

## The Fire Within: The Consequences of Chronic Inflammation



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Chair: Dietary  
Supplements/Botanicals  
Expert Information Panel  
Admissions Sub-  
Committee

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# Inflammation.....



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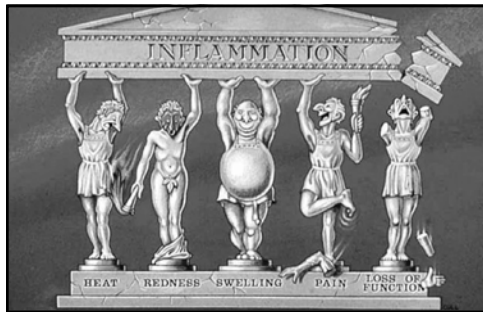
## Chronic Inflammatory Diseases

- Complex conditions that involve multiple causal components interacting with each other, often in an unpredictable way.
- Result of complex interactions between genetics and environment, such as microbial communities (biofilms) and the host response, which is hard to explain by a few individual factors.
- Some of these factors include:
  - Pattern of **central obesity**
  - Western-dietary pattern, **high fructose**
  - **Sedentary lifestyle**, lack of exercise
  - Prolonged **psychosocial stress**
  - **Alterations in gut flora and intestinal permeability**
  - **Environmental exposures** (smoke, toxins, endocrine disrupting chemicals)

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## Chronic Inflammation

- Inflammatory response crucial for our survival. But there is a dark side.
- When **inflammation becomes chronic** it contributes to conditions as varied as **gum disease, osteoporosis, cardiovascular disease, Alzheimer's disease, type-2 diabetes, autoimmune disorders, cancer, and more.**

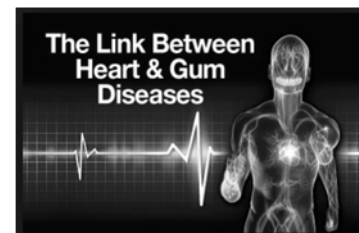
Chang SC, Yang WV. *Crit Rev Oncol Hematol* 2016; 108:146-153

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## Periodontitis and Systemic Disease



- Periodontitis recognized as inflammatory disease of bacterial origin.
- Plausibility of periodontal bacteria influencing vascular inflammation strengthened when *Porphyromonas gingivalis* isolated from human atheromatous plaques.
- Periodontal disease associated with: rheumatoid arthritis, cardiovascular-disease, diabetes, chronic respiratory diseases, and pre-term birth and pre-eclampsia.

Friedewald VE, et al. *J Periodontol* 2009; 80:1021-1032

Parihar AS, et al. *J Int Oral Health* 2015; Jul;7(7)

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## Periodontitis and Cancer

- Almost 60,000 Americans develop **head and neck cancer** annually and 12,000 die from the disease.
- **Chronic periodontitis** may be independently associated with HNSCC through direct **toxic effects of bacteria and their products**, and/or through **indirect effects of inflammation**.
- May facilitate the **acquisition and persistence of oral HPV infection**, a recently recognized risk factor for HNSCC.

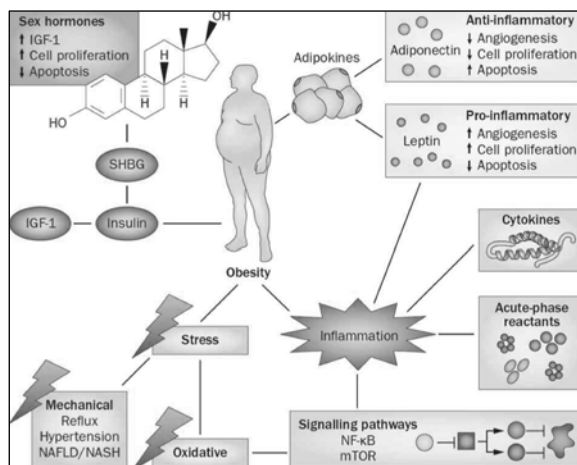
Han YW, et al. *Adv Dent Res* 2014; 26(1):47-55

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## Inflammaging



- **Obesity + aging** drastically increases **chronic low-grade inflammation**: a key link between **obesity, insulin resistance, elevated blood sugar, insulin-growth factors (IGF), and age-associated diseases**.
- **Elevated insulin and IGF** increases **tumor growth and aggressiveness**.

Frasca D, et al; Aging, Obesity and Inflammatory Age-Related Diseases. *Front Immunol* 2017 Dec 7;8:1745.

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# Inflammation and Cancer

- **Poorly regulated blood sugar** often accompanied by increased **inflammatory markers** (e.g., interleukin (IL)-1 $\beta$ , IL-6, TNF- $\alpha$ )
- Inflammation is strongly linked with cancer.
- Nuclear factor- $\kappa$ B (**NF- $\kappa$ B**) is one of the most important molecules **linking chronic inflammation to cancer**
- Activation of NF- $\kappa$ B primarily initiated by bacterial endotoxins such as **lipopolysaccharide (LPS)** and **pro-inflammatory cytokines**.
- NF- $\kappa$ B activation occurs in **cancer cells and tumor microenvironments**.

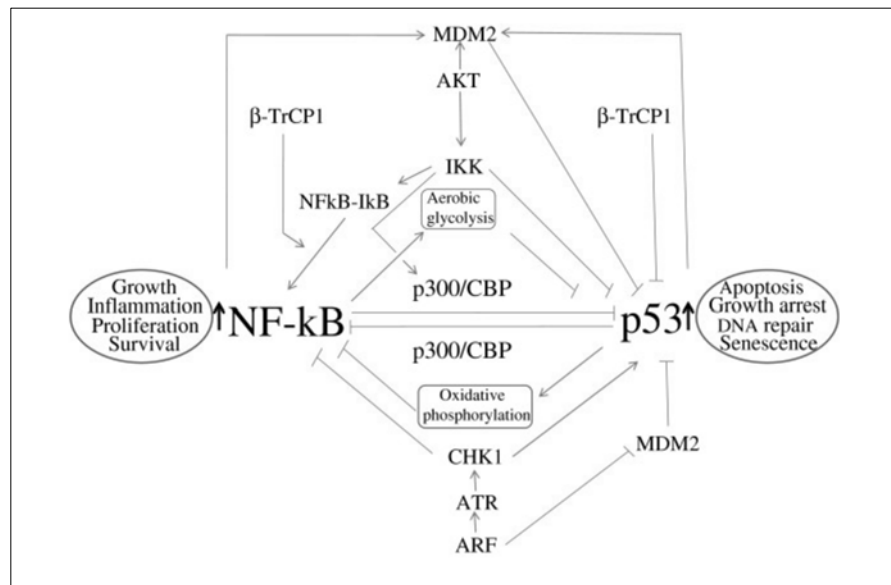
Taniguchi K, et al. NF- $\kappa$ B, inflammation, immunity and cancer: coming of age. *Nature Reviews Immunology* 2018; 18: 309–324

Chang SC, Yang WV. *Crit Rev Oncol Hematol* 2016; 108:146-153

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Pal S, et al. *J Inflamm* 2014; Aug 9;11:23.

