Optimal Cardiovascular Health

"A man is as old as his blood vessels." *~Thomas Sydenham, MD, English Physician, 1624-1689*

The health of your heart and blood vessels is paramount to optimal aging.

Your heart beats approximately 100,000 times a day, pumping 1,900 gallons of blood through more than 60,000 miles of blood vessels. This astonishing ability of your cardiovascular system makes life possible—healthy blood vessels and heart function enable your cells to receive vital oxygen and nutrients and to remove waste. Without preventive measures, the blood vessels and heart undergo changes with aging. These changes include a decline in heart function, thickening and stiffening of arteries, plaque development, and a tendency toward clotting. Declining heart and blood vessel function don't just affect the heart itself—they contribute to brain degeneration and poor blood flow to all vital organs and tissues.

According to the American Heart Association, nearly half of American adults have some form of cardiovascular disease which includes coronary artery disease, heart failure, stroke, and high blood pressure.[1] **Cardiovascular disease is the #1 cause of death and disability in the US accounting for 1 in 3 deaths.** In fact, every 40 seconds (approximately the time it took for you to read to this point) someone in the US has a heart attack or stroke. **Cardiovascular disease kills 2,303 Americans daily**. This is equivalent to 10 full-capacity Boeing 737 airplanes crashing, killing everyone aboard—every single day. More Americans die from cardiovascular disease than all forms of cancer combined. This ebook will provide you with effective tools to prevent you from being a cardiovascular statistic.

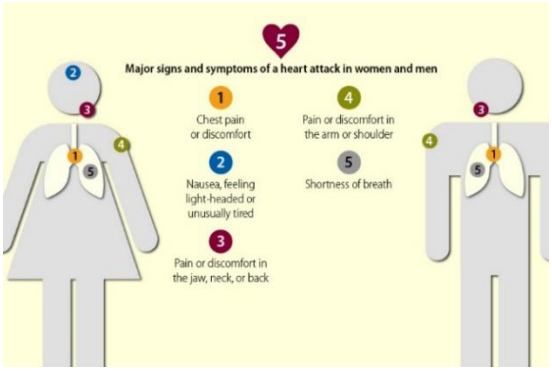
What is a heart attack or stroke?

Most heart attacks or strokes are caused by "atherosclerosis"—a buildup or rupture of plaque in the arteries that feed the heart and brain. Plaque is a sticky substance made of oxidized cholesterol and fat, inflammatory molecules, and immune cells. When plaque ruptures and blood clots form in the arteries, blood supply is choked off and the heart muscle or brain (depending on the location of plaque rupture or clot) begins to die. Plaque, calcification, and arterial stiffening can worsen over time, limiting or choking off blood supply, oxygen, and nutrient delivery to the heart and brain.

Symptoms of heart disease include shortness of breath, chest pain on exertion (e.g., walking upstairs), fatigue, dizziness, abnormal heartbeat, and fluid retention in the legs or ankles. Unfortunately, roughly half of all people who have a heart attack have no prior symptoms of heart disease and 20% of heart attacks are "silent," causing only mild or no symptoms. This is why a thorough assessment of your risk is critical.

Heart attack symptoms include chest pain, shortness of breath and tightness, and aching in the chest or arms that may spread to the neck, jaw, or back. Sweating and dizziness may can

also occur. Digestive symptoms, such as nausea, heartburn, or abdominal pain, are also possible. Women are less likely to have crushing chest pain and more likely to experience shortness of breath, lightheadedness, upper back pressure, extreme fatigue, or nausea and vomiting than men.

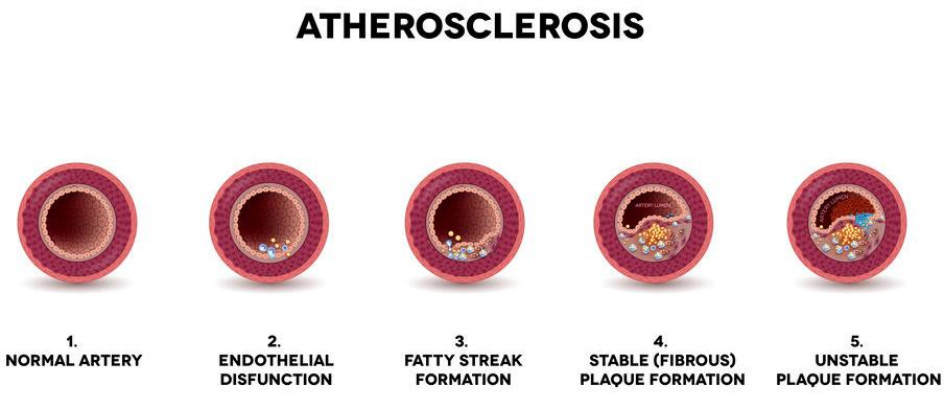


Symptoms of a stroke are usually sudden including trouble walking, difficulty talking, confusion, and numbness or paralysis of the face, arm, or leg. Blurry, blackened, or double vision, or severe headache may also be symptoms of a stroke.

How does a heart attack or stroke happen?

Heart attacks and strokes are most often caused by rupture of atherosclerotic plaque. Although heart attacks and strokes seem to happen in an instant, they are the result of years or decades of blood vessel damage. In other words, **heart attacks and strokes are events that occur as part of a process.** This process is treatable and possibly reversible.

How does atherosclerosis develop?



A few key steps are involved in the development and progression of plaque in the arteries:

1. Initially, injury to the endothelial layer occurs from a toxin, dyslipidemia, high blood sugar, or oxidative stress (from poor diet, obesity, smoking, sleep deprivation, infections, or heavy metals).
2. An apoB containing particle (mostly LDL particles) carrying cholesterol slips through the endothelium into the artery wall.
3. This particle is modified by oxidation or glycation (sugar) and the immune system sends cells to the scene to ingest the modified particle/cholesterol, provoking inflammation.

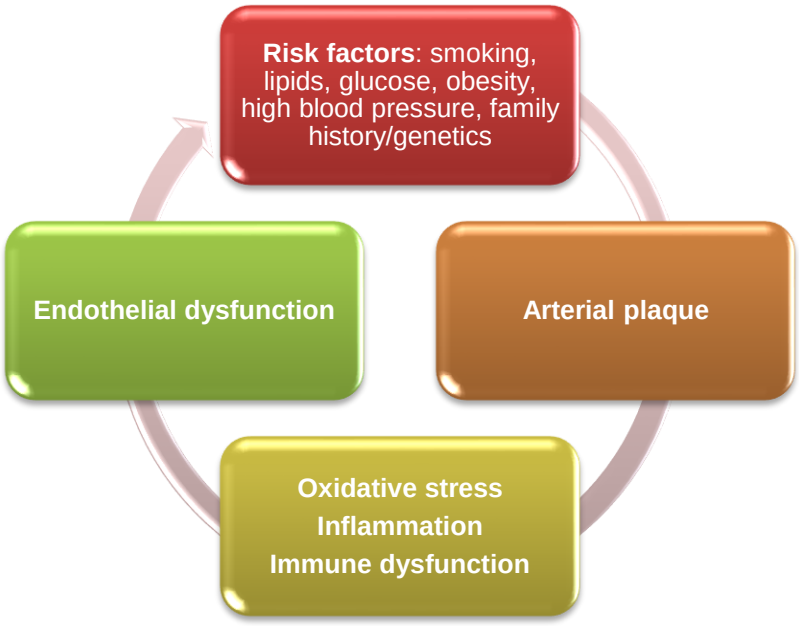
Endothelial damage also releases inflammatory compounds increasing white blood cell recruitment.

4. Immune cells (macrophages) begin to coalesce creating “foam cells” and causing a “fatty streak” in the artery wall. Smooth muscle cells migrate to the plaque surface creating a “fibrous cap.” The atherosclerotic plaque is like a pimple on the inside wall of the artery and the fibrous plaque is like a scab. When this cap is thick, the plaque is stable. When it thins, the plaque can erode or rupture, causing a clot to form.

What is your risk?

Besides preventing heart attack and stroke, your goal should be to minimize or reverse aging blood vessels and vascular disease. Knowing your arterial health and risk factors will enable you to take control of this process.

Arguably, the biggest risk factor for cardiovascular disease is ignorance and denial. To estimate your risk and how well your blood vessels are aging, it’s helpful to evaluate your **risk factors, plaque burden, oxidative stress (free radical activity), blood vessel inflammation, and endothelial function.** These areas influence each other and are like pieces of a puzzle, giving you a better picture of your heart and blood vessel health than just traditional cholesterol levels.



Risk factors

Genetics and family history play a significant role in cardiovascular risk. If you have a strong family history, especially of premature cardiovascular disease (father <55 years, mother <65 years), your risk is 60-75% higher. It’s imperative that you have a thorough workup and adopt a blood vessel protection plan as young as possible.

80% of the risk for heart attacks is caused by the top 5 modifiable risk factors: abnormal lipids, cigarette smoking, abdominal obesity, hypertension, and diabetes with 90% of risk due to these 5 factors plus stress, lack of daily fruit and vegetable intake, inadequate exercise, and lack of alcohol intake (although heavy or binge drinking increases risk).[2,3]

The two most important non-modifiable risk factors for vascular disease are having a strong family history and getting older (the longer the blood vessels are exposed to insults, the more likely they become diseased).

Are you at high, intermediate, or low risk?

Unfortunately, relying on symptoms to determine your heart attack and stroke risk is dangerous. **62% of men and 46% of women with heart disease experience a heart attack as their initial symptom**.[4] In addition, **50% of people who have a heart attack have normal cholesterol levels**. Therefore, your risk must be determined by thoroughly evaluating all risk factors and current disease state.

Heart attack and stroke risk can be classified into **3 categories: high, intermediate, or low (optimal) risk.** Check the box that corresponds with your risk (note that risk factors are additive):

☐ **High risk:**

- Prior heart attack or stroke
- Significant plaque in coronary arteries (feed the heart) or carotid arteries (feed the brain), or peripheral vascular disease (including most cases of erectile dysfunction in men older than 50)
- Significantly increased carotid intima media thickness (CIMT)
- Abdominal aortic aneurysm
- Chronic kidney disease
- Diabetes
- Heart failure
- 10 year predicted risk for cardiovascular disease (free online risk assessment calculators: www.cvriskcalculator.com and www.reynoldsriskscore.org

☐ **Intermediate risk (one or more of the following; risk is additive):**

- Family history of heart disease or stroke
- Unfavorable genes (e.g., Apo E4, 9p21, 6p24, and others)
- Calcium score >0 on coronary artery CT
- Increased carotid intima media thickness (CIMT)
- Elevated Lp(a)
- High LDL-C, LDL-P, Apo B, sdLDL
- Low HDL-C, HDL-P, Apo A-1
- High triglycerides
- Cigarette smoking
- Visceral (around the waist) obesity
- High stress level
- Hypertension
- High blood sugar
- Elevated inflammation
- High oxidative stress
- High homocysteine
- High fibrinogen
- Poor diet
- Physical inactivity
- Heavy alcohol use
- Untreated sleep apnea
- Poor exercise capacity
- Abnormal heart rate recovery
- Collagen-vascular autoimmune disease (e.g., rheumatoid arthritis or Lupus)
- History of pre-eclampsia or gestational diabetes
- Pregnancy-induced hypertension

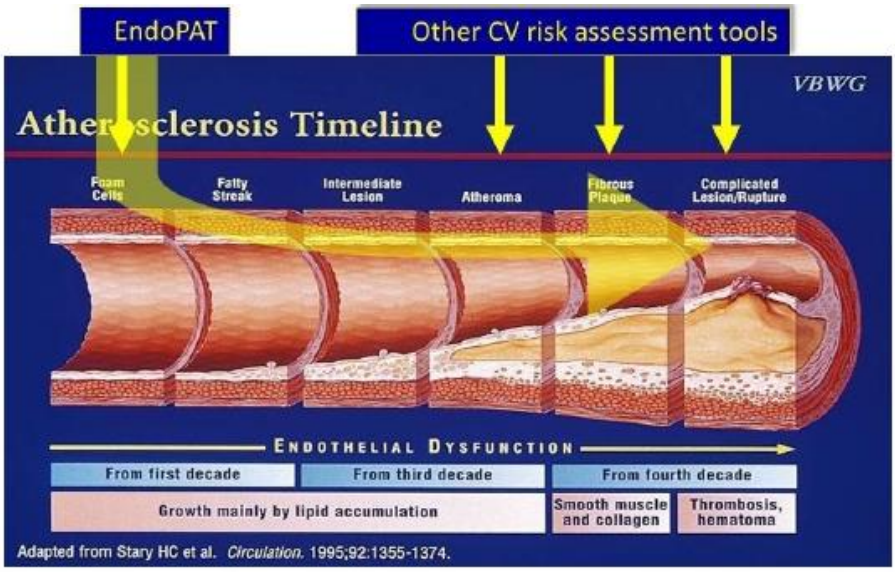
- **Optimal (low) risk:**

  - No calcified plaque in the coronary arteries (zero calcium score)
  - No carotid plaque or increased carotid intima media thickness (CIMT)
  - Low inflammation (no elevated inflammatory markers)
  - Low oxidative stress markers
  - Blood pressure ≤120/80 (untreated)
  - Low LDL-C, LDL-P, apoB
  - High HDL-P
  - Fasting blood sugar <90 (untreated)
  - Fasting insulin ≤5.0
  - Non-smoker
  - Optimal body mass (fat and muscle %)
  - Adequate exercise
  - Ideal diet
  - Good stress management

Measuring endothelial function, blood pressure, arterial thickness and stiffness, and plaque burden:

Ideally, abnormal blood vessel function would be detected early before structural changes are seen. In addition to measuring risk factors, the following tests can help determine unhealthy vascular function and extent of disease in the vessels.

- **Endothelial function testing:** The endothelium is a single layer of cells that line all blood vessels. These highly specialized cells detect physical, chemical, and mechanical stimuli to protect blood vessels and facilitate exchange between blood gasses (oxygen and nitric oxide or "NO") and nutrients. NO released from endothelial cells causes blood vessels to relax (which dilates arteries and lowers blood pressure). Endothelial cells also play a critical role in promotion or prevention of white blood cell adherence to the vessel wall, platelet activation (blood clotting), oxidation, inflammation, and plaque formation.[5]



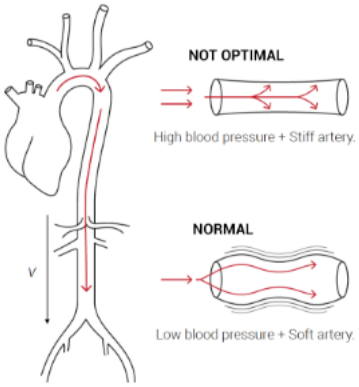
Endothelial dysfunction may be considered the **"ultimate risk of the risk factors"** since it is the earliest detectable stage of vascular disease,[6] and testing endothelial function helps predict heart attacks and strokes.[7-11] Endothelial dysfunction can improve; therefore, repeat testing

helps determine treatment effectiveness.[12] The most commonly used machine in a clinical setting is called EndoPAT, although other machines are available.

- **24-hour ambulatory blood pressure monitoring (24-hour ABPM):** Blood pressure is reported as systolic (pressure in the arteries when the heart pumps) over diastolic (pressure in the arteries when the heart relaxes).

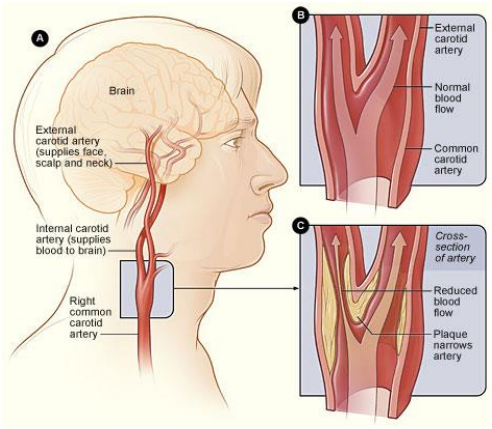
  - **Normal blood pressure (BP) is <120/80 mmHg**
  - **Elevated is 120-129/<80**
  - **Stage I hypertension is 130-139/80-89**
  - **Stage 2 is ≥140/≥90**

A 24-hour ABPM provides significantly more information than a single office blood pressure reading since it measures blood pressure throughout the day and night. Normally, blood pressure decreases approximately 10% at night compared to the daytime. If blood pressure is elevated at night or doesn't decrease (a phenomenon called "non-dipping"), cardiovascular disease risk increases.[13] 24-hour ABPM also identifies morning blood pressure surges and significant BP variability throughout the day



- **Pulse wave velocity (PWV) analysis:** This test provides information about the stiffness and loss of elasticity of arteries. When the left ventricle contracts, it ejects blood into the ascending aorta, dilating the aortic wall and generating a pressure wave that moves along the arteries. As artery walls become stiffer, pressure wave speed increases. Age, high blood pressure, and atherosclerosis are the most important factors influencing PWV.

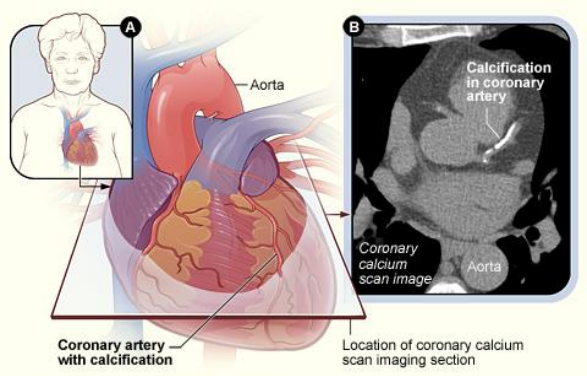
- **Carotid artery ultrasound & CIMT:** Ultrasound of the carotid arteries measures plaque and arterial thickness (carotid intima media thickness or "CIMT"). The carotid arteries provide a "window" to the coronary and other arteries. Increased carotid intima media thickness (CIMT) is an independent predictor of future cardiovascular events, including heart attack, cardiac death, and stroke.[14] In addition, increased CIMT is independently associated with mild cognitive impairment and dementia[15] (thicker, stiffer arteries decrease blood flow to the brain).



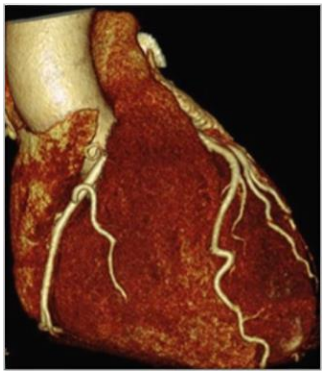
An abnormal IMT indicates soft plaque accumulation and endothelial dysfunction. If your CIMT is significantly worse than typical for your age and gender, developing an aggressive strategy to decrease risk factors is imperative. Repeat CIMT measurements every 6 months to 1 year can help gauge progress.

- **Coronary calcium scan (calcium score):** This 10-minute test is a CT scan that takes pictures of the coronary arteries. No contrast dye is used. If the calcium score is zero (meaning no calcium is detected in any artery feeding the heart) and you're not at high risk, you get a "15

year warranty," meaning your risk of dying from a heart attack in the next 15 years is very low.[16] If the calcium score is >0, the score helps assess risk since significant calcification (hardened plaque) can narrow arteries and it's a footprint for soft, rupture-prone plaque. The downside of this imaging tool is that soft plaque is not detected (only calcification can be seen) and that people may mistakenly believe they have no risk with a zero calcium score, possibly ignoring risk factors.



- **Coronary artery CT (CT angiogram):** A computerized tomography (CT) coronary angiogram evaluates the coronary arteries for the presence, location, and type of plaque and amount of narrowing of arteries. Unlike traditional coronary angiograms, CT angiograms don't use a catheter threaded through blood vessels. CT angiograms do, however, expose a person to radiation and contrast material (dye). The benefit of the CT angiogram over calcium score is the detection of both soft and calcified plaque and degree of arterial stenosis (narrowing).



- **CORUS test:** This is a blood test measuring the activity of 23 genes that change when there is a significant narrowing or blockage in the coronary arteries. The test is highly correlated with QCA (quantitative coronary artery angiogram) and degree of stenosis.[17-19]

How can you reduce cardiovascular disease risk and improve your heart and blood vessel health?

Your goal to reduce your heart attack and stroke risk and slow the aging of your blood vessels is to minimize blood vessel injury and improve their repair. This includes **decreasing risk factors**, **healing dysfunctional endothelium, stabilizing and reversing plaque, and decreasing arterial thickening and stiffness.** With solid commitment and accountability, following this plan will help you achieve those goals.

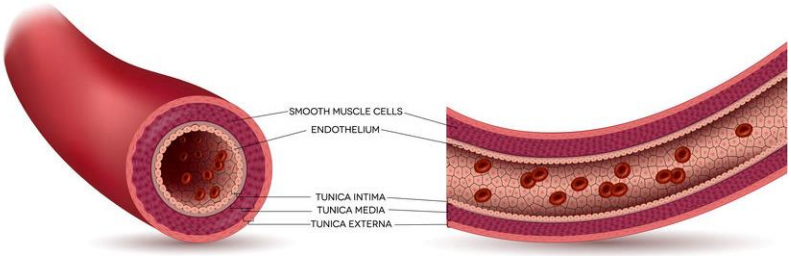
1. **If you smoke, you must quit. Avoid all second-hand smoke (don't allow another person's habit or addiction to damage your blood vessels).**

   Smoking is like sandblasting your arteries, increasing heart attack and stroke risk 2 to 4 times and directly causing atherosclerosis.[20] Cigarette smoking dramatically increases inflammation and oxidative stress (free radical damage), reduces circulation, and damages the endothelial lining of blood vessels. This leads to a greater chance of developing atherosclerosis and peripheral vascular disease, obstructing arteries in the arms and legs leading to pain or even gangrene. In a recent randomized trial, smoking cessation improved endothelial dysfunction after one year, significantly reducing cardiovascular risk.[21]

If you do smoke, there are many tools to help you quit including nicotine replacement (gum, patches, or compounded lollipops), medications to decrease cravings (Chantix® or Wellbutrin®), natural options (such as taking cannabidiol or CBD, the non-hallucinogenic component of hemp and marijuana[22]), as well as cell phone apps and self-help books and programs. Hypnosis with a trained hypnotist can be effective, especially if treatment is individualized and you attend follow-up sessions after you've quit.[23]

2. Improve endothelial dysfunction and optimize blood pressure.

The endothelium is a continuous, single layer of one to two trillion cells that lines all your vessels of your circulatory system from large arteries to small capillaries. These cells stretch over more than 1,300 square feet (more than the surface area of 6 tennis courts!) These cells provide a barrier between the blood and blood vessel. The endothelium is a metabolically active endocrine organ secreting substances such as nitric oxide and cyclooxygenase that regulate immune responses and inflammation, blood vessel tone, and coagulation (blood clot formation).



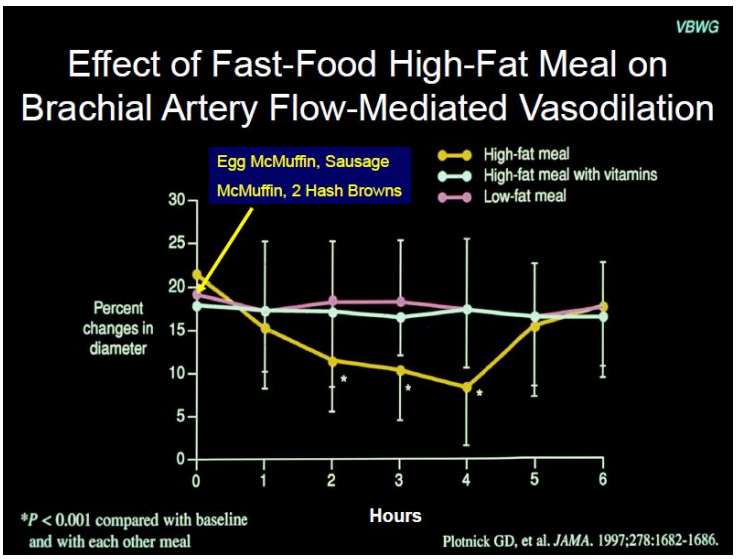
Endothelial dysfunction contributes to the formation and promotion of atherosclerosis by causing cell permeability (allowing LDL particles to get into the arterial wall to deposit cholesterol), increasing white blood cell attraction (which causes foam cell and eventual plaque formation), enhancing LDL oxidation (contributing to unstable plaque), and promoting platelet activation and clot formation. Endothelial dysfunction reduces nitric oxide production. This can prevent dilation of blood vessels and promote vascular smooth muscle cell proliferation, causing high blood pressure and thicker, stiffer, stickier arteries.

The following approach can <u>improve endothelial dysfunction</u>:

- **If you smoke, you must become a non-smoker.**
- **Besides not smoking, the most important step you can take to improve endothelial function is to optimize your diet.** This means avoiding refined carbohydrates, especially processed grains, sugar, and high fructose corn syrup. If you do eat sugar on special occasions, make sure you exercise to prevent the sugar from damaging the endothelium.[24]

  Avoid all trans fat and high amounts of saturated animal fat. These fats induce inflammation and cause endothelial dysfunction.[25-27]

Interestingly, the "McDonald's study" showed that taking antioxidants (in this study, vitamins C and E) reduced endothelial damage caused by eating an Egg McMuffin with sausage and hash browns.[28] Although the antioxidants blunted the damage from the McDonald's breakfast, the take home message should be not to eat at McDonald's in the first place!



Increase intake of dietary flavonoids from colorful fruits and vegetables, especially berries, pomegranate seeds and juice, green tea, and dark chocolate.[29,30] Anti-oxidants from colorful fruits and vegetables and even those found in red wine can protect the endothelium and improve nitric oxide production.[31-33] In addition, green leafy vegetables and beets, a source of dietary nitrates, are especially helpful to boost nitric oxide production and improve endothelial function.[34]

- **Treat high blood pressure.** If you have hypertension you have a bigger problem than just increased pressure in your blood vessels—<u>you have diseased blood vessels.</u> You must restore ideal blood pressure to reverse the detrimental impact on your blood vessels, heart, kidneys, and brain. If blood pressure remains elevated, it further damages the endothelial lining and disrupts nitric oxide production. Ideal blood pressure to decrease heart attack, stroke, congestive heart failure, and cardiovascular death is <120/80 mm Hg.[35]

  Lowering blood pressure to a healthy range (preferably <120/80) significantly improves endothelial dysfunction over 6 months.[36] Meta-analysis of 147 trials revealed an average of 22% reduction in heart attack and 41% reduction in stroke by lowering blood pressure 10 mm Hg systolic or 5 mm diastolic.[37] In addition to lowering your risk for heart attack and stroke, keeping systolic blood pressure below 120 reduces the risk of mild cognitive impairment, a precursor to dementia, although it may not decrease dementia risk.[38,39]

  Note that some blood pressure medications, such as ACE inhibitors like quinapril, enalopril, or ramipril, or angiotensin II receptor blockers (ARBs) like irbesartan and telmisartan improve endothelial health besides just lowering blood pressure.[40-43] Telmisartan (generic Micardis®) may be an ideal medication for people with metabolic syndrome or diabetes since it may improve insulin sensitivity and help with weight loss.[44-46]

- **Do not take long-term proton pump inhibitors (PPIs) such as Prilosec® (generic is omeprazole), Prevacid,® Protonix,® and Nexium.®** These medications suppress nitric oxide production by inhibiting DDAH (dimethylarginine dimethylaminohydrolase), the enzyme that clears ADMA (asymmetric dimethylarginine, a naturally occurring product of metabolism).[47] High levels of ADMA inhibit nitric oxide production by the endothelium and are a strong predictor of cardiovascular events and death in people with coronary artery disease.[48]

Long-term use of PPIs is associated with an increase in heart attack, stroke, cardiovascular death, and kidney disease risk.[49-52] This doesn't mean that PPIs cause cardiovascular or kidney disease (it's possible that many people who need these drugs eat an unhealthy diet and have poor lifestyle habits accounting for the association). However, it doesn't make good sense to take medication that suppresses stomach acid production and may end up contributing to endothelial dysfunction if you can treat the cause.

If you've taken PPIs for longer than 4 to 8 weeks (which is how long the FDA-approval is for these drugs), your stomach acid may be completely suppressed; abruptly stopping the drug can cause severe rebound acid secretion. Taper the medication over time and replace it as needed with Rhizinate, Glutamine Synergy, or Leaky Gut Formula (natural products that contain deglycyrrhizinated licorice, glutamine, and aloe vera that soothe and heal the intestinal lining) or take Tums®. Above all, avoid the most common triggers of esophageal reflux (GERD) and heartburn—overeating, eating late at night, coffee and other acidic food such as tomato sauce, spicy food, and alcohol.

- **Improve your resiliency to stress.** Even brief episodes of stress, like those encountered in everyday life, cause transient endothelial dysfunction for up to 4 hours.[53] Hormones and chemicals released at times of stress, such as glucocorticoids, pro-inflammatory cytokines, and endothelin-1 decrease synthesis and function of nitric oxide.[54] For help with stress management, see section below on stress reduction or Dr. Retzler's handout, "Emptying Your Stress Bucket."

- **Improve cardiovascular exercise** (preferably, interval training—see exercise section below). Exercise improves endothelium-dependent vasodilation of arteries in healthy people and in people with heart disease.[55,56] The right type and amount of exercise increases nitric oxide production and function and reverses blood vessel damage by increasing endothelial progenitor (stem) cells.[57,58]

- **Lower LDL particles.** LDL that's been oxidized promotes endothelial dysfunction and contributes to plaque formation, progression, and rupture by several mechanisms. This includes downregulation of eNOS activity, the enzyme that synthesizes nitric oxide.[59] Statin medications (such as Lipitor® or Crestor®) may improve this negative effect of LDL[60] and may improve endothelial function beyond lowering LDL.[61,62]

- **Reduce elevated homocysteine.** Homocysteine is a metabolite of a common amino acid called methionine. High homocysteine is an independent risk factor for the development of atherosclerosis.[63] Elevated homocysteine can injure the endothelium and decrease nitric oxide production and may promote coagulation and clot formation.[64-66] Taking active folate, vitamin B6, and vitamin B12 lowers homocysteine. Active folate (5MTHF or methyltetrahydrofolate) has pleiotropic effects on blood vessels other than homocysteine lowering, increasing nitric oxide production and scavenging superoxide radicals.[67]

- **Avoid heavy metals and remove them if present.** Heavy metals, such as lead, mercury, and cadmium damage endothelial function and overall blood vessel health through mechanisms such as increasing oxidative stress and inflammation, decreasing nitric oxide formation, and causing immune dysfunction.[68] This may lead to hypertension, atherosclerosis, and elevated heart attack and stroke risk.[69-71] Testing for heavy metals can be performed via blood, hair, and urine (via Quicksilver Scientific Lab) or by urine testing following a chelation challenge with EDTA & DMPS (through Doctor's Data). Please discuss your possible heavy metal exposure and testing options with Dr. Retzler.

- **Use pharmaceutical-quality supplements** to improve endothelial function and nitric oxide production, decrease inflammation, and minimize free radical activity/oxidation. Beets

contain nitrate which is reduced to nitrite by oral bacteria, then reduced to NO in stomach acid. Some forms of beet root extract such as Neo40® may improve endothelial function.[72] Other supplements (vitamins C, D, and E, CoQ10, lycopene, flavonoids, garlic, magnesium, and omega 3 fatty acids)[73-81] may be particularly effective in improving endothelial function.[82]

- **Balance hormones.** Estradiol and testosterone supplementation improve endothelial function in women.[83–85] Testosterone induces nitric oxide and promotes healthy endothelial function in men. Testosterone may also promote recruitment of endothelial progenitor cells which repair blood vessels.[86] Although low testosterone is associated with endothelial dysfunction, studies are mixed regarding testosterone supplementation improving endothelial function in men.[87,88] Physiologic doses of testosterone may work well because testosterone is aromatized into estrogens which positively impacts the endothelium and blood vessel dilation.[89,90]

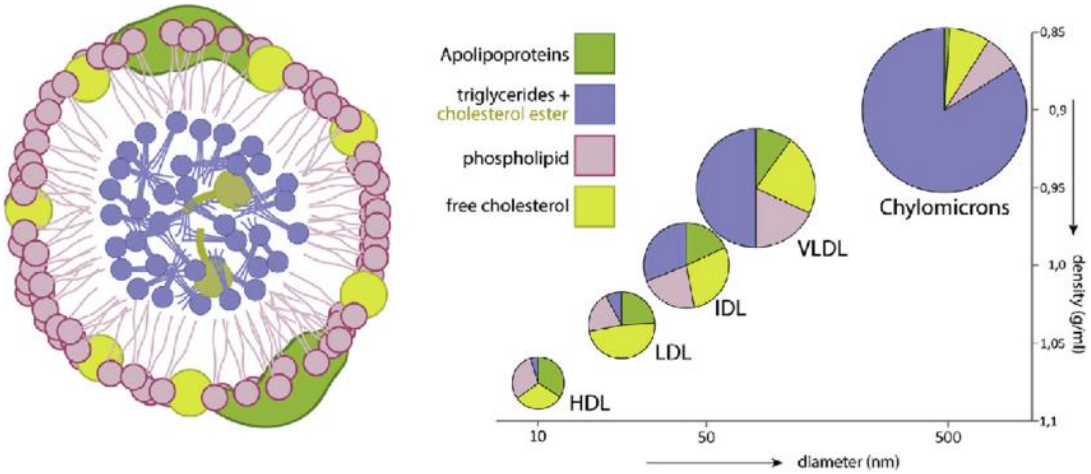
3. Improve "good" and "bad" cholesterol.

Cholesterol is a paradox—when it forms plaque that becomes oxidized and inflamed it is detrimental to your blood vessels, heart, and brain; however, cholesterol is also necessary for normal body functions.

Rather than floating around in your bloodstream or clogging your arteries, by far, most of the cholesterol in your body is found in your cell membranes. Cholesterol is essential for life, which is why all cells make their own. Cholesterol provides the following important functions:

- It's the backbone for production of hormones such as adrenal hormones (cortisol and DHEA,) aldosterone (which helps regulate blood pressure,) and sex hormones (estrogen, progesterone, and testosterone.)
- It's a component of bile acids which are necessary for proper fat digestion and absorption of fat-soluble vitamins—A,D,E, and K.
- It provides structure to cell membranes, modulating membrane integrity and fluidity, and organelles (tiny specialized parts of a cell that carry out its functions).
- It's necessary for brain and nervous system function.
- It provides a natural water repellent for skin and is a precursor for vitamin D synthesis.

Cholesterol is carried through the bloodstream by attaching to particles called "lipoproteins." Besides cholesterol, lipoproteins are spherical molecules that contain triglycerides, phospholipids, and apolipoproteins. There are four different types of lipoproteins that transport cholesterol in the bloodstream; they differ based on their protein content which determines their densities (they also differ in their triglyceride and cholesterol content). The higher the density, the higher the protein and the lower the lipid it contains. Note that lipoproteins are not just cholesterol.



- High density lipoprotein (HDL) are the smallest particles and have the highest percentage of protein (hence the name "high density") and lowest percentage of triglycerides.
- Low density lipoprotein (LDL) carry the majority of cholesterol in circulation. LDL particles consist of varying sizes and densities. Smaller, denser particles can be more atherogenic than larger ones.
- Very low density lipoprotein (VLDL) have the lowest percentage of protein with the main job of carrying triglycerides to cells.
- Chylomicrons are the largest particles and mainly carry triglycerides and cholesterol from the gut to the liver. They also transport triglycerides from the liver to the heart and skeletal muscle to use as fuel, and to fat cells for storage.

High levels of HDL particles reduce cardiovascular risk and low levels are associated with increased risk. Properly functioning HDL particles are beneficial because they:

- Traffic triglycerides to cells to use as an energy source.
- Deliver cholesterol to the adrenal glands and testicles or ovaries to make hormones, especially in situations of high demand.
- Remove cholesterol from the artery wall and transport it back to the liver for breakdown or to the intestines for reabsorption or excretion. HDL can also facilitate transport of cholesterol to LDL particles so they can bring it back to the liver or intestines.
- Inhibit LDL oxidation and minimize inflammation.
- Promote repair of endothelial cells and stimulate nitric oxide production.

The level of HDL isn't as important as how well it functions. Unfortunately, measuring HDL-C (cholesterol bound to HDL) or HDL-P (HDL particles) does not reflect HDL function—currently no test determines HDL function (although assays are currently being developed[91]) and artificially increasing HDL cholesterol levels doesn't reduce cardiovascular events[92,93] (although raising HDL particle count may).[94,95]

LDL's main purpose is to deliver triglycerides (energy) and phospholipids to cells. Most of the time, they carry cholesterol back to the liver. If LDL particles are too abundant, especially if the endothelium is dysfunctional, they can deposit cholesterol in the wall of arteries. The LDL

particles that are retained initiate atherosclerosis.[96] Deposited cholesterol can then be modified (oxidized or glycated) and engulfed by a white blood cell, starting plaque development. When plaque becomes calcified (as the body attempts to stabilize rupture-prone soft plaque) the arteries become "hardened." Plaque can also become inflamed and oxidized, festering like a wound in the artery wall, eventually breaking through the "scab" or fibrous plaque. This can cause a blood clot to form, chocking off the artery.

Besides delivering triglycerides and phospholipids to cells, LDL particles play a role in the innate immune system. LDL particles may protect against infection from bacteria, viruses, and parasites, and neutralize lipopolysaccharide (LPS) from gut bacteria (in the case of "leaky gut"), preventing tissue damage from endotoxins.[97,98] If high LDL is caused by infection or inflammation, periodontal disease, or intestinal hyperpermeability ("leaky gut"), treating the underlying cause is necessary to lower LDL.

LDL particles are made and cleared by the liver. If your LDL level is high, treating the cause is key. Very high LDL may be due to genetics, known as "familial hypercholesterolemia" or FH, requiring medication. Heterozygous FH affects 1 in 250 people and homozygous FH 1 in 160,000 to 1 in a million.[99,100] Therefore, most cases of elevated LDL are not due to genetics.

There are 5 major subgroups of LDL—IDL (or "intermediate density lipoprotein"), and LDL I, II, III, and IV. IDL is the largest, least dense, and most buoyant; LDL IV is the smallest and most dense. The smaller the LDL particle, the more dangerous it is. Small-dense LDL (LDL III and IV) is more atherogenic because it can penetrate the endothelium easier (similar to a golf ball fitting through a net, whereas a beach ball would bounce off of it). In addition, small LDL particles stay in circulation longer than large, buoyant ones.

Regardless of the type of LDL particles you produce, over time, **LDL particles cause atherosclerosis and cardiovascular disease.[101]** Note that LDL particles (LDL-P) cause atherosclerosis and are more important to measure than the cholesterol level of these particles (LDL cholesterol or LDL-C).[102] If your LDL particle count is high, you need to lower production or improve its clearance. If your high LDL is not due to genetics (remember, familial hypercholesterolemia is uncommon), there is much you can do to reach your LDL goal.

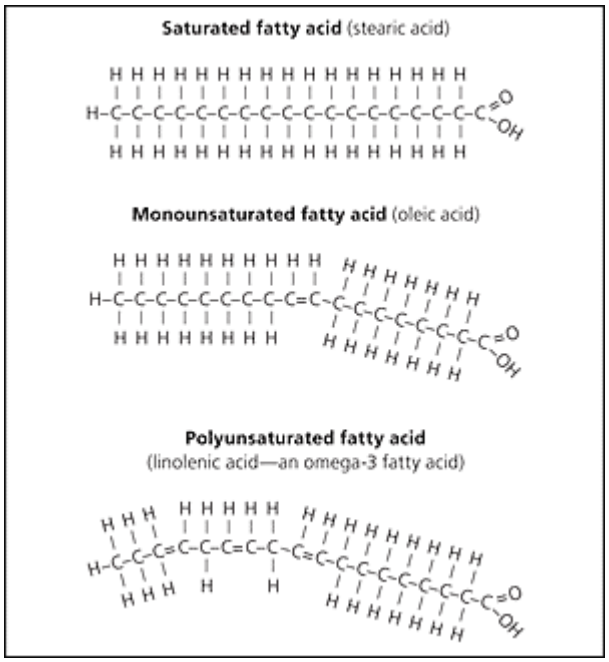
The most important step to improve protective HDL and reduce atherogenic LDL is to optimize your diet and exercise. Although the Treatment section will give you specifics on fine tuning your diet and ideal exercise habits, some diet guidelines specifically focused on optimizing lipids will be offered here.

Many people believe that limiting their intake of food-sources of cholesterol is the most important way to obtain healthy cholesterol levels. However, **dietary cholesterol has very little impact on your cholesterol levels** [103,104] and does not increase cardiovascular disease risk.[105] Most of the cholesterol (approximately 85%) in your body is made by your body—reabsorption of self-made cholesterol that's excreted into the intestines via bile is the main source of cholesterol in circulation. So, limiting high cholesterol foods such as egg yolks won't impact your serum cholesterol levels that much. In fact, most people who eat more cholesterol-containing food will decrease their body's production of cholesterol.[106] However, some people are cholesterol hyperabsorbers, meaning they tend to over-absorb cholesterol from the intestines. Measuring cholesterol production markers

(lathosterol and desmosterol) and absorption markers (beta-sitosterol, campesterol, and cholestanol) can determine if you are a cholesterol over-producer or over-absorber.

The most contentious issue regarding nutrition and cardiovascular risk surrounds type and amount of fats in the diet. All fats are not equal. A recent analysis published in the British Medical Journal summarizes this fact succinctly: *" . . . Researchers and public health authorities now agree that to consider the effect of total fat intake alone on health is meaningless; different types of fats must be considered*."[107]

Fats differ based on the number of double bonds in their carbon chain (saturated fats have no double bonds, monounsaturated fats have one, polyunsaturated fats have multiple), whether the double bonds are on the opposite position (as in trans fats), and the length of the carbon chain. Many foods contain different types of fat but one source may predominate (e.g., olive oil is mostly monounsaturated but also contains polyunsaturated fat).



There's no debate about the need to significantly limit or avoid all trans fat from fried or packaged food (any "hydrogenated" or partially hydrogenated" oil). Trans fats not only raise LDL and triglycerides and lower HDL, they also impair endothelial function, promote blood clots, and increase cardiovascular disease risk and death (from any cause!)[108,109]

Saturated fat may or may not influence your lipid levels. The source of saturated fat (e.g., dairy, eggs, coconut, beef), the length of the carbon chain (medium or long), and what replaces saturated fat in the diet can all influence results.[110] The most abundant saturated fats in the diet are long-chain—16-carbon atoms (palmitic acid found in palm oil, red meat, and dairy) or 18 carbon atoms (stearic acid found in animal fat and coconuts). Palmitic acid may raise LDL whereas stearic acid appears to have a neutral effect.[111]

Medium-chain fatty acids or medium-chain triglycerides, "MCT oils," contain 6 to 12 carbon atoms and are found in high amounts in coconuts and smaller amounts in dairy products. These fats go straight to the liver and can be used for energy or turned into ketones, an alternative energy source for the brain. They're less likely to be stored as fat and appear to improve insulin sensitivity and help with weight loss.[112] Overall, most studies do not link eating saturated fat and increased risk of heart attack or cardiovascular disease.[113-115]

Monounsaturated fats found in nuts, olives/olive oil, and avocadoes are beneficial for your heart and arteries for many reasons—they lower LDL, oxidation, inflammation, and clotting risk, and may improve endothelial function and blood pressure.[116,117]

Polyunsaturated fats (PUFAs) are essential, meaning they must come from the diet since they can't be made by the body. There are 2 types—omega 3 and omega 6. These are found in fatty fish such as wild salmon and sardines, vegetables, nuts, and seeds. PUFAs lower LDL while improving HDL, and lower cardiovascular risk, especially if they're eaten instead of saturated fat.[118]

Avoiding processed food, particularly processed grains or refined carbohydrates and sugar, is critical to improve your lipid profile. Timing, type and amount of carbohydrates eaten, and other foods eaten with the carbohydrate determine the impact on your body. For example, if you exercise, your body uses carbohydrates as fuel, or stores them in muscles as an easily accessible form or energy called "glycogen." However, if you don't exercise, if you eat excessive carbohydrates, or if you have high blood sugar and insulin levels, your liver converts glucose from carbohydrates into triglycerides (this is called "de novo lipogenesis"). The liver creates VLDL particles to transport these triglycerides to cells to use them as energy or store them in fat cells. After VLDL particles release triglycerides, they are cleared by the liver or converted to LDL particles. Therefore, high insulin levels produce high triglyceride levels and most people with high triglycerides have the more atherogenic form of LDL (small dense LDL). In other words, if you have elevated blood sugar and insulin production, your triglycerides increase and your liver must produce more LDL particles to traffic cholesterol (since more triglyceride content means less cholesterol is carried; therefore, more LDL particles are needed to transport cholesterol).

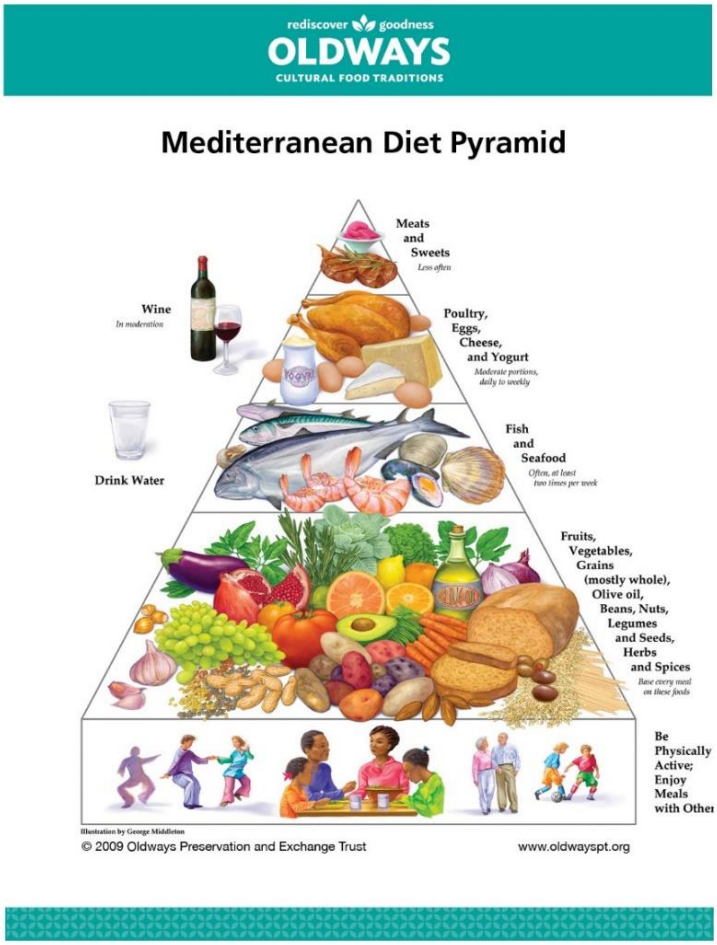
Research on low-carbohydrate diets and lipid levels is conflicting with meta-analyses showing lower triglycerides and higher HDL-C, with either no change, or increased LDL-C.[119-122] This is likely because of different carbohydrate quality (fiber content, glycemic impact) amount consumed (different definitions of "low-carb" diets), populations studied (although most studies were of insulin resistant, diabetic people), and other factors (e.g., amount of fat or fiber in other foods consumed with carbohydrates, exercise vs no exercise).

Refined carbohydrates include grains that have been processed to remove the fiber—this is how flour is made. Refined carbs are found in bread, pasta, white rice, pastries, cereal, processed corn and many snack items. High fructose-containing beverages such as pop or fruit juice not only spike blood sugar and insulin, they can cause your liver to become congested with fat. This condition called "fatty liver" is found in at least 25% of American adults and 70-90% of people who are obese and can lead to cirrhosis and liver cancer.[123,124]

Not all carbs are bad or cause LDL elevation, especially in people with normal insulin sensitivity. Healthy carbohydrates are great sources of fiber, vitamins, minerals, and plant compounds that lower LDL and improve endothelial function. These include vegetables, some fruit (especially berries), legumes (beans, chickpeas, lentils), and unprocessed whole grains such as steel-cut oats, wild rice, and quinoa.

It's important to note that foods are not just isolated macronutrients and that eating food is more than the sum of individual nutrients—a concept known as "**food synergy**"[125]. The most important dietary pattern you can adopt to lower LDL production, improve LDL particle size, enhance HDL activity, and lower your risk for heart attack and stroke (as well as erectile dysfunction, diabetes, obesity, several forms of cancer, and dementia) is to implement a Mediterranean diet.[126] Studies linking the Mediterranean diet with impressive cardiovascular benefit are abundant.[127] In fact, the PREDIMED trial showed that when people at high risk for cardiovascular disease eat a Mediterranean diet, especially if they supplement with extra virgin olive oil or nuts, they significantly lower their risk for heart attack, stroke, and death.[128]

There are, of course, many different countries and cultures that surround the Mediterranean and confusion exists about the definition of this diet. Consensus is that the ideal Mediterranean diet is high in unprocessed grains, vegetables and fruit, legumes, nuts and seeds, and olives and olive oil. Moderate consumption (at least twice per week) of fish and seafood, eggs, poultry, dairy (especially fermented such as yogurt and cheese) is encouraged. Infrequent intake of red meat and sweets is also a focus as well as beverages being mainly water and red wine in moderation. The Mediterranean Diet Pyramid was created by Oldways, a food and nutrition nonprofit organization, in partnership with the Harvard School for Public Health & the World Health Organization. In addition to emphasizing the above diet, the pyramid highlights regular exercise and physical activity, community involvement, and enjoying meals with others.



Treatment for dyslipidemia in addition to diet and exercise: The foundation for improving lipid levels should be to optimize your diet and exercise habits as much as possible. If this isn't enough, or if the presence of atherosclerosis is significant, other therapies may be needed. This includes medications or natural supplements. You may grimace at the thought of adding medications to your treatment plan. Good medicine is using the right treatment at the appropriate time for each individual patient—while adhering to the oath, "first do no harm" (which includes not enabling a person to have a premature heart attack, stroke, or develop dementia due to fear or misinformation about medications). Using the right treatment at the appropriate time is the best medicine.

Medication options: The enzyme that controls cholesterol production is called "HMG-CoA reductase." Statin medications, such as Lipitor® or Crestor,® block this enzyme in the liver, reducing cholesterol synthesis. The liver then increases LDL receptors to take in cholesterol from the bloodstream, lowering LDL particles in circulation.

Several naturally occurring statins (called "monacolins") are found in red yeast rice, as well as the phytosterols—beta-sitosterol, campesterol, and stigmasterol. More information on red yeast rice can be found in the supplement section.

Zetia® blocks intestinal absorption of cholesterol. Recall that approximately 85% of cholesterol in your body was made by your body—reabsorption of this self-made cholesterol that's excreted into the intestines via bile is the main source of cholesterol in circulation. Zetia block this excreted cholesterol from being absorbed, as well as pulling cholesterol back out of bile and mildly increasing LDL receptors in the liver. If your LDL-P is not at goal, taking Zetia in addition to a statin may lower your risk.[129] Unfortunately, in some people, Zetia can shift the ratio of large, buoyant LDL to more atherogenic, small dense LDL particles.[130]

Fenofibrate (Tricor®) activates lipoprotein lipase, increasing fat breakdown and elimination of triglyceride-rich particles from the bloodstream. This promotes a shift from small, dense LDL particles to large buoyant ones. Fenofibrate also increases HDL particles and reduces serum uric acid levels in people with high uric acid. Fibrate medications are best used in people with persistent high triglycerides and low HDL cholesterol levels.[131,132] Fibrates can lower microvascular disease (retinopathy and kidney disease) in diabetics.[133]

Natural therapies: There are many natural therapies that can help lower production of LDL, convert small LDL to large particles, and upregulate LDL receptors in the liver (therefore, lowering LDL in circulation). In addition, some natural substances have been shown to decrease triglycerides, reduce intestinal absorption of cholesterol, and possibly enhance HDL activity to remove cholesterol from the arteries. See the supplement section for more information.

4. Maintain optimal blood sugar and insulin (reverse metabolic syndrome).

Remarkably, only 4 grams of sugar (~3/4 teaspoon) circulates in the blood of an insulin-sensitive 150-pound person.[134] When you're sedentary and fasted, your brain consumes approximately 60% of blood glucose. If the level falls significantly, symptoms such as heart racing, sweating, dizziness, and confusion can occur with severely low blood sugar causing seizures and death. Your body has a sophisticated control system to protect itself from running out of glucose that involves communication between your brain, muscle, fat cells, intestines, liver, and pancreas. The most important pancreatic hormones regulating blood glucose are glucagon and insulin. During sleep or in between meals when blood sugar is normally low, the pancreas secretes glucagon causing your liver to release stored glucose. If demand for glucose is great, glycogen in the liver and muscles can be broken down. If glycogen stores become critically low (for example, after long bouts of exercise), your liver can make more glucose.

After you eat a meal with carbohydrates, insulin is secreted enabling your liver and muscle to take up glucose for immediate fuel or fat cells to store it as triglycerides for later use. Your abdomen contains a lot of insulin receptors, which is the reason high insulin production leads to fat accumulation around your waist.

Insulin resistance and type 2 diabetes are now an epidemic. Among all US adults, more than a third currently have impaired fasting glucose and insulin resistance, often referred to as

prediabetes. More than 12% of US adults are diabetic. Among people over 65, the percentage of prediabetics jumps to nearly 50% and the number of diabetics is more than 25%. This means that more than 100 million American adults have insulin resistance and prediabetes or type 2 diabetes.[135] In 2017, the cost of caring for diabetic Americans was $327 billion, with medical expenditure per diabetic patient of nearly $17,000.[136] This trend is obviously not sustainable.

Insulin resistance, which precedes diabetes, occurs in a step-wise fashion: initially, high blood sugar (from eating too much sugar and refined carbohydrates or excess calories, lack of exercise, or long-term stress) causes the pancreas to secrete excessive amounts of insulin. If this continues, eventually muscle then liver cells won't respond to the high level of insulin—they become resistant.[137] Over time, high blood sugar causes a decline in muscle mass, worsening elevated glucose (since muscle takes up the most glucose after a meal).[138] Excess glucose is shunted to the liver and adipose cells which turn it into fat. To overcome resistance, higher levels of insulin are secreted, which becomes a self-perpetuating cycle.

Most people with diabetes die from cardiovascular disease. Even, if your blood sugar level isn't high enough to be considered diabetes or prediabetes, elevated glucose and insulin in the bloodstream (known as "hyperinsulinemia") is harmful to your blood vessels and heart. In fact, even without diabetes, insulin resistance is a good predictor of cardiovascular disease[139] causing several overlapping problems. For example, chronically elevated blood sugar triggers oxidative stress and inflammation. High insulin levels alter lipid metabolism, known as dyslipidemia, increasing triglycerides, lowering HDL particles, and raising small dense LDL particles.[140] Elevated blood sugar and insulin also impair proper endothelial function, promoting plaque development, high blood pressure, and clot formation.[141]

Don't use genetics as an excuse. When it comes to metabolic syndrome and diabetes risk, genetics may load the gun but your diet and lifestyle choices pull the trigger.

Besides damaging blood vessels and contributing to atherosclerosis, hyperinsulinemia can damage the heart muscle itself, preventing it from pumping properly. Consider the fact that your heart must pump non-stop from the moment you're born, requiring a constant supply of energy (ATP). There is no way to store this energy in the heart; therefore, the mitochondria in heart cells require a continual supply of substrate to make ATP. Normally, the heart prefers making ATP from fatty acids rather than glucose.[142] The level of free fatty acids in circulation determines uptake in the heart. In a state of hyperinsulinemia, the heart has a rich fatty acid supply and glucose use is inhibited. This causes glucotoxicity from a buildup of glucose. In addition, accumulation of fatty acids leads to their storage in lipid droplets inside heart cells (called "lipotoxicity").[143] This can cause dysfunction of heart cells, enlargement of the heart itself (cardiac hypertrophy or cardiomyopathy), and impairment of the heart's ability to pump blood. Eventually, this leads to heart failure.[144]

Insulin resistance is caused by a variety of factors. Although some people may be genetically prone, most cases are due to eating an unhealthy diet, overeating, lack of exercise, and being overweight. The good news is that insulin sensitivity can be restored and insulin production lowered. This requires modifying what and how often you eat (restricting sugar and processed carbohydrates and preferably, practicing time-restricted eating), reducing abdominal fat, optimizing exercise intensity and frequency including weight training to build muscle, improving resiliency to stress, and maintaining healthy hormone levels. Even if you have a strong family history of diabetes, the Nurses' Health Study suggests that 90% of type 2 diabetes can be

attributed to four factors within your control: excess weight, lack of exercise, poor diet, and smoking.[145] Remember, you are not your genes—you are how your genes express themselves.

5. Achieve an ideal weight.

Fat tissue needs blood vessels to feed it. If you accumulate fat, your body must continue remodeling the vascular network (arteries, arterioles, capillaries, veins, etc.) to create new vessels and dilate existing capillaries.[146] Every extra pound of fat requires many extra miles of blood vessels to feed it—the number of miles is debatable, up to 200 miles per pound of fat is cited.[147] Excess fat tissue strains your heart and deprives other tissues of oxygen and nutrients. Losing as little as 5 to 10 percent of your body weight can reduce insulin levels and blood pressure and decrease your risk of heart attack, stroke, and diabetes.

What's more important than the extra pumping your heart must endure to feed fat tissue is that fat, especially visceral fat around your waist, produces more than 35 adipokines—most of these are inflammatory chemicals and hormones that directly participate in the development of insulin resistance and cardiovascular disease.[148,149] In addition, the presence of visceral fat reflects epicardial fat, meaning **the more belly fat you have, the more fat you have encasing your heart.[150]**

There are many contributing factors to being overweight, including stress, emotional eating, lack of exercise, poor diet choices, toxicity, and hormone imbalances. Genetics may play a role; however, how your genes express themselves is largely within your control—influenced by your diet, lifestyle, nutrient intake, and toxicity level.

Perhaps you believe that weight gain is common with aging due to the age-related slowing of metabolism and loss of muscle mass. It is true that after age 45 the average person loses 10% of their muscle mass per decade.[151] Some research indicates that body weight changes as early as age 25, with a gradual gain of 30 pounds between ages 25 and 55.[152] Because muscle burns more calories than fat, the total calories you burn each day declines with aging which is why small dietary changes—adding only 10 extra calories per day (that's one Lifesaver, two M&Ms, or one-half Hershey's kiss) rather than eliminating that many—**can lead to one pound of weight gain every year or 30 pounds by the time you reach your mid-50s.**

The good news is that aerobic exercise and strength training can offset some of the decline in metabolism associated with aging.[153,154] Restoring hormones to youthful levels can also improve muscle mass and bone health. In addition, some supplements may be beneficial at reducing appetite, lowering blood sugar and promoting insulin sensitivity, and optimizing mitochondrial production and function. This includes fiber, MCT oil, beta hydroxybutyrate, fish oil, berberine, nicotinamide riboside, resveratrol, pterostilbene, and coenzyme Q10 (more on supplements later).

If you are overweight, commit to a plan to reduce it. Nearly all studies show that eating a calorie-restricted diet high in nutrients can slow signs of aging and lead to weight loss.[155–158] No single diet is best for everyone. One long-term study that compared diets with different compositions of fat, protein, and carbohydrates, suggests that weight loss may be related to calories, not which macronutrient (fat, protein, or

carbs) is emphasized.[159] However, low carbohydrate diets are often more effective and easier to stick with than low fat diets.[160-162]

Two low carbohydrate diets that can help with weight loss include the Paleo and very low carb, high fat or "ketogenic" diet. The Paleo diet eliminates grains, sugar, legumes and dairy, and emphasizes unprocessed, whole foods including meat and fish, vegetables, low-glycemic fruit, nuts, and seeds. People following this diet tend to eat fewer calories per day and lose weight, especially visceral fat, and improve their blood sugar, blood pressure, and lipid levels.[163-168] The ketogenic diet is a high-fat diet, restricting carb intake to 20-150 grams per day (depending on overall calories), sticking to a ratio of 75-90% fat, 5-15% protein, and 5-10% carbohydrates. After adjusting to the diet, the body will use fat instead of carbohydrate to generate ATP or energy. This is because fatty acids are transported to the liver and turned into ketones which can be used by the heart and brain as fuel. The ketogenic diet can decrease blood sugar and insulin levels, improving insulin sensitivity.[169-171] This diet is often easier to follow than low-calorie diets since fat improves satiety, decreasing hunger and appetite.[172,173] There is good evidence that following a ketogenic diet is very effective for long-term weight loss.[174]

Regarding cardiovascular risk, the ketogenic diet may improve lipids (triglycerides, LDL cholesterol, and HDL cholesterol), especially in overweight or obese patients.[175,176] This is expected due to reducing blood sugar and insulin release and promoting fat loss (see the sections on lipoproteins and insulin resistance for more information). However, in some people, the diet increases LDL cholesterol (LDL-C) and LDL particle number (LDL-P). In a study of highly-trained athletes following the ketogenic diet for more than a year, LDL-C and LDL-P increased, although particle size was the large, buoyant rather than small dense type.[177] The significance of the LDL increase in this study is uncertain since it's possible that increased LDL in elite athletes without other cardiovascular risk factors has a different impact than in people without such a high level of fitness (for example, the study points out that the dramatically accelerated rate of fatty acid oxidation due to extreme exercise requires increased lipid metabolism). In any case, if you follow a ketogenic diet, it's probably best to eat healthy forms of polyunsaturated and monounsaturated fat (fish, nuts, seeds, avocados, olives and olive oil) rather than very high amounts of saturated fat (butter, cream, fatty meat, "Bulletproof coffee") to optimize weight loss and glycemic control without significantly boosting potentially atherogenic LDL particles.

The most successful weight loss programs combine changes in behavior, diet, nutritional education, and exercise.[178] In other words, just following a diet is usually not enough to maintain weight loss—it's more effective to learn about nutrition, improve your food choices, implement more exercise, and enhance self-awareness. In addition, accountability—through frequent group attendance or individual sessions—leads to a much better likelihood of achieving weight loss goals.[179] If you want to achieve and maintain your ideal weight, here is a plan that can work:

- Commit to losing weight. If this has been your story, "*It doesn't matter what I do, I can't lose weight…"* **stop telling it.** You know this story isn't true and it doesn't serve your health goals to reinforce it. Instead, write a new story that includes the fact that vibrant health feels exponentially better than self-medicating with unhealthy food, remaining sedentary, or "checking out" with self-destructive behaviors. As you develop a new story, tell others. The more you repeat your health-affirming story, the more it becomes your reality.

- At minimum, stop eating refined carbohydrates and sugar. Wheat and other high-glycemic grains and starches (e.g., white rice, potatoes, corn) and sugar increase blood glucose causing a corresponding spike in insulin. This leads to fat accumulation, especially around

the waist, decreased satiety (feeling full), and rebound hunger. For some people, wheat, refined carbohydrates, and sugar hijack the brain and can feel like an addiction. Oftentimes, cravings will subside after a few days of avoiding these substances. Targeted amino acid therapy to increase the brain's production of dopamine and serotonin may help with cravings. To uncover emotional eating triggers and eliminate them, see Roger Gould's book *Shrink Yourself* and interactive, web-based program www.shrinkyourself.com.

- Eat based on internal hunger, not your watch. The old advice of eating every 2 to 3 hours to "increase" metabolism may lead to weight gain and does not increase metabolism, thermogenesis (energy expenditure), or weight loss.[180-182] At minimum, eating every 2 to 3 hours trains people to eat by their watch not internal hunger cues. Your body preferentially burns recently ingested carbohydrates rather than stored fat when you eat often. Therefore, limiting carbohydrates and frequency of eating (unless you binge when hungry) is ideal.

- Identify and manage hunger. Overweight patients often tell me they never get hungry. This is because they eat for reasons other than physical hunger. There are 3 types of hunger: physical, psychological, or mouth hunger. Physical hunger causes growling in the stomach and an empty feeling inside. When you experience physical hunger, it's easier to make healthy food choices. If you don't experience physical hunger, don't eat. If you are ready to perform time-restricted eating or intermittent fasting (discussed below), you'll need to learn to tolerate physical hunger, reassuring yourself you're not starving and knowing the physical hunger cues are temporary.

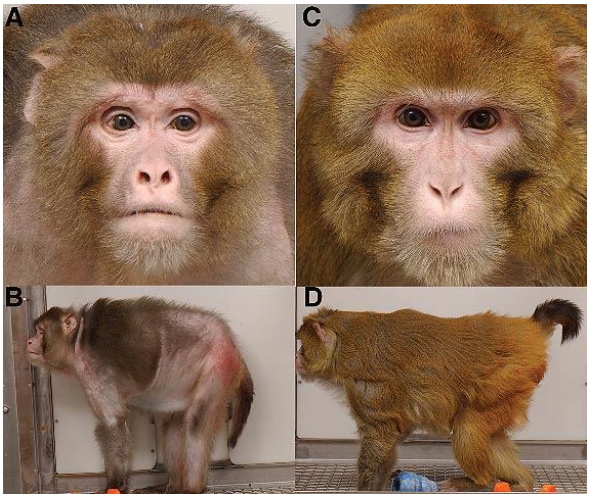
  Psychological hunger drives a person to eat to satisfy underlying emotions or feelings. Mouth hunger is the urge to eat more of food that tastes good. If you eat to satisfy psychological or mouth hunger, identify this and work on the underlying cause. If you overeat due to mouth hunger, improve mindfulness. Savoring food, chewing well, and eating more slowly can help. If you are an emotional eater, you can change this pattern. It can be valuable to record how you feel or what events precipitated unhealthy food choices in a diet diary. Ask for a copy of Dr. Retzler's handout "Ways to Break Free from Unhealthy Food Dependencies." Geneen Roth's books offer remarkable tools and new ways of thinking to break free from emotional eating.[183] In addition, psychiatrist Roger Gould, developed an, evidence-based program to permanently change emotional eating behavior. See: www.shrinkyourself.com or www.pockethungercoach.com

- Exercise regularly, at least 20-30 minutes every 24-48 hours. Not only will exercise enable you to burn more calories and increase muscle mass, but you're less likely to make poor food choices when you know the effort it takes to burn them off. For example, you need to run the length of a football field to burn off just one Lifesaver, two M&Ms, or one-half Hershey's kiss! Emphasize cardiovascular exercise to improve endothelial dysfunction and insulin resistance and weight training to increase basal metabolic rate (calories burned at rest). More on exercise below.

- Set up accountability for yourself by reporting to a group, weight loss coach, nutritionist, or Online program. You may also benefit from keeping a blog or posting your progress on Facebook or social media.

- Weigh yourself every day. This single accountability tool has been one of the most effective for me personally and in my clinical practice. Daily weighing doesn't allow you to develop "Ostrich Syndrome"—sticking your head in the sand about your weight. You may also want

to take body measurements or perform bioimpedence analysis (BIA), DEXA, or Bod Pod to monitor fat and muscle percentages throughout your weight loss journey. Don't fall prey to the thinking you don't need to measure your weight or fat and muscle mass because you know how your clothes feel. If you've become overweight, paying attention to how your clothes feel has not been an effective strategy.



- Perform calorie restriction, time-restricted eating, or periods of fasting. The science behind calorie restriction reaches across species—from protozoa and worms to hamsters, dogs, and primates. In most animal studies, calorie restriction (CR) is the most effective, reproducible intervention to delay age-related diseases and extend lifespan.

  2 studies—one conducted by the National Institute on Aging (NIA) and the other by the University of Wisconsin (UW)--involved rhesus monkeys kept on CR diet versus a control group for more than 20 years.[184,185] Both studies showed lower rates of cancer, heart disease, and diabetes. As expected, CR monkeys had decreased body fat; interestingly, they also had better preservation of muscle mass that normally declines with aging. Regarding cardiovascular risk specifically, CR monkeys had lower blood pressure, , lower LDL and higher HDL, and improved glucose regulation with better insulin sensitivity and lower blood sugar.

  The UW study monkeys lived longer than typical monkeys in captivity, however the NIA study didn't show CR lenghthened lifespan. A paper published online suggests several factors that could've led to the different longevity outcomes including the monkeys ages when the studies started (NIH monkeys included young, adolescent, and old monkeys whereas the UW study monkeys were all adults), genetic background (Chinese vs Indian), type of diet (NIA diet was naturally sourced to ensure phytochemicals and micronutriets were provided vs UW semi-purified diet to provide consistency), macronutrients in diet (NIA diet was lower in fat and sugar and higher in protein and fiber than UW), and timing of feeding (NIA monkeys fed 2 meals with afternoon meal allowed to be eaten overnight, UW monkeys were food deprived overnight).[186] Meal timing suggests a possible connecting between the circadian rhythm, metabolism, and longevity.

  Calorie restriction in humans seems to have similar benefits as animal studies. People from Okinawa eat a diet with 20% fewer calories than mainland Japanese and 40% fewer than Americans and have the longest life expectancy and greatest percentage of centenarians (people who live to be 100).[187] Results in human studies echo other species. One 6-month randomized study where the intervention group ate 25% fewer calories compared to the control group led to less DNA damage, inflammation, and blood clot risk as well as lower LDL and blood pressure. The calorie-restricted group also had improved insulin sensitivity and more mitochondrial production in skeletal muscles.[188,189] Results from another recent 2-year trial in young and middle aged (21-50 years), healthy, non-obese men and women underscored these benefits in cardiovascular risk reduction. With an average 12% calorie reduction, participants improved lipids (lower triglycerides and LDL, increased HDL), decreased hsCRP (therefore, lower inflammation), enhanced insulin sensitivity, and improved blood pressure.[190]

The bottom line is that calorie restriction—that doesn't lead to malnutrition or nutrient deficiencies—is an excellent way to improve blood vessel and heart health, probably improves your health span, and may improve your life span.

In addition to calorie restriction, time restricted eating (often referred to as "intermittent fasting) may be an effective weight loss and disease prevention tool. This diet restricts calories to a 6 to 12-hour eating window and is based on following the circadian clock, an area called the suprachiasmatic nucleus in the hypothalamus that keeps the body on a 24-hour schedule.[191] Researcher Satchidananda Panda has discovered that confining calorie consumption to an 8 to 12-hour window may reduce diabetes, obesity, and cardiovascular disease.[192]

In one study, obese adults who ate between 10 am and 6 pm and drank only water for the remaining 16 hours for 12 weeks lost weight; unfortunately, lipids, blood sugar, insulin, and homocysteine levels were unchanged.[193] In another crossover study of prediabetic men, eating all food during a 6-hour window, ending by 3:00 pm versus eating over 12 hours for 5 weeks led to improved insulin sensitivity, blood pressure, oxidative stress, and appetite.[194] The results were seen even without weight loss, suggesting a connection with circadian rhythms in metabolism.

Nearly all studies on time restricted eating or fasting regimens lead to weight loss without harmful side effects.[195] Alternate day fasting (eating a very reduced calorie diet or drinking only water every other day) can cause intense hunger on fasting days and has not been shown to be more effective for weight loss than overall calorie restriction.

There are many forms of calorie restriction, time-restricted eating, and intermittent fasting. Experiment with what works best for your lifestyle and body and perform lab and body composition testing to determine your ideal regimen. Following are some options to try:

1. Reduce calories by 10-40% every day while ensuring optimal micronutrient, protein, fiber, and healthy fat intake. To determine your calorie allotment, deduct 10-40% of your daily calorie expenditure. Your daily calorie expenditure is the calories you burn through daily activity and exercise plus basal metabolic rate (BMR, the number of calories you burn just to survive). There are different equations used to estimate your BMR—the Harris-Benedict formula is a common one:

   Women: BMR = 655 + (9.6 × weight in kg) + (1.8 × height in cm) – (4.7 × age in years)

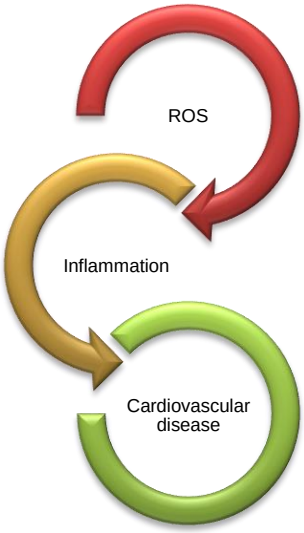
   Men: BMR = 66 + (13.7 × weight in kg) + (5 × height in cm) – (6.8 × age in years)

2. Practice intermittent fasting. Two options include eating a 40% calorie-reduced diet for two days per week or the method advocated by Michael Mosley, MD—limiting calories to 500 per day for two days per week (referred to as the "5:2 diet"). For more information on Dr. Mosley's perspective on intermittent fasting, see his book, *The Fast Diet.*

3. Practice time-restricted eating by consuming all calories within a 6 to 10-hour window. Ideally, early eating vs later eating may be more effective to improve blood sugar and insulin response.[196] In addition, allow 3 hours between your last meal and bedtime.

If you've tried unsuccessfully to lose weight on your own in the past, consider investing in a program such as the **HormoneSynergy Ideal Weight Brain Balance program**. This

program is comprehensive, covering all the above topics. Natural and pharmaceutical appetite suppressants enable a person to follow a lower calorie diet with emphasis on permanent weight loss. Remember that maintaining an ideal weight requires daily (often, moment-to-moment) commitment to healthy eating and exercise habits—there are no shortcuts.



6. Reduce inflammation & oxidative stress.

Oxidative stress and inflammation are interconnected and interdependent. Oxidative stress occurs due to an imbalance between reactive oxygen species (ROS—different types of free radicals) and the availability of antioxidants that neutralize them. ROS are produced from normal cellular metabolism, sun or radiation exposure, excess calorie intake, poor diet, obesity, cigarette smoking, toxin exposure, and over-exercising.

In normal cells, ROS are produced in a controlled manner, serving many useful purposes. For example, they are signaling molecules that regulate cell division, inflammation, immune function, and autophagy (degradation of old or damaged cells). Excess ROS or oxidative stress induces endothelial dysfunction, high blood pressure, and vascular disease, and triggers the onset and progression of inflammation.

Next time you get a cut or splinter, observe your body's healthy acute inflammatory response. A splinter represents a foreign invader—your body launches an attack by increasing white blood cell activity and releasing chemicals that cause redness and swelling to attempt to rid the body of the intruder and heal the injury. This is normal and healthy. Unfortunately, in blood vessels, inflammation draws immune cells such as monocytes to the site of injury, where they slip through the artery wall. These monocytes consume modified LDL particles and cholesterol becoming macrophages, eventually forming foam cells and creating plaque. Other immune cells, such as T cells, further the inflammatory process.

Chronic or sustained inflammation is a well-recognized contributor to atherosclerosis and cardiovascular events such as heart attacks and strokes.[197] Heart surgeon Dwight Lundel, MD likens the chronic inflammatory process inside arteries to "a stiff brush repeatedly being rubbed over soft skin until it becomes red and nearly bleeding."[198]

Inflammation is the result of several, overlapping causes that damage the endothelial lining and promote plaque. Inflamed atherosclerotic plaque is like a wound that smolders until it causes the plaque to rupture and a clot to form. There are several tests that reflect oxidative stress and inflammation including F2-isoprostanes, oxidized LDL, hsCRP, $LpPLA_2$, fibrinogen, myeloperoxidase, TNFα, interleukin-6 (IL-6), and IL-17.

Causes of oxidative stress and inflammation overlap. Major causes that are within your control include obesity, excess calories, and poor diet choices. Excess body fat, especially around the waist, produces inflammatory molecules called "adipokines" (such as TNF-alpha, IL-6, & CRP) causing a type of "smoldering inflammation," contributing to cardiovascular disease.[199,200]

Eating sugar, refined carbohydrates, fast food, processed meats (e.g., hot dogs, bacon, lunch meat), and trans fat all increase inflammation.[201-204] In addition, eating omega-6-containing vegetable oils (e.g., soybean, safflower, sunflower, cottonseed, and corn oil) can cause an imbalance in essential fatty acid levels. If the ratio of omega-6 to omega-3 level is high, proinflammatory molecules can be created. The most common omega-6 fatty acid is linoleic acid—this is the fatty acid that becomes oxidized in LDL. Oxidized LDL causes atherosclerosis and inflammation.[205] Although randomized controlled trials have not shown an association between omega-6 intake and increased inflammatory makers, the ratio of omega-6 to omega-3 intake is 16:1 in today's Western diet.[206,207] For prevention of cardiovascular disease, the ideal ratio is likely 4:1 or lower. Note that our ancestors who ate mostly land animals had a ratio of 2:1 to 4:1.[208] The easiest way to achieve a healthier omega-6-to-omega-3 fatty acid ratio is to stick to olive oil and eat fish, avoiding all other added vegetable oils.

Modestly restricting calories without causing malnutrition can significantly reduce oxidative stress and inflammation.[209-212] See information above regarding periodic fasting, calorie restriction, and time-restricted eating.

Toxin exposure including excess alcohol, cigarette smoke, ozone, radiation, pollution, pesticides, and some household cleaners create ROS and can tip the balance toward inflammation. Avoid these toxins whenever possible.

Moderate exercise boosts antioxidant enzymes made by the body to minimize the impact of free radicals. Although the function of these enzymes diminishes with aging, exercise has been shown to maintain these antioxidant enzymes with advancing age.[213] On the other hand, overtraining actually increases oxidative stress and reduces total antioxidant capacity.[214]

Intestinal hyperpermeability, often referred to as "leaky gut" is another common cause of inflammation.[215,216] The primary function of the intestinal barrier is to modulate what gets into the bloodstream and what stays out. If the barrier is breached, lipopolysaccharide (LPS) from gram-negative bacteria in the gut gets into circulation provoking an immune response, increasing inflammation. Interestingly, LDL particles can bind to LPS, acting as scavengers to neutralize endotoxin.[217] More on leaky gut causes and treatment below.

It's best to identify and treat the causes of oxidative stress and inflammation and shift to an anti-inflammatory diet and lifestyle. Focus on a predominantly Mediterranean, whole-foods diet rich in healthy fat (nuts, seeds, avocados, olives, and coconut), vegetables, low-glycemic fruit, free-range protein, wild caught, fish, and legumes. In addition, just 20 minutes of moderate exercise daily can decrease inflammation.[218] Stress management tools such as mindfulness meditation, yoga, and improving heart rate variability can all mitigate inflammation.[219-221]

Supplements and some herbal medicines have been shown to effectively reduce oxidative stress and inflammation. Upregulation of Nrf2, a protein that is the master regulator of antioxidant responses, may be the most beneficial way to minimize ROS damage. Besides calorie restriction, Nrf2 can be upregulated by eating a Mediterranean diet including lots of olive oil and moderate intake of red wine.[222] In addition, resveratrol, pterostilbene, sulforaphane, curcumin, green tea, and quercetin can boost Nrf2 activity.[223] The most potent supplement to induce Nrf2 seems to be sulforaphane, a sulfur-rich compound abundant in raw cruciferous vegetables such as broccoli and broccoli seed sprouts, cauliflower, cabbage, and kale.[224] Coenzyme Q10 may be particularly helpful to reduce oxidative stress in people with cardiovascular disease.[225] In addition, glutathione is the most potent antioxidant made in your body. You can increase glutathione production or function from eating sulfur-rich food (garlic, onions, cruciferous vegetables, eggs, whey protein) or supplementing with n-acetyl cysteine

(NAC, the precursor for glutathione synthesis). Bioavailable forms of glutathione (liposomal, nano-sized, or s-acetyl glutathione) may reduce damage from oxidative stress.[226-229]

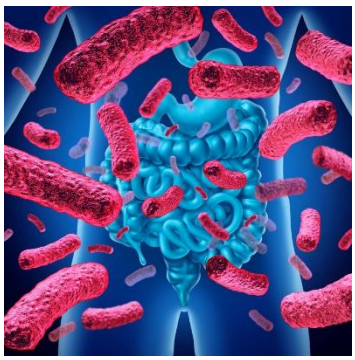
Besides lowering oxidative stress to reduce inflammation, curcumin (a component of the spice turmeric), ginger, and fish oil are all potent anti-inflammatory agents.[230--232] Statin medications have also been shown to reduce inflammation, atherosclerosis progression, and cardiovascular events, [233,234] even in people without high LDL.[235]

7. Treat underlying infections and autoimmune diseases and optimize gut health.

Chronic or frequent infections and autoimmune diseases may contribute to atherosclerosis by increasing inflammation and through a process known as "molecular mimicry."[236] This means that foreign viruses or bacteria induce an immune response that may cross react with the body's tissues including blood vessels. Autoimmune diseases (such as rheumatoid arthritis and lupus), the result of an imbalanced immune system, can also cause atherosclerosis.[237]

Bacteria that lead to periodontal disease provoke an immune response along with chronic, low-grade local and systemic inflammation. This is linked with an increased likelihood for developing atherosclerosis[238,239] In fact, periodontal bacteria have been found in atherosclerotic plaque in the arteries.[240.241] It's critical to have a dentist performs a thorough exam of your gums since approximately 50% of American adults have periodontal disease.[242]

Besides periodontal microbes, herpes, cytomegalovirus, H. pylori, Chlamydia pneumonia, HIV, Mycoplasma pneumonia, Epstein Bar virus, and hepatitis A, B, and C are all associated with heart disease.[243,244] In fact, bacterial DNA from more than 50 different species have been identified in atherosclerotic plaque.[245] The greater the number and duration of chronic infections (the "pathogenic burden"), the more likely a person will develop coronary artery disease.[246] This doesn't mean that atherosclerosis is caused by infections. Since lipoproteins are part of the innate immune system,[247] microbes may end up in blood vessels from lipoproteins binding them. However, infections can induce LDL oxidation and raise inflammation, promoting atherosclerosis and plaque rupture.



Besides autoimmune diseases and chronic infections, an unhealthy milieu of gut bacteria or poor intestinal lining can contribute to atherosclerosis and heart disease through "the heart-gut axis."[248] In fact, the gut contains approximately the same number of normal flora or bacteria (called the "microbiota") as cells in the human body.[249] An imbalance of this bacteria called "dysbiosis" is implicated in type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), and obesity.[250-252] Dysbiosis also contributes to hypertension, atherosclerosis, cardiovascular disease, and heart failure through several mechanisms. [253,254]

Recall that most cholesterol in the bloodstream is reabsorbed from self-made cholesterol eliminated in bile that's excreted into the small intestine. Bile helps with fat digestion and most bile acids and cholesterol are reabsorbed with some being eliminated in the stool. Cholesterol that reaches the large intestine is transformed by intestinal bacteria into coprostanone and coprostanol, which are poorly absorbed from the intestine and are, therefore, excreted.[255] This activity decreases blood cholesterol levels.

More than 90% of gut bacteria is made up of 2 phyla, *Bacteroidetes* and *Firmicutes,* with the remainder being remarkably diverse. Greater bacterial diversity in the gut is associated with

lower body fat and triglycerides and increased HDL levels.[256] People with low gut bacterial diversity are more likely to be obese and have insulin resistance and lipid abnormalities.[257] Specifically, fewer *Bacteroidetes* species are found in obese people and this type of bacteria increases with weight loss on a low-calorie diet.[258] Mouse studies have demonstrated a causal link between gut bacteria and weight gain. For example, if germ-free mice are given bacteria from obese mice, their body fat increases, whereas germ free mice given bacteria from lean mice do not become obese.[259]

Besides intestinal bacteria playing a role in cardiometabolic disease, the health of the intestinal lining influences blood vessel health. If the intestinal lining is impaired (as in "leaky gut") pathogen-associated molecules drive an immune response leading to systemic and tissue-specific inflammation. For example, if lipopolysaccharide (LPS), a component of intestinal bacterial cell walls, ends up in the bloodstream due to leaky gut, it's a strong risk factor for cardiovascular disease.[260]

Leaky gut has several causes. One class of medications—non-steroidal anti-inflammatory drugs (NSAIDs) such as celecoxib, meloxicam, diclofenac, ibuprofen, and naproxen—should be highlighted. More than 30 million people take NSAIDs daily.[261] Although these medications are very effective as short-term anti-inflammatory pain-relievers, they can damage the cardiovascular system, kidneys, liver, and GI tract, increasing the risk for heart attack, stroke, heart failure, and GI issues.[262] Many people know that NSAIDs can cause stomach problems such as ulcers and gastritis. Unfortunately, NSAIDs also increase intestinal permeability within 24 hours of ingestion and can cause severe leaky gut if taken long-term.[263,264]

Development and function of the intestinal barrier depends upon gut bacteria. Therefore, anything that contributes to dysbiosis or an imbalance of normal flora can lead to leaky gut. This includes antibiotics which can affect gut microbiota in the short-term and possibly long-term.[265,266] Proton pump inhibitors ("PPIs"), such as Prilosec®, Prevacid®, and Nexium®, were designed to suppress acid production in the stomach. These drugs significantly alter the gut microbiota,[267] including increasing the risk for overgrowth of potentially life-threatening *Clostridium difficile*. This serious consequence of long-term PPI use was summarized in a meta-analysis of 42 studies, prompting the FDA to issue a drug safety warning about these medications.[268] Unfortunately, PPIs are still available over-the-counter and are widely used.

In susceptible people, gluten/gliadin-containing grains, such as wheat, barley, and rye, can cause leaky gut, regardless of Celiac disease diagnosis.[269,270] Food allergies can also contribute to leaky gut.[271] Heavy alcohol use can disrupt the intestinal barrier through several mechanisms including release of histamine, inflammatory chemicals, and reactive oxygen species (free radicals), increasing the likelihood of leaky gut.[272]

You can optimize your intestinal barrier by avoiding these medications that harm healthy gut bacteria. In addition, diet and lifestyle factors significantly impact the microbiota. For example, gut bacteria normally ferment fiber from food into short chain fatty acids (SCFA). The most abundant SCFAs—aetate, propionate, and butyrate—are metabolized in the colon and help maintain the barrier of the small and large intestine. Eating plenty of healthy fiber from food, not supplements, with every meal is critical to improve gut bacteria and intestinal cell health. Focus on getting at least 25-30 grams of fiber per day, depending on your overall food intake. There are 2 types of fiber—soluble and insoluble. Most plants contain both soluble and insoluble fiber in different amounts. Soluble fiber absorbs water and becomes a gel or dissolves in water and is digested by gut bacteria into SCFA. Sources of soluble fiber include beans, lentils, oats, fruit, and all vegetables. Insoluble fiber adds bulk to the stool and shortens transit time but is not digested. Insoluble fiber is found in beans, vegetables, whole (unprocessed) grains, seeds, and

nuts. Although technically fiber is a form of carbohydrate, it's not absorbed and, therefore, doesn't increase blood sugar or calorie intake.

Supplementing with certain live beneficial bacteria called "probiotics," can improve tight junctions and help heal leaky gut. *Lactobacillus salvarius UCC118* strain has been shown to adhere to intestinal cells and improve barrier function.[273,274] In addition, several strains of probiotics can impact cardiovascular risk factors, lowering blood pressure, LDL-cholesterol, blood sugar, and inflammation.[275,276] For example, *Lactobacillus reuteri* and *Lactobacillus plantarum* can reduce triglycerides and LDL cholesterol and improve HDL levels.[277] *Lactobacillus reuteri* (NCIMB 30242 strain) has also been shown to lower serum cholesterol and hsCRP and fibrinogen (markers of inflammation).[278] Specific strains of *Lactobacillus rhamnosus* (ATCC53102 & 103) and *Bifidobacterium lactis 420* have been shown to help with weight loss, specifically visceral fat.[279,280]

8. Optimize hormone levels.

The most important hormones for healthy blood vessel and heart function include thyroid hormone, estrogen, DHEA, and testosterone. Age-related hormone decline contributes to cardiovascular disease and supplementing with bioidentical hormones may protect blood vessels and heart health.

Arguably, thyroid is the most critical hormone for ideal cardiovascular health. Hypothyroidism (low thyroid hormone) promotes atherosclerosis due to effects on endothelial function, blood pressure regulation, and lipid metabolism. Hypothyroidism can increase apoB-containing particles (mainly LDL-P) due to decreased clearance of LDL in the liver.[281] Endothelial dysfunction and elevated CRP are seen in hypothyroid patients.[282] Inadequate thyroid hormone promotes stiffening of arteries and decreases the heart's contractility and output.[283] If untreated, hypothyroidism increases heart attack and stroke risk and causes heart failure.[284-286] With adequate thyroid supplementation, these risk factors can improve and atherosclerosis progression can be delayed.[287] In fact, abnormal carotid artery-intima media thickness (CIMT) can be reversed in hypothyroid patients treated with thyroid hormone.[288] Since T3 is the active thyroid hormone that enters the heart cell, it's important to make sure T3 levels are optimal in addition to ideal T4 levels.

Estradiol protects the heart and blood vessels by inducing vasodilation (blood vessel relaxation), improving blood flow, and enhancing endothelial function.[289-294] Testosterone supplementation may improve endothelial function in women[295] and may enhance strength and endurance in women with congestive heart failure.[296] Women with higher estrogen levels and those who use estrogen therapy have been shown to have lower calcification of the coronary arteries (the arteries feeding the heart).[297-299]

Estradiol supplementation increases HDL (more with oral than transdermal) and decreases total and LDL cholesterol.[300] Oral estradiol increases clotting factors and CRP whereas transdermal estradiol does not.[301,302] Although oral estradiol seems to favor blood clot formation, some studies show it also improves fibrinolysis (prevention of blood clots).[303,304] Transdermal (through the skin) estradiol may be a better choice than oral supplementation for heart disease risk.[305]

Estradiol replacement can also lower blood sugar levels and risk of developing diabetes.[306] Higher levels of androgens, specifically DHEA-sulphate and testosterone in women, are associated with lower CIMT (arterial wall thickness).[307] Supplementing with DHEA may improve endothelial function, independent of androgen and estrogen receptors.[308] Women with low testosterone are more likely to experience a cardiovascular event than women with the highest levels.[309]

Age-related testosterone decline can contribute to cardiovascular disease risk in men. Men with low testosterone have been shown by meta-analysis to have an increased risk of death from all causes, including cardiovascular disease.[310] Somewhat recently, two observational studies published in the Journal of the American Medical Association (JAMA) and PLoS One reported that testosterone supplementation increased heart attack risk.[311,312] It's worth discussing the JAMA study in detail since men with cardiovascular risk may be denied testosterone by their doctors due to the incorrect assumption that testosterone supplementation will harm them.

The authors of the JAMA study published the wrong conclusion which has been poorly reported in the media and misunderstood by countless physicians. This study concluded that men who received testosterone had a higher risk of heart attack, stroke, and death. The study looked at approximately 8,700 veterans with low testosterone (<300 ng/dL) who underwent coronary angiograms from 2005 to 2011. Testosterone prescriptions were given to 1,223 men; 7,468 men did not receive testosterone therapy. The study's authors published the wrong conclusion, stating a higher event rate (25.7%) in men who received testosterone prescriptions vs 20% event rate in men who did not receive testosterone therapy. This was incorrect. Of the 7,486 patients who did not receive testosterone prescriptions, 681 died, 420 had heart attacks, and 486 had strokes. This was an absolute event rate of 21.2% (681 + 420 + 486 = 1587 events divided by 7486 men = 21.2%). Of the 1,223 men who received testosterone prescriptions, 67 died, 23 had heart attacks, and 33 had strokes. This was an absolute event rate of 10.1% (67 + 23 + 33 = 123 events divided by 1223 men = 10.1%). Therefore, men who did not receive testosterone prescriptions had more than double the risk for an event than men who did receive prescriptions. More than 160 leading experts from 32 countries have asked JAMA to retract this paper;[313] unfortunately, as of the date of this writing, JAMA has not done so.

In contrast, another recent observational study following 25,000 men over age 65 found that men on testosterone injections did not have an increased risk for heart attack. In fact, in men with high cardiovascular risk, testosterone was modestly protective.[314]

Note that these studies are observational, not intervention, studies. In an observational study, investigators observe subjects and measure their outcomes—the researchers do not actively manage the study. In an intervention study (e.g., a randomized controlled trial), the investigators give the research subjects a particular drug or other intervention and compare the treated subjects to subjects who receive no treatment (placebo). Researchers then measure how the subjects' health changes. Observational studies do not prove causation; they can, however, reveal the need for intervention trials. Ideally, physicians should base treatment decisions on the results of many studies after weighing an individual patient's risks and benefits.

Clear associations between low endogenous (made in the body) testosterone and higher risk for heart disease, heart attack, stroke, and death from cardiovascular disease exist.[315-320] This is likely due to the conditions and cardiovascular risk factors associated with low testosterone including endothelial dysfunction, increased atherosclerosis and arterial thickness, increased inflammation, dyslipidemia, insulin resistance and metabolic syndrome, type 2 diabetes, and obesity.[321-328] Testosterone deficiency is considered by some authors to be a major risk

factor for cardiovascular disease.[329,330] Low testosterone is also associated with increased risk of death from cardiovascular disease.[331]

Many observational and several intervention studies show no increased risk of heart attack or stroke in men with higher endogenous testosterone levels or men treated with testosterone. Most studies are consistent when it comes to testosterone supplementation improving cardiovascular risk factors and decreasing heart attack and stroke risk. One 14-year observational study reported decreased cardiovascular and all-cause mortality in men using testosterone supplementation.[332] Another observational study of 1,031 veterans reported twice the mortality risk for men with low testosterone who were untreated (20.7%) versus those who were treated (10.3%) over 2 to 4 years of therapy.[333]

A deficiency of testosterone likely plays a role in the development of insulin resistance and type 2 diabetes, and testosterone therapy improves metabolic syndrome parameters such as high blood sugar, insulin resistance, hsCRP, and blood pressure.[334-338] Testosterone therapy has also been shown to improve survival in men with type 2 diabetes.[339]

Regarding lipids and inflammation, testosterone supplementation has been shown to lower LDL cholesterol and triglyceride levels, as well as reduce inflammation.[340,341] Physiological doses of testosterone may also improve synthesis of nitric oxide and, therefore, endothelial function.[342,343] Testosterone replacement increases lean body mass (muscle) and reduces visceral fat percentage.[344-346] In men with heart disease, testosterone supplementation improves angina (chest pain) symptoms, likely because it dilates coronary arteries.[347-350] Testosterone also improve exercise capacity, insulin resistance, and muscle performance in men with congestive heart failure and can improve their survival.[351,352]

Diet

The relationship between diet and coronary artery disease is more complex than cholesterol intake, involving genetics, vitamins, antioxidants, fiber, other fatty acids, flavonoids, and phytosterols.[353] Eating a diet high in vegetables and low-glycemic fruit, quality protein, and healthy fats is **the most important step** in optimizing cardiovascular health. As preventive cardiology guru Dr. Mark Houston states, "*Atherosclerosis and vascular disease are post-prandial phenomena.*" Dr. Houston is referring to the fact that every time you eat you influence lipid levels, generate free radicals and inflammation, and introduce bacteria and toxins into your body, possibly causing blood vessel damage. Put another way, eating inflammatory food (especially high trans-fat or sugar) increases systemic and vascular inflammation, oxidation (free radical damage), endotoxemia (especially if you have "leaky gut"), and autoimmune responses in blood vessels. These effects are cumulative and contribute to endothelial dysfunction and atherosclerosis.[354] This means that the food you eat and the amount eaten are critical choices affecting your cardiovascular system in real time.

What's the best diet—Ornish, Paleo, Gluten-free, Ketogenic, Mediterranean . . .?

It seems that a new study is published weekly about the "best" diet to follow and gurus with great social media influence spread their opinions provoking confusion, frustration, and arguments. There may be a best diet for you as an individual based on your health status and genetics. Despite seemingly conflicting information in self-help books, solid, evidence-based nutritional tenets do exist. For example, **plant-centered diets** high in fiber and low in saturated fat, sugar, and refined grains can reduce diabetes.[355] You've learned that a high-fat ketogenic diet can improve blood sugar, insulin sensitivity, and weight loss; however, low-fat, vegan diets have also been shown to do this.[356,357] If you already have cardiovascular disease, Drs. Dean

Ornish and Caldwell Esselstyn have been effectively reversing plaque, lowering cardiovascular disease risk, and extending lives for decades with a low-fat, plant-based diet (consisting of whole grains, legumes, vegetables, fruit, with 10-15% of calories coming from fat).[358,359]

So where should you start? Regarding overall diet, it seems most data points to a low refined carbohydrate, healthy fat, Mediterranean-style diet as the most effective way to reduce cardiovascular disease risk. Following are ideas to help you adopt this type of diet.

Check the boxes next to the following dietary suggestions you will follow:

☐ **Focus on what you know you need to eat**, rather than just trying to avoid unhealthy foods. Ask yourself if you've met your body's nutritional needs—minimum of 5-7 servings of vegetables and low-glycemic fruit (such as berries), good quality protein, healthy fats, and minimal whole (not refined) grains or high fiber food—every day.

☐ **Eat more produce.** Consider making a smoothie for breakfast or lunch. Include colorful berries (blueberries, cranberries, blackberries, raspberries, or strawberries), protein powder, unsweetened Greek yogurt (if not dairy intolerant), nuts, and green leafy vegetables (e.g., kale or spinach). You can add unsweetened coconut or almond milk. Avoid bananas, mangoes, pineapple, and rice milk—they increase blood sugar too much.

A simple way to boost your vegetable intake is to order a vegetable platter every week from a natural foods market or cut vegetables in advance. Store them in Debbie Meyer Green Bags® or other containers that preserve freshness. Bring hummus or other high-protein dip (consider edamame pureed with avocado, lime, Greek yogurt and cilantro) to work or serve with dinner. Convenience is key—if vegetables are washed and cut in advance, you're more likely to eat them for lunch or snacks.

You can also make **salad in a jar.** This is a simple way to make sure you eat several servings of vegetables per day:

1. Gather several wide-mouthed jars, such as a Mason jars.
2. Put salad dressing on bottom. Consider using 50% EVOO, 50% balsamic vinegar or lemon or coconut oil mixed with lemon juice or mustard.
3. Add harder vegetables (such as radishes, carrots, celery, broccoli, cabbage,), nuts, beans (black, pinto, edamame, garbanzos), and cherry tomatoes or blueberries next. These are least likely to become soggy over time. Avoid high water content fruits and vegetables (such as strawberries, cut tomatoes, and cucumbers).
4. Put greens on top. Consider romaine, arugula, kale, or spinach. Tear leaves rather than cutting them with a knife to prevent browning of edges.
5. Sprinkle flax or chia seeds on top for omega 3 oils and fiber, or other raw seeds, such as pumpkin seeds, or nuts (pecans, hazelnuts, almonds, or walnuts) on top.
6. Top with lid. When ready to serve, shake jar and empty contents onto plate.

- **Eat at least 2 cups of green leafy vegetables and/or 1 cup of beet root juice per day.** These vegetables are especially high in nitrates which get converted to nitrites increasing nitric oxide and endothelial function.[360-362]

- **Eat healthy protein sources.** Protein needs vary based on age gender, muscle mass, weight goals, and activity level; most adults need 45 to 90 grams per day. Good quality protein includes vegetarian options such as whey, non-GMO soy, beans, and nuts. Animal products such as wild-caught fish, dairy, eggs, poultry, and free-range meat may also good protein options. To minimize your exposure to toxins, it's best to eat free-range meat and wild caught fish, and to avoid fish high in heavy metals such as tuna and swordfish. Remember the pneumonic SMASH to stick to fish low in mercury (salmon, mackerel, anchovies, sardines, and herring).

- **If you're hungry when you wake up, start your day with a real heart-healthy breakfast (not Cheerios!).** Emphasize protein and avoid carbohydrates. Avoid all cereals, including instant oatmeal—they're usually high in refined carbohydrates and added sugar, and they dramatically increase blood glucose. In addition, granola is <u>not</u> a health food. Consider substituting unsweetened, high-protein yogurt (such as Greek yogurt) for milk or start your day with a protein smoothie (with kale and berries).Whey or pea protein are excellent protein powders to use. If you're not hungry in the morning, don't force yourself to eat breakfast. The old advice of eating every 2 to 3 hours to "increase" metabolism, may lead to weight gain, and certainly trains people to eat by their watch, not internal hunger cues. Rather than eating by the clock it's most important to plan healthy food for when you do get hungry.

- **Drink 8 ounces of pomegranate juice or eat pomegranate seeds often.** Pomegranate is full of compounds such as flavanols, which includes proanthocyanidins, that are powerful antioxidants. Eating or drinking pomegranate can decrease oxidized and glycosylated LDL and remove it from the arterial wall and reduce carotid IMT.[363,364] Pomegranate juice also increases the production of nitric oxide, decreases inflammation, and helps lower blood pressure.[365,366]

- **Increase your intake of berries**. Berries are high in proanthocyanidins and antioxidants and can help strengthen the inner walls and endothelial lining of blood vessels. Randomized, placebo-controlled, double-blind trials have shown that flavonoids from blueberries improved endothelial and blood vessel function.[367]Aim for eating at least one-half cup of berries every day.

- **Eat healthy fat.** "Unhealthy fats" include excessive saturated fat (from animal products) and omega-6 fatty acids such as soybean, canola, cottonseed, corn, and vegetable oils, and all trans fats.[368,369] Trans fats are made by heating liquid vegetable oils in the presence of hydrogen (hence the name, "hydrogenated oil"). It's relatively easy to avoid eating any trans fats—stay away from commercially packaged baked goods, snack foods, and fast food. Don't eat any food with "partially hydrogenated oil" on the label, avoid margarine and shortening, and don't eat fried food in restaurants.

The total amount of fat you eat may not be as important as the type of fat. "Healthy fats" include monounsaturated and polyunsaturated fatty acids. Monounsaturated fats are found in olives and avocados (and their oils) as well as nuts such as almonds, cashews, pistachios, pecans, cashews, pumpkin seeds, and sunflower seeds.. Good sources of polyunsaturated fats high in omega-3 fatty acids include salmon, herring, and sardines.

- **Avoid advanced glycation end products (AGEs).** These compounds are formed inside and outside the body from sugar attaching to proteins or lipids. AGEs damage blood vessels by increasing permeability and stiffness, preventing nitric oxide formation and blood vessel dilation, oxidizing LDL, and promoting free radical activity (oxidative stress) and inflammation. Besides contributing to cardiovascular disease and diabetes, AGEs literally cause aging. AGEs form during frying, roasting, and baking (especially any “browning” of food).

  Foods that you should avoid due to very high AGE levels include bacon, fast food hamburgers and hot dogs, cheese, pizza, fried food (especially meat, chicken, and potatoes).[370]

- **Do not drink any soft drinks.** High fructose corn syrup (HFCS) is the main sweetener used in the soft drink industry. It causes greater fat deposition than glucose and negatively impairs carbohydrate, triglyceride, and lipid metabolism.[371] Over time, drinking soft drinks and HFCS increases the risk of metabolic syndrome, fatty liver, atherosclerosis, diabetes, and erectile dysfunction.[372] Excess intake of calories and HCFS leads to the deposition of fat—abdominal or “visceral fat” and fatty liver.

- **Eat lots of herbs and spices.** Many spices have high polyphenol contents with antioxidant, immune system modulating activity. Spices, such as clove, cinnamon, oregano, rosemary, ginger, black pepper, paprika, and garlic have been shown to prevent endothelial dysfunction caused by high-fat meat.[373] Another study using a high-antioxidant spice blend (including black pepper, cinnamon, cloves, garlic powder, ginger, oregano, paprika, rosemary, and turmeric) significantly decreased postprandial insulin and triglyceride levels.[374] Adding these spices and a daily dose of Cassia cinnamon (1-2 teaspoons or 1-6 grams) can lower blood sugar, LDL cholesterol, and triglyceride levels.[375,376]

- **Enjoy dark chocolate.** Eating 1.6 ounces of dark chocolate high in flavonoids has been shown to improve endothelial function.[377] Dark chocolate has a high antioxidant content (1 oz. has an ORAC value of 4,000-5,900—more than berries, green tea, and red wine). Dark chocolate may enhance insulin sensitivity, lower LDL and raise HDL, and improve blood flow to the heart and brain.[378-381] Meta-analysis of 40 studies has shown that cocoa effectively lowers blood pressure, although the reduction is mild.[382]

- **Drink green tea.** Green tea is one of the healthiest beverages you can drink. Green tea and green tea extracts have been shown to improve endothelial function, reduce insulin and glucose, improve

high blood pressure, decrease inflammation (hsCRP& TNF-α), and reduce oxidative stress.[383-386] Green tea also lowers LDL and triglycerides and raises HDL. Drinking a minimum of 3 cups green tea per day may minimize heart attack and stroke risk.[387,388] In fact, a Japanese study of 203 patients found that the more green tea a person drinks, the less likely they are to have heart disease.[389] Consider brewing a fresh pot of green tea (or a mixture of green tea and peppermint) each morning, pouring into a glass jar, and sipping on it throughout the day for a refreshing alternative to water, soda, or coffee.

- **Moderate intake of eggs is okay.** Studies have shown that up to 3 eggs per day may increase HDL and, therefore, decrease the LDL-to-HDL cholesterol ratio.[390] A recent meta-analysis concluded that up to one egg per day does not increase risk of death from heart disease or stroke.[391,392]

- **Avoid or significantly limit simple or refined carbohydrates** such as sugar, wheat, and high-glycemic grains. This includes crackers, pastries, pretzels, corn chips, bread, pasta, and white rice. These foods dramatically raise blood sugar, damage the endothelium, and stimulate your body to boost unhealthy cholesterol production. Recall that low-carbohydrates may be more effective for weight loss and cardiovascular risk reduction than low-fat diets.[393]

- **Limit salt.** Excess salt intake impairs dilation of blood vessels and enhances their constriction, regardless of blood pressure.[394,395] Salt also damages the endothelial lining, decreasing nitric oxide production, and increases blood pressure, atherosclerosis and blood clot risk.[396] Unless your exercise and sweating is extreme, keep salt intake to a <u>maximum of 1500 mg per day</u>. If you ingest more than this, some of the detrimental effects may be augmented by potassium and magnesium supplementation.

- **Drink red wine in moderation.** If you don't have a problem with alcohol, red wine is likely beneficial for your heart and blood vessel health. A recent meta-analysis of 84 studies suggests that, overall, red wine drinking (one glass for women, two glasses for men per day) lowers the risk of dying from a heart attack or blood vessel disease by 25% compared with non-drinkers.[397] Meta-analyses has also shown that light or moderate alcohol consumption also protects against ischemic stroke risk, although heavy drinking may increase stroke risk.[398]

Exercise

If exercise were a drug, it would be a blockbuster. Research has shown that exercise **improves weight loss, decreases visceral and abdominal fat, lowers unhealthy cholesterol, repairs endothelial dysfunction, decreases blood pressure, reduces inflammation, and improves insulin sensitivity.**[399-404] Exercise also promotes mitochondrial health, stimulating production of new mitochondria and improves mitochondrial antioxidant systems. In addition, exercise influences the number and function of endothelial progenitor cells (EPCs). EPCs decrease with aging and are responsible for repairing blood vessel damage.[405,406] The number of circulating EPCs is critical in predicting cardiovascular risk.[407]

For exercise to become a way of life, it's important to start slowly and **think of yourself as an active person.** In other words, begin to incorporate changes into your lifestyle such as walking instead of driving and using stairs instead of escalators or elevators when possible.

If you want to get the most benefit from exercise, consider the results of a study comparing moderate continuous exercise and high intensity aerobic interval training.[408] **Interval training** was superior in enhancing endothelial function (arterial dilation, decreased clotting, and decreased likelihood of plaque formation), insulin sensitivity, muscle mass, and reducing blood sugar. Both exercise programs were equally effective at lowering blood pressure and reducing body weight and fat.

Interval training involves a series of low-to-high-intensity exercise interspersed with rest or recovery periods. One option is to warm up by walking, running, or biking at a low intensity pace for 5 minutes, then increase to high-intensity for 30 to 60 seconds, followed by lower intensity for 60-90 seconds. Repeat this pattern for a total of 8 times (if you're out of shape, start with 4 cycles and work up).

For maximum cardiovascular and brain benefit, you must exercise for at least 20-30 minutes every 24–48 hours. Your heart rate should be 65-75% of maximum during warmup and between interval bursts, and 84-92% of maximum during interval bursts. To determine your target heart rate, fill in these blanks:

Maximum heart rate = 208 – (0.7 x age): _____

Multiply by 0.84 = _____

Multiply by 0.92 = _____

My target heart rate to warm up and between intervals is: ____ beats per minute (bpm).

My target heart rate for intervals is: ___ to ___ bpm.

Goals:

- My immediate goal that I begin today and will continue for the next 2-3 weeks is to exercise for _____ minutes, by _____, _____ times per week.
- My long-term goal that I will implement by _____ is to exercise _____ minutes, a minimum of _____ times per week.

Lifestyle

Psychological stress, in the areas of work, home, finances, and major life events within the past year, has been shown to be a **more potent predictor of heart attack** than diabetes, hypertension, and obesity.[409,410] Stress can contribute to elevated blood sugar, insulin resistance, and endothelial dysfunction. Brief episodes of stress, such as those encountered in everyday life, cause transient endothelial dysfunction for up to 4 hours.[411] Chronic stress deteriorates endothelial function because hormones and chemicals released

under stress, such as glucocorticoids, pro-inflammatory cytokines, and endothelin-1, decrease synthesis and function of nitric oxide.[412]

It may be helpful to remember that the feelings and symptoms of stress are due to a sequence of biochemical events in your body. Technically, stress is not an actual event or circumstance—it's your body's reaction to an event or circumstance. This means that stress is not what happens to you—it's how you respond to what happens to you. You can control how you respond to events and circumstances in your life and you can diminish the impact stress has on your body.

One way to reduce your stress response is to minimize triggers. Consider these wise words from Earnest Holmes:

> *Some individuals, in spite of the pressures…around them, are able to master them, and literally become masters of their own lives. Others seem to let life overwhelm them….The difference can be traced to a way of thinking.*
>
> *Are you a slave or a master? Do you let external situations control you or do you control them?*

Becoming a master of your external circumstances takes time. If you feel easily overwhelmed or unempowered in your life, consider seeing a therapist or life coach trained in neurolinguistic programming (NLP). You can reprogram thinking patterns and develop a life-affirming, empowered way of being.

Since breathing controls your autonomic nervous system, one simple way to neutralize stress (and turn off the "fight or flight" response in the moment) is to **focus on your breathing**. Transcendental meditation (deep breathing while reciting a specific mantra) has been shown to reduce the incidence of heart disease, heart attack, stroke, and death.[413] Your heartbeat speeds up with every inhalation and slows down with every exhalation. When you feel stressed, focus on lengthening your outbreath. You may want to count—4 counts for each inbreath, 5 counts for each outbreath. After only 5 breath cycles you will significantly minimize the impact of stress.

If you need help minimizing stress, please see Dr. Retzler's "Emptying Your Stress Bucket" handout.

Sleep duration and quality are critical to cardiovascular health. Testing for and treating sleep apnea can literally save your life. At a minimum, 1 in 5 adults has at least mild obstructive sleep apnea (OSA) and 1 in 15 has moderate to severe OSA. Unfortunately, more than 85% of patients with OSA have never been diagnosed or treated. OSA can cause endothelial dysfunction, systemic inflammation, oxidative stress, insulin resistance, hypercoagulability (increased chance of blood clots), and can cause or contribute to kidney disease, stroke, hypertension, heart failure, arrhythmias, and heart attacks.[414]

The prevalence of sleep apnea in people with cardiovascular disease is startling—sleep apnea is found in 50% of people with hypertension, 30% of people with coronary artery disease, 30-40% of people with heart failure, and 50% of people who have a stroke.[415-417]

Symptoms of sleep apnea include:

- Disruptive snoring
- Witnessed apnea (episodes of not breathing) or gasping
- Obesity and/or enlarged neck size
- Sleepiness or fatigue during the day

When it comes to sleep duration, less than 6hours increases the risk for hypertension, diabetes, obesity, heart disease, heart attack, and stroke.[418-422] Sleeping more than 10 hours increases stroke risk. It seems that 8 hours is an ideal amount. If you're struggling with sleep, please ask for help. Request a copy of Dr. Retzler's handout "Getting a Good Night's Sleep" which contains information on sleep hygiene, natural remedies, and medication options. Consider using guided visualization or the Holosync® or Hemi-Sync® programs, or purchase an Alpha-Stim to help your brain produce calming brainwaves and turn off the stress response.

Alcohol can be a tonic or a poison, depending on the dosage. Red wine is, indeed, a good source of antioxidants and resveratrol. Moderate alcohol intake has been shown to reduce the risk of heart attack, stroke, and diabetes.[423–425]

Since alcohol is socially acceptable, many people overindulge without regard for the negative health consequences or the excess, "empty" calories it contains.

Meta-analysis has shown that, while moderate alcohol use (12 to 24 grams or approximately ½ to 1 ounce per day) reduces ischemic stroke, heavy use (>60 grams or 2 ounces per day) increases the risk.[426] One Canadian study looked at the health effects of binge drinking (8 or more drinks at one sitting) versus non-binge drinking. Binge drinking increased coronary heart disease in men and women and hypertension in men.[427]

How Is "Moderate" Defined?

Moderate drinking is usually defined as: ≤ 1 drink per day for women (≤ 2 per day for men) in the absence of binge drinking. One drink is defined as 12 oz. of regular beer, 5 oz. of wine (12% alcohol), and 1.5 oz. of 80-proof spirits, all equivalent to about 15 g of alcohol.

If you feel like your alcohol intake is excessive, commit to "**alcohol free nights**" at least 3 to 4 days during the week. If you're unable to stick to this commitment you may have an unhealthy dependence on alcohol or an actual addiction. Help in cutting down or quitting is available with medications and many effective programs, support groups, and cognitive behavioral. Please reach out and ask for help if you need it—alcohol dependency and addiction is nearly as common as sugar and carbohydrate addiction. You are not alone if you have a problem and need support.

Supplements/Nutraceuticals

As the word "supplement" implies, nutrients or herbs that improve cardiovascular health are meant to be used in addition to—not in place

of—eating a healthy diet, achieving ideal body composition, and improving exercise and lifestyle habits.

It's important to keep in mind that not all products are alike, no matter what the manufacturer or label may claim. In July 2016 Consumer Reports magazine published a guide to supplement safety stating that there are 15,000 supplement manufacturers whose products are sold in the US.[428] Very few of these facilities have been inspected by the FDA. So how do you know if the supplements you purchase are safe and of high quality?

FDA law requires supplement companies to follow current good manufacturing practices (cGMP). The purpose of cGMP is to prevent wrong or contaminated ingredients to be sold as supplements and to assure packages are correctly labeled and ingredient amounts are not greater or less than listed on labels. The Natural Products Association (NPA) is an organization that inspects facilities to make sure they comply with cGMP. The National Sanitation Foundation (NSF) tests products to verify accuracy and dosage of labeled ingredients and ensures there are no pathogens (such as bacteria, fungi, or other microbes), pesticides, heavy metals, or other contaminants in the bottle. The US Pharmacopeia (USP) also verifies that supplements contain ingredients stated on the label, in stated amounts, and that they're not contaminated. "Pharmaceutical grade ingredients" means the ingredient meets a specific monograph (or standard set of test parameters) set forth by USP, however, not all ingredients have a monograph. Lastly, the Therapeutic Goods Administration of Australia or TGA is part of the Australian government. In Australia, herbs, vