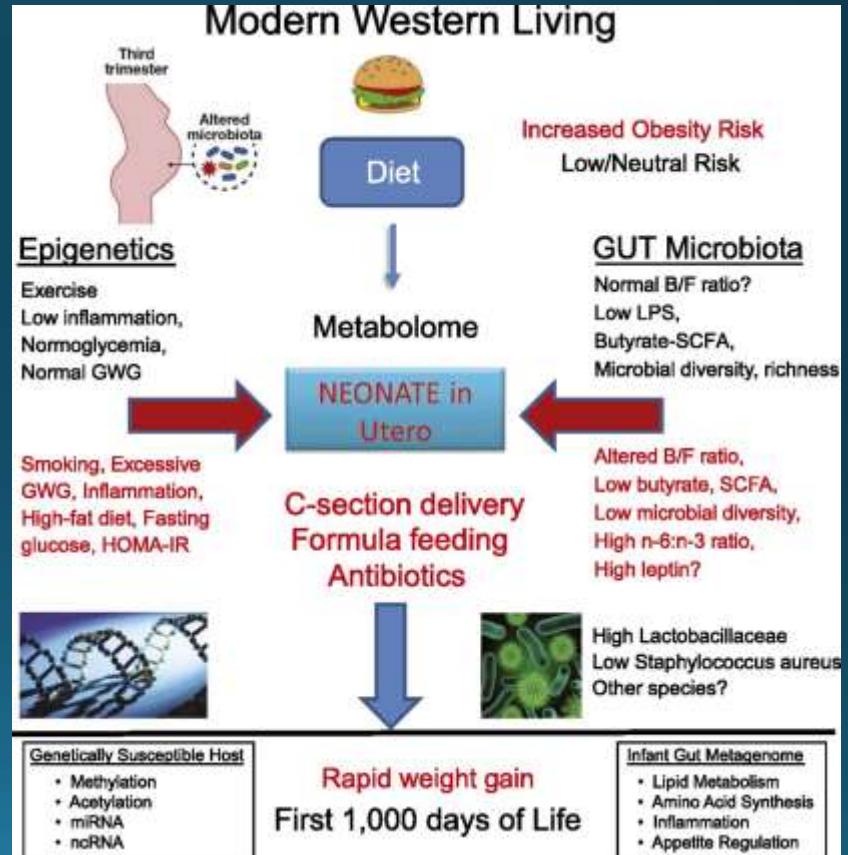
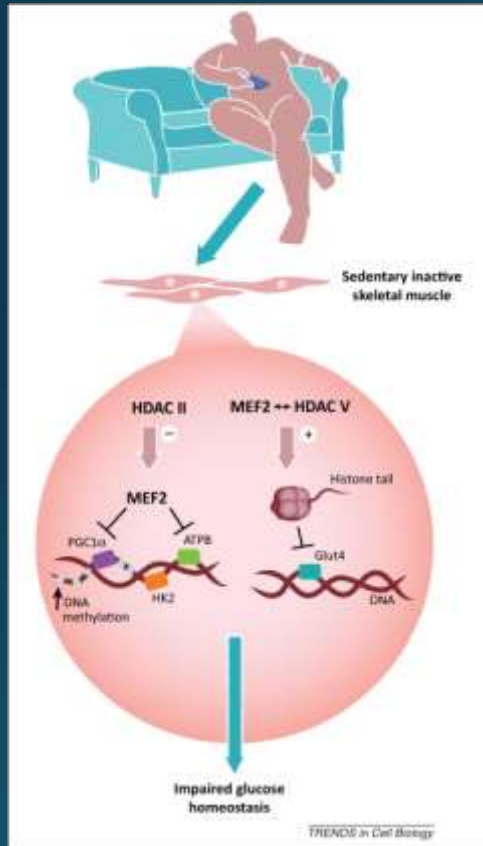


# Exercise, Nutrition, Gut Microbiome – Keys to Good Health



# Most People – Mentally Tired but NOT Physically Tired



# We Are Becoming More “Well Rounded”

Research produced by the President’s Council on Fitness, Sports & Nutrition, reveals that less than 5% of the U.S. adult population participate in 30 minutes of physical activity per day

For children, it’s far worse thanks to wireless technology and all these computer gadgets – kids spend around 7 hours per day on computer screens, cell phones and T.V.’s

Physical exercise and education is not a priority in schools

Biologically, we are able to walk 10,000 steps per day and do moderate manual labor for 4 hrs yet according to the CDC, 4 in 5 adults lead sedentary or minimally active lifestyles that fall short of the recommended 2.5 hours of moderate aerobic exercise each week

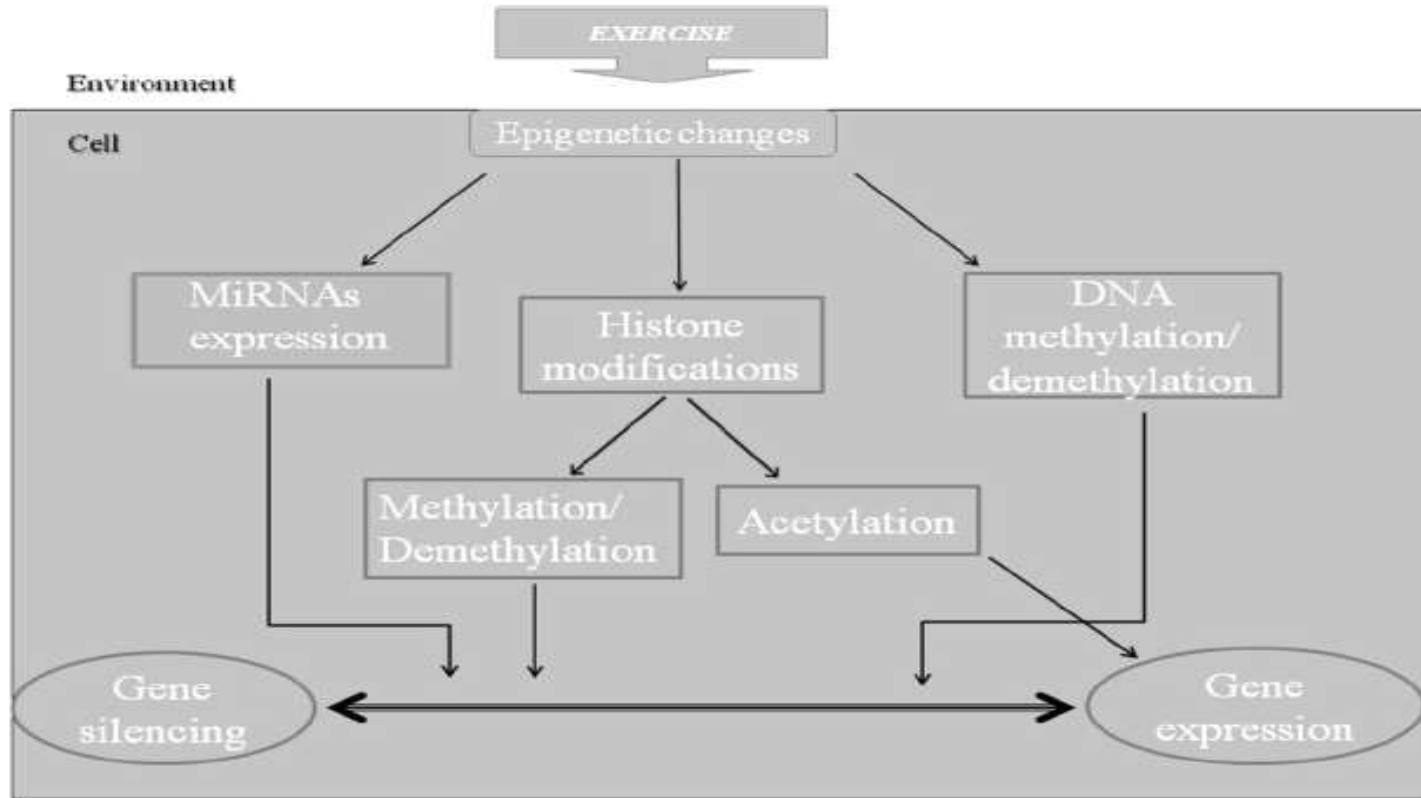


# Reported Benefits of Regular Exercise

- Exercise exerts positive effects on CV, immune, and nervous systems and minimizes risk of obesity and metabolic syndrome
- Enhances cognition and protects against neurodegeneration
- Modifies the genome-wide DNA methylation pattern in humans
- Affects metabolic phenotypes and risk of disease
- Alters the gene expression pattern in multiple tissues

The health benefits of physical exercise, especially on a long term and strenuous basis, has a positive effect on epigenetic mechanisms and ultimately may reduce incidence and severity of disease

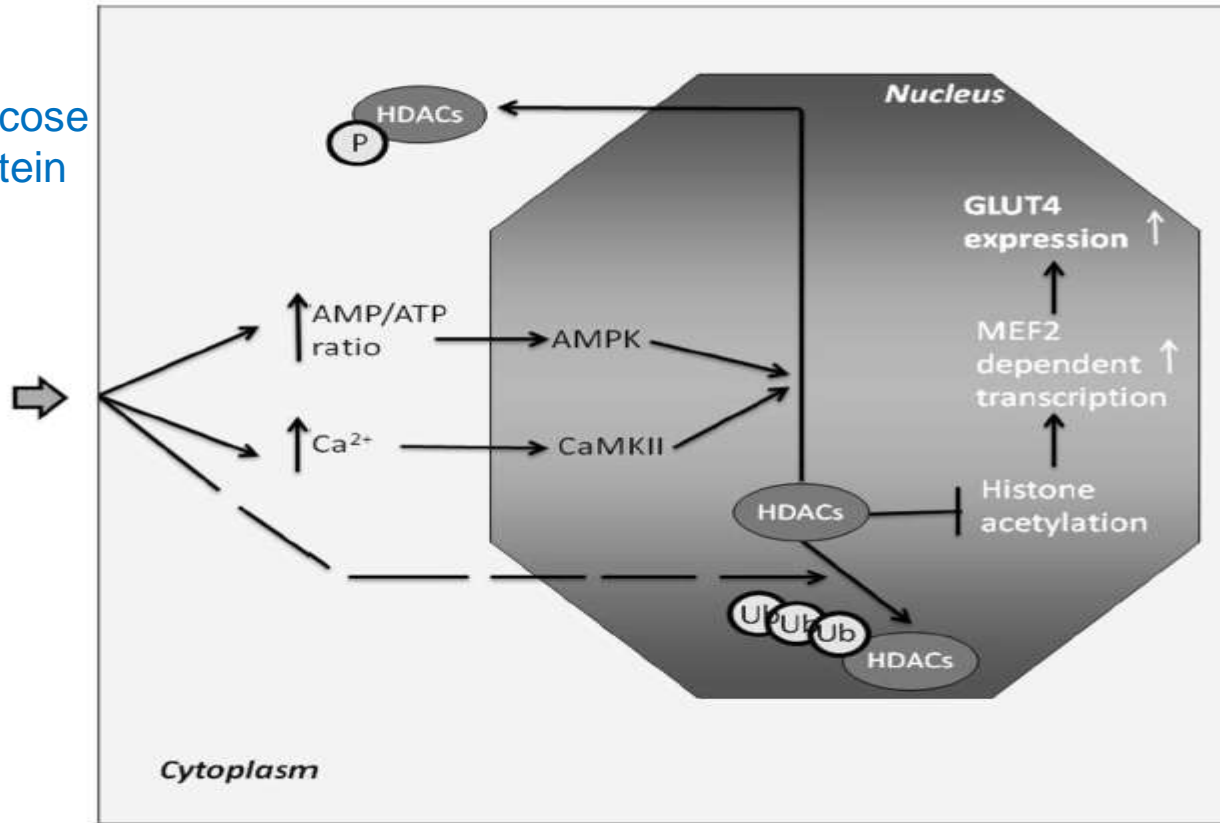
# Possible Epigenetic Changes Induced by Exercise