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## Green Tea (*Camellia sinensis*)



Butt MS, et al. *Crit Rev Food Sci Nutr* 2015; 55(6):792-805.  
Pellicore LS, Giancaspro GI, Low Dog T. *Drug Saf.* 2008;31(6):469-84.

- **White, green, oolong and black teas** contain polyphenols and flavonoids, particularly catechins.
- Epigallocatechin gallate (**EGCG**) **potent anti-inflammatory and antioxidant activity.**
- Potent **inhibitor NF- $\kappa$ B** and **inducer of P53.**
- Inhibits every step of carcinogenesis. **Stimulates DNA repair** and inhibits two proteins that promote tumor cell growth and migration.
- Green tea **extracts** should be taken with **food** to avoid liver problems.

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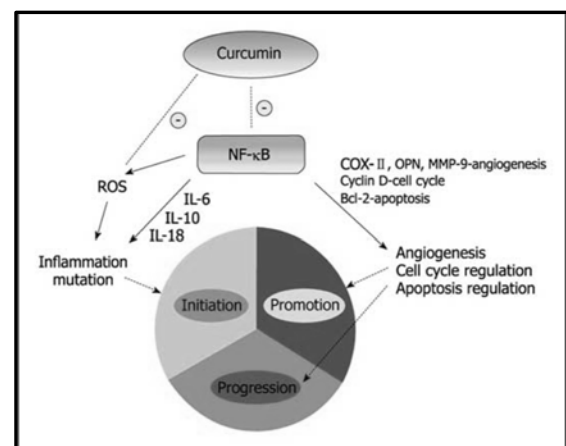
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## Turmeric: the Curcuminoids

- Potent anti-inflammatory.
- **Beneficial for osteoarthritis, gut inflammation, improving microbial diversity, and topically for wounds.**
- May prevent/beneficial adjunctive treatment for **colorectal cancer.**
- Acts alone/synergistically with EGCG (green tea) to **inhibit malignant changes in oral epithelium.**

Gupta S, et al. Curcumin, a Component of Turmeric: From Farm to Pharmacy. *Biofactors* 2013; 39(1):2-13

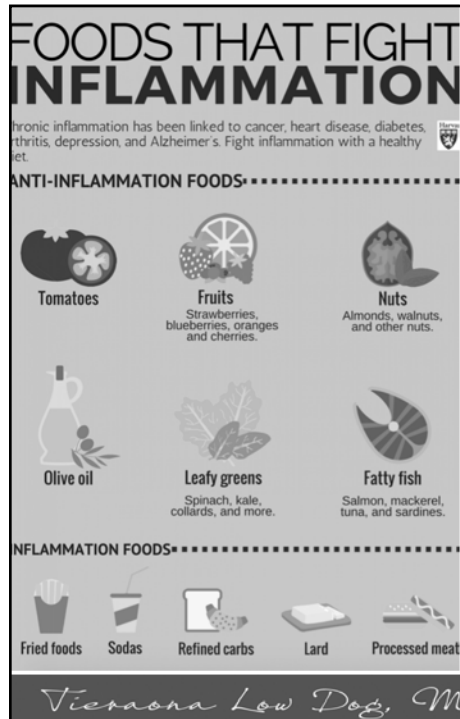
Bannuru RR, et al. Efficacy of curcumin and Boswellia for knee osteoarthritis: Systematic review and meta-analysis. *Semin Arthritis Rheum* 2018 Mar 10. pii: S0049-0172(18)30002-7



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## Diet and Inflammation

- High intake of **animal fats, red meat, salt, refined carbohydrates, fried foods, and low intake of fruit, vegetables, fiber, vitamin C, and other antioxidants, and shortage of vitamin D,** results in **increased inflammation.**
- **Exercise, low-calorie diets, and probiotics and prebiotics,** can act on the nuclear receptors and enzymes **that upregulate oxidative metabolism and reduce the production of pro-inflammatory molecules.**

Loos BG, et al. The role of inflammation and genetics in periodontal disease. *Periodontol* 2019;00:1–14

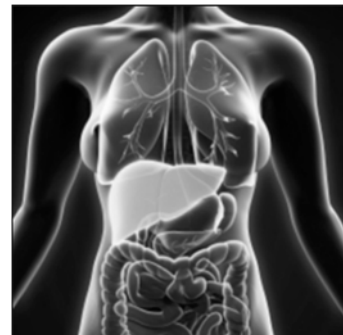
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## Sugars



- Table sugar (sucrose): **one glucose + one fructose** molecule
- **High fructose corn syrup:** 55% fructose, 42% glucose and 3% other sugars.
- Every cell in body readily converts glucose into energy. But *liver cells are one of few types of cells that can convert fructose to energy.*
- Large amounts of “free” fructose *taxes the liver and increases risk of non-alcoholic fatty liver disease.*

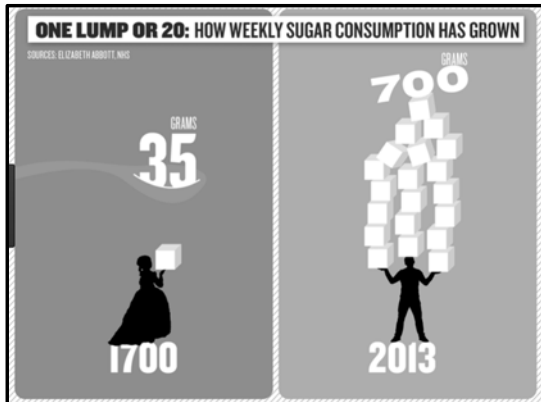


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## Too Little Fiber, Too Much Sugar



Canadians average daily sugar intake:

- 101 grams (24 tsp) children 1-8 years
- 115 grams (27 tsp) children 9-18 years
- 85 grams (20 tsp) for adults - lower due to increase intake “diet” sodas.

Langlois K, et al. Change in total sugars consumption among Canadian children and adults. *Health Rep* 2019 Jan 16;30(1):10-19.

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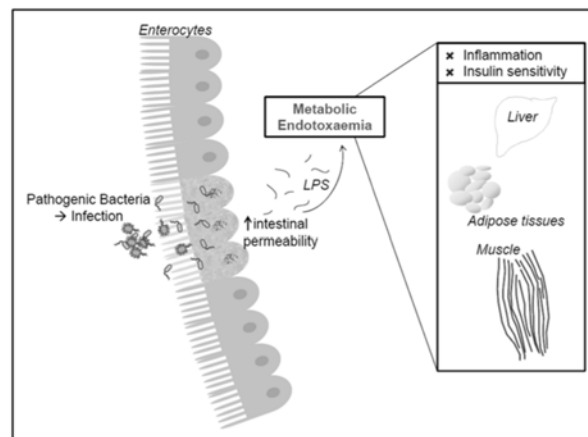
15

- **High fructose diet increases intestinal permeability.**
- **Bacterial endotoxin (LPS) enters bloodstream, inflammation is activated** by changing **insulin** signaling and triggering **inflammatory** mediators.

Jin R, et al. *Nutrients* 2014; 6:3187–3201

Boroni Moreira AP, et al. *Nutr Hosp* 2012; 27(2):382-90

Jegatheesan P, et al. *Nutrients* 2017; Mar 3;9(3)



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## Dietary Inflammatory Index (DII)

- Anti-inflammatory diet may reduce **inflammation** and improve **cardiovascular, metabolic, and neurologic parameters**.
- **Dietary Inflammatory Index** based on measuring inflammation in the body in response to specific foods (1900 studies)
- **Higher DII scores increased risk of oral/pharyngeal CA.**
- NHANES – those with highest DII score had **16% more teeth lost compared to those with lowest scores.**
- Shivappa N, et al. Inflammatory potential of diet and risk of oral and pharyngeal cancer in a large case-control study from Italy. *Int J Cancer* 2017; 141(3):471-479; Kotsakis GA, et al. Diet-borne systemic inflammation is associated with prevalent tooth loss. *Clin Nutr* 2018 Aug;37(4):1306-1312.

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## INFLAMMATION INDEX

FOOD	SERVING SIZE	SERVING SIZE (GRAMS)	IF RATING
AGAVE NECTAR	1 TBSP	21	-74
ALMOND BUTTER	¼ CUP	64	100
CHEESE, CHEDDAR	1 OUNCE	28.35	-20
CHICKEN BREAST, RSTD	3 OUNCES	85	-19
MILK, WHOLE	1 CUP	246	-46
OLIVE OIL	1 TBSP	14	74
ONIONS, COOKED	½ CUP	105	240
RICE, WHITE	1 CUP	158	-153
SPINACH	1 CUP	30	75
SALMON, SOHO BAKED	3 OUNCES	85	450
TURMERIC	½ TSP	1.5	338

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## Inflammation & Memory




- Researchers evaluated inflammatory potential of diet in relation to mild cognitive impairment/dementia risk using **DII during average follow up of 9.7 years during Women's Health Initiative Memory Study.**
- **Higher inflammatory scores** were significantly associated with *greater cognitive decline and earlier onset of cognitive impairment.*

Hayden KM, et al. The association between an inflammatory diet and global cognitive function and incident dementia in older women: The Women's Health Initiative Memory Study. *Alzheimers Dement* 2017 May 19. pii: S1552-5260(17)30185-1.

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Designed for those who want to monitor their DII® on an on-going basis, DII-on-Demand™ is an in-depth, online food frequency questionnaire that generates a DII® score calculated by CHI scientists along with a detailed report.

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DII on Demand™



Designed for those who want to monitor their DII score on an on-going basis, DII-on-Demand™ is an in-depth, online food frequency questionnaire that generates a DII® score calculated by CHI scientists. Typically, DII-on-Demand™ is repeated monthly, though sometimes, twice a month, based on your doctor's or nutritionist's recommendations

Users receive a personalized report that includes their DII® score, dietary recommendations and next steps for reducing the inflammatory potential of one's diet.

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*All disease begins in the gut.*

*Hippocrates*

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## Probiotics

- **Regulate/modulate immune functions**, reduce risk intestinal infection.
- Improve **intestinal barrier functions**, reduce endotoxemia
- Induce hypo-responsiveness to **food antigens**
- Improve glucose control and **reduce inflammatory cytokines**.
- Inhibit tumorigenesis and **may inhibit cancer progression**
- 81 obese postmenopausal women randomized to high or low dose multi-strain probiotics or placebo for 12 weeks. Statistically significant differences **in LPS, uric acid, glucose, insulin** found for both doses compared to placebo.

Gianotti L. et al. *World J Gastroenterol*. 2010;16:167–175

Szulinska M, et al. *Nutrients* 2018, 10(6), 773; <https://doi.org/10.3390/nu10060773>

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## It's the Fiber Folks!



- Diets **high in fiber** and **low in sugar** increase *Bifidobacteria*, preventing toxins from passing through **intestinal wall** into **bloodstream**.
- Prebiotics: **un-digestible plant fiber** acts as food for microbiota.
- Bananas, onions, garlic, leeks, Jerusalem artichoke, apple skin, chicory root, dandelion greens, beans, wheat flour just a few examples of prebiotic foods.

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## Sugar Substitutes – Better?



- Sugar substitutes frequently **1000 times sweeter** than sucrose.
- Despite GRAS status by regulatory agencies, sugar substitutes **can have negative effects** on gut microbiota.
- **Sucralose** and **saccharin** disrupt balance and **diversity** of gut microbiota. **Sucralose increases bacterial pro-inflammatory genes**.

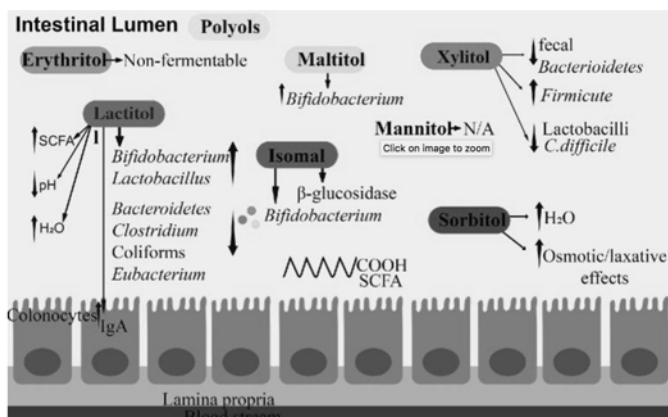
Nettleton JE, et al. Reshaping the gut microbiota: Impact of low calorie sweeteners and the link to insulin resistance? *Physiol Behav* 2016;164(Pt B):488-93.

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## Stevia and the Polyols



Ruiz-Ojeda F, et al. Effects of sweeteners on the gut microbiota: a review of experimental studies and clinical trials. *Adv Nutr* 2019; 10(S1): PMC6363527

- Erythritol, mannitol and sorbitol have **no effect** on gut microbiota.
- Isomaltose and maltitol, increase *bifidobacteria* and may have **prebiotic actions**.
- Stevia extracts may **negatively impact** gut microbiota composition.

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**Table 1 | Examples of foods, nutrients, and dietary patterns that influence human health linked to their effects on the gut microbiome**

Dietary element	Effect on gut microbiome	Effect on health outcomes mediated by gut microbiome
Low FODMAP diet	Low FODMAP diet increased Actinobacteria; high FODMAP diet decreased abundance of bacteria involved in gas consumption <sup>58</sup>	Reduced symptoms of irritable bowel syndrome <sup>56</sup>
Cheese	Increased <i>Bifidobacteria</i> , <sup>97,98</sup> which are known for their positive health benefits to their host through their metabolic activities. <sup>99</sup> Decrease in <i>Bacteroides</i> and <i>Clostridia</i> , some strains of which are associated with intestinal infections <sup>98</sup>	Potential protection against pathogens. <sup>100</sup> Increased production of SCFA and reduced production of TMAO <sup>99</sup>
Fibre and prebiotics	Increased microbiota diversity and SCFA production <sup>22,101,102</sup>	Reduced type 2 diabetes <sup>22</sup> and cardiovascular disease <sup>103</sup>
Artificial sweeteners	Overgrowth of Proteobacteria and <i>Escherichia coli</i> . <sup>104</sup> <i>Bacteroides</i> , <i>Clostridia</i> , and total aerobic bacteria were significantly lower, and faecal pH was significantly higher <sup>47</sup>	Induced glucose intolerance <sup>105</sup>
Polyphenols (eg, from tea, coffee, berries, and vegetables such as artichokes, olives, and asparagus)	Increased intestinal barrier protectors ( <i>Bifidobacteria</i> and <i>Lactobacillus</i> ), butyrate producing bacteria ( <i>Faecalibacterium prausnitzii</i> and <i>Roseburia</i> ) and <i>Bacteroides vulgatus</i> and <i>Akkermansia muciniphila</i> . <sup>107</sup> Decreased lipopolysaccharide producers ( <i>E coli</i> and <i>Enterobacter cloacae</i> ) <sup>106</sup>	Gut micro-organisms alter polyphenol bioavailability resulting in reduction of metabolic syndrome markers and cardiovascular risk markers <sup>108</sup>
Vegan	Very modest differences in composition and diversity in humans and strong differences in metabolomic profile compared with omnivore diet in humans <sup>50</sup>	Some studies show benefit of vegetarian over omnivore diet, <sup>109</sup> others fail to find a difference <sup>110</sup>

