

How Not to Age

Michael Greger, M.D. FACLM

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Research on the basic biology of aging aims to understand the mechanisms that cause organisms to decline in function over time and lead to increasing risk of morbidity and mortality.⁶¹ This is, of course, intimately connected to pathology because aging promotes disease. Most leading causes of mortality in developed nations share a single greatest risk factor, and it isn't how much you eat, drink, smoke, or exercise; it's how old you are.³⁹ Diabetes, heart disease, kidney disease, stroke, Alzheimer disease, Parkinson disease, and most forms of cancer, along with several other diseases, all show an exponential increase in risk with age over much of the human life span (Figs. 1, 2).

Understanding why this relationship between age and

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Kaeberlein M. The biology of aging: citizen scientists and their pets as a bridge between research on model organisms and human subjects. *Vet Pathol.* 2016;53(2):291-298.

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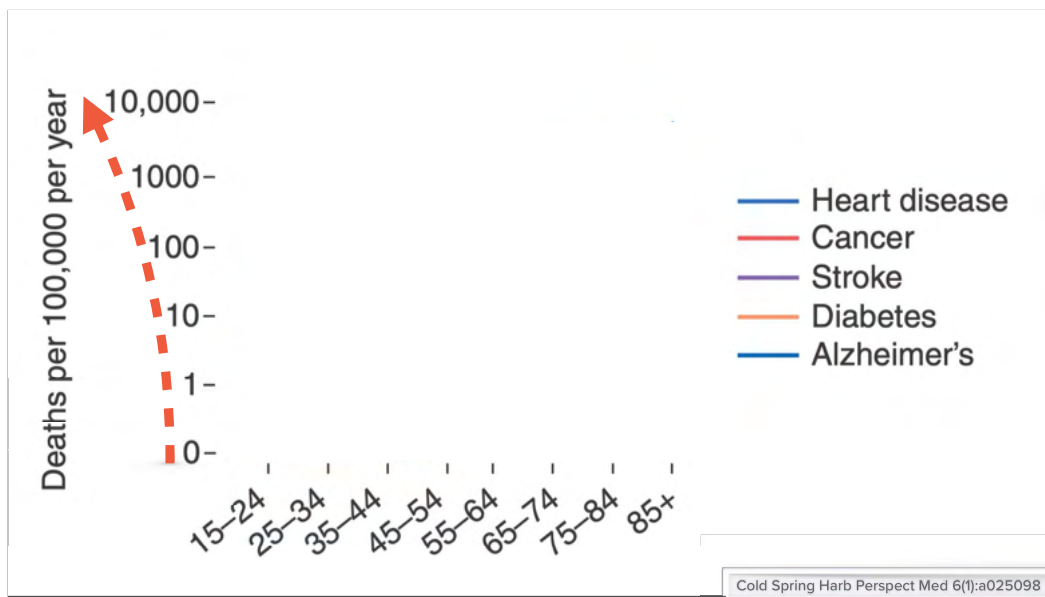
Understanding why this relationship between age and

that lives, ages, and then dies. Although they may appear similar, the two concepts differ in one important regard – the rate of death. The latter depicts a mortality rate that increases with age, while the former depicts one in which death can occur with equal probability at any age (Fig. 1). Empirically, we know that death is much more likely at advanced age (and intuitively we all know that our grandparents are more likely to die than our parents). And though it may seem strange to say, old age is the single greatest risk factor for death.

While today we take it for granted that this biological phenomenon which we call aging, is amenable to scientific study, just thirty years ago this question itself was hotly debated. Pre-existing theories based on evolutionary biology painted a gloomy picture for the early scientists that attempted to develop this nascent field.

Evolutionary theory attributed aging to the concomitant breakdown of multiple biological systems due to the declining investment in repair and maintenance of these systems over the life span.

Exp Gerontol 104:35-42



Cold Spring Harb Perspect Med 6(1):a025098

Circulation

AHA STATISTICAL UPDATE

Heart Disease and Stroke Statistics—2022
Update: A Report From the American Heart
Association

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Mechanisms of Ageing and Development

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The impact of nutrients on the aging rate: A complex interaction of demographic, environmental and genetic factors



Serena Dato, Dina Bellizzi, Giuseppina Rose, Giuseppe Passarino*

Department of Ecology, Biology and Earth Sciences, Ponte Pietro Bucci cubo 4C, 87036 Rende, CS, Italy

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REVIEW

Interventions to Slow Aging in Humans: Are We Ready?

Valter D. Longo,^{1,2} Adam Antebi,³ Andrzej Bartke,⁴ Nir Barzilai,⁵ Holly M. Brown-Borg,⁶ Calogero Caruso,⁷ Tyler J. Curiel,⁸ Rafael de Cabo,⁹ Claudio Franceschi,¹⁰ David Gems,¹¹ Donald K. Ingram,¹² Thomas E. Johnson,¹³ Brian K. Kennedy,¹⁴ Cynthia Kenyon,¹⁵ Samuel Klein,¹⁶ John J. Kopchick,¹⁷ Guenter Lepperdinger,¹⁸ Frank Madeo,^{19,20} Mario G. Mirisola,²¹ James R. Mitchell,²² Giuseppe Passarino,²³ Karl L. Rudolph,²⁴ John M. Sedivy,²⁵ Gerald S. Shadel,^{26,27} David A. Sinclair,^{28,29} Stephen R. Spindler,³⁰ Younsin Suh,^{31,32,33} Jan Vijg,³⁴ Manlio Vinciguerra³⁵ and Luigi Fontana^{36,37,38}

¹Davis School of Gerontology and Department of Biological Sciences, Longevity Institute, University of Southern California, Los Angeles, CA 90089, USA

²IFOM, FIRC Institute of Molecular Oncology, Via Adamello 16, 20139, Milano, Italy

³Max Planck Institute for Biology of Ageing, Joseph Stelzmann Strasse 9b, 50931, Koeln, Germany

⁴Department of Internal Medicine, Southern Illinois University-School of Medicine, Springfield, IL 62794, USA

²³Department of Biology, Ecology and Earth Science, University of Calabria, 87036, Rende, Italy

²⁴Leibniz Institute for Age Research, Fritz Lipmann Institute, D-07745, Jena, Germany

²⁵Laboratories for Molecular Medicine, Department of Molecular Biology, Cell Biology and Biochemistry, Brown University, 70 Ship Street, Providence, RI 02903, USA

²⁶Department of Pathology, Yale University School of Medicine, New Haven, CT 06520, USA

²⁷Department of Genetics, Yale University School of Medicine, New Haven, CT 06520, USA

²⁸Laboratory for Ageing Research, Department of Pharmacology, School of Medical Sciences, UNSW Australia, Sydney, NSW, Australia

²⁹Australia Glenn Labs for the Biological Mechanisms of Aging, Department of Genetics, Harvard Medical School, Boston, MA, Australia

³⁰Department of Biochemistry, University of California at Riverside, Riverside, CA, USA

³¹Department of Genetics, Albert Einstein College of Medicine, Bronx, NY, USA

³²Department of Medicine, Diabetes Research and Training Center, Albert Einstein College of Medicine, Bronx, NY, USA

³³Institute for Aging Research, Diabetes Research and Training Center, Albert Einstein College of Medicine, Bronx, NY, USA



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³¹Department of Genetics, Albert Einstein College of Medicine, Bronx, NY, USA

³²Department of Medicine, Diabetes Research and Training Center, Albert Einstein College of Medicine, Bronx, NY, USA

³³Institute for Aging Research, Diabetes Research and Training Center, Albert Einstein College of Medicine, Bronx, NY, USA

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Summary

The workshop entitled 'Interventions to Slow Aging in Humans: Are We Ready?' was held in Erice, Italy, on October 8–13, 2013, to bring together leading experts in the biology and genetics of aging and obtain a consensus related to the discovery and development of safe interventions to slow aging and increase healthy lifespan in humans. There was consensus that there is sufficient evidence that aging interventions will delay and prevent disease onset for many chronic conditions of adult and old age. Essential pathways have been identified, and behavioral, dietary, and pharmacologic approaches have emerged. Although many gene targets and drugs were discussed and there was not complete consensus about all interventions, the participants selected a subset of the most promising strategies that could be tested in humans for their

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... targets will continue to emerge as research progresses; and (iv) it is now necessary to cautiously proceed to test these interventions in humans.

Based on a vote taken on the last day of the workshop, the strategies believed to be most promising by the panel of invited experts and authors of this manuscript are as follows:

- 1 Pharmacological inhibition of the GH/IGF-1 axis
- 2 Protein restriction and Fasting Mimicking Diets
- 3 Pharmacological inhibition of the TOR -S6K pathway
- 4 Pharmacological regulation of certain sirtuin proteins and the use of spermidine and other epigenetic modulators
- 5 Pharmacological inhibition of inflammation
- 6 Chronic metformin use

These choices were based in part on: (i) consistent evidence for their pro-longevity effects in simple model organisms and rodents; (ii) evidence for their ability to prevent or delay multiple age-related

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ture of cells. The hallmark of aging is the shortening of telomeres.¹ Telomeres shorten because of various factors such as cell division, oxidative stress, and defective DNA damage response proteins.² The unspoiled maintenance of protein homeostasis is critical to sustaining the function and structure of the cell. At any given point in time, mammalian cells synthesize and assemble more than 10 000 functionally and structurally different proteins. As proteins are sensitive, fragile, and at risk of misfolding, protecting them in various conditions is a challenging task.³ Three major mechanisms are involved in maintaining protein homeostasis: the molecular chaperones, the proteasome proteolytic system, and the lysosome autophagy proteolytic system.^{3,4} Mechanisms that promote proteome homeostasis can be helpful in slowing down the aging

Cell Biochem Funct 37(6):452-8

With this finding, exacerbated oxidative damage has been implicated in the upregulation of sterol-regulatory-element-binding protein 1 (SREBP) and fatty acid synthase (FAS)-dependent lipogenic pathways, thereby worsening the obese condition [32].

Of note, it is plausible to speculate that ROS over production tied to obesity represents one of the major risk factors for the development of numerous obesity-related diseases such as diabetes, systemic arterial hypertension, ischemic heart diseases, liver failure or asthma.

3. Autophagy, between Obesity and Oxidative stress

3.1. Mechanism and Main Functions of Autophagy

Autophagy, a term acquired from the Greek words “auto (self)” and “phagein (to eat)”, literally meaning “self-eating”, refers to an evolutionary conserved catabolic mechanism that allows cells to remove their own unnecessary or dysfunctional components [33]. This tightly regulated process underlies the sequestration of intracellular entities within double-membraned vesicles (called autophagosomes) and their incorporation into lysosomes for final degradation [34]. Autophagy can be classified into different subtypes, according to the modality of cargo delivery to the lysosome: macroautophagy (the main regulated form of autophagy that responds to environmental and physiological signals), microautophagy (i.e., the direct absorption of cytoplasmic contents by lysosomes), and chaperone-mediated autophagy (CMA; chaperone-assisted translocation of substrate proteins into the lyso-

It is worthy to note that macroautophagy (henceforth referred to as autophagy) further classified based on the material that is to be degraded [12] is non-selective

dysfunctional proteins, which is detrimental to cells and affects organismal metabolism [1]. Proteostasis is supported by autophagy, a conserved machinery that helps to eliminate dysfunctional proteins and cellular organelles via lysosomal degradation. The rejuvenating power of cleaning up garbage and replacing it with recycled and newly synthesized cellular components speaks to the imagination and is an attractive explanation for the positive correlation between autophagy and lifespan. This connection is highly conserved and well reflected by research utilizing model organisms that confirms the positive impact of increased autophagy on aging in yeast, worms, flies, zebrafish, and mice. The life expanding potenti

Aging 12(22): 22350-1

Lysosomes Mediate Benefits of Intermittent Fasting in Cardiometabolic Disease: The Janitor Is the Undercover Boss

Kartik Mani,^{1,2} Ali Javaheri,² and Abhinav Diwan^{*2,3}

ABSTRACT

Adaptive responses that counter starvation have evolved over millennia to permit organismal survival, including changes at the level of individual organelles, cells, tissues, and organ systems. In the past century, a shift has occurred away from disease caused by insufficient nutrient supply toward overnutrition, leading to obesity and diabetes, atherosclerosis, and cardiometabolic disease. The burden of these diseases has spurred interest in fasting strategies that harness physiological responses to starvation, thus limiting tissue injury during metabolic stress. Insights gained from animal and human studies suggest that intermittent fasting and chronic caloric restriction extend lifespan, decrease risk factors for cardiometabolic and inflammatory disease, limit tissue injury during myocardial stress, and activate a cardioprotective metabolic program. Acute fasting activates autophagy, an intricately orchestrated lysosomal degradative process that sequesters cellular constituents for degradation, and is critical for cardiac homeostasis during fasting. Lysosomes are dynamic cellular organelles that function as incinerators to permit autophagy, as well as degradation of extracellular material internalized by endocytosis, macropinocytosis, and phagocytosis.

Self-Digestion for Lifespan Extension: Enhanced Autophagy Delays Aging

Michael D. Arensman¹ and Christina H. Eng^{1,*}

¹Oncology Research & Development, Pfizer, Pearl River, NY 10965, USA

*Correspondence: christina.eng@pfizer.com

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By systemically boosting autophagy with a knockin mutation that prevents binding of beclin 1 to BCL2, Fernández et al. (2018) demonstrate that enhanced autophagy prolongs lifespan in mammals.

Autophagy, a term coined by Christian de Duve and derived from the Greek meaning of "to eat self," orchestrates the delivery of cytosolic components to the lysosome for degradation and subsequent recycling. This process enables cells to survive during periods of nutrient deprivation by mobilizing endogenous macro-

to assess the impact of whole-body loss of critical autophagy genes on lifespan in mammals, as loss of such genes results in embryonic or neonatal lethality. Autophagy generally declines with age, and this decline can be circumvented by caloric restriction and rapamycin. Although these treatments prolong life-

observed along with improvements in metabolic outcomes such as insulin sensitivity (Pyo et al., 2013). The improvement in metabolic phenotypes was accompanied by body weight reduction in the Atg5 transgenic mice. As F121A BECN1 mice also appeared leaner (Fernández et al., 2018), it would be inter-

been shown to be necessary for maintenance of cellular homeostasis, clearance of damaged intracellular components, for cellular processes involving major cellular remodeling (such as development or differentiation), and as part of both innate and acquired immunity, because it contributes to the defense against intracellular and extracellular insults, including common pathogens (2).

A decrease in autophagy with age has been described in almost all organisms and tissues analyzed (7,8). Although the reasons for this functional decline still remain elusive, alterations with age, both in particular autophagy effectors and in the signaling mechanisms that usually modulate this process, have been described (8). Based on the plethora of cellular functions in which autophagy participates, it is easy to infer that a gradual decrease in autophagic activity

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neurodegenerative diseases are known to be caused by or correlated with mutations and dysregulation of ATG proteins, selective autophagy, and their receptors (reviewed in Deng et al. 2017; Menzies et al. 2017). To circumvent such diseases of aging, efforts to pharmacologically modulate autophagy are at the forefront of multiple research programs in academia and the pharmaceutical industry (reviewed in Galluzzi et al. 2017b). In this review, we highlight the latest links between autophagy and metabolism, the recent elucidation of transcriptional regulatory mechanisms governing autophagy and the emerging evidence of the impact of

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In answer to your question I do not think that the small amount of leucine present in your stevia preparation is sufficient to interfere with autophagy. There is already a substantial amount of leucine present in blood and cells in your body, and the small amount of leucine in the stevia will not have much of an effect. Another comment is that 5 days of fasting is too long for activating autophagy. The greatest acceleration of autophagy takes place after 24–48 h of fasting. During prolonged fasting autophagy declines again because proteins, many of which are enzymes essential for survival of the cells in our body, need to be spared. The brain, which normally uses glucose as a fuel in the fed state, obtains glucose from glycogen during the first period of fasting; this is followed by glucose produced from amino acids (derived from

Autophagy 15(12):2043

protecting cells from DNA damage, suppressing cell growth, and enhancing apoptosis of damaged cells, fasting could retard and/or prevent the formation and growth of cancers.

However, studies of fasting regimens have not been performed in children, the very old, and underweight individuals, and it is possible that IF and PF would be harmful to these populations. Fasting periods lasting longer than 24 hr, and particularly those lasting 3 or more days, should be done under the supervision of a physician and preferably in a clinic. IF- and PF-based approaches toward combating the current epidemics of overweight, diabetes, and related diseases should be pursued in human research studies and medical treatment plans. Several variations of potential “fasting prescriptions” that have been adopted for overweight subjects revolve around the common theme of abstaining from food and caloric beverages for a

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may be due in part to increased sensitivity to the drug (Feibush, 1959). We found, however, that blood levels in patients aged 60 and over with controlled atrial fibrillation were closely similar to the levels in younger patients (Fig. 4). The blood levels in the older age group were attained with a smaller mean dose, and the blood urea of these patients tended to be higher than those found in the under-60 group. This observation is consistent with the findings of Ewy,

Marcus, F. L., Burkhalter, L., Cuccia, C., Pavlovich, J., and Kapadia, G. G. (1966). *Circulation*, **34**, 865.
Marcus, F. L., Kapadia, G. I., and Kapadia, G. G. (1964). *Journal of Pharmacology and Experimental Therapeutics*, **145**, 203.
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Smith, T. W., Butler, V. P., and Haber, E. (1970). *Biochemistry (Washington)*, **9**, 331.
Soffer, A. (1961). *Archives of Internal Medicine*, **107**, 681.

Prolonged Starvation—A Dangerous Procedure?

J. RUNCIE,* M.B., CH.B., M.R.C.P.GLASG. ; T. J. THOMSON,† M.B., CH.B., F.R.C.P.(LOND., GLASG.)

British Medical Journal, 1970, **3**, 432-435

Summary: Experience with 18 obese patients who have undergone prolonged (60 days) therapeutic starvation shows that in general this is a safe procedure, but there are significant associated hazards, particularly a breakdown in electrolyte homeostasis. The need for close biochemical control of such patients is stressed.

Introduction

Spencer (1968) reported the deaths of two patients while they were undergoing therapeutic starvation. Garnett *et al.* (1969) reported the death of a young woman on the seventh day of

* Lecturer in Materia Medica, University of Glasgow, at Stobhill General Hospital, Glasgow N.1.
† Consultant Physician, Stobhill General Hospital, Glasgow N.1.

refeeding following a fast of 30 weeks. At necropsy fragmentation of the cardiac myofibrils was found. This led them to stigmatize therapeutic starvation as an unsafe procedure. These reports have stimulated us to review our experience in particular the possible hazard to the patient during therapeutic starvation. We also wish to describe some side-effects of fasting which, to our knowledge, have not previously been reported.

Probably the incidence of any hazard due to therapeutic starvation will rise with increasing length of fast of patients. In this context we have arbitrarily defined prolonged starvation as for a minimum period of 60 days. To date, in this series, 18 patients have undergone periods of fasting of at least 60 days. The details of these patients—length of fast and weight loss—are shown in the Table.

The association between the hyperuricaemia of fasting and acute gout is well known. This has led some workers to use uricosuric or other antigout agents routinely in fasting patients (Gilliland, 1968). In our view this is unnecessary (Runcie and Thomson, 1969). It is potentially dangerous in that such drugs may impair or abnormally stress the renal adaptive response to fasting. Cases 5 and 9 show a hitherto unrecognized hazard of fasting—namely, that the renal response to starvation—that is, electrolyte conservation—may break down. Unless urinary sodium excretion is being measured routinely the significance of such non-specific symptoms as dizziness, weakness, and lethargy may be misinterpreted and a dangerous degree of sodium depletion allowed to develop.

All the patients who have died during or in association with therapeutic starvation (Spencer, 1968; Garnett *et al.*, 1969) have manifested abnormalities of the extracellular fluid

Exercise induces autophagy in peripheral tissues and in the brain

Congcong He,¹ Rhea Sumpter, Jr.² and Beth Levine^{3,*}

¹Howard Hughes Medical Institute; Department of Internal Medicine; Center for Autophagy Research; University of Texas Southwestern Medical Center; Dallas, TX USA; ²Department of Internal Medicine; Center for Autophagy Research; University of Texas Southwestern Medical Center; Dallas, TX USA; ³Howard Hughes Medical Institute; Departments of Internal Medicine and Microbiology; Center for Autophagy Research; University of Texas Southwestern Medical Center; Dallas, TX USA

We recently identified physical exercise as a newly defined inducer of autophagy *in vivo*. Exercise induced autophagy in multiple organs involved in metabolic regulation, such as muscle, liver, pancreas and adipose tissue. To study the physiological role of exercise-induced autophagy, we generated mice with a knock-in nonphosphorylatable mutation in BCL2 (Thr69Ala, Ser70Ala and Ser84Ala) (BCL2 AAA) that are defective in exercise- and starvation-induced autophagy but not in basal autophagy. We found that BCL2 AAA mice

has numerous health benefits, such as lifespan expansion, and protection against cardiovascular diseases, diabetes, cancer and neurodegenerative diseases.¹ Many of these health benefits overlap with known protective functions of the cellular pathway of macroautophagy (herein referred to as autophagy).^{2,3} Thus, we proposed that some of the health benefits of exercise may be due to autophagy activation.

To test this hypothesis, we exercised wild-type mice that transgenically express the fluorescent autophagy marker GFP-LC3⁴ on a treadmill, using a running

AUTOPHAGY

Explaining Exercise

Cellular "self-eating" may account for some benefits of exercise

Few would contest that exercise is a healthy habit. It strengthens muscles, keeps weight down, and, population studies suggest, protects against diabetes, cancer, and Alzheimer's disease. Still, the mechanisms behind exercise's many benefits remain murky.

Beth Levine of the University of Texas Southwestern Medical Center in Dallas had a hunch that her research interest might help solve the mystery of exercise. Since 1998, Levine has studied autophagy, the "self-eating" process by which cells recycle used or flawed organelles, membranes, and other internal structures. She has largely focused on its role in cancer and infectious

Science 335:281 but elevated autophagy last in animal models,

maintain a background level of autophagy, then boost it under stress.

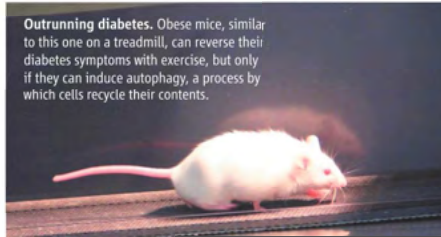
Exercise is one such stress, Levine found. Running mice for short periods on a treadmill sharply elevated autophagy in many organs, her group reports. The Italian group documented a similar effect in skeletal muscle of

Levine fattened normal mice and the autophagy mutants, which gave both groups a form of diabetes, then put them through 2 months of daily treadmill workouts. Only the normal were able to reverse their diabetes through physical training. Such exercise also brought down elevated cholesterol and triglyceride levels in these mice, but not in the autophagy-impaired mice. Autophagy may also be required to produce the lasting beneficial effects of exercise in diabetes, Levine concludes.

How do exercise and autophagy cooperate? Levine found that, after short-term exercise, normal mice activate in muscle the enzyme AMP-activated protein kinase (AMPK) but the autophagy-defective rodents don't. AMPK reprograms cells to boost energy production, and its induction by autophagy, Levine says, could explain how exercise training reverses diabetes.

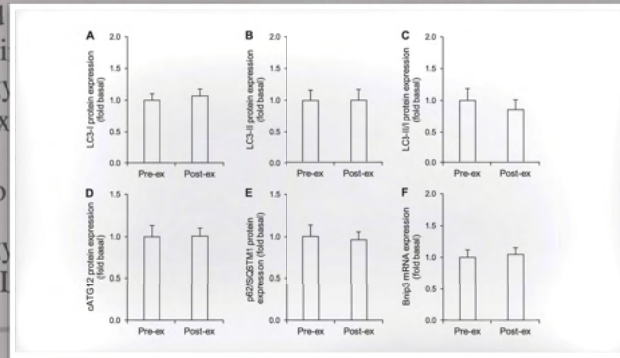
Exercise training also causes lasting adaptations in muscle,

Outrunning diabetes. Obese mice, similar to this one on a treadmill, can reverse their diabetes symptoms with exercise, but only if they can induce autophagy, a process by which cells recycle their contents.



during a 36-h fast, and 2) during continuous glucose infusion at 0.2 kg/h. Physical exercise increased ULK1 phosphorylation at Ser⁵⁵⁵ and decreased lipidation of light chain 3B. ULK1 phosphorylation at Ser⁵⁵⁵ correlated positively with AMP-activated protein kinase- α Thr¹⁷² phosphorylation and negatively with light chain 3B lipidation. ULK1 phosphorylation at Ser⁷⁵⁷ was not affected by exercise. Fasting

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FASEB J 28(2):1022-34

Masschelein E, Van Thienen R, D'Hulst G, Hespel P, Thomis M, Deldicque L. Acute environmental hypoxia induces LC3 lipidation in a genotype-dependent manner. FASEB J 28(2):1022-34



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Ecotoxicology and Environmental Safety

journal homepage: www.elsevier.com/locate/ecoenv



Research Paper

Acrylamide inhibits autophagy, induces apoptosis and alters cellular metabolic profiles

Dan Song^{a,d}, Chao Xu^a, Askild L. Holck^e, Rong Liu^{a,b,c,*}

^a College of Food Science and Technology, Nanjing Agricultural University, Nanjing, China

^b National center for international research on animal gut nutrition, Nanjing, China

^c Jiangsu collaborative innovation center of meat production and processing, Nanjing, China

^d College of Animal Science and Technology, Zhejiang Agriculture and Forestry University, Hangzhou, China

^e Norwegian Institute of Food, Fisheries and Aquaculture Research (NOFIMA), P.O. Box 210, N-1431 Aas, Norway

ARTICLE INFO

Edited by: Dr. Caterina Faggio

Keywords:

ABSTRACT

Acrylamide (ACR) is generated during thermal processing of carbohydrate-rich foods at high temperature and can directly enter the body through ingestion, inhalation and skin contact. The toxicity of ACR has been widely studied. The main results of these studies show that exposure to ACR can cause neurotoxicity in both animals and



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Nutrition

journal homepage: www.nutritionjrn.com



Editorial

Fried potato chips and French fries—Are they safe to eat?

The impact of contaminants on food quality and safety throughout the human food chain, from raw to cooked and processed foods, is an area of growing concern. Recently, Palazoglu et al. showed that the acrylamide content of fried potato chips prepared by heating increases dangerously with frying temperature [1]. Acrylamide has several harmful health effects including neurotoxicity, reproductive toxicity, carcinogenicity, genotoxicity, and mutagenicity [2–4]. It is used in the production of

the diet, drugs, or infections. It is widely known that perinatal brain injury remains one of the common complications causing developmental disabilities, neurocognitive delay, and lifelong handicaps [7] in functions such as general activity, fine and gross motor skills, cognitive function, language, reasoning and memory, concentration, attention, and school performance [8]. As the neuropathologic correlations with these observations are still missing, the study of El-Sayyad et al. in the current issue



Contents lists available at [ScienceDirect](#)

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol



Associations of hemoglobin biomarker levels of acrylamide and all-cause and cardiovascular disease mortality among U.S. adults: National Health and Nutrition Examination Survey 2003–2006[☆]

Mengmeng Huang^a, Jingjing Jiao^b, Jun Wang^a, Xinyu Chen^a, Yu Zhang^{a,*}

^a National Engineering Laboratory of Intelligent Food Technology and Equipment, Zhejiang Key Laboratory for Agro-Food Processing, Fuli Institute of Food Science, College of Biosystems Engineering and Food Science, Zhejiang University, Hangzhou, Zhejiang, China

^b Department of Nutrition and Food Hygiene, School of Public Health, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

ARTICLE INFO

Article history:

Received 6 August 2017

ABSTRACT

Background: The potential hazards of acrylamide (AA) have been proposed due to its lifelong exposure.

Chronic intake of potato chips in humans increases the production of reactive oxygen radicals by leukocytes and increases plasma C-reactive protein: a pilot study¹⁻³

Marek Naruszewicz, Danuta Zapolska-Downar, Anita Kosmider, Grażyna Nowicka, Małgorzata Kozłowska-Wojciechowska, Anna S Vikström, and Margareta Törnqvist

ABSTRACT

Background: Relatively high concentrations of acrylamide in commonly ingested food products, such as French fries, potato chips, or cereals, may constitute a potential risk to human health.

Objective: The objective of this pilot study was to investigate the possible connection between chronic ingestion of acrylamide-containing potato chips and oxidative stress or inflammation.

Design: Fourteen healthy volunteers (mean age: 35 y; 8 women and 6 smokers of >20 cigarettes/d) were given 160 g of potato chips containing 157 mg acrylamide daily for 4 wk

reported that acrylamide could be formed in various heat-treated, carbohydrate-rich foods (3, 4). A particularly high concentration of acrylamide was found in potato chips, breakfast cereals, and crisp bread (5). It has been shown that acrylamide content in food results from heat-induced reactions between the amino group of the free amino acid asparagine and the carbonyl group of a reducing sugar (6). In humans, acrylamide is absorbed mainly via ingestion or inhalation and forms adducts with hemoglobin, which appear to be useful biomarkers of acrylamide

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Am J Clin Nutr 89:773-7

containing 100 µg acrylamide daily for 4 wk

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elevated CRP concentrations >5 mg/L at baseline and a body mass index (BMI; in kg/m²) >25 were also excluded.

The study period was divided into 3 phases. In the first 2 wk, all study subjects were required to ingest 400 g of boiled potatoes daily with amounts of fat [a mixture of liquid and hardened vegetable

(POV) < 1.0 mg/kg of potato chips corresponding to the amount of fat ingested

Variables	Before consumption	28 d after consumption
hs CRP (mg/L)	1.53 ± 0.75	2.39 ± 0.78 ²

² P < 0.01

batch purchased from a shop. The potato chips contained 878 kcal, of which 4.3% was energy from protein, 65.6% was energy from fat with a polyunsaturated/saturated fatty acid ratio of 0.51, and 30.1% was energy from carbohydrates, together with 1374 sodium and 5 mg of vitamin E. The acrylamide content

were found after intake of potato chips. Twenty-eight days from the discontinuation of the experiment, the variables under study decreased to some extent. It has been shown also that acrylamide increases the production of reactive oxygen species in isolated human monocyte-macrophages in vitro and decreases the cellular glutathione concentration.

Conclusion: These novel findings seem to indicate that chronic ingestion of acrylamide-containing products induces a proinflammatory state, a risk factor for progression of atherosclerosis. *Am J Clin Nutr* 2009;89:773–7.

DISCUSSION

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Further investigations on the effect of frying time on the generation of the toxicologically relevant acrylamide and glycidamide showed that a prolonged frying time resulted in a much higher generation of both analytes in chips (Table 9).

Lowering the Frying Temperature: A Suitable Tool for a Better Product? As shown in the present study, deep-frying of potatoes led to the formation of the desired typical aroma expected by the consumers but also to the formation of undesired food-borne toxicants. Thus, adapting the frying conditions toward minimizing the generation of toxicologically relevant compounds (as acrylamide) and, simultaneously, maintaining the sensory properties of the fried food is a challenge, but it would improve its quality and safety and lead to an increased acceptance by consumers.

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LONDON:
SCIATICA AND OTHER NEURALGIC AFFECTIONS,
AND CERTAIN FORMS OF PARALYSIS.

BY

GEORGE E. DAY, M.D.

FELLOW OF THE ROYAL COLLEGE OF PHYSICIANS, AND PHYSICIAN
TO THE WESTERN GENERAL DISPENSARY.

*The reasons why Persons in this age fall so soon into this decrepit state, and why the
miseries thereof are so multiplied and magnified upon them, is, because either they call not
to soon enough for help, or because those that are called in either understand not, or misde-
not what they ought to do. An honest and an able Physician may easily approve himself
to his ancient Patient a restorer of life and nourisher of old age."*

King Solomon's Description of Old Age.

LONDON :

T. AND W. BOONE, 29, NEW BOND STREET.

1849.

Effect of Pretreatments and Air-Frying, a Novel Technology, on Acrylamide Generation in Fried Potatoes

M. Sansano, M. Juan-Borrás, I. Escriche, A. Andrés, and A. Heredia

Abstract: This paper investigated the effect of air-frying technology, in combination with a pretreatment based of soaking the samples in different chemical agent solutions (citric acid, glycine, calcium lactate, sodium chloride, or nicotinic acid [vitamin B3]), on the generation of acrylamide in fried potatoes. The influence of reducing sugars on the development of surface's color was also analyzed. The experiments were conducted at 180 °C by means of air-frying and deep-oil-frying, as a reference technology. Based on the evolution of color crust with frying time, it could be concluded that the rate of Maillard reaction decreased as the initial reducing sugars content increased in the raw material, and was also lower for deep-oil-frying than for air-frying regardless of pretreatments applied. Air-frying reduced acrylamide content by about 90% compared with conventional deep-oil-frying without being necessary the application of a pretreatment. However, deep-oil fried potatoes pretreated with solutions of nicotinic acid, citric acid, glycine at 1%, and NaCl at 2% presented much lower acrylamide levels (up to 80% to 90% reduction) than nonpretreated samples.

Keywords: acrylamide, air-frying, additives, color, reducing sugars

Introduction

in the fried product (Pedreschi and others 2005). Some alterna-

Sansano M, Juan-Borrás M, Escriche I, Andrés A, Heredia A. Effect of pretreatments and air-frying, a novel technology, on acrylamide generation in fried potatoes: acrylamide generation in air-frying.... Journal of Food Science. 2015;80(5):T1120-T1128.

tamine stretch of huntingtin display elevated autophagy levels in the brain that were coupled to increased longevity (57). However, it is unknown whether the pathologically expanded polyglutamine stretch of mutant huntingtin associated with Huntington's disease is responsible for the commonly observed autophagy defects (58).

CR is a simple nutritional intervention that potently stimulates autophagy, but it is generally judged to be contraindicated for broad clinical application because it causes weight loss, compromises wound healing, and generates discomfort (59). Therefore, pharmacologic induction of autophagy has been pursued extensively in the last decade for the treatment of age-associated pathologies, in particular neurodegenerative diseases. The TOR inhibitor rapamycin is a potent autophagy inducer (via inhibition

J Clin Invest 125(1):85-93

C1) that extends life span in a variety of organisms (Figure 3

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Coffee induces autophagy in vivo

Federico Pietrocola^{1,2,3,4}, Shoaib Ahmad Malik^{1,2,3,4,1}, Guillermo Mariño^{1,2}, Erika Vacchelli^{1,2,3}, Laura Senovilla⁵, Kariman Chaba^{1,2}, Mireia Niso-Santano^{1,2}, Maria Chiara Maiuri^{1,2}, Frank Madeo⁶, and Guido Kroemer^{1,2,7,8,*}

¹Equipe 11 labellisée par la Ligue Nationale Contre le Cancer; INSERM U1138; Centre de Recherche des Cordeliers; Paris, France; ²Metabolomics and Molecular Cell Biology Platforms; Gustave Roussy; Villejuif, France; ³Université de Paris Sud; Villejuif, France; ⁴Directorate of Medical Sciences; Government College University; Faisalabad, Pakistan; ⁵INSERM U1015; Gustave Roussy; Villejuif, France; ⁶Institute of Molecular Biosciences; University of Graz; Graz, Austria; ⁷Pôle de Biologie; Hôpital Européen Georges Pompidou; AP-HP; Paris, France; ⁸Université Paris Descartes; Sorbonne Paris Cité; Paris, France

*These authors contributed equally to this paper.

Keywords: acetyl-coenzyme A, acetylation, mTOR, macroautophagy

Epidemiological studies and clinical trials revealed that chronic consumption coffee is associated with the inhibition of several metabolic diseases as well as reduction in overall and cause-specific mortality. We show that both natural and decaffeinated brands of coffee similarly rapidly trigger autophagy in mice. One to 4 h after coffee consumption, we observed an increase in autophagic flux in all investigated organs (liver, muscle, heart) in vivo, as indicated by the increased lipidation of LC3B and the reduction of the abundance of the autophagic substrate sequestosome 1 (p62/SQSTM1). These changes were accompanied by the inhibition of the enzymatic activity of mammalian target of rapamycin complex 1 (mTORC1), leading to the reduced phosphorylation of p70^{S6}, as well as by the global deacetylation of cellular proteins detectable by immunoblot. Immunohistochemical analyses of transgenic mice expressing a GFP-LC3B fusion protein confirmed the coffee-induced relocation of LC3B to autophagosomes, as well as general protein deacetylation. Altogether, these results indicate that coffee triggers 2 phenomena that are also induced by nutrient depletion, namely a

TABLE 3. EFFECT OF DIET AND COFFEE UPON LIFE SPAN OF RATS

Group	Diet	Coffee	No.	Sex	Mean life span, days
1	Average	-	20	F	582
2	Average	+	20	F	786

J Gerontol 1(4 Pt 1):426-32

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J Gerontol 1(4 Pt 1):426-32

Li Q, Liu Y, Sun X, et al. Caffeinated and decaffeinated coffee consumption and risk of all-cause mortality: a dose-response meta-analysis of cohort studies. J Hum Nutr Diet. 2019;32(3):279-287.

REVIEW - SYSTEMATIC REVIEW - META-ANALYSIS

Caffeinated and decaffeinated coffee consumption and risk of all-cause mortality: a dose-response meta-analysis of cohort studies

Q. Li,¹ Y. Liu,² X. Sun,² Z. Yin,² H. Li,² C. Cheng,¹ L. Liu,¹ R. Zhang,³ F. Liu,³ Q. Zhou,³ C. Wang,¹ L. Li,¹ B. Wang,¹ Y. Zhao,¹ M. Zhang³ & D. Hu¹ 

¹Department of Epidemiology and Health Statistics, College of Public Health, Zhengzhou University, Zhengzhou, Henan, China

²The Affiliated Luohu Hospital of Shenzhen University Health Science Center, Shenzhen, Guangdong, China

³Department of Preventive Medicine, Shenzhen University Health Science Center, Shenzhen, Guangdong, China

Keywords

all-cause mortality, coffee, cohort studies, dose-response meta-analysis.

Abstract

Background: Previous meta-analysis showed an inverse association between coffee consumption and all-cause mortality. However, the relationship

Liu

authors reported relative risks (RRs) of all-cause mortality for at least three levels of coffee consumption were eligible. Random-effects models were used to estimate the pooled RR of all-cause mortality with coffee consumption. Restricted cubic splines were used to model the dose-response association.

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Results: We included 21 cohort study articles (10 103 115 study participants and 240 303 deaths). We found a nonlinear association between coffee consumption and all-cause mortality ($P_{\text{nonlinearity}} < 0.001$). Compared with no or rare coffee consumption, with a consumption of 3 cups day⁻¹, the risk of all-cause mortality might reduce 13% (RR = 0.87; 95% confidence interval = 0.84–0.89).

Conclusions: The findings of the present study provide quantitative data suggesting that coffee consumption plays a role in reducing the risk of all-cause mortality. Similar inverse associations are found for caffeinated coffee and decaffeinated coffee.

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Coffee is one of the most commonly consumed beverages worldwide.¹ As such, even small individual health effects could be important on a population scale. There have been mixed conclusions as to whether coffee consumption is beneficial or harmful to health, and this varies between outcomes.² Roasted coffee is a complex mixture of over 1000 bioactive compounds,³ some with potentially therapeutic antioxidant, anti-inflammatory, antifibrotic, or anticancer effects that provide biological plausibility for recent epidemiological associations. Key active compounds include caffeine, chlorogenic acids, and the diterpenes, cafestol and kahweol. The biochemistry

BMJ 359:j5024

Chlorogenic acid enhances autophagy by upregulating lysosomal function to protect against SH-SY5Y cell injury induced by H₂O₂

LI-JUAN GAO^{1,2*}, YUAN DAI^{2*}, XIAO-QIONG LI^{1,2}, SHI MENG^{1,2}, ZHAN-QIONG ZHONG^{1,3} and SHI-JUN XU^{1,2}

¹Institute of Material Medica Integration and Transformation for Brain Disorders;

²School of Pharmacy; ³School of Basic Medical Sciences, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan 611137, P.R. China

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DOI: 10.3892/etm.2021.9843

Abstract. Autophagy serves an important role in amyloid- β (A β) metabolism and τ processing and clearance in Alzheimer's disease. The progression of A β plaque accumulation and hyperphosphorylation of τ proteins are enhanced by oxidative stress. A hydrogen peroxide (H₂O₂) injury cell model was established using SH-SY5Y cells. Cells were randomly divided into normal, H₂O₂, and chlorogenic acid

Importantly, these effects of CGA on H₂O₂-treated SH-SY5Y cells were mediated via the mTOR-transcription factor EB signaling pathway. These results indicated that CGA protected cells against H₂O₂-induced oxidative damage via the upregulation of autophagosomes, which promoted autophagocytic degradation and increased autophagic flux.

Cite this: *Food Funct.*, 2014, 5, 1718

Variations in caffeine and chlorogenic acid contents of coffees: what are we drinking?

Iziar A. Ludwig,^a Pedro Mena,^b Luca Calani,^b Concepción Cid,^c Daniele Del Rio,^b Michael E. J. Lean^d and Alan Crozier^{*a}

The effect of roasting of coffee beans and the extraction of ground coffee with different volumes of hot pressurised water on the caffeine and the total caffeoylquinic acids (CQAs) content of the resultant beverages was investigated. While caffeine was stable higher roasting temperatures resulted in a loss of CQAs so that the caffeine/CQA ratio was a good marker of the degree of roasting. The caffeine and CQA content and volume was determined for 104 espresso coffees obtained from coffee shops in Scotland, Italy and Spain, limited numbers of cappuccino coffees from commercial outlets and several instant coffees. The caffeine content ranged from 48–317 mg per serving and CQAs from 6–188 mg. It is evident that the ingestion of 200 mg of caffeine per day can be readily and unwittingly exceeded by regular coffee drinkers. This is the upper limit of caffeine intake from all sources recommended by US and UK health agencies for pregnant women. In view of the variable volume of serving sizes, it is also

the extraction of ground coffee with different volumes of hot water. The total caffeoylquinic acids (CQAs) content of the resultant coffee was stable. Higher roasting temperatures resulted in a loss of caffeine, a good marker of the degree of roasting. The caffeine and CQAs content for 104 espresso coffees obtained from coffee shops in London, 104 cappuccino coffees from commercial outlets and several other coffee types ranged from 48–317 mg per serving and CQAs from 6–188 mg. It is noted that caffeine per day can be readily and unwittingly exceeded by the amount of caffeine intake from all sources recommended by US health authorities. In view of the variable volume of serving sizes, it is also noted that caffeine is not a reproducible measurement for consumption, yet it is the most common marker of coffee consumption and to link the potential effects of the

main the 66–276 mg range in Scotland indicated much greater outlet-
e not to-outlet variability than in Italy or Spain. Coffees prepared in
phenol Spain were very lightly roasted compared to the beans used to
make Italian espressos. As with volume, there was much more
variability in Scotland where the median caffeine/CQA was 1.8
and the range 0.8–11.0. The major contributor to this wide
range were the espressos purchased from Starbucks which had
an extremely low CQA content (Table 3) and the resultant very
health high caffeine/CQA ratio indicated that the beans had been
feine subjected to intensive roasting. Assuming that globally Star-
health bucks use a standard roast procedure, this is likely to be a
y.^{24,25} feature of Starbucks coffee worldwide, rather than a uniquely
but Scottish phenomenon.

and beans used in the different countries may lead to CF/CGAs
day, ratio ranging from 0.7 to 11 (Ludwig et al. 2014).

Conversely, the processing used to obtain instant coffee
ted (freeze or spray-drying) does not significantly affect the level
of CGAs, especially in the case of dark roasted coffee
ulti- (Vignoli, Bassoli, and Benassi 2011), and when compared to
on, fresh coffee differences of less than 1 mg/100 mL have been
09; registered (Mills et al. 2013).

De Considering decaffeinated coffee, some reports indicated
are a consistent loss of CGAs (Farah et al. 2005) while others
nd reported only a not significant reduction (Azevedo et al.

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THE CHOLESTEROL-RAISING FACTOR FROM COFFEE BEANS

R. Urgert and M. B. Katan

Wageningen Agricultural University, Department of Human Nutrition, Bomenweg 2,
6703 HD, Wageningen, The Netherlands

KEY WORDS: cafestol, serum lipids, liver enzymes, lipid metabolism

Coffee consumption and mortality from cardiovascular diseases and total mortality: Does the brewing method matter?

Aage Tverdal¹, Randi Selmer², Jacqueline M Cohen² and Dag S Thelle³

Abstract

Aim: The aim of this study was to investigate whether the coffee brewing method is associated with any death and cardiovascular mortality, beyond the contribution from major cardiovascular risk factors.

Methods and results: Altogether, 508,747 men and women aged 20–79 participating in Norwegian cardiovascular surveys were followed for an average of 20 years with respect to cause-specific death. The number of deaths was 46,341 for any cause, 12,621 for cardiovascular disease (CVD), 6202 for ischemic heart disease (IHD), and 2894 for stroke. The multivariate adjusted hazard ratios (HRs) for any death for men with no coffee consumption as reference were

Tverdal A, Selmer R, Cohen JM, Thelle DS. Coffee consumption and mortality from cardiovascular diseases and total mortality: Does the brewing method matter? European Journal of Preventive Cardiology. 2020;27(18):1986–1993.

Aage Tverdal¹, Randi Selmer², Jacqueline M Cohen² and
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The multivariate adjusted hazard ratios (HRs) for any death for men with no coffee consumption as reference were 0.85 (0.82–0.90) for filtered brew, 0.84 (0.79–0.89) for both brews, and 0.96 (0.91–1.01) for unfiltered brew. For women, the corresponding figures were 0.85 (0.81–0.90), 0.79 (0.73–0.85), and 0.91 (0.86–0.96) for filtered, both brews, and unfiltered brew, respectively. For CVD, the figures were 0.88 (0.81–0.96), 0.93 (0.83–1.04), and 0.97 (0.89–1.07) in men, and 0.80 (0.71–0.89), 0.72 (0.61–0.85), and 0.83 (0.74–0.93) in women. Stratification by age raised the HRs for ages ≥ 60 years. The HR for CVD between unfiltered brew and no coffee was 1.19 (1.00–1.41) for men and 0.98 (0.82–1.15) for women in this age group. The HRs for CVD and IHD were raised when omitting total cholesterol from the model, and most pronounced in those drinking ≥ 9 of unfiltered coffee, per day where they were raised by 9% for IHD mortality.

Conclusion: Unfiltered brew was associated with higher mortality than filtered brew, and filtered brew was associated with lower mortality than no coffee consumption.