# Effect of Exercise on Glut4 Expression In Skeletal Muscle

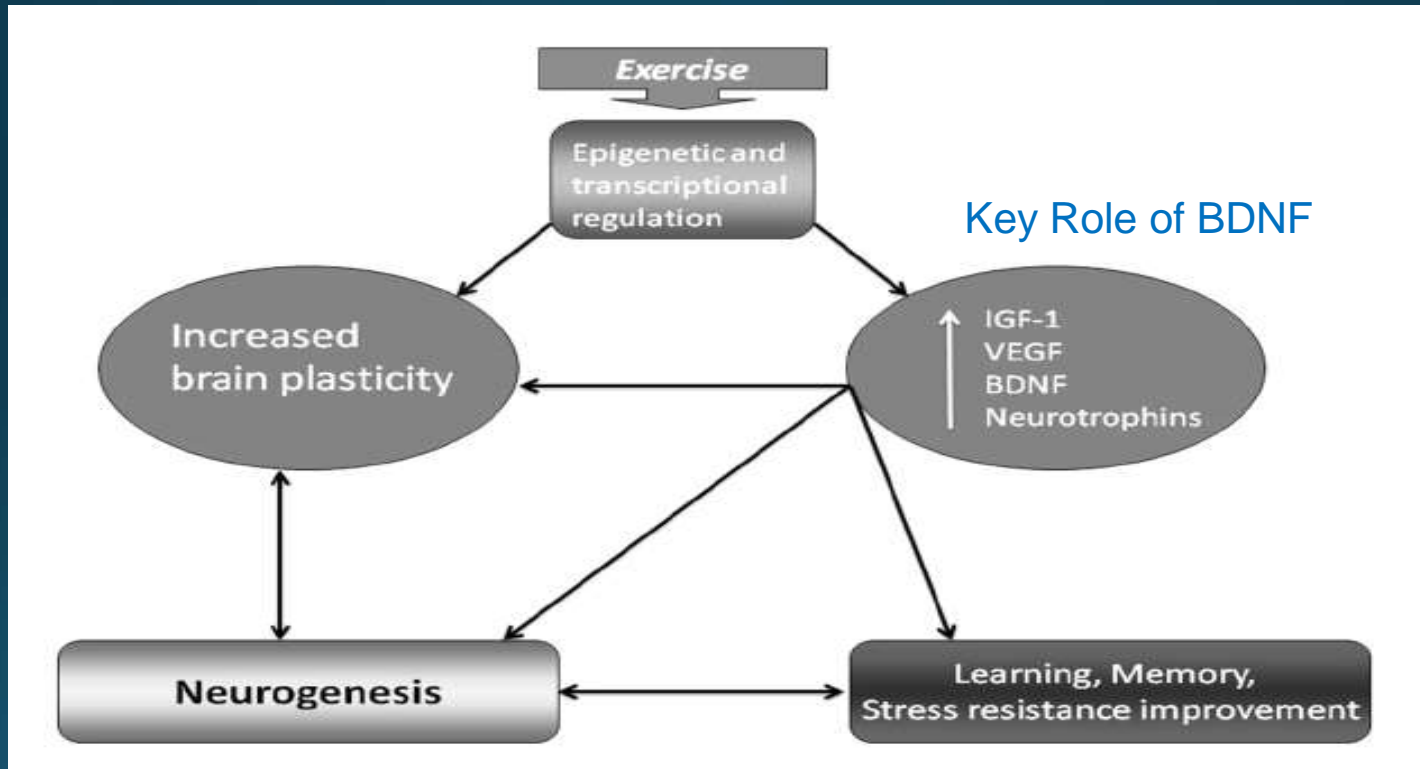
GLUT4 – glucose transport protein

*Physical exercise - muscle contraction*

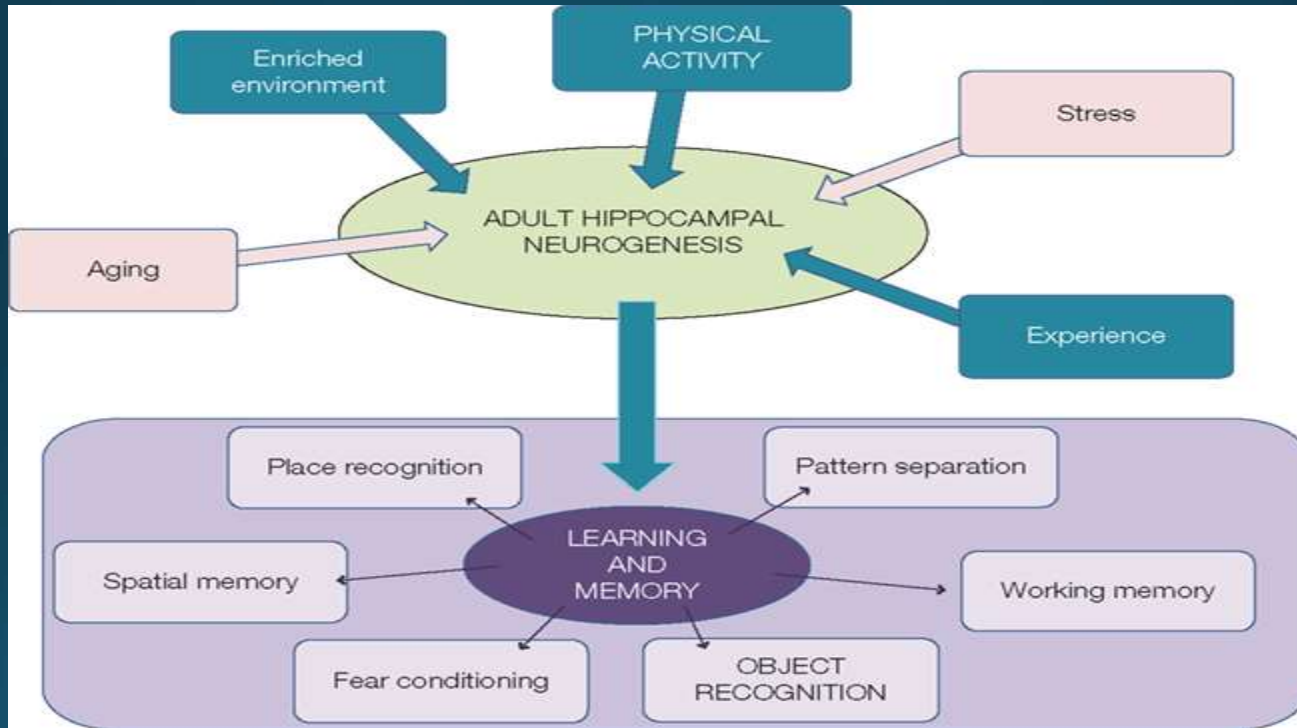




# Effect of Exercise on Molecular, Neuroplastic and Cognitive Patterns through Epigenetics

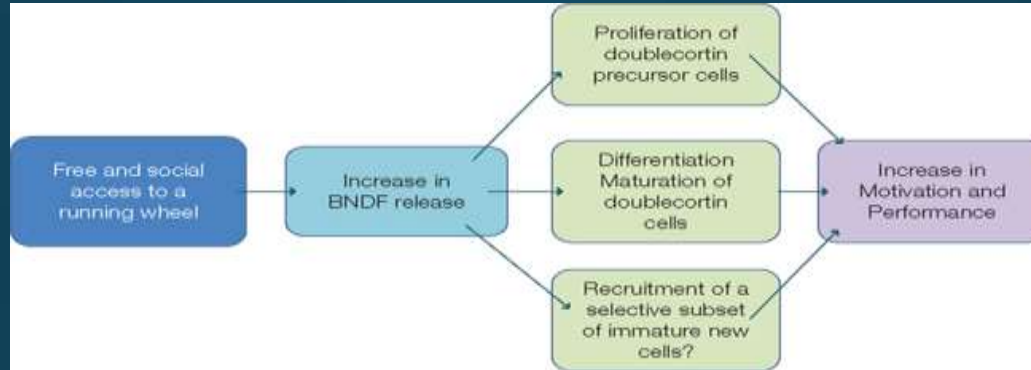


# Physical Exercise Exerts Positive Influence on Neurogenesis and Minimizes Negative Affect of Stress

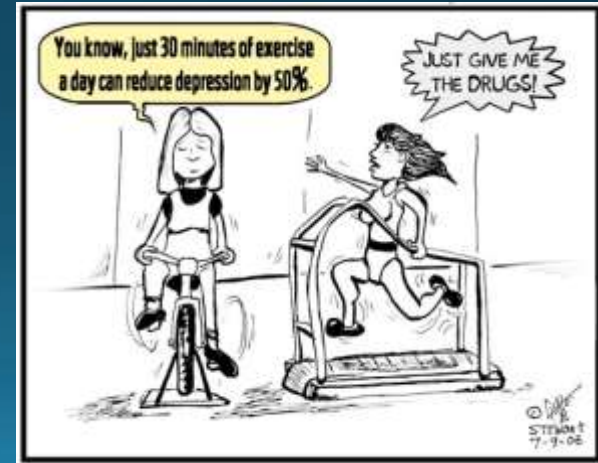
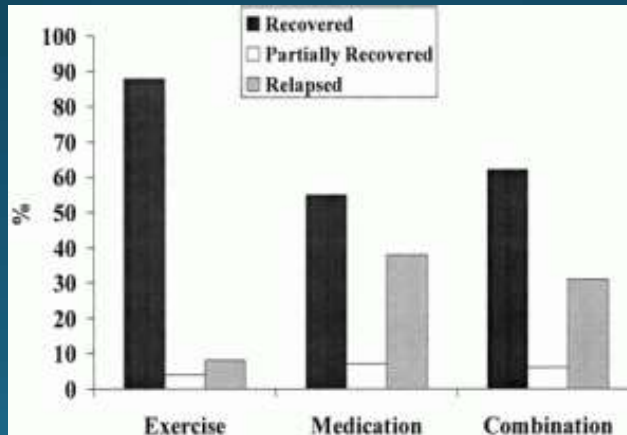
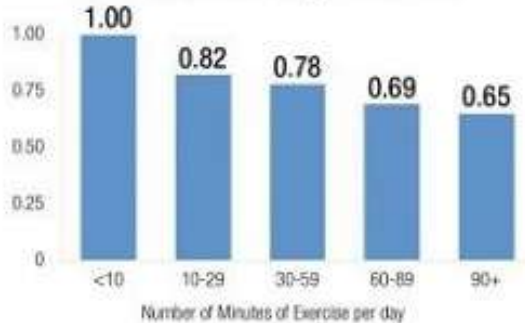