Valdes AM, et al. Role of gut microbiota in nutrition and health. *British Medical Journal* 2018;361:j2179

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## Summary of Systematic Review Analyzing the Role of Probiotics on Clinical Outcomes

Outcome	Reference	No of studies/ participants	Evidence of benefit?
<i>Clostridium difficile</i> associated diarrhoea in adults and children	Goldenberg et al (2017) <sup>111</sup>	39/9955	Yes
Necrotising enterocolitis	Al Faleh et al (2014) <sup>112</sup> Rees et al (2017) <sup>113</sup>	17/5338	Yes
Antibiotic associated diarrhoea in children	Goldenberg et al (2015) <sup>114</sup>	26/3898	Yes
Probiotics for preventing acute upper respiratory tract infections	Hao et al (2015) <sup>115</sup>	12/3720	Yes
Urinary tract infections	Schwenger et al (2015) <sup>116</sup>	9/735	No
Prevention of asthma and wheeze in infants	Azad et al (2013) <sup>117</sup>	6/1364	No
Prevention of eczema in infants and children	Mansfield et al (2014)	16/2797	Yes
Prevention of invasive fungal infections in preterm neonates	Agrawal et al (2015) <sup>119</sup>	19/4912	Unclear
Prevention of nosocomial infections	Manzanares et al (2015) <sup>120</sup>	30/2972	Yes
Treatment of rotavirus diarrhoea in infants and children	Ahmadi et al (2015) <sup>121</sup>	14/1149	Yes
Prevention and treatment of Crohn's disease and ulcerative colitis	Saez Lara et al (2015) <sup>122</sup>	14/821 ulcerative colitis 8/374 Crohn's disease	Yes
Pulmonary exacerbations in children with cystic fibrosis	Ananathan et al (2016) <sup>123</sup>	9/275	Yes
Type 2 diabetes (fasting glucose, glycated haemoglobin test)	Akbari et al (2016) <sup>124</sup>	13/805	Yes
Type 2 diabetes (insulin resistance, insulin levels)	Zhang et al (2016) <sup>125</sup>	7/425	Yes
Necrotising enterocolitis in pre-term neonates with focus on <i>Lactobacillus reuteri</i>	Athalye-Jape et al (2016) <sup>126</sup>	6/1778	Yes
Reduction of serum concentration of C reactive protein	Mazidi et al (2017) <sup>127</sup>	19/935	Yes
Cardiovascular risk factors in patients with type 2 diabetes	Hendijani et al (2017) <sup>128</sup>	11/641	Yes
Reduction of total cholesterol and low density lipoprotein cholesterol	Wu et al (2017) <sup>129</sup>	15/976	Yes
Depressive symptoms	Wallace and Milev (2017) <sup>79,130</sup>	6/1080	Yes
Vulvovaginal candidiasis in non-pregnant women	Xie et al (2018) <sup>131</sup>	10/1656	Yes


From: Valdes AM, et al. Role of gut microbiota in nutrition and health. *BMJ* 2018;361:j2179

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## Clinical Resource Tool: [www.usprobioticguide.com](http://www.usprobioticguide.com)

 <b>Clinical Guide to Probiotic Products Available in USA</b> Indications, Dosage Forms and Clinical Evidence to Date - 2019 Edition						
<a href="#">Introduction</a> <a href="#">Adult Health</a> <a href="#">Women's Health</a> <a href="#">Pediatric Health</a> <a href="#">Functional Foods</a> <a href="#">References</a> <a href="#">About</a>						
INDICATIONS FOR PEDIATRIC HEALTH						
Show 10 entries						
Brand Name	Probiotic Strain	Dosage Form	CFU/Dose	No of Doses/Day	Indications (Level of Evidence)	
Bio-Kult® Infantis <sup>1</sup>	L. casei PXNB 37™ L. rhamnosus PXNB 54™ Streptococcus thermophilus PXNB 66™ L. acidophilus PXNB 35™ B. breve PXNB 25™ L. delbrueckii ssp. bulgaricus PXNB 39™ B. infantis PXNB 27™	Sachet	1B/sachet	1/1 sachet	CE/AD - Childhood eczema/ Atopic dermatitis (I) Colic - Colic (I) HP - Helicobacter pylori - Adjunct to standard eradication therapy (II)	
BioGaia® ProTectis® Baby Drops with Vitamin D <sub>3</sub> <sup>1</sup>	L. reuteri DSM 17938	Drops	100M/drops	5 drops	AAD - Antibiotic associated diarrhea - Prevention (I) C - Constipation (I) CE/AD - Childhood eczema/ Atopic dermatitis (II) CID - Common infectious disease - community acquired (I) Colic - Colic (I) IBS/FAP - Irritable bowel syndrome/Functional abdominal pain (I) ID - Infectious diarrhea (I) Regurg/ GI Mot - Reduces regurgitation/ Improves gastrointestinal motility (I)	
BioGaia® ProTectis® <sup>1</sup>	L. reuteri DSM 17938	Chew. tabs Drops	100M/tab 100M/drops	1 tab 5 drops	AAD - Antibiotic associated diarrhea - Prevention (I) C - Constipation (I) CE/AD - Childhood eczema/ Atopic dermatitis (II) CID - Common infectious disease - community acquired (I) Colic - Colic (I) IBS/FAP - Irritable bowel syndrome/Functional abdominal pain (I) ID - Infectious diarrhea (I) Regurg/ GI Mot - Reduces regurgitation/ Improves gastrointestinal motility (I)	
Gerber® Good Start® Soothe Powder Infant Formula <sup>2</sup>	L. reuteri DSM 17938	Powder	1Migram	Routine feeding if alternative to breast milk is required	AAD - Antibiotic associated diarrhea - Prevention (I) Colic - Colic (I) ID - Infectious diarrhea (I) Regurg/ GI Mot - Reduces regurgitation/ Improves gastrointestinal motility (I)	
Gerber® Soothe Probiotic Colic Drops <sup>1</sup>	L. reuteri DSM 17938	Drops	100M/drops	5 drops	AAD - Antibiotic associated diarrhea - Prevention (I) C - Constipation (I) CE/AD - Childhood eczema/ Atopic dermatitis (II) CID - Common infectious disease - community acquired (I) Colic - Colic (I) IBS/FAP - Irritable bowel syndrome/Functional abdominal pain (I) ID - Infectious diarrhea (I) Regurg/ GI Mot - Reduces regurgitation/ Improves gastrointestinal motility (I)	

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Click next to brand name to see evidence.....

Colic - Colic	I	<p>82. Savino, F., E. Pelle, E. Palumeri, R. Oggero, and R. Miniero. "Lactobacillus reuteri (American Type Culture Collection Strain 55730) versus simethicone in the treatment of infantile colic: a prospective randomized study." <i>Pediatrics</i> 119.1 (2007): e124-e130.</p> <p>85. Chau, K., E. Lau, S. Greenberg, S. Jacobson, P. Yazdani-Brojeni, N. Verma, and G. Koren. "Probiotics for infantile colic: a randomized, double-blind, placebo-controlled trial investigating <i>Lactobacillus reuteri</i> DSM 17938." <i>The Journal of pediatrics</i> 166.1 (2015): 74-78.</p> <p>84. Sung, V., H. Hiscock, M.L.K. Tang, F.K. Mensah, M.L. Nation, C. Satzke, R.G. Heine, A. Stock, R.G. Barr, and M. Wake. "Treating infant colic with the probiotic <i>Lactobacillus reuteri</i>: double blind, placebo controlled randomised trial." <i>BMJ</i> 348 (2014): g2107.</p> <p>83. Savino, F., L. Cordisco, V. Tarasco, E. Palumeri, R. Calabrese, R. Oggero, S. Roos, and D. Matteuzzi. "Lactobacillus reuteri DSM 17938 in infantile colic: a randomized, double-blind, placebo-controlled trial." <i>Pediatrics</i> 126.3 (2010): e526-e533.</p>
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Evidence is ranked using grading system of I, II, III. You can then see the references for your review.

[http://www.usprobioticguide.com/PBCPediatricHealth.html?utm\\_source=pediatric\\_ind&utm\\_medium=civ&utm\\_campaign=USA\\_CHART](http://www.usprobioticguide.com/PBCPediatricHealth.html?utm_source=pediatric_ind&utm_medium=civ&utm_campaign=USA_CHART) Accessed January 17, 2019

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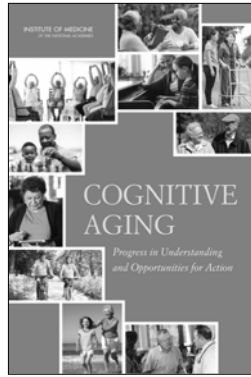
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## Cognitive Aging: Progress in Understanding and Opportunities for Action

[www.iom.edu/cognitiveaging](http://www.iom.edu/cognitiveaging)



Cognitive aging NOT a disease, no neurodegeneration

- 87% those 65 and older have cognitive changes
- 13% of those 65 and older develop AD

Reduce known risk factors, promote health:

- Physical activity/restorative sleep
- Stay socially and intellectually engaged
- Reduce CV risk factors
- Manage meds/conditions that can affect cognition

IOM (Institute of Medicine). 2015. *Cognitive aging: Progress in understanding and opportunities for action*. Washington, DC: The National Academies Press.

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### The Who's Who of Brain Cells

Glial cells outnumber neurons by 9 to 1. Once thought of as mere helper cells, glia are now known to play key roles in shaping brain circuitry and controlling neurons' behavior.

#### Neuron

Forms networks with other neurons and transmits messages through rapid electrochemical signals across connections known as synapses.

#### Astrocyte

Provides structural support, nutrients and oxygen to neurons. Enables synapse formation and prunes weak synapses. Can help heal — or destroy — injured or diseased neurons.

#### Microglia

Prunes excess synapses in developing nervous system. Removes molecular debris. During infections, gobbles up invading pathogens. May also prune functional synapses in cases of neurodegenerative disease.

#### Oligodendrocyte

Insulates axons (nerve fibers) with myelin, improving transmission of nerve impulses. Damage to oligodendrocytes leads to demyelination, implicated in neurological disorders such as multiple sclerosis and Charcot-Marie-Tooth disease. — K.M.

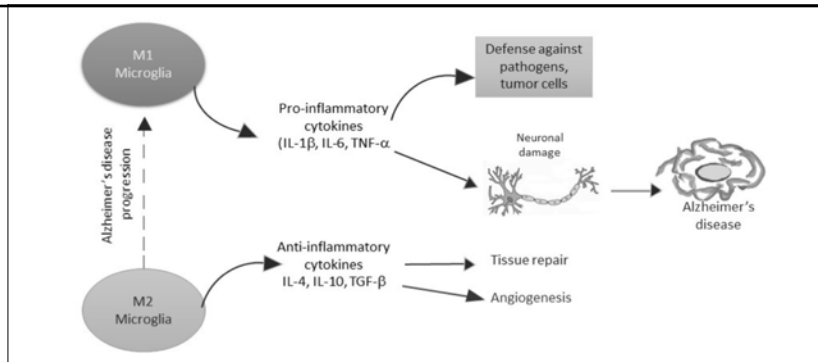
From: <https://www.discovermagazine.com/mind/the-brain-of-ben-barres>

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# Neuro-inflammation



- Mediated principally by **reactive astrocytes and microglial cells**.
- CNS threatened - **microglia migrate to site** and assume activated phenotype.
- **Chronic neuroinflammation** *linked to* Alzheimer's disease; anxiety, depression, and bipolar disorder. **Neuroinflammation *generally precedes* neurodegeneration.**

From: Chandra Mohan at [www.sigmaaldrich.com/technical-documents/articles/biology/microglia-in-neuroinflammation.html](http://www.sigmaaldrich.com/technical-documents/articles/biology/microglia-in-neuroinflammation.html). Accessed 12/22/19

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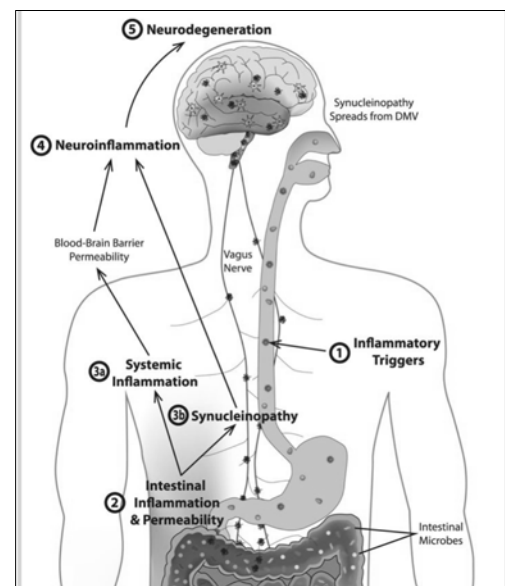
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# Brain-GutAxis

- Human studies/animal models of depression show **increased inflammatory mediators in both periphery and CNS**.
- **Microglial activation** key event triggering changes in signaling cascades and gene expression that **mediate onset of depressive symptoms**.
- **Gut microbes and dietary fiber** help prevent disruption of intestinal lining and blood-brain barrier.

Carlessi AS, et al. *Eur J Neurosci* 2019; doi: 10.1111/ejn.14631.