Keywords

Ischemic heart disease, stroke, smoking, unfiltered brew, filtered brew

Received 15 January 2020; accepted 2 March 2020

Spermidine

A novel autophagy inducer and longevity elixir

Frank Madeo,^{1,*} Tobias Eisenberg,¹ Sabrina Büttner,¹ Christoph Ruckenstuhl¹ and Guido Kroemer^{2-4,*}

¹Institute of Molecular Biosciences; University of Graz; Graz, Austria; ²INSERM, U848; Villejuif, France; ³Institut Gustave Roussy; Villejuif, France;

⁴University Paris Sud; Villejuif, France

Spermidine is a ubiquitous polycation that is synthesized from putrescine and serves as a precursor of spermine. Putrescine, spermidine and spermine all are polyamines that participate in multiple known and unknown biological processes. Spermidine is known to be involved in cell growth, differentiation, and it retarded necrotic cell death. In addition, spermidine could rejuvenate replicatively old yeast cells as their replicative life span was increased (that is the number of daughter cells generated from one single mother cell). *Chronological Aging*

CXLVIII. NOTES ON SPERMINE.

By HAROLD WARD DUDLEY AND OTTO ROSENHEIM.

*From the National Institute for Medical Research, Mount Vernon,
Hampstead, N.W. 3.*

(Received October 28th, 1925.)

**I. THE IDENTITY OF MUSCULAMINE, NEURIDINE AND GERONTINE
WITH SPERMINE.**

(a) *Musculamine*. Étard and Vila [1902] isolated this base as a benzoyl compound from hydrolysed calf's muscle, and gave it the formula $C_8H_{21}N_3$. Posternack [1902] pointed out the agreement of the analytical figures with



Polyamine-rich food decreases age-associated pathology and mortality in aged mice

Kuniyasu Soda^{a,b,*}, Yoh Dobashi^c, Yoshihiko Kano^b, Shingo Tsujinaka^b, Fumio Konishi^b

^a Department of Cardiovascular Research Institute, Saitama Medical Center, Jichi Medical University, Japan

^b Department of Surgery, Saitama Medical Center, Jichi Medical University, Japan

^c Department of Pathology, Saitama Medical Center, Jichi Medical University, Japan

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ABSTRACT

The purpose of this study was to test whether oral intake of foods rich in polyamines (spermine and spermidine) suppresses age-associated pathology in aged mice. Synthetic polyamines were mixed into experimental chows, and 24-week-old Jc1:ICR male mice were fed one of three chows containing differing polyamine concentrations. The spermine and spermidine concentrations in the low, normal, and high polyamine chows were 143 and 224 nmol/g, 160 and 434 nmol/g, and 374 and 1540 nmol/g, respectively.

Priority Research Paper

The metabolomic signature of extreme longevity: naked mole rats *versus* mice

Mélanie Viltard^{1,*}, Sylvère Durand^{2,3,*}, Maria Pérez-Lanzón^{2,3,4}, Fanny Aprahamian^{2,3}, Deborah Lefevre^{2,3}, Christine Leroy⁵, Frank Madeo^{6,7}, Guido Kroemer^{2,3,8,9,10}, Gérard Friedlander^{5,11,12}

¹Fondation pour la Recherche en Physiologie, Brussels, Belgium

²Metabolomics and Cell Biology Platforms, Institut Gustave Roussy, Villejuif, France

³Equipe Labellisée par la Ligue contre le Cancer, Université de Paris, Sorbonne Université, INSERM U1138, Centre de Recherche des Cordeliers, Paris, France

⁴Faculté de Médecine, Université de Paris Saclay, Kremlin Bicêtre, France

⁵INSERM UMR_S1151 CNRS UMR8253 Institut Necker-Enfants Malades (INEM), Paris, France

⁶Institute of Molecular Biosciences, University of Graz, NAWI Graz, Graz, Austria

⁷BioTechMed Graz, Graz, Austria

⁸Pôle de Biologie, Hôpital Européen Georges Pompidou, AP-HP, Paris, France

⁹...

In an unflattering light, a naked mole rat looks like a wrinkly sausage with oversized teeth, legs and a tail. And given that it spends all of its extraordinarily long life short of air in dark and overcrowded underground tunnels, where it frequently eats its own excrement, an unflattering light is probably the best that a naked mole rat can hope for. Still, the best science, like love and justice, is blind, so this week the naked mole rat (*Heterocephalus glaber*; also known as the sand puppy or desert mole rat) joins the illustrious list of animals judged to be of sufficient significance for an analysis of their genome sequence to be published.

And what an animal it is. Unfortunately, the research paper that describes its genetic insides, published online by *Nature* this week (E. B. Kim *et al.* *Nature* doi:10.1038/nature10533; 2011), finds no room to feature a clear image of its extraordinary outsides. So those readers unfamiliar with this bizarre burrowing rodent native to parts of east Africa are highly recommended to look up its image on the Intern

Nature 478:156



rodent native to East Africa that lives strictly underground in social colonies (Kenya, Ethiopia and Somalia). Although this rodent has a similar size as the laboratory mouse (*Mus musculus*), it lives 10-20 times longer without showing any visible signs of aging [4]. Furthermore, the naked mole-rat can live for over 32 years in captivity [5], without facing any increased age-related risk of mortality, challenging Gompertz's mortality law, and thus establishing the naked mole-rat as a non-aging mammal [6].

Not only naked mole-rats can live an extremely long life, but they also show a remarkably long healthspan associated with almost no decline in physiologic

Spermidine and Spermine Are Enriched in Whole Blood of Nona/Centenarians

Stefania Pucciarelli,¹ Benedetta Moreschini,¹ Daniela Micozzi,¹ Giusi S. De Fronzo,¹ Francesco M. Carpi,¹
Valeria Polzonetti,¹ Silvia Vincenzetti,² Fiorenzo Mignini,³ and Valerio Napolioni¹

Abstract

Polyamines (putrescine, spermidine, and spermine) are a family of molecules that derive from ornithine through a decarboxylation process. They are essential for cell growth and proliferation, stabilization of negative charges of DNA, RNA transcription, translation, and apoptosis. Recently, it has been demonstrated that exogenously administered spermidine promotes longevity in yeasts, flies, worms, and human cultured immune cells. Here, using a cross-sectional observational study, we determined whole-blood polyamines levels from 78 sex-matched unrelated individuals divided into three age groups: Group 1 (31–56 years, $n=26$, mean age 44.6 ± 6.07), group 2 (60–80 years, $n=26$, mean age 68.7 ± 6.07), and group 3 (90–106 years, $n=26$, mean age 96.5 ± 4.59). The total content of poly-

its participation and in-person follow-up rates >90% (20–24), facilitated by annual population mobility proportions as low as 0.2%. Moreover, for all participants, full medical records from general practitioners and Bruneck Hospital, the only hospital in the region, were available for review. For this analysis, we defined the baseline as the year of the first detailed dietary assessment (1995) involving 829 women and men aged 45–84 y with a follow-up of 20 y (1995–2015; **Supplemental Figure 1**). The study protocol conformed to the Declaration of Helsinki and was approved by the local ethics committees (Bolzano and Verona). Participants gave their written informed consent and did not receive financial compensation. Participant characteristics were assessed by standard procedures (20–24) detailed in the online supporting material (page 3).

Higher spermidine intake is linked to lower mortality: a prospective population-based study

Stefan Kiechl,¹ Raimund Pechlaner,^{1,3} Peter Willeit,^{1,3,4} Marlene Notdurfter,⁵ Bernhard Paulweber,⁶ Karin Willeit,¹ Philipp Werner,⁷ Christoph Ruckstuhl,^{8,9} Bernhard Iglseder,⁶ Siegfried Weger,⁵ Barbara Mairhofer,⁵ Markus Gartner,⁵ Ludmilla Kedenko,⁶ Monika Chmelikova,¹⁰ Slaven Stekovic,^{8,9} Hermann Stuppner,^{11,12} Friedrich Oberhollenzer,⁵ Guido Kroemer,^{13,14,15,16,17,18} Manuel Mayr,³ Tobias Eitsenberger,^{8,9} Herbert Tilg,² Frank Madeo,^{8,9} and Johann Willeit¹

Departments of ¹Neurology and ²Internal Medicine I, Gastroenterology, Endocrinology and Metabolism, Medical University of Innsbruck, Innsbruck, Austria; ³King's British Heart Foundation Center, King's College London, London, United Kingdom; ⁴Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom; ⁵Department of Internal Medicine, Bruneck Hospital, Bruneck, Italy; ⁶First Department of Internal Medicine and Department of Geriatric Medicine, Paracelsus Medical University, Salzburg, Austria; ⁷Department of Acute Neurology and Stroke, Feldkirch Academic Teaching Hospital, Feldkirch, Austria; ⁸Institute of Molecular Biosciences, University of Graz, NAWI Graz, Graz, Austria; ⁹BioTechMed Graz, Graz, Austria; ¹⁰Department of Pathological Physiology, Faculty of Medicine, Masaryk University Brno, Brno, Czech Republic; ¹¹Institute of Pharmacy/Pharmacognosy and ¹²Department of Medicinal Chemistry, Faculty of Science, Masaryk University Brno, Brno, Czech Republic; ¹³Department of Pathology, University of Innsbruck, Innsbruck, Austria; ¹⁴Department of Pathology, University of Salzburg, Salzburg, Austria; ¹⁵Department of Pathology, University of Vienna, Vienna, Austria; ¹⁶Department of Pathology, University of Zurich, Zurich, Switzerland; ¹⁷Department of Pathology, University of Basel, Basel, Switzerland; ¹⁸Department of Pathology, University of Bern, Bern, Switzerland

Induction of autophagy by spermidine promotes longevity

Tobias Eisenberg¹, Heide Knauer¹, Alexandra Schauer¹, Sabrina Büttner¹, Christoph Ruckenstuhl¹, Didac Carmona-Gutierrez¹, Julia Ring¹, Sabrina Schroeder¹, Christoph Magnes², Lucia Antonacci¹, Heike Fussi¹, Luiza Deszcz^{3,4}, Regina Hartl^{3,4}, Elisabeth Schraml⁵, Alfredo Criollo^{6,7,8}, Evgenia Megalou⁹, Daniela Weiskopf¹⁰, Peter Laun¹¹, Gino Heeren¹¹, Michael Breitenbach¹¹, Beatrix Grubeck-Loebenstein¹⁰, Eva Herker¹², Birthe Fahrenkrog¹³, Kai-Uwe Fröhlich¹, Frank Sinner², Nektarios Tavernarakis⁹, Nadege Minois^{3,4,14}, Guido Kroemer^{6,7,8,15} and Frank Madeo^{1,15}

Ageing results from complex genetically and epigenetically programmed processes that are elicited in part by noxious or stressful events that cause programmed cell death. Here, we report that administration of spermidine, a natural polyamine whose intracellular concentration declines during human ageing, markedly extended the lifespan of yeast, flies and worms, and human immune cells. In addition, spermidine administration potently inhibited oxidative stress in ageing mice. In ageing yeast, spermidine treatment triggered epigenetic deacetylation of histone H3 through inhibition of histone acetyltransferases (HAT), suppressing oxidative stress and necrosis. Conversely, depletion of endogenous polyamines led to hyperacetylation, generation of reactive oxygen species, early necrotic death and decreased lifespan. The altered acetylation status of the chromatin led to significant upregulation of various autophagy-related transcripts, triggering autophagy in yeast, flies, worms and human cells. Finally, we found that enhanced autophagy is crucial for polyamine-induced suppression of necrosis and enhanced longevity.

As an organism ages, the fate of individual cells is dictated by apoptotic or ... is known to negatively regulate autophagy, the major lysosomal degra-

have or cells treated with spermidine exhibited a relative increase in
t, and MAP1S stability and autophagy signaling via depletion of cyto-
simple solic HDAC4. Extending recent evidence that orally adminis-
autop- tered spermidine can extend lifespan in mice, we determined
h and that life extension of up to 25% can be produced by lifelong
phagic administration, which also reduced liver fibrosis and HCC foci
ociated as induced by chemical insults. Genetic investigations estab-
flux in lished that these observed impacts of oral spermidine adminis-
raction tration relied upon MAP1S-mediated autophagy. Our findings
efficient offer a preclinical proof of concept for the administration of oral
devel- spermidine to prevent liver fibrosis and HCC and potentially
e mice extend lifespan. *Cancer Res*; 77(11); 2938–51. ©2017 AACR.

Spermidine: a physiological autophagy inducer acting as an anti-aging vitamin in humans?

Frank Madeo^{a,b}, Maria A. Bauer^a, Didac Carmona-Gutierrez^a, and Guido Kroemer^{c,d,e,f,g,h}

^aInstitute of Molecular Biosciences, University of Graz, Graz, Austria; ^bBioTechMed Graz, Graz, Austria; ^cEquipe 11 labellisée Ligue contre le Cancer, Centre de Recherche des Cordeliers, INSERM U, Paris, France; ^dMetabolomics and Cell Biology Platforms, Gustave Roussy Comprehensive Cancer Center, Villejuif, France; ^eSorbonne Paris Cité, Université Paris Descartes, Paris, France; ^fUniversité Pierre et Marie Curie, Paris, France; ^gPôle de Biologie, Hôpital Européen Georges Pompidou, Paris, France; ^hDepartment of Women's and Children's Health, Karolinska University Hospital, Stockholm, Sweden

ABSTRACT

Spermidine is a natural polyamine that stimulates cytoprotective macroautophagy/autophagy. External supplementation of spermidine extends lifespan and health span across species, including in yeast, nematodes, flies and mice. In humans, spermidine levels decline with aging, and a possible connection between reduced endogenous spermidine concentrations and age-related deterioration has been suggested. Recent epidemiological data support this notion, showing that an increased uptake of this polyamine with spermidine-rich food diminishes overall mortality associated with cardiovascular diseases and cancer. Here, we discuss nutritional and other possible routes to counteract the age-mediated decline of spermidine levels.

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gression of age-associated diseases and prolong the lifespan of humans. Epidemiologic studies have suggested the relation between several foods and prolonged longevity (Hu and Willett, 2002; Renaud and Lanzmann-Petithory, 2001). Eating beans such as soy may help decrease the incidence of age-associated diseases, such as atherosclerotic plaque in arteries, and prolong longevity (Papanikolaou and Fulgoni, 2008; Sacks et al., 2006).

Beans, especially soybeans, have the highest amount of the polyamines (spermine and spermidine) present in natural foods (Bardócz et al., 1993; Okamoto et al., 1997). Because spermine and spermidine are not enzymatically degraded in the alimentary tract, oral spermine and spermidine are absorbed quickly from intestinal lumen and distributed to all organs and tissues (Bardocz et al., 1990, 1995). And, we recently found that long-term intake of polyamine-rich foods gradually increases blood polyamine levels in humans and animals (Soda et al., 2009).

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foods free of or rich in polyamines; for example, the production of transgenic potatoes with a high content of spermidine seems feasible [79]. Nevertheless, before making any recommendation concerning the use of supplements or enrichment with these substances that are so strictly regulated by the organism, more studies on their therapeutic and nutritional effects are needed.

Top Spermidine Sources

(mg per 100 g serving unless otherwise specified)

9.7 mg: tempeh ^{356,357}	3.7 mg: broccoli ^{377,378,379}
9.2 mg: mushroom ^{358,359}	3.4 mg: cow intestine ³⁸⁰
9.2 mg: pig pancreas (1 oz) ³⁶⁰	2.9 mg: chickpeas ³⁸¹
8.2 mg: natto (1 oz) ³⁶¹	2.8 mg: cauliflower ^{382,383}
6.1 mg: mango (one 210 g) ^{362,363}	2.7 mg: celeriac ³⁸⁴
5.9 mg: edamame ^{364,365}	2.6 mg: yellow peas ³⁸⁵
5.8 mg: green peas ^{366,367}	2.5 mg: wheat germ (1 Tb) ³⁸⁶
5.7 mg: cheddar (aged 1 year, 1 oz) ³⁶⁸	2.5 mg: french fries ³⁸⁷
5.5 mg: lentil soup (1 cup) ³⁶⁹	2.4 mg: oysters ³⁸⁸
5.1 mg: soybeans ³⁷⁰	2.4 mg: lentils ³⁸⁹
4.4 mg: lettuce ³⁷¹	2.4 mg: adzuki beans ^{390,391,392}
4.3 mg: polenta ³⁷²	2.3 mg: eel livers (1 oz) ³⁹³
4.3 mg: corn ^{373,374}	2.2 mg: salad ³⁹⁴
3.8 mg: soymilk (1 cup) ³⁷⁵	2.1 mg: popcorn (50 g) ³⁹⁵
3.8 mg: mussels ³⁷⁶	2.0 mg: kidney beans

This represents an exhaustive list of virtually every food I could find that consistently,


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<https://doi.org/10.1007/s00508-020-01758-y>



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The Central European Journal of Medicine

The positive effect of spermidine in older adults suffering from dementia

First results of a 3-month trial

Thomas Pekar  · Katharina Bruckner · Susanne Pauschenwein-Frantsich · Anna Gschaider · Martina Oppliger · Julia Willesberger · Petra Ungersbäck · Aribert Wendzel · Alexandra Kremer · Walter Flak · Felix Wantke · Reinhart Jarisch

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Wien Klin Wochenschr
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the study, relatives of legal guidelines provided con-
sent.

In the implementation of the study, the 92 subjects were divided into two random groups. One group received a grain roll with wheat germ (Schalkmühle, Ilz, Austria; 1075 mg/kg spermidine) for breakfast 6 times a week (roll A). Each roll A contained 3.3 mg of spermidine after baking. To scrutinize the success of spermidine, the second group received rolls baked with wheat bran (Schafler Mühle, Feistritz, Austria; 115 mg/kg spermidine) instead of wheat germ (roll B). Each finished roll B contained 1.9 mg of spermidine. Both the wheat germ and the wheat bran were added to the dough mixture during preparation.

On average, the subjects ate 69 rolls during the 9

midine level in group B was consistent during the study. The medians in this group were always around 40 ng/ml ($p < 0.106$).

The most substantial improvement in test performance for the group with higher spermidine substitution was found in the group of subjects with mild dementia with an increase of 2.23 ($p = 0.026$) in the Mini Mental test. The improvement by more than 2 points is way beyond all available antedementia treatments so far. In a comparable study over the same period, the results were not as promising [17]. In our opinion, these differences are due to the different dosages of spermidine intake. Our group A received 2.75 times more spermidine as the inter-

Aducanumab Fails to Produce Efficacy Results Yet Obtains US Food and Drug Administration Approval

Mark Angelo, MD, MHA, FACP^{1,i} and Lawrence Ward, MD, MPH, FACP^{2,ii}

Keywords: aducanumab, dementia, Aduhelm, Alzheimer's disease, amyloid plaque, Medicare

THE US FOOD AND DRUG Administration (FDA) recently approved use of the first new drug for the treatment of Alzheimer's dementia in almost 2 decades. This infusion from Biogen, Aduhelm (R) (aducanumab) is a monoclonal antibody, administered monthly, that targets amyloid-beta oligomers and fibrils in the brain that are considered patho-

early-stage dementia.¹ Despite there being no evidence to support use in advanced or even moderate disease, the FDA ultimately approved aducanumab for all stages of disease severity. In response, at the time of this writing, 3 experts from the FDA advisory committee have since resigned in protest, and the FDA has commissioned an inspector general

Angelo M, Ward L. Aducanumab fails to produce efficacy results yet obtains us food and drug administration approval. Population Health Management. 2021;24(6):638-639.

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In large trials of other Alzheimer's drug candidates, amyloid lowering has not led to cognitive benefits, and this has made it a sticking point for researchers.

Biogen can now sell its US\$56,000-per-year drug to 6 million people with Alzheimer's in the United States. As a condition of the accelerated approval, the firm has until 2030 to report the results of a 'post marketing' trial to prove the drug's cognitive benefit.

Internal memos released last week by the FDA shed some light on the decision. Clinical review-

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tional brain MRIs before their 7th and 12th
infusions. The scans are needed to monitor
for amyloid-related imaging abnormalities
(ARIAs). As the AAN document notes, 35%
of clinical trial participants who received
aducanumab (compared with 3% of those
who received a placebo) developed ARIAs,
with either swelling or bleeding in the
brain, within the first 4 months of treat-
ment with aducanumab. ARIA symptoms
include confusion, altered mental status,
and disorientation.

ARIAs usually resolved over time, but at

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My head just exploded, now what? Aducanumab

Nancy E. Lundebjerg MPA 

American Geriatrics Society, 40 Fulton Street, 18th Floor, New York, New York, 10038, USA

Correspondence

Nancy E. Lundebjerg, American Geriatrics Society, 40 Fulton Street, 18 Floor, New York, NY 10038, USA.
Email: nlundebjerg@americangeriatrics.org

Have you ever pushed a person in a wheelchair while in search of a diagnosis which would then (hopefully) lead to a cure?

I have. And, after seemingly endless visits to specialists and corresponding tests, the diagnosis was scarring

drug with the requirement that Biogen conduct an additional trial.⁴⁻⁶

It is important to note that although aducanumab was studied only in patients with mild cognitive impairment or early-stage Alzheimer's disease, FDA has

ubiquitous, evolutionarily conserved, catabolic, and self-degradative process that mediates the destruction of cytoplasmic macromolecules to preserve genomic integrity, achieve cell metabolism, and ensure cell survival [30,79–81]. It is a natural regulatory mechanism which retains beneficial substances and removes harmful substances from body, whilst playing a housekeeping role in the elimination of misfolded or aggregated proteins, the eradication of damaged organelles, proteins [82–84], and cancerous materials [7], and the elimination of foreign pathogens such as viruses via a degradative lysosomal pathway [21,85–87].

Numerous physiobiological roles of autophagy have been identified, such as the disposal of endogenous wastes and exogenous agents to maintain homeostasis; however, disturbing the natural balance of this mechanism can result in pathological consequences [88].

Since it is the primary system for cleaning the body, autophagy can prevent or treat cancer by killing cancerous cells and degrading endogenous or exogenous carcinogens; thus, favoring the development of healthy cells. However, autophagy may have dual roles in cancer as it is involved in stem cell-related resistance to anti-cancer therapy (radioresistance and chemoresistance), metastasis, and tumor recurrence [89]. As obligate intracellular pathogens, viruses interact with multiple host cell processes for their survival, including metabolism, cellular trafficking, and immunity-related responses [54,90]. Furthermore, autophagy is a major degradative cellular process, with essential roles in many innate and adaptive immune processes [91–93]. Autophagy also regulates the phosphorylation of p38 and ERK1/2 MAPKs in BV2 microglial cells, required for nitric oxide production [94,95]. Thus, it can affect the activation of neuronal cells by microglia and suppress neurotoxicity. Moreover, it can downregulate pro-inflammatory mediators in BV2 microglial cells to rescue them from LPS- and α -synuclein-induced neuronal cell death [94].

Autophagy can either be selective or non-selective [96]. In selective autophagy, cargo is recognized

Cells 8:674

...equivalent, cytoplasmic constituents, and can be a degradative process that involves the destruction of cytoplasmic macromolecules to preserve genomic integrity, achieve cell metabolism, and ensure cell survival [30,79–81]. It is a natural regulatory mechanism which retains beneficial substances and removes harmful substances from body, whilst playing a housekeeping role in the elimination of misfolded or aggregated proteins, the eradication of damaged organelles, proteins [82–84], and cancerous materials [7], and the elimination of foreign pathogens such as viruses via a degradative lysosomal pathway [21,85–87].

Numerous physiobiological roles of autophagy have been identified, such as the disposal of endogenous wastes and exogenous agents to maintain homeostasis; however, disturbing the natural balance of this mechanism can result in pathological consequences [88].

Since it is the primary system for cleaning the body, autophagy can prevent or treat cancer by killing cancerous cells and degrading endogenous or exogenous carcinogens; thus, favoring the development of healthy cells. However, autophagy may have dual roles in cancer as it is involved in stem cell-related resistance to anti-cancer therapy (radioresistance and chemoresistance), metastasis, and tumor recurrence [89]. As obligate intracellular pathogens, viruses interact with multiple host cell processes for their survival, including metabolism, cellular trafficking, and immunity-related responses [54,90]. Furthermore, autophagy is a major degradative cellular process, with essential roles in many innate and adaptive immune processes [91–93]. Autophagy also regulates the phosphorylation of p38 and ERK1/2 MAPKs in BV2 microglial cells, required for nitric oxide production [94,95]. Thus, it can affect the activation of neuronal cells by microglia and suppress neurotoxicity. Moreover, it can downregulate pro-inflammatory mediators in BV2 microglial cells to rescue them from LPS- and α -synuclein-induced neuronal cell death [94].

Autophagy can either be selective or non-selective [96]. In selective autophagy, cargo is recognized

ubiquitous, evolutionarily conserved, autophagic, and self-degradative process that mediates the destruction of cytoplasmic macromolecules to preserve genomic integrity, achieve cell metabolism, and ensure cell survival [30,79–81]. It is a natural regulatory mechanism which retains beneficial substances and removes harmful substances from body, whilst playing a housekeeping role in the elimination of misfolded or aggregated proteins, the eradication of damaged organelles, proteins [82–84], and cancerous materials [7], and the elimination of foreign pathogens such as viruses via a degradative lysosomal pathway [21,85–87].

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though. While some have suggested the general use of spermidine, such as in the form of potatoes,⁷³³ there are already a plethora of naturally spermidine-rich foods.

Autophagy Takeaways

To help slow this aging pathway, on a daily basis, consider:

- 60 min or more of moderate to vigorous (55%–70% VO₂ max) aerobic exercise
- minimizing your intake of french fries and potato chips
- drinking three cups of regular or decaffeinated coffee
- trying to consume at least 20 mg of spermidine by incorporating foods such as tempeh, mushrooms, peas, and wheat germ into your diet
- instituting the recommendations to activate AMPK (see chapter 1)
- following the recommendations to suppress mTOR (see chapter 8)

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Editorial

Centenarian Studies: Important Contributors to Our Understanding of the Aging Process and Longevity

Donald Craig Willcox,^{1,2,3} Bradley J. Willcox,^{2,3,4,5,6} and Leonard W. Poon⁷

¹ Okinawa International University, Okinawa 901-2701, Japan

² Okinawa Research Center for Longevity Science, Okinawa 901-2114, Japan

³ Pacific Health Research and Education Institute, Honolulu, HI 96813, USA

⁴ Department of Research, Kuakini Medical Center, Honolulu, HI 96817, USA

⁵ Department of Research, Planning and Development, The Queen's Medical Center, Honolulu, HI 96813, USA

⁶ Department of Geriatric Medicine, John A. Burns School of Medicine, University of Hawaii, HI 96817, USA

⁷ The Institute of Gerontology, University of Georgia, UGA, Athens, GA 30602, USA

Correspondence should be addressed to Donald Craig Willcox; d.willcox@okiui.ac.jp

Willcox DC, Willcox BJ, Poon LW. Centenarian studies: important contributors to our understanding of the aging process and longevity. *Current Gerontology and Geriatrics Research*. 2010;2010:1-6.

Longevity Studies in GenomEUtwin

Axel Skytthe¹, Nancy L. Pedersen², Jaakko Kaprio⁴, Maria Antonietta Stazi³, Jacob v.B. Hjelmberg¹, Ivan Lachaine², James W. Vaupel¹, and Kaare Christensen¹

¹ The Danish Twin Registry, Epidemiology Unit, Institute of Public Health, University of Southern Denmark, Odense, Denmark

² The Department of Statistics, Institute of Public Health, University of Southern Denmark, Odense, Denmark

³ The Swedish Twin Registry, Karolinska Institutet, Stockholm, Sweden

⁴ The Finnish Twin Cohort Study, University of Helsinki, Finland

⁵ The Italian Twin Registry, Istituto Superiore di Sanità, Roma, Italia

Previous twin studies have indicated that approximately 25% of the variation in life span can be attributed to genetic factors and recent studies have also suggested a moderate clustering of extreme longevity within families. Here we discuss various definitions of extreme longevity and some analytical approaches with special attention to the challenges due to censored data. Lexis diagrams are provided for the Danish, Dutch, Finnish, Italian, Norwegian, and Swedish Twin registries hereby outlining possibilities for longevity studies within GenomEUtwin. We extend previous analyses of lifespan for

A large ongoing research effort is underway to identify the genetic, environmental, and behavioral determinants of extreme survival by comparing centenarians with younger cohorts (association studies). However, such studies suffer from the lack of an appropriate comparison group as cohort specific characteristics may confound the comparison between the centenarians and younger cohorts. To date, only one common polymorphism, namely Apo-E e2 [ARG158CYS] of the ApoE e2/e3/e4 polymorphism, has

will provide a resource for identifying unusual sibships (i.e., dizygotic twin pairs) where both survived to extreme ages, as a basis for discovering genetic variants of importance for extreme survival.

During the last decade a series of twin studies has shown that approximately 25% of the variation in lifespan is caused by genetic differences. This seems to be a rather consistent finding in various Nordic countries across different time periods among other species not living in the wild (Finch & Tanzi, 1997; Herskind et al., 1996; Iachine et al., 1998; Ljungquist et al., 1998).

For extreme longevity, moderate familial clustering has

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Genetic and Environmental Determinants of Healthy Aging

Editorial

Secrets of Healthy Aging and Longevity From Exceptional Survivors Around the Globe: Lessons From Octogenarians to Supercentenarians

Bradley J. Willcox,^{1,2,3,4} D. Craig Willcox,^{1,4,5} and Luigi Ferrucci⁶

¹Pacific Health Research Institute, Honolulu, Hawaii.

²Department of Research Planning and Development, Queen's Medical Center, Honolulu, Hawaii.

³Department of Geriatric Medicine, John A. Burns School of Medicine, University of Hawaii, Manoa.

⁴Okinawa Research Center for Longevity Science, Japan.

⁵Department of Human Welfare, Okinawa International University, Japan.

⁶Longitudinal Studies Section, Clinical Research Branch, National Institute on Aging, Baltimore, Maryland.

The Blue Zones: areas of exceptional longevity around the world

*Michel Poulain, Anne Herm and Gianni Pes**

Abstract

The aim of this study was to compare the level of population longevity and the characteristics of four geographic areas where unusually high proportions of long-lived individuals have been observed. For these areas (Ogliastra in Sardinia, Okinawa in Japan, the Nicoya peninsula in Costa Rica and the island of Ikaria in Greece). The term of 'blue zone' (BZ) given to these areas is defined as a limited region where the population shares a common lifestyle and environment and whose exceptional

S.F. Vatner et al.

Rica; Sardinia, Italy; Ikaria, Greece; Okinawa, Japan (Buettner and Skemp, 2016; Huang and Mark Jacquez, 2017). In these areas the number of centenarians, i.e., those reaching the age of 100 is 10 times greater than the average in the United States. These regions are characterized by cultural preferences which discourage over-eating and excessive alcohol consumption, while encouraging active lifestyles. While the characteristics shared by these regions extend beyond diet and exercise, both a healthy diet and exercise training have been shown to reduce oxidative stress and protect against the deleterious effects of aging.

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Ageing Res Rev 64:101194

STATE OF THE ART
REVIEWS

Dan Buettner, BA, and Sam Skemp, BA

Blue Zones: Lessons From the World's Longest Lived

Abstract: *What began as a National Geographic expedition, lead by Dan Buettner, to uncover the secrets of longevity, evolved into the discovery of the 5 places around the world where people consistently live over 100 years old, dubbed the Blue Zones. Dan and his team of demographers, scientist*

lives is dictated by our genes, whereas the other 80% is dictated by our lifestyle. In 2004, Dan Buettner, CEO of Blue Zones LLC, was determined to uncover the specific

might explain longevity. They found that the lifestyles of all Blue Zones residents shared 9 specific characteristics. These are called the Power 9.



However, many individuals have



Food Guidelines

We distilled more than 150 dietary surveys of the world's longest-lived people to discover the secrets of a longevity diet.

These 11 simple guidelines reflect how the world's longest-lived people ate for most of their lives. We make it easy to eat like the healthiest people in the world with the [Blue Zones Meal Planner](#), where you'll find thousands of recipes that follow these guidelines while making plant-slant food delicious and accessible. By adopting some of the healthy eating principles into your daily life, you too can *Live Better, Longer*. Click [here](#) to download our free printable of the Blue Zones Food Guidelines so you can post it in your home as a daily reminder.

WEEKLY

Slash sugar: Consume only 28 grams (7 teaspoons) of added sugar daily



Eliminate eggs:
No more than 3 per week



Go easy on fish:
Fewer than 3 oz, up to 3 times weekly



Snack on nuts:
About 1-2 handful a day



Drink mostly water: About 7 glasses / day; coffee, tea, and wine in moderation



Daily dose of beans: Half-cup to one cup / day



Go wholly whole: Single-ingredient, raw, cooked, ground, or fermented, and not highly processed



DAILY

95-100% plant-based



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eat often with family and friends

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meta-analyses, but inevitably they rely on published results that may be contentious, particularly in dietary studies.

Smoking works out at about 10 microlives for every 20 cigarettes smoked, around 15 minutes per cigarette (a previous basic analysis⁸ estimated 11 minutes pro rata loss in life expectancy per cigarette). The table[↓] shows that, averaged over a lifetime habit, a microlife can be “lost” from smoking two cigarettes, being 5 kg overweight, having the second and third alcoholic drink of the day, watching two hours of television, or eating a burger. On the other hand microlives can be “gained” by drinking coffee, eating fruit and vegetables, exercising, and taking statins. Air pollution has been placed under “behaviour” since exposure is, in principle, optional.

BMJ 345:e8223

REVIEW



Diet and Dermatology: The Role of a Whole-food, Plant- based Diet in Preventing and Reversing Skin Aging—A Review

ABSTRACT

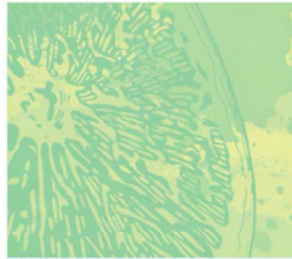
BACKGROUND: Previous studies have demonstrated that a whole-food, plant-based (WFPB) diet can aid in the prevention, and in some cases reversal, of some of the leading chronic diseases in the United States. The medical literature on the relationship between diet and disease is steadily growing. Over the last decade, the possible connection between diet and many dermatological

by **JASON SOLWAY, DO; MICHAEL MCBRIDE, DO; FURQAN HAQ, PhD, MPH; WAHEED ABDUL, MD; and RICHARD MILLER, DO**

Drs. Solway, Haq, Abdul, and Miller are with Largo Medical Center in Largo, Florida. Dr. McBride is with Riverside Methodist Hospital in Columbus, Ohio.

J Clin Aesthet Dermatol. 2020;13(5):38–43

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lengthen telomeres and reverse the aging
process of deoxyribonucleic acid (DNA).⁵⁻⁷ It is
also responsible for preventing and reversing
the leading chronic diseases in America,
specifically coronary artery disease (CAD).⁸⁻¹¹
Additionally, WFPB diet has been shown to
reduce the amount of gerontotoxins measured
in the blood, making them biomarkers of
accelerated cellular skin aging, as well as
increase the amount of antioxidants, which
ultimately can translate into healthier and
more youthful skin. Although various factors

with the amino acids in the lens which destroyed the pristine clear quality of lens proteins and resulted in yellow and finally brown cataracts, the AGE food colors of roasted turkey. The researchers became more and more impressed with the toxic nature of these chemicals. They were so impressed they gave these chemicals the acronym AGE for advanced glycation end products and to emphasize their toxic role in age-related disease. They did notice the chemical similarity to Maillard's "browning products" in cooking foods; so

pathological endothelial cell dysfunction and apoptosis of macrophages [9, 10].

Exogenous formation of AGEs

AGEs are naturally occurring chemicals in raw animal-origin foods, and cooking propagates and accelerates the generation of more AGEs within them. Studies have shown that dry heating results in the formation of more than ten to hundred times of new AGEs in foods as compared to the uncooked state [1]. For the food industry AGEs are greatly desirable owing to the profound effect of AGEs on safety and convenience

Nutr Metab 15:72

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heterogeneous that one molecule alone cannot fully represent the real AGE content in foods. This is a very important limitation that can hardly be solved, even using other current chromatographic and immunochemical assays [85]. Another marker for AGE content in foods is MG, but, in contrast with other AGEs like CML, which have an estimated 10% absorption rate in the intestine, reactive dicarbonyls appear not to be absorbable. It is believed that MG cannot reach circulation because it reacts with free amino groups present in the intestine and, therefore, does not exert any effect on the serum AGE levels in vivo [86]. Based on tables and database analysis included in research papers, fats, meat, cheese, and nuts (if processed, canned, or toasted at high temperatures) had the highest AGE content, while dairy, grains, fruits, and vegetables the lowest. Within the meat group the CML contents decrease gradually in poultry, pork, fish, eggs, and lamb [2,87]. The reason for this high AGE content in red meats and poultry is probably given by the fact that, when cooked under dry heat, these release high amounts of highly reactive amino-lipids and reducing sugars, like fructose or glucose-6-phosphate, due to the rupture of lean muscle cells. Even if the fat group is the one that contains the most adducts, it is the meat group that could account more for a high AGE intake since fats cannot make a meal by themselves and the quantities ingested are substantially lower. The fat group, however, can increase the contents of other food groups if the cooking method used requires it. The data shows a substantial rise in AGEs in those foods that have been cooked using butter or oil [83,85]. What appears clear from these first statements is that the fat group and meat group, which have a high lipid and protein content, are more prone to having high AGEs. These foods have a high quantity of lysine and arginine residues, which are, together with cysteine, tryptophan and histidine, favorable glycation targets [88]. Modifications of amino acids (including the essential ones) limit their bioavailability and may lower nutritive value of a food product. An interesting point can rise from the analysis of protein rich

Nutrients 11:1748

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which attenuate protein glycation and prevent the biosynthesis of AGEs^{265–270}. As mentioned above, cooking methods can play a critical role in regulating the levels of AGE formation, with effects ranging from those caused by oven-frying > frying > broiling > roasting > boiling/poaching/stewing/steaming. For example, cooking meat (e.g., chicken, pork, or beef) by boiling or stewing can reduce the AGE contents to one-half of that prepared by broiling^{1,271}. In addition, the water content, cooking method, temperature and time, and food pH are crucial to the final amount of AGEs. Marinating food or meat with acidic ingredients such as lemon juice and vinegar can decrease the amounts of dietary AGEs produced during to

Exp Mol Med 53:168-88

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HAGE and LAGE meals

The 2 meals were isocaloric, had identical ingredients, and differed only by the temperature and time of cooking. Each meal consisted of 200 g chicken breast, 250 g potatoes, 100 g carrots, 200 g tomatoes, and 15 g vegetable oil and provided 580 kcal, 54 g protein, 17 g fat, 48 g carbohydrates, 60 mg cholesterol, and 10 g fibers. The HAGE meal (15.100 kU AGE) was prepared by frying or broiling at 230 °C for 20 min, whereas the LAGE meal (2750 kU AGE) was prepared by steaming or boiling at 100 °C for 10 min. The subjects were instructed to eat the test meal within 30 min.

Assessment of vascular function

Am J Clin Nutr 85:1236-43

macrocirculatory function was assessed by measuring

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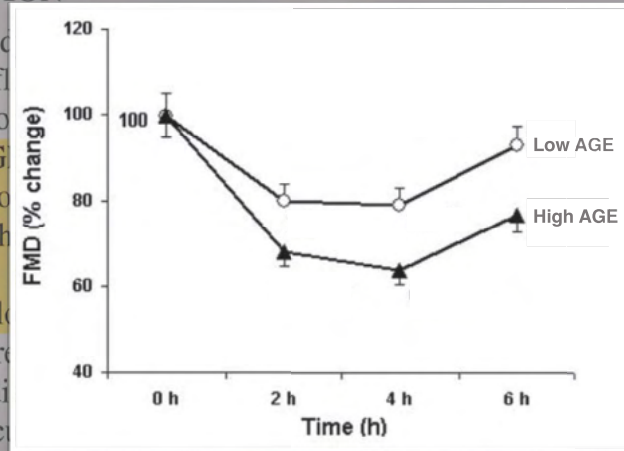
Am J Clin Nutr 85:1236-43

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DISCUSSION

Our study shows that a meal induces endothelial dysfunction in “real-life” HAGE and microvascular dysfunction (reduced by five-fold).

These results show that postprandial hypertriglycerolemia (7, 28, 29) and add AGEs and dicarbonyls (methylglyoxal) as new factors responsible for these effects. To our



method of measurement of microvascular function in “real-life” conditions is a “real-life” method of measurement of microvascular function in “real-life” conditions. The results show that postprandial hypertriglycerolemia (7, 28, 29) and add AGEs and dicarbonyls (methylglyoxal) as new factors responsible for these effects. To our

understanding of the mechanisms underlying the microvascular dysfunction in “real-life” conditions, at least in the elderly, the role of triglycerides and microvascular dysfunction is already well established. The results show that postprandial hypertriglycerolemia (7, 28, 29) and add AGEs and dicarbonyls (methylglyoxal) as new factors responsible for these effects. To our

food restriction in mice studies enjoys BOTH the benefits of reduction of mTOR plus the benefits of 40% reduction in AGEs.

The AGE Less diet is the name given to diet with reduced AGEs. The AGE Less diet involves no caloric restriction and no medication. It involves avoiding the very worst foods (fried bacon) a reduction in very high AGE foods and cooking with moist heat instead of dry heat. It is about using chemistry to produce less AGEs in foods instead of more AGEs. Anybody who is willing to substitute having a poached egg instead of a fried egg can rather easily adjust to an AGE Less diet.

Am J Clin Nutr 85:1236-43

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The AGE Less diet is the name given to diet with reduced AGEs. The AGE Less diet involves no caloric restriction and no medication. It involves avoiding the very worst foods (fried bacon) a reduction in very high AGE foods and cooking with moist heat instead of dry heat. It is about using chemistry to produce less AGEs in foods instead of more AGEs. Anybody who is willing to substitute having a poached egg instead of a fried egg can rather easily adjust to an AGE Less diet.

restriction show excellent synergy between caloric restriction which reduces mTOR when inadvertently combined with AGE reduction. Although the science of AGEs is very well documented with over 8000 papers listed in PubMed, it is little known to both health care professionals and the general public. In an important regard, the science of AGEs shares a common characteristic with rapamycin; both have zero commercial value.

I consider the combined use of oral intermittent rapamycin and the AGE Less diet to have the best potential to treat aging. However, I do not expect either to become very popular as they both suffer from the



Oral administration of AST-120 (Kremezin) is a promising therapeutic strategy for advanced glycation end product (AGE)-related disorders

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^a Department of Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan

^b Radioisotope Institute for Basic and Clinical Medicine, Kurume University School of Medicine, Kurume, Japan



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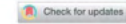
^b *Radioisotope Institute for Basic and Clinical Medicine, Kurume University School of Medicine, Kurume, Japan*

**Oral Activated Charcoal Adsorbent (AST-120)
Ameliorates Chronic Kidney Disease-Induced
Intestinal Epithelial Barrier Disruption**

Nosratola D. Vaziri^a Jun Yuan^a Mahyar Khazaeli^a Yuichi Masuda^b
Hirohito Ichii^b Shuman Liu^a

^aDivision of Nephrology and Hypertension, and ^bDepartment of Surgery, University of California, Irvine, Calif., USA

PERSPECTIVE



Plant-Based Diets for Healthy Aging

Hana Kahleova^a, Susan Levin^a, and Neal D. Barnard^{a,b}

^aDepartment of Medicine, Physicians Committee for Responsible Medicine, Washington, DC, USA; ^bSchool of Medicine and Health Sciences, George Washington University, Washington, DC, USA

ARTICLE HISTORY

Received 24 June 2020
Accepted 29 June 2020

KEYWORDS

Diets; preventative nutrition and chronic disease; general nutrition; aging; plant-based

The world population of adults 60 years old or older is expected to double from 841 million to 2 billion by 2050. The number of individuals 80 or older will more than triple, reaching almost 400 million (1). This demographic shift

Particularly intriguing is emerging evidence that diet plays a major role in the prevention of age-related cognitive decline and Alzheimer's disease. It has been shown that a diet rich in fruits, grains, legumes, vegetables, nuts, and

PERSPECTIVE



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JAMA | Original Investigation

The State of US Health, 1990-2016

Burden of Diseases, Injuries, and Risk Factors Among US States

The US Burden of Disease Collaborators

INTRODUCTION Several studies have measured health outcomes in the United States, but none have provided a comprehensive assessment of patterns of health by state.

OBJECTIVE To use the results of the Global Burden of Disease Study (G6D) to report trends in the burden of diseases, injuries, and risk factors at the state level from 1990 to 2016.

DESIGN AND SETTING A systematic analysis of published studies and available data sources estimates the burden of disease by age, sex, geography, and year.


MAIN OUTCOMES AND MEASURES Prevalence, incidence, mortality, life expectancy, healthy life expectancy (HALE), years of life lost (YLLs) due to premature mortality, years lived with disability (YLDs), and disability-adjusted life-years (DALYs) for 333 causes and 84 risk factors with 95% uncertainty intervals (UIs) were computed.