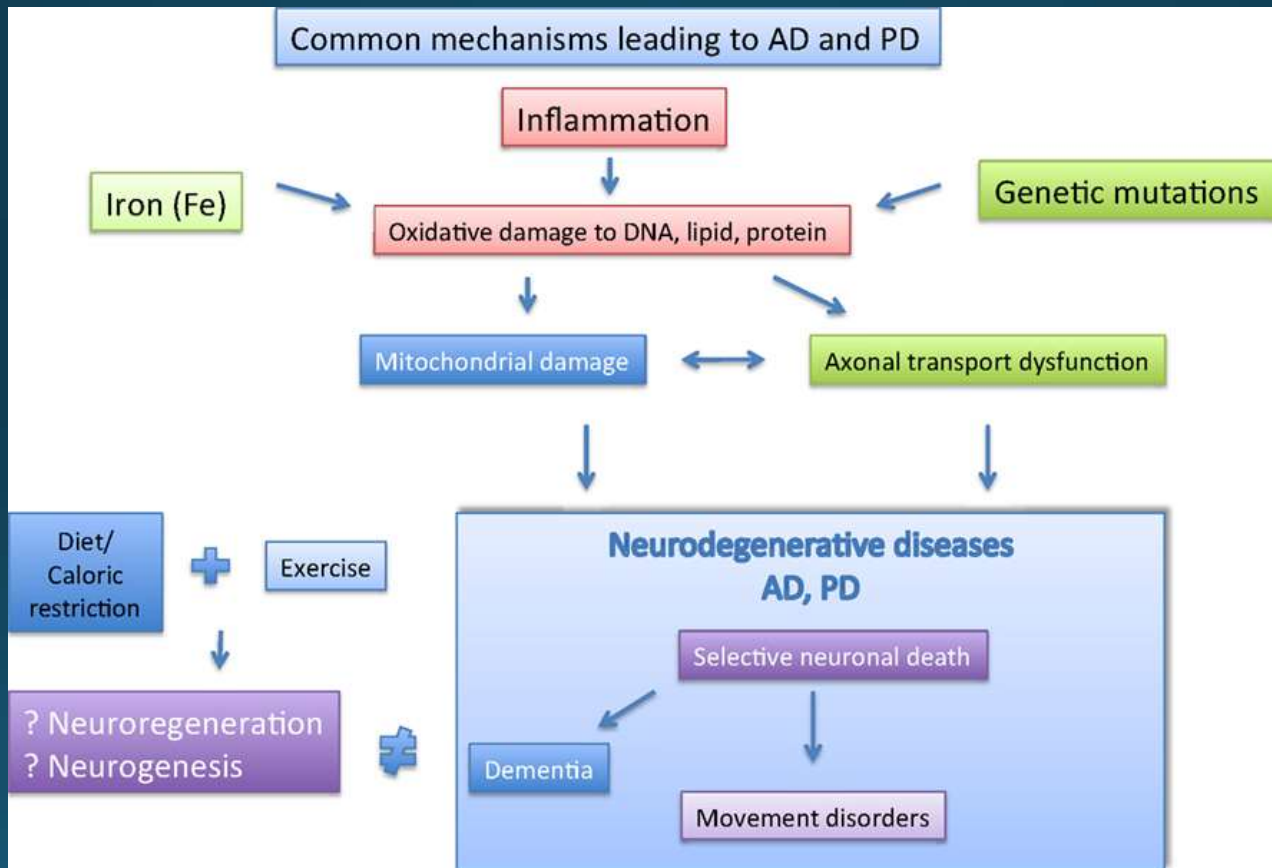
# Physical Exercise Increases Motivation and Decreases Depression

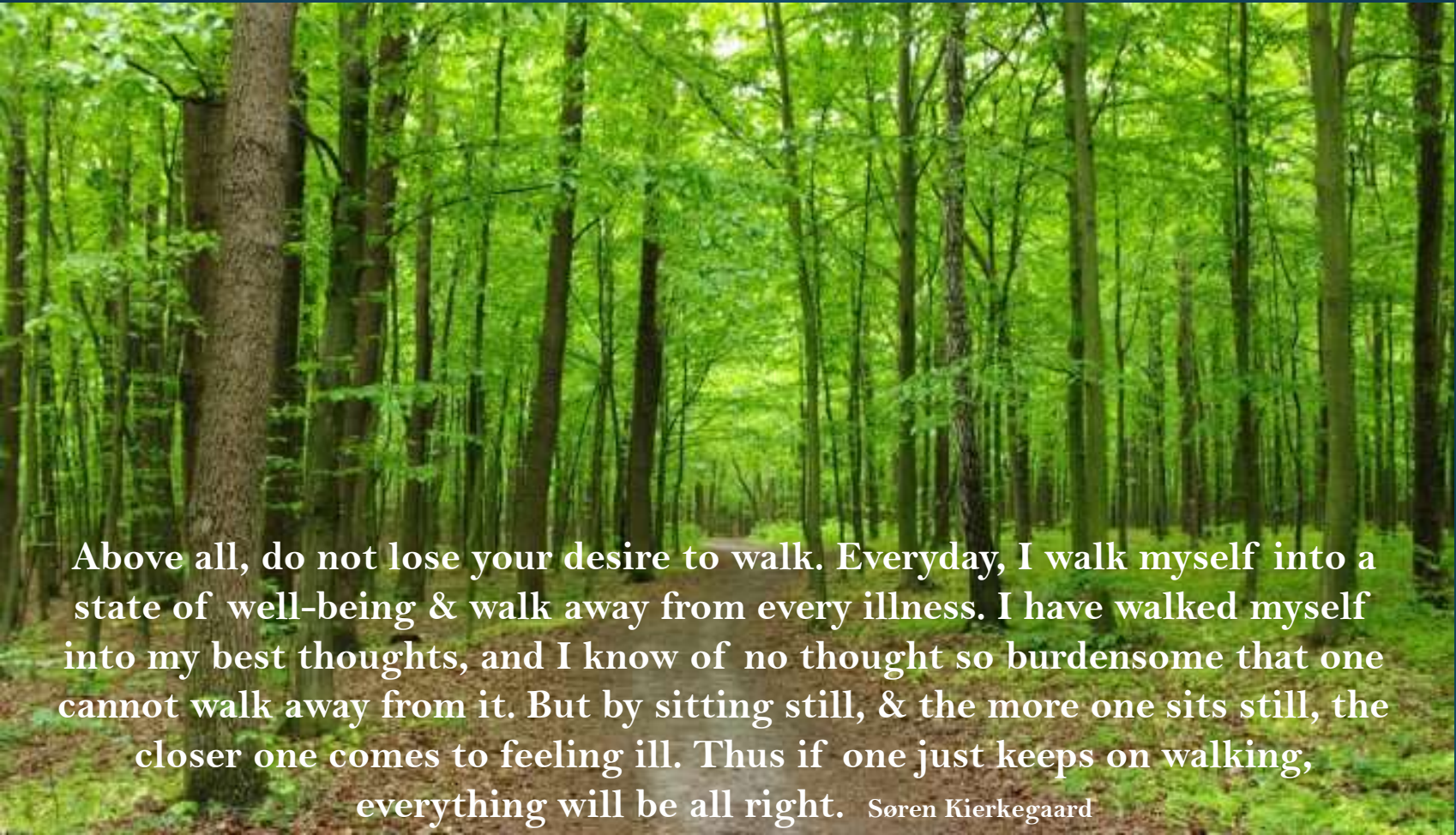


**Clinical Depression in Women by Amount of Daily Exercise**



# Physical Exercise - Beneficial Therapy for AD and PD

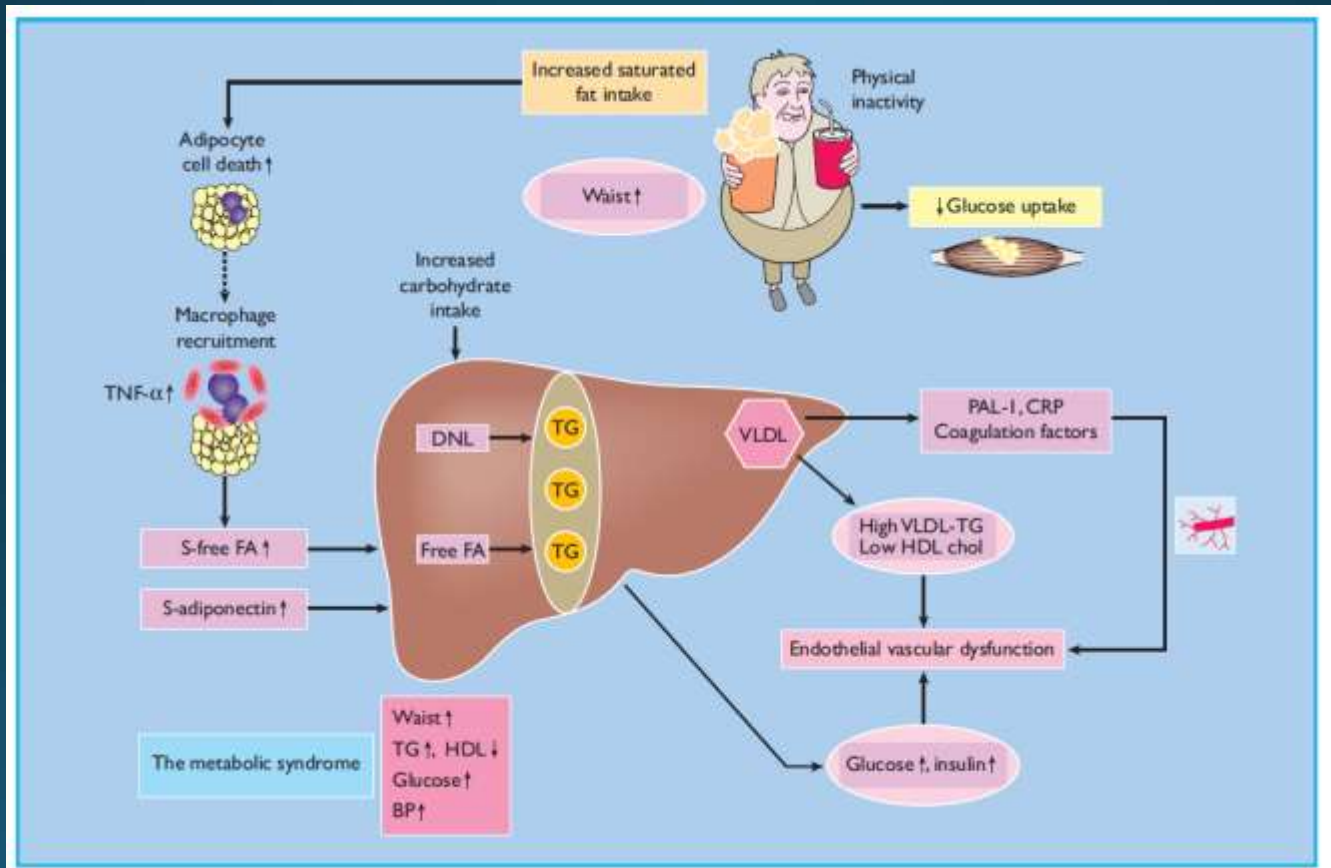


A photograph of a dense forest with tall, thin trees and vibrant green foliage. A path leads through the trees towards the background. The scene is bright and natural, with sunlight filtering through the leaves.

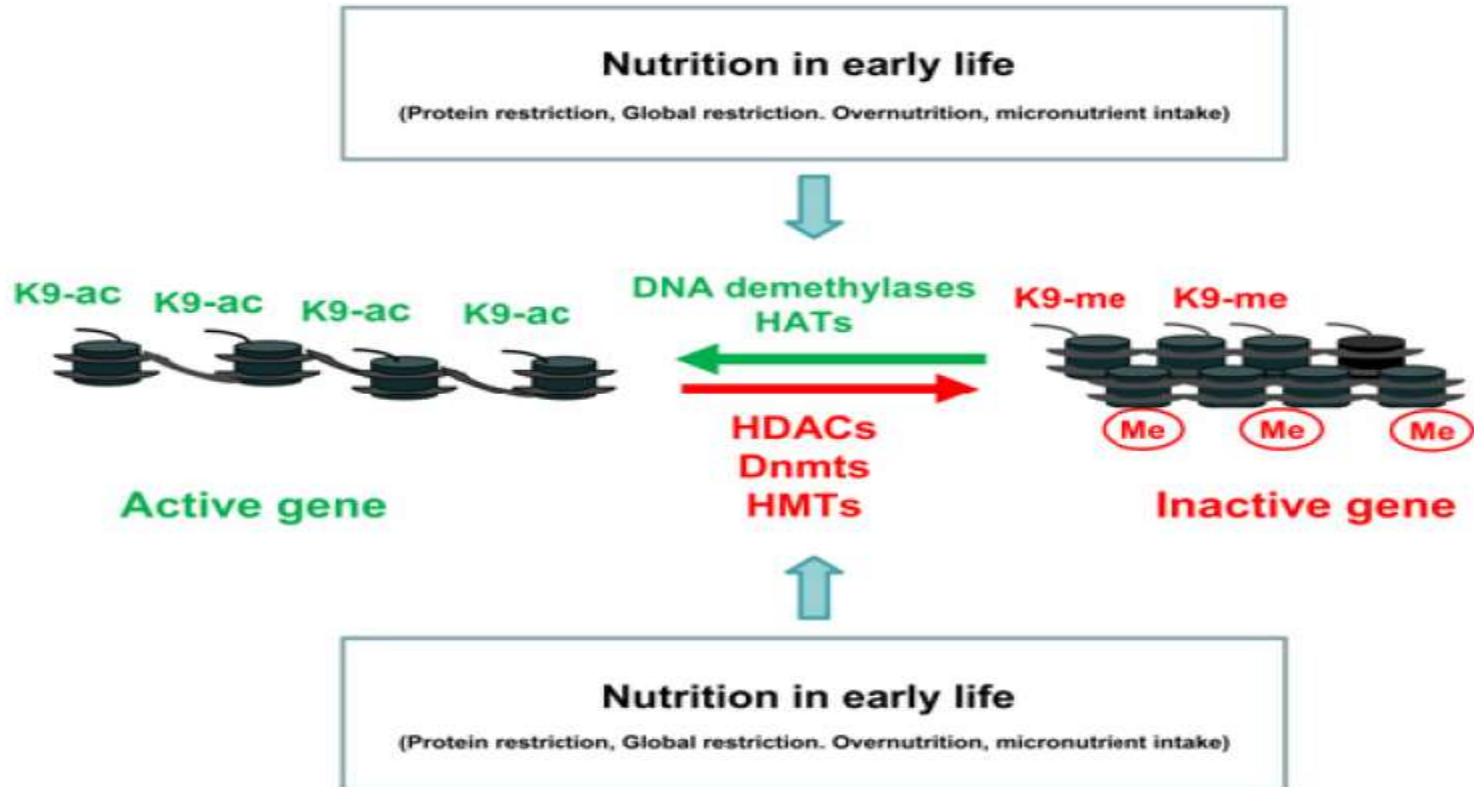
Above all, do not lose your desire to walk. Everyday, I walk myself into a state of well-being & walk away from every illness. I have walked myself into my best thoughts, and I know of no thought so burdensome that one cannot walk away from it. But by sitting still, & the more one sits still, the closer one comes to feeling ill. Thus if one just keeps on walking, everything will be all right. Søren Kierkegaard



