



# THE 10 KEY BIOMARKERS OF A HEALTHY BRAIN



## HOW DOES YOUR BODY HEALTH RELATE TO YOUR BRAIN HEALTH?

Our bodies provide the essential nutrients our brains need. When our body systems are working well, they support the creation of more neurons and stronger connections between them. People with strongly connected brains feel happier, calmer, sharper and more energetic.

If you want to know if your body is healthy enough for your brain, you can check 10 key biomarkers through routine blood tests. These biomarkers measure your nutrient levels, circulatory, metabolic and digestive health. If you can get your biomarkers on target, you can support your mood, wit, and energy levels today as well as your brain health in the long run.

The brain is the final frontier of medicine. We are still learning a lot about how to improve brain health and function. Today, you can take matters into your own hands by discussing the following tests with your doctor.



# BIOMAKERS OF NUTRITION



Vitamin B12, RBC Magnesium and Omega 3 Index are three key biomarkers of nutrition.

## 1. VITAMIN B12

### WHAT IS THE VITAMIN B12 LEVEL BIOMARKER?

Vitamin B12 level is a blood test that measures your levels of cobalamin, or Vitamin B12.

### WHY IS VITAMIN B12 IMPORTANT?

Vitamin B12 helps the body convert food into neurotransmitters. When we get enough B12, our bodies and brains can make enough dopamine, norepinephrine and serotonin, which are the neurotransmitter chemicals that help us make brain connections. When our brain connections are strong, we feel energetic, happy and smart.

Having the right amount of B12 is so important that it can help reduce age-related brain shrinkage.<sup>1</sup>

### WHO IS TYPICALLY LOW ON B12?

According to traditional medical guidelines, about 20% of adults are low on B12.<sup>2</sup> According to newer neuroscientific guidelines, up to 40% of people may have low B12 levels. It is also possible to have normal levels of B12 intake, but inadequate absorption or conversion of B12 into neurotransmitters.<sup>3</sup>

People who follow a vegan diet or take common reflux medications, such as antacids or proton pump inhibitors like “the purple pill”, are more likely to be B12 deficient.

### WHAT IS A BRAIN-HEALTHY B12 LEVEL?

A level of 400 ng/mL is required for the nerves and the brain. To maintain your B12 levels, the recommended dietary allowance of Vitamin B12 is 2.4 mcg per day.

### WHAT ARE THE BEST SOURCES OF VITAMIN B12?

The best sources of B12 come from eggs, dairy and meat.

At Honeybrains, we make sure to use foods high in B12 across our menu, to help you get to your target. You can check the B12 levels of individual dishes by consulting our Honeybrains Food Periodic Table.

### WHAT TYPES OF SUPPLEMENTS ARE AVAILABLE?

Two types of B12 supplements are generally available. The first is regular B12. The second is called “methylated B12.” People who have a variation of a gene known as MTHFR may need to supplement with methylated B12 (see MTHFR test below). You can supplement with methylated B12 daily by using the HB Healthy Brain supplement, which works for people with and without the MTHFR gene and contains other essential brain nutrients.

*Worth mentioning: Doctor are typically taught in medical school that a level of 200 ng/mL is enough for the body. If you had your B12 level checked and were told it was “normal,” you can check again to be sure it was at least 400 ng/mL, which is the new normal for your brain.*

## 2. RED BLOOD CELL (“RBC”) MAGNESIUM

### WHAT IS THE RBC MAGNESIUM BIOMARKER?

The RBC magnesium biomarker is a blood test that measures how much of the mineral magnesium is inside your cells. When the body has enough magnesium, almost all organ systems, including the brain, benefit.<sup>4</sup>

Magnesium is an essential mineral that we need for every metabolic process in the body and brain. The ability to measure red blood cell magnesium levels at the cellular level is a new technology. Most doctors don't routinely test for it.

### WHO IS TYPICALLY LOW ON MAGNESIUM?

Around half of the U.S. population consumes less than the recommended amount of magnesium.<sup>5</sup> We used to get enough magnesium from our food. Today, many of our industrially-farmed soils have lower levels of this essential nutrient, so we aren't getting enough from the regular food we eat. Anybody who gets regular belly aches or headaches may be particularly susceptible to low magnesium levels.<sup>6</sup>

### WHAT IS A BRAIN-HEALTHY RBC MAGNESIUM LEVEL?

Your target for a brain-healthy RBC Magnesium level is at least 4.3 mg/dL. To maintain a brain-healthy level, you need to get approximately 400mg of magnesium per day.