RESULTS Between 1990 and 2016, overall death rates in the United States declined from 745.2 (95% UI, 740.6 to 749.8) per 100,000 persons to 578.0 (95% UI, 569.4 to 587.1) per

 [Editorial page 1438](#)

 [Author Audio Interview](#)

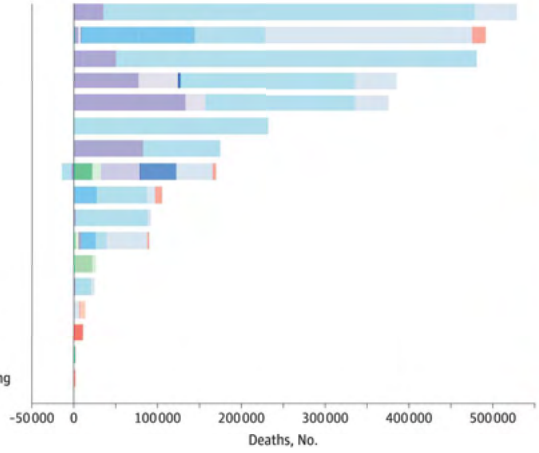
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A Risk factors and related deaths

Risk factors

- Dietary risks
- Tobacco use
- High systolic blood pressure
- High body mass index
- High fasting plasma glucose
- High total cholesterol
- Impaired kidney function
- Alcohol and drug use
- Air pollution
- Low physical activity
- Occupational risks
- Low bone mineral density
- Residential radon and lead exposure
- Unsafe sex
- Child and maternal malnutrition
- Sexual abuse and violence
- Unsafe water, sanitation, and handwashing



Communicable, maternal, neonatal, and nutritional diseases

- HIV/AIDS and tuberculosis
- Diarrhea, lower respiratory tract, and other common infectious diseases
- Maternal disorders
- Neonatal disorders
- Nutritional deficiencies
- Other communicable maternal, neonatal, and nutritional diseases

Noncommunicable diseases

- Neoplasms
- Cardiovascular diseases
- Chronic respiratory diseases
- Cirrhosis and other chronic liver diseases
- Digestive diseases
- Neurological disorders
- Mental and substance use disorders
- Diabetes, urogenital, blood, and endocrine diseases
- Musculoskeletal disorders
- Other noncommunicable diseases

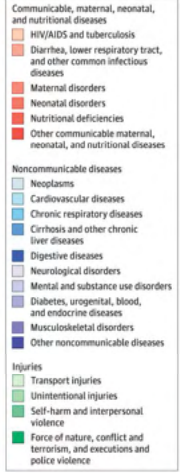
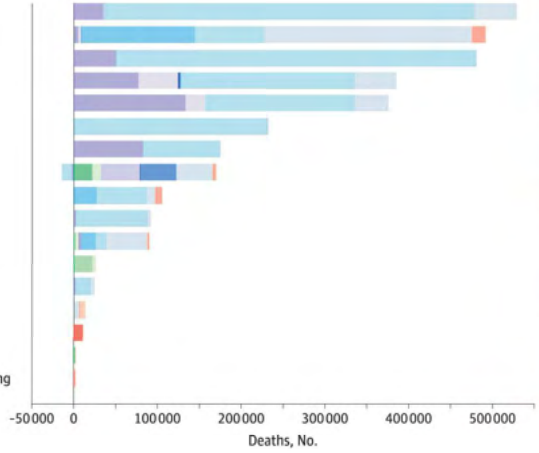
Injuries

- Transport injuries
- Unintentional injuries
- Self-harm and interpersonal violence
- Force of nature, conflict and terrorism, and executions and police violence

A Risk factors and related deaths

Risk factors

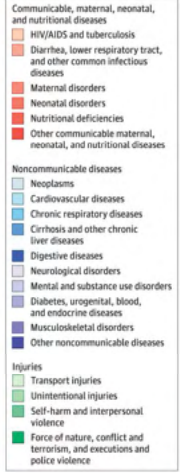
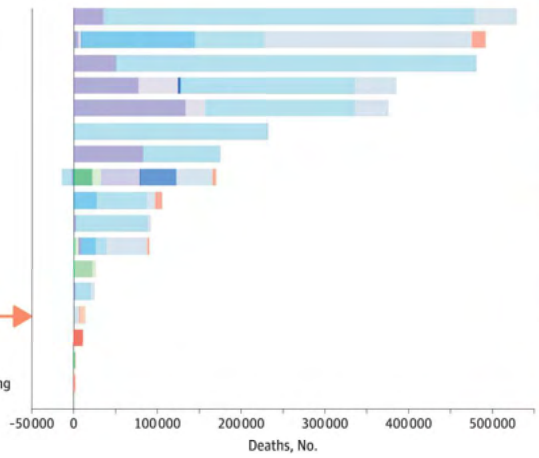
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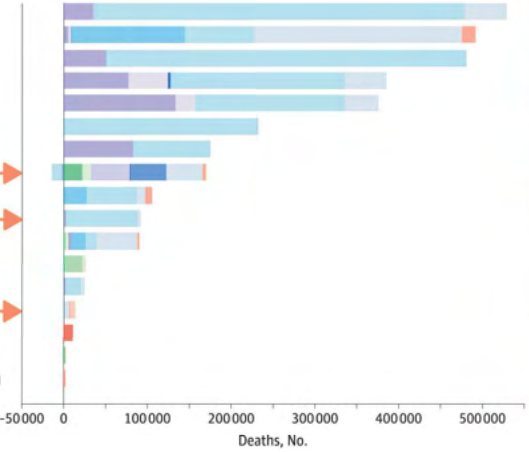
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RESEARCH ARTICLE

Estimating impact of food choices on life expectancy: A modeling study

Lars T. Fadnes^{1,2*}, Jan-Magnus Økland^{1,3}, Øystein A. Haaland^{1,3}, Kjell Arne Johansson^{1,2,3}

1 Department of Global Public Health and Primary Care, University of Bergen, Norway, **2** Bergen Addiction Research, Department of Addiction Medicine, Haukeland University Hospital, Bergen, Norway, **3** Bergen Center for Ethics and Priority Setting, University of Bergen, Norway

☉ These authors contributed equally to this work.

* lars.fadnes@uib.no



Abstract

Background

Interpreting and utilizing the findings of nutritional research can be challenging to clinicians,

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RESEARCH ARTICLE

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© These authors contributed equally to this work.

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Abstract

Background

Interpreting and utilizing the findings of nutritional research can be challenging to clinicians,

the diet. An optimal diet had substantially higher intake than a typical diet of whole grains, legumes, fish, fruits, vegetables, and included a handful of nuts, while reducing red and processed meats, sugar-sweetened beverages, and refined grains. A feasibility approach diet was a midpoint between an optimal and a typical Western diet. A sustained change from a typical Western diet to the optimal diet from age 20 years would increase LE by more than a decade for women from the United States (10.7 [95% UI 8.4 to 12.3] years) and men (13.0 [95% UI 9.4 to 14.3] years). The largest gains would be made by eating more legumes (females: 2.2 [95% UI 1.1 to 3.4]; males: 2.5 [95% UI 1.1 to 3.9]), whole grains (females: 2.0 [95% UI 1.3 to 2.7]; males: 2.3 [95% UI 1.6 to 3.0]), and nuts (females: 1.7 [95% UI 1.5 to 2.0]; males: 2.0 [95% UI 1.7 to 2.3]), and less red meat (females: 1.6 [95% UI 1.5 to 1.8]; males: 1.9 [95% UI 1.7 to 2.1]) and processed meat (females: 1.6 [95% UI 1.5 to 1.8]; males: 1.9 [95% UI 1.7 to 2.1]). Changing from a typical diet to the optimized diet at age 60 years would increase LE by 8.0 (95% UI 6.2 to 9.3) years for women and 8.8 (95% UI 6.8 to 10.0) years for men, and 80-year-olds would gain 3.4 years (95% UI females: 2.6 to 3.8/ males: 2.7 to 3.9). Change from typical to feasibility approach diet would increase LE by 6.2 (95% UI 3.5 to 8.1) years for 20-year-old women from the United States and 7.3 (95% UI 4.7

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NIH-AARP Diet and Health Study Reaches Milestone

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October 24, 2019, by Justine E. Yu

In 1995, the NCI launched the NIH-AARP Diet and Health study, a cohort that was, and remains, the largest prospective in-depth study examining the relationship between diet, lifestyle, and cancer risk.

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- [Breaking Ground for a Large Prospective Study](#)
- [Study Characteristics](#)
- [Redefining Diet and Health Research](#)
- [A Resource for Intramural and Extramural Scientists](#)
- [Evolution and Growth with the Advancement of Research and Technology](#)
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Association Between Plant and Animal Protein Intake and Overall and Cause-Specific Mortality

Jiaqi Huang, PhD; Linda M. Liao, PhD, MPH; Stephanie J. Weinstein, PhD; Rashmi Sinha, PhD; Barry I. Graubard, PhD; Demetrius Albanes, MD

[+](#) Supplemental content

IMPORTANCE Although emphasis has recently been placed on the importance of high-protein diets to overall health, a comprehensive analysis of long-term cause-specific mortality in association with the intake of plant protein and animal protein has not been reported.

OBJECTIVE To examine the associations between overall mortality and cause-specific mortality and plant protein intake.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study analyzed data from 416 104 men and women in the US National Institutes of Health–AARP Diet and Health Study from 1995 to 2011. Data were analyzed from October 2018 through April 2020.

EXPOSURES Validated baseline food frequency questionnaire dietary information, including intake of plant protein and animal protein.

MAIN OUTCOMES AND MEASURES Hazard ratios and 16-year absolute risk differences for overall mortality and cause-specific mortality.

RESULTS The final analytic cohort included 237 036 men (57%) and 179 068 women. Their

Huang J, Liao LM, Weinstein SJ, Sinha R, Graubard BI, Albanes D. Association between plant and animal protein intake and overall and cause-specific mortality. JAMA Intern Med. 2020;180(9):1173.

Research

JAMA Internal Medicine | [Original Investigation](#)

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RESULTS The final analytic cohort included 237 036 men (57%) and 179 283 women. Overall median (SD) ages were 62.2 (5.4) years for men and 62.0 (5.4) years for women. Based on 6 009 748 person-years of observation, 77 614 deaths (18.7%) were analyzed. Adjusting for several important clinical and lifestyle factors, greater dietary plant protein intake was associated with reduced overall mortality in both sexes (hazard ratio per 1 SD was 0.95 [95% CI, 0.94-0.97] for men and 0.93-0.96] for women; adjusted absolute risk difference per 1 SD was -0.48% to -0.25%] for men and -0.33% [95% CI, -0.48% to -0.21%] for women). The hazard ratio per 10 g/1000 kcal was 0.88 [95% CI, 0.84-0.91] for men and 0.8

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RESEARCH ARTICLE

Open Access

Association between plant-based dietary pattern and biological aging trajectory in a large prospective cohort



Sicong Wang^{1,2†}, Wenyuan Li^{1†}, Shu Li¹, Huakang Tu¹, Junlin Jia¹, Wenting Zhao¹, Andi Xu¹, Wenxin Xu¹, Min Kuang Tsai³, David Ta-Wei Chu⁴, Chi Pang Wen^{3,5,6*} and Xifeng Wu^{1,7,8*} 

Abstract

Background Aging is a dynamic and heterogeneous process that may better be captured by trajectories of aging biomarkers. Biological age has been advocated as a better biomarker of aging than chronological age, and plant-based dietary patterns have been found to be linked to aging. However, the associations of biological age trajectories with mortality and plant-based dietary patterns remained unclear.



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ORIGINAL PAPER

Aging Cell  WILEY

DNA methylation-based biomarkers of aging were slowed down in a two-year diet and physical activity intervention trial: the DAMA study

Giovanni Fiorito^{1,2}  | Saverio Caini³ | Domenico Palli³  | Benedetta Bendinelli³ | Calogero Saieva³ | Ilaria Ermini³ | Virginia Valentini⁴ | Melania Assedi³ | Piera Rizzolo⁴ | Daniela Ambrogetti³ | Laura Ottini⁴ | Giovanna Masala³

¹Laboratory of Biostatistics, Department of Biomedical Sciences, University of Sassari, Sassari, Italy

²MRC-PHE Centre for Environment 43 and Health, Imperial College London, London, UK

Abstract

Several biomarkers of healthy aging have been proposed in recent years, including the epigenetic clocks, based on DNA methylation (DNAm) measures, which are getting increasingly accurate in predicting the individual biological age. The recently

(diet, PA, diet+PA, and control) according to a permuted-block randomization scheme stratified by age (50–59 vs. 60–69 years) and body mass index (BMI) category (<25 vs. ≥ 25 kg/m²), with a constant block size (n=4).

Study participants assigned to the dietary intervention (*arm 1*) were counseled to adopt a diet based on the consumption of plant foods, with a low glycemic load, low in saturated- and *trans*-fats and alcohol, and rich in antioxidants. The change in dietary habits was aimed to be achieved in an isocaloric context, as no advice was given about the quantity of food to be consumed. The intervention objectives included: (a) replacement of refined grains with whole grains; (b) consumption of at least one portion of raw vegetables and one

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the delta DNAmGrimAA and delta EML as the outcomes (control group as the reference). The dietary intervention led to a significant reduction of delta DNAmGrimAA ($\beta = -0.66$, 95% CI -1.15 to -0.17, $p = 0.01$, Table 3), whereas the PA intervention caused a significant reduction of the delta EML ($\beta = -2.06$, 95% CI -2.84 to -1.28, $p < 0.0001$, Table 3). There was no significant reduction of DNAmGrimAA associated with the PA intervention nor reduced EML associated with the dietary intervention (Table 3). For both DNAmGrimAA and EML, the estimated differences presented in Table 3 (i.e., the β coefficients) can be interpreted as the change in biological age (in years) compared with the reference group (see Methods for more details).

Changes in Dietary Intake of Animal and Vegetable Protein and Unhealthy Aging



Rosario Ortolá, MD, PhD,^{a,b} Ellen A. Struijk, PhD,^{a,b} Esther García-Esquinas, MD, PhD,^{a,b}
Fernando Rodríguez-Artalejo, MD, PhD,^{a,b,c} Esther Lopez-García, PhD^{a,b,c}

^aDepartment of Preventive Medicine and Public Health, Universidad Autónoma de Madrid and IdiPAZ, Madrid, Spain; ^bCIBER of Epidemiology and Public Health (CIBERESP), Madrid, Spain; ^cIMDEA Food Institute, CEI UAM + CSIC, Madrid, Spain.

ABSTRACT

BACKGROUND: Animal and vegetable-based proteins differ on their effect on many health outcomes, but their relationship with unhealthy aging is uncertain. Thus, we examined the association between changes in animal and vegetable protein intake and unhealthy aging in older adults.

METHODS: Data came from 1951 individuals aged ≥ 60 years recruited in the Seniors-ENRICA cohort in 2008-2010 (wave 0) and followed-up in 2012 (wave 1), 2015 (wave 2), and 2017 (wave 3). Dietary protein intake was measured with a validated diet history at waves 0 and 1, and unhealthy aging was measured

both animal and vegetable protein.³⁰

Macronutrients were expressed as percentages of total energy intake, and changes in total energy and macronutrient intake from wave 0 to wave 1 were calculated.

Deficit Accumulation Index. At each wave, unhealthy aging was measured using a 52-item DAI with 4 domains: functional impairments, self-reported health/vitality, mental health, and morbidities/use of health services. The overall and domain-specific DAI scores were calculated as the total sum of points assigned to each deficit divided by the number of deficits considered and further multiplied by 100 to obtain a range from 0 (lowest) to 100% (highest deficit accumulation). A detailed description of this index is provided in the Methodological

0.97), and dementia mortality (HR, 0.79; 95% CI, 0.67–0.94) (Table 2). Plant protein intake was not associated with cancer mortality (Table 3). Competing risk analysis for dementia mortality revealed similar results (Table S1).

Substituting 5% energy of animal protein with plant protein was associated with a lower risk of all-cause mortality (HR, 0.86; 95% CI, 0.81–0.91), CVD mortality (HR, 0.78, 95% CI, 0.70–0.87), and dementia mortality (HR, 0.81, 95% CI, 0.68–0.97) (Figure 1). Substituting 5% energy of animal protein with plant protein was not associated with cancer mortality. The results of sensitivity analyses were similar when women in the CT were excluded or deaths occurring within 3 years after base-

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Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017



GBD 2017 Diet Collaborators*

Summary

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This online publication has been corrected. The corrected version first appeared at [thelancet.com](http://www.thelancet.com) on June 24, 2021.

See [Comment](#) page 1916

*Collaborators listed at the end

Background Suboptimal diet is an important preventable risk factor for non-communicable diseases (NCDs); however, its impact on the burden of NCDs has not been systematically evaluated. This study aimed to evaluate the consumption of major foods and nutrients across 195 countries and to quantify the impact of their suboptimal intake on NCD mortality and morbidity.

Methods By use of a comparative risk assessment approach, we estimated the proportion of disease-specific burden attributable to each dietary risk factor (also referred to as population attributable fraction) among adults aged 25 years or older. The main inputs to this analysis included the intake of each dietary factor, the effect size of the dietary factor on disease endpoint, and the level of intake associated with the lowest risk of mortality. Then, by use of disease-specific population attributable fractions, mortality, and disability-adjusted life-years (DALYs), we calculated the



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CLINICAL RESEARCH

Epidemiology and prevention

Adding salt to foods and hazard of premature mortality

Hao Ma¹, Qiaochu Xue¹, Xuan Wang¹, Xiang Li¹, Oscar H. Franco², Yanping Li³,
Yoriko Heianza¹, JoAnn E. Manson^{3,4,5}, and Lu Qi^{1,6*}

¹Department of Epidemiology, School of Public Health and Tropical Medicine, Tulane University, 1440 Canal Street, Suite 1724, New Orleans, LA, USA; ²Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland; ³Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; ⁴Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA; ⁵Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; and ⁶Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA

Received 14 September 2021; revised 11 March 2022; accepted 7 April 2022

Abstract

Aims

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Results

A total of 501 379 participants from UK biobank who completed the questionnaire on the frequency of adding salt to foods at baseline. The information on the frequency of adding salt to foods (do not include salt used in cooking) was collected through a touch-screen questionnaire at baseline. We found graded relationships between higher frequency of adding salt to foods and higher concentrations of spot urinary sodium or estimated 24-h sodium excretion. During a median of 9.0 years of follow-up, 18 474 premature deaths were documented. The multivariable hazard ratios [95% confidence interval (CI)] of all-cause premature mortality across the increasing frequency of adding salt to foods were 1.00 (reference), 1.02 (0.99, 1.06), 1.07 (1.02, 1.11), and 1.28 (1.20, 1.35) (P -trend < 0.001). We found that intakes of fruits and vegetables significantly modified the associations between the frequency of adding salt to foods and all-cause premature mortality, which were more pronounced in participants with low intakes than those with high intakes of these foods (P -interaction = 0.02). In addition, compared with the never/rarely group, always adding salt to foods was related to 1.50 (95% CI, 0.72–2.30) and 2.28 (95% CI, 1.66–2.90) years lower life expectancy at the age of 50 years in women and men, respectively.

Conclusions

Our findings indicate that higher frequency of adding salt to foods is associated with a higher hazard of all-cause premature mortality and lower life expectancy.

Effect of potassium-enriched salt on cardiovascular mortality and medical expenses of elderly men¹⁻³

Hsing-Yi Chang, Yu-Whuei Hu, Ching-Syang Jack Yue, Yu-Wen Wen, Wen-Ting Yeh, Li-San Hsu, Shin-Yin Tsai, and Wen-Harn Pan

ABSTRACT

Background: The beneficial effects of potassium-enriched salt on blood pressure have been reported in a few short-term trials. The long-term effects of potassium-enriched salt on cardiovascular mortality have not been carefully studied.

Objective: The objective was to examine the effects of potassium-enriched salt on cardiovascular disease (CVD) mortality and medical expenditures in elderly veterans.

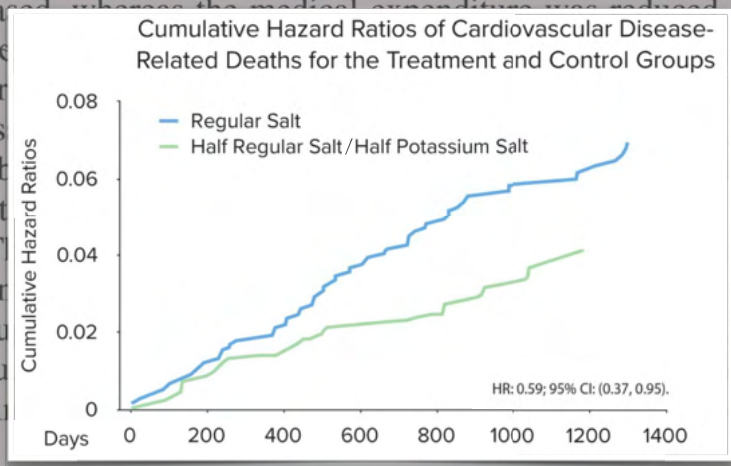
Design: Five kitchens of a veteran retirement home were randomized into 2 groups (experimental or control) and veterans assigned to those kitchens were given either potassium-enriched salt (experi-

sodium, potassium, calcium, and fatty acid composition and obesity are considered among the contributing factors for the development of hypertension (5). Both observational and experimental studies have repeatedly shown that the level of sodium intake is positively associated with blood pressure (6-9). Although there were many contradictory findings, they were primarily due to the limitations of the study designs and methods such as not measuring confounders, low statistical power of within-population studies, and regression dilution bias caused by large within-person variations in sodium intake.

The Nutrition and Health Survey in Taiwan found that the



proportional hazard models confirmed the results: the effect in CVD mortality reduction was statistically significant. Compared with the control group, the estimated life expectancy was increased, whereas the medical expenditure was reduced in the experimental group. The blood pressure in the experimental group was lower than in the control group. The estimated life expectancy was increased by 17% in the experimental group. The medical expenditure was reduced by 17% in the experimental group. The results were consistent with the results of the previous study.



mortality, although the relative risk of all-cause mortality did not reach statistical significance.

The estimated life expectancy for the group of veterans aged 70 y could be used to show how potassium-enriched salt substantially reduces mortality risks. In Taiwan, the average male life expectancy at age 70 y improved 0.05 y naturally in the past 20 y (29). The life expectancy difference at age 70 y between the 2 groups (0.90 y) is equivalent to that which would have naturally occurred in 14 y.

Many researchers have provided strong evidence on the relation between sodium and blood pressure (17, 18, 30) to contradict the arguments by Alderman (15) and Freeman (16). However, most of these studies were observational epidemiologic studies. In addition, most sodium reduction trials were short-term and used blood pressure reduction as the primary endpoint. Recently,

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Again, we appreciate the opportunity to present the views of our industry, both in formal comments and in the personal meeting with the committee staff.

Sincerely,

WILLIAM E. DICKINSON, *President.*

Enclosure.

STATEMENT OF THE SALT INSTITUTE—RE: "DIETARY GOALS FOR THE UNITED STATES"

The Salt Institute is a trade association that represents the interests of the world's major salt producers. It is concerned with all salt uses, including the nutritional value of salt as a food, and with criticism of salt.

Salt is essential to life, so much so, that the body has a built-in regulator—the kidneys—to remove excess salt or to retain salt if the amount in the body is deficient. It is a scientifically supported fact that too little salt can have a serious effect on the human body and, in some cases, loss of too much salt could even be fatal.

The role of sodium in hypertension has been the subject of debate for many years. Positions in the medical profession range from little or no concern for the role of sodium intake to suggestions that high sodium intake may be a cause of hypertension.

ment that "improved nutrition might cut the nation's health bill by one third." This is a laudable objective, but it is not realistic. Degenerative diseases inevitably accompany old age. Indeed, health care expenditures increase if the lifespan is prolonged. Dr. John Cairns pointed out that if tobacco were banned from the United Kingdom, the increase in the expected lifespan would simultaneously increase the cost of care of old people, which comes under the category of health care expenditures.

On page 10 the following quotation from Canada's Minister of National Health and Welfare appears:

Even such a simple question as whether one should severely limit his consumption of butter and eggs can be a subject of endless scientific debate.

Faced with conflicting scientific opinions of this kind, it would be easy for health educators and promoters to sit on their hands; it certainly makes it easy for those who abuse their health to find a real "scientific" excuse.

But many of Canada's health problems are sufficiently pressing that action has to be taken even if all scientific evidence is not in.

This is the kind of talk that leads to the popularity of fake "cancer cures."

Page 12 lists the "United States Dietary Goals" (see above)—in other words, the Committee's own dietary goals for Americans. The

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Bone Quality: An Empty Term

Harri Sievänen, Pekka Kannus, Teppo L. N. Järvinen*

Although the concept of “bone quality” is at least 15 years old [1], the term has recently sparked much discussion and debate among clinicians and clinical researchers [2–5]. At a recent National Institutes of Health conference on bone quality, the term was defined as: “The sum total of *characteristics of the bone* that influence the *bone’s resistance to fracture*” [6].

Where Did the Definition Come From?

This definition arose from the results of multicenter clinical trials that evaluated the effects of two classes of drugs—antiresorptive bisphosphonate therapy (alendronate and risedronate) and selective estrogen receptor

a solution to the classic paradox of osteoporosis: while low BMD values are associated with increased relative risk of fracture at the *population level*, the predictive value of BMD in an *individual patient* remains quite marginal [13–15]. And to further support the concept of bone quality, inclusion of increased bone turnover in fracture-predicting models has somewhat improved the ability to predict fracture risk independently of BMD [8,16–19].

Flaws in the Concept

Although the concept of bone quality might seem attractive for all of the reasons discussed above, nevertheless the notion has three major conceptual flaws.

fallacy. Basically, BMD reflects the bulk of material (bone mass) of which the bone, as an organ, is made [22]. BMD thus denotes a lumped measure of virtually everything within the measured bone site (i.e., bone cross-sectional size and dimensions, cortical thickness and porosity, trabecular thickness and number, mineralization of bone material), but it denotes nothing specifically. Thus, there is not much left to be accounted for by subtle architectural and material properties (i.e., factors that allegedly account for bone quality). This simply means that BMD and most bone quality characteristics, measurable *in vivo*, are intertwined and largely *inseparable*.

Flaws in defining bone quality. Third,

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doi: 10.1111/joim.12366

Watch Dr. Järvinen talk about the 11th Key Symposium: Osteoporosis: the emperor has no clothes [here](#).

Osteoporosis: the emperor has no clothes

■ T. L. N. Järvinen¹, K. Michaëlsson², P. Aspenberg³ & H. Sievänen⁴

From the ¹Department of Orthopaedics and Traumatology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland, ²Section of Orthopaedics, Department of Surgical Sciences, Uppsala University, Uppsala; ³Clinical Sciences, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden, and ⁴The UKK Institute for Health Promotion Research, Tampere, Finland

Abstract. Järvinen TLN, Michaëlsson K, Aspenberg P, Sievänen H (University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland; Uppsala University, Uppsala; Linköping University, Linköping, Sweden; and The UKK Institute for Health Promotion Research, Tampere, Finland). Osteoporosis: the emperor has no clothes. (Key Symposium). *J Intern Med* 2015; **277**: 662–673.

Current prevention strategies for low-trauma fractures amongst older persons depend on the notions that fractures are mainly caused by osteoporosis (pathophysiology), that patients at high risk can be identified (screening) and that the risk is amenable

multifactorial prediction tools are unable to identify a large proportion of patients who will sustain a fracture, whereas many of those with a high fracture risk score will not sustain a fracture.

Treatment. The evidence for the viability of bone-targeted pharmacotherapy in preventing hip fracture and other clinical fragility fractures is mainly limited to women aged 65–80 years with osteoporosis, whereas the proof of hip fracture-preventing efficacy in women over 80 years of age and in men at all ages is meagre or absent. Further, the antihip fracture efficacy shown in clinical trials is absent in real-life studies. Many drugs for the treatment of osteoporosis have also been associated with

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Osteoporosis: the emperor has no clothes

■ T. L. N. Järvinen¹, K. Michaëlsson², P. Aspenberg³ & H. Sievänen⁴

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Fig. 2 Fractures are primarily due to falling, not osteoporosis. Despite a wide consensus that fractures in adults are 'osteoporotic', evidence indisputably shows that both hip and vertebral fractures are predominantly traumatic (caused by an injury).

vertebra [35, 37] (Fig. 1). Only one-third of the X-ray changes termed vertebral fractures are symptomatic [38], and the occurrence of vertebral fractures poorly predicts either the existence of back pain or the functional status of the spine [39, 40].

Although it is commonly argued that vertebral fractures increase the risk of death, it should be noted that almost every illness in older adults, by virtue of the definition of the word 'illness' as an indicator of frailty and weakness, is related to increased morbidity and mortality, but is seldom a truly independent risk factor or direct cause of death. Accordingly, the more relevant question is, how much of the increased *morbidity and mortality* risk associated with vertebral fractures can be reduced by bone-targeted pharmacotherapy? As demonstrated herein, there is no evidence that pharmacotherapy would either provide a clinically relevant reduction in vertebral fractures or reduce the related mortality risk (see below).

Do fractures cause excess mortality?

One of the most common arguments for screening and treatment of osteoporosis is that fractures cause excess mortality, and therefore, bone-tar-



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REVIEW ARTICLE

The effectiveness of exercises on fall and fracture prevention amongst community elderlies: A systematic review and meta-analysis



R.M.Y. Wong, K.C. Chong, S.W. Law, W.T. Ho, J. Li, C.S. Chui, S.K.H. Chow, W.H. Cheung*

Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong, Hong Kong

ARTICLE INFO

Keywords:
Exercise
Fall
Fracture
Prevention
Systematic review

SUMMARY

Objective: To analyze the effectiveness of exercise interventions on falls and fall-related fracture prevention among community-dwelling elderlies.
Methods: Literature search was conducted in Pubmed and Embase. Keywords used for literature search were "fracture" AND "fall" AND "exercise". Randomized controlled trials involving community-dwelling elderlies older than 60 years old with physical exercises as intervention were included. A systematic review and meta-analysis was performed. The primary outcomes were falls and fractures.

Combined resistance and balance-jumping exercise reduces older women's injurious falls and fractures: 5-year follow-up study

SAIJA KARINKANTA¹, PEKKA KANNUS^{1,2}, KIRSTI UUSI-RASI¹, ARI HEINONEN³, HARRI SIEVÄNEN¹

¹The UKK Institute for Health Promotion Research, Tampere 33501, Finland

²Medical School, University of Tampere, and Department of Orthopaedics and Trauma Surgery, Tampere University Hospital, Tampere, Finland

³Department of Health Sciences, University of Jyväskylä, Jyväskylä, Finland

Address correspondence to: S. Karinkanta. Tel: (+358) 328291111. Email: saija.karinkanta@uta.fi

Abstract

Background and objective: resistance and balance-jumping exercise study (RCT) showed that combined

Abstract

Background and objective: previously, a randomised controlled exercise intervention study (RCT) showed that combined resistance and balance-jumping training (COMB) improved physical functioning and bone strength. The purpose of this follow-up study was to assess whether this exercise intervention had long-lasting effects in reducing injurious falls and fractures.

Design: five-year health-care register-based follow-up study after a 1-year, four-arm RCT.

Setting: community-dwelling older women in Finland.

Subjects: one hundred and forty-five of the original 149 RCT participants; women aged 70–78 years at the beginning.

Methods: participants' health-care visits were collected from computerised patient register. An injurious fall was defined as an event in which the subject contacted the health-care professionals or was taken to a hospital, due to a fall. The rate of injured fallers was assessed by Cox proportional hazards model (hazard ratio, HR), and the rate of injurious falls and fractures by Poisson regression (risk ratio, RR).

Results: eighty-one injurious falls including 26 fractures occurred during the follow-up. The rate of injured fallers was 62% lower in COMB group compared with the controls (HR 0.38, 95% CI 0.17 to 0.85). In addition, COMB group had 51% less injurious falls (RR 0.49, 95% CI 0.25 to 0.98) and 74% less fractures (RR 0.26, 95% CI 0.07 to 0.97).

Conclusions: home-dwelling older women who participated in a 12-month intensive multi-component exercise training showed a reduced incidence for injurious falls during 5-year post-intervention period. Reduction in fractures was also evident. These long-term effects need to be confirmed in future studies.

Keywords: exercise, injurious falls, fractures, older adults

Introduction

Fall-related injuries of older adults cause a lot of suffering and costs [1, 2]. Every third older adult aged 65 years or

Many risk factors for falls and fall-induced injuries are related to physical inactivity and decreased functional capacity, and also to bone fragility. All these can be modified by physical activity [12]. Many epidemiological studies show the

Is there any *real-life* evidence? Whilst confounding by indication is an obvious risk in these studies, they actually provide pertinent evidence about the feasibility of using bone-modifying drugs to prevent fractures. However, existing real-life data do not support clear clinically relevant antifracture (including hip fracture) effects of bisphosphonates or any other compounds [74–80]. For example, in a recent Canadian study it was found that despite greater than fourfold differences between provinces in prescribing rates of osteoporosis medication in those aged >55, there were still no between-prov-
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J Intern Med 277:662-73

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Medical News & Perspectives

Amid Osteoporosis Treatment Crisis, Experts Suggest Addressing Patients' Bisphosphonate Concerns

Jennifer Abbasi

Several times a month, orthopedic surgeon Anna N. Miller, MD, repairs an unusual type of thigh bone break that can afflict elderly patients being treated for osteoporosis. Known as atypical femur fractures, these breaks occur not after a fall or other trauma, but during routine activities, like walking, twisting at the waist, or even just standing still. The injuries are devastating, Miller says, often requiring multiple surgeries, a stay at a rehabilitation facility, and months to walk normally again.

Worse yet, many atypical femur fractures can feel like a too-cruel joke to patients because they aren't directly caused by

It's not clear why the adverse effects occur. Bisphosphonates and the monoclonal antibody denosumab are the first-line drugs prescribed for osteoporosis. They inhibit bone resorption and turnover, reducing the disease's hallmark bone loss. Some believe the drugs slow the remodeling process needed to repair tiny cracks that occur in bones. According to Miller, the thigh bone is one of the skeleton's highest stressed regions, making it particularly vulnerable to these microcracks. Over years of use, antiresorptive drugs essentially freeze bone repair in place, she says. Occasionally, minuscule cracks may progress, giving rise to atypical femur fractures

preventing approximately 100 osteoporotic fractures.

Yet for many patients who have heard about the snapped femurs and crumbling jaws—both have been the subject of news reports and lawsuits—the statistics aren't reassuring. "I think the patient mindset is, 'Yeah, the risk is low, but what if it happens to me?'" says Sundeep Khosla, MD, an osteoporosis clinician and researcher at the Mayo Clinic.

Physicians report that fearful patients are turning down prescriptions they need to prevent life-limiting fractures. Qualms about bisphosphonates, and by extension all osteoporosis drugs, could be adding to what

that can afflict elderly patients being treated for osteoporosis. Known as atypical femur fractures, these breaks occur not after a fall or other trauma, but during routine activities, like walking, twisting at the waist, or even just standing still. The injuries are devastating, Miller says, often requiring multiple surgeries, a stay at a rehabilitation facility, and months to walk normally again.

Worse yet, many atypical femur fractures can feel like a too-cruel joke to patients because they aren't directly caused by their bone disease. Rather, they may be an adverse effect of bisphosphonates—the very medications that treat osteoporosis.

That's one side of the story, the one that

drugs prescribed for osteoporosis inhibit bone resorption and reduce the disease's hallmark pain. Some believe the drugs slow the healing process needed to repair the microcracks that occur in bones. According to Miller, the thigh bone is one of the skeleton's most stressed regions, making it particularly vulnerable to these microcracks. Because of this, she says, antiresorptive drugs essentially freeze bone repair in place, and even minuscule cracks may progress to atypical femur fractures.

Osteonecrosis of the jaw occurs only in people taking high-dose bisphosphonates, a common side effect of chemotherapy-related bone treatments that has spread to

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Atypical bilateral femoral fractures: a rare adverse effect of long-term bisphosphonate use

Oluwatobi O Onafowokan 

Department of Orthopaedic Surgery, Salford Royal Hospital, Salford, UK

Correspondence to
Oluwatobi O Onafowokan;
tonafowokan7@gmail.com

Accepted 19 August 2021

DESCRIPTION

A 69-year-old man presented with deformities to his mid-thighs bilaterally and inability to weight-bear. He had fallen from standing height after tripping over a loose rug at his home. He suffered no other injuries and examination indicated no neurovascular deficits. Prior to injury, he had been independently mobile and fully weight-bearing without issue. Plain radiographs indicated bilateral femoral shaft fractures ([figures 1 and 2](#)). There was no clinical or radiographical evidence of pelvic or proximal femoral fractures. His medical history included osteoporosis, coronary angioplasty and hypertension. His current medication included:



RESEARCH

Open Access



A randomized trial of the effects of flaxseed to manage constipation, weight, glycemia, and lipids in constipated patients with type 2 diabetes

Noureddin Soltanian and Mohsen Janghorbani*

Abstract

Background: To compare the effects of baked flaxseed versus those who received a placebo on constipation symptom scores, weight, glycemic and lipid control in constipated patients with type 2 diabetes (T2D).

Methods: In a single-blinded, randomized controlled trial, 53 constipated patients with T2D with body mass index (BMI) 20.5–48.9 kg/m² received either 10 g of flaxseed pre-mixed in cookies twice per day or placebo cookies for

Abstract

Background: To compare the effects of baked flaxseed versus those who received a placebo on constipation symptom scores, weight, glycemic and lipid control in constipated patients with type 2 diabetes (T2D).

Methods: In a single-blinded, randomized controlled trial, 53 constipated patients with T2D with body mass index (BMI) 20.5–48.9 kg/m² received either 10 g of flaxseed pre-mixed in cookies twice per day or placebo cookies for 12 weeks. The constipation symptom scores, BMI, fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), and lipid profile were determined at the beginning and end of 4, 8, and 12-week period. Constipation was evaluated with a stool diary (ROME III).

Results: After the 12-week intervention, constipation symptom scores (2.46), weight (– 3.8 kg), BMI (– 1.5 kg/m²), FPG (– 26.7 mg/dl), cholesterol (– 37.3 mg/dl), triglycerides (– 10.4 mg/dl), LDLC (– 21.0 mg/dl), HDLC (4.7 mg/dl), cholesterol/ HDLC ratio (– 1.4 mg/dl) significantly decreased from baseline in the flaxseed group (all *P*-values < 0.05). The differences of absolute change of constipation symptom scores (2.46 vs. 0.41), weight (– 3.8 vs. 0.0 kg), BMI (– 1.5 vs. -0.1 kg/m²), FPG (– 26.7 vs. -1.9 mg/dl), >HbA1c (– 0.8 vs. 1.0%), cholesterol (– 37.3 vs. -10.4 mg/dl), LDLC (– 21.0 vs. -4.3 mg/dl), and HDLC (4.7 vs. -4.4 mg/dl) between the flaxseed and placebo groups were statistically significant (all *P*-values < 0.05). The compliance was good and no adverse effects were observed.

Conclusion: In constipated patients with T2D, flaxseed cookies used as a snack may be a useful tool for decreasing constipation symptoms, weight, glycemic and lipid levels.

Trial registration: irct.ir: IRCT20110416006202N2.

Keywords: Flaxseed, Efficacy, Constipation, Diabetes, Lipid, Glucose



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Randomized Controlled Trial

Effect of flaxseed or psyllium vs. placebo on management of constipation, weight, glycemia, and lipids: A randomized trial in constipated patients with type 2 diabetes



Noureddin Soltanian, Mohsen Janghorbani*

Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

ARTICLE INFO

Article history:
Received 20 October 2018
Accepted 2 November 2018

SUMMARY

Background: Both flaxseed and psyllium have previously been shown to reduce constipation symptoms, weight, glycemic and lipid levels, and we postulate that treatment with flaxseed and psyllium may have similar benefits.

Original Article

Effects of flaxseed supplementation on functional constipation and quality of life in a Chinese population: A randomized trial

Jianqin Sun MS¹, Huijing Bai PhD¹, Jianxia Ma PhD², Ruiyu Zhang BSN¹, Hua Xie PhD¹, Yanmei Zhang PhD³, Mingquan Guo PhD³, Jianfeng Yao MS²

¹Clinical Nutrition Center, Hua Dong Hospital affiliated to Fu Dan University, Shanghai, PR China

²Department of Gastroenterology, Hua Dong Hospital affiliated to Fu Dan University, Shanghai, PR China

³Clinical Laboratory, Hua Dong Hospital affiliated to Fu Dan University, Shanghai, PR China

Background and Objectives: This prospective, randomized, controlled study aimed to evaluate the effects of flaxseed supplementation on functional constipation and quality of life in adult men and women in China. **Methods and Study Design:** 90 subjects with functional constipation diagnosed by the Rome IV criteria were enrolled. Subjects were randomly assigned to receive either 50 g/day flaxseed flour with meals (n=60) or 15 mL/day of a

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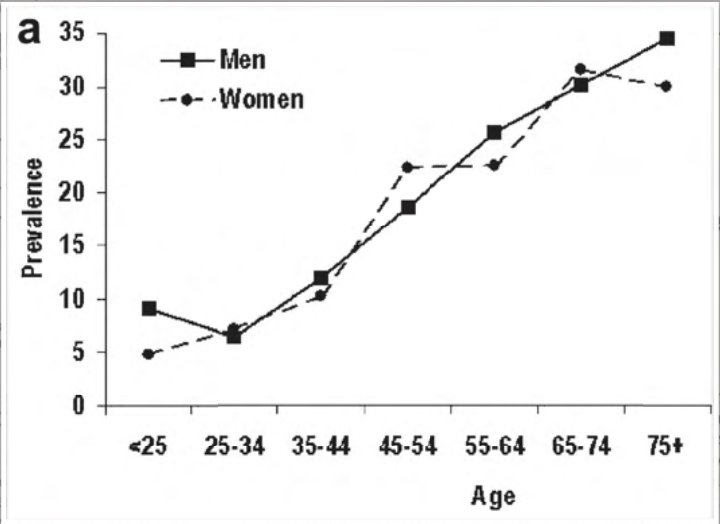
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Abstract Co
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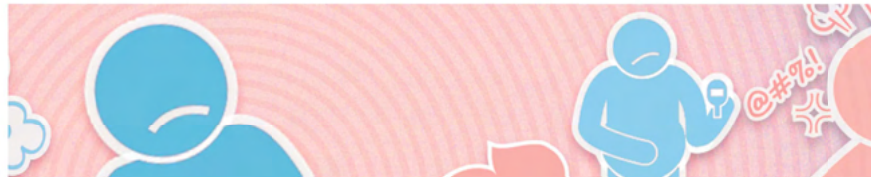
Drug firms helped create \$3 billion overactive bladder market

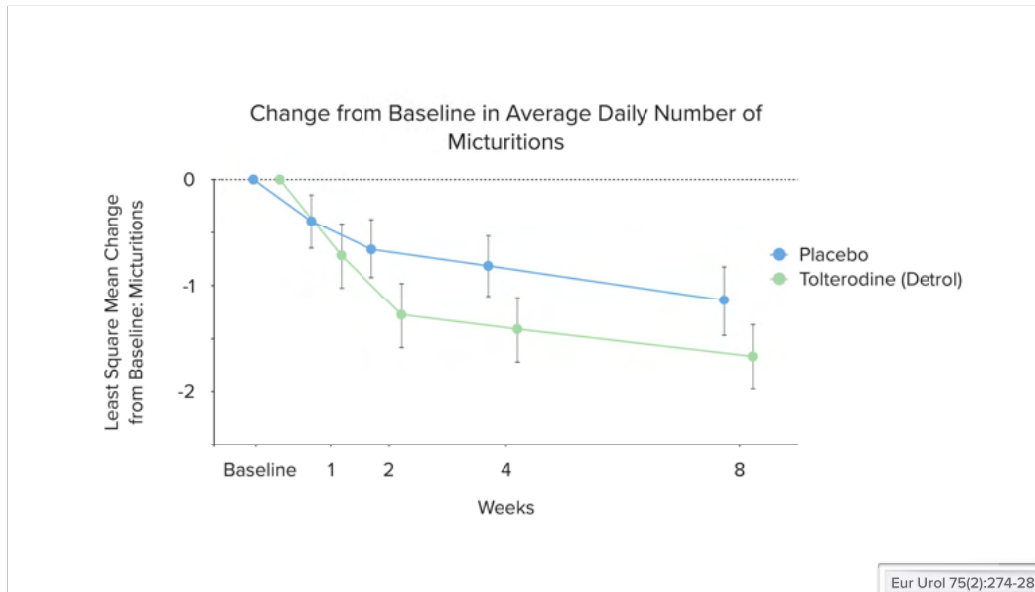
In the push to expand the definition of the condition, and the people who need treatment, even the name 'overactive bladder' was created with marketing in mind.

Kristina Fiore, John Fauber and Matt Wynn MedPage Today and Milwaukee Journal Sentinel

Published 11:04 p.m. CT Oct. 15, 2016 | Updated 3:42 p.m. CT Jan. 6, 2017

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Mitcheson HD, Samanta S, Muldowney K, et al. Vibegron (RVT-901/MK-4618/KRP-114V) administered once daily as monotherapy or concomitantly with tolterodine in patients with an overactive bladder: a multicenter, phase iib, randomized, double-blind, controlled trial. Eur Urol 75(2):274-282

Efficacy of Daily Intake of Dried Cranberry 500 mg in Women with Overactive Bladder: A Randomized, Double-Blind, Placebo Controlled Study



Ahra Cho, Andrew Eidelberg, Daniel J. Butler, David Danko, Ebrahim Afshinnekoo, Christopher E. Mason and Bilal Chughtai*,†

From the Department of Urology (AC, AE, BC), Weill Cornell Medical College-New York Presbyterian Hospital, New York, New York, Tri-Institutional Computational Biology & Medicine Program (DJB, DD, EA, CEM), Weill Cornell Medicine, New York, New York, Department of Physiology and Biophysics (DD), Weill Cornell Medicine, New York, New York, The HHH Prince Alwaleed Bin Talal Bin Abdulaziz Alsaud Institute for Computational Biomedicine (EA, CEM), Weill Cornell Medicine, New York, New York, WorldQuant Initiative for Quantitative Prediction (EA, CEM), Weill Cornell Medicine, New York, New York, and The Feil Family Brain and Mind Research Institute (CEM), Weill Cornell Medicine, New York, New York

Purpose: We sought to determine the efficacy of dried cranberry on reducing symptoms of overactive bladder in women.

Materials and Methods: Eligible women aged 18 or older with overactive bladder were randomized to either daily dried cranberry powder (500 mg) or placebo (500 mg)

**Abbreviations
and Acronyms**

a.u. = arbitrary unit

Cho A, Eidelberg A, Butler DJ, et al. Efficacy of daily intake of dried cranberry 500 mg in women with overactive bladder: a randomized, double-blind, placebo controlled study. Journal of Urology. 2021;205(2):507-513.

DISCUSSION

Overall, we found that dried cranberry powder reduced the mean number of daily micturitions by 1.91 ($p=0.0406$) compared to placebo at 24 weeks (table 5). The reduction of mean micturitions resulting from antimuscarinic agents such as solifenacin 5 mg (-0.78 , $p=0.0018$), solifenacin 10 mg (-1.22 , $p=0.0001$)¹⁷ and tolterodine (-0.54 , $p=0.026$)¹⁸ were at the expense of adverse events such as dry mouth, constipation,



Cochrane Database of Systematic Reviews

Oestrogen therapy for urinary incontinence in post-menopausal women (Review)

Cody JD, Jacobs ML, Richardson K, Moehrer B, Hextall A



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the period after oestrogen treatment had finished and no information about the long-term effects of this therapy was given. Conversely, systemic hormone replacement therapy using conjugated equine oestrogen may worsen incontinence. There were too few data to reliably address other aspects of oestrogen therapy, such as oestrogen type and dose, and no direct evidence comparing routes of administration. The risk of endometrial and breast cancer after long-term use of systemic oestrogen suggests that treatment should be for limited periods, especially in those women with an intact uterus.