Houser MC, et al. *Parkinson's Disease* 2017; doi:10.1038/s41531-016-0002-0

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# LPS and Neuroinflammation

- LPS enter circulation due to **increased intestinal permeability**.
- Highly immunogenic, bind TLR-4, trigger systemic inflammation and **degrades BOTH intestinal and blood brain barriers**.
- **TLR-4 expressed on microglia** and neurons: **once activated, produce pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , NO)**.
- LPS induces **cognitive impairment, anxiety, depression in animal models**.
- **Systemic inflammation/infection can change microglial phenotype and disrupt BBB integrity** in absence of precipitating neuronal damage/infection

Zhao J, et al. *Sci Rep* 2019; 9:5790 doi:10.1038/s41598-019-42286-8

Kure C, et al. *Front Pharmacol* 2017; doi.org/10.3389/fphar.2017.00117

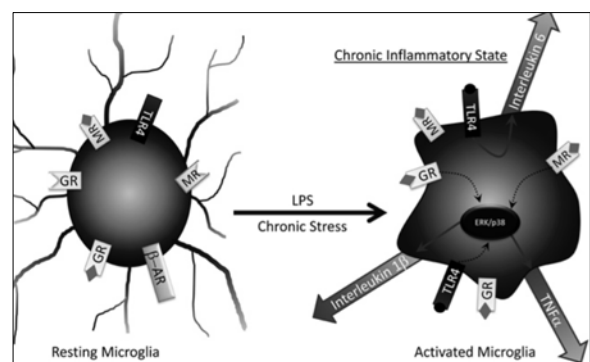
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# Stress and Microglia

- Microglia constant surveillance mode; biosensors for stress effects on CNS.
- Mouse study: **repeated unpredictable stress caused prefrontal cortex neurons triggered microglia** to remodel neural circuits, limiting synaptic connections. **All animals showed signs of anxiety and depression.**
- **Microglia hold “memories” of stress** and have larger and more rapid response when exposed to future stressors.



Wohleb ES, et al. *Biol Psychiatry* 2018; 83(1) 38-49

Weber MD, et al. *Biol Psychiatry* 2018;

doi.org/10.1016/j.biopsych.2018.10.009

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## Turmeric (*Curcuma longa*)

- Dietary consumption linked to reduced AD rates.
- Animal models: **suppresses LPS induced neuroinflammation; reduces amyloid- $\beta$ -stimulated inflammatory responses** in primary astrocytes.
- **Most studies older adults show improvement in memory & mood BUT those with AD, no benefit** – trend showed patients did worse than control on Mini-Mental State Examination.
- Use nanoparticle or bound to phospholipid. If using with piperine 20mg/d increase risk drug interactions.



Zhu LN, et al. *Phytother Res* 2019; Mar;33(3):524-533.

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## Ashwagandha (*Withania somnifera*)

Preclinical studies:

- Maintained/restored BBB integrity by **inhibiting expression of microglial inflammatory factors.**
- Inhibited **microglial migration** and **induced apoptosis of inflamed microglial cells**
- Anti-inflammatory **against systemic LPS-induced neuroinflammation;** ameliorated associated behavioral abnormalities (anxiety in rodent model)



Gupta M, et al. *Neuromolecular Med* 2018  
Sep;20(3):343-362

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## Ashwagandha in MCI

- Prospective RDBPCT: 50 adults MCI
- 300 mg BID ashwagandha extract or placebo for 8 weeks.
- Ashwagandha: **significant improvement in both immediate and general memory (Wechsler Memory Scale III) and significantly greater improvement in executive function, sustained attention, and information-processing speed compared to placebo (p=0.006)**
- *Potential effect on **thyroid hormones***



Choudhary D, et al. *J Diet Suppl* 2017; Nov 2;14(6):599-612

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## Bacopa Herb *Bacopa monnieri*



- Medhya rasayana, nootropic, in Ayurveda: enhance brain's cognitive function and memory; ease tension, promote concentration.
- **Studies in adults/children suggest beneficial effects on cognition.**
- **Reduces TNF- $\alpha$  and IL-6, ROS; modulates release of pro-inflammatory cytokines from activated microglia.**
- Modulates brain-derived neurotrophic factor (BDNF).
- No significant risk of clinically relevant drug interactions known.

Aguilar S, *Rejuvenation Res* 2013; Aug; 16(4): 313–326.

Nemetchek MD, et al. *J Ethnopharmacol* 2017 Feb 2;197:92-100.

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## Bacopa Research

- RDBPCT **60 healthy elders** (mean 62.6 years) given one of two doses of **bacopa extract (300 or 600 mg)** or placebo once daily for 12 weeks.
  - Bacopa **improved power, speed, and continuity of attention, and quality and speed of memory** at both doses, compared to placebo.
- **Meta-analysis RCTS** (518 participants) found **bacopa improved cognition and speed of attention**.
  - Overall quality of reported information was high with low risk of bias.

Peth Nui T, et al. *Evid Based Complement Alternat Med* 2012; 606424

Kongkeaw C, et al. *J Ethnopharmacol* 2014; 151(1):528-35.

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## Reduce Triggers (Where Possible) That Drive Neuroinflammation

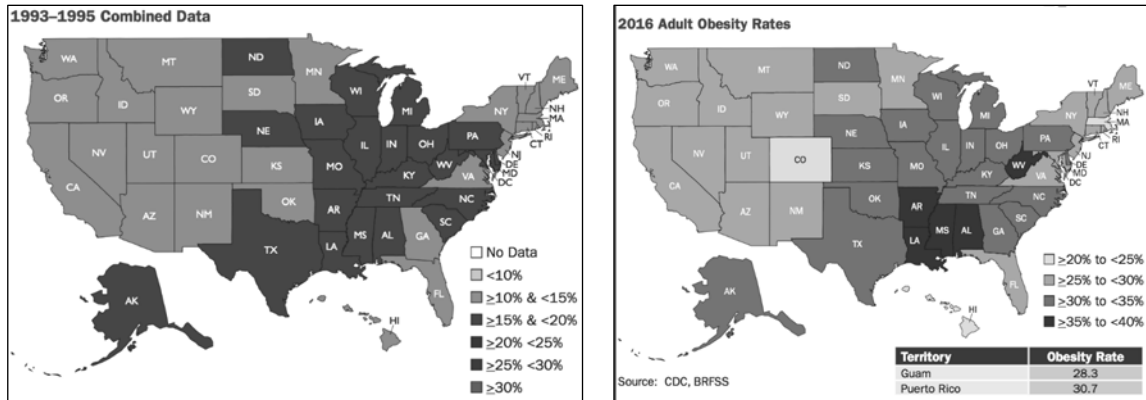
- |                               |   |
|-------------------------------|---|
| • Air pollution/passive smoke | • Obesity                               |
| • Allergens                   | • Poor nutrition                        |
| • Aging                       | • Stress/poor sleep                     |
| • Autoimmunity                | • Toxic exposures                       |
| • ↑ Intestinal Permeability   | • Traumatic brain or spinal cord injury |
| • Microbes/Infections/Viruses | • Type 2 diabetes                       |
| • Mycotoxins                  |   |