### WHAT ARE THE BEST SOURCES OF MAGNESIUM?

Nuts and seeds provide good sources of magnesium.

At Honeybrains, we use nuts and seeds extensively to ensure that sufficient magnesium, along with other essential brain nutrients, are in what we serve.

### WHAT TYPES OF SUPPLEMENTS ARE AVAILABLE?

Magnesium supplements come in the form of magnesium oxide, magnesium citrate or magnesium glycinate. Any of these can be effective in restoring magnesium levels as long as they get you to your target biomarker level.

You can also help ensure that you get enough magnesium daily by using the HB Healthy Brain or HB Headache Therapy supplements.

*Worth mentioning: Kids with ADHD tend to have lower levels of magnesium in their blood.<sup>7</sup> Supplementing with magnesium may be a natural way to improve behavior and focus.<sup>8</sup>*



## 3. OMEGA 3 INDEX

### WHAT IS THE OMEGA 3 INDEX BIOMARKER?

The Omega 3 Index biomarker measures how much DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid) Omega 3 healthy fats are in the red blood cell membranes. People who maintain higher levels of Omega 3 in their body tend to have a healthier brain, for life.<sup>9</sup> The amount of Omega 3 in your blood cells depends on your diet and your genes.

### WHO IS TYPICALLY LOW ON OMEGA 3 INDEX?

Most adults in the U.S., but especially women and children, get less than half of the Omega 3 daily target in their diet.<sup>10</sup>

### WHAT IS A BRAIN-HEALTHY OMEGA 3 INDEX?

Your target for a brain-healthy Omega 3 Index level is > 8%. For a brain-healthy Omega 3 level, you need about 250 to 500mg of EPA and/or DHA per day.

### WHAT ARE GOOD SOURCES OF OMEGA 3?

Fatty fish are the best sources of Omega 3 in the diet because they contain both EPA & DHA. Plant sources of Omega 3 provide ALA (Alpha-linolenic acid), which requires conversion by the body into DHA.

Top fatty fish sources of Omega 3 include Herring, Salmon, Sardines, Mackerel, Anchovy, and Caviar. Top plant sources include Walnuts, Chia Seeds, & Flax Seeds.

At Honeybrains, we use salmon, walnuts, chia seeds, flax seeds, and omega 3 free range eggs in many of our dishes, which helps ensure that they contain sufficient Omega 3 healthy fats. You can check the Omega 3 levels of individual dishes by consulting our Honeybrains Food Periodic Table.

### WHAT TYPES OF SUPPLEMENTS ARE AVAILABLE?

There are a number of Omega 3 supplements available on the market, generally in the form of fish oil or fish powder. We also included Omega 3 in the form of fish oil powder in the HB Healthy Brain supplement, for those who do not want to take multiple separate supplements to target a healthy brain.



# BIOMAKERS OF CIRCULATORY HEALTH

*ApoB:ApoA, homocysteine and MTHFR are three key biomarkers of circulatory health. Circulatory health means having smooth, inflammation-free arteries.*

## 4. APOB:APOA

### WHAT IS THE THE APOB:APOA RATIO BIOMARKER?

The ApoB:ApoA ratio biomarker measures the balance of inflammatory vs. non-inflammatory cholesterol particles we carry in our blood. People with optimal ApoB:ApoA ratios tend to have healthier hearts, for life.<sup>11</sup> Healthier hearts create healthier brains.<sup>12</sup> This test gives more information than routine cholesterol level testing.<sup>13</sup>

### WHO TYPICALLY HAS SUBOPTIMAL APOB:APOA RATIOS?

Our genetics, lifestyle and metabolic health determine the ratio of ApoB:ApoA. People who have a genetic risk (strong family history) of heart disease, cholesterol problems or diabetes are likely to have abnormal ApoB:ApoA ratios. Also, people with high intake of processed foods and/or low levels of physical activity are likely to have abnormal ApoB:ApoA levels.