PLAIN LANGUAGE SUMMARY

Oestrogens for urinary incontinence in women

Urinary incontinence is the leakage of urine when coughing or exercising (stress urinary incontinence) or after a strong uncontrollable urge to urinate (urgency urinary incontinence). In women who have gone through the menopause, low oestrogen levels may contribute to urinary incontinence. The review found 34 trials including more than 19,000 women of whom over 9000 received oestrogen. The review found that significantly more women who received local (vaginal) oestrogen for incontinence reported that their symptoms improved compared to placebo. There was no evidence about whether the benefits of local oestrogen continue after stopping treatment but this seems unlikely as women would revert to having naturally low oestrogen levels. Trials investigating systemic (oral) administration, on the other hand, found that women reported worsening of their urinary symptoms. The evidence comes mainly from two very large trials including 17,642 incontinent women. These trials were investigating other effects of hormone replacement therapy as well as incontinence, such as prevention of heart attacks in women with coronary heart disease, bone fractures, breast and colorectal cancer. In addition, in one large trial women who did not have incontinence at first were more likely to develop incontinence. There may be risks from long-term use of systemic oestrogen, such as heart disease, stroke and cancer of the breast and uterus.

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Table. Overall results of conservative treatment of genuine stress incontinence

	<i>Pelvic floor exercises (n=26)</i>	<i>Oestrogen (n=24)</i>	<i>Controls (n=25)</i>
Cured and improved	17 (65%)*	3 (12%)	nil
Unchanged	9 (35%)	21 (87%)	25 (100%)

* $P < 0.001$

Summary

The use of three different non-operative techniques for the treatment of female genuine urinary stress incontinence has been assessed by objective means.

One hundred and four patients complaining of stress incontinence were allocated at random to four groups. Sixty-five per cent of patients treated with pelvic floor exercises were significantly improved after 3 months; interferential therapy was effective in 32 per cent of cases. Oestrogen treatment was initially beneficial in 12 per cent

recently that this method has gained international support.

There is conflicting data in the literature regarding the use of oestrogens for the treatment of urinary stress incontinence due to different doses used, routes of administration and methods of investigations (Wilson, 1984).

PATIENTS AND METHODS

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PATIENTS AND METHODS

...based on in vitro studies on rat bladders showing increased muscle contraction.³⁴⁵³

JACKED IN THE BOX

Drugs that inhibit the bladder muscle from contracting can be prescribed for urge incontinence.³⁴⁵⁴ The average cure rate is nearly 50 percent, but they have the list of common side effects I describe above.³⁴⁵⁵ This may help explain why only 14 to 35 percent of people prescribed these drugs are still on them one year later.³⁴⁵⁶ There are no FDA-approved drugs for stress incontinence,³⁴⁵⁷ but surgical interventions have a cure rate exceeding 80 percent.³⁴⁵⁸

Surprisingly, there is considerable evidence that systemic (oral) estrogen therapy may actually worsen incontinence.³⁴⁵⁹ For example, in the Women's Health Initiative, continent women receiving estrogen were approximately twice as likely to develop stress incontinence within the first year, compared to placebo.³⁴⁶⁰ Topical (vaginal) estrogens do seem to help, though, reducing one or two accidents a day.³⁴⁶¹ However, first-line management for urinary incontinence is nonpharmacological and nonsurgical.³⁴⁶² Working five times better than local estrogens in a head-to-head test: pelvic floor (Kegel) exercises.

In 1948, Dr. Arnold H. Kegel published a paper describing a successful therapy for urinary incontinence that involved exercising the hammock of muscles extending from the pubic bone in the front, down and around to the tailbone in the back.³⁴⁶³ To find the right muscles, stop urination midstream. The Mayo Clinic suggests you imagine sitting on a marble and trying to lift it up with your vaginal muscles.³⁴⁶⁴ Contractions held for ten seconds and followed by at least ten seconds

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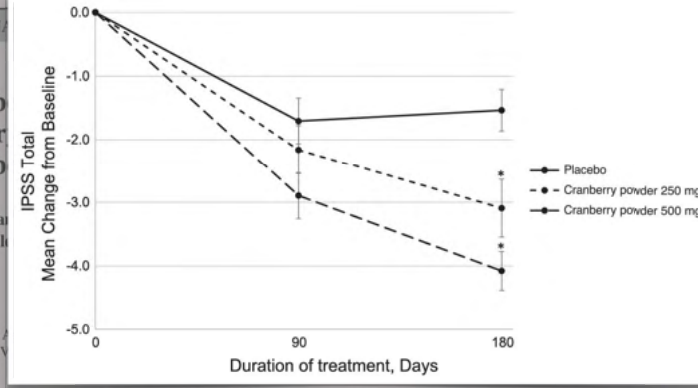
Unfortu-

ORIGINAL

Cranberry powder improves lower urinary tract symptoms in men: a double-blind, randomized, placebo-controlled study

Ales Vidlar
Marc Roll

Received: 9 July 2015
© Springer-Verlag Berlin Heidelberg 2015



Abstract

Background Lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia increase with age. To date, several medications are available to treat LUTS, including

500-mg groups, $p = 0.05$ and $p < 0.001$, respectively) versus the placebo group (-1.5), and a dose-response effect was observed. There were significant differences in Q_{max} , Q_{ave} , PVR, and Vol in the Flowens™ 500-mg group ver-

Vidlar A, Student V, Vostalova J, et al. Cranberry fruit powder (Flowens™) improves lower urinary tract symptoms in men: a double-blind, randomized, placebo-controlled study. World J Urol. 2016;34(3):419-424.

Special Article

Investig Clin Urol 2021;62:520-534.
https://doi.org/10.4111/icu.20210254
pISSN 2466-0493 • eISSN 2466-054X

INVESTIGATIVE AND CLINICAL UROLOGY
ICUROLOGY



***Serenoa repens* for the treatment of lower urinary tract symptoms due to benign prostatic enlargement: A systematic review and meta-analysis**

Leonel Fabrizio Trivisonno¹, Nadia Sgarbossa¹, Gustavo Ariel Alvez², Cecilia Feiras²,
Camila Micaela Escobar Liquitay², Jae Hung Jung^{3,4}, Juan Víctor Ariel Franco^{1,2}

¹Department of Health Science, Universidad Nacional de La Matanza, San Justo, Buenos Aires, ²Department of Research, Instituto Universitario Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, ³Department of Urology, Yonsei University Wonju College of Medicine, Wonju, ⁴Center of Evidence Based Medicine, Institute of Convergence Science, Yonsei University, Seoul, Korea

Purpose: To assess the effects of *Serenoa repens* alone or in combination with other phytotherapy compared to placebo in men

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Effects of Pumpkin Seed in Men with Lower Urinary Tract Symptoms due to Benign Prostatic Hyperplasia in the One-Year, Randomized, Placebo-Controlled GRANU Study

Winfried Vahlensieck^a Christoph Theurer^b Edith Pfitzer^c Brigitte Patz^d
Norbert Banik^e Udo Engelmann^f

^aDepartment of Urology, Kurpark Hospital, Bad Nauheim, ^bPharmaceutical chemist, Cologne, ^cFood engineer, Schwäbisch Gmünd, ^dFreelance Scientific Consulting, Gäufelden, ^eWinicker Norimed Medical Research GmbH, Munich, and ^fDivision of Urologic Oncology, Department of Urology, University of Cologne, Cologne, Germany

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Abstract


Introduction: The German Research Activities on Natural Urologicals (GRANU) study was a randomized, partially blinded, placebo-controlled, parallel-group trial that investigated the efficacy of pumpkin seed in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (BPH/LUTS). **Subjects and Methods:** A total of 1,431 men (50–80 years) with BPH/LUTS were randomly assigned to either pumpkin seed (5 g b.i.d.), capsules with pumpkin seed extract (500 mg b.i.d.) or matching placebo. The primary response criterion was a decrease in International Prostate Symptom Score (IPSS) of ≥ 5 points from baseline after 12 months. Secondary outcome measures included IPSS-related quality of life, IPSS single items and diary-recorded nocturia. **Results:** After 12 months, the response rate (intention to treat/last observation carried forward)

duction in IPSS could not fully justify a recommendation to seed to treat moderate BPH/LUTS. This was substantiated in a cost-effectiveness analysis.

Introduction

Pumpkin seed oil is used for various disorders and has been shown to improve symptoms of lower urinary tract symptoms in men with benign prostatic hyperplasia (BPH). The improvement in symptoms was confirmed in clinical trials. The seed contains a high amount of lycopene, which is a natural antioxidant.

Pumpkin seed oil vs. minoxidil 5% topical foam for the treatment of female pattern hair loss: A randomized comparative trial

Ibrahim M. Ibrahim MD¹ | Mohamed S. Hasan MD¹ | Khaled I. Elsabaa MSc¹ |
Mohamed L. Elsaie MD² 

¹Department of Dermatology, Al-Azhar University, Cairo, Egypt

²Department of Dermatology, National Research Centre, Cairo, Egypt

Correspondence


Mohamed L. Elsaie, Department of Dermatology, National Research Centre,

Abstract

Background: Pumpkin (*Cucurbita pepo* L.) is an annual climber plant, and its seeds have considerable amount of oil with nutritional and medicinal importance.

Aim: The present study aimed to investigate the clinical efficacy of pumpkin seed oil (PSO) in the treatment of female pattern hair loss (FPHL) and compare its effects with

Pumpkin seed oil vs. minoxidil 5% topical foam for the treatment of female pattern hair loss: A randomized comparative trial

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2.4.1 | Procedure

- Group A: Were instructed to apply 1 mL of topical pumpkin seed oil once daily and for three consecutive months.
- Group B: Were instructed to apply 1 mL of minoxidil 5% foam once daily and for three consecutive months.

TABLE 1 Age and disease duration

ORIGINAL CONTRIBUTION

Rosemary Oil vs Minoxidil 2% for the Treatment of Androgenetic Alopecia: A Randomized Comparative Trial

Yunes Panahi, PhD;¹ Mohsen Taghizadeh, PhD;² Eisa Tahmasbpour Marzony, MSc;¹ Amirhossein Sahebkar, PharmD, PhD³

ABSTRACT

Rosmarinus officinalis L. is a medicinal plant with diverse activities including enhancement microcapillary perfusion. The present study aimed to investigate the clinical efficacy of rosemary oil in the treatment of androgenetic alopecia (AGA) and compare its effects with minoxidil 2%. Patients with AGA were randomly assigned to rosemary oil (n=50) or minoxidil 2% (n=50) for a period of 6 months. After a baseline visit, patients returned to the clinic for efficacy and safety evaluations every 3 months. A standardized professional microphotographic assessment of each volunteer was taken at the initial interview and after 3 and 6 months of the trial. No significant change was observed in the mean hair count at the 3-month endpoint, neither in the rosemary nor in the minoxidil group ($P>.05$). In contrast, both groups experienced a significant increase in hair count at the 6-month endpoint compared with the baseline and 3-month endpoint ($P<.05$). No significant difference was found between the study groups regarding hair count either at month 3

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Amirhossein Sahebkar, PharmD, PhD³

ABSTRACT

Rosmarinus officinalis L. is a medicinal plant with diverse activities including enhancement microcapillary perfusion. The present study aimed to investigate the clinical efficacy of rosemary oil in the treatment of androgenetic alopecia (AGA) and compare its effects with minoxidil 2%. Patients with AGA were randomly assigned to rosemary oil (n=50) or minoxidil 2% (n=50) for a period of 6 months. After a baseline visit, patients returned to the clinic for efficacy and safety evaluations every 3 months. A standardized professional microphotographic assessment of each volunteer was taken at the initial interview and after 3 and 6 months of the trial. No significant change was observed in the mean hair count at the 3-month endpoint, neither in the rosemary nor in the minoxidil group ($P>.05$). In contrast, both groups experienced a significant increase in hair count at the 6-month endpoint compared with the baseline and 3-month endpoint ($P<.05$). No significant difference was found between the study groups regarding hair count either at month 3 or month 6 ($P>.05$). The frequencies of dry hair, greasy hair, and dandruff were not found to be significantly different from baseline at either month 3 or month 6 trial in the groups ($P>.05$). The frequency of scalp itching at the 3- and 6-month trial points was significantly higher compared with baseline in both groups ($P<.05$). Scalp itching, however, was more frequent in the minoxidil group at both assessed endpoints ($P<.05$). The findings of the present trial provided evidence with respect to the efficacy of rosemary oil in the treatment of AGA. (*SKINmed*. 2015;13:15–21)

Androgenetic alopecia (AGA) is the most common type of hair loss in both men and women, affecting about 50% of patients before the age of 50.¹ This type of hair loss is more

Rosmarinus officinalis L. (rosemary) is an aromatic evergreen and perennial herb belonging to the family Labiateae. Rosemary is native to the Mediterranean region but is also extensively culti-

A Randomized Comparative Trial

Yunes Panahi, PhD;¹ Mohsen Taghizadeh, PhD;² Eisa Tahmasbpour Marzony, MSc;¹
Amirhossein Sahebkar, PharmD, PhD³

ABSTRACT

Rosmarinus officinalis L. is a medicinal plant with diverse activities including enhancement microcapillary perfusion. The present study aimed to investigate the clinical efficacy of rosemary oil in the treatment of androgenetic alopecia (AGA) and compare its effects with minoxidil 2%. Patients with AGA were randomly assigned to rosemary oil (n=50) or minoxidil 2% (n=50) for a period of 6 months. After a baseline visit, patients returned to the clinic for efficacy and safety evaluations every 3 months. A standardized professional microphotographic assessment of each volunteer was taken at the initial interview and after 3 and 6 months of the trial. No significant change was observed in the mean hair count at the 3-month endpoint, neither in the rosemary nor in the minoxidil group ($P>.05$). In contrast, both groups experienced a significant increase in hair count at the 6-month endpoint compared with the baseline and 3-month endpoint ($P<.05$). No significant difference was found between the study groups regarding hair count either at month 3 or month 6 ($P>.05$). The frequencies of dry hair, greasy hair, and dandruff were not found to be significantly different from baseline at either month 3 or month 6 trial in the groups ($P>.05$). The frequency of scalp itching at the 3- and 6-month trial points was significantly higher compared with baseline in both groups ($P<.05$). Scalp itching, however, was more frequent in the minoxidil group at both assessed endpoints ($P<.05$). The findings of the present trial provided evidence with respect to the efficacy of rosemary oil in the treatment of AGA. (*SKINmed*. 2015;13:15–21)

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Table 1. Estimated Event Rate Difference Associated With Combined Estrogen and Progestin Use vs Placebo in Postmenopausal Women

Outcome	Absolute Event Rate Difference per 10 000 Woman-Years (95% CI)
Harms	
Breast cancer (invasive)	9 (1 to 19)
Coronary heart disease	8 (0 to 18)
Dementia (probable)	22 (4 to 53)
Gallbladder disease	21 (10 to 34)
Stroke	9 (2 to 19)
Venous thromboembolism	21 (12 to 33)
Urinary incontinence	876 (606 to 1168)



Cochrane Database of Systematic Reviews

**Oral oestrogen and combined oestrogen/progestogen therapy
versus placebo for hot flushes (Review)**

MacLennan AH, Broadbent JL, Lester S, Moore V

MacLennan AH, Broadbent JL, Lester S, Moore V.

Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD002978.

in the Japanese sample, but the prevalence of these symptoms is low and night sweats does not load on the same factor as hot flushes. In Canada and the United States, few women and few physicians doubt the inevitability of hot flushes or their association with menopause. By contrast, no one word in Japanese unequivocally signifies a hot flush. In the questionnaire several words were used as synonyms. The lack of a word is remarkable in a language which is infinitely more sensitive than is English in its ability to describe body states. Whether the low incidence of vasomotor symptoms reflects cultural, psychological, or physiological differences, or some combination of all three, requires further examination. Japanese women may not perceive these heat changes as remarkable and/or they may experience them at a much lower rate, possibly due to the much lower fat content in their diets.

The major differences found are:

Baillieres Clin Endocrinol Metab 7(1):17-32



Soy Product Intake and Hot Flashes in Japanese Women: Results from a Community-based Prospective Study

Chisato Nagata, Naoyoshi Takatsuka, Norito Kawakami, and Hiroyuki Shimizu

The association between soy product intake and the occurrence of hot flashes was examined in a cohort of 1,106 female residents of Takayama, Gifu, Japan. The women were aged 35–54 years and premenopausal at their entry into the study in 1992. Diet, including intake of soy products and isoflavones, was assessed by means of a validated semiquantitative food frequency questionnaire at study entry. A follow-up mail questionnaire asking about experiences of hot flashes was sent in 1998. During the 6 years of the study period, 101 women had new moderate or severe hot flashes according to the Kupperman test of menopausal distress. After data were controlled for age, total energy intake, and menopausal status, hot flashes were significantly inversely associated with consumption of soy products in terms of both total amount (highest tertile of soy product intake (g/day) vs. lowest: hazard ratio = 0.47; 95% confidence interval: 0.28, 0.79; p for trend = 0.005) and isoflavone intake (highest tertile of isoflavone intake (mg/day) vs. lowest: hazard ratio = 0.42; 95% confidence interval: 0.25, 0.72; p for trend = 0.002). These data suggest that consumption of soy products has a protective effect against hot flashes. *Am J Epidemiol* 2001;153:790–3.



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The Association between Soy Nut Consumption and Decreased Menopausal Symptoms

FRANCINE K. WELTY, M.D., Ph.D.,¹ KAREN S. LEE, M.D.,¹ NATALIE S. LEW, B.A.,¹
MELITA M. NASCA, Ph.D.,¹ and JIN-RONG ZHOU, Ph.D.²

ABSTRACT

Background: Epidemiological studies suggest a low incidence of hot flashes in populations that consume dietary soy. The present study examined the effect of soy nuts on hot flashes and menopausal symptoms.

Methods: Sixty healthy postmenopausal women were randomized in a crossover design to a therapeutic lifestyle changes (TLC) diet alone and a TLC diet of similar energy, fat, and pro-

ical Center approved the protocol, and all subjects gave informed consent.

Study design and diets

This was a randomized, controlled, crossover trial of the effect of one-half cup soy nuts daily for 8 weeks on systolic and diastolic BP and lipid levels in 60 postmenopausal women. A registered dietitian instructed subjects to eat a TLC diet, which consisted of 30% of energy from total fat ($\leq 7\%$ saturated fat, 12% monounsaturated fat, and 11% polyunsaturated fat). 15% of energy

ORIGINAL STUDY

The Women's Study for the Alleviation of Vasomotor Symptoms (WAVS): a randomized, controlled trial of a plant-based diet and whole soybeans for postmenopausal women

Neal D. Barnard, MD, FACC,^{1,2} Hana Kahleova, MD, PhD,¹ Danielle N. Holtz, BS,¹
Fabiola del Aguila, PhD,¹ Maggie Neola, BS, RD,¹ Lelia M. Crosby, BA, RD,¹
and Richard Holubkov, PhD³

Abstract

Objective: This study aimed to assess the effects of the combination of a low-fat plant-based diet and soybeans on the frequency and severity of menopausal hot flashes.

Methods: Postmenopausal women ($n = 38$) reporting two or more hot flashes/day were randomly assigned to a low-fat, vegan diet, including $1/2$ cup (86 g) of cooked soybeans daily, or to no diet changes for 12 weeks. Frequency and severity of hot flashes were recorded using a mobile application, and vasomotor, psychosocial, physical, and sexual symptoms were assessed using the Menopause-Specific Quality of Life Questionnaire. Significance was assessed using *t*-tests (continuous outcomes) and chi-squared/McNemar tests (binary outcomes).

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ORIGINAL STUDY

A dietary intervention for vasomotor symptoms of menopause: a randomized, controlled trial

Neal D. Barnard, MD, FACC,^{1,2} Hana Kahleova, MD, PhD,² Danielle N. Holtz, BS,² Tatiana Znayenko-Miller, MSHS,² Macy Sutton, MS,² Richard Holubkov, PhD,³ Xueheng Zhao, PhD,⁴ Stephanie Galandi, MS,⁴ and Kenneth D. R. Setchell, PhD, FAASLD^{4,5}

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Results: Total hot flashes decreased 79% in the intervention group ($P < 0.001$) and 49% in the control group ($P = 0.002$; between-group $P = 0.01$). Moderate-to-severe hot flashes decreased 84% in the intervention group ($P < 0.001$) and 42% in the control group ($P = 0.009$; between-group $P = 0.01$). From 0 to 12 weeks, 59% (10/17) of intervention-group participants reported becoming free of moderate and severe hot flashes ($P = 0.002$). There was no change in this variable in the control group (between-group $P < 0.001$). The Menopause-Specific Quality of Life Questionnaire revealed significantly greater reductions in the intervention group in vasomotor ($P < 0.0001$), psychosocial ($P = 0.04$), physical ($P < 0.002$), and sexual ($P = 0.01$) domains compared to a control group making no dietary changes. During a 12-week period, a mobile application was used to record hot flashes (frequency and severity), and vasomotor, psychosocial, physical, and sexual symptoms were assessed with the Menopause-Specific Quality of Life questionnaire. Between-group differences were assessed for continuous (t tests) and binary (χ^2 /McNemar tests) outcomes. In a study subsample, urinary equol was measured after the consumption of $1/2$ cup (86 g) of cooked whole soybeans twice daily for 3 days.

Results: In the intervention group, moderate-to-severe hot flashes decreased by 88% ($P < 0.001$) compared with 34% for the control group ($P < 0.001$; between-group $P < 0.001$). At 12 weeks, 50% of completers in the intervention group reported no moderate-to-severe hot flashes at all. Among controls, there was no change in this variable from baseline (χ^2 test, $P < 0.001$). Neither seasonality nor equol production status was associated with the degree of improvement. The intervention group reported greater reductions in the Menopause-Specific Quality of Life questionnaire vasomotor ($P = 0.004$), physical ($P = 0.01$), and sexual ($P = 0.03$) domains.

Conclusions: A dietary intervention consisting of a plant-based diet, minimizing oils, and daily soybeans signifi-

the frequency and severity of menopausal hot flashes.

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s requested by their

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Software (Qualtrics,
Qualtrics account.

ors' knowledge, had

with soybeans on va-

between-group $P < 0.001$).

The number of intervention-group study completers who were free of moderate-to-severe hot flashes, based on mobile application reports, increased from 1 of 38 at week 1 to 19 of 38 (50%) at week 12. This variable remained unchanged among controls (1 of 33 [3%] at each time point, $P < 0.0001$ for χ^2 test comparing the proportion free of moderate-to-severe hot flashes at week 12). These changes, reported with the mobile application, were paralleled by changes in MENQOL questionnaire findings

ORIGINAL STUDY

The effect of Fennel seed powder on estradiol levels, menopausal symptoms, and sexual desire in postmenopausal women

Parvin Ghaffari, MD,¹ Maryam Hosseinik, MSc,² Ardashir Afrasiabifar, PhD,³
Hossein Sadeghi, PhD,⁴ Amar Hosseinik, MSc,⁵ Seyedeh Marzieh Tabatabaei, MD,⁶
and Nazafarin Hosseini, PhD⁷

Abstract

Objectives: The present study was designed to determine the effect of Fennel seed powder on menopausal symptoms, sexual desire, and serum estradiol levels in postmenopausal women.

Methods: The present study was conducted on 80 eligible women (45-60 y) who were referred to the Mofatteh Gynecology Clinic in Yasuj, Iran. Participants were randomized into equal intervention and control (control) groups. The intervention and control groups received four capsules of Fennel seed powder (2 gr) and starch-containing capsules (2 gr) daily over 8 weeks, respectively. Menopausal symptoms and sexual desire of the participants were evaluated using both the menopausal Kupperman index and Hurlbert index of sexual desire. The questionnaires were completed at baseline, week 4 and week 8 of the study by the participants. The serum estradiol levels were measured at baseline and also at the end of the study. The Chi-square test, independent *t* test, and

Effect of Fenugreek on vasomotor symptoms in menopausal women

A protocol for systematic review and meta-analysis

Tingchao Wu, PhD , Rensong Yue, PhD*, Mingmin He, BS, Chenyi Xu, PhD

Abstract

Background: Vasomotor symptoms (hot flashes or night sweats) are closely related to the impaired quality of life in menopausal women. Fenugreek is the ripe seed of *Trigonella foenum graecum* Linn. In China, this plant is used to relieve menopausal symptoms in women. Although recent studies have shown that fenugreek may have a good effect on the menopausal symptoms, there is no meta-analysis to systematically evaluate its efficacy in improving menopausal vasomotor symptoms.

Methods: Randomized controlled trials that met the inclusion criteria will be retrieved in 5 English online databases and 4 Chinese online databases. The primary outcomes are changes in frequency and intensity of vasomotor symptoms that measured by validated scales. The secondary outcomes will include quality of life, blood hormone parameters, blood biochemical parameters, and adverse events. Heterogeneity of data will be assessed by I^2 and Cochrane Q statistics. Sensitivity analysis and subgroup analysis will be performed to explore the sources of heterogeneity. Egger test and Begg test will be used to assess the publication bias. Finally, we will evaluate the quality of evidence by the GRADE approach. All the data statistics will be performed using the STATA 15.0 software.

Results: All the results of will be published in a peer-reviewed journal.

Effect of Fenugreek on vasomotor symptoms in menopausal women: a protocol for systematic review and meta-analysis. *Medicine* 2020;99:23(e20526).

increase risk of tumor development in estrogen- sensitive tissues. Phytoestrogens are one of the alternative therapies in HRT. Phytoestrogens are herbal compounds that have estrogenic activity. Fenugreek is one of the herbs that contains phytoestrogen compounds but its effect has not been assessed on early menopausal symptoms yet. This study aimed to investigate the effect of Fenugreek seed on early menopausal symptoms. In this quasi experimental study, 2 groups of perimenopausal women were selected. Each group contained 25 patients. Women in control group received 2 periods consist of 0.625 mg conjugated estrogen and 10 mg medroxy progesterone acetate. Women in Fenugreek group received 6 g fenugreek seed powder in granulated form for 8 weeks. The Greene menopausal scale was used to assess change in early menopausal symptoms at baseline and after 4, 8 weeks of treatment. Statistical analysis was used for comparison between control and fenugreek groups. Greene score between control and Fenugreek groups at baseline was not significantly different ($p=0.776$). After 4 and 8 weeks of treatment on control group compared to Fenugreek group Greene score showed significant decrease ($p<0.001$, $p<0.001$). Greene score within control and Fenugreek groups showed a significant decrease after 4 and 8 weeks ($p<0.001$, $p<0.001$). Use of Fenugreek seed for 4 and 8 weeks caused significant reduction of total Green menopausal score but this effect was less than HRT. Further studies using double blind placebo-controlled clinical trial are needed.

Key words: Fenugreek, Perimenopausal stage, Phytoestrogens, HRT.

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Sotolon is a lactone derivative and a powerful aromatic compound, with a typical smell of curry or fenugreek and is the major aroma component of fenugreek seed. It is also present in roast tobacco, aged sake and white wine, and dried fruiting bodies of the mushroom.⁵⁷ Sotolon can pass through the body relatively unchanged, and consumption of foods high in sotolon, such as fenugreek, can impart a maple syrup aroma to one's sweat and urine. In some individuals with genetic disorder, it is spontaneously produced in their bodies and excreted in their urine, leading to the characteristic smell caused by the disease.⁵⁷

Use in the Lactation Period. Fenugreek can enhance breast milk production. However, with regard to

J Evid Based Complementary Altern Med 21(1):53-62

Antihypertensive and antioxidant effects of dietary black sesame meal in pre-hypertensive humans

Jatuporn Wichitsranoi¹, Natthida Weeraprecyakul², Patcharee Boonsiri³, Chatri Settasatian⁴, Nongnuch Settasatian⁵, Nantarat Komanasin⁶, Suchart Sirijaichingkul⁷, Yaovalak Teerajetgul⁵, Nuchanart Rangkadilok⁸ and Naruemon Leelayuwat^{9*}

Abstract

Background: It has been known that hypertension is an independent risk factor for cardiovascular disease (CVD). CVD is the major cause of morbidity and mortality in developed and developing countries. Elevation of blood pressure (BP) increases the adverse effect for cardiovascular outcomes. Prevention of increased BP plays a crucial role in a reduction of those outcomes, leading to a decrease in mortality. Therefore, the purpose of this study was to investigate the effects of dietary black sesame meal on BP and oxidative stress in individuals with prehypertension.

Methods: Twenty-two women and eight men (aged 49.8 ± 6.6 years) with prehypertension were randomly divided into two groups, 15 subjects per group. They ingested 2.52 g black sesame meal capsules or placebo capsules each day for 4 weeks. Blood samples were obtained after overnight fasting for measurement of plasma lipid, malondialdehyde (MDA) and vitamin E levels. Anthropometry, body composition and BP were measured before and after 4-week administration of black sesame meal or a placebo.

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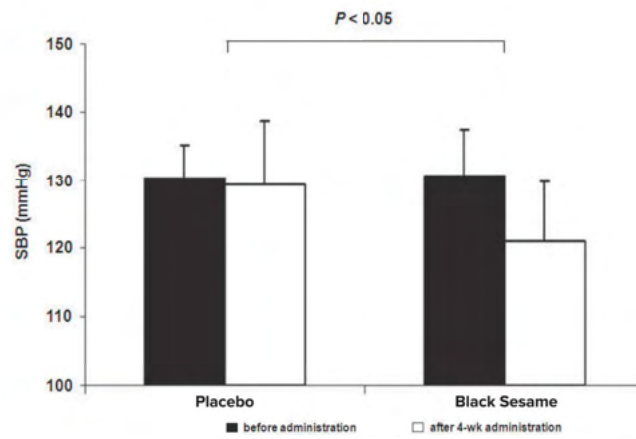


Figure 1 Average levels of SBP (A) and DBP (B) before and after 4-week administration of black sesame meal and a placebo in subjects with prehypertension. Values are expressed as means \pm SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; PG, placebo group; SG, black sesame meal group.

Article

Strawberries Improve Pain and Inflammation in Obese Adults with Radiographic Evidence of Knee Osteoarthritis

Jace Schell ¹, R. Hal Scofield ^{2,3,4}, James R. Barrett ⁵, Biji T. Kurien ², Nancy Betts ¹, Timothy J. Lyons ⁶, Yan Daniel Zhao ⁷ and Arpita Basu ^{1,8,*}

¹ Nutritional Sciences, Oklahoma State University, Stillwater, OK 74078, USA; jace.schell@okstate.edu (J.S.); nancy.betts@okstate.edu (N.B.)

² Section of Endocrinology and Diabetes, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA; Hal-Scofield@omrf.org (R.H.S.); biji-kurien@omrf.org (B.T.K.)

³ Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK 73104, USA

⁴ Medical Service, US Department of Veterans Affairs Medical Center, Oklahoma City, OK 73102, USA

⁵ Department of Family and Preventive Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA; jim-barrett@ouhsc.edu

⁶ Division of Endocrinology, Medical University of South Carolina, Charleston, SC 29425, USA

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³ Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK 73104, USA

⁴ Medical Service, US Department of Veterans Affairs Medical Center, Oklahoma City, OK 73102, USA

⁵ Department of Family and Preventive Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA; jim-barrett@ouhsc.edu

⁶ Division of Endocrinology, Medical University of South Carolina, Charleston, SC 29425, USA



Cochrane Database of Systematic Reviews

Paracetamol versus placebo for knee and hip osteoarthritis (Review)

Leopoldino AO, Machado GC, Ferreira PH, Pinheiro MB, Day R, McLachlan AJ, Hunter DJ, Ferreira ML

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Citation on next slide.



Cochrane Database of Systematic Reviews

Paracetamol versus placebo for knee and hip osteoarthritis (Review)

Leopoldino AO, Machado GC, Ferreira PH, Pinheiro MB, Day R, McLachlan AJ, Hunter DJ, Ferreira ML

evidence for practice in rehabilitation?

6.

Paracetamol is widely considered the first choice for treating hip and knee pain due to osteoarthritis. However, this review confirms that the effect of paracetamol for immediate and short-term pain is minimal and probably not clinically relevant. Despite high-quality evidence demonstrating no risk of adverse events, paracetamol should be avoided in monotherapy for hip and knee osteoarthritis and other drugs should be preferred.

7.

Research

JAMA | Original Investigation

Effect of Intra-articular Triamcinolone vs Saline on Knee Cartilage Volume and Pain in Patients With Knee Osteoarthritis

A Randomized Clinical Trial

Timothy E. McAlindon, DM, MPH; Michael P. LaValley, PhD; William F. Harvey, MD; Lori Lyn Price, MAS; Jeffrey B. Driban, PhD; Ming Zhang, PhD; Robert J. Ward, MD

IMPORTANCE Synovitis is common and is associated with progression of structural characteristics of knee osteoarthritis. Intra-articular corticosteroids could reduce cartilage damage associated with synovitis but might have adverse effects on cartilage and periarticular bone.

OBJECTIVE To determine the effects of intra-articular injection of 40 mg of triamcinolone acetate every 3 months on progression of cartilage loss and knee pain.

DESIGN, SETTING, AND PARTICIPANTS Two-year, randomized, placebo-controlled, double-blind trial of intra-articular triamcinolone vs saline for symptomatic knee osteoarthritis with ultrasonic features of synovitis in 140 patients. Mixed-effects regression

 Author Video Interview and JAMA Report Video

 Supplemental content

 CME Quiz at jamanetwork.com/learning

thickness of -0.21 mm vs -0.10 mm (between-group difference, -0.11 mm; 95% CI, -0.20 to -0.03 mm); and no significant difference in pain (-1.2 vs -1.9 ; between-group difference, -0.6 ; 95% CI, -1.6 to 0.3). The saline group had 3 treatment-related adverse events compared with 5 in the triamcinolone group and had a small increase in hemoglobin A_{1c} levels (between-group difference, -0.2% ; 95% CI, -0.5% to -0.007%).

CONCLUSIONS AND RELEVANCE Among patients with symptomatic knee osteoarthritis, 2 years of intra-articular triamcinolone, compared with intra-articular saline, resulted in significantly greater cartilage volume loss and no significant difference in knee pain. These findings do not support this treatment for patients with symptomatic knee osteoarthritis.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: [NCT01230424](https://clinicaltrials.gov/ct2/show/study/NCT01230424)

JAMA. 2017;317(19):1967-1975. doi:[10.1001/jama.2017.5283](https://doi.org/10.1001/jama.2017.5283)

Osteoarthritis and Cartilage



Increased risk for knee replacement surgery after arthroscopic surgery
for degenerative meniscal tears: a multi-center longitudinal
observational study using data from the osteoarthritis initiative



J.J. Rongen ^{†*}, M.M. Rovers [‡], T.G. van Tienen [§], P. Buma [†], G. Hannink ^{||}

[†] Radboud University Medical Center, Radboud Institute for Molecular Life Sciences, Orthopaedic Research Lab, PO Box 9101, 6500 HB Nijmegen, The Netherlands

[‡] Radboud University Medical Center, Radboud Institute for Health Sciences, Department for Health Evidence, PO Box 9101, 6500 HB Nijmegen, The Netherlands

[§] Kliniek Viasana, PO Box 4, 5450 AA Mill, The Netherlands

^{||} Radboud University Medical Center, Radboud Institute for Health Sciences, Orthopaedic Research Lab, PO Box 9101, 6500 HB Nijmegen, The Netherlands

A R T I C L E I N F O S U M M A R Y

Article

Strawberries Improve Pain and Inflammation in Obese Adults with Radiographic Evidence of Knee Osteoarthritis

Jace Schell¹, R. Hal Scofield^{2,3,4}, James R. Barrett⁵, Biji T. Kurien², Nancy Betts¹, Timothy J. Lyons⁶, Yan Daniel Zhao⁷ and Arpita Basu^{1,8,*}

¹ Nutritional Sciences, Oklahoma State University, Stillwater, OK 74078, USA; jace.schell@okstate.edu (J.S.); nancy.betts@okstate.edu (N.B.)

² Section of Endocrinology and Diabetes, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA; Hal-Scofield@omrf.org (R.H.S.); biji-kurien@omrf.org (B.T.K.)

³ Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK 73104, USA

⁴ Medical Service, US Department of Veterans Affairs Medical Center, Oklahoma City, OK 73102, USA

⁵ Department of Family and Preventive Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA; jim-barrett@ouhsc.edu

⁶ Division of Endocrinology, Medical University of South Carolina, Charleston, SC 29425, USA

Systematic Review

 **Effectiveness of Ginger on Pain and Function in Knee Osteoarthritis: A PRISMA Systematic Review and Meta-Analysis**

Felipe Araya-Quintanilla, MSc^{1,2}, Héctor Gutiérrez-Espinoza, PhD^{1,3},
María Jesús Muñoz-Yanez, MSc¹, Úrsula Sánchez-Montoya, MSc⁴,
and Juan López-Jeldes, MSc⁴

From: ¹Rehabilitation and Health Research Center (CIRES), Universidad de las Américas, Santiago, Chile; ²Faculty of Health Sciences, Universidad SEK, Santiago, Chile; ³Physical Therapy Department, Clinical Hospital San Borja Arriarán, Santiago, Chile; ⁴Faculty of Health, School of Nutrition, Universidad de las Américas, Santiago, Chile

Background: Ginger has been proposed as a complementary treatment for musculoskeletal pain. However, efficacy, type, and safety remains unclear.

Objectives: To determine the effectiveness of consumption or topical application of ginger for pain relief and knee function improvement in patients with knee osteoarthritis.

Study Design: Systematic review with meta-analysis of randomized clinical trials.

Methods: An electronic search was performed on Medline, Central, CINAHL, PEDro,

A SYSTEMATIC REVIEW OF THE EVIDENCE FOR TOPICAL USE OF GINGER

Mingshuang Ding, RM, BMid, MMid,¹ Matthew J. Leach, RN, BN(Hons), ND, DipClinNutr, PhD,^{2#}
and Helen Bradley, RN, RM, DipTeach, BEd, MEdStud, PhD²

Background: The use of ginger as a topical intervention is widely advocated in the popular media. However, there has been no attempt to date to synthesize the evidence for topically administered ginger.

Objective: To systematically review and synthesize the best available evidence of effectiveness for topical ginger in any condition.

Data Sources: CAM on PubMed, CINAHL, Google Scholar, MEDLINE, National Library of Australia, The Cochrane Library, TRIP, pertinent texts, and bibliographies of relevant papers.

Study Selection: Data sources were systematically searched for studies investigating the clinical effectiveness of topical ginger, in any form and for any condition, regardless of study design. Studies were limited to those published between 1980 and 2010,

randomized controlled trial. All studies differed in terms of study population, outcome measures, comparative interventions, and dose and form of ginger used, and thus, were not amenable to meta-analysis. Findings from all trials favored usage of ginger for most outcomes. However, the small sample sizes and inadequate methodological reporting indicate a high risk of bias and the need for caution when interpreting these results.

Conclusions: Few studies have investigated the effectiveness of topically administered ginger for any condition. Until the findings of these studies are corroborated by more robust research, and the safety of ginger is adequately established, clinicians should remain cautious about using topical ginger

REVIEW ARTICLE

A SYSTEMATIC REVIEW OF THE EVIDENCE FOR TOPICAL USE OF GINGER

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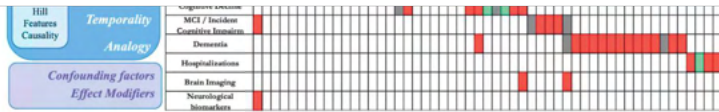
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24 male subjects with orchitis were assigned either ginger treatment (i.e., application of six–ten fresh ginger slices, 0.2-mm thick, over the affected testes) ($n = 20$) or no treatment ($n = 4$), until the condition had resolved. Resolution of symptoms occurred within three days in the ginger group, compared to 8.5 days in the control group.¹² However, it is not clear if the difference between the groups was statistically significant.

Level IV Evidence

24 male subjects with orchitis were assigned either ginger treatment (i.e., application of six–ten fresh ginger slices, 0.2-mm thick, over the affected testes) ($n = 20$) or no treatment ($n = 4$), until the condition had resolved. Resolution of symptoms occurred within three days in the ginger group, compared to 8.5 days in the control group.¹² However, it is not clear if the difference between the groups was statistically significant.

Level IV Evidence

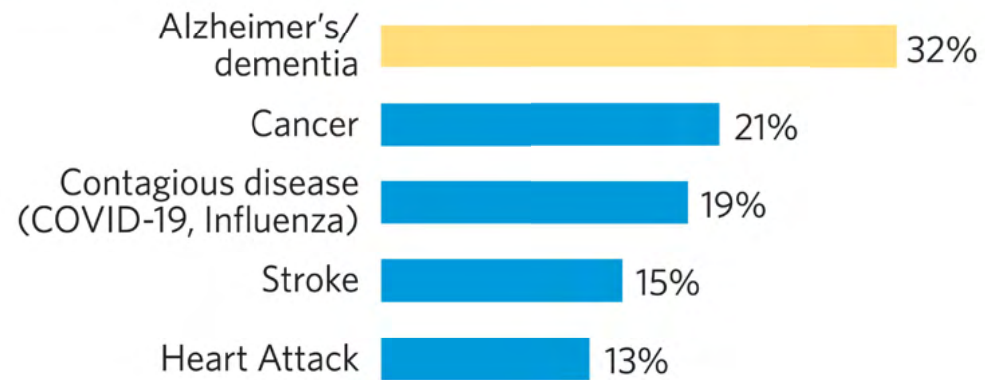


ABSTRACT

Dementia is arguably the most pressing public health challenge of our age. Since identifying risk factors that can be controlled has become paramount to reduce the economic burden of dementia. The relationship between exposure to air pollution and cognitive decline and dementia has stimulated increasing scientific interest in the literature critically examines the available epidemiological evidence of association between ambient air pollutants, cognitive performance, acceleration of cognitive decline, risk of hospitalizations and neurological biomarker studies, following Bradford Hill guidelines for causal inference. The evidence reviewed has been consistent in reporting associations between chronic exposure to air pollution and reduced global cognition, as well as impairment in specific

Sci Total Environ 757:143734

Retirees' most feared condition of later life



diagnose and treat illnesses such as dementia, often experience similar concerns.⁵⁵⁻⁵⁷ Several of the studies reviewed also demonstrated a limited understanding of early onset dementia.^{5,24,30} Given the widespread erroneous belief found across many of the studies that dementia is a normal part of aging, this finding is not entirely surprising.

The studies reviewed also revealed that another common misconception held by the general public is that individuals have no control over whether or not they develop dementia. The review showed that while the public's knowledge of genetic risk factors seems to be fair to good, knowledge of modifiable risk factors for dementia is poor.^{26,32,36,37,39,52,58} For example, in one study³⁷ only about one quarter of respondents were aware that hypertension and high cholesterol increase the individual's risk of developing dementia and in another study i

Review

Alzheimer's Disease is Incurable but Preventable

Jack C. de la Torre*

Center for Alzheimer's Research, Banner Sun Health Research Institute, Sun City, AZ, USA

Accepted 30 December 2009

Abstract. The dramatic rising incidence and costs of Alzheimer's disease (AD) require that research efforts and funding be primarily directed on either finding a cure or applying preventive measures to curb this disorder. A cure for AD appears unlikely when significant cognitive loss has occurred because the neuronal networks that controlled the perturbed cognitive abilities are either dead or irreversibly damaged and replacing them, even if it were technically possible, would not reconstruct the

biomarkers or cognitive profiles that accurately predict dementia.³⁻³⁶ Nevertheless, there is enough evidence to show the importance of healthy lifestyles and cardiovascular risk factors in adulthood for dementia.^{35 36} For some of these risk factors, such as obesity, hypertension, and hypercholesterolaemia, it is mid-life levels that seem to be more important than those measured at older ages.³⁵ There is emerging consensus that “what is good for our hearts is also good for our heads,”^{36 37} making aggressive control of behavioural and cardiovascular risk factors as early as possible key targets for clinical practice and public health.

