (from berberine HCl)	500 mg*
Silymarin (from Milk Thistle seed extract)	200 mg*
Green Tea leaf extract (50% EGCG)(low caffeine)	125 mg*
Curcumin (Curcuma longa root extract, emulsified†)	100 mg*
Resveratrol (fermented)	50 mg*
Ginger root	50 mg*

* Daily Value not established

Other ingredients:

Capsule shell (gelatin and water), medium chain triglycerides and silica.

Cardiac Longevity Plan - Let's Do This Together

60 minute office visit

Recorded laboratory review call

2 health coaching visits

\$200 testing credit

CIMT study

~~\$3200~~

\$2497



Ultimate Longevity Tests

<https://www.wolfsonintegrativecardiology.com/free-health-coaching/>

Wheat Zoomer- Leaky gut

Environmental toxins

Gut Zoomer

Genetic testing

Neural Zoomer

CV analysis

Toxic Metals

Micronutrient

Mold mycotoxins

Nine cellular and molecular hallmarks of aging:

Genomic instability

Mitochondrial dysfunction

Telomere attrition

Cellular senescence

Epigenetic alterations

Stem cell exhaustion

Loss of proteostasis

Altered intercellular communication

Deregulated nutrient sensing