### WHAT IS A BRAIN-HEALTHY APOB:APOA RATIO?

Your target for a brain-healthy ApoB:ApoA ratio is less than 0.6.

### WHAT CAN I DO TO OPTIMIZE MY APOB:APOA RATIO?

Our metabolic health, the amount we exercise, and the types of alcohol, sugars and fats we ingest can affect ApoB:ApoA ratios.<sup>14</sup> Eating more HDL-raising (which is our “good cholesterol”) foods, such as fatty fish, is a delicious way to improve ApoB:ApoA ratios. Eating more herbs and spices can also help; for example, getting more saffron can improve ApoB:ApoA ratios because it can increase the levels of HDL.<sup>15</sup>

Eating more foods high in fiber is also good for ApoB:ApoA ratios because foods high in fiber are good for your metabolism. Top fiber sources include legumes such as peas and beans.

The Honeybrains menu features many types of fatty fish, herbs, spices, and legumes. The HB Power House supplement also may help you optimize your ApoB:ApoA ratio because it contains ingredients that promote metabolic health.

*Worth mentioning: Doctors traditionally check for cholesterol levels in the form of testing LDL (the bad type of cholesterol) and HDL (the good type of cholesterol). If you don't ask for it, your doctor will most likely not check your ApoB:ApoA ratio, which gives you even more information than a routine test.*

## 5. HOMOCYSTEINE

### WHAT IS THE HOMOCYSTEINE BIOMARKER?

The homocysteine biomarker tests the amount of homocysteine, an amino acid, in the blood. Higher than normal levels are harmful to circulation. If someone's homocysteine is elevated, they are at a much higher risk of developing brain shrinkage, stroke, and Alzheimer's Disease.<sup>16</sup> People with low homocysteine can avoid damage to the arteries of the brain that occurs over time with aging.<sup>17</sup>

### WHO TYPICALLY HAS HIGH HOMOCYSTEINE LEVELS?

People who have a history of vitamin B12 deficiency, or any of the risk factors listed above for vitamin B12 deficiency, are at risk for a high homocysteine level. Vitamin B12 is required for homocysteine metabolism so when it gets low, homocysteine goes up.

The following groups of people may have higher homocysteine levels:

Anybody with chronic headaches, chronic fatigue, and/or chronic pain.<sup>18</sup>

Anybody with migraines or a family history of migraines.<sup>19</sup>

Anybody with a family history of stroke or dementia.

Inflammatory conditions such as rheumatoid arthritis or tobacco smoking can increase homocysteine. People with the MTHFR mutation are at high risk for high homocysteine because MTHFR is the enzyme needed to metabolize homocysteine. (see MTHFR test below).

### WHAT IS A BRAIN-HEALTHY HOMOCYSTEINE LEVEL?

A homocysteine of 10 mmol/L or below is required to promote healthy brain aging over time.<sup>20</sup> Adults need about 400 mcg of folate in their diet to support healthy homocysteine levels.

### WHAT ARE HOMOCYSTEINE-LOWERING FOODS?

Eating a variety of plant-based foods can help to lower homocysteine, naturally.<sup>21</sup> Eating foods that are particularly rich in folate and/or B12 are anti-inflammatory because B12 and folate help to metabolize homocysteine.<sup>22</sup>

Top sources of folate include dark leafy vegetables (spinach, asparagus, brussels sprouts, broccoli).

At Honeybrains, many of our ingredients are high in folate. You can check the folate and B12 levels of individual dishes by consulting our Honeybrains Food Periodic Table. You can also take nutrient supplements to ensure that you get enough B12 and folate. The HB Healthy Brain supplement contains 500mcg of vitamin B12 and 800 mcg of folate, along with other essential brain nutrients that, when taken daily, can support healthier homocysteine levels.

## 6. MTHFR

### WHAT IS THE MTHFR MUTATION?

The MTHFR gene encodes for a protein known as methyl-tetra-hydrofolate reductase, which uses B12 and folate in order to convert homocysteine into neurotransmitters. Some people have mutations in this gene that cause the protein to be less efficient at converting homocysteine into neurotransmitters. These people can have high homocysteine even when they have normal levels of B12 and folate. People who have the MTHFR mutation with high homocysteine will not benefit from taking regular B12 because their genes don't process regular B12 well; people with the MTHFR mutation require a special B12, called methylated B12, which bypasses their gene defect.