Our results have profound implications for the design of research used in studies of ageing. Much research in this domain, including that on dementia, assesses both putative risk factors

BMJ 344:d7622



Intracranial atherosclerosis as a contributing factor to Alzheimer's disease dementia

Alex E. Roher^{a,*}, Suzanne L. Tyas^{b,c}, Chera L. Maarouf^a, Ian D. Dausg^a, Tyler A. Kokjohn^{a,d},
Mark R. Emmerling^a, Zsolt Garami^e, Marek Belohlavek^f, Marwan N. Sabbagh^g,
Lucia I. Sue^h, Thomas G. Beach^h

^aThe Longtime Center for Neurodegenerative Biochemistry, Banner Sun Health Research Institute, Sun City, AZ, USA

^bDepartment of Health Studies and Gerontology, University of Waterloo, Waterloo, Ontario, Canada

^cDepartment of Psychology, University of Waterloo, Waterloo, Ontario, Canada

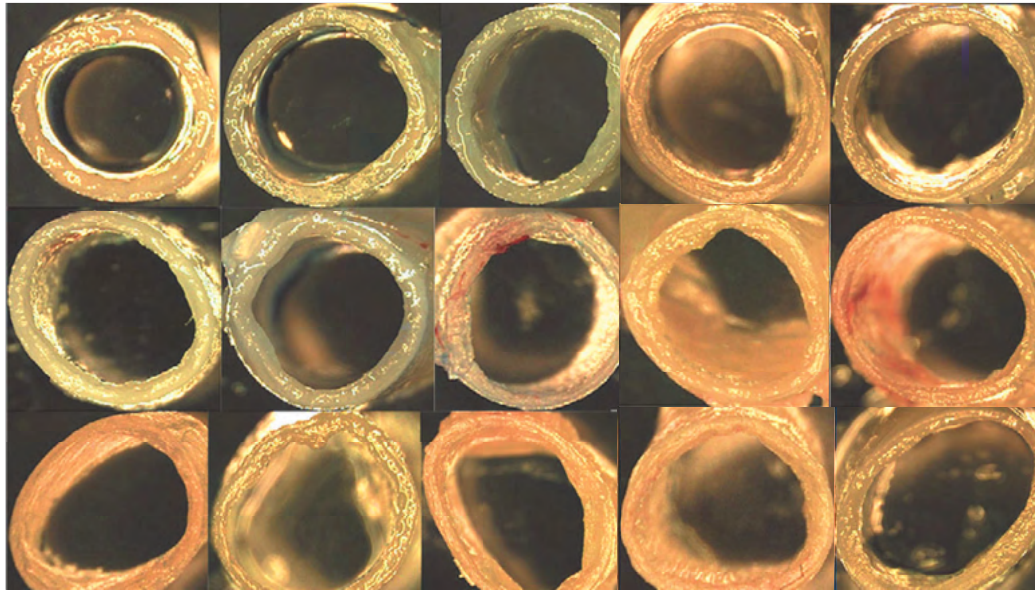
^dDepartment of Microbiology, Midwestern University, Glendale, AZ, USA

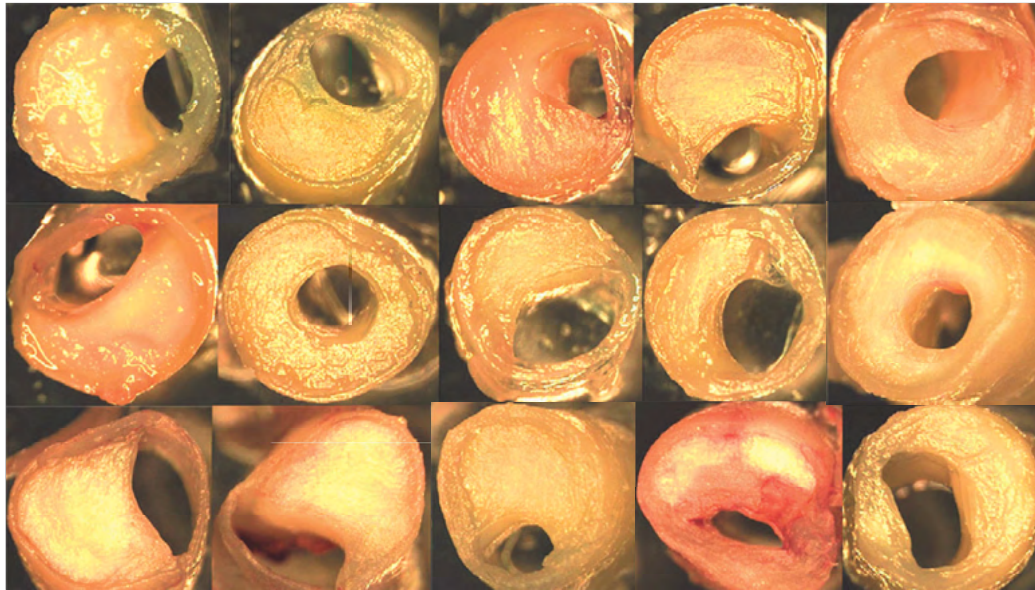
^eTranscranial Doppler Center, Methodist DeBakey Heart and Vascular Center, The Methodist Hospital, Houston, TX, USA

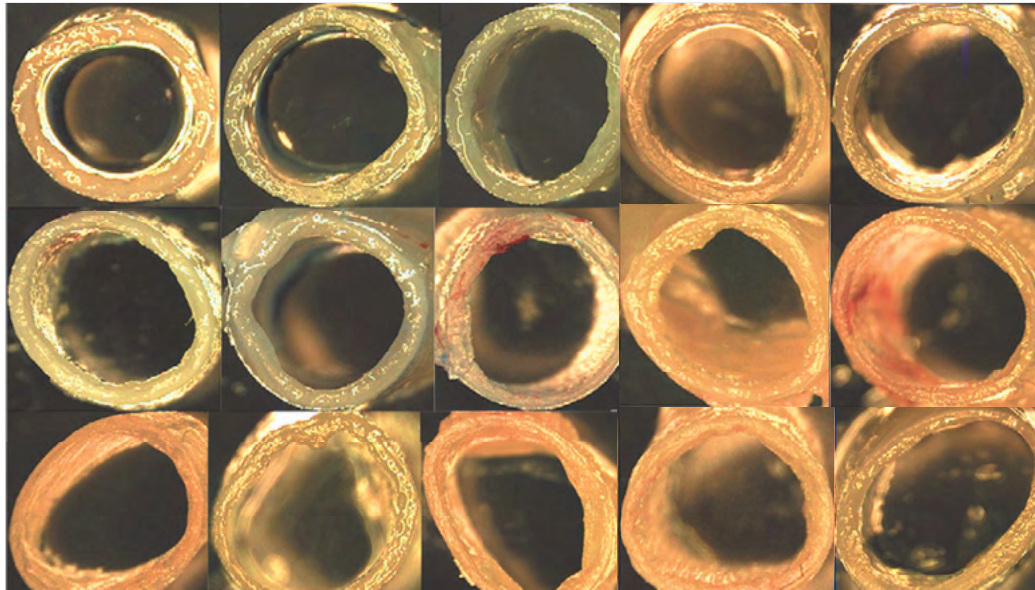
^fTranslational Ultrasound Research Laboratory, Division of Cardiovascular Diseases, Mayo Clinic, Scottsdale, AZ, USA

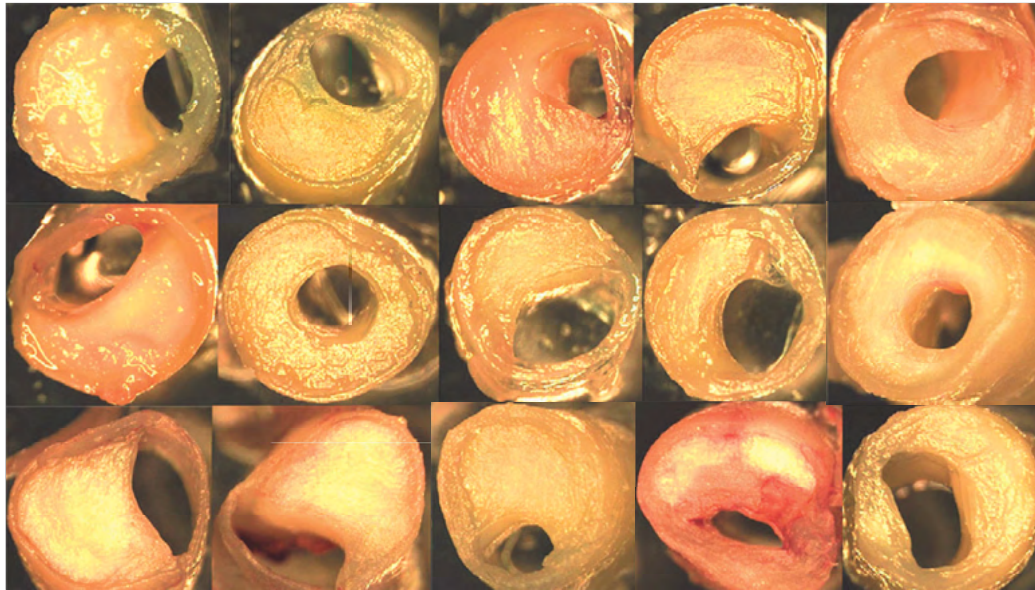
^gCleo Roberts Center for Clinical Research, Banner Sun Health Research Institute, Sun City, AZ, USA

^hHarold Civin Laboratory of Neuropathology, Banner Sun Health Research Institute, Sun City, AZ, USA









Association of Alzheimer disease pathology with abnormal lipid metabolism

The Hisayama Study

T. Matsuzaki, MD, PhD
K. Sasaki, MD, PhD
J. Hata, MD, PhD
Y. Hirakawa, MD
K. Fujimi, MD, PhD
T. Ninomiya, MD, PhD
S.O. Suzuki, MD, PhD
S. Kanba, MD, PhD
Y. Kiyohara, MD, PhD
T. Iwaki, MD, PhD

Address correspondence and
reprint requests to Dr. Kensuke
Sasaki, Department of
Neuropathology, Neurological

ABSTRACT

Objective: The relationship between lipid profiles and Alzheimer disease (AD) pathology at the population level is unclear. We searched for evidence of AD-related pathologic risk of abnormal lipid metabolism.

Methods: This study included brain specimens from a series of 147 autopsies performed between 1998 and 2003 of residents in Hisayama town, Japan (76 men and 71 women), who underwent clinical examinations in 1988. Lipid profiles, such as total cholesterol (TC), triglycerides, and high-density lipoprotein cholesterol (HDL-C), were measured in 1988. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula. Neuritic plaques (NPs) were assessed according to the Consortium to Establish a Registry for Alzheimer's Disease guidelines (CERAD) and neurofibrillary tangles (NFTs) were assessed according to Braak stage. Associations between each lipid profile and AD pathology were examined by analysis of covariance and logistic regression analyses.

Results: Adjusted means of TC, LDL-C, TC/HDL-C, LDL-C/HDL-C, and non-HDL-C (defined as TC-

Table 4 Multivariate-adjusted ORs and 95% CIs for presence of NPs (CERAD score 1-3 vs 0) according to lipid profile levels*

Quantiles of lipid profiles	Range	OR (95% CI)	p Value
TC, mmol/L			
Q4 (vs Q1-3)	>5.8	24.8 (4.7-130.5)	0.0002

that all relevant tests have been carried out and the data submitted.

Other opponents of the GEAC approval include two organizations backed by right-wing supporters of the ruling government led by prime minister Narendra Modi: the Swadeshi Jagaran Manch (the Forum for National Awakening), and the Bharatiya Kisan Sangh (Indian Farmers Association).

Scientists observing the case say that if the court is satisfied, or simply requests clarifications of existing data or minor additional data, the case could be resolved two or three months after the hearings begin. But should the court seek new data, such as on the effects of GM mustard oil in monkeys or chimpanzees, the process could take up to five years.

It's not the first time the GEAC has cleared transgenic mustard for evaluation in open fields: it gave its first approval in 2017. But the GEAC itself then went on to request further data on the impact on honeybees and other pollinators, and on soil microbial diversity, following feedback from both supporters and opponents.

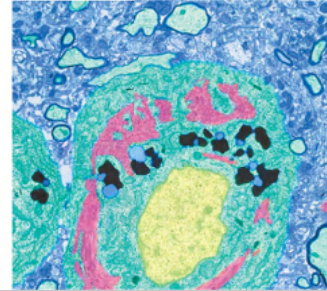
THIS IS HOW AN ALZHEIMER'S GENE RAVAGES THE BRAIN



Work in cells and mice suggests that the variant *APOE4* affects the insulation around neurons.

By Elie Dolgin

No gene variant is a bigger risk factor for Alzheimer's disease than one called *APOE4*. A study has now linked *APOE4* with faulty cholesterol processing in the brain, which leads to defects in the insulating sheaths that surround nerve fibres and facilitate the cells' electrical activity.

Preliminary results hint that these changes could cause memory and learning deficits. And the work suggests that drugs that restore the brain's cholesterol processing could treat the disease. "This fits in with the picture that



Ma Fe Lanfranco, Christi Anne Ng  and G. William Rebeck * 

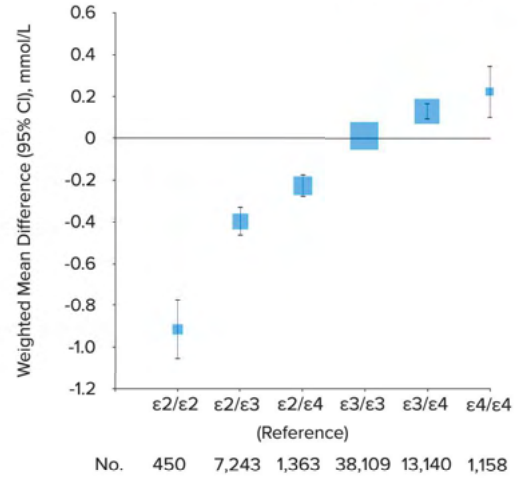
Department of Neuroscience, Georgetown University Medical Center, 3970 Reservoir Road NW, Washington, DC 20057, USA; ml1358@georgetown.edu (M.F.L.); cn472@georgetown.edu (C.A.N.)
Correspondence: gwr2@georgetown.edu; Tel.: +1-202-687-1534

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Abstract: Apolipoprotein E (*APOE*) is the major cholesterol carrier in the brain, affecting normal cellular processes including neuronal growth, repair and remodeling of synapses, neurogenesis, clearance and degradation of amyloid β ($A\beta$) and neuroinflammation. The *APOE* gene has three common allelic variants, termed E2, E3, and E4. *APOE4* is the strongest genetic risk factor for Alzheimer's disease (AD), whereas *APOE2* is neuroprotective. To perform its normal functions, apoE must be secreted and properly lipidated, a process that is affected by the structural differences associated with apoE isoforms. Here we highlight the importance of apoE lipidation as well as the *APOE*-lipidation targeted therapeutic approaches that have been developed.

Int J Mol Sci 21:6336

Low-Density Lipoprotein Cholesterol



Total Plasma Cholesterol Concentrations and Changes During Dietary Study

Diet	E4/E4 (n = 8)	E4/E3 (n = 42)	E3/E3 (n = 48)	E3/E2 (n = 12)	ANOVA
Baseline	7.63 ± 1.32	6.31 ± 1.15	6.07 ± 1.00	5.86 ± 1.48	0.003
Intervention	5.79 ± 0.86	5.12 ± 0.85	4.99 ± 0.94	4.73 ± 1.10	0.069

Values are in mmol/L and are the means ± SD.

three alleles in populations. The *APO E*4* allele is associated with higher mean cholesterol levels in populations, and one might expect that a higher *APO E*4* allele frequency would be associated with a higher mean cholesterol value, as was observed by Ehnholm et al. (1986) in Finns. To date, Nigerian blacks have the highest observed frequency of the *APO E*4* allele in world populations, but their adjusted mean cholesterol level is among the lowest reported in studies of the cholesterol/*APO E* relationship. This is probably due to a diet that is low in animal fat and high in saturated

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TABLE 4. Prevalence of Alzheimer's Disease Among Different Age Groups of Nigerian African Subjects (Ibadan) and African American Subjects (Indianapolis)

Age Group (years)	Ibadan	Indianapolis
	% With Alzheimer's Disease	Total % With Alzheimer's Disease
65-74	0.52	1.58
75-84	1.69	8.02
≥85	5.91	28.85
Overall, age-adjusted	1.41	6.24

Am J Psychiatry 152:1485-92

three alleles in populations. The *APO E*4* allele is associated with higher mean cholesterol levels in populations, and one might expect that a higher *APO E*4* allele frequency would be associated with a higher mean cholesterol value, as was observed by Ehnholm et al. (1986) in Finns. To date, Nigerian blacks have the highest observed frequency of the *APO E*4* allele in world populations, but their adjusted mean cholesterol level is among the lowest reported in studies of the cholesterol/*APO E* relationship. This is probably due to a diet that is low in animal fat and high in saturated

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of Cardiology

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doi:10.1093/eurheartj/ehy479

CURRENT OPINION

Why is hypercholesterolaemia so prevalent? A view from evolutionary medicine

Ulrich Laufs^{1*}, Ricardo Dent², Paul J. Kostenuik^{3,4}, Peter P. Toth^{5,6},
Alberico Luigi Catapano^{7,8}, and M. John Chapman⁹

¹Klinik und Poliklinik für Kardiologie; Universitätsklinikum Leipzig, Liebigstr. 20, 04103 Leipzig, Germany; ²Amgen Inc., Thousand Oaks, CA 91320, USA; ³University of Michigan School of Dentistry, Ann Arbor, MI 48109, USA; ⁴Phylon Pharma Services, Newbury Park, CA, USA; ⁵CGH Medical Center, Sterling, IL 61081, USA; ⁶Johns Hopkins University School of Medicine, Ciccarone Center for the Prevention of Cardiovascular Disease, Baltimore, MD, USA; ⁷Department of Pharmacological and Biomolecular Sciences, University of Milano, Via Balzaretti 9, 20133 Milan, Italy; ⁸Multimedica IRCCS Via Milanese, 300 20099 Sesto San Giovanni, Milano, Italy; and ⁹National Institute for Health and Medical Research (INSERM), University of Pierre and Marie Curie, Pitié-Salpêtrière University Hospital, Paris, France

Received 8 February 2018; revised 7 May 2018; editorial decision 21 July 2018; accepted 23 August 2018

Introduction

Hypercholesterolaemia is highly prevalent, particularly in affluent

... serious illnesses later in life.⁸ This phenomenon, antagonistic pleiotropy, is an important tenet of evolutionary medicine, which applies evolutionary principles to understand health and disease.^{8,9} An ex-



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The top 10 causes of death

9 December 2020

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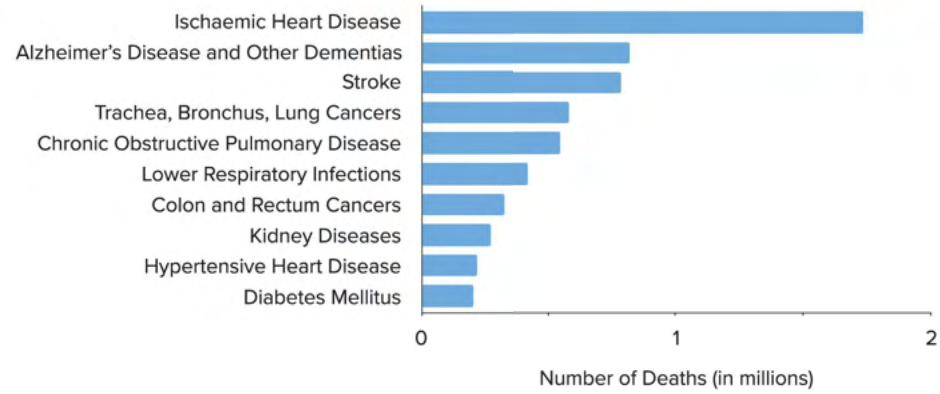
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Leading Causes of Death in High-Income Countries



Source: WHO Global Health Estimates.
Note: World Bank 2020 income classification.



Contents lists available at [ScienceDirect](#)

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging



Review

Dietary and lifestyle guidelines for the prevention of Alzheimer's disease



Neal D. Barnard^{a,b,*}, Ashley I. Bush^c, Antonia Ceccarelli^d, James Cooper^a,
Celeste A. de Jager^{e,1}, Kirk I. Erickson^f, Gary Fraser^g, Shelli Kesler^h, Susan M. Levin^b,
Brendan Luceyⁱ, Martha Clare Morris^j, Rosanna Squitti^{k,1}

^aDepartment of Medicine, George Washington University School of Medicine, Washington, DC, USA

^bPhysicians Committee for Responsible Medicine, Washington, DC, USA

^cFlarey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, Australia

^dDepartment of Neurology, Brigham and Women's Hospital, Laboratory for Neuroimaging Research, Partners MS Center, Harvard Medical School, Boston, MA, USA

^eOxford Project to Investigate Memory and Ageing (OPTIMA), Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK

^fDepartment of Psychology, University of Pittsburgh, Pittsburgh, PA, USA

^gDepartment of Epidemiology and Biostatistics, School of Public Health, Loma Linda University, Loma Linda, CA, USA

^hDepartment of Psychology, University of Pittsburgh, Pittsburgh, PA, USA

ⁱDepartment of Psychology, University of Pittsburgh, Pittsburgh, PA, USA

^jDepartment of Psychology, University of Pittsburgh, Pittsburgh, PA, USA

^kDepartment of Psychology, University of Pittsburgh, Pittsburgh, PA, USA

The Impact of the Six Pillars of Lifestyle Medicine on Brain Health

Ecler Jaqua¹, Edna Biddy², Clare Moore¹, Genise Browne³

¹. Family Medicine, Loma Linda University Medical Center, Loma Linda, USA ². Geriatrics, University of California Irvine, Irvine, USA ³. Family Medicine, Loma Linda University School of Medicine, Loma Linda, USA

Corresponding author: Ecler Jaqua, eclerjaqua@gmail.com

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Abstract

Dementia is growing exponentially worldwide. Unfortunately, the treatment available does not reverse any type of cognitive impairment. As a result, healthcare professionals are focusing on other evidence-based options, such as lifestyle medicine (LM). Current evidence demonstrates improvement in neurocognitive decline by applying the six pillars of LM, which include plant-based nutrition, physical activity, stress management, avoidance of risky substances, restorative sleep, and social connections.

Plant-based nutrition has a positive impact on cognition by decreasing the risk for Alzheimer's disease (AD) with high adherence to the Mediterranean-Dietary Approach to Systolic Hypertension (DASH) Intervention for Neurodegenerative Delay (MIND). Physical activity also might prevent neurocognitive decline by increasing fibronectin type III domain-containing protein 5 (FNDC5) and Irisin in the hippocampus, which increases energy expenditure and prolongs endurance.

Review

Plants, Plants, and More Plants: Plant-Derived Nutrients and Their Protective Roles in Cognitive Function, Alzheimer's Disease, and Other Dementias

Helen Ding, Allison B. Reiss , Aaron Pinkhasov and Lora J. Kasselman *

NYU Long Island School of Medicine, Mineola, NY 11501, USA; helen.ding@nyulangone.org (H.D.); allison.reiss@nyulangone.org (A.B.R.); aron.pinkhasov@nyulangone.org (A.P.)

* Correspondence: lora.kasselman@nyulangone.org

Abstract: *Background and Objectives:* Alzheimer's disease (AD) is the most common form of dementia, with the risk of developing it attributed to non-modifiable and modifiable factors. Currently, there is no cure for AD. A plant-based diet may protect against cognitive decline, due to the effects of plant-based nutrients such as vitamins, antioxidants, and fiber. The aim of the review is to summarize current literature on plant-based nutrients and their impact on cognition. *Materials and Methods:* A search was conducted on PubMed for clinical and murine studies, using combinations of the following words: "Alzheimer's disease", "dementia", "cognition", "plant-based diet", "mild cognitive impairment", "vitamin B", "vitamin C", "vitamin E", "beta carotene", "antioxidants", "fiber",

Preventing Alzheimer's: Our Most Urgent Health Care Priority

Abstract: Dementia is the fastest growing epidemic in the developed nations, and if not curtailed, it will single handedly collapse our health care system. The prevalence of dementia is 1 in 10 individuals older than 65 years and increases to 50% of all individuals older than 85 years. The prevalence of Alzheimer's dementia (AD), the most common form of dementia, has been increasing rapidly and is projected to reach 16 million individuals by the year 2050. Several prevailing myths about the

and social activity. The evidence base for each of the components is reviewed.

Keywords: Alzheimer's, brain health, prevention, longevity, cognitive impairment

Background

We have learned more about the brain, this 3-pound organ that is the source of human consciousness, in the first quarter of the 21st century than ever before in

discovered that our brains may consist of around 86 billion neurons, potentially as many as 1 trillion supporting cells such as glial cells, and more than 1 quadrillion connections. Therein lies the potential protection against the trauma and wear and tear that accumulate with aging. These connections can confer tremendous cognitive resilience that could enable the brain to withstand much of a lifetime's trauma. In the 20th century, we have seen a sharp rise in life expectancy that came about with

Article

Effect of a Strawberry and Spinach Dietary Supplement on Spatial Learning in Early and Late Middle-Aged Female Rats

Paula M. Millin ^{1,*} and Gina T. Rickert ²

¹ Department of Psychology, Kenyon College, Gambier, OH 43022, USA

² Chicago College of Osteopathic Medicine, Midwestern University, Chicago, IL 60515, USA;
grickert39@midwestern.edu

* Correspondence: millin@kenyon.edu; Tel.: +1-330-317-0411

Received: 12 November 2018; Accepted: 18 December 2018; Published: 20 December 2018



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RESEARCH ARTICLE

Open Access

Increased habitual flavonoid intake predicts attenuation of cognitive ageing in twins



Amy Jennings¹, Claire J. Steves², Alexander Macgregor³, Tim Spector² and Aedin Cassidy^{1*}

Abstract

Background: Although the pathophysiology of cognitive decline is multifactorial, and modifiable by lifestyle, the evidence for the role of diet on cognitive function is still accumulating, particularly the potentially preventive role of constituents of plant-based foods.

Methods: We aimed to determine whether higher habitual intake of dietary flavonoids, key components of plant-based diets, were associated with improved cognition and medial temporal lobe volumes using three complementary approaches (longitudinal, cross-sectional and co-twin analyses). In 1126 female twins ($n=224$ with a 10-year follow-up of diet and cognition data) aged 18–89 years, habitual intakes of total flavonoids and seven subclasses (flavanones, anthocyanins, flavan-3-ols, flavonols, flavones, polymeric flavonoids (and proanthocyanidins

Review

Effects of Berry Anthocyanins on Cognitive Performance, Vascular Function and Cardiometabolic Risk Markers: A Systematic Review of Randomized Placebo-Controlled Intervention Studies in Humans

Sanne Ahles ^{1,2}, Peter J. Joris ¹ and Jogchum Plat ^{1,*}

¹ Department of Nutrition and Movement Sciences, School of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University, 6200 MD Maastricht, The Netherlands, s.ahles@maastrichtuniversity.nl (S.A.); p.joris@maastrichtuniversity.nl (P.J.J.)

² BioActor BV, Gaetano Martinolaan 85, 6229 GS Maastricht, The Netherlands

* Correspondence: j.plat@maastrichtuniversity.nl

Abstract: Supplementation with anthocyanins, which are a type of flavonoids mainly found in various berries, is hypothesized to be a promising approach to lower the risk of developing cognitive decline. The aim of this systematic review was to provide a comprehensive overview of dietary

Table 2. The effect of berry anthocyanins on cognitive performance outcomes, compared to control.

Author (Year)	Intervention	Anthocyanin Dose	Attention and Psychomotor Speed				Executive Function				Memory			Other		
			TRFA	MFT	CPT	ICERT	Manikin	DMFB	Stony	DAMANT	Go-No-Go	Manikin	RAVLT - HVLT - CVLT		VFAL and VFAL	WET
Radford (2019) [11]	Freeze-dried wild blueberry juice	253 mg						†			† (G)					= (TOWER-2)
Emerging (2018) [12]	freeze-dried strawberry powder	249 mg											††			
Bowell (2017) [13]	Blueberry extract	387 mg					=						†	= (BKT)		= (Cohen-Mans)
Kalishian (2016) [14]	Blueberry juice	428-998 mg ¹									† (K)	† (V)				
Kalishian (2016) [14]	Freeze-dried blueberry fruit powder	258 mg	††				=		† (CCWAT)		= (B)	† (B)				
McNamee (2016) [15]	Freeze-dried blueberry powder	249 mg							= (CCWAT)			† (B)				
Miller (2016) [16]	Freeze-dried blueberry powder	230 mg ¹	=				=	=	† (DST)	† (K)				= (DST)		= (VMWMT)
Whyte (2015) [17]	Blueberry juice	143 mg							=	=	= (B)			= (DLT)		
Whyte (2016) [17]	Freeze-dried wild blueberry powder	127 mg	=					†† (PMT)	†† (PMT)	†† (B)						
Whyte (2016) [17]	Wild blueberry powder	254 mg	†					=	†† (PMT)	†† (B)						
Whyte (2017) [18]	Wild blueberry powder	253 mg						†								
Whyte (2018) [17]	Wild blueberry powder and extract	1.35 mg 2.7 mg 7 mg						=	=	= (B)	=	=	= (CBT, SST, SMST)	=	= (CBT, SST, SMST)	†† (CBT), = (SST, SMST)
Whyte (2018) [17]	Wild blueberry powder	479 mg						=	†		† (B)					
Whyte (2018) [17]	Wild blueberry powder	253 mg									= (B)			† (VNCLE) = (PFL, PFL)		
Whyte (2018) [18]	Wild blueberry powder	253 mg						††	=	=	= (B)					

† or †† or = indicates statistically significant improved or deteriorated values or no significant change in the intervention group compared to control. † indicates a trend. # indicates that the value was calculated. ¹ indicates that the dosage was dependent on body weight. Abbreviations: AMY: attention matrices test; DPT: brown potpourri task; CBT: Corsi blocks test; CCWAT: controlled word association; CVLT: California verbal learning test; DST: digit span task; DVT: digit vigilance test; PCRT: five-choice reaction time task; CPT: go/no-go task; HVLT: Hopkins verbal learning test; SET: international shopping list task; MANT: modified attention network test; MFT: modified fuster test; n-back: n-back test; n-back: n-back test; NCT: number connect test; PRT: picture recognition task; RAVLT: ray auditory verbal learning test; RVT: rapid visual information processing; SMST: Sternberg memory scanning task; VFAL: spatial pattern associates learning; SST: simple reaction time task; SST: serial subtraction task; SVL: spatial working memory task; TMT: trail making test; TOWER-2: test of word reading efficiency; TWT: task switching test; VMWMT: Virtual Morris Water Maze test; VFAL: verbal paired associates learning; VNCLE: visuo-spatial grid task; WET: word recognition task.

Enhanced suppleme impairme

Erin L. Boespflug
Shidler¹, Wilhelm
Amanda N. Stove

¹Department of Psychia
Cincinnati, OH 45267-0
Canada, Kentville, Nova
Hospital Medical Cente

Objectives: Preclinical
performance and neur
and such benefits. Pre

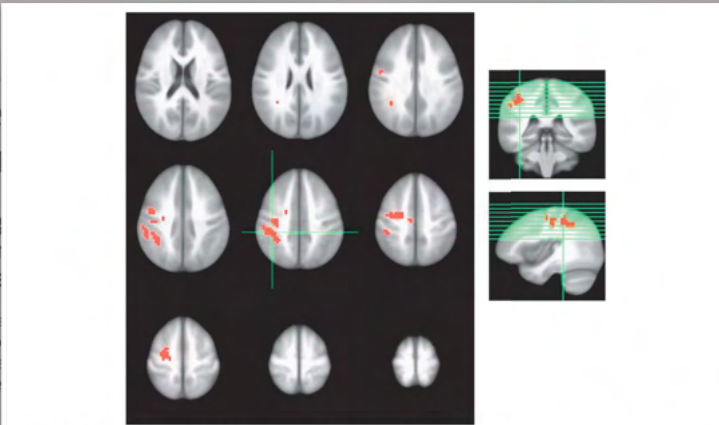


Figure 1 Increased BOLD signal during memory loading conditions in blueberry-treated group in the left pre-central gyrus, left middle frontal gyrus, and left inferior parietal lobe after intervention relative to pre-intervention baseline (corrected $P < 0.01$).

Boespflug EL, Eliassen JC, Dudley JA, et al. Enhanced neural activation with blueberry supplementation in mild cognitive impairment. Nutritional Neuroscience. 2018;21(4):297-305.



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Nutrition

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Pilot study

Effects of a single dose of a flavonoid-rich blueberry drink on memory in 8 to 10 y old children



Adrian R. Whyte M.Sc., Claire M. Williams Ph.D. *

School of Psychology and Clinical Language Sciences, University of Reading, Earley Gate, Whiteknights, Reading, United Kingdom

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ABSTRACT

Objective: Recent evidence from animals and adult humans has demonstrated potential benefits to cognition from flavonoid supplementation. The aim of this study was to investigate whether these cognitive benefits extended to a sample of school-aged children.

Method: Using a crossover design, with a washout of at least 7 d between drinks, 14 children ages 8



Addition of milk prevents vascular protective effects of tea

Mario Lorenz¹, Nicoline Jochmann¹, Amélie von Krosigk¹, Peter Martus², Gert Baumann¹, Karl Stangl¹, and Verena Stangl^{1*}

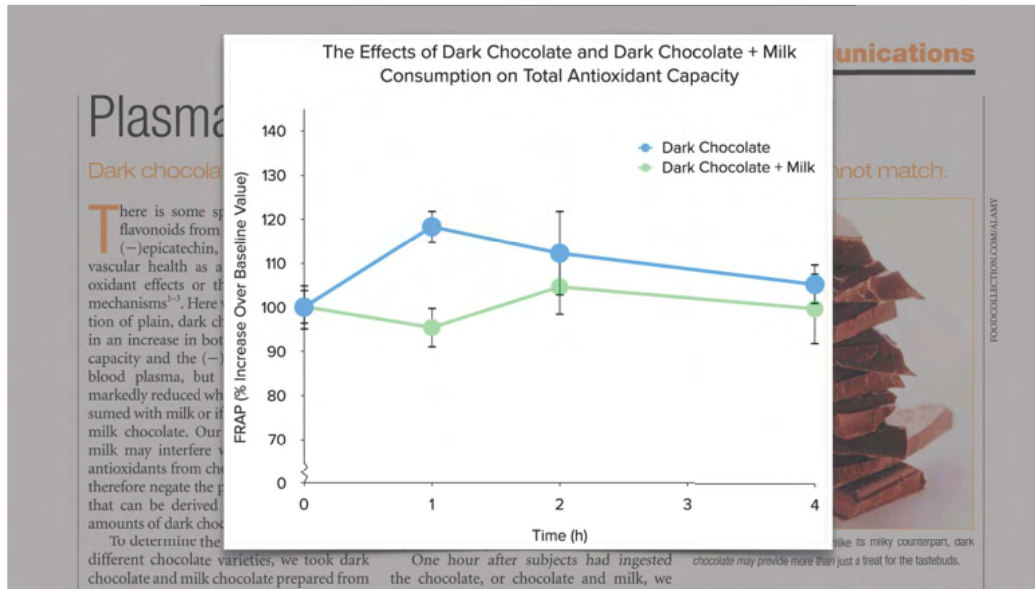
¹Medizinische Klinik mit Schwerpunkt Kardiologie und Angiologie, Charité—Universitätsmedizin Berlin, CCM, Charitéplatz 1, D-10117 Berlin, Germany and ²Institut für Biometrie und Klinische Epidemiologie, Charité—Universitätsmedizin Berlin, CCM, Charitéplatz 1, D-10117 Berlin, Germany

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KEYWORDS

Endothelial function;
Nitric oxide;
Tea;
Milk;

Aims Experimental and clinical studies indicate that tea exerts protection against cardiovascular diseases. However, a question of much debate is whether addition of milk modifies the biological activities of tea. We studied the vascular effects of tea, with or without milk, in humans and elucidated the impact of individual milk proteins in cell culture experiments, with isolated rat aortic rings and by HPLC analysis.



Effect of Simultaneous Consumption of Milk and Coffee on Chlorogenic Acids' Bioavailability in Humans

Giselle S. Duarte[†] and Adriana Farah^{*,†,‡}

[†]Instituto de Química and [‡]Instituto de Nutrição, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brazil

ABSTRACT: Different studies have shown that milk may interact with polyphenols and affect their bioavailability in humans. The present study investigated the effect of the simultaneous consumption of coffee and milk on the urinary excretion of chlorogenic acids (CGA) and metabolites. Subjects were submitted to consumption of water, instant coffee (609 mmol of CGA) dissolved in water, and instant coffee dissolved in whole milk. Urine was collected for 24 h after consumption of each treatment for analysis of CGA and metabolites by HPLC/LC–MS. The amount of CGA and metabolites recovered after consumption of combined coffee–milk ($40\% \pm 27\%$) was consistently lower in all subjects compared to that of coffee alone ($68\% \pm 20\%$). Concluding, the simultaneous consumption of milk and coffee may impair the bioavailability of coffee CGA in humans.

KEYWORDS: chlorogenic acids, bioavailability, coffee, coffee and milk interaction, polyphenols

■ INTRODUCTION

In the past few years, coffee began to be considered by many as a

the effect of the simultaneous consumption of coffee and milk on the urinary excretion of CGA and metabolites.



Original Contribution

Antioxidant activity of blueberry fruit is impaired by association with milk

Mauro Serafini ^{a,*}, Maria Francesca Testa ^a, Debora Villaño ^a, Monia Pecorari ^a, Karin van Wieren ^b,
Elena Azzini ^a, Ada Brambilla ^c, Giuseppe Maiani ^a

^a Antioxidant Research Laboratory, Unit of Human Nutrition, Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione, 00178 Rome, Italy

^b Friesland College, Leeuwarden, The Netherlands

^c Consiglio per la Ricerca e la Sperimentazione in Agricoltura, Istituto Sperimentale per la Valorizzazione Tecnologica dei Prodotti Agricoli, Milan, Italy

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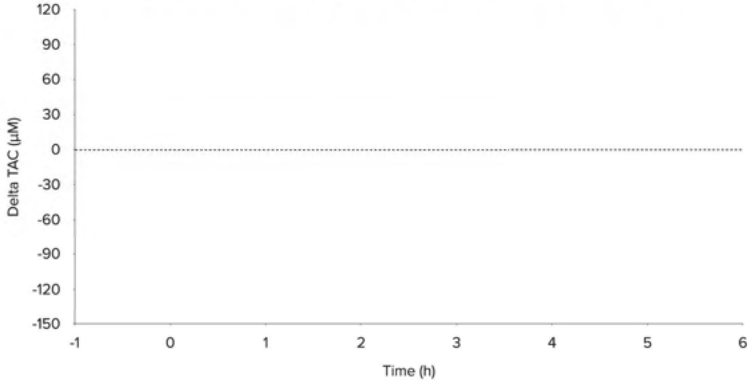
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Available online 11 December 2008

ABSTRACT

The antioxidant properties of dietary phenolics are believed to be reduced in vivo because of their affinity for proteins. In this study we assessed the bioavailability of phenolics and the in vivo plasma antioxidant capacity after the consumption of blueberries (*Vaccinium corymbosum* L.) with and without milk. In a crossover design, 11 healthy human volunteers consumed either (a) 200 g of blueberries plus 200 ml of water or (b) 200 g of blueberries plus 200 ml of whole milk. Venous samples were collected at baseline and at 1, 2,

Antioxidant Capacity Relative to Baseline After Ingestion of 200g Blueberries Plus
200 ml of Water vs 200 g of Blueberries Plus 200 ml of Whole Milk



Review of Neuro-nutrition Used as Anti-Alzheimer Plant, Spinach, *Spinacia oleracea*

Wanee Jiraungkoorskul

Department of Pathobiology, Faculty of Science, Mahidol University, Bangkok 10400, Thailand

ABSTRACT

Neuro-nutrition is the nutrition needed to achieve health brain and neurocognitive function. Diets rich in antioxidants, vitamins, flavonoids, and polyphenolic compounds will help suppress the onset of Alzheimer's disease. *Spinacia oleracea* (Family: *Amaranthaceae*) commonly known as spinach or Buai Leng (in Thai), one of the traditional medicinal plants with high in those mention nutrients. The micronutrients in spinach include a range of vitamins and minerals, which can prevent deficiency diseases and are essential for normal physiological function. Its phytochemicals are carotenoids, flavonoids, and phenolic compounds, which can prevent chronic health problems, as well as other diseases associated with aging. The objective of this article was to conduct a review on various ethnomedicinal uses of the spinach and its influences on the pathophysiology of Alzheimer's disease based on a literature review.

Key words: Alzheimer, herb, neuro-nutrition, plant, spinach, *Spinacia oleracea*

INTRODUCTION

Popeye, the popular cartoon sailor man, who famously attributed his strength after his consumption of spinach. This dark green leafy vegetable, *Spinacia oleracea* (SO), referred as "power food" is packed

to the hyperphosphorylation of microtubule-associated Tau protein in neurons.^[9] These processes lead, respectively, to the formation of neuritic plaques or senile plaques and neurofibrillary tangles, oxidative and inflammatory processes, neurotransmitter disturbances, and cholinergic deficit, which are the pathological hallmarks of

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Nitric Oxide

journal homepage: www.elsevier.com/locate/yniox



Acute effect of a high nitrate diet on brain perfusion in older adults

Tennille D. Presley^{a,b}, Ashley R. Morgan^c, Erika Bechtold^d, William Clodfelter^d, Robin W. Dove^{b,e},
Janine M. Jennings^{b,e}, Robert A. Kraft^f, S. Bruce King^{b,d}, Paul J. Laurienti^{b,c}, W. Jack Rejeski^{b,g},
Jonathan H. Burdette^{b,c,*}, Daniel B. Kim-Shapiro^{a,b,*}, Gary D. Miller^{b,g,*}

^a Department of Physics, Wake Forest University, Winston-Salem, NC 27109, USA

^b Translational Science Center, Reynolda Campus, Wake Forest University, Winston-Salem, NC 27109, USA

^c Department of Radiology, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA

^d Department of Chemistry, Wake Forest University, Winston-Salem, NC 27109, USA

^e Department of Psychology, Wake Forest University, Winston-Salem, NC 27109, USA

^f Department of Biomedical Engineering, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA

^g Department of Health and Exercise Science, Wake Forest University, Winston-Salem, NC 27109, USA

ARTICLE INFO

ABSTRACT

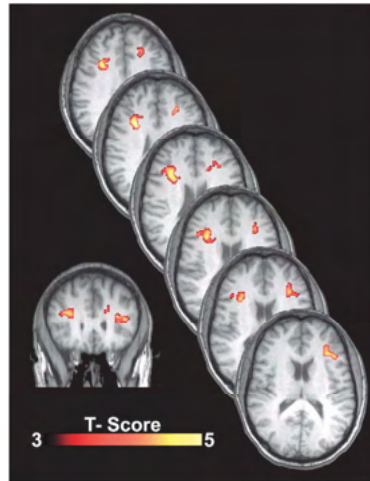


Fig. 5. Cerebral blood flow (CBF) differences between the high nitrate diet and low nitrate diet states. Statistical maps show significant differences in regional blood flow for the $n = 14$ subjects on the high nitrate diet vs. on the low nitrate diet. Note the increased CBF (ml/100 g/min) within the bilateral white matter of the frontal lobes, areas known to be at risk for chronic ischemia in the elderly. The bottom left image is a coronal slice at the level of genu of the corpus callosum. The diagonal stacked images are axial slices extending from the uppermost portions of the lateral ventricles superiorly to the basal ganglia/mid-body of the lateral ventricles inferiorly. Although there are some asymmetries to the findings, the effects on CBF from the high nitrate diet clearly manifest bilaterally within the white matter. Statistical analyses were performed at $p < 0.005$, extent corrected at 180 voxels. Color scale represents the t -score from a voxel-wise paired-samples t -test.

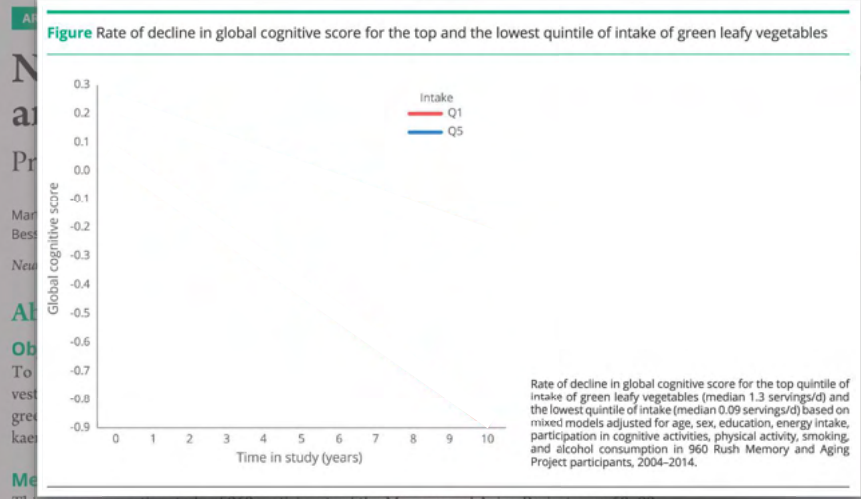


Effects of Lutein/Zeaxanthin Supplementation on the Cognitive Function of Community Dwelling Older Adults: A Randomized, Double-Masked, Placebo-Controlled Trial

Billy R. Hammond Jr.¹, L. Stephen Miller^{1,2}, Medina O. Bello¹, Cutter A. Lindbergh¹, Catherine Mewborn¹ and Lisa M. Renzi-Hammond^{1*}

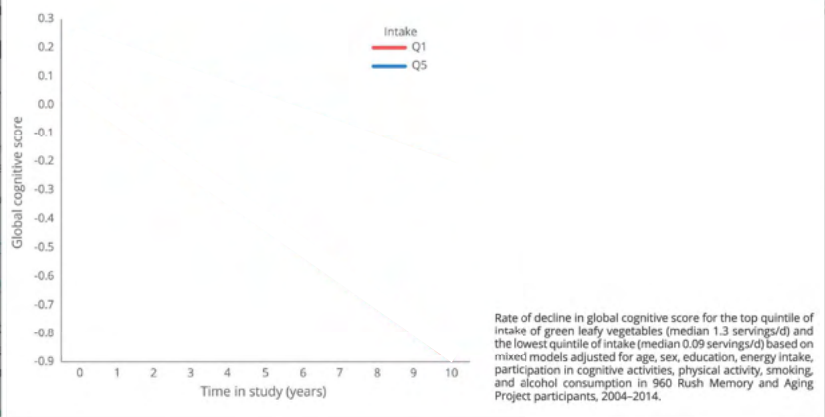
¹ Department of Psychology, University of Georgia, Athens, GA, United States, ² Bio-Imaging Research Center, Paul D. Coverdell Center for Biomedical and Health Sciences, University of Georgia, Athens, GA, United States

Background: High levels of xanthophyll carotenoids lutein (L) and zeaxanthin (Z) in the



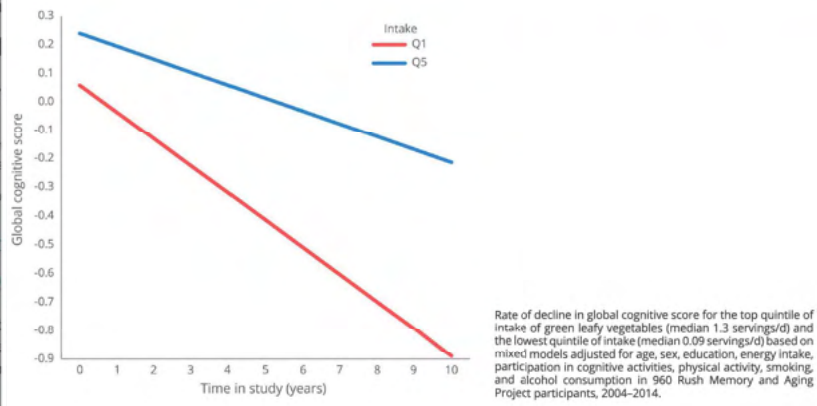
This was a prospective study of 960 participants of the Memory and Aging Project, ages 58-99 years, who completed a food frequency questionnaire and had ≥ 2 cognitive assessments over 10 years.

Figure Rate of decline in global cognitive score for the top and the lowest quintile of intake of green leafy vegetables



This was a prospective study of 960 participants of the Memory and Aging Project, ages 58-99 years, who completed a food frequency questionnaire and had ≥ 2 cognitive assessments over a mean 4.7 years.