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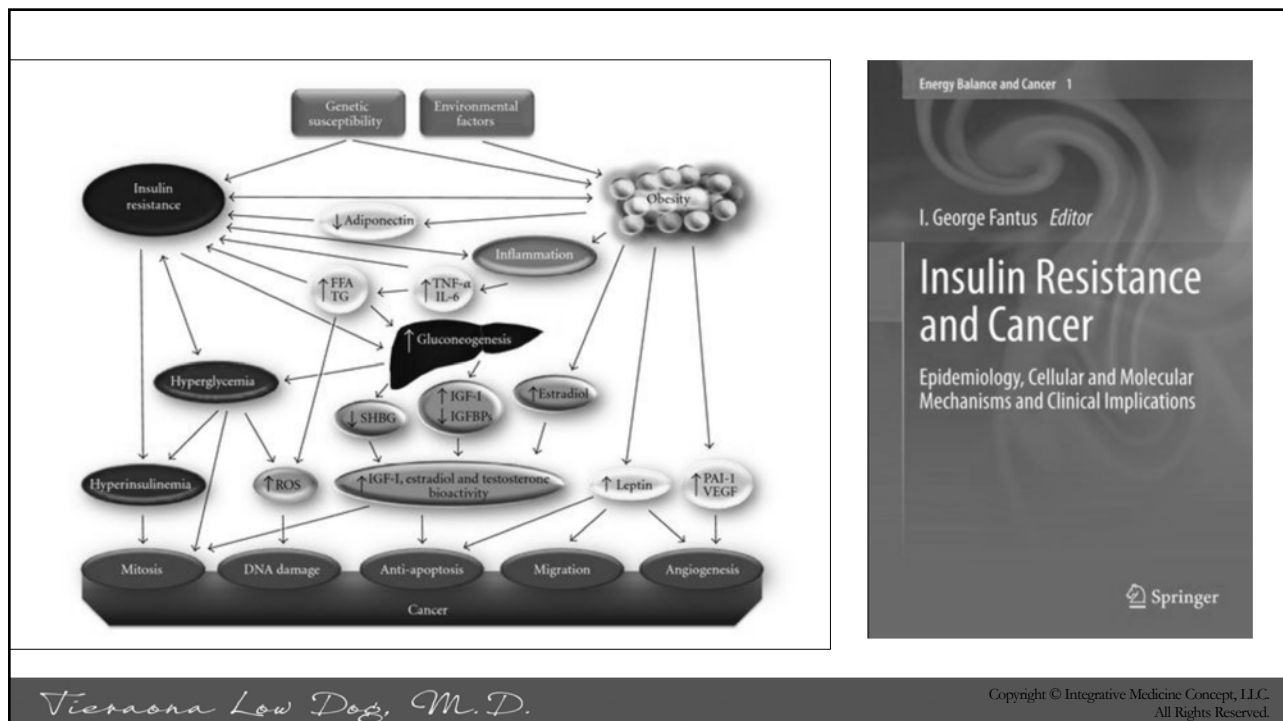
# The Changing Landscape of Adult Weight



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## Mechanisms?

- **Fat tissue produces excess estrogen**, high levels are associated with increased risks of breast, endometrial, ovarian, and some other cancers.
- Obese people often have increased blood levels of **insulin and insulin-like growth factors (IGF-1)**. High levels of insulin and IGF-1 may promote the development of **colon, kidney, prostate, and endometrial cancers**.
- **Obesity** strongly linked with **chronic inflammation**, which can damage DNA
- Fat cells produce adipokines. **Leptin promotes cell proliferation**. Adiponectin less abundant in obese than normal weight—may have **anti-proliferative effects**.

[www.cancer.gov/about-cancer/causes-prevention/risk/obesity/obesity-fact-sheet](http://www.cancer.gov/about-cancer/causes-prevention/risk/obesity/obesity-fact-sheet)

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## Insulin Resistance and Cancer

- Obesity and metabolic syndrome **associated with prostate cancer development and poorer outcomes for cancer survivors**.
- Strong association: **higher BMI in adolescence and increased cancer risk in adulthood**
- **Hyperinsulinemia**: increased risk for **breast cancer, double the risk for endometrial cancer; and increased risk for prostate cancer development, progression and aggressiveness**.

Di Sebastiano, KM, et al. *Obesity Reviews* 2018; 19: 1008–1016; Kabat, GC, et al. *Eur J Cancer Prev* 2018; 27(3): 261-268  
Weihrach-Bluhner, et al. *Metabolism* 2019; 92: 147-52

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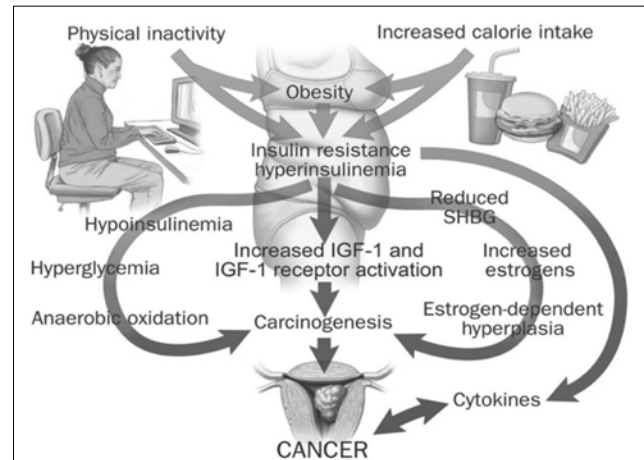
48



## Obesity and Insulin Growth Factors

- **Increase cancer risk** and cancer-related **mortality** via **insulin resistance, high blood sugar** and **insulin-growth factors (IGF)**.
- **Elevated insulin** increases tumor growth and aggressiveness.
- **IGF-1, IGF-2** identified as **tumor promoters** in multiple studies.

Belardi V, et al. *J Mammary Gland Biol Neoplasia* 2013; 18(3-4):277-89

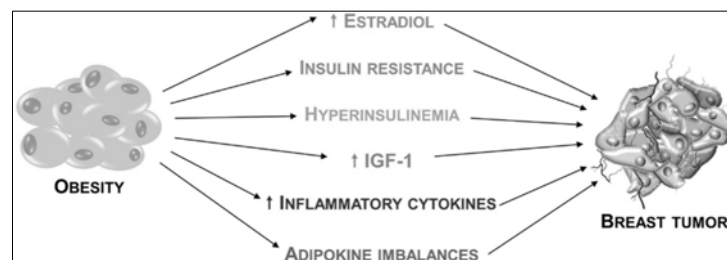


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## Women's Healthy Eating and Living (WHEL)



- **Carbohydrate restriction** associated with **striking five-fold reduction in breast cancer recurrence in 50% of subjects**, specifically those whose tumors expressed the **IGF-1 receptor**.

Edmond JA, et al. *Cancer Epidemiol, Biomarkers Prev* 2014

Image from: Mauro L, et al. *Front. Oncol* 2015; doi.org/10.3389/fonc.2015.00157

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## BENEFITS OF PHYSICAL ACTIVITY



- Maintain healthy **body weight and muscle tone.**
- **Reduces risk of heart disease**
- **Lowers risk of diabetes** by enhancing skeletal uptake of blood sugar.
- American Cancer Society, ***exercise may reduce risk of cancer by reducing insulin and insulin-like growth factors levels, associated with increased cell/tumor growth.***
- Review 73 studies: **25% average risk reduction** for breast cancer amongst physically active women.
- Aim for 30-45 minutes of moderate (or more) physical activity most days of the week.