You can supplement with methylated B12 daily by using the HB Healthy Brain supplement, which works for people with and without the MTHFR gene and contains other essential brain nutrients.

# BIOMAKERS OF METABOLIC HEALTH

*HOMA-IR and adiponectin are two biomarkers that measure metabolic health. The better our metabolism while we are young and healthy, the better our brains function throughout life.<sup>23</sup>*

## 7. HOMA-IR

### WHAT IS THE HOMA-IR BIOMARKER?

The HOMA-IR biomarker helps doctors understand how much insulin your body is making in response to how much sugar you are eating. Specifically, the HOMA-IR ratio is the ratio of fasting blood sugar vs. insulin. A body with an efficient metabolism responds to dietary sugars sensitively with minimal insulin use. If insulin sensitivity is low, the metabolism isn't efficient, and sugar levels go up. Higher than normal blood sugar levels can cause inflammation in the circulatory system. Inflammation in the circulatory system is bad for brain health.

### WHO TYPICALLY HAS A SLOW METABOLISM?

About 34% of U.S. adults have a slow metabolism.<sup>24</sup> When someone has an inefficient metabolism, the medical term is called prediabetes or Type II diabetes, depending on how inefficient their metabolism is.

Anybody can have suboptimal metabolism, even if they diet and exercise, because our genes and our lifestyle combine to determine our metabolic efficiency. Anybody with a close family member with prediabetes or diabetes has a higher risk for metabolic inefficiency. People with higher fat to muscle ratios are more likely to have metabolic inefficiency because having a lot of muscle helps the body to use insulin well.

### WHAT IS A BRAIN-HEALTHY HOMA-IR LEVEL?

A brain-healthy HOMA-IR level is less than 1.9.

### HOW DO I GET TO MY TARGET HOMA-IR LEVEL?

When it comes to metabolism, your diet, lifestyle and body fitness make all the difference.

Colorful fruits and vegetables, coffees and teas may be particularly good for your metabolism because color pigments within these foods and drinks help our body to process other nutrients such as healthy fats.<sup>25</sup>

Supplementing with colorful spices like cinnamon, saffron and turmeric can improve your body's use of insulin.<sup>26, 27, 28</sup>

When it comes to body fitness, building muscle mass is a surefire way to improve metabolism.

At Honeybrains, we love foods that are high in color and use them extensively. You can check the color nutrient levels of individual dishes by consulting our Honeybrains Food Periodic Table. The HB Power House supplement can also help you get to your target HOMA-IR level, because it includes goji berry and green coffee bean extract, which are food-based ingredients proven to promote metabolic health. The HB Healthy Brain supplement also contains five different colors of plant pigments to help you get your daily dose of color.

## 8. ADIPONECTIN

### WHAT IS THE ADIPONECTIN BIOMARKER?

The adiponectin biomarker measures the levels of adiponectin, a hormone that is made by fat cells. People whose adiponectin levels are at target tend to have more skeletal muscle and less fat around the organs.<sup>29</sup> Having more muscle and less organ fat leads to healthier metabolic and circulatory systems.<sup>30,31</sup>

Our body uses adiponectin to convert sugar and fat into energy. When fat cells get too much energy, they make less adiponectin. Low levels of adiponectin is a sign that metabolic efficiency is low. Having a normal adiponectin level is critical for the brain because the energy supply of the brain depends on an efficient metabolism. People with optimal adiponectin levels tend to have sharper brains.<sup>33</sup>

### WHO TYPICALLY HAS ABNORMAL LEVELS OF ADIPONECTIN?

Women or men with low muscle mass are likely to have abnormal adiponectin levels. Women or men who feel they have too much fat on their body are also more likely to have abnormal adiponectin.

### WHAT IS A BRAIN-HEALTHY TARGET FOR ADIPONECTIN LEVELS?

A brain-healthy target for adiponectin is at least 14 ug/mL.