Figure Rate of decline in global cognitive score for the top and the lowest quintile of intake of green leafy vegetables



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CHAPTER SEVEN

**Nutrition and the aging retina:
A comprehensive review of the
relationship between nutrients
and their role in age-related
macular degeneration and retina
disease prevention**

Chelsey Walchuk^{a,b}, Mivoung Suh^{a,b,*}



**Nutrition and the aging retina:
A comprehensive review of the
relationship between nutrients
and their role in age-related
macular degeneration and retina
disease prevention**

Chelsey Walchuk^{a,b}, Mivoung Suh^{a,b,*}

Emerging Science

Phytochemicals and age-related eye diseases

Michael Rhone and Arpita Basu

Cataracts, glaucoma, and age-related macular degeneration (AMD) are common causes of blindness in the elderly population of the United States. Additional risk factors include obesity, smoking, and inadequate antioxidant status. Phytochemicals, as antioxidants and anti-inflammatory agents, may help prevent or delay the progression of these eye diseases. Observational and clinical trials support the safety of higher intakes of the phytochemicals lutein and zeaxanthin and their association with reducing risks of cataracts in healthy postmenopausal women and improving clinical features of AMD in patients. Additional phytochemicals of emerging interest, like green tea catechins, anthocyanins, resveratrol, and Ginkgo biloba, shown to ameliorate ocular oxidative stress, deserve more attention in future clinical trials.

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Contents lists available at ScienceDirect

Food Chemistry

journal homepage: www.elsevier.com/locate/foodchem



Short communication

In vitro liberation of carotenoids from spinach and Asia salads after different domestic kitchen procedures



Jane N. Eriksen^{a,b}, Amy Y. Luu^a, Lars O. Dragsted^a, Eva Arrigoni^{b,*}

^a University of Copenhagen, Department of Nutrition, Exercise and Sports, Rolighedsvej 30, DK-1958 Frederiksberg C, Denmark

^b Agroscope, Institute of Food Sciences, Schloss 1, CH-8820 Wädenswil, Switzerland

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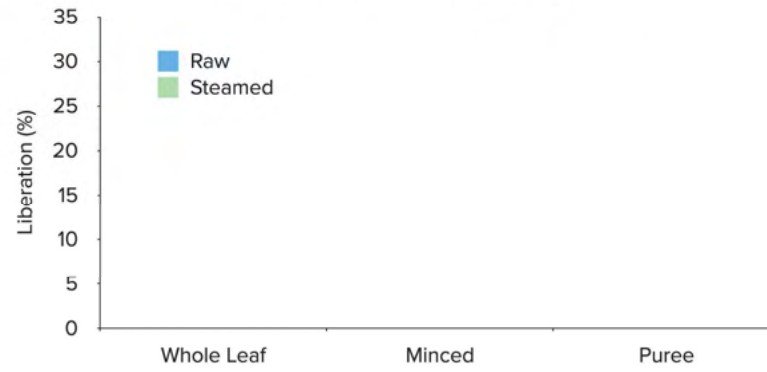
Accepted 3 February 2016

Available online 4 February 2016

ABSTRACT

Green-leafy vegetables are rich in nutritionally important constituents including carotenoids. Their potential health benefits depend among others on their liberation from the plant matrix. The aim of the present study was to evaluate the effect of particle size and heat treatments on lutein and β -carotene liberation from spinach and Asia salads by applying an *in vitro* digestion protocol and UHPLC analysis. Reduction of particle size resulted in a three- to fourfold increase in liberation of lutein

Effect of Domestic Heat Treatment and Particle Size on Lutein from Spinach After in vitro Digestion Simulating Upper Gastro-Intestinal Enzymatic Degradation



Dietary nitrate reduces resting metabolic rate: a randomized, crossover study in humans¹⁻³

Filip J Larsen, Tomas A Schiffer, Björn Ekblom, Mathias P Mattsson, Antonio Checa, Craig E Wheelock, Thomas Nyström, Jon O Lundberg, and Eddie Weitzberg

ABSTRACT

Background: Nitrate, which is an inorganic anion abundant in vegetables, increases the efficiency of isolated human mitochondria. Such an effect might be reflected in changes in the resting metabolic rate (RMR) and formation of reactive oxygen species. The bioactivation of nitrate involves its active accumulation in saliva followed by a sequential reduction to nitrite, nitric oxide, and other reactive nitrogen species.

Objective: We studied effects of inorganic nitrate, in amounts that represented a diet rich in vegetables, on the RMR in healthy volunteers.

respiration by its reversible binding and inhibition of cytochrome *c* oxidase (8). NO generation is catalyzed by specific NO synthases but is also generated by serial reductions of the inorganic anions nitrate (NO_3^-) and nitrite (NO_2^-) (9). Nitrate is abundant in our everyday diet, particularly in green leafy vegetables that are naturally rich in nitrate. Ingested nitrate is actively taken up from blood by the salivary glands and accumulates in saliva. In the oral cavity, nitrate is reduced to the more-reactive nitrite anion by commensal bacteria, and swallowed nitrite is absorbed in the gut and rapidly distributed throughout tissues. Therefore, number of biochemical pathways in blood and tissues contrib-



Acute dietary nitrate supplementation improves dry static apnea performance

Harald K. Engan^{a,b,*}, Andrew M. Jones^d, Fanny Ehrenberg^a, Erika Schagatay^{a,c}

^a Department of Engineering and Sustainable Development, Mid Sweden University, Östersund, Sweden

^b Raros Rehabilitation, The Norwegian Heart and Lung Patient Organization-LHL Health, Norway

^c Swedish Winter Sports Research Centre, Östersund, Sweden

^d College of Life and Environmental Sciences, University of Exeter, Exeter, United Kingdom

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Keywords:

Oxygen consumption

ABSTRACT

Acute dietary nitrate (NO_3^-) supplementation has been reported to lower resting blood pressure, reduce the oxygen (O_2) cost of sub-maximal exercise, and improve exercise tolerance. Given the proposed effects of NO_3^- on tissue oxygenation and metabolic rate, it is possible that NO_3^- supplementation might enhance the duration of resting apnea. If so, this might have important applications both in medicine and sport. We investigated the effects of acute NO_3^- supplementation on pre-apnea blood pressure, apneic

Dietary Inorganic Nitrate Improves Mitochondrial Efficiency in Humans

Filip J. Larsen,^{1,2,3,*} Tomas A. Schiffer,^{1,3} Sara Bomniquel,¹ Kent Sahlin,^{1,2} Björn Eklom,^{1,2} Jon O. Lundberg,¹ and Eddie Weitzberg^{1,*}

¹Department of Physiology and Pharmacology

²Swedish School of Sport and Health Sciences

Karolinska Institutet, 14186 Stockholm, Sweden

³These authors contributed equally to this work

*Correspondence: filip.larsen@ki.se (F.J.L.), eddie.weitzberg@ki.se (E.W.)

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SUMMARY

Nitrate, an inorganic anion abundant in vegetables, is converted in vivo to bioactive nitrogen oxides including NO. We recently demonstrated that dietary nitrate reduces oxygen cost during physical exercise, but the mechanism remains unknown. In

been increasingly appreciated (Gladwin et al., 2005; Lundberg et al., 2008; van Faassen et al., 2009). Circulating nitrate, normally derived both from endogenous NO production and from dietary intake, is actively taken up by the salivary glands, excreted in saliva, and reduced to nitrite by commensal bacteria in the oral cavity (Lundberg et al., 2004). By this route nitrate intake elevates systemic nitrite levels (Lundberg and Govoni,

Dietary nitrate reduces resting metabolic rate: a randomized, crossover study in humans¹⁻³

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Fruit and vegetable intake and risk of frailty in women 60 years old or older

Teresa T Fung,¹ Ellen A Struijk,^{2,3} Fernando Rodriguez-Artalejo,^{2,3,4} Walter C Willett,^{5,6} and Esther Lopez-Garcia^{2,3,4}

¹Department of Nutrition, Simmons University, Boston, MA, USA; ²Department of Preventive Medicine and Public Health, School of Medicine, Universidad Autónoma de Madrid-Idi Paz, Madrid, Spain; ³CIBERESP (CIBER of Epidemiology and Public Health), Madrid, Spain; ⁴Instituto Madrileño De Estudios Avanzado-Food Institute, Campus de Excelencia Internacional Universidad Autónoma de Madrid+Centro Superior de Investigaciones Científicas, Madrid, Spain; ⁵Channing Division of Network Medicine, Department of Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, MA, USA; and ⁶Department of Nutrition, Harvard TH Chan School of Public Health, Boston, MA, USA

ABSTRACT

Background: Prior research has suggested that the antioxidative and anti-inflammatory potential of fruits and vegetables may ameliorate

compromise the ability to handle stressors such as acute illnesses (2). Frailty has been associated with a poor quality of life, as well as increased morbidity and mortality (3–6).

Research Article

A Single Dose of Dietary Nitrate Increases Maximal Knee Extensor Angular Velocity and Power in Healthy Older Men and Women

Andrew R. Coggan, PhD,^{1,2,*} Richard L. Hoffman, MS,¹ Derrick A. Gray, BS,¹ Ranjani N. Moorthi, MD,³ Deepak P. Thomas, MD,⁴ Joshua L. Leibowitz, MD,^{4,5} Dakkota Thies, AAS,⁵ and Linda R. Peterson, MD,^{4,5}

¹Department of Kinesiology, ²Department of Cellular and Integrative Physiology, and ³Department of Internal Medicine, Indiana University—Purdue University Indianapolis. ⁴Department of Medicine and ⁵Department of Radiology, Washington University School of Medicine, St. Louis, Missouri.

*Address correspondence to: Andrew R. Coggan, PhD, Department of Kinesiology, Indiana University—Purdue University Indianapolis, IF 101C, 250 University Boulevard, Indianapolis, IN 46112. E-mail: acoggan@iupui.edu

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**THE IMPACT OF DIETARY PROTEIN OR AMINO ACID SUPPLEMENTATION
ON MUSCLE MASS AND STRENGTH IN ELDERLY PEOPLE: INDIVIDUAL
PARTICIPANT DATA AND META-ANALYSIS OF RCT'S**

M. TIELAND¹, R. FRANSSSEN^{1,2}, C. DULLEMEIJER¹, C. VAN DRONKELAAR³, H. KYUNG KIM⁴,
T. ISPOGLOU⁵, K. ZHU⁶, R.L. PRINCE⁶, L.J.C. VAN LOON², L.C.P.G.M. DE GROOT¹

1. Division of Human Nutrition, Wageningen University, Wageningen, the Netherlands; 2. NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Centre+, Maastricht, the Netherlands; 3. Department of Nutrition & Dietetics, School of Sports and Nutrition, Amsterdam University of Applied Sciences, Amsterdam, The Netherlands; 4. Research Team for Promoting Independence of the Elderly, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan; 5. Carnegie Faculty, School of Sport, Leeds Beckett University, Leeds, UK; 6. School of Medicine and Pharmacology, University of Western Australia, Perth, Australia. Corresponding author: Prof. Lisette C.P.G.M. de Groot, PhD, Wageningen University, Division of Human Nutrition, PO Box 8129, 6700 EV Wageningen (the Netherlands), Telephone: +31 317 482577, E-mail: lisette.degroot@wur.nl

Abstract: *Objectives:* Increasing protein or amino acid intake has been promoted as a promising strategy to increase muscle mass and strength in elderly people, however, long-term intervention studies show inconsistent findings. Therefore, we aim to determine the impact of protein or amino acid supplementation compared to placebo on muscle mass and strength in older adults by combining the results from published trials in a meta-analysis and pooled individual participant data analysis. *Design:* We searched Medline and Cochrane databases and performed a meta-analysis on eight available trials on the effect of protein or amino acid supplementation on muscle mass and strength in older adults. Furthermore, we pooled individual data of six of these randomized double-blind placebo-controlled trials. The main outcomes were change in lean body mass and change in muscle strength for both the meta-analysis and the pooled analysis. *Results:* The meta-analysis of eight studies (n=557)

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Review

Sarcopenia among the Elderly Population: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Di-Ya Tu ¹, Fa-Min Kao ¹, Shih-Tzer Tsai ^{1,2} and Tao-Hsin Tung ^{3,*}

¹ Department of Nutrition Therapy, Cheng-Hsin General Hospital, Taipei 112, Taiwan; snoopy5386@hotmail.com (D.-Y.T.); felix19940728@gmail.com (F.-M.K.); tsais60@gmail.com (S.-T.T.)

² Department of Internal Medicine, Cheng-Hsin General Hospital, Taipei 112, Taiwan

³ Evidence-Based Medicine Center, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Linhai 317000, China

* Correspondence: ch2876@gmail.com; Tel.: +86-576-8512-0120

Abstract: *Purpose.* This systematic review and meta-analysis was conducted to explore the effect of protein intake on the prevention and improvement of sarcopenia. *Methods.* We searched the Cochrane Library, PubMed, and EMBASE from inception to 20 May 2021. Two authors independently selected studies, assessed the quality of included studies, and extracted data. Any disagreement was resolved by discussion with a third author. *Results.* There were 33 studies that met the selection criteria.

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Review Article

Exercise interventions in healthy older adults with sarcopenia: A systematic review and meta-analysis

Lara Vlietstra  and Wendy Hendrickx

Physical Therapy Sciences, Program in Clinical Health Sciences, University Medical Center Utrecht, Utrecht, The Netherlands

Debra L Waters

Department of Medicine; and School of Physiotherapy, University of Otago, Dunedin, New Zealand

Objective: To systematically assess the effects of exercise interventions on body composition and functional outcomes in older adults with sarcopenia.

Methods: PubMed/Medline, Embase and Cochrane Library were searched from 2006 to 2017 for exercise randomised controlled trials and controlled clinical trials in adults 60 years and older with sarcopenia. Preferred Reporting Items for Systematic Review and Meta-Analysis protocol (PRISMA-P) and Physiotherapy

However, the existing evidence is based on populations of differing ages. The inconsistent findings limit our understanding. There is currently insufficient evidence to enable definitive exercise intervention recommendations to be made.

Key words: exercise, frail older adults, meta-analysis, review, sarcopenia, systematic.

Introduction

Sarcopenia is a well-known geriatric syndrome and is recognised worldwide [1]. The European Working Group on Sarcopenia in Older People (EWGSOP) is one of several groups that has provided a working definition of sarcopenia as 'a syndrome characterised by progressive and gen-



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Review Article

Protein Supplementation Does Not Significantly Augment the Effects of Resistance Exercise Training in Older Adults: A Systematic Review



Danielle K. Thomas MSc^{a,*}, Marcus A. Quinn MBChB^b, David H. Saunders PhD^c,
Carolyn A. Greig PhD^a

^a MRC-ARUK Centre for Musculoskeletal Ageing Research and School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Edgbaston, Birmingham, United Kingdom

^b School of Clinical Sciences and Community Health, University of Edinburgh, Edinburgh, United Kingdom

^c Institute for Sport, Physical Education and Health Sciences, University of Edinburgh, Edinburgh, United Kingdom

ABSTRACT

Keywords:

Elderly
muscle strength
protein

Background and aims: Physical activity and nutritional supplementation interventions may be used to ameliorate age-related loss of skeletal muscle mass and function. Previous reviews have demonstrated the beneficial effects of resistance exercise training (RET) combined with protein or essential amino acids (EAA) in younger populations. Whether or not older adults also benefit is unclear. The aim of this review

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WHAT DIET HELPS PEOPLE LIVE THE LONGEST?

BY ALEXANDRA SIFFERLIN

WE'RE ACCUSTOMED TO THINKING ABOUT DIETS as a short-term fix for unwanted weight gain, but

protein, which provided on average just 17% of daily calories, compared with up to 35% in the standard American diet. Also raising questions about protein is a 2014 study in *Cell Metabolism*. It showed that middle-aged Americans who ate a lot of animal protein were more likely to die of cancer and other causes, compared with people who opted for more plant-based protein. Study author Valter Longo, director of the University of Southern California's Longevity Institute, recommends that people cut down on protein overall to live longer.

That advice may raise eyebrows, since many diets for weight loss, including the popular paleo diet, advocate high protein. "There's a misconception that it's O.K. to eat a lot of it," Longo says. "People don't understand it could lead to some major aging factors." One such factor is the impact of the growth hormone IGF-1 (insulin-like growth factor 1). While it's important for early development, getting too much from high-

AT DIET PS PEOPLE E THE GEST?

DRA SIFFERLIN

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Mark F. McCarty*

Practical prospects for boosting hepatic production of the “pro-longevity” hormone FGF21

DOI 10.1515/hmbci-2015-0057

Received October 25, 2015; accepted November 20, 2015

Keywords: ATF4; bilirubin; FGF21; FXR; GLP-1; glucagon; PPAR α ; vegan.

Abstract: Fibroblast growth factor-21 (FGF21), produced mainly in hepatocytes and adipocytes, promotes leanness, insulin sensitivity, and vascular health while down-regulating hepatic IGF-I production. Transgenic mice overexpressing FGF21 enjoy a marked increase in median and maximal longevity comparable to that evoked by calorie restriction – but without a reduction in food intake. Transcriptional factors which promote hepatic FGF21 expression include PPAR α , ATF4, STAT5, and FXR; hence, fibrate drugs, elevated lipolysis, moderate-protein vegan diets, growth hormone, and bile acids may have potential to

FGF21 – a hormone with intriguing potential

In recent years, fibroblast growth hormone-21 (FGF21) has emerged as a key agent for promotion of metabolic and vascular health, leanness, and longevity [1–5]. Produced primarily by hepatocytes and adipocytes, FGF21 activates hybrid receptors comprised of an isoform of the FGF receptor and the transmembrane protein *BK10b*.

Mark F. McCarty*

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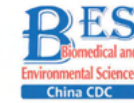
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Original Article



IGF-1 Accelerates Cell Aging by Inhibiting POLD1 Expression*

HOU Yu Li¹, WANG Yi Fei², SONG Qiao¹, ZHANG Xiao Min¹, LIU Jing¹, WANG Ya Qi¹, CUI Yu Ting¹,
FU Jing Xuan¹, FENG Zi Yi², ZHANG Chi¹, and WANG Pei Chang^{1,#}

1. Department of Clinical Laboratory, Xuanwu Hospital, National Clinical Research Center for Geriatric Diseases, Capital Medical University, Beijing 100053, China, 2. Clinical Laboratory Diagnostics, Capital Medical University, Beijing 100053, China

Abstract

Objective The individual cascades of the insulin-like growth factor-1 (IGF-1) signaling pathway and the molecular mechanism of aging have not been fully clarified. In the current study, we explored the effect of DNA polymerase delta 1 (POLD1) on the IGF-1 signaling pathway in cell aging.

Methods First, we analyzed the relationship between IGF-1 and POLD1 expression in aging. To

M(o)TOR of aging: MTOR as a universal molecular hypothalamus

Mikhail V. Blagosklonny

Department of Cell Stress Biology, Roswell Park Cancer Institute, BLSC, L3-312, Elm and Carlton Streets, Buffalo, NY, 14263, USA

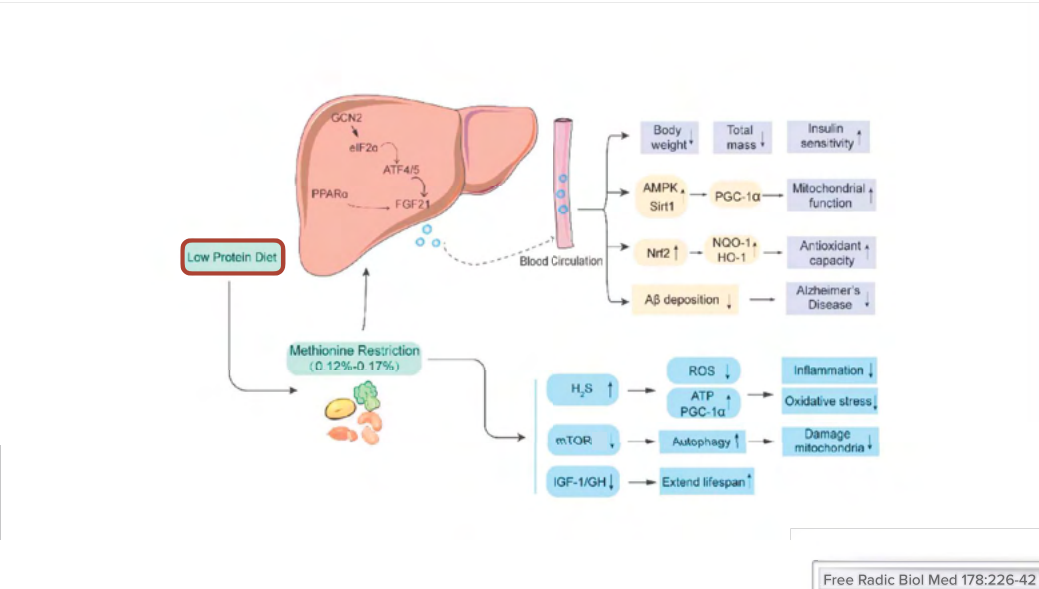
Key words: senescence, geroconversion, rapamycin, diseases, molecular hypothalamus

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Correspondence to: Mikhail V. Blagosklonny, MD/PhD; **E-mail:** blagosklonny@oncotarget.com

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Abstract: A recent ground-breaking publication described hypothalamus-driven programmatic aging. As a Russian proverb goes "everything new is well-forgotten old". In 1958, Dilman proposed that aging and its related diseases are programmed by the hypothalamus. This theory, supported by beautiful experiments, remained unnoticed just to be re-discovered recently. Yet, it does not explain all manifestations of aging. And would organism age without hypothalamus? Do sensing pathways such as MTOR (mechanistic Target of Rapamycin) and IKK-beta play a role of a "molecular hypothalamus" in every cell? Are hypothalamus-driven alterations simply a part of quasi-programmed aging manifested by hyperfunction and secondary signal-resistance? Here are some answers.



Interventions to Regulate the Eleven Aging Pathways

	Exercise	Smoking Cessation	Caloric Restriction	Protein Restriction	Decrease in Certain Animal Foods	Decrease in Certain Processed Foods	Increase in Certain Plant Foods
AMPK	✓		✓	✓	✓	✓	✓
Autophagy	✓		✓	✓	✓	✓	✓
Cellular Senescence	✓	✓	✓	✓		✓	✓
Epigenetics	✓	✓	✓	✓	✓		✓
Glycation	✓	✓	✓	✓	✓	✓	✓
IGF-1				✓	✓		
Inflammation	✓	✓	✓	✓	✓	✓	✓
mTOR		✓	✓	✓	✓		✓
Oxidation	✓	✓	✓	✓	✓	✓	✓
Sirtuins	✓	✓	✓	✓	✓	✓	✓
Telomeres	✓	✓		✓	✓	✓	✓

REVIEW

Open Access

Impact of caloric and dietary restriction regimens on markers of health and longevity in humans and animals: a summary of available findings

John F Trepanowski, Robert E Canale, Kate E Marshall, Mohammad M Kabir and Richard J Bloomer*

Abstract

Considerable interest has been shown in the ability of caloric restriction (CR) to improve multiple parameters of health and to extend lifespan. CR is the reduction of caloric intake - typically by 20 - 40% of *ad libitum* consumption - while maintaining adequate nutrient intake. Several alternatives to CR exist. CR combined with exercise (CE) consists of both decreased caloric intake and increased caloric expenditure. Alternate-day fasting (ADF) consists of two interchanging days; one day, subjects may consume food *ad libitum* (sometimes equaling twice the normal intake); on the other day, food is reduced or withheld altogether. Dietary restriction (DR) -

REVIEW

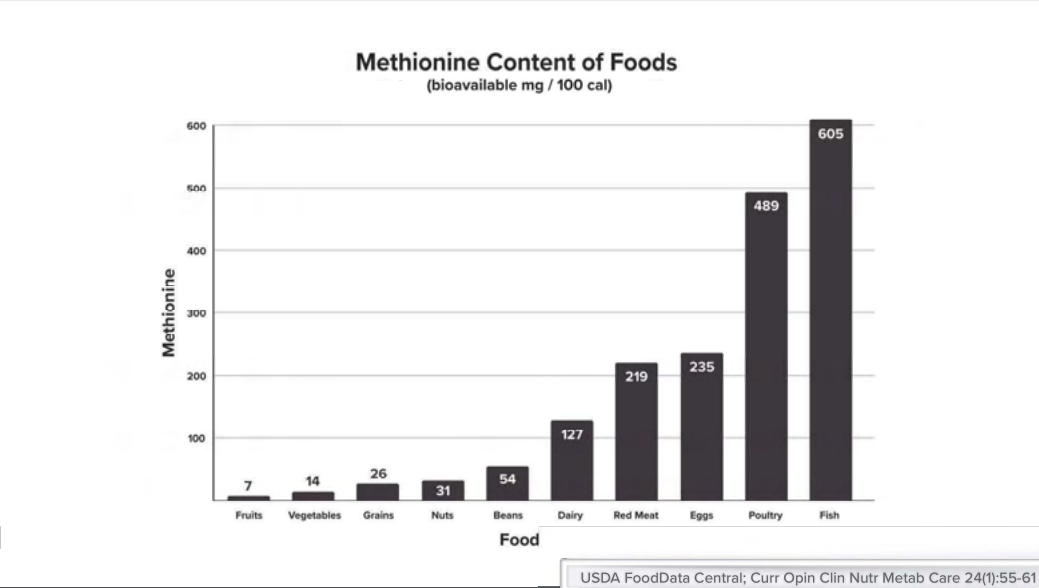
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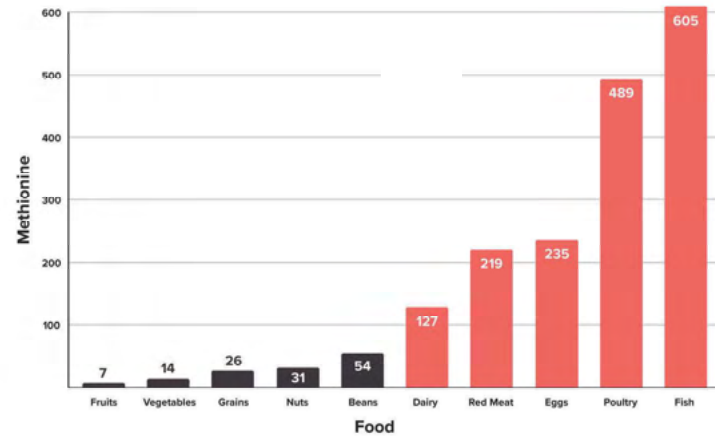
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USDA FoodData Central; Curr Opin Clin Nutr Metab Care 24(1):55-61

Methionine Content of Foods (bioavailable mg / 100 cal)





Laboratory–Clinic Interface

A review of methionine dependency and the role of methionine restriction in cancer growth control and life-span extension

Paul Cavuoto^a, Michael F. Fenech^{*}

^aCSIRO Food and Nutritional Sciences, P.O. Box 10041, Adelaide BC, SA 5000, Australia

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ABSTRACT

Methionine is an essential amino acid with many key roles in mammalian metabolism such as protein synthesis, methylation of DNA and polyamine synthesis. Restriction of methionine may be an important strategy in cancer growth control particularly in cancers that exhibit dependence on methionine for survival and proliferation. Methionine dependence in cancer may be due to one or a combination of deletions, polymorphisms or alterations in expression of genes in the methionine *de novo* and *salvage*



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The low-methionine content of vegan diets may make methionine restriction feasible as a life extension strategy

Mark F. McCarty*, Jorge Barroso-Aranda, Francisco Contreras

Oasis of Hope Hospital, Tijuana, Mexico

ARTICLE INFO

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SUMMARY

Recent studies confirm that dietary methionine restriction increases both mean and maximal lifespan in rats and mice, achieving "aging retardant" effects very similar to those of caloric restriction, including a suppression of mitochondrial superoxide generation. Although voluntary caloric restriction is never likely to gain much popularity as a pro-longevity strategy for humans, it may be more feasible to achieve moderate methionine restriction, in light of the fact that vegan diets tend to be relatively low in this amino acid. Plant proteins – especially those derived from legumes or nuts – tend to be lower in methionine than animal proteins. Furthermore, the total protein content of vegan diets, as a function of calorie content, tends to be lower than that of omnivore diets, and plant protein has somewhat lower bioavailability

Protein restriction and branched-chain amino acid restriction promote geroprotective shifts in metabolism

Michaela E. Trautman^{1,2,3}  | Nicole E. Richardson^{1,2,4} | Dudley W. Lamming^{1,2,4} 

¹Department of Medicine, University of Wisconsin-Madison, Madison, Wisconsin, USA

²William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin, USA

³Interdepartmental Graduate Program in Nutritional Sciences, University of Wisconsin-Madison, Madison, Wisconsin, USA

⁴Endocrinology and Reproductive Physiology Graduate Training Program,

Abstract

The proportion of humans suffering from age-related diseases is increasing around the world, and creative solutions are needed to promote healthy longevity. Recent work has clearly shown that a calorie is not just a calorie—and that low protein diets are associated with reduced mortality in humans and promote metabolic health and extended lifespan in rodents. Many of the benefits of protein restriction on metabolism and aging are the result of decreased consumption of the three branched-chain amino acids (BCAAs), leucine, isoleucine, and valine. Here, we discuss the emerging

protein restriction

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and stave off frailty, while athletes may need to consume more BCAAs to build and maintain muscle. These protein or BCAA recommendations may be personalized based on one's circulating amino acid levels and genes, allowing us to find the best diet for each person. Further research into the molecular mechanisms which underlie the benefits of BCAA and protein restriction may allow the development of pharmaceuticals to mimic these dietary interventions.

Research Article

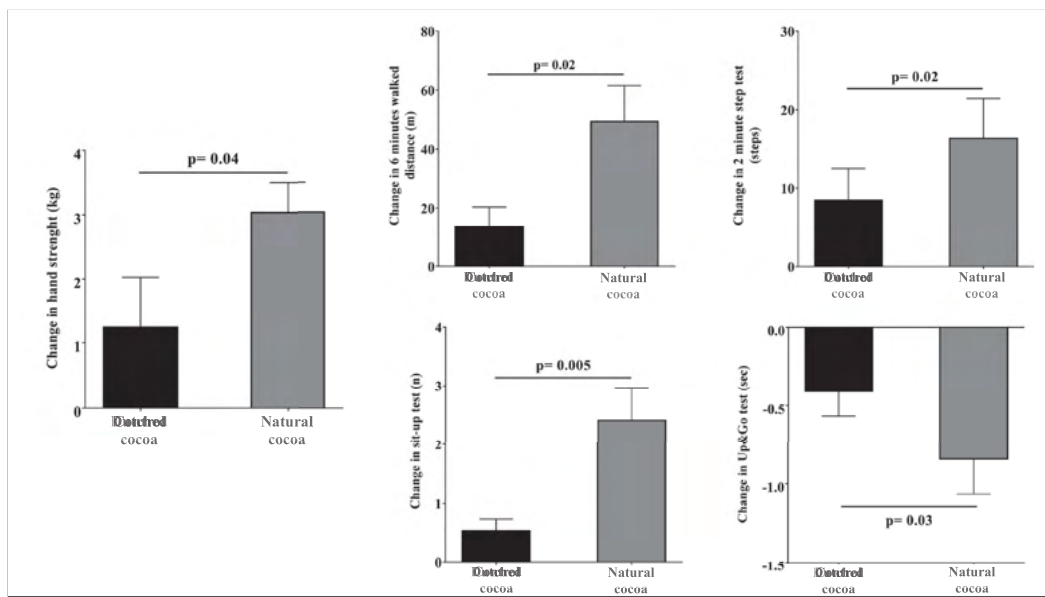
High Flavonoid Cocoa Supplement Ameliorates Plasma Oxidative Stress and Inflammation Levels While Improving Mobility and Quality of Life in Older Subjects: A Double-Blind Randomized Clinical Trial

Levy Munguia, MD, PhD,¹ Ivan Rubio-Gayosso, PhD,¹ Israel Ramirez-Sanchez, PhD,¹ Alicia Ortiz, PhD,² Isabel Hidalgo, MSc,¹ Cristian Gonzalez, MSc,¹ Eduardo Meaney, PhD,¹ Francisco Villarreal, MD, PhD,^{3,4} Nayelli Najera, PhD,^{1,†} and Guillermo Ceballos, MD, PhD^{1,*†,®}

¹Seccion de Estudios de Posgrado e Investigacion, Escuela Superior de Medicina and ²Departamento de Ingenieria Bioquimica, Escuela Nacional de Ciencias Biologicas, Instituto Politecnico Nacional, Mexico. ³Department of Medicine, School of Medicine, University of California San Diego, La Jolla. ⁴VA San Diego Healthcare System, California.


The initial study used a double-blind, placebo-controlled design enrolling male and female subjects aged 55–70 years. [Supplementary Table 1](#) delineates the end points measured (collected at the beginning and end of the study). All volunteers were evaluated for dietary habits and instructed to maintain their usual lifestyle, limiting high caloric foods, and the intake of flavonoid-containing foods and beverages (ie, chocolate and tea). Subjects were also instructed to walk for 30 min/day as vigorously as possible. Participants were randomly assigned to consume once a day a powder-based beverage for 12 weeks containing either (i) a cocoa-free skim milk-based powder (with coloring

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Cocoa to Improve Walking Performance in Older People With Peripheral Artery Disease

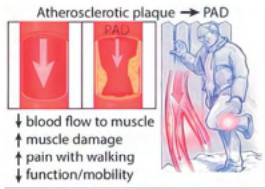
The COCOA-PAD Pilot Randomized Clinical Trial

Mary M. McDermott, Michael H. Criqui, Kathryn Domanchuk, Luigi Ferrucci, Jack M. Guralnik, Melina R. Kibbe, Kate Kosmac, Christopher M. Kramer, Christiaan Leeuwenburgh, Lingyu Li, Donald Lloyd-Jones, Charlotte A. Peterson, Tamar S. Polonsky, James H. Stein, Robert Sufit, Linda Van Horn, Francisco Villarreal, Dongxue Zhang, Lihui Zhao, Lu Tian 

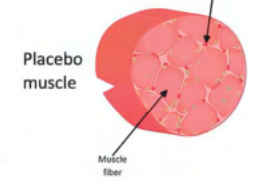
RATIONALE: Cocoa and its major flavanol component, epicatechin, have therapeutic properties that may improve limb perfusion and increase calf muscle mitochondrial activity in people with lower extremity peripheral artery disease (PAD).

OBJECTIVE: In a phase II randomized clinical trial, to assess whether 6 months of cocoa improved walking performance in people with PAD, compared with placebo.

METHODS AND RESULTS: Six-month double-blind, randomized clinical trial in which participants with PAD were randomized to either

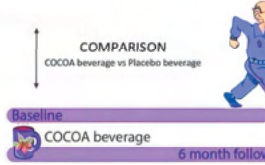
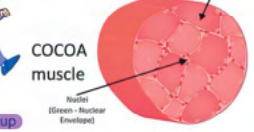


The COCOA-PAD Pilot Randomized Clinical Trial



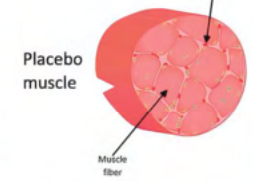
Improved by COCOA relative to placebo

- Muscle fibers with central nuclei
- Capillaries/fiber
- MRI muscle perfusion
- Mitochondrial activity (COX)



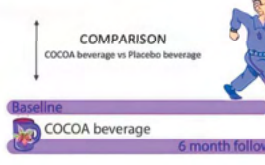
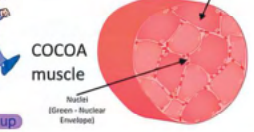


The COCOA-PAD Pilot Randomized Clinical Trial



Improved by COCOA relative to placebo

- Muscle fibers with central nuclei
- Capillaries/fiber
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- Mitochondrial activity (COX)



Alterations in Skeletal Muscle Indicators of Mitochondrial Structure and Biogenesis in Patients with Type 2 Diabetes and Heart Failure: Effects of Epicatechin Rich Cocoa

Pam R. Taub, M.D.^{1,2}, Israel Ramirez-Sanchez, Ph.D.^{1,3}, Theodore P. Ciaraldi, Ph.D.^{1,2}, Guy Perkins, Ph.D.¹, Anne N. Murphy, Ph.D.¹, Robert Naviaux, M.D., Ph.D.¹, Michael Hogan, Ph.D.¹, Alan S. Maisel, M.D.^{1,2}, Robert R. Henry, M.D.^{1,2}, Guillermo Ceballos, M.D., Ph.D.³, and Francisco Villarreal, M.D., Ph.D.¹

Abstract

(-)-Epicatechin (Epi), a flavanol in cacao stimulates mitochondrial volume and cristae density and protein markers of skeletal muscle (SkM) mitochondrial biogenesis in mice. Type 2 diabetes mellitus (DM2) and heart failure (HF) are diseases associated with defects in SkM mitochondrial structure/function. A study was implemented to assess perturbations and to determine the effects of Epi-rich cocoa in SkM mitochondrial structure and mediators of biogenesis. Five patients with DM2 and stage II/III HF consumed dark chocolate and a beverage containing approximately 100 mg of Epi per day for 3 months. We assessed changes in protein and/or activity levels of oxidative phosphorylation proteins, porin, mitofilin, nNOS, nitric oxide, cGMP, SIRT1, PGC1 α , Tfam, and mitochondria volume and cristae abundance by electron microscopy from SkM. Apparent major losses in normal mitochondria structure were observed before treatment. Epi-rich cocoa increased protein and/or activity of mediators of biogenesis and cristae abundance while not changing mitochondrial volume density. Epi-rich cocoa treatment improves SkM mitochondrial structure and in an orchestrated manner, increases molecular markers of mitochondrial biogenesis resulting in enhanced cristae density. Future controlled studies are warranted using Epi-rich cocoa (or pure Epi) to translate improved mitochondrial structure into enhanced cardiac and/or SkM muscle function. Clin Trans Sci 2012; Volume 5: 43–47

Keywords: heart failure, type 2 diabetes, epicatechin, mitochondrial biogenesis, skeletal muscle

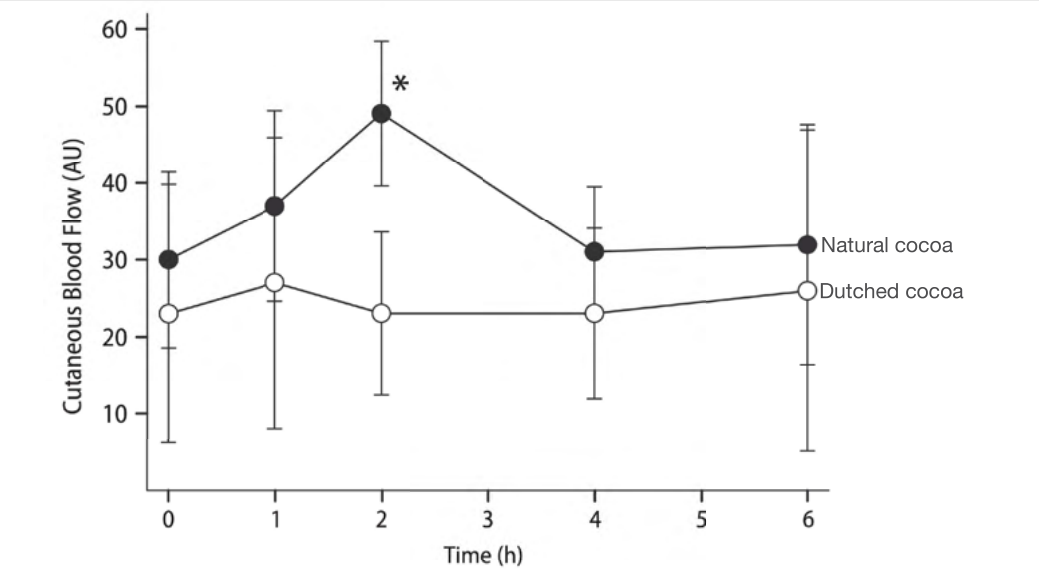
Karin Neukam
Wilhelm Stahl
Hagen Tronnier
Helmut Sies
Ulrike Heinrich

Consumption of flavanol-rich cocoa acutely increases microcirculation in human skin

Received: 2 June 2006
Accepted: 27 October 2006
Published online: 11 December 2006

■ **Abstract** *Background* Long term cocoa ingestion leads to an increased resistance against UV-induced erythema and a lowered transepidermal water loss. *Aim of the study* To investigate the acute effects of a single dose of cocoa

were measured by means of HPLC. *Results* Subsequent to the intake of high flavanol cocoa, dermal blood flow was significantly increased by 1.7-fold at $t = 2$ h and oxygen saturation was elevated 1.8-fold. No statistically significant



Nutrition and Disease

Long-Term Ingestion of High Flavanol Cocoa Provides Photoprotection against UV-Induced Erythema and Improves Skin Condition in Women¹

Ulrike Heinrich,* Karin Neukam,[†] Hagen Tronnier,* Helmut Sies,[†] and Wilhelm Stahl^{†2}

**Institut für Experimentelle Dermatologie, Universität Witten-Herdecke, D-58455 Witten, Germany and*

[†]Institut für Biochemie und Molekularbiologie I, Heinrich-Heine-Universität Düsseldorf, D-40001 Düsseldorf, Germany

ABSTRACT Dietary antioxidants contribute to endogenous photoprotection and are important for the maintenance of skin health. In the present study, 2 groups of women consumed either a high flavanol (326 mg/d) or low flavanol (27 mg/d) cocoa powder dissolved in 100 mL water for 12 wk. Epicatechin (61 mg/d) and catechin (20 mg/d) were the major flavanol monomers in the high flavanol drink, whereas the low flavanol drink contained 6.6 mg epicatechin and 1.6 mg catechin as the daily dose. Photoprotection and indicators of skin condition were assayed before and during the intervention. Following exposure of selected skin areas to 1.25 × minimal erythral dose (MED) of radiation from a solar simulator, UV-induced erythema was significantly decreased in the high flavanol group, by 15 and 25%, after 6 and 12 wk of treatment, respectively, whereas no change occurred in the low flavanol group. The ingestion of high flavanol cocoa led to increases in blood flow of cutaneous and subcutaneous tissues, and to increases in skin density and skin hydration. Skin thickness was elevated from 1.11 ± 0.11 mm at wk 0 to 1.24 ± 0.13 mm at wk 12; transepidermal water loss was diminished from 8.7 ± 3.7 to 6.3 ± 2.2 g/h · m² within the same time frame. Neither

*Variables related to skin structure and texture determined by
ultrasound B-scan surface evaluation of the skin
and corneometry of women at wk 0 and
after 6 and 12 wk of consuming Natural or Dutched
cocoa beverages¹*

	Time, wk		
	0	6	12
	<i>arbitrary units</i>		
Natural			
Density, <i>pixel</i>	10.2 ± 1.7	11.3 ± 2.1 ^{2,3}	11.9 ± 1.6 ^{2,3}
Thickness, <i>mm</i>	1.11 ± 0.11	1.20 ± 0.14 ^{2,3}	1.24 ± 0.13 ^{2,3}
Roughness, <i>AU</i>	0.27 ± 0.20	0.20 ± 0.17	0.19 ± 0.18 ²
Scaling, <i>AU</i>	0.14 ± 0.09	0.10 ± 0.07	0.08 ± 0.06 ²
Smoothness, <i>AU</i>	20.3 ± 1.9	20.9 ± 1.9	21.2 ± 2.5
Wrinkles, <i>AU</i>	42.2 ± 5.1	41.8 ± 4.1	41.8 ± 4.1
Hydration, <i>AU</i>	39 ± 4	40 ± 6	44 ± 8 ^{2,3}
Transepidermal water loss, <i>g/(h · m²)</i>	8.7 ± 3.7	7.8 ± 3.5	6.3 ± 2.2 ^{2,3}
Dutched			
Density, <i>pixel</i>	12.5 ± 1.2	12.3 ± 1.4	12.4 ± 1.2
Thickness, <i>mm</i>	1.05 ± 0.10	1.05 ± 0.10	1.04 ± 0.11
Roughness, <i>AU</i>	0.13 ± 0.20	0.17 ± 0.17	0.15 ± 0.13
Scaling, <i>AU</i>	0.18 ± 0.22	0.11 ± 0.08	0.13 ± 0.11
Smoothness, <i>AU</i>	19.6 ± 3.1	20.7 ± 2.1	20.5 ± 1.9
Wrinkles, <i>AU</i>	44.4 ± 5.4	44.0 ± 5.1	43.7 ± 4.4
Hydration, <i>AU</i>	38 ± 5	36 ± 4	36 ± 6
Transepidermal water loss, <i>g/(h · m²)</i>	7.2 ± 4.2	7.4 ± 3.2	6.9 ± 2.0

¹ Values are means ± SD, n = 12.

² Different from wk 0, P < 0.05.

³ Change compared with wk 0 is significantly different from dutched group, P < 0.05.

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ultrasound B-scan surface evaluation of the skin
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¹ Values are means ± SD, *n* = 12.

² Different from wk 0, *P* < 0.05.

³ Change compared with wk 0 is significantly different from dutched group,
P < 0.05.



Cocoa Flavanol Supplementation Influences Skin Conditions of Photo-Aged Women: A 24-Week Double-Blind, Randomized, Controlled Trial¹⁻³

Hyun-Sun Yoon,⁴⁻⁶ Jong Rhan Kim,^{7,9} Gyeong Yul Park,⁵ Jong-Eun Kim,^{7,9} Dong Hun Lee,^{5,6} Ki Won Lee,⁷⁻⁹ and Jin Ho Chung^{5,6,8*}

⁴Department of Dermatology, Seoul National University Boramae Hospital, Seoul, Korea; ⁵Department of Dermatology, Seoul National University College of Medicine, Seoul, Korea; ⁶Institute of Human-Environment Interface Biology, ⁷Center for Food and Bioconvergence, Department of Agricultural Biotechnology, and ⁸Institute on Aging, Seoul National University, Seoul, Korea; and ⁹Advanced Institutes of Convergence Technology, Seoul National University, Suwon, Korea

Abstract

Background: The consumption of dietary antioxidants is considered to be a good strategy against photo-aging. However, the results of previous clinical trials that investigated the effects of oral consumption of high-flavanol cocoa products on skin photo-aging have been contradictory.

Objective: The aim of this study was to investigate whether high-flavanol cocoa supplementation would improve the moderately photo-aged facial skin of female participants by assessing skin wrinkles and elasticity.



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An Anti-Wrinkle Diet: Nutritional Strategies to Combat Oxidation, Inflammation and Glycation

Rajani Katta, MD^{1,2,3}; Ariadna Perez Sanchez, MD³; Evelyne Tantry⁴

¹*McGovern Medical School at The University of Texas Health Sciences Center at Houston, Houston, TX, USA*

²*Baylor College of Medicine, Houston, TX, USA*

³*Katta Dermatology, Bellaire, TX, USA*

⁴*Rice University, Houston, TX, USA*

Conflicts of interest: Rajani Katta is the author of a book for the general public on diet and dermatology and has been an advisory board member for Vichy Laboratories. Ariadna Perez Sanchez and Evelyne Tantry have no conflicts to declare for this work.