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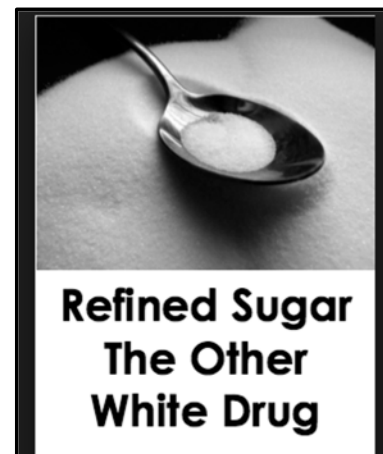
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## “Cancer Loves Sugar”

- Tumor cells have remarkable **up regulation of glucose transporter molecules on surface.** Predominant use of **glucose** anaerobically by cancer cells (Warburg effect) important characteristic cancer cells have in common.
- **Ketogenic diet** is promising. Some tumor types may be more responsive.

Oliviera CL, et al. A Nutritional Perspective of Ketogenic Diet in Cancer: A Narrative Review. *J Acad Nutr Diet* 2018; 118(4):668-688.



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## Keto Diet: Clinical Trial

- **RCT women with ovarian or endometrial cancer** randomly assigned to ketogenic diet (**70:25:5** energy from fat, protein, and carbohydrate) or American Cancer Society diet (high-fiber, low-fat).
- **Body composition, fasting serum insulin and IGF-I** obtained at baseline and at end of 12 weeks.
- Those on keto diet **had statistically significant reduction in fasting insulin and IGF-1 levels, and greater reduction in visceral fat.**

Cohen CW, et al. A Ketogenic Diet Reduces Central Obesity and Serum Insulin in Women with Ovarian or Endometrial Cancer. *J Nutr* 2018; 148(8):1253-1260.

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## Ask for Advanced Tumor Testing

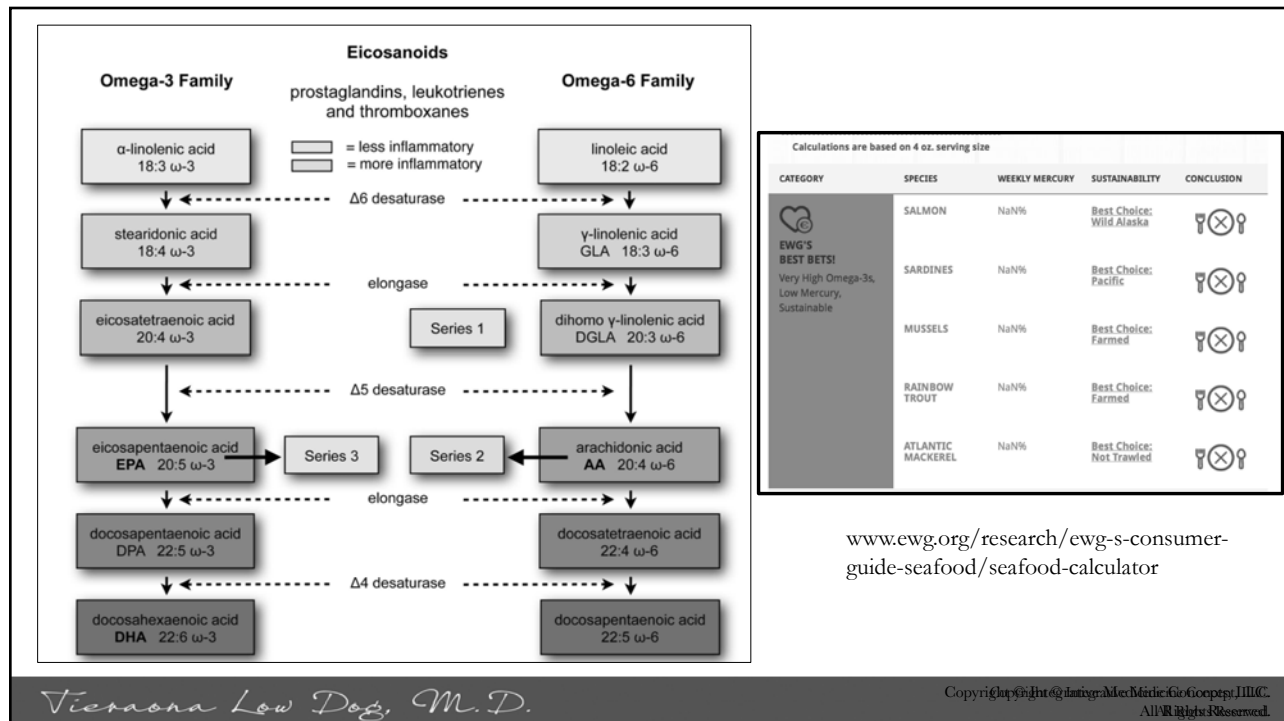
- **FDA approved companion testing for cancer.** Understanding what mutations and biomarkers you have can help choose the best therapy.
  - **Comprehensive genomic testing**
  - **Molecular profiling**
  - **Immunotherapy biomarkers**
- Also covered by Medicare, Medicaid.

[www.foundationmedicine.com](http://www.foundationmedicine.com)

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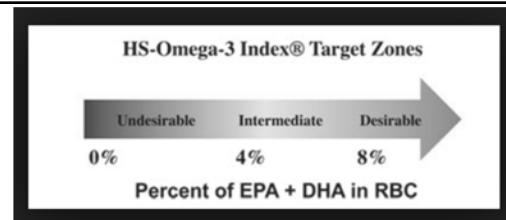
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## No Fish Story



- Omega-3 Index test is now the gold standard for omega-3 biostatus testing. It is used as a compliance marker for randomized controlled trials with fish oil supplements, and in epidemiological research.
- In 2008 Dr. Bernadine Healy, cardiologist and past President of the AHA and first woman Director of the NIH said, “Before long, your personal Omega-3 Index just could be the new cholesterol—the number you want to brag about.”

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**Dr. Low Dog's: Nutrition Prescription**

**Supplements:**  
 Multi-Vitamin: Basic, Gender & Age Specific  
 Vitamin D3: 1,000-2,000 IU/day  
 Omega 3s: EPA 400g-600mg  
 DHA 200g-500mg

**Lifestyle:**  
 Movement  
 Meditation  
 Community

**Beverages:**  
 Water: 4-8 servings (8 oz/serving)  
 Tea & Coffee: 0-3 servings (< 300 mg Caffeine)  
 Alcohol: 0-2 servings

**Healthy Fats & Oils:**  
 Olive Oil (Extra Virgin)  
 Grape Seed (Cold Pressed)  
 Butter (Organic)

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Patient: Doctor, I don't feel well and I'm not sure why.

Doctor: I want you to meditate for 20 minutes, twice a day, exercise for at least 30 minutes a day, avoid processed foods, eat plenty of organic fruit and veg, spend more time in nature and less indoors, stop worrying about things you can't control and ditch your T.V. Come back in 3 weeks.

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