### HOW CAN YOU IMPROVE YOUR ADIPONECTIN LEVELS?

Building more muscle leads to improvements in adiponectin.<sup>34</sup> An ideal muscle mass for a male athlete is at least 43% and for a female athlete is at least 37%. An ideal body fat percentage for men is less than 13% and for women is less than 20%. Even though we all aren't athletes, when it comes to brain fitness, we should all strive to be like athletes because that gives us the most control of the fate of our brain health.

The HB Power House supplement includes goji berry and green coffee bean extract, which are food-based ingredients proven to promote metabolic health that can help you improve your adiponectin levels. The HB Good Mood supplement, designed to positively impact your mood, is also good for metabolism because it contains both turmeric and saffron. Supplementing with curcumin may improve adiponectin.<sup>35</sup>





## BIOMAKERS OF DIGESTIVE HEALTH

*Celiac Disease and Food Allergy Antibodies are two biomarkers of digestive system health and can be checked by anybody who has belly symptoms.*

### 9. CELIAC DISEASE

#### WHAT IS CELIAC DISEASE?

Celiac disease is an autoimmune disorder – the body’s immune system attacks its own organs. People with celiac disease have developed antibodies to gluten, which is a type of protein found in grains such as wheat, barley, rye and spelt. These antibodies (anti-gliadin and tissue transglutaminase) are made by the immune system to recognize foreign invaders. With celiac disease, auto-antibodies accidentally attack healthy cells in the lining of the digestive system which, over time, can harm the body. Celiac disease can influence how much essential brain nutrients are absorbed from food every day.

#### HOW CAN I TEST FOR CELIAC DISEASE?

Celiac disease can be tested for with a blood test that measures levels of the anti-gliadin and tissue transglutaminase antibodies. People who test negative for these antibodies do not have celiac disease.

For people with abnormal levels of anti-gliadin antibodies, avoiding all gluten-containing foods (while still consuming whole grains) is the best way to optimize body and brain health. Avoiding all whole grains is not recommended – people who eat more whole grains tend to live longer.<sup>37</sup> Whole grains have special sugars that feed the bacteria in our digestive system that absorb critical brain nutrients. People with celiac disease can still eat certain non-gluten whole grains such as amaranth, buckwheat, brown or wild rice, polenta, and oats.

### 10. FOOD ALLERGIES

#### WHAT ARE FOOD ALLERGIES?

Food allergies are allergic disorders. This is when the body’s immune system attacks a foreign allergen. When a dietary allergen triggers an immune response in the digestive system, it can cause inflammation and discomfort. When you have inflammation, nutrients can’t be absorbed as efficiently. The most common food allergies include cow’s milk, eggs, tree nuts, peanuts, shellfish, wheat, soy and fish.

#### HOW CAN I TEST FOR FOOD ALLERGIES?

Food allergies can be tested for using skin and/or blood tests. The blood tests measure the presence of IgE antibodies to specific foods (IgE, short for “immunoglobulin E,” is the antibody that triggers food allergy symptoms).

#### COULD IRRITABLE BOWEL SYNDROME, NOT CELIAC DISEASE OR FOOD ALLERGIES, BE THE REAL CAUSE OF MY BELLY SYMPTOMS?

If you test negative for food allergies and celiac disease, and you still have belly discomfort, especially when stressed, you should ask your doctor about irritable bowel syndrome (IBS). IBS is a stress-related disorder that affects the large intestine. Common signs and symptoms include bloating, cramping, excess gas, diarrhea or constipation. It can also feel like reflux, but will almost never wake you up at night. People with IBS typically have a personal or family history of migraines.

IBS is often treatable by supplementing with magnesium, which you can find in the HB Healthy Brain or the HB Headache Therapy supplements.

# TABLE 1: A SUMMARY OF THE BRAIN HEALTH BIOMARKERS

	BODY SYSTEM	WHAT QUESTION IT ANSWERS	HEALTHY TARGET	HOW TO NORMALIZE WITH LIFESTYLE	RECOMMENDED HB SUPPLEMENT
NUTRIENTS	Vitamin B12	Does my body have enough B12 to support my brain?	> 400 ng/mL	More eggs, dairy & meat	HB Healthy Brain
	RBC Magnesium	Does my body have enough magnesium to support my brain?	> 4.2 mg/dL	More nuts & seeds	HB Headache Therapy
	Omega 3 Index	Does my body have enough Omega 3 to support my brain?	> 8%	More fatty fish, walnuts, chia seeds, and flax seeds	HB Healthy Brain
CIRCULATION	ApoB:ApoA ratio	Even if I have normal cholesterol levels, do I have normal cholesterol particle sizes?	< 0.6 (ratio)	More fatty fish, herbs, spices & legumes	HB Power House
	Homocysteine	Do I have a toxin in my blood that could cause my brain to shrink over time?	< 10 mmol/L	More dark leafy greens & more B12	HB Healthy Brain
	MTHFR mutation	A gene that determines how you process B12	Normal	More dark leafy greens	HB Healthy Brain
METABOLISM	HOMA-IR	Insulin sensitivity	< 1.9 (ratio)	More colorful fruits and vegetables, teas & coffees	HB Power House
	Adiponectin	Fat distribution	> 14 ug/mL	Build more muscle	HB Good Mood
DIGESTION	Celiac disease panel	Autoimmune anti-bodies to the gluten protein	Negative	Avoid gluten	
	Food Allergy panel	Measures the presence of IgE antibodies to specific foods. IgE is the antibody that triggers food allergy symptoms.	Negative	Avoid food allergens	