ABSTRACT

There is growing awareness of the complex link between nutrition and skin. In the last few decades, our understanding of this link has grown significantly with research findings from multiple laboratory, animal, and human studies. From the impact of diet on clinical features of aging skin, to documentation of the biochemical and histologic changes that occur, our understanding of this link continues to expand and evolve. In this paper, we review the research on the impact of diet on skin aging. A number of long-term observational population studies have documented that healthier diets are linked to fewer signs of skin aging. Animal and laboratory studies have elucidated the biochemical processes that play a large role in the development of these clinical findings. A number of studies have also reported on the role of specific dietary compounds in impacting these processes, whether by combating or potentiating these forces. This body of research serves as guidance in recommending nutritional strategies that can combat the skin aging forces of oxidation, inflammation, and glycation.

Jéssica Eleonora Pedrosa Sanches Silveira* and Débora Midori Myaki Pedrosa

UV light and skin aging

Abstract: This article reviews current data about the relationship between sun radiation and skin, especially with regards ultraviolet light and the skin aging process. The benefits of sun exposition and the photoaging process are discussed. Finally, the authors present a review of photoprotection agents that are commercially available nowadays.

Keywords: photoaging; sun protection; ultraviolet (UV) exposure.

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Aging

However, skin transformations are the most perceptible signs of aging. Physiological changes in aged skin include structural and biochemical changes as well as changes in neurosensory perception, permeability, response to injury, repair capacity, and increased incidence of some skin diseases (5).

The skin aging process occurs in the epidermis and dermis. Although the number of cell layers remains stable, the skin thins progressively over adult life at an accelerating rate. The epidermis decreases in thickness by about 6.4% per decade on average, with an associated reduction in epidermal cell numbers (6), particularly in women. Further, dermis thickness decreases with age, and thinning is accompanied by a decrease in both vascularity and cellularity (5).

Aged skin turns dryer (7), and this can be proven by transdermal water loss (TEWL) measurements. Base-



Natural anti-aging skincare: role and potential

Idris Adewale Ahmed · Maryam Abimbola Mikail · Norhisam Zamakshshari · Al-Shwyeh Hussah Abdullah

Received: 3 January 2020 / Accepted: 22 February 2020
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Abstract The deterioration of the skin morphology and physiology is the first and earliest obvious and to elaborate on the relevance of *natural beauty and natural anti-aging skincare approaches that will help*

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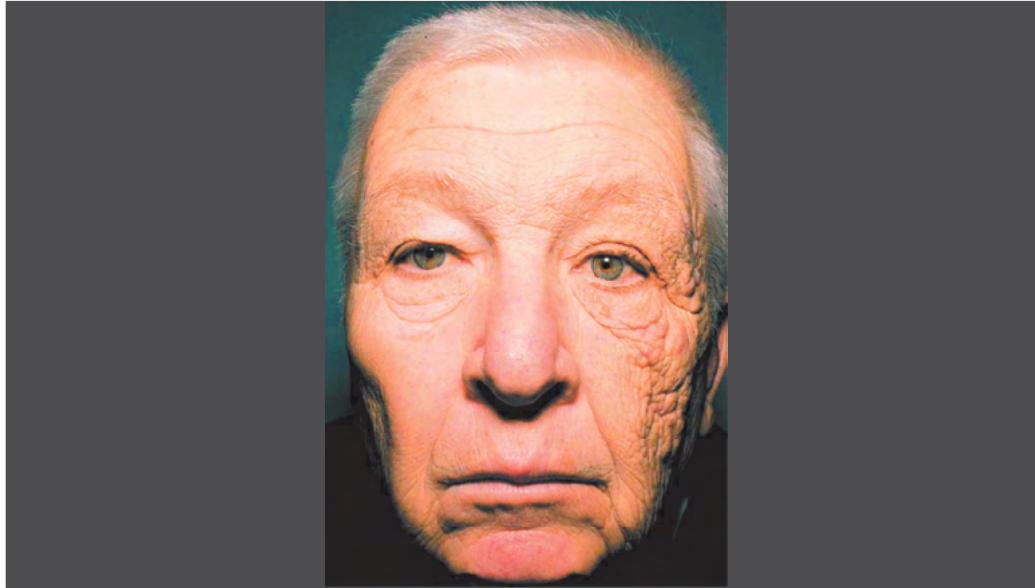


Natural anti-aging skincare: role and potential

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use these products in a complementary manner to retinoids, which, although approved by the FDA to improve the appearance of photoaged skin, often cause dryness and irritation. When compliance with retinoids is improved, clinical results improve. In a comprehensive skin care program for photoaged skin, the daily use of sunscreens in the daytime and retinoids at night is the gold standard. The addition of cosmeceuticals such as peptides may speed visible results either by enhancing collagen production, relaxing mimetic wrinkling, improving hydration and barrier function, or by a combination of these benefits. Unless intolerance to

Continuing Medical Education Article—Skin Care

Review Article

**The Truth About Over-the-Counter Topical
Anti-Aging Products: A Comprehensive Review**

Catherine K. Huang, MD; and Timothy A. Miller, MD

Dr. Huang is a resident in the Department of Head & Neck Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA. Dr. Miller is Professor and Chief, Division of Plastic & Reconstructive Surgery, at the same institution.

Learning Objectives:

The reader is presumed to have knowledge of the basic concepts of skin aging. After studying this article, the participant should be able to:

Vitamins

Vitamin A/retinols

Vitamin A is a naturally occurring antioxidant in the skin. The biologically active form of vitamin A is all-trans retinoic acid or tretinoin (Retin-A). Retinoic acid aids in epidermal proliferation, keratinization, and peeling. It also modifies keratin synthesis, fibroblastic proliferation, and collagen metabolism.¹⁰ Topical application of retinoic acid has been widely proven to improve global appearance, fine and coarse wrinkling, roughness, pig-

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STUDY

Topical Tretinoin Therapy and All-Cause Mortality

Martin A. Weinstock, MD, PhD; Stephen F. Bingham, PhD; Robert A. Lew, PhD; Russell Hall, MD; David Eilers, MD; Robert Kirsner, MD, PhD; Mark Naylor, MD; James Kalivas, MD; Gary Cole, MD; Kimberly Marcolivio, MEd; Joseph Collins, ScD; John J. DiGiovanna, MD; Julia E. Vertrees, PharmD; for the Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) Trial Group

Objective: To evaluate the relation of topical tretinoin, a commonly used retinoid cream, with all-cause mortality in the Veterans Affairs Topical Tretinoin Chemoprevention Trial (VATTC). The planned outcome of this trial was risk of keratinocyte carcinoma, and systemic administration of certain retinoid compounds has been shown to reduce risk of this cancer but has also been associated with increased mortality risk among smokers.

Design: The VATTC Trial was a blinded randomized chemoprevention trial, with 2- to 6-year follow-up. Oversight was provided by multiple independent committees.

Setting: US Department of Veterans Affairs medical centers.

Main Outcome Measures: Death, which was not contemplated as an end point in the original study design.

Results: The intervention was terminated 6 months early because of an excessive number of deaths in the tretinoin-treated group. Post hoc analysis of this difference revealed minor imbalances in age, comorbidity, and smoking status, all of which were important predictors of death. After adjusting for these imbalances, the difference in mortality between the randomized groups remained statistically significant.

Conclusions: We observed an association of topical tretinoin therapy with death, but we do not infer a

**Topical
blotching
facial sk**

D. L. Bissett, K. M.
The Procter & Gam

Received 6 May 20

Keywords: aging

**Wrinkling, red
ging**

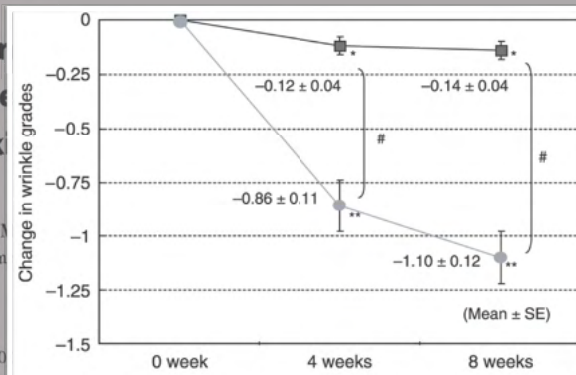


Figure 1. Change in wrinkle grades after treatments with the tested preparation (●) and the control (■).

* $P < 0.001$ compared with the control.

J Dermatol 35:637-42

Synopsis

Résumé

DISCUSSION

This study revealed the efficacy for wrinkles and tolerability of a cosmetic containing niacinamide, SSTT, in Japanese women. Overall, 64% of subjects who used the test substances showed marked or moderate improvement with the combination of observation and photographs based on the guideline of the JCIA.⁵ No subjects who used the control showed marked or moderate improvement. Significant reduction of wrinkle grades was seen both in the tested and control areas as compared with pre-

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Use of Topical Ascorbic Acid and Its Effects on Photodamaged Skin Topography

Steven S. Traikovich, DO

Objective: To determine the efficacy of topical ascorbic acid application in treating mild to moderate photodamage of facial skin using an objective, computer-assisted image analysis of skin surface topography and subjective clinical, photographic, and patient self-appraisal questionnaires.

Design: A 3-month, randomized, double-blind, vehicle-controlled study.

Setting: Facial plastic surgery private practice.

Patients: Nineteen evaluable volunteer sample patients aged between 36 and 72 years with Fitzpatrick skin types I, II, and III who were in good physical and mental health with mild to moderately photodamaged facial skin were considered for analysis.

ffects (burning, stinging, redness, peeling, dryness, discoloration, itching, and rash). Standard photographs were taken at baseline, including anteroposterior and left and right oblique views to facilitate subsequent clinical evaluations, and at the end of therapy for comparison. Optical profilometry analysis was performed on the skin surface replicas of the lateral canthal (crow's feet) region, comparing baseline to end-of-study specimens. Using this computer-based system, the resulting image was digitally analyzed, and numeric values were assigned to reflect surface features. The parameters obtained included R_z , R_a , and shadows. These values provided objective data that document pretreatment and posttreatment texture changes proportional to the degree of wrinkling, roughness, and other surface irregularities.

Results: Optical profilometry image analysis demon-

is the amount synthesized per day by a 130-lb goat.)

Only primates, guinea pigs, and the Indian fruit-eating bat lack the enzyme (L-glucono-gamma-lactone oxidase) required to self-synthesize vitamin C. Vitamin C (L-ascorbic acid) is the body's major aqueous-phase antioxidant and is essential for life. We humans get vitamin C solely from our diet, but even large doses (6000 mg/day, or 80 oranges) do not increase the concentration to optimal levels in the skin. Furthermore, exposure to sunlight and environmental pollution deplete vitamin C from the center layers of the skin. Even minimal UV exposure of 1.6 minimal erythema dose (MED) decreases the level of vitamin C to 70% of the normal level, and exposure to 10 MED decreases the vitamin C to only 54%.⁸⁶ Exposure to ozone at a dose of 10 parts per million in city pollution decreases the level of epidermal vitamin C by 55%.⁸⁷

Active L-ascorbic acid is such an excellent antioxidant that it is inherently unstable, turning brown as it is oxidized to dihydroascorbic acid when exposed to air. Therefore, the shelf life of most formulations containing pure vitamin C is short, so esterified forms of vitamin C are usually used for topical application in lotions, creams, serums, and patches to overcome this problem. However, these more stable, esterified derivatives (ascorbyl-6-palmitate and magnesium ascorbyl phosphate) are not well absorbed¹⁰³ and are only minimally metabolized by the skin to the active, free acid form. To achieve photoprotection and other benefits to the skin with topical vitamin C, the formulation must contain L-ascorbic acid in a high enough concentration (at least 10%), be stable, and be at an acid pH—less than the pKa (4.2) of vitamin C.¹⁰³ (The optimal pH is 3.5.)

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vert to L-ascorbic acid (the only form that can be used by the body), and/or are not delivered in adequate concentration. These ascorbic acid substitutes include ascorbyl palmitate, magnesium ascorbyl phosphate, ascorbic acid sulfate, ascorbyl stearate, ascorbyl dipalmitate, and ascorbic acid magnesium phosphate, which are easily stabilized but must be converted to L-ascorbate to be effectively useful. There is no direct evidence that ascorbic acid derivatives enter the skin in appreciable amounts, and it seems that their conversion to L-ascorbate is largely inefficient, thus precluding effective concentration delivery.

This 3-month study demonstrated and evaluated topographic improvement in photodam

Arch Otolaryngol Head Neck Surg 125(10):1091-8

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Details

Finally, a Regimen to Extend Human Life Expectancy

James W. Larrick^{1,2} and Andrew R. Mendelsohn^{1,2}

Abstract

The United States has the most expensive healthcare system worldwide. Yet measures of health span and life expectancy are well below the major industrialized nations. With the U.S. population aged 65 years and older projected to double by mid-century, a healthcare crisis is looming. Within this context, huge interest and investment have emerged in technologies and drugs to address aging with an expected benefit to health span. The thesis being that such basic interventions will reduce morbidity caused by many chronic diseases wherein biological age itself is the major risk factor. In the light of limited progress to date, a recent study out of the Harvard School of Public Health is quite refreshing: less than half dozen lifestyle interventions can greatly increase health span. Perhaps these are familiar: cessation of smoking, ≥ 30 minutes of moderate daily exercise,



Impact of Healthy Lifestyle Factors on Life Expectancies in the US Population

BACKGROUND: Americans have a shorter life expectancy compared with residents of almost all other high-income countries. We aim to estimate the impact of lifestyle factors on premature mortality and life expectancy in the US population.

METHODS: Using data from the Nurses' Health Study (1980–2014; n=78865) and the Health Professionals Follow-up Study (1986–2014,

Yanping Li, MD, PhD*
An Pan, PhD*
Dong D. Wang, MD, ScD
Xiaoran Liu, PhD
Klodian Dhana, MD, PhD
Oscar H. Franco, MD, PhD
Stephen Kaptoge, PhD

low-risk factors was 60.7% (95% CI, 53.6–66.7) for all-cause mortality, 51.7% (95% CI, 37.1–62.9) for cancer mortality, and 71.7% (95% CI, 58.1–81.0) for cardiovascular disease mortality. We estimated that the life expectancy at age 50 years was 29.0 years (95% CI, 28.3–29.8) for women and 25.5 years (95% CI, 24.7–26.2) for men who adopted zero low-risk lifestyle factors. In contrast, for those who adopted all 5 low-risk factors, we projected a life expectancy at age 50 years of 43.1 years (95% CI, 41.3–44.9) for women and 37.6 years (95% CI, 35.8–39.4) for men. The projected life expectancy at age 50 years was on average 14.0 years (95% CI, 11.8–16.2) longer among female Americans with 5 low-risk factors compared with those with zero low-risk factors; for men, the difference was 12.2 years (95% CI, 10.1–14.2).

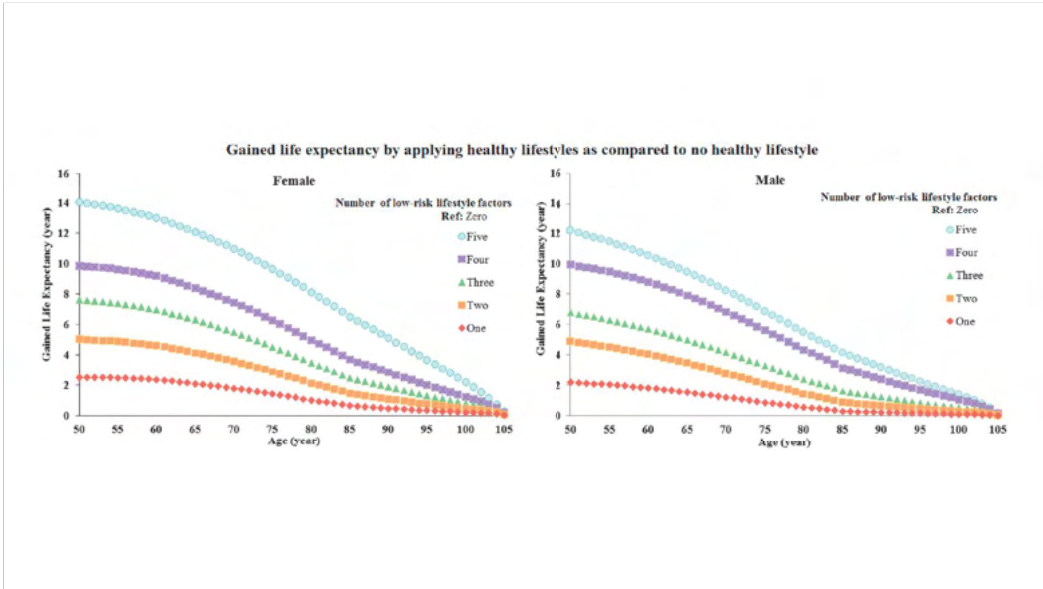
CONCLUSIONS: Adopting a healthy lifestyle could substantially reduce premature mortality and prolong life expectancy in US adults.

Circulation. 2018;138:345–355. DOI: 10.1161/CIRCULATIONAHA.117.032047

low-risk factors was 60.7% (95% CI, 53.6–66.7) for all-cause mortality, 51.7% (95% CI, 37.1–62.9) for cancer mortality, and 71.7% (95% CI, 58.1–81.0) for cardiovascular disease mortality. We estimated that the life expectancy at age 50 years was 29.0 years (95% CI, 28.3–29.8) for women and 25.5 years (95% CI, 24.7–26.2) for men who adopted zero low-risk lifestyle factors. In contrast, for those who adopted all 5 low-risk factors, we projected a life expectancy at age 50 years of 43.1 years (95% CI, 41.3–44.9) for women and 37.6 years (95% CI, 35.8–39.4) for men. The projected life expectancy at age 50 years was on average 14.0 years (95% CI, 11.8–16.2) longer among female Americans with 5 low-risk factors compared with those with zero low-risk factors; for men, the difference was 12.2 years (95% CI, 10.1–14.2).

CONCLUSIONS: Adopting a healthy lifestyle could substantially reduce premature mortality and prolong life expectancy in US adults.

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RESEARCH ARTICLE

Measuring Burden of Unhealthy Behaviours Using a Multivariable Predictive Approach: Life Expectancy Lost in Canada Attributable to Smoking, Alcohol, Physical Inactivity, and Diet

Douglas G. Manuel^{1,2,3,4,5,6,7,*}, Richard Perez^{1,2,5}, Claudia Sanmartin³, Monica Taljaard^{1,5}, Deirdre Hennessy^{1,3}, Kumanan Wilson¹, Peter Tanuseputro^{1,2,5}, Heather Manson⁷, Carol Bennett^{1,2}, Meltem Tuna^{1,2}, Stacey Fisher^{1,5}, Laura C. Rosella^{2,7,8}

1 Ottawa Hospital Research Institute, Ottawa, Ontario, Canada, **2** Institute for Clinical Evaluative Sciences, Ottawa and Toronto, Ontario, Canada, **3** Statistics Canada, Ottawa, Ontario, Canada, **4** Department of Family Medicine, University of Ottawa, Ottawa, Ontario, Canada, **5** School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Ottawa, Ontario, Canada, **6** Bruyère Research Institute, Ottawa, Ontario, Canada, **7** Public Health Ontario, Toronto, Ontario, Canada, **8** University of Toronto, Toronto, Ontario, Canada



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1 Ottawa Hospital Research Institute, Ottawa, Ontario, Canada, **2** Institute for Clinical Evaluative Sciences, Ottawa and Toronto, Ontario, Canada, **3** Statistics Canada, Ottawa, Ontario, Canada, **4** Department of Family Medicine, University of Ottawa, Ottawa, Ontario, Canada, **5** School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Ottawa, Ontario, Canada, **6** Bruyère Research Institute, Ottawa, Ontario, Canada, **7** Public Health Ontario, Toronto, Ontario, Canada, **8** University of Toronto, Toronto, Ontario, Canada



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subgroups. Discrimination was maintained or improved in the validation cohorts. For the 2010 Canadian population, unhealthy behaviour attributable life expectancy lost was 6.0 years for both men and women (for men 95% CI: 5.8 to 6.3 for women 5.8 to 6.2). The Canadian life expectancy associated with health behaviour recommendations was 17.9 years (95% CI: 17.7 to 18.1) greater for people with the most favourable risk profile compared to those with the least favourable risk profile (88.2 years versus 70.3 years). Smoking, by itself, was associated with 32% to 39% of the difference in life expectancy across social groups (by education achieved or neighbourhood deprivation).

Conclusions

Multivariable predictive algorithms such as MPoRT can be used to assess health burdens for sociodemographic groups or for small changes in population exposure to risks, thereby addressing some limitations of more commonly used measurement approaches. Unhealthy behaviours have a substantial collective burden on the life expectancy of the Canadian

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Because of this relationship, slowing aging is predicted to be more effective at improving both quality and quantity of life compared to treating or curing any individual disease. Indeed, for a typical 50-year-old woman, completely curing all forms of cancer would only increase life expectancy by a few years, whereas slowing the aging process itself comparable to what has been accomplished in laboratory animals may yield 15–20 extra years of life (Martin et al. 2003). Importantly, these extra years are relatively healthy, due to the fact that slowing biological aging would also slow the onset and progression of all age-associated disorders. If realized, this “longevity dividend”

Mamm Genome 27(7-8):279-288

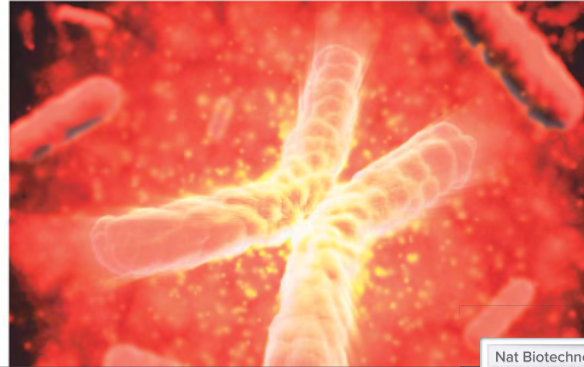
slowing biological aging is expected to yield sig-

Selling long life

Christopher Thomas Scott & Laura DeFrancesco

A new generation of commercial entities is beginning to explore opportunities for new types of interventions and services in a graying world.

Aging research has a new face: longevity. What began as a breathless expectation of the discovery of aging genes in the 1990s has yielded to a far more ambitious effort fueled by a bolus of baby boomers faced with an incomplete picture of their golden years—extended lifetimes, surely, but with the potential that some of those years will be spent in suffering decline. And what distinguishes longevity research from its aging counterpart is its sudden embrace of big science. Two high-profile companies with undisclosed amounts of private capital have set up shop: Craig Venter's Human Longevity (HLI; San Diego) and Google's super stealthy Calico (S. San Francisco, CA, USA). In addition, several large-scale projects are gearing up to collect massive data sets of healthy human populations—the 100K Wellness Project, spearheaded by



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CLINICAL RESEARCH STUDY

 **AJM Theme Issue: Diabetes/Metabolism**

Turning Back the Clock: Adopting a Healthy Lifestyle in Middle Age

Dana E. King, MD, MS, Arch G. Mainous, III, PhD, Mark E. Geesey, MS

Department of Family Medicine, Medical University of South Carolina, Charleston, SC.

ABSTRACT

PURPOSE: To determine the frequency of adopting a healthy lifestyle (5 or more fruits and vegetables daily, regular exercise, BMI 18.5-29.9 kg/m², no current smoking) in a middle-aged cohort, and determine the subsequent rates of cardiovascular disease (CVD) and mortality among those who adopt a healthy lifestyle.

METHODS: We conducted a cohort study in a diverse sample of adults age 45-64 in the Atherosclerosis Risk in Communities survey. Outcomes are all-cause mortality and fatal or non-fatal cardiovascular disease.

RESULTS: Of 15,200 subjects, 13.4% (5%) adopted a healthy lifestyle. Mortality rates were significantly lower in those who adopted a healthy lifestyle compared to those who did not (10.7% vs 13.4%, p < 0.001).

tality (OR 0.75, 95% CI, 0.58-0.97). Individuals adopting all 4 healthy habits experienced reductions in both ($P < .01$).

DISCUSSION

In this study, we found that a midlife switch to a healthy lifestyle that includes a diet of at least 5 daily fruits and vegetables, exercise, maintaining a healthy weight, and not smoking results in a substantial reduction in mortality and cardiovascular disease over the subsequent 4 years. This benefit was independent of age, race, gender, socioeconomic status, a history of hypertension, hypercholesterolemia, diabetes, or previous cardiovascular disease. The study adds 3 new features to the current literature: first, that

ing, and only 8.4% newly adopt such a lifestyle past age 45.

- Adopting a healthy lifestyle in middle age has substantial benefits: Mortality and cardiovascular disease risk was significantly reduced (40% and 35% respectively) after only 4 years compared to people with less healthy lifestyles.
- Men, African-Americans, and individuals with less than college education, lower

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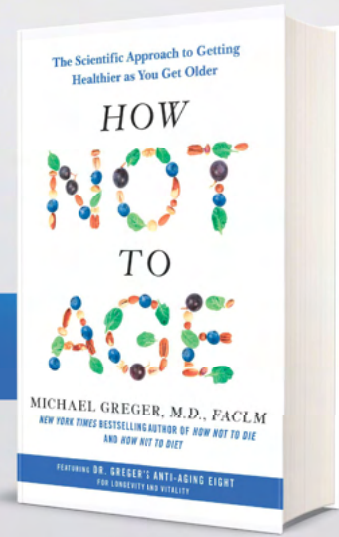
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The potential public health benefit from adopting a healthier lifestyle in middle age is substantial. The current study demonstrated that adopting 4 modest healthy habits considerably lowers the risk of cardiovascular disease and mortality in relatively short-term 4-year follow up period. The findings emphasize that making the necessary changes to adhere to a healthy lifestyle is extremely worthwhile, and that middle-age is not too late to act.

ACKNOWLEDGMENTS

The Atherosclerosis Risk in Communities Study (ARIC) is


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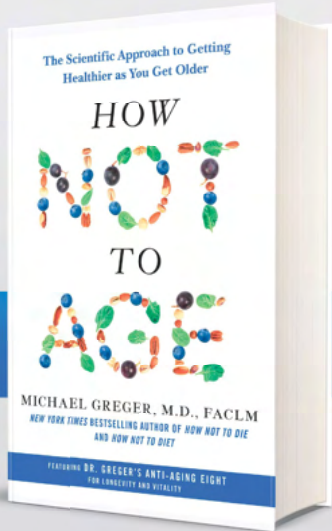

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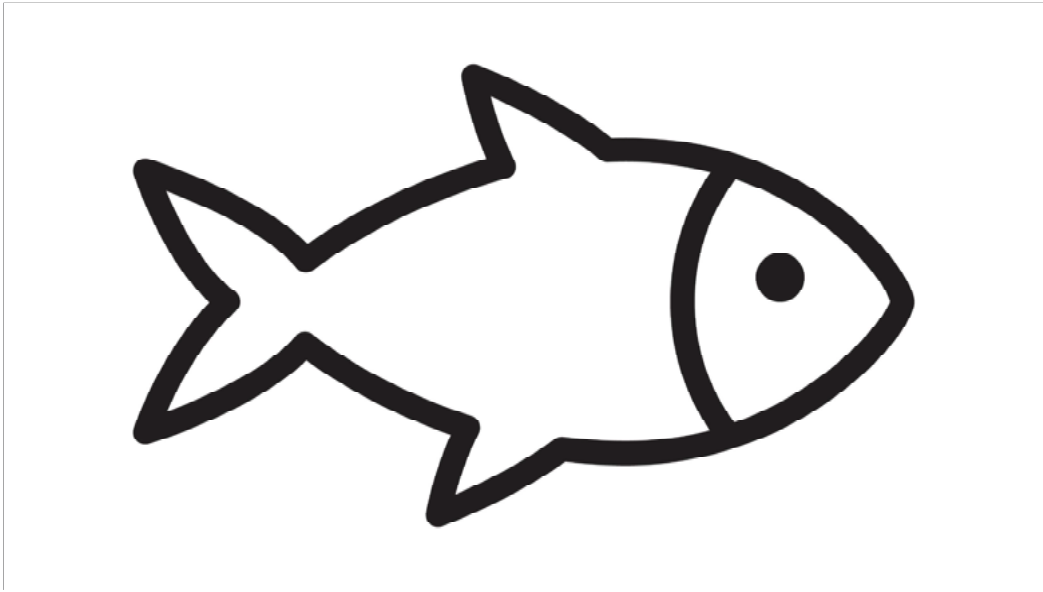


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REVIEW

Human Health and Ocean Pollution

Philip J. Landrigan*, John J. Stegeman†, Lora E. Fleming^{‡,§}, Denis Allemand¶, Donald M. Anderson†, Lorraine C. Backer¶, Françoise Brucker-Davis^{**††}, Nicolas Chevalier^{**††}, Lilian Corra^{**§§}, Dorota Czerucka¶, Marie-Yasmine Dechraoui Bottein¶¶¶¶¶, Barbara Demeneix^{†††.†††}, Michael Depledge[§], Dimitri D. Deheyn^{§§§}, Charles J. Dorman¶¶¶¶, Patrick Fénichel^{**††}, Samantha Fisher*, Françoise Gaill^{†††}, François Galgani^{¶¶¶}, William H. Gaze^{****}, Laura Giuliano^{††††}, Philippe Grandjean^{††††}, Mark E. Hahn†, Amro Hamdoun^{§§§§}, Philipp Hess^{¶¶¶}, Bret Judson*, Amalia Laborde^{¶¶¶¶}, Jacqueline McGlade^{¶¶¶¶.*****}, Jenna Mu*, Adetoun Mustapha^{††††.††††}, Maria Neira^{§§§§§}, Rachel T. Noble^{¶¶¶¶¶}, Maria Luiza Pedrotti^{†††.¶¶¶¶¶}, Christopher Reddy^{*****}, Joacim Rocklöv^{†††††}, Ursula M. Scharler^{†††††}, Hariharan Shanmugam*, Gabriella Taghian*, Jeroen A.J.M. van de Water¶, Luigi Vezzulli^{§§§§§}, Pál Weihe^{¶¶¶¶¶}, Ariana Zeka^{¶¶¶¶¶}, Hervé Raps^{¶.*****} and Patrick Rampa^{¶.*****}

1. **Pollution of the oceans is widespread, worsening, and poorly controlled. Human activity that releases unwanted, often dangerous waste materials into the sea is the major source.**

- Ocean pollution is a complex mixture of plastic waste, toxic metals, manufactured chemicals, oil spills, urban and industrial wastes, pesticides, fertilizers, pharmaceutical chemicals, agricultural runoff, and sewage. More than 80% arises from land-based sources. Chemical and plastic pollutants have become ubiquitous in the earth's oceans and contaminate seas and marine organisms from the high Arctic to the abyssal depths.

Polychlorinated Biphenyls in Food

Panithi Saktrakulka, Tuo Lan, Jason Hua, Rachel F. Marek, Peter S. Thorne,* and Keri C. Hornbuckle*

 Cite This: *Environ. Sci. Technol.* 2020, 54, 11443–11452

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ABSTRACT: We measured the concentrations of 205 polychlorinated biphenyl (PCB) congeners in 26 food items: beef steak, butter, canned tuna, catfish, cheese, eggs, french fries, fried chicken, ground beef, ground pork, hamburger, hot dog, ice cream, liver, luncheon meat, margarine, meat-free dinner, milk, pizza, poultry, salmon, sausage, shrimp, sliced ham, tilapia, and vegetable oil. Using Diet History Questionnaire II, we calculated the PCB dietary exposure in mothers and children participating in the AESOP Study in East Chicago, Indiana, and Columbus Junction, Iowa. Salmon had the highest concentration followed by canned tuna, but fish is a minor contributor to exposure. Other animal proteins are more important sources of PCB dietary exposure in this study population. Despite the inclusion of few congeners and food types



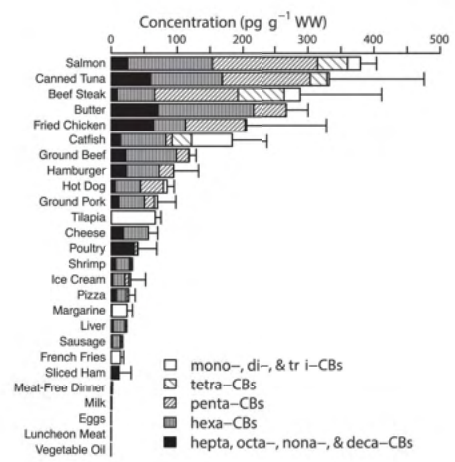


Table 18: Expression of result (ER), sample size (N), mean levels of dioxins (PCDD), furans (PCDF), dioxins and furans (PCDD/F), non-ortho PCB (NO PCB), mono-ortho PCB (MO PCB), dioxin-like PCB (DL PCB), and total TEQ_{WHO98} values (in pg/g) in a number of food subgroup.

Food group	Food sub-group	ER	N	PCDD	PCDF	PCDD/F	NO PCB	MO PCB	DL PCB	Total
Meat and meat products ruminants	Bovine fat		130	0.31	0.55	0.86	0.94	0.24	1.18	2.03
	Ovine fat		40	0.53	0.39	0.91	0.56	0.26	0.82	1.73
	Caprine fat		3	1.29	0.34	1.63	0.46	0.05	0.52	2.15
Muscle meat fish and fish products excluding eels	Seafood ww		98	0.56	0.80	1.36	0.94	0.24	1.18	2.54
	Farmed salmon ww		144	0.15	0.29	0.44	0.91	0.20	1.11	1.55
	Farmed trout ww		25	0.11	0.21	0.31	0.78	0.11	0.88	1.20
	Farmed other ww		125	0.64	1.25	1.89	3.84	1.09	4.92	6.82
	Herring ww		389	1.20	3.73	4.93	1.83	0.89	2.72	7.65
	Salmon, other ww		95	0.94	2.34	3.28	3.47	1.24	4.71	7.99
	Sprat ww		48	0.79	2.27	3.05	2.65	0.61	3.26	6.31
	Trout ww		71	0.33	1.00	1.33	1.44	0.79	2.23	3.56
	Other fish ww		980	0.26	0.57	0.83	0.84	0.50	1.34	2.17
Raw milk and dairy products including butter	Milk not specified fat		420	0.50	0.55	1.05	1.28	0.09	1.37	2.42
	Butter fat		141	0.28	0.26	0.54	0.65	0.07	0.72	1.26
	Cheese fat		71	0.35	0.32	0.68	0.74	0.13	0.87	1.54
	Milk from farm fat		123	0.18	0.26	0.43	0.69	0.14	0.84	1.27
	Milk bulk fat		61	0.20	0.42	0.62	0.56	0.12	0.68	1.30
	Milk from retail fat		36	0.28	0.22	0.51	0.35	0.09	0.44	0.95
	Other milk products fat		79	0.30	0.37	0.67	0.33	0.06	0.40	1.07
Hen eggs and egg products	Caged fat		26	0.19	0.11	0.30	0.10	0.01	0.11	0.41
	Free range fat		34	0.21	0.09	0.30	0.13	0.03	0.16	0.46
	Not specified fat		725	0.50	0.50	1.00	0.86	0.31	1.17	2.16

EFSA J 8(3):1385



Invited Commentary

The secret story of fish: decreasing nutritional value due to pollution?

(First published online 24 May 2012)

Fish, especially fatty fish, have long been viewed as a healthy dietary component because of their unique content of long-chain *n*-3 PUFA (*n*-3 fatty acids). An observation in 852 male residents of Zutphen, The Netherlands, aged 40–59 years in 1960 indicated that fish intake was inversely associated with the incidence of CHD over 20 years of follow-up⁽¹⁾. On the other hand, fish may also contain diverse environmental pollutants such as heavy metals and persistent organic pollutants (POP), including organochlorine pesticides, polychlorinated biphenyls (PCB), dioxins, polybrominated diphenylether (PBDE) and perfluorinated compounds (PFCO). Therefore,

metabolic profile⁽¹¹⁾. In addition, consumption of salmon protein hydrolysate containing less than 0.2% of lipids, and therefore very low concentrations of POP, was found to protect rats against insulin resistance induced by a high-fat diet containing lard and 'corn oil'⁽¹²⁾. Taken together, these findings emphasise that background levels of POP, which many people consider to be at safe levels, can completely counteract the potential benefits of *n*-3 fatty acids and other nutrients present in fish, in particular leading to the serious metabolic features which often precede type 2 diabetes. Thus, these animal feeding studies are consistent with the recent human

The secret story of fish: decreasing nutr

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Chronic Consumption of Farmed Salmon Containing Persistent Organic Pollutants Causes Insulin Resistance and Obesity in Mice

Mohammad Madani Ibrahim^{1,2}, Even Fjære^{1,3}, Erik-Jan Lock¹, Danielle Naville⁴, Heidi Amlund¹, Emmanuelle Meugnier⁴, Brigitte Le Magueresse Battistoni⁴, Livar Frøyland¹, Lise Madsen^{1,3}, Niels Jessen⁵, Sten Lund⁶, Hubert Vidal⁴, Jérôme Ruzzin^{1,7*}

1 National Institute of Nutrition and Seafood Research, Bergen, Norway, **2** Institute of Biomedicine, University of Bergen, Bergen, Norway, **3** Department of Biology, University of Copenhagen, Copenhagen, Denmark, **4** INSERM U-1060, INRA U-1235, CarMeN Laboratory, Lyon1 University, Oullins, France, **5** Department of Clinical Pharmacology, Aarhus University Hospital, Aarhus, Denmark, **6** Department of Internal Medicine and Diabetes and Institute of Experimental Clinical Research, Aarhus University Hospital, Aarhus, Denmark, **7** Department of Biology, University of Bergen, Bergen, Norway

Abstract

Background: Dietary interventions are critical in the prevention of metabolic diseases. Yet, the effects of fatty fish consumption on type 2 diabetes remain unclear. The aim of this study was to investigate whether a diet containing farmed salmon prevents or contributes to insulin resistance in mice.

Methodology/Principal Findings: Adult male C57BL/6J mice were fed control diet (C), a very high-fat diet without or with farmed Atlantic salmon fillet (VHF and VHF/S, respectively), and Western diet without or with farmed Atlantic salmon fillet (WD and WD/S, respectively). Other mice were fed VHF containing farmed salmon fillet with reduced concentrations of

vary depending on the presence or absence of POP. Rats exposed to contaminated salmon oil (containing background levels of POP) developed metabolic complications linked to type 2 diabetes, whereas animals exposed to decontaminated salmon oil (treated to achieve very low levels of POP) did not show such disturbances⁽¹⁰⁾. Furthermore, mice fed commercially available farmed salmon fillet with common POP levels were found to develop insulin resistance, glucose intolerance, visceral obesity, fatty liver and chronic low-grade inflammation, in contrast to mice fed farmed salmon fillet containing lower levels of POP, which showed a better

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Public Health and Economic Consequences of Methyl Mercury Toxicity to the Developing Brain

Leonardo Trasande,^{1,2,3,4} Philip J. Landrigan,^{1,2} and Clyde Schechter⁵

¹Center for Children's Health and the Environment, Department of Community and Preventive Medicine, and ²Department of Pediatrics, Mount Sinai School of Medicine, New York, New York, USA; ³Division of General Pediatrics, Children's Hospital, Boston, Massachusetts, USA; ⁴Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA; ⁵Department of Family Medicine, Albert Einstein College of Medicine, Bronx, New York, USA

Methyl mercury is a developmental neurotoxicant. Exposure results principally from consumption by pregnant women of seafood contaminated by mercury from anthropogenic (70%) and natural (30%) sources. Throughout the 1990s, the U.S. Environmental Protection Agency (EPA) made steady progress in reducing mercury emissions from anthropogenic sources, especially from power plants, which account for 41% of anthropogenic emissions. However, the U.S. EPA recently proposed to slow this progress, citing high costs of pollution abatement. To put into perspective the costs of controlling emissions from American power plants, we have estimated the economic costs of methyl mercury toxicity attributable to mercury from these plants. We used an environmentally attributable fraction model and limited our analysis to the neurodevelopmental impacts—specifically loss of intelligence. Using national blood mercury prevalence data from the Centers for Disease Control and Prevention, we found that between 316,588 and 637,233 children each year have cord blood mercury levels > 5.8 µg/L, a level associated with loss of IQ. The resulting loss of intelligence causes diminished economic productivity that persists over the entire lifetime of these children. This lost productivity is the major cost of methyl mercury toxicity, and it amounts to \$8.7 billion annually (range, \$2.2–43.8 billion; all costs are in 2000 US\$). Of this total, \$1.3 billion (range, \$0.1–6.5 billion) each year is attributable to mercury emissions from American power

U.S. exposure levels. The first of these studies, a cohort in New Zealand, found a 3-point decrement in the Wechsler Intelligence Scale-Revised (WISC-R) full-scale IQ among children born to women with maternal hair mercury concentrations > 6 µg/g (Kjellstrom et al. 1986, 1989). A second study in the Seychelles Islands in the Indian Ocean found only one adverse association with maternal hair mercury concentration among 48 neurodevelopmental end points examined (prolonged time to complete a grooved pegboard test with the nonpreferred hand) (Myers et al. 2003). However, the grooved pegboard test was one of the few neurobehavioral instruments in the Seychelles study not subject to the vagaries of translation that can degrade

(30%) sources. Throughout the 1990s, the U.S. Environmental Protection Agency (EPA) made steady progress in reducing mercury emissions from anthropogenic sources, especially from power plants, which account for 41% of anthropogenic emissions. However, the U.S. EPA recently proposed to slow this progress, citing high costs of pollution abatement. To put into perspective the costs of controlling emissions from American power plants, we have estimated the economic costs of methyl mercury toxicity attributable to mercury from these plants. We used an environmentally attributable fraction model and limited our analysis to the neurodevelopmental impacts—specifically loss of intelligence. Using national blood mercury prevalence data from the Centers for Disease Control and Prevention, we found that between 316,588 and 637,233 children each year have cord blood mercury levels > 5.8 µg/L, a level associated with loss of IQ. The resulting loss of intelligence causes diminished economic productivity that persists over the entire lifetime of these children. This lost productivity is the major cost of methyl mercury toxicity, and it amounts to \$8.7 billion annually (range, \$2.2–43.8 billion; all costs are in 2000 US\$). Of this total, \$1.3 billion (range, \$0.1–6.5 billion) each year is attributable to mercury emissions from American power plants. This significant toll threatens the economic health and security of the United States and should be considered in the debate on mercury pollution controls. *Key words:* children's health, cognitive development, cord blood, electrical generation facilities, environmentally attributable fraction, fetal exposure, lost economic productivity, mercury, methyl mercury, power plants. *Environ Health Perspect* 113:590–596 (2005). doi:10.1289/ehp.7743 available via <http://dx.doi.org/> [Online 28 February 2005]

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Short Communication

One man's swordfish story: The link between Alzheimer's disease and mercury exposure



Madeline M. Foley^{a,b}, Ilana Seidel^c, Justin Sevier^{a,d}, Julie Wendt^e, Mikhail Kogan^{f,*}

^a Intern, George Washington University Center for Integrative Medicine, 908 New Hampshire Ave NW #200, Washington D.C., 20037, USA

^b MS2, University of Utah School of Medicine, 20 N 1900 E, SLC, UT 84132, USA

^c San Francisco Veterans Affairs, 4150 Clement St, San Francisco, CA 94121, Integrative Health Service, USA

^d MS1, The George Washington University School of Medicine and Health Sciences, 2300 I St. NW, Washington, DC 20052, USA

^e JW Nutrition, 1098 Taft Street, Rockville, MD 20850, USA

^f George Washington Center for Integrative Medicine, 908 New Hampshire Ave NW #200, Washington D.C., 20037, USA

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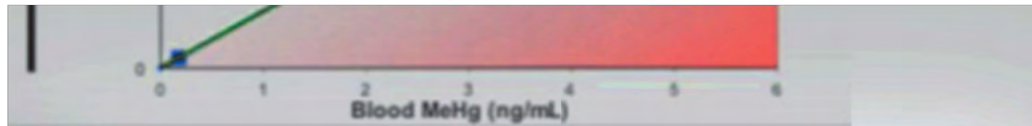
ABSTRACT

It is well-documented that when mercury levels surpass the permissible value, individuals experience a myriad of symptoms that include chronic fatigue, dizziness, and loss of appetite. Mercury is also known to be one of the

report discusses a clinical scenario in which decreasing the mercury load in a 91-year-old man diagnosed with Alzheimer's led to an improvement in his Mini-Mental State Examination (MMSE) performance.

2. Presenting concerns

A 91-year-old white male was brought in by his wife to the physician's clinic with a chief complaint of progressive memory loss during the past several years. Upon initial assessment, we learned that the patient was originally a strong and physically healthy three-war veteran. He lacked a number of important AD risk factors such as cardiac disease and family history of AD. Although the patient possessed good strength overall, his energy and cognition had declined. He also complained of sleeplessness during the night, which was possibly due to



blood, and urine compared to CDC average. over time.

initially, his substantial functional decline had prevented him from maintaining his prior lifestyle, and his friends and relatives assumed that he was nearing end of his life. Because no one anticipated or accepted his cognitive recovery, he could not reintegrate into his previous lifestyle and became deeply depressed.

The ReCode protocol, pioneered by Dr. Dale Bredesen ¹³ constitutes the first functional treatment of Alzheimer's disease and may represent the only mechanism of Alzheimer's disease reversal at present time. Given this development, the authors advocate for an early ethical discussion with patients and families to address the criticality of re-es-

AREDS 2, Saw Palmetto, and Vitamin D3. The patient's only known allergy was to penicillin. The patient's father died from a stroke at the age of 57. The patient was a veteran of three wars but had never been diagnosed with PTSD, had never smoked cigarettes, and did not drink alcohol. He had lived with his wife for the past 25 years and had five children that range in age from 44 to 66 years old. His diet was generally healthy and was mostly managed by his wife, who tried to maintain an anti-inflammatory diet. A detailed history revealed that he had consumed swordfish once or twice a week for several years.

Upon initial evaluation, the 91-year-old patient appeared strong and capable with slight difficulty standing or sitting, possibly due to his past bilateral knee replacement. He walked into the room with a slight shuffle in his gait and when asked to sit, he understood the question but did not comply by sitting. On examination of verbal and physical response, the patient's understanding of commands was intact, yet he could not initiate physical movements. A detailed physical exam

urine test demonstrated an elevated RBC mercury level in addition to CoQ10 and magnesium deficiency. Specialized mercury testing via Quicksilver Mercury Tri-Testing (hair, blood, and urine) revealed a severely elevated level, more than ten times greater than the CDC recommended level of total mercury. In addition, both methylmercury, an organic form found in fish, and inorganic mercury, presumably from amalgams, were highly elevated (Fig. 1).