# Metabolic Syndrome – Global Health Epidemic Caused by Physical Inactivity and Poor Diet



# Epigenetic Changes Mediated by Nutrition



# Nutrition Studies – What Are We To Believe?

Focus should be on nutrition and not just calories.



Need to feed self and also provide nutrients for gut microbiota - fiber



# Defining Powerhouse Fruits and Vegetables: A Nutrient Density Approach

Jennifer Di Noia, PhD



Centers for Disease Control and Prevention

CDC 24/7: Saving Lives. Protecting People.™

**PREVENTING CHRONIC DISEASE**

PUBLIC HEALTH RESEARCH, PRACTICE, AND POLICY

## Abstract

National nutrition guidelines emphasize consumption of powerhouse fruits and vegetables (PFV), foods most strongly associated with reduced chronic disease risk; yet efforts to define PFV are lacking. This study developed and validated a classification scheme defining PFV as foods providing, on average, 10% or more daily value per 100 kcal of 17 qualifying nutrients. Of 47 foods studied, 41 satisfied the powerhouse criterion and were more nutrient-dense than were non-PFV, providing preliminary evidence of the validity of the classification scheme. The proposed classification scheme is offered as a tool for nutrition education and dietary guidance.

## Objective

Powerhouse fruits and vegetables (PFV), foods most strongly associated with reduced chronic disease risk, are described as green leafy, yellow/orange, citrus, and cruciferous items, but a clear definition of PFV is lacking (1). Defining PFV on the basis of nutrient and phytochemical constituents is suggested (1). However, uniform data on food phytochemicals and corresponding intake recommendations are lacking (2). This article describes a classification scheme defining PFV on the basis of 17 nutrients of public health importance per the Food and Agriculture Organization of the United Nations and Institute of Medicine (ie, potassium, fiber, protein, calcium, iron, thiamin, riboflavin, niacin, folate, zinc, and vitamins A, B<sub>6</sub>, B<sub>12</sub>, C, D, E, and K) (3).

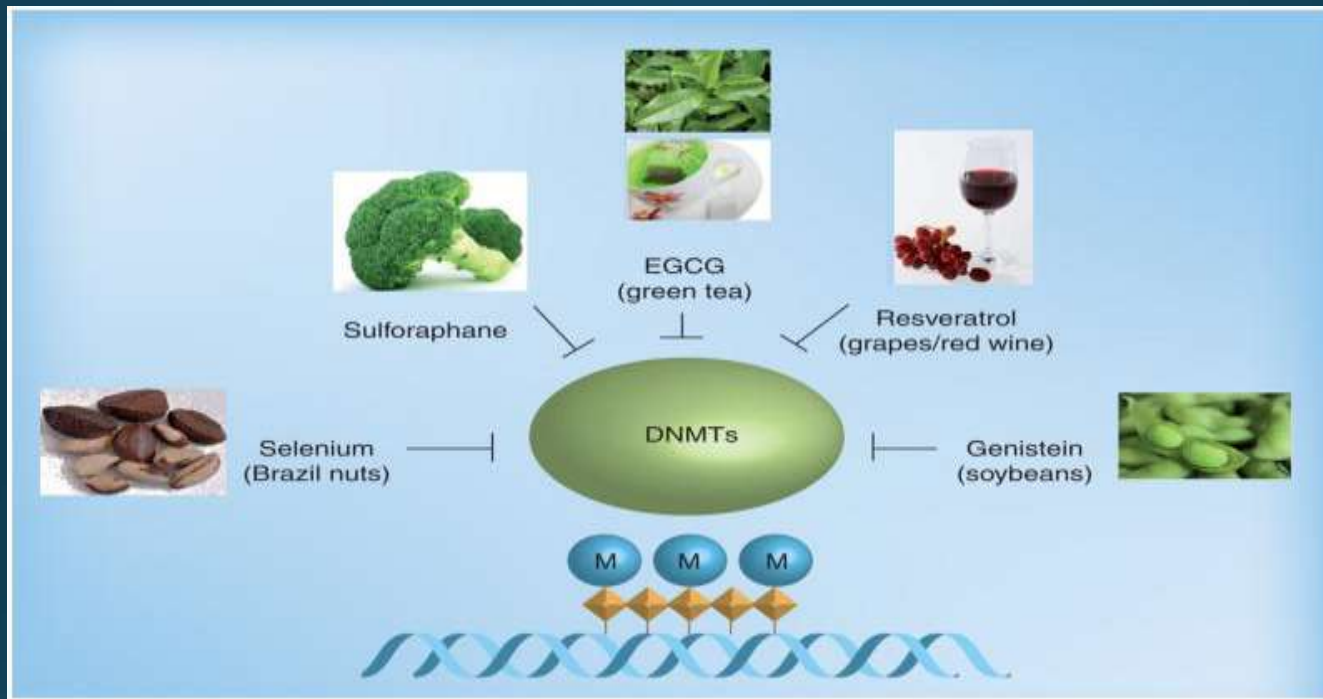
# Epigenetic diet: impact on the epigenome and cancer

Tabitha M Hardy<sup>1</sup> and Trygve O Tollefsbol<sup>1,2,3,4,5,†</sup>

*Epigenomics*. 2011 August 1; 3(4): 503–518. doi:10.2217/epi.11.71.

## Epigenetic diet compounds

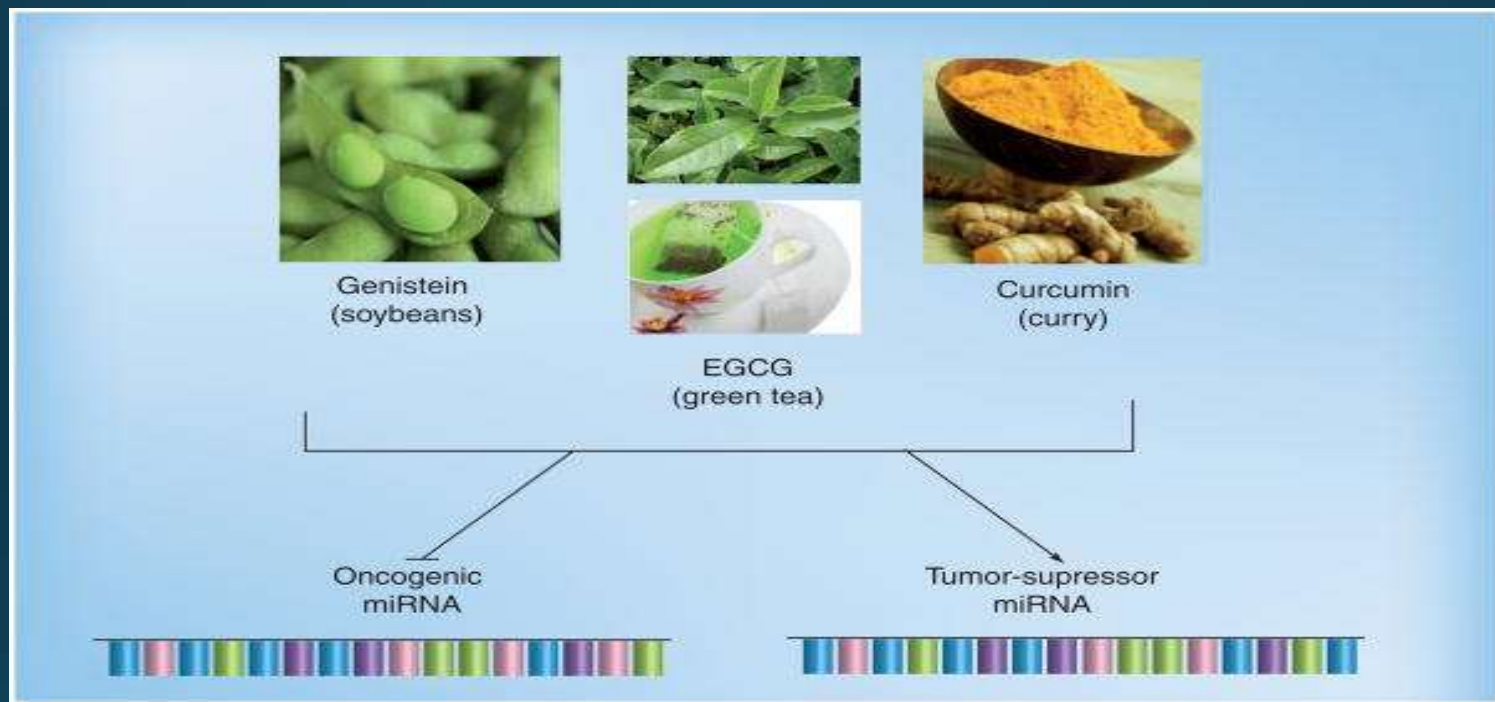
- Dietary polyphenols such as tea polyphenols (i.e., epicatechin, epicatechin-3-gallate, epigallocatechin and epigallocatechin-3-gallate), resveratrol and curcumin can inhibit DNA methyltransferases and act as histone modifiers and demonstrate potential as anticancer therapeutic as well as chemopreventive agents.
- Isoflavones such as genistein are found in soybeans, fava beans and kudzu and have been demonstrated to have anticancer properties that, in part, involve DNA methylation.
- Isothiocyanates including sulforaphane are known to affect the epigenome and to have anticancer properties and act as a histone deacetylase inhibitor.
- Other dietary factors including those found in Brazilian nuts, chicken, cereals, coffee, cashews, garlic, parsley, milk thistle and rosemary, have also been reported to have epigenetic targets in cancer. While most natural dietary products have shown beneficial effects on the epigenome, some dietary components (i.e., alcohol) are associated with harmful epigenetic modifications.



**Figure 1. Dietary inhibitors of DNA methyltransferases**

DNMTs catalyze DNA methylation by adding a methyl group (CH<sub>3</sub>; indicated by M) to cytosines of CpG dinucleotides (diamond shapes). Hypermethylation of CpG dinucleotides or CpG islands by DNMTs usually results in transcriptional gene silencing and gene inactivation. Several bioactive compounds found in foods (e.g., EGCG in green tea) act as dietary inhibitors of DNA methyltransferases and also alter gene expression via epigenetic mechanisms.

DNMTs: DNA methyltransferases; EGCG: Epigallocatechin-3-gallate; M: Methylation.