## REFERENCES

- Nutritional determinants of cognitive aging and dementia. Morris MC. *Proc Nutr Soc.* 2012 Feb;71(1):1-13. doi: 10.1017/S002966511003296. Epub 2011 Nov 9. Review.
- How common is vitamin B-12 deficiency? Allen LH. *Am J Clin Nutr.* 2009 Feb;89(2):693S-6S. doi: 10.3945/ajcn.2008.26947A. Epub 2008 Dec 30. Review.
- Metabolic vitamin B12 deficiency: a missed opportunity to prevent dementia and stroke. Spence JD. *Nutr Res.* 2016 Feb;36(2):109-16. doi: 10.1016/j.nutres.2015.10.003. Epub 2015 Oct 21. Review.
- Subclinical magnesium deficiency: a principal driver of cardiovascular disease and a public health crisis. DiNicolantonio JJ, O'Keefe JH, Wilson W. *Open Heart.* 2018 Jan 13;5(1):e000668.
- Suboptimal magnesium status in the United States: are the health consequences underestimated? Rosanoff A, Weaver CM, Rude RK. *Nutr Rev.* 2012 Mar;70(3):153-64. doi: 10.1111/j.1753-4887.2011.00465.x. Epub 2012 Feb 15. Review.
- Role of magnesium in the pathogenesis and treatment of migraine. Sun-Edelstein C, Mauskop A. *Expert Rev Neurother.* 2009 Mar;9(3):369-79. doi: 10.1586/14737175.9.3.369. Review. PMID: 19271946
- Significantly lower serum and hair magnesium levels in children with attention deficit hyperactivity disorder than controls: A systematic review and meta-analysis. Huang YH, Zeng BY, Li DJ, Cheng YS, Chen TY, Liang HY, Yang WC, Lin PY, Chen YW, Tseng PT, Lin CH. *Prog Neuropsychopharmacol Biol Psychiatry.* 2019 Mar 2;90:134-141.
- The Role of Nutritional Supplements in the Treatment of ADHD: What the Evidence Says. Lange KW, Hauser J, Lange KM, Makulska-Gertruda E, Nakamura Y, Reissmann A, Sakaue Y, Takano T, Takeuchi Y. *Curr Psychiatry Rep.* 2017 Feb;19(2):8. doi: 10.1007/s11920-017-0762-1. Review.
- Red blood cell  $\omega$ -3 fatty acid levels and markers of accelerated brain aging. Tan ZS, Harris WS, Beiser AS, Au R, Himali JJ, Debette S, Pikula A, Decarli C, Wolf PA, Vasani RS, Robins SJ, Seshadri S. *Neurology.* 2012 Feb 28;78(9):658-64. doi: 10.1212/WNL.0b013e318249f6a9.
- Omega-3 Fatty Acid Intake by Age, Gender, and Pregnancy Status in the United States: National Health and Nutrition Examination Survey 2003-2014. Thompson M, Hein N, Hanson C, Smith LM, Anderson-Berry A, Richter CK, Stessy Bisselou K, Kusi Appiah A, Kris-Etherton P, Skulas-Ray AC, Nordgren TM. *Nutrients.* 2019 Jan 15;11(1). pii: E177.
- Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet.* 2001;358:2026-2033.
- From Heart Health to Brain Health: Legacy of the North Karelia Project for Dementia Research. Kivipelto M, Ngandu T. *Glob Heart.* 2016 Jun;11(2):235-42. doi: 10.1016/j.ghheart.2016.04.013. Review.
- The apoB/apoA-I ratio is better than the cholesterol ratios to estimate the balance between plasma proatherogenic and antiatherogenic lipoproteins and to predict coronary risk. Walldius G, Jungner I, Aastveit AH, Holme I, Furberg CD, Sniderman AD.
- Lifestyle and Dietary Determinants of Serum Apolipoprotein A1 and Apolipoprotein B Concentrations: Cross-Sectional Analyses within a Swedish Cohort of 24,984 Individuals. Frondelius K, Borg M, Ericson U, Borné Y, Melander O, Sonestedt E. *Nutrients.* 2017 Feb 28;9(3). pii: E211.
- The effect of saffron on weight and lipid profile: A systematic review, meta-analysis, and dose-response of randomized clinical trials. Rahmani J, Manzari N, Thompson J, Clark CCT, Villanueva G, Varkaneh HK, Mirmiran P. *Phytother Res.* 2019 Sep;33(9):2244-2255. doi: 10.1002/ptr.6420. Epub 2019 Jul 2. Review.
- Brain atrophy in cognitively impaired elderly: the importance of long-chain  $\omega$ -3 fatty acids and B vitamin status in a randomized controlled trial. Jernerén F, Elshorbagy AK, Oulhaj A, Smith SM, Refsum H, Smith AD. *Am J Clin Nutr.* 2015 Jul;102(1):215-21. doi: 10.3945/ajcn.114.103283. Epub 2015 Apr 15.
- Homocysteine, B Vitamins, and Cognitive Impairment. Smith AD, Refsum H. *Annu Rev Nutr.* 2016 Jul 17;36:211-39. doi: 10.1146/annurev-nutr-071715-050947. Review.
- Increased concentrations of homocysteine in the cerebrospinal fluid in patients with fibromyalgia and chronic fatigue syndrome. Regland B, Andersson M, Abrahamsson L, Bagby J, Dyrehag LE, Gottfries CG. *Scand J Rheumatol.* 1997;26(4):301-7.
- Homocysteine and migraine: A narrative review. Lippi G, Mattiuzzi C, Meschi T, Cervellin G, Borghi L. *Clin Chim Acta.* 2014 Jun 10;433:5-11. doi: 10.1016/j.cca.2014.02.028. Epub 2014 Mar 5. Review.
- Homocysteine and Dementia: An International Consensus Statement. Smith AD, Refsum H, Bottiglieri T, Fenech M, Hooshmand B, McCaddon A, Miller JW, Rosenberg IH, Obeid R. *J Alzheimers Dis.* 2018;62(2):561-570. doi: 10.3233/JAD-171042.
- Effect of dietary patterns on serum homocysteine: results of a randomized, controlled feeding study. Appel LJ, Miller ER 3rd, Jee SH, Stolzenberg-Solomon R, Lin PH, Erlinger T, Nadeau MR, Selhub J. *Circulation.* 2000 Aug 22;102(8):852-7.