The treatment involved removing swordfish and other high-mercury fish from his diet¹⁵ and the patient was prescribed comprehensive nutritional detoxification support and additional nutrients to correct identified deficiencies. This program consisted of CoQ10; a high potency methylated multivitamin/multimineral complex; probiotics; and a supplement form of a metal binder consisting of cilantro, Modified Citrus Pectin, Chlorella, alpha-lipoic acid, and N-acetyl- cysteine (NAC). In addition, the patient was given oral glutathione and liver protective formula consisting of milk thistle, burdock, and cordyceps.

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Repeat Mercury Tri-Test showed an 80 % reduction in the patient's total mercury level six months later and normal mercury levels four months after that (Fig. 2). At a follow-up visit one month after the last mercury test, the patient's wife reported substantial memory improvement and the MMSE score improved to a 27/30 (Graph 1). The patient's memory unexpectedly declined in 2015 with his lowest MMSE score of a 21/30. A computed tomography (CT) of the head was performed but interpreted as negative by the radiologist. A head CT completed one year later showed old infarcts, indicating that the patient had incurred mini strokes that caused memory decline and increased cognitive impairment. A second examination of the initial CT

CASE REPORT

Reversible alopecia associated with high blood mercury levels and early menopause: a report of two cases

Jane B. Peters, BA,² and Michelle P. Warren, MD¹

Abstract

Objective: The aim of this study was to report on two women in early menopause with alopecia and high mercury (Hg) levels which reversed with a decrease in toxic levels.

Methods: Retrospective chart review and case studies in a reproductive endocrinology practice.

Results: A 43-year-old woman initially evaluated for early menopause later experienced sudden circumscribed hair loss on the scalp. Blood tests indicated elevated Hg levels and further investigation revealed a diet high in tuna. Levels fell with elimination of dietary tuna. Another woman, 39 years old was complaining of severe hot flashes, night sweats, and menstrual irregularity also developed alopecia. Treated unsuccessfully for low testosterone, blood tests indicated high Hg levels and simultaneous hair loss was observed; recommendation to alter diet, including fish intake, was followed by a reversal of alopecia, along with a decrease in blood Hg levels. Literature searches were conducted with a focus on Hg toxicity or poisoning with symptom of alopecia.

Conclusions: Women of reproductive age frequently seek treatment for what is thought to be hormone-related hair loss especially at menopause. Two women demonstrated a strong temporal correlation to high Hg levels

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Conclusions: Women of reproductive age frequently seek treatment for what is thought to be hormone-related hair loss especially at menopause. Two women demonstrated a strong temporal correlation to high Hg levels associated with early menopause, which was reversible. The development of alopecia in the setting of mild Hg intoxication has not been reported in the medical literature despite its appearance in the popular press. Measurement of Hg levels should be considered in women with alopecia and its relationship to early menopause is unclear but bears further research.

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Patient 2

Patient 2 was seen at age 39 for severe hot flashes, night sweats, and recent amenorrhea for 3 months. Laboratory evalu

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level with reversal upon normalization of Hg levels. One patient showed only a localized and sudden loss. Clinicians should recognize diffuse and localized alopecia as unusual, but possible symptoms of Hg toxicity even in the absence of concomitant neurologic manifestations. Screening for Hg toxicity should be considered, as it is reversible. Instructing patients to reduce fish intake and repeat blood tests could offer relief of symptoms and uncover dietary habit as a potential source of heavy metal intoxication and alopecia. Contamination of water supplies is an issue of recent concern to environmentalists.¹² As alopecia is a regular occurrence in gynecologic and reproductive endocrine practices, it should be included in differential diagnosis. Monitoring of frequency and types of seafood consumption should be advised. Identi-





Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016



GBD 2016 Alcohol Collaborators*

Summary

Background Alcohol use is a leading risk factor for death and disability, but its overall association with health remains complex given the possible protective effects of moderate alcohol consumption on some conditions. With our comprehensive approach to health accounting within the Global Burden of Diseases, Injuries, and Risk Factors Study 2016, we generated improved estimates of alcohol use and alcohol-attributable deaths and disability-adjusted life-years (DALYs) for 195 locations from 1990 to 2016, for both sexes and for 5-year age groups between the ages of 15 years and 95 years and older.

Methods Using 694 data sources of individual and population-level alcohol consumption, along with 592 prospective and retrospective studies on the risk of alcohol use, we produced estimates of the prevalence of current drinking, abstinence, the distribution of alcohol consumption among current drinkers in standard drinks daily (defined as 10 g

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See Comment page 987

*Collaborators listed at the end of the Article

Correspondence to:
Prof Emmanuela Gakidou,
Institute for Health Metrics and

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Alcohol in Men a

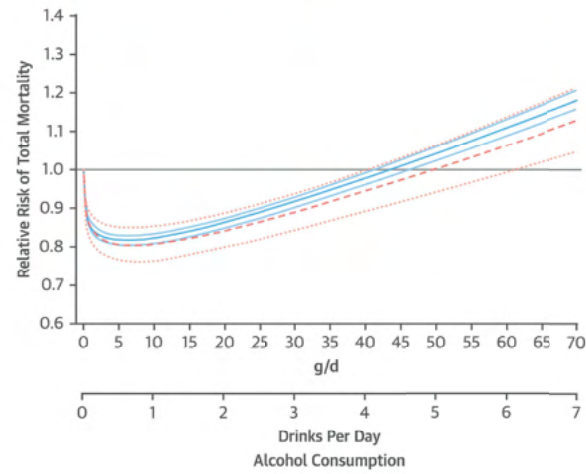
An Updated

Augusto Di Castel
Maria Benedetta L

Background: M
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with mortality is
analysis of prospec
mortality.

Methods: We sea
til December 2005
selected articles. Thirty-four studies on men and women,

FIGURE 2 All-Cause Mortality Risk: Alcohol



06;166:2437-2445

d, 13%-22%) and
5%-19%). Higher
increased mortal-
appeared at doses
unadjusted data
ion was only re-
ssociation in men
Europe.

Alcohol's contribution to cancer is underestimated for exactly the same reason that its contribution to cardioprotection is overestimated

Connor discusses whether it is consistent to doubt epidemiological studies that low-dose alcohol is cardioprotective while accepting similar evidence that it also causes cancer. We show that misclassification of former and occasional drinkers as abstainers is widespread in alcohol epidemiology. This practice leads to a systematic underestimation of health risks from drinking (e.g. for cancer) and overestimation of health benefits. Correction of this problem in future studies should lead to significantly larger estimates of alcohol's contribution to chronic disease.

We greatly appreciate Dr Connor's thoughtful analysis of the evidence that alcohol consumption can be considered a cause of cancer and not just a possible link or association

Such individuals are often still classified as 'abstainers' and used as a reference against which all current drinkers are compared. In simple terms, they make drinkers at all levels of consumption 'look good' by comparison. This, in turn, results in both the appearance of protection at low levels of drinking and reduced risk at higher levels (assuming an underlying dose-response risk relationship applies). It is worth noting that the misclassification of former and occasional drinkers as abstainers is virtually the norm in alcohol epidemiology. In a new meta-analysis on alcohol and prostate cancer, we found that 21 of 27 included studies contained abstainer bias [8]. In a recent meta-analysis of alcohol and all-cause mortality, we reported abstainer biases in 74 of 87 studies [5].

It is thus entirely consistent to be sceptical about

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Mortality in relation to smoking: 50 years' observations on male British doctors

Richard Doll, Richard Peto, Jillian Boreham, Isabelle Sutherland

Abstract

Objective To compare the hazards of cigarette smoking in men who formed their habits at different periods, and the extent of the reduction in risk when cigarette smoking is stopped at different ages.

Design Prospective study that has continued from 1951 to 2001.

Setting United Kingdom.

Participants 34 439 male British doctors. Information about their smoking habits was obtained in 1951, and periodically thereafter; cause specific mortality was monitored for 50 years.

Main outcome measures Overall mortality by *smoking habit*, considering separately men born in different periods.

Results The excess mortality associated with smoking chiefly involved vascular, neoplastic, and respiratory diseases that can be caused by smoking. Men born in 1900-1930 who smoked only cigarettes and continued smoking died on average about 10 years younger than lifelong non-smokers. Cessation at age 60, 50, 40, or 30 years gained, respectively, about 3, 6, 9, or 10

Kingdom (where the disease became by the 1940s a major cause of death). Throughout the first half of the 20th century the hazards of smoking had remained largely unsuspected.¹ Around the middle of the century, however, several case-control studies of lung cancer were published in Western Europe²⁻⁶ and North America,⁷⁻¹⁰ leading to the conclusion in 1950 that smoking was "a cause, and an important cause" of the disease.⁵

1951 prospective study

This discovery stimulated much further research into the effects of smoking (not only on lung cancer but also on many other diseases), including a UK prospective study of smoking and death among British doctors that began in 1951 and has now continued for 50 years.¹¹⁻¹⁷ The decision that this study would be conducted among doctors was taken partly because it was thought that doctors might take the trouble to describe their own smoking habits accurately, but principally because their subsequent mortality would be relatively easy to follow, as they had to keep their names on the medical register if they were to

Short of breath hurrying†	17.2	4
Phlegm in winter†	25.5	1

NA=not applicable.

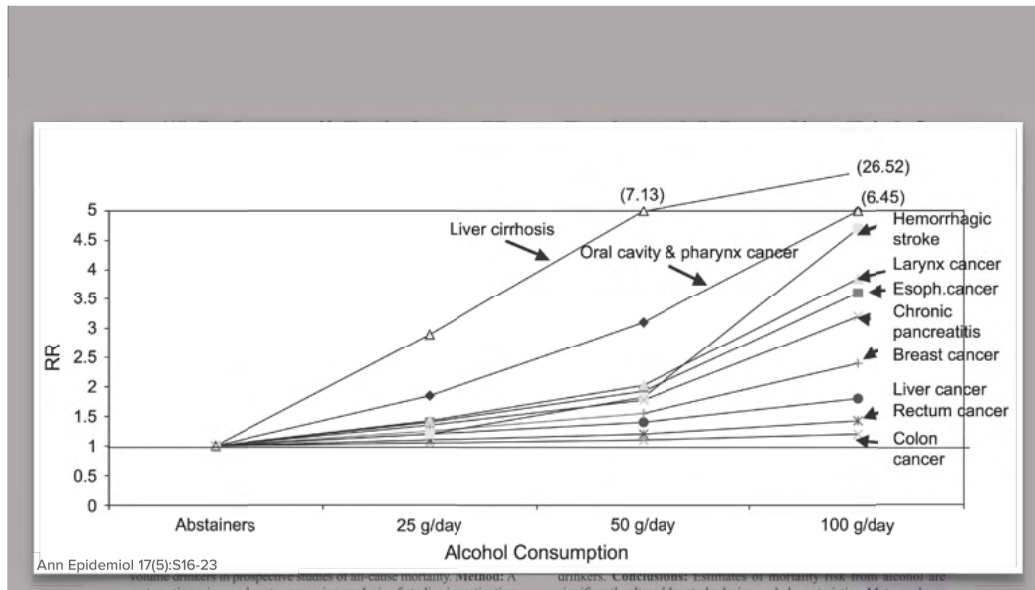
*Body mass index=weight (kg)/(height(m)²).

†Are you short of breath when hurrying; and, do you usually bring up phlegm from your chest during t

causality”—that is, some reduction in the apparent risk of death among current smokers because of a tendency for people to give up smoking after they begin to be affected by some life threatening condition (table 2), whether or not their illness was caused by smoking.

When all 11 categories in table 1 are added together, however, yielding overall mortality, the combined effects of all these non-causal factors—acting to increase or decrease the apparent hazards among smokers—are unlikely to have influenced greatly the absolute difference between the overall

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Ann Epidemiol17(5):S16-23

Acute Effect of Drinking Red and White Wines on Circulating Levels of Inflammation-Sensitive Molecules in Men With Coronary Artery Disease

Michael J.A. Williams, Wayne H.F. Sutherland, Alan P. Whelan, Maree P. McCormick, and Sylvia A. de Jong

There is evidence that moderate consumption of red wine with its high content of polyphenolic antioxidants may be more protective than white wine against development of coronary artery disease (CAD). The aim of this study was to compare the acute effects of ingestion of red wine and white wine on markers of inflammation in men with CAD. Thirteen men with angiographically-proven CAD were studied in a cross-over trial. The men consumed 4 mL/kg (2 to 3 glasses) red wine and white wine in random order during a light meal and with at least a week between interventions. Later, the men also consumed an isoenergetic nonalcoholic beverage (control) in the same study protocol. Venous blood was taken at baseline, 1 hour, and 6 hours after the drinks. Plasma interleukin-6 (IL-6), vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), blood alcohol, plasma lipids, and plasma polyphenols were measured. Mean \pm SD blood alcohol was 6.5 ± 2.2 mmol/L and 6.9 ± 1.1 mmol/L at 1 hour and returned to baseline at 6 hours after intake of red wine and white wine, respectively. Plasma IL-6 concentration increased significantly ($P = .01$) during 6 hours after ingestion of red wine (56%) and white wine (63%). The increase in plasma IL-6 concentration after ingestion of wine was significantly higher ($P = .045$) compared with the corresponding increase (11%) following intake of the nonalcoholic beverage. Plasma IL-6 levels at 6 hours ($r = .631$, $P = .02$) were correlated significantly with plasma alcohol levels at 1 hour after ingestion of red wine. These data suggest that moderate wine intake may acutely increase plasma levels of IL-6 in men with CAD. It is possible that this increase in plasma IL-6 is a response to alcohol-induced oxidative stress in the liver.

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EPIDEMIOLOGIC STUDIES indicate that regular consumption of moderate amounts of alcoholic beverages (1 is postulated to play a role in atherogenesis.¹⁴ Plasma concentrations of IL-6¹⁵ and soluble cell adhesion molecules¹⁶ are

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EPIDEMIOLOGIC STUDIES indicate that regular consumption of moderate amounts of alcoholic beverages (1 to 2 drinks per day) is associated with lower risk of coronary heart disease (CHD).¹⁻⁵ There is evidence that red wine provides extra cardioprotection compared with other alcoholic beverages.⁴⁻⁶ High content of polyphenolic antioxidants in red wine is thought to decrease the risk of CHD by attenuating the

is postulated to play a role in atherogenesis.¹⁴ Plasma concentrations of IL-6¹⁵ and soluble cell adhesion molecules¹⁶ are elevated in patients with coronary artery disease (CAD) compared with matched controls. Whether or not ingestion of red wine decreases plasma concentrations of IL-6 and cell adhesion molecules is unclear. Few studies have examined the acute effect of red wine and white wine intake on circulating levels of



Atherosclerosis 177 (2004) 461–468

ATHEROSCLEROSIS

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The effect of acute red wine polyphenol consumption on postprandial lipaemia in postmenopausal women

Mary Naissides, John C.L. Mamo, Anthony P. James, Sebely Pal*

*Department of Nutrition, Dietetics and Food Science, School of Public Health,
Curtin University of Technology, Kent Street, Bentley, Western Australia 6102*

Received 1 March 2004; received in revised form 21 June 2004; accepted 16 July 2004
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Abstract

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Abstract

Postprandial lipoproteins are potentially atherogenic. The aim of this study was to elucidate whether acute consumption of red wine (RW) and dealcoholised red wine (DRW) regulates postprandial lipid and lipoprotein metabolism in 17 dyslipidaemic postmenopausal women. A mixed meal accompanied by either water, RW or DRW was consumed on three separate visits, in random order, 2 weeks apart. One fasting and 6 hourly postprandial blood samples were taken for lipid analysis. Results showed no significant quantitative changes in postprandial apolipoprotein (apo) B48 levels following the consumption of DRW or RW compared to water. However, qualitatively, DRW may reduce arterial exposure to apoB48-containing lipoproteins over the 6-h postprandial period measured. DRW consumption did not significantly change postprandial TG or insulin levels. A 35% ($p = 0.02$) increase in postprandial triglyceride (TG) levels and a 54% ($p = 0.02$) increase in insulin levels were observed following RW consumption, compared to water. In conclusion, acute DRW consumption had no effect on postprandial lipid and lipoprotein metabolism in dyslipidaemic postmenopausal women. However, the consumption of full-compliment RW exacerbated the postprandial lipaemic and insulin response over the 6-h period. Collectively, our findings suggest that neither polyphenols nor red wine reduce atherosclerotic risk by acutely modulating postprandial lipaemia over a 6-h period.
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Keywords: Cardiovascular disease; Postprandial lipaemia; Apolipoprotein B48; Chylomicrons; Polyphenols; Red wine; Postmenopausal women

1. Introduction

Cardiovascular disease (CVD) is characterised by endothelial dysfunction and cholesterol accumulation in the arterial wall possibly resulting from elevated levels of chy-

lomicrons enter circulation as enlarged triglyceride-rich particles. Lipoprotein lipase hydrolyses these particles to form smaller, cholesterol-rich CMR. Under normal conditions, CMR are rapidly cleared from plasma predominantly via the LDL-receptor, however, in the case of CVD, increased

A randomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer disease

OPEN ▲

R. Scott Turner, MD,
PhD
Ronald G. Thomas, PhD
Suzanne Craft, PhD
Christopher H. van Dyck,
MD
Jacobo Mintzer, MD
Brigid A. Reynolds, NP
James B. Brewer, MD,
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Robert A. Rissman, PhD
Rema Raman, PhD
Paul S. Aisen, MD
For the Alzheimer's
Disease Cooperative

ABSTRACT

Objective: A randomized, placebo-controlled, double-blind, multicenter 52-week phase 2 trial of resveratrol in individuals with mild to moderate Alzheimer disease (AD) examined its safety and tolerability and effects on biomarker (plasma A β 40 and A β 42, CSF A β 40, A β 42, tau, and phospho-tau 181) and volumetric MRI outcomes (primary outcomes) and clinical outcomes (secondary outcomes).

Methods: Participants (n = 119) were randomized to placebo or resveratrol 500 mg orally once daily (with dose escalation by 500-mg increments every 13 weeks, ending with 1,000 mg twice daily). Brain MRI and CSF collection were performed at baseline and after completion of treatment. Detailed pharmacokinetics were performed on a subset (n = 15) at baseline and weeks 13, 26, 39, and 52.

Results: Resveratrol and its major metabolites were measurable in plasma and CSF. The most common adverse events were nausea, diarrhea, and weight loss. CSF A β 40 and plasma A β 40 levels declined more in the placebo group than the resveratrol-treated group, resulting in a

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REVIEW

Tea Consumption

Molecular Nutrition
Food Research
www.mnf-journal.com

Tea Consumption and Health Outcomes: Umbrella Review of Meta-Analyses of Observational Studies in Humans

Mengshi Yi, Xiaoting Wu, Wen Zhuang, Lin Xia, Yi Chen, Rui Zhao, Qianyi Wan, Liang Du, and Yong Zhou*

Scope: The aim of this article is to conduct an umbrella review to study the strength and validity of associations between tea consumption and diverse health outcomes.

Methods and results: Meta-analyses of observational studies examining associations between tea consumption and health outcomes in all human populations and settings are screened. The umbrella review identifies 96 meta-analyses with 40 unique health outcomes. Tea consumption shows greater benefits than harm to health in this review. Dose-response analyses of tea consumption indicates reduced risks of total mortality, cardiac death, coronary artery disease, stroke, and type 2 diabetes mellitus with increment of

polyphenols, including catechins such as (-)-epigallocatechin-3-gallate (EGCG), have been shown to be protective against cardiovascular disease (CVD) and cancer,¹⁻³ to exert immunomodulatory effects under conditions of immune dysfunction caused by transplanted tumors or carcinogen treatment,⁶ and to affect lipid metabolism^{7,8} and glucose metabolism⁹ in early vivo animal studies. Tea is generally divided into categories based on processing, among which the green tea and black tea are

3.2. Total Mortality

Tea consumption was related to a marked 41% reduction in total mortality risk (RR 0.59, 95% CI 0.40–0.97).^[19] Dose–response analysis showed that an increment in tea consumption by three cups per day was related to a 24% reduction in total mortality (0.76, 0.63–0.91). Consumption of green tea^[20] and black tea^[20] were both associated with reduced total mortality, and an increase of one cup of green tea or black tea per day could reduce the risk of total mortality by 4% or 3%, respectively. The maximum reduction in total mortality was observed at two to three cups per day, and with higher degree of tea consumption (more than five cups per day), this association became null or positive.^[20]

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Results: Over 12 y of follow-up, we documented 400 deaths from pneumonia. In women, the multivariate HRs of death from pneumonia that were associated with different frequencies of green tea consumption were 1.00 (reference) for <1 cup/d, 0.59 (95% CI: 0.36, 0.98) for 1–2 cups/d, 0.55 (95% CI: 0.33, 0.91) for 3–4 cups/d, and 0.53 (95% CI: 0.33, 0.83) for ≥ 5 cups/d, respectively (*P* for trend: 0.008). In men, no significant association was observed.

Conclusion: Green tea consumption was associated with a lower risk of death from pneumonia in Japanese women. *Am J Clin Nutr* 2009;90:672–9.

INTRODUCTION

Pneumonia ranks as the fourth-leading cause of death in Japan, where it is responsible for $\approx 10\%$ of total deaths, despite the

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Article

Anti-Influenza with Green Tea Catechins: A Systematic Review and Meta-Analysis

Anchalee Rawangkan ^{1,2}, Kirati Kengkla ^{3,4,5}, Sukrit Kanchanasurakit ^{3,4,5,6}, Acharaporn Duangjai ^{1,2,4} and Surasak Saokaew ^{2,3,4,5,6,7,8,*}

¹ School of Medical Sciences, University of Phayao, Phayao 56000, Thailand; ewmedsci@gmail.com (A.R.); achara.phso@gmail.com (A.D.)

² Unit of Excellence on Clinical Outcomes Research and IntegratioN (UNICORN), School of Pharmaceutical Sciences, University of Phayao, Phayao 56000, Thailand

³ Division of Pharmacy Practice, Department of Pharmaceutical Care, School of Pharmaceutical Sciences, University of Phayao, Phayao 56000, Thailand; kirati.ke@gmail.com (K.K.); sukrit.ka@up.ac.th (S.K.)

⁴ Center of Health Outcomes Research and Therapeutic Safety (Cohorts), School of Pharmaceutical Sciences, University of Phayao, Phayao 56000, Thailand

⁵ Unit of Excellence on Herbal Medicine, School of Pharmaceutical Sciences, University of Phayao, Phayao 56000, Thailand

⁶ Division of Pharmaceutical Care, Department of Pharmacy, Phrae Hospital, Phrae 54000, Thailand

⁷ Division of Medical Education, Department of Pharmacy, Phrae Hospital, Phrae 54000, Thailand

⁸ Division of Pharmaceutical Care, Department of Pharmacy, Phrae Hospital, Phrae 54000, Thailand

FOOD & FUNCTION

Effects of single dose and regular intake of green tea (*Camellia sinensis*) on DNA damage, DNA repair, and heme oxygenase-1 expression in a randomized controlled human supplementation study

Cyrus K. Ho, Siu-wai Choi, Parco M. Siu and Iris F. F. Benzie

Department of Health Technology and Informatics, The Hong Kong Polytechnic University, Kowloon, Hong Kong

Regular intake of green tea (*Camellia sinensis*) lowers DNA damage in humans, but molecular mechanisms of genoprotection are not clear. Protection could be via direct antioxidant effects of tea catechins, but, paradoxically, catechins have pro-oxidant activity in vitro, and it is hypothesized that mechanisms relate to redox-sensitive cytoprotective adaptations. We investigated this hypothesis, focusing particularly on effects on the DNA repair enzyme human oxoguanine glycosylase 1 (hOGG1), and heme oxygenase-1, a protein that has antioxidant and anti-inflammatory effects. A randomized, placebo-controlled, human supplementation study of

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Keywords:

DNA damage and repair / Green tea / Heme oxygenase-1 / hOGG1 / Redox tone



Additional supporting information may be found in the online version of this article at

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Additional supporting information may be found in the online version of this article at

Genoprotective effects of green tea (*Camellia sinensis*) in human subjects: results of a controlled supplementation trial

K. C. Han, W. C. Wong and Iris F. F. Benzie*

Department of Health Technology and Informatics, The Hong Kong Polytechnic University, Kowloon, Hong Kong

(Received 10 May 2010 – Revised 19 July 2010 – Accepted 21 July 2010 – First published online 1 September 2010)

Abstract

Green tea is rich in polyphenolic antioxidants and has widely reported but largely unsubstantiated health benefits. In the present study, genoprotective effects of two types of green tea were studied both in an *in vitro* and in a human supplementation trial. For the *in vitro* study, human lymphocytes were pre-incubated in tea (0.005–0.1%, w/v), washed and subjected to oxidant challenge induced by H₂O₂. In a placebo-controlled, cross-over supplementation study, eighteen healthy volunteers took 2 × 150 ml/d of 1% (w/v) green tea ('Longjing' green tea or 'screw-shaped' green tea) or water (control) for 4 weeks (*n* 6). Subjects took all the three treatments in a random order, with 6 weeks' washout between each treatment. Fasting blood and urine were collected before and after each treatment. The comet assay was used to measure the resistance of lymphocytic DNA to H₂O₂-induced challenge. Basal oxidation-induced DNA damage was measured using the formamidopyrimidine glycosylase (Fpg) enzyme-assisted comet assay. Urine 7,8-dihydro-2-deoxyguanosine (8-oxodG,

tea and screw-shaped tea) showed significant genoprotective effects of similar magnitude in both the *in vitro* and supplementation studies. In *in vitro* experiments, there was approximately 30% less DNA damage in H₂O₂-challenged cells that had been pre-incubated for 30 min in low concentration (0.01% or less, w/v) green tea. More importantly, this increase in resistance to oxidant challenge was also seen in lymphocytes collected after 4 weeks' supplementation with green tea. Furthermore, pre-existing oxidation-induced DNA damage was approximately 30% lower after 4 weeks' supplementation with green tea. The effect of each tea was similar, as was their antioxidant content.

The finding that very similar effects were observed with



Public health response to ultra-processed food and drinks

Growing evidence confirms a link between consumption of ultra-processed food and drinks and non-communicable diseases. **Jean Adams and colleagues** explore the implications for public health action

People have used food processing to make food safe, palatable, and longer lasting since prehistoric times.¹ Common modern food processing to achieve similar safety, palatability, and preservation goals includes pasteurisation of milk to reduce harmful microbes, milling of wheat to remove indigestible components, and canning fruit to increase its shelf life. However, in the past 100 years industrial techniques have been increasingly used

is associated with increased risk of non-communicable disease, presenting a public health challenge.

Several definitions and classifications of food processing exist, but in this article we use the Nova system (table 1). Despite some debate,^{8,9} Nova is emerging as the most conceptually coherent, operationally useful, and widely used in dietary public health research and policy.¹⁰

Global changes in eating patterns

with increased risk of obesity and non-communicable diseases. For example, a longitudinal analysis of country level data from 2002 to 2016 found a positive association between sales of ultra-processed foods and mean body mass index (BMI) in men, and between ultra-processed drinks sales and mean BMI in both men and women.¹¹ This is consistent with the findings of a recent randomised controlled trial of unrestricted ultra-processed versus unprocessed diets (matched for total energy, macronutrients

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Global changes in eating patterns

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OBESITY/**C**OMORBIDITIES/**N**UTRITION

OBESITY **WILEY**

Ultraprocessed food and chronic noncommunicable diseases: A systematic review and meta-analysis of 43 observational studies

Melissa M. Lane¹ | Jessica A. Davis¹ | Sally Beattie⁴ | Clara Gómez-Donoso^{2,3} |
Amy Loughman¹ | Adrienne O'Neil¹ | Felice Jacka^{1,6,7,8} | Michael Berk^{1,9} |
Richard Page^{1,4,5} | Wolfgang Marx¹ | Tetyana Rocks¹

¹The Institute for Mental and Physical Health and Clinical Translation (IMPACT), Food and Mood Centre, School of Medicine, Barwon Health, Deakin University, Geelong, Victoria, Australia

²Department of Preventive Medicine and Public Health, School of Medicine, University of Navarra, Pamplona, Spain

³CIBER Physiopathology of Obesity and Nutrition (CIBEROBN), Carlos III Health Institute, Madrid, Spain

⁴The Barwon Centre of Orthopaedic Research and Education (B-CORE), Barwon Health and St John of God Hospital Geelong, Geelong, Victoria, Australia

⁵School of Medicine, Deakin University, Geelong, Victoria, Australia

Plant-Based Diets Are Associated With a Lower Risk of Incident Cardiovascular Disease, All-Cause Mortality, and All-Cause Mortality in Middle-Aged Adults

Hyunju Kim, PhD; Laura E. Caulfield, PhD; Casey M. Rebholz, PhD

Coresh, MD, PhD;

Background—Previous studies have been conducted in selected study

based diets; however, these studies

Methods and Results—We used data from the Atherosclerosis Risk in Communities (ARIC) study. Participants were classified into 4 diet indexes. In the overall population, those in the highest quintile of plant-based diet index received higher scores; in the healthiest quintile, those in the less healthy plant-based diet index received higher scores. In all indexes, those in the highest versus lowest quintile of plant-based diet index had a 16%, 31% to 32%, and 18% to 25% lower risk of cardiovascular disease, respectively, after adjusting for important confounders. In all indexes, those in the highest versus lowest quintile of plant-based diet index had a 19% and 11% lower risk of cardiovascular disease ($P < 0.05$ for all outcomes).

adults (n=12 168) in the ARIC study. Participants' diet was classified using 4 diet indexes of all or selected plant foods. In all indexes, those in the highest versus lowest quintile of plant-based diet index received higher scores. In all indexes, those in the highest versus lowest quintile of plant-based diet index had a 16%, 31% to 32%, and 18% to 25% lower risk of cardiovascular disease, respectively, after adjusting for important confounders. In all indexes, those in the highest versus lowest quintile of plant-based diet index had a 19% and 11% lower risk of cardiovascular disease, respectively, but not incident cardiovascular disease and the

Variable	All-Cause Mortality
Healthy plant-based diet index	1 (Reference)
	0.99 (0.92–1.08)
	0.97 (0.89–1.05)
	0.92 (0.84–1.01)
	0.89 (0.81–0.98)
Unhealthy plant-based diet index	1 (Reference)
	1.01 (0.94–1.10)
	0.94 (0.87–1.02)
	0.95 (0.88–1.03)
	0.94 (0.87–1.03)
	0.10

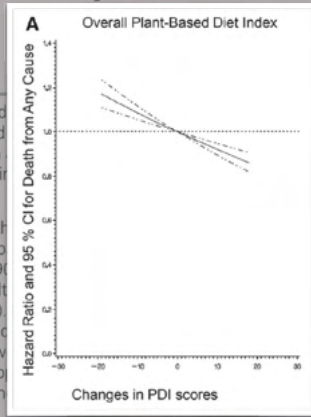
Changes in Plant-Based Diet Quality and Total and Cause-Specific Mortality

ORIGINAL RESEARCH
ARTICLE

BACKGROUND: Plant-based diets are associated with lower risk of type 2 diabetes mellitus and cardiovascular disease, but the association between changes in diet quality and mortality remains unclear.

METHODS: We investigated the association between changes in plant-based diet indices (score range, 18–90) and total and cause-specific mortality (1998–2014) in the Nurses’ Health Study (NHS) and Nurses’ Health Study II (NHSII) and Health Professionals Follow-Up Study (HPFS) who were followed up from 1986 to 1998. We used multivariable-adjusted Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

RESULTS: We documented 10 555 deaths, including 2046 CVD deaths.



Megu Y. Baden, MD, PhD
Gang Liu, PhD
Ambika Satija, ScD
Yanping Li, PhD
Qi Sun, MD, ScD
Teresa T. Fung, ScD
Eric B. Rimm, ScD
Walter C. Willett, MD, DrPH
Frank B. Hu, MD, PhD
Shilpa N. Bhupathiraju, PhD

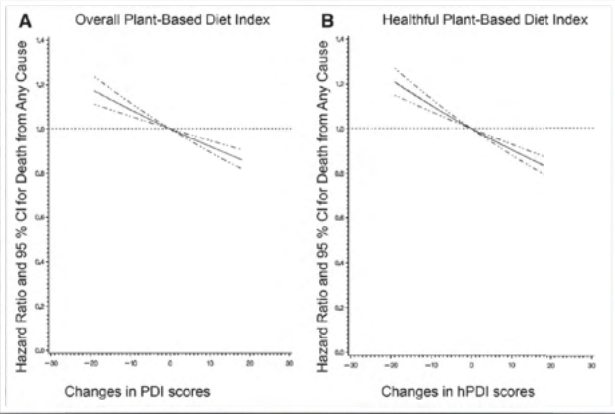
Changes in Plant-Based Diet Quality and Total and Cause-Specific Mortality

ORIGINAL RESEARCH
ARTICLE

BACKGROUND: The association of type 2 diabetes with mortality is well established, but the association of type 2 diabetes with mortality remains unclear. The association of type 2 diabetes with mortality remains unclear.

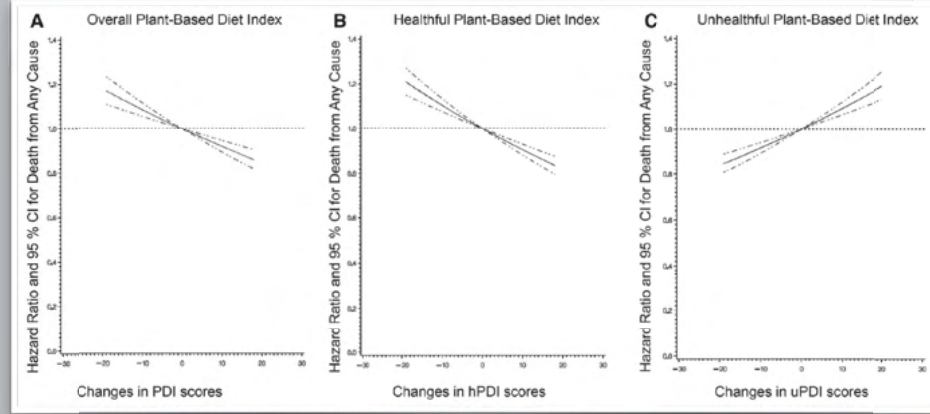
METHODS: We used data from the Nurses' Health Study (from 1980 to 2012) to estimate a healthful plant-based diet index (hPDI) and a less healthful plant-based diet index (lPDI) using a healthy eating index approach. We used multivariable Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI) for death from any cause, cardiovascular disease (CVD), and cancer.

RESULTS: We documented 10,686 deaths including 2,046 CVD deaths.



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Changes in Plant-Based Diet Quality and Total and Cause-Specific Mortality



RESULTS: We documented 10,686 deaths including 2,046 CVD deaths

Degree of adherence to plant-based diet and total and cause-specific mortality: prospective cohort study in the Million Veteran Program

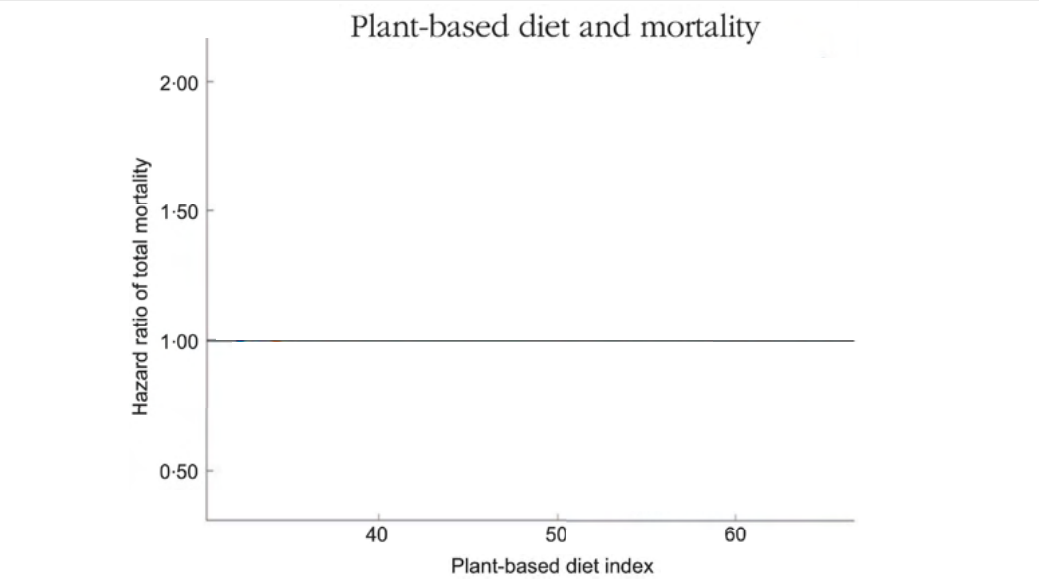
Dong D Wang^{1,2,3,*}, Yanping Li^{1,3}, Xuan-Mai T Nguyen^{1,4,5}, Rebecca J Song^{1,6}, Yuk-Lam Ho¹, Frank B Hu^{2,3,7}, Walter C Willett^{2,3,7}, Peter Wilson^{8,9}, Kelly Cho^{1,4,5}, J Michael Gaziano^{1,4,5}, Luc Djoussé^{1,3,4,5} and on behalf of the Million Veteran Program

¹Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, Boston, MA, USA; ²The Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA; ³Departments of Nutrition, Harvard T. H. Chan School of Public Health, Boston, MA, USA; ⁴Department of Medicine, Division of Aging, Brigham and Women's Hospital, Boston, MA, USA; ⁵Harvard Medical School, Boston, MA, USA; ⁶Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA; ⁷Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA, USA; ⁸Atlanta VA Medical Center, Atlanta, GA, USA; ⁹Emory Clinical Cardiovascular Research Institute, Atlanta, GA, USA

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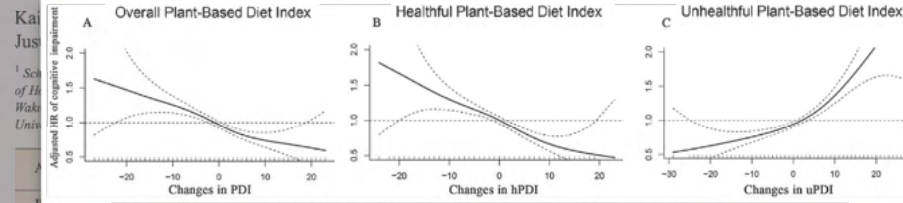
Abstract

Objective: To examine the association between adherence to plant-based diets and



Original Research Article

Changes in Plant-Based Dietary Quality and Subsequent Risk of Cognitive Impairment Among Older Chinese Adults: a National Community-Based Cohort Study



Objectives: This study aims to evaluate this relationship using data from the Chinese Longitudinal Healthy Longevity Survey.

Methods: A total of 6662 participants free of cognitive impairment in 2008 were included and followed ≤ 2018 . Plant-based dietary quality was assessed by 3 indices: overall plant-based diet index (PDI), healthful PDI (hPDI), and unhealthful PDI (uPDI). Changes in plant-based diet quality from 2008 to

RESEARCH PAPER

Quality of plant-based diet and the risk of dementia and depression among middle-aged and older population

HANZHANG WU^{1,2,3}, YEQING GU¹, GE MENG^{1,4}, HONGMEI WU^{1,2}, SHUNMING ZHANG^{1,2}, XUENA WANG^{1,2}, JUANJUAN ZHANG^{1,2}, TAO HUANG⁵, KAIJUN NIU^{1,2,3,6,7}

¹Institute of Radiation Medicine, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China

²School of Public Health of Tianjin University of Traditional Chinese Medicine, Tianjin, China

³Nutritional Epidemiology Institute and School of Public Health, Tianjin Medical University, Tianjin, China

⁴Department of Toxicology and Sanitary Chemistry, School of Public Health, Tianjin Medical University, Tianjin, China


⁵Department of Epidemiology and Biostatistics, School of Public Health, Peking University Health Science Center, Beijing, China

⁶Tianjin Key Laboratory of Environment, Nutrition and Public Health, Tianjin, China

⁷Center for International Collaborative Research on Environment, Nutrition and Public Health, Tianjin, China



Plant-based diets and risk of frailty in community-dwelling older adults: the Seniors-ENRICA-1 cohort

Javier Maroto-Rodríguez · Mario Delgado-Velandia ·
Rosario Ortolá · Adrián Carballo-Casla · Esther García-Esquinas ·
Fernando Rodríguez-Artalejo · Mercedes Sotos-Prieto 

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Abstract Frailty is a geriatric syndrome that leads to increased risk of hospitalization, disability, and healthy plant foods. Incident frailty was defined with the Fried phenotype. Study associations were sum-

RESEARCH ARTICLE

Open Access

Association between plant-based dietary pattern and biological aging trajectory in a large prospective cohort



Sicong Wang^{1,2*}, Wenyuan Li^{1†}, Shu Li¹, Huakang Tu¹, Junlin Jia¹, Wenting Zhao¹, Andi Xu¹, Wenxin Xu¹, Min Kuang Tsai³, David Ta-Wei Chu⁴, Chi Pang Wen^{3,5,6*} and Xifeng Wu^{1,7,8*} 

Abstract

Background Aging is a dynamic and heterogeneous process that may better be captured by trajectories of aging biomarkers. Biological age has been advocated as a better biomarker of aging than chronological age, and plant-based dietary patterns have been found to be linked to aging. However, the associations of biological age trajectories with mortality and plant-based dietary patterns remained unclear.

Table 2 Associations between quintiles of PDI, hPDI, and uPDI and aging trajectories based on multinomial logistic regression model

Diet index	High-degree vs slow aging		
	N ^a	OR (95% CI)	p-trend
Quintile of PDI (N)			
Q1 (2402)	145	Ref	0.0050
Q2 (2038)	96	0.67 (0.49, 0.92)	
Q3 (2072)	93	0.67 (0.50, 0.91)	
Q4 (1753)	71	0.62 (0.45, 0.86)	
Q5 (1926)	89	0.63 (0.46, 0.86)	
Per 10, unit increment of PDI		0.70 (0.53, 0.92)	
Quintile of hPDI (N)			
Q1 (2080)	118	Ref	0.0004
Q2 (1787)	92	0.79 (0.59, 1.06)	
Q3 (2144)	99	0.62 (0.42, 0.91)	
Q4 (1981)	85	0.58 (0.43, 0.78)	
Q5 (2199)	100	0.62 (0.44, 0.88)	
Per 10, unit increment of hPDI		0.65 (0.50, 0.85)	
Quintile of uPDI (N)			
Q1 (1851)	78	Ref	0.0114
Q2 (2059)	109	1.27 (0.92, 1.74)	
Q3 (1809)	72	0.93 (0.65, 1.31)	
Q4 (2316)	114	1.24 (0.90, 1.70)	
Q5 (2156)	121	1.70 (1.21, 2.38)	
Per 10, unit increment of uPDI		1.39 (1.11, 1.75)	

Slow aging: slow aging trajectory, Medium-degree: medium-degree accelerated aging trajectory, High-degree: high-degree accelerated aging trajectory. N^a: Number of participants in medium-degree accelerated aging trajectory or high-degree accelerated aging trajectory. Model adjusted for age, gender, education level, marital status, smoking status, drinking status, and chronic disease count

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Q4 (2316)	114	1.24 (0.90, 1.70)	
Q5 (2156)	121	1.70 (1.21, 2.38)	
Per 10, unit increment of uPDI		1.39 (1.11, 1.75)	

Slow aging: slow aging trajectory, Medium-degree: medium-degree accelerated aging trajectory, High-degree: high-degree accelerated aging trajectory. N^a: Number of participants in medium-degree accelerated aging trajectory or high-degree accelerated aging trajectory. Model adjusted for age, gender, education level, marital status, smoking status, drinking status, and chronic disease count

Table 2 Associations between quintiles of PDI, hPDI, and uPDI and aging trajectories based on multinomial logistic regression model

Diet index	High-degree vs slow aging		
	N ^a	OR (95% CI)	p-trend
Quintile of PDI (N)			
Q1 (2402)	145	Ref	0.0050
Q2 (2038)	96	0.67 (0.49, 0.92)	
Q3 (2072)	93	0.67 (0.50, 0.91)	
Q4 (1753)	71	0.62 (0.45, 0.86)	
Q5 (1926)	89	0.63 (0.46, 0.86)	
Per 10, unit increment of PDI		0.70 (0.53, 0.92)	
Quintile of hPDI (N)			
Q1 (2080)	118	Ref	0.0004
Q2 (1787)	92	0.79 (0.59, 1.06)	
Q3 (2144)	99	0.62 (0.42, 0.91)	
Q4 (1981)	85	0.58 (0.43, 0.78)	
Q5 (2199)	100	0.62 (0.44, 0.88)	
Per 10, unit increment of hPDI		0.65 (0.50, 0.85)	
Quintile of uPDI (N)			
Q1 (1851)	78	Ref	0.0114
Q2 (2059)	109	1.27 (0.92, 1.74)	
Q3 (1809)	72	0.93 (0.65, 1.31)	
Q4 (2316)	114	1.24 (0.90, 1.70)	
Q5 (2156)	121	1.70 (1.21, 2.38)	
Per 10, unit increment of uPDI		1.39 (1.11, 1.75)	

Slow aging: slow aging trajectory, Medium-degree: medium-degree accelerated aging trajectory, High-degree: high-degree accelerated aging trajectory. N^a: Number of participants in medium-degree accelerated aging trajectory or high-degree accelerated aging trajectory. Model adjusted for age, gender, education level, marital status, smoking status, drinking status, and chronic disease count

Article

Evaluation of an Eight-Week Whole-Food Plant-Based Lifestyle Modification Program

	Vegetarian or Vegan		
	Baseline	Final	Change
Weight, kg	88.9 (22.1)	84.4 (20.6)	−4.5 (2.8) ****
LDL cholesterol, mg/dL	103.8 (30.4)	88.3 (22.8)	−15.6 (16.2) ***

**** $p < 0.0001$, *** $p < 0.001$

from an eight-week group program utilizing an ad-hoc whole-food plant-based dietary pattern, were reviewed. There were 79 participants, all self-referred from the community, including 24 (30.4%) who were already vegetarian or vegan at baseline. Seventy-eight participants (98.7%) completed the eight-week program. Among completers, those with higher BMI at baseline lost a larger...