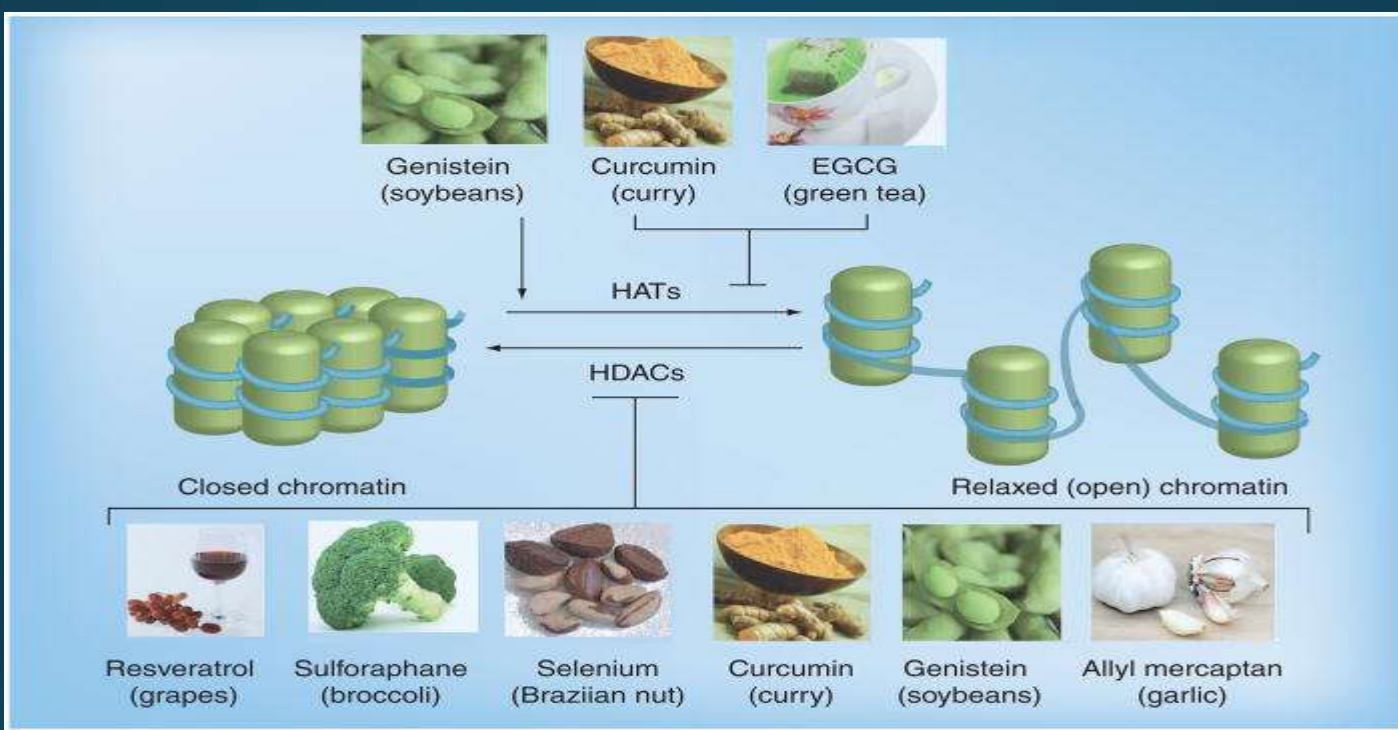


**Figure 2. Dietary effectors of miRNAs**

miRNAs serve as regulators of gene expression. Evidence has been reported supporting the fact that dietary agents target the miRNA of oncogenes and/or tumor suppressors and impact the expression level of miRNAs.

EGCG: Epigallocatechin-3-gallate.





### Figure 3. Dietary modifiers of histones

Bioactive compounds including resveratrol, sulforaphane and curcumin have the ability to alter (indicated by cylinders) HATs as well as HDACs. These histone modifications cause conformational changes in chromatin structure that lead to changes in DNA accessibility. HATs induce a relaxed chromatin state allowing transcriptional factors access to DNA (blue cords) and activate gene expression whereas chromatin in its closed state is indicative of gene silencing and repression. Dietary compounds can inhibit and/or enhance (arrow) HATs and HDACs thereby altering gene expression.

# The Effect of Chromosome 9p21 Variants on Cardiovascular Disease May Be Modified by Dietary Intake: Evidence from a Case/Control and a Prospective Study

Ron Do<sup>1</sup>, Changchun Xie<sup>2,3</sup>, Xiaohe Zhang<sup>2</sup>, Satu Männistö<sup>4</sup>, Kennet Harald<sup>4</sup>, Shofiqul Islam<sup>2,3</sup>, Swneke D. Bailey<sup>1</sup>, Sumathy Rangarajan<sup>2</sup>, Matthew J. McQueen<sup>2</sup>, Rafael Diaz<sup>5</sup>, Liu Lisheng<sup>6</sup>, Xingyu Wang<sup>7</sup>, Kaisa Silander<sup>4,8</sup>, Leena Peltonen<sup>4,8†</sup>, Salim Yusuf<sup>2</sup>, Veikko Salomaa<sup>4</sup>, James C. Engert<sup>1,9,10\*</sup>, Sonia S. Anand<sup>2,3\*</sup>, on behalf of the INTERHEART investigators

## Abstract

**Background:** One of the most robust genetic associations for cardiovascular disease (CVD) is the Chromosome 9p21 region. However, the interaction of this locus with environmental factors has not been extensively explored. We investigated the association of 9p21 with myocardial infarction (MI) in individuals of different ethnicities, and tested for an interaction with environmental factors.

**Methods and Findings:** We genotyped four 9p21 SNPs in 8,114 individuals from the global INTERHEART study. All four variants were associated with MI, with odds ratios (ORs) of 1.18 to 1.20 ( $1.85 \times 10^{-8} \leq p \leq 5.21 \times 10^{-7}$ ). A significant interaction ( $p = 4.0 \times 10^{-4}$ ) was observed between rs2383206 and a factor-analysis-derived "prudent" diet pattern score, for which a major component was raw vegetables. An effect of 9p21 on MI was observed in the group with a low prudent diet score (OR = 1.32,  $p = 6.82 \times 10^{-7}$ ), but the effect was diminished in a step-wise fashion in the medium (OR = 1.17,  $p = 4.9 \times 10^{-3}$ ) and high prudent diet scoring groups (OR = 1.02,  $p = 0.68$ ) ( $p = 0.014$  for difference). We also analyzed data from 19,129 individuals (including 1,014 incident cases of CVD) from the prospective FINRISK study, which used a closely related dietary variable. In this analysis, the 9p21 risk allele demonstrated a larger effect on CVD risk in the groups with diets low or average for fresh vegetables, fruits, and berries (hazard ratio [HR] = 1.22,  $p = 3.0 \times 10^{-4}$ , and HR = 1.35,  $p = 4.1 \times 10^{-3}$ , respectively) compared to the group with high consumption of these foods (HR = 0.96,  $p = 0.73$ ) ( $p = 0.0011$  for difference). The combination of the least prudent diet and two copies of the risk allele was associated with a 2-fold increase in risk for MI (OR = 1.98,  $p = 2.11 \times 10^{-9}$ ) in the INTERHEART study and a 1.66-fold increase in risk for CVD in the FINRISK study (HR = 1.66,  $p = 0.0026$ ).

**Conclusions:** The risk of MI and CVD conferred by Chromosome 9p21 SNPs appears to be modified by a prudent diet high in raw vegetables and fruits.



# A Need for Better Treatments

- Need for novel Migraine – TMD – TN treatments
- Many currently used drugs exhibit adverse side effects
- Few FDA approved effective pharmacological treatments
- Most drugs used do not target underlying neuron-glia inflammatory cycle
  
- FDA Approved Drugs
  - Many patients don't respond to these drugs and other common therapies
- Many patients have turned to alternative medicine because their prescription medications are not effective
  
- Any compound that inhibits sensitization of trigeminal nociceptive neurons may be useful in managing TN - TMD – Migraine Pathology



# “Let Food Be Thy Medicine” Hippocrates





Dietary Cocoa and Grape Seed Extract Increase  
Expression of Phosphatases and Repress Kinases  
Inhibition of Peripheral and Central Sensitization

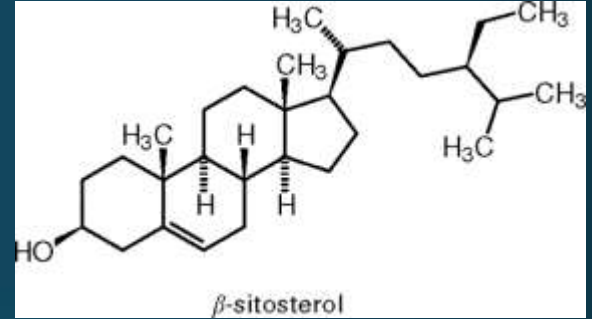
# *Theobroma cacao* (Cocoa)

- Possible treatment for variety of diseases
  - Insulin insensitivity, cardiovascular disease, and inflammation
- Data from *in vitro* studies from our lab show cocoa blocks activation of trigeminal neurons
  - Abbey et al., 2008
  - J Ethnopharmacol, 115:238-248
- Data from *in vivo* studies demonstrate that Cocoa can increase phosphatases and inhibit inflammatory proteins; inhibit neurogenic inflammatory pain in rats
  - Cady and Durham, 2010
  - Brain Research, 1323: 18-32
  
  - Bowmen et al, 2017 (Neubert)
  - Orthod Craniofac Res. 2017



# Active Compound – $\beta$ -Sitosterol

- Common plant phytosterol
- Found in pumpkin seeds, wheat germ, soybeans, corn oils, rice bran
- Increased basal expression of MKP-1 and IL-10
- $\beta$ -sitosterol has the similar cellular effects as dexamethasone
- Thus, adding a natural product to the diet could have the same health benefits as a prescription drug





# Dietary Grape Seed Extract Represses Neuronal Sensitization

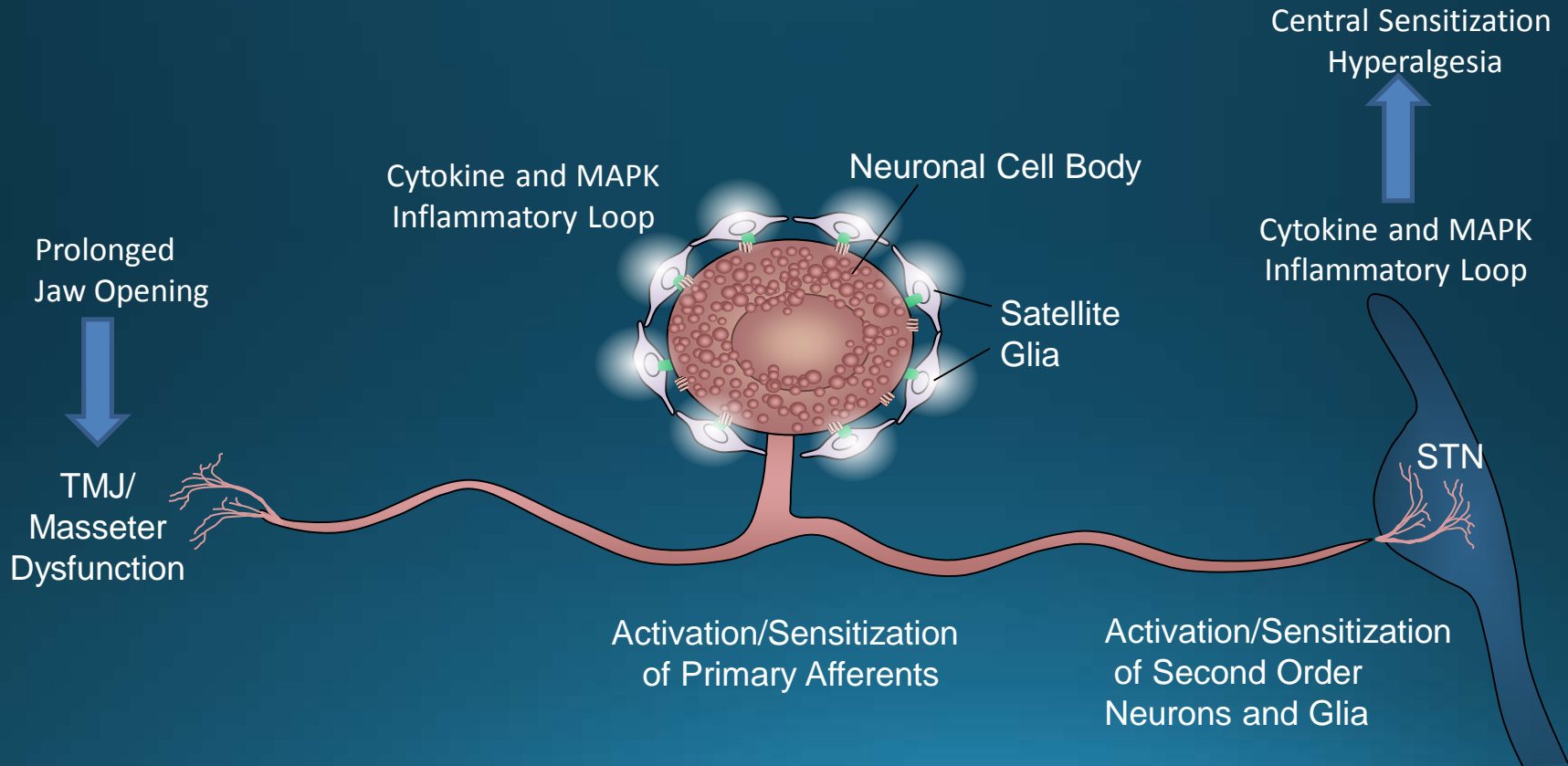
- Dietary Grape Seed Polyphenols Repress Neuron and Glia Activation in Trigeminal Ganglion and Trigeminal Nucleus Caudalis
- *Cady et al., Molecular Pain 2010*



Dietary Grape Seed Extract  
Enriched Chicken Bone Broth (AAC1)

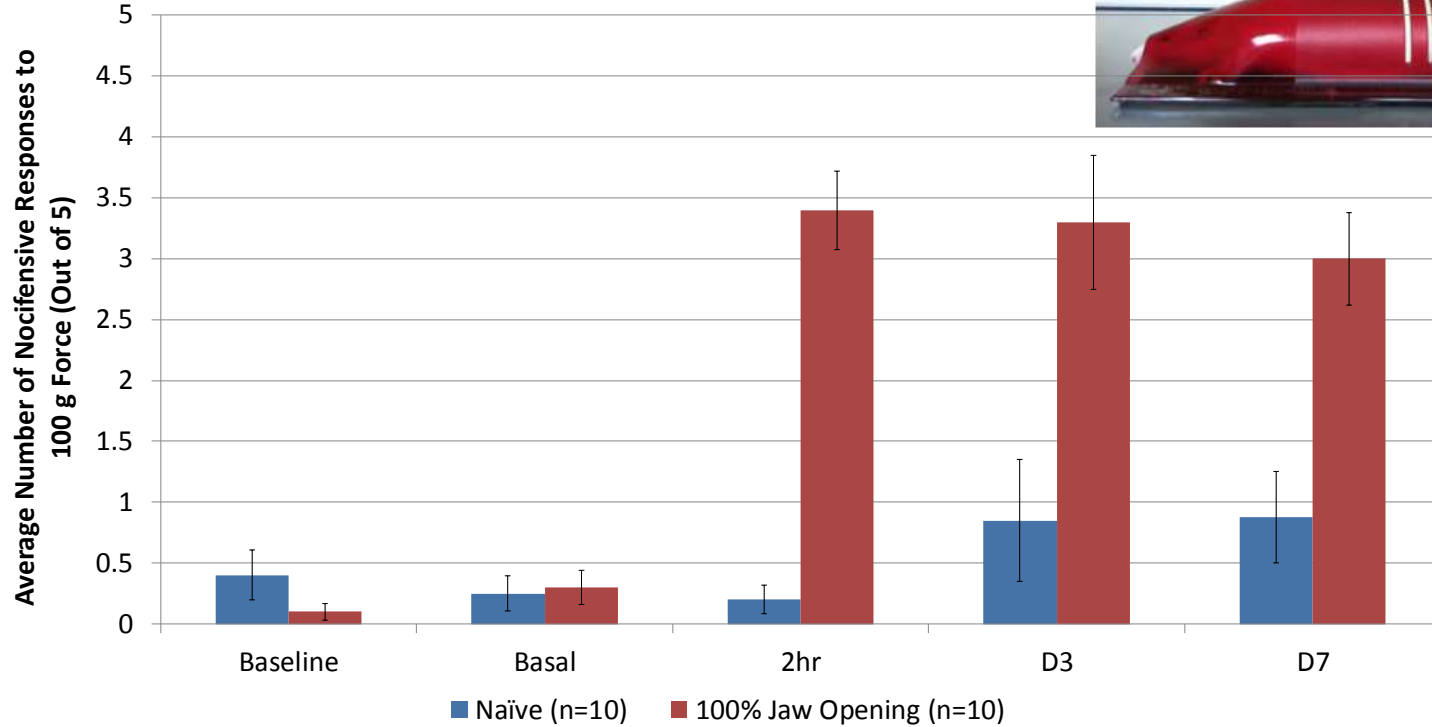
Repress Nocifensive Responses  
Following Prolonged Jaw Opening

# TMD Pathology Involves Activation of Trigeminal System

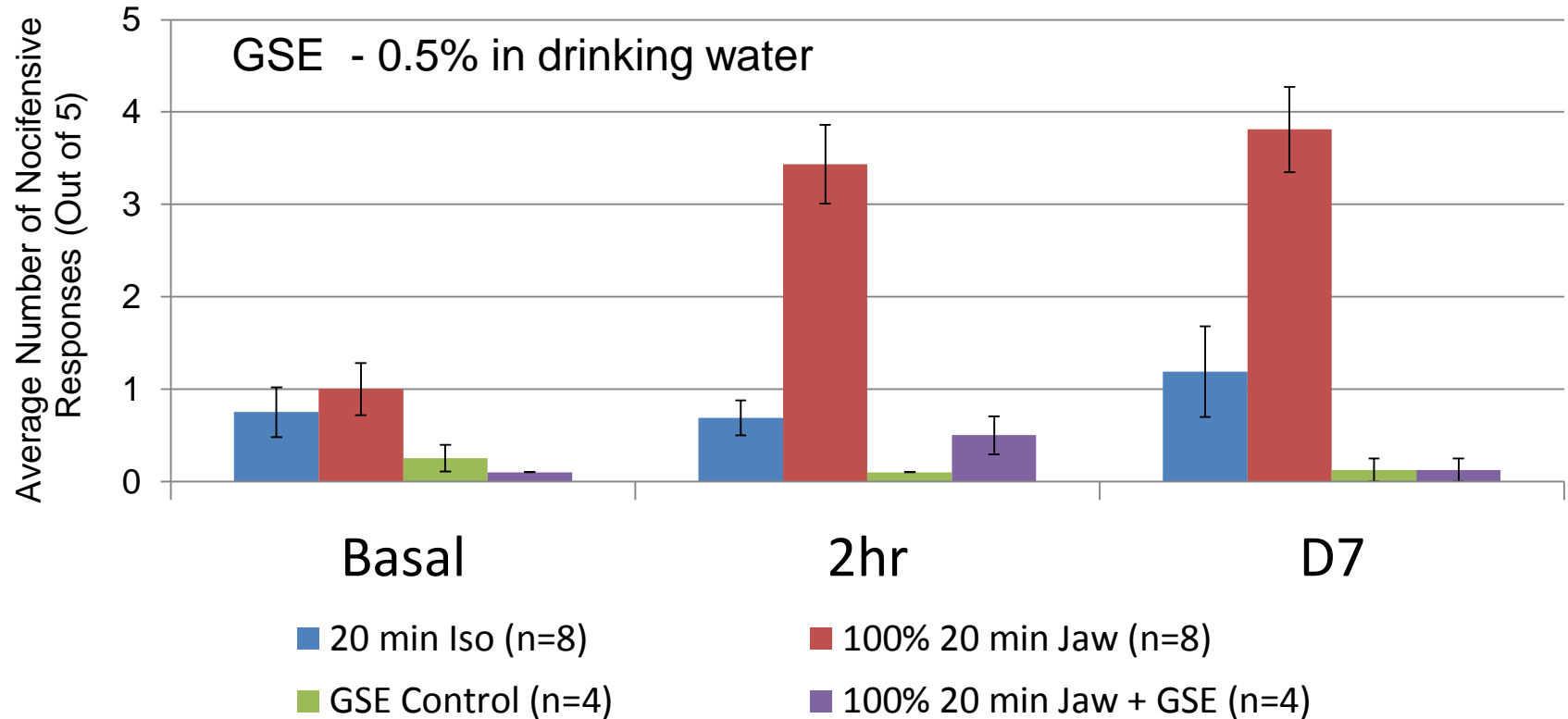




# Protracted Jaw Opening Results in a Prolonged Increase in Nocifensive Head Withdrawal Responses to Mechanical Stimulation of V3 Region



# Dietary Grape Seed Extract Represses Nocifensive Responses Following Prolonged Jaw Opening



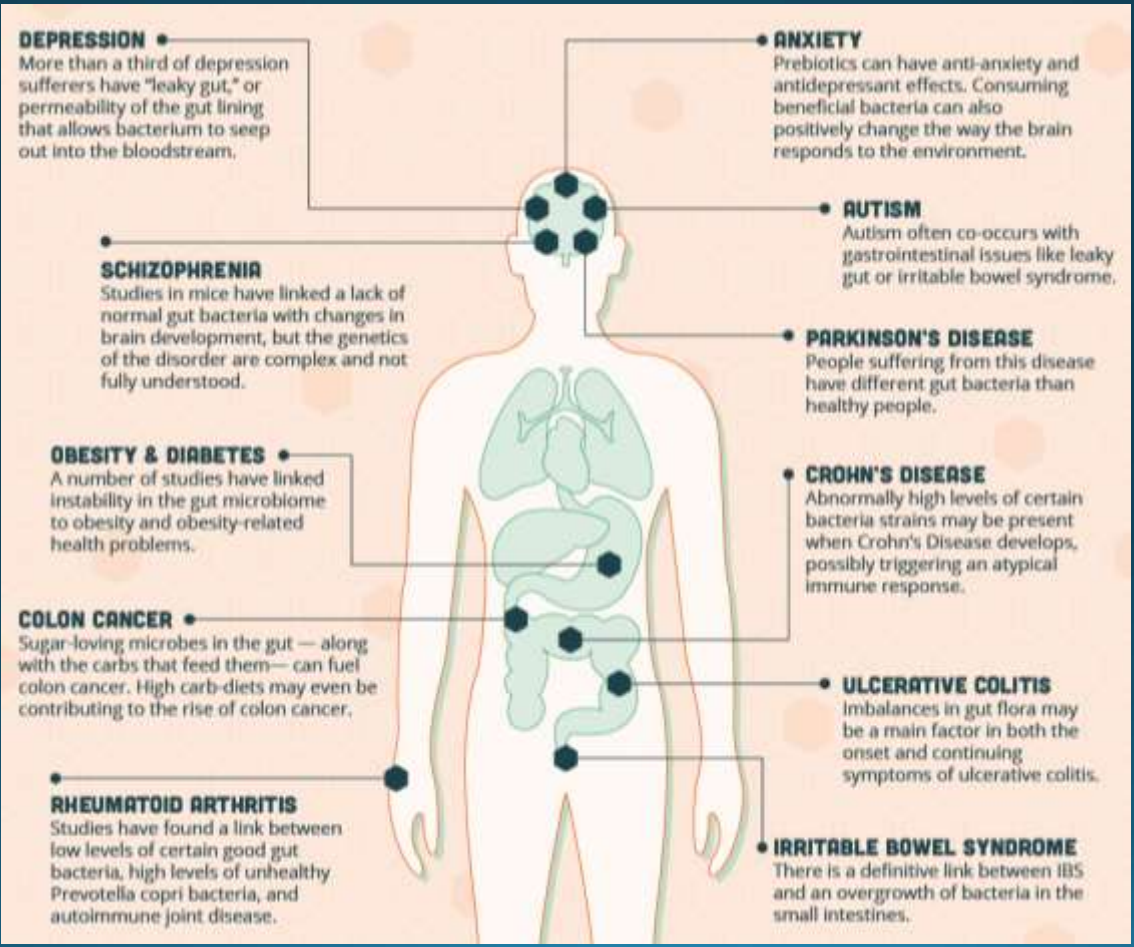


# Commensal Bacteria Can Affect the Epigenetic Modification of Host Genes

1. An overwhelming 100 trillion commensal bacteria live within the human gastrointestinal tract - >400 species
2. In addition to diet, pollution, and infections, the intestinal microbiota are another factor affecting epigenetic gene modification
3. Maintenance of the symbiosis between the intestinal immune system and the commensals is required for intestinal homeostasis
4. Disorders in this system lead to increased risk of onset or aggravated symptoms of various diseases, including allergy, inflammatory bowel disease, autoimmune disease, and metabolic syndrome
5. Many of these conditions involve excessive inflammation, indicating that regulation of inflammation is indispensable for the maintenance of the intestinal symbiotic system