22. Dietary determinants of plasma homocysteine concentrations. Verhoef P, de Groot LC. *Semin Vasc Med.* 2005 May;5(2):110-23. Review.
23. Blood glucose levels and cortical thinning in cognitively normal, middle-aged adults. Wennberg AM, Spira AP, Pettigrew C, Soldan A, Zipunnikov V, Rebok GW, Roses AD, Lutz MW, Miller MM, Thambisetty M, Albert MS. *J Neurol Sci.* 2016 Jun 15;365:89-95. doi: 10.1016/j.jns.2016.04.017. Epub 2016 Apr 14.
24. <https://www.cdc.gov/diabetes/data/statistics-report/prevalence.html>. Accessed Nov 2019.
25. Effects of Coffee and Tea Consumption on Glucose Metabolism: A Systematic Review and Network Meta-Analysis. Yoshinobu Kondo, Atsushi Goto, Hisashi Noma, Hiroyasu Iso, Kunihiko Hayashi, Mitsuhiro Noda. *Nutrients.* 2019 Jan; 11(1): 48. Published online 2018 Dec 27.
26. Clinical evidence on the effects of saffron (*Crocus sativus* L.) on cardiovascular risk factors: A systematic review meta-analysis. Pourmasoumi M, Hadi A, Najafgholizadeh A, Kafeshani M, Sahebkar A. *Pharmacol Res.* 2019 Jan;139:348-359. doi: 10.1016/j.phrs.2018.11.038. Epub 2018 Nov 28.
27. Saffron (*Crocus sativus* L.) increases glucose uptake and insulin sensitivity in muscle cells via multipathway mechanisms. Kang C, Lee H, Jung ES, Seyedian R, Jo M, Kim J, Kim JS, Kim E. *Food Chem.* 2012 Dec 15;135(4):2350-8. doi: 10.1016/j.foodchem.2012.06.092. Epub 2012 Jul 3.
28. Metabolic benefits of curcumin supplementation in patients with metabolic syndrome: A systematic review and meta-analysis of randomized controlled trials. Azhdari M, Karandish M, Mansoori A. *Phytother Res.* 2019 May;33(5):1289-1301. doi: 10.1002/ptr.6323. Epub 2019 Apr 2.
29. Adiponectin—Consideration for its Role in Skeletal Muscle Health. Matthew P. Krause, Kevin J. Milne, Thomas J. Hawke. *Int J Mol Sci.* 2019 Apr; 20(7): 1528. Published online 2019 Mar 27. doi: 10.3390/ijms20071528
30. Beneficial Effects of Adiponectin on Glucose and Lipid Metabolism and Atherosclerotic Progression: Mechanisms and Perspectives. Yanai H, Yoshida H. *Int J Mol Sci.* 2019 Mar 8;20(5). pii: E1190. doi: 10.3390/ijms20051190. Review.
31. Association of Metabolic Syndrome with the Adiponectin to Homeostasis Model Assessment of Insulin Resistance Ratio. Ding YS, Guo SX, Ma RL, Li SG, Guo H, Zhang JY, Zhang M, Liu JM, He J, Yan YZ, Zhang WJ, Liu LG. *Mediators Inflamm.* 2015;2015:607364.
32. The Role of Leptin and Adiponectin in Obesity-Associated Cognitive Decline and Alzheimer's Disease. Forny-Germano L, De Felice FG, Vieira MNDN. *Front Neurosci.* 2019 Jan 14;12:1027. doi: 10.3389/fnins.2018.01027. eCollection 2018. Review.
33. Serum Adiponectin Levels, Neuroimaging, and Cognition in the Mayo Clinic Study of Aging. Wennberg AM, Gustafson D, Hagen CE, Roberts RO, Knopman D, Jack C, Petersen RC, Mielke MM. *J Alzheimers Dis.* 2016 May 4;53(2):573-81. doi: 10.3233/JAD-151201.
34. Enhanced skeletal muscle for effective glucose homeostasis. Yang J. *Prog Mol Biol Transl Sci.* 2014;121:133-63. doi: 10.1016/B978-0-12-800101-1.00005-3. Review.
35. The effect of curcumin supplementation on circulating adiponectin: A systematic review and meta-analysis of randomized controlled trials. Clark CCT, Ghaedi E, Arab A, Pourmasoumi M, Hadi A. *Diabetes Metab Syndr.* 2019 Jul 30;13(5):2819-2825.
36. Anti-Gliadin Antibodies Identify Celiac Patients Overlooked by Tissue Transglutaminase Antibodies. Brian C Benson, Christopher J Mulder, Jeffrey T Laczek. *Hawaii J Med Public Health.* 2013 Sep; 72(9 Suppl 4): 14-17.
37. Consumption of whole grains in relation to mortality from all causes, cardiovascular disease, and diabetes: Dose-response meta-analysis of prospective cohort studies. Li B, Zhang G, Tan M, Zhao L, Jin L, Tang X, Jiang G, Zhong K. *Medicine (Baltimore).* 2016 Aug;95(33):e4229. doi: 10.1097/MD.00000000000004229.