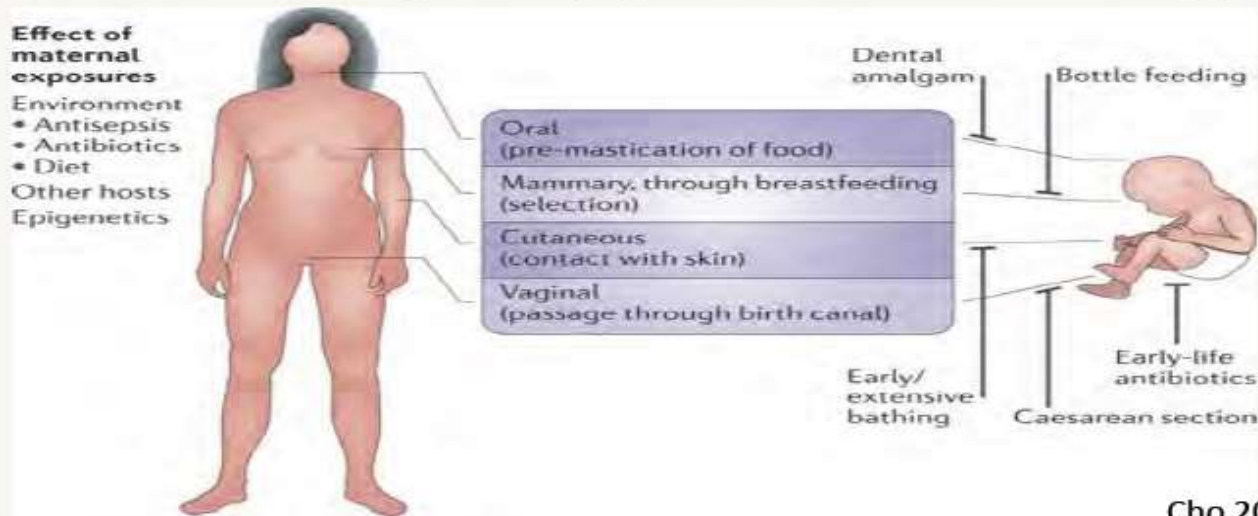


# Diseases Linked with Gut Microbiome Imbalance

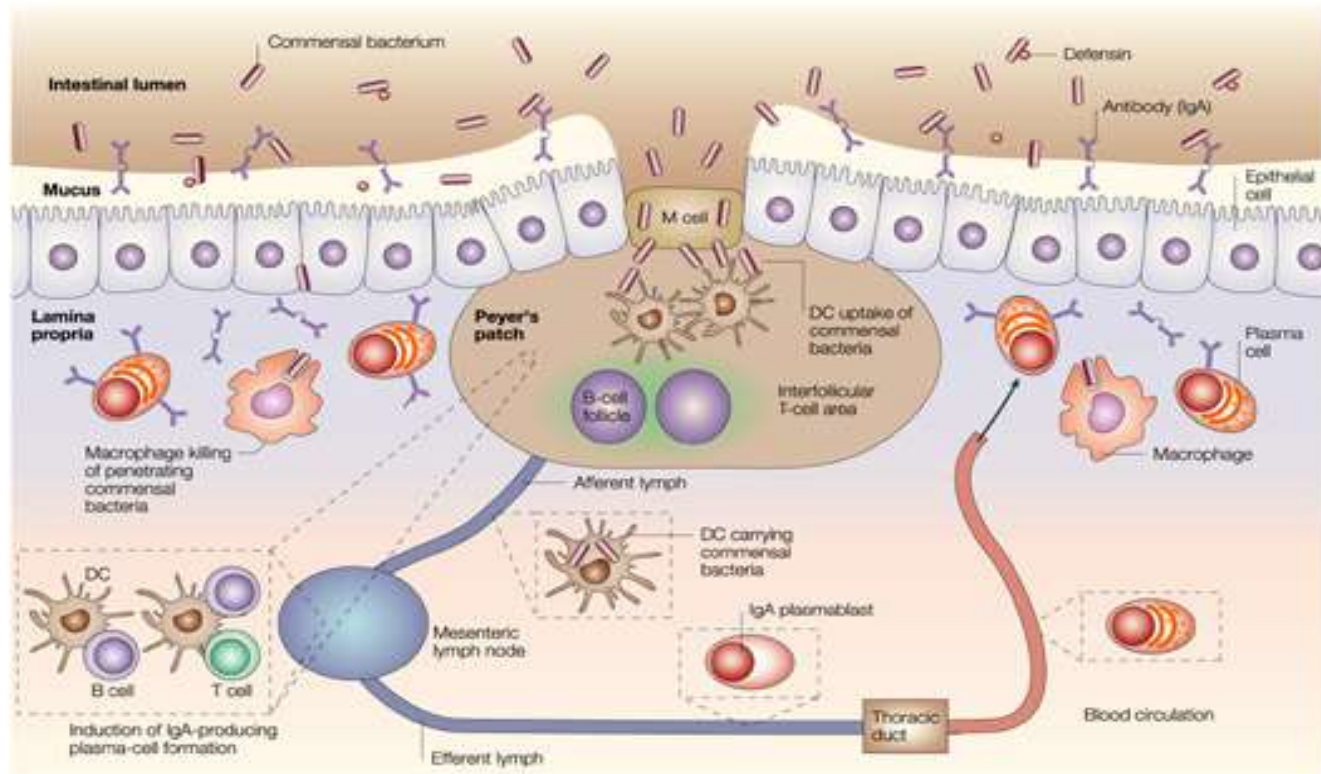


# How Do We Acquire Our Microbiome?

- Different for C section vs. vaginal birth
- Initial colonization can be rapidly altered by diet, disease etc.
- Early microbiome programming influences HPA responsiveness
- Evolves to relative stability in adults, declines in elderly
- Evolves over lifespan like population succession in ecology



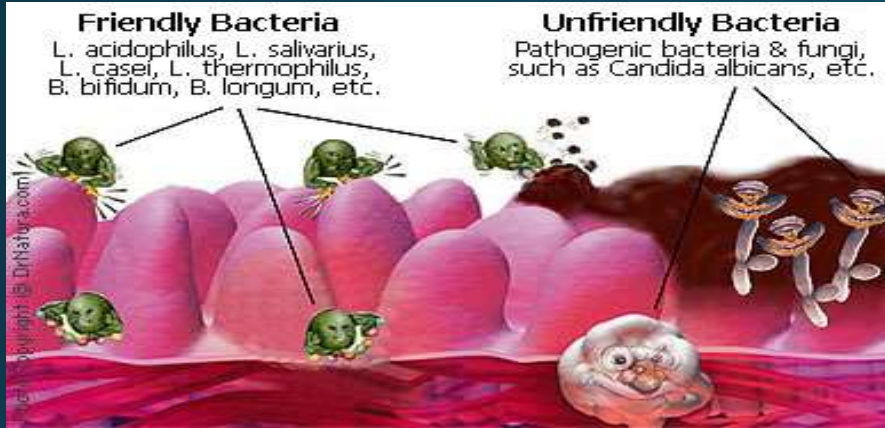
# Commensal Bacteria and Your Immune System



Nature Reviews | Immunology



# Maintaining Your Commensal Bacteria – Key to Good Health



Thus, commensal bacteria play a novel role in the regulation of intestinal inflammation through their effect on epigenetic modification of the host gene, thereby providing a mechanism for the maintenance of the intestinal symbiotic system

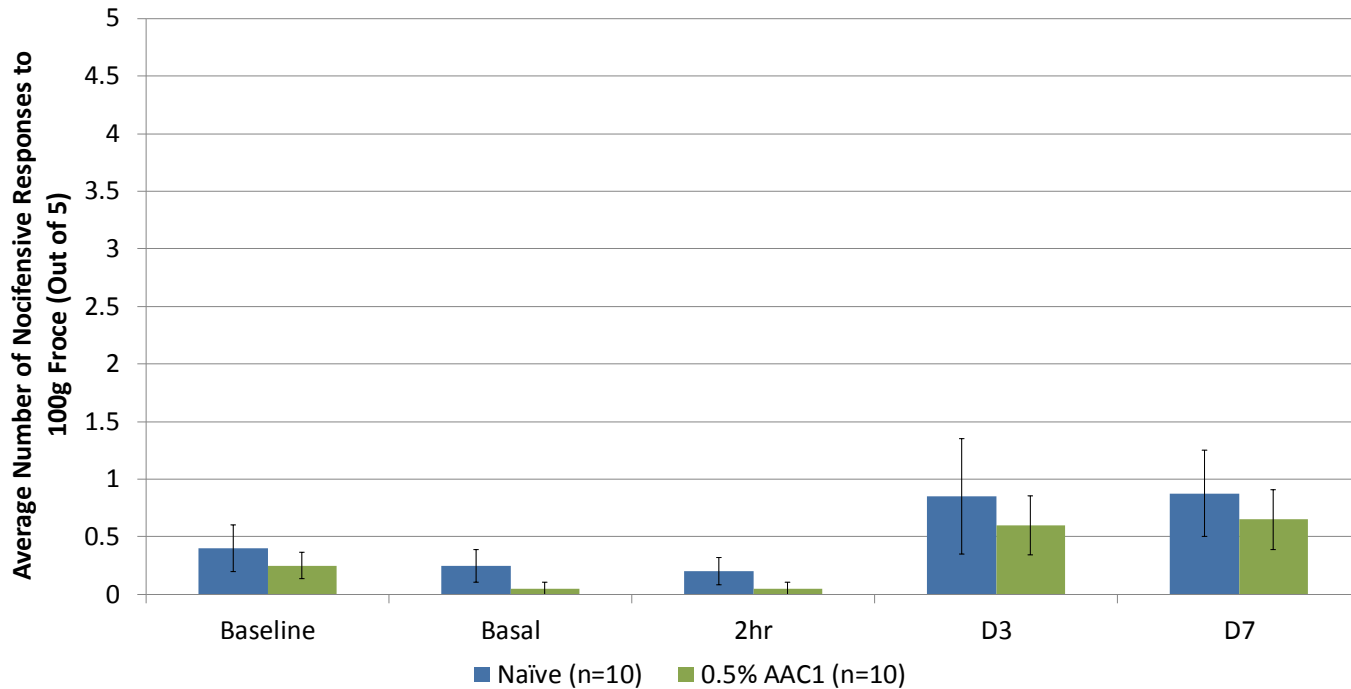
# Chicken Broth AAC1 as a Dietary Supplement Suppresses Nocifensive Behaviors and PKA Expression Caused by Prolonged Jaw Opening

Hawkins, Durham. J Oral Facial Pain Headache 2018

- ❖ Administration of AAC1 for 14 days was able to suppress mechanical nocifensive hypersensitivity at 2 hours, 3 days, and 7 days post jaw opening.
- ❖ Importantly, AAC1 inhibited elevated PKA expression induced by prolonged jaw opening at 7 days, a time point that correlated with nocifensive behavioral responses.
- ❖ Taken together, our results demonstrate that prolonged jaw opening promotes persistent trigeminal sensitization to mechanical stimuli that can be suppressed by dietary modifications. Thus, the use of AAC1 chicken broth and GSE may provide a novel way to treat TMD and other inflammatory joint conditions.

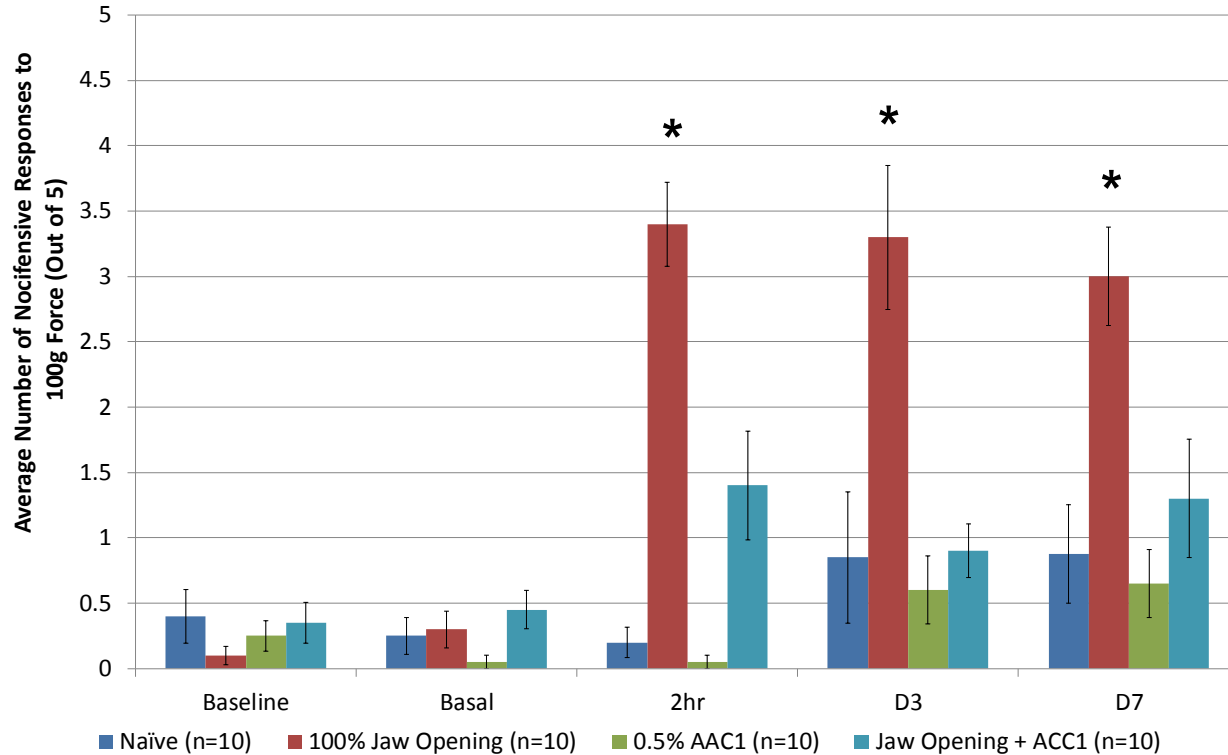


# Inclusion of Chicken Broth AAC1 Did Not Change Nocifensive Responses in Control Animals

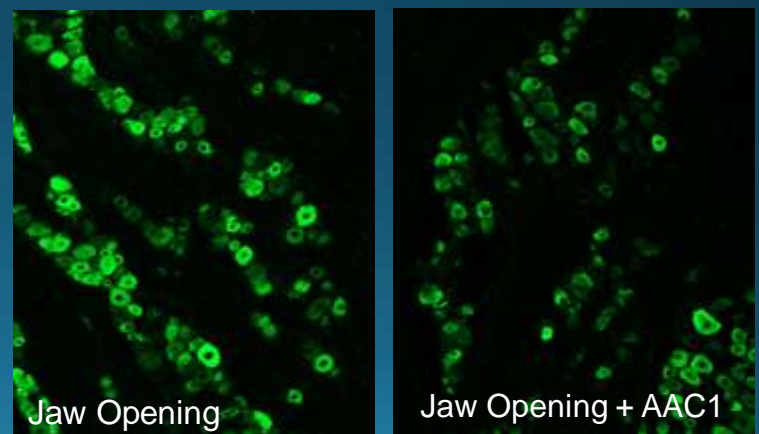
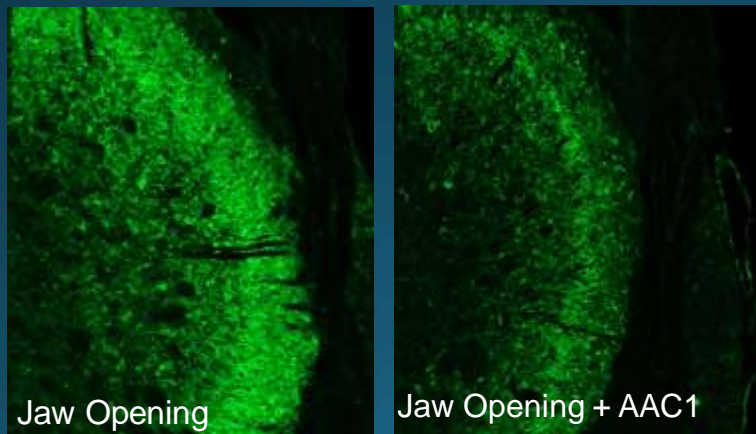
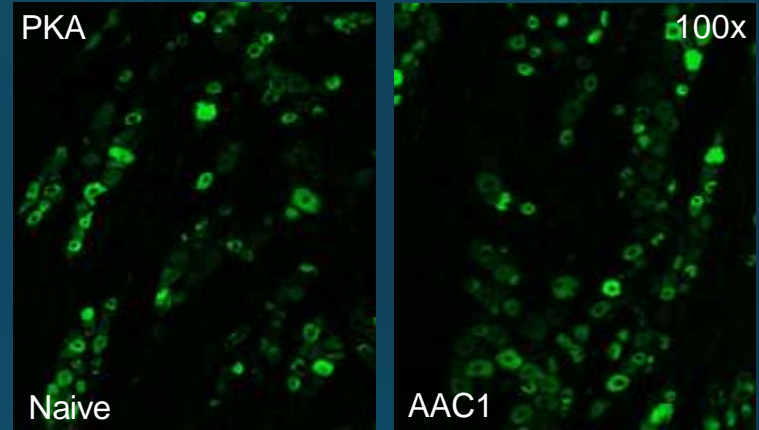
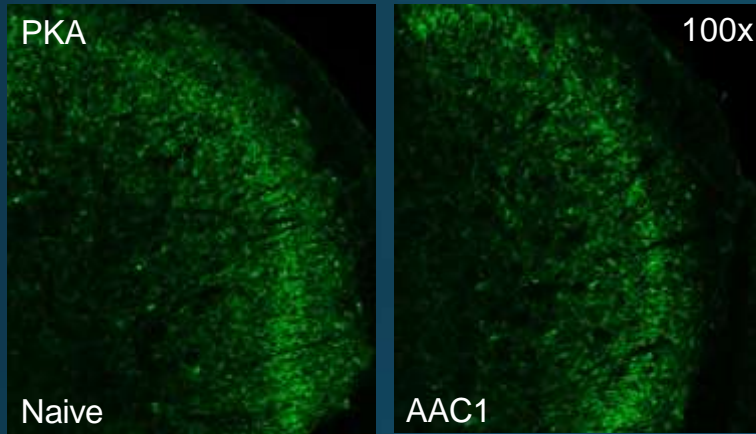




# Dietary AAC1 Represses Nocifensive Responses Following Protracted Jaw Opening



# Dietary AAC1 Inhibits Increased PKA Expression in the Upper Spinal Cord and Trigeminal Ganglion Following Prolonged Jaw Opening



# Bioactive Epigenetic Diet Compounds

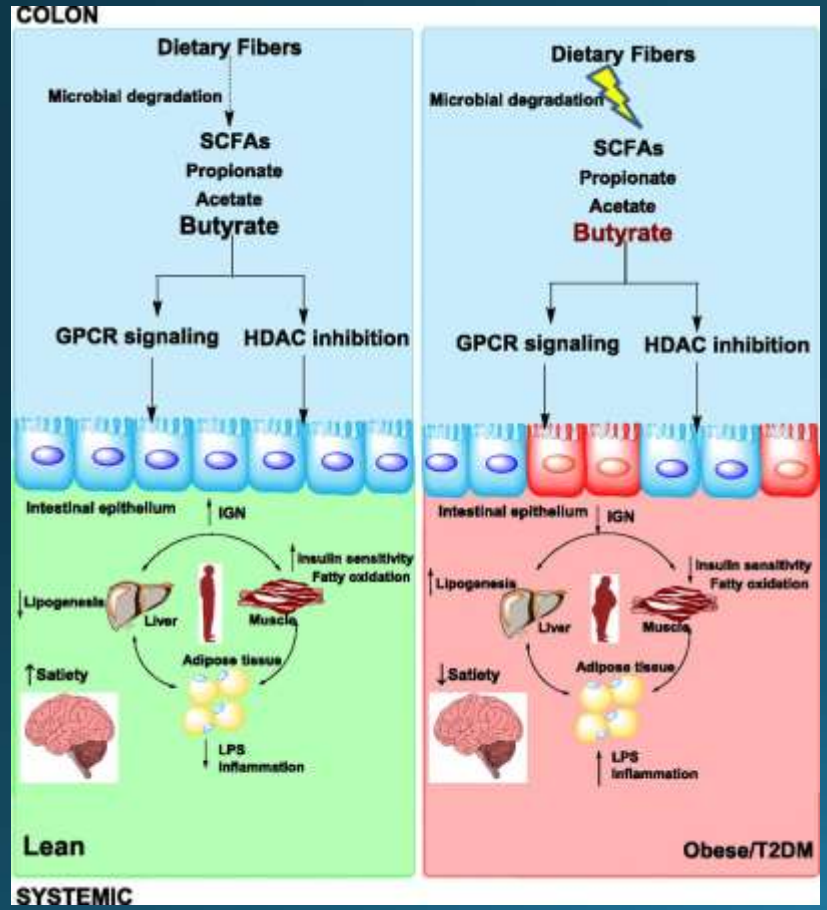
**Table 1**

Bioactive epigenetic diet compounds, food sources and epigenetic functions.

Epigenetic diet compounds	Food sources	Epigenetic functions
EC, ECG, EGC and EGCG	Green tea	DNMT and HAT inhibitor, modulates miRNA
Resveratrol	Grapes, peanuts, mulberries, cranberries, blueberries	DNMT and HDAC inhibitor
Curcumin	Tumeric, curry	DNMT inhibitor and miRNA modulator
Genistein	Soybeans, fava beans	DNMT and HDAC inhibitor, enhances HATs, modulates miRNA
Isothiocyanates, sulforaphane	Broccoli, cabbage, kale, watercress	DNMT and HDAC inhibitor
Selenium	Brazilian nuts, chicken, game meat, beef	DNMT and HDAC inhibitor
Allyl mercaptan, organosulfur compounds	Garlic	HDAC inhibitor
Folate	Beans, grains, fortified breakfast cereals, pastas, green vegetables	Deficiencies alter DNA methylation patterns
Alcohol	Alcoholic beverages	High consumption increases promoter hypermethylation

DNMT: DNA methyltransferase; EC: Epicatechin; ECG: Epicatechin-3-gallate; EGC: Epigallocatechin; EGCG: Epigallocatechin-3-gallate; HAT: Histone acetyltransferase; HDAC: Histone deacetylase.

# Dietary Fibers - Food for the Gut Microbiota



<https://www.naturalfoodseries.com/21-best-foods-gut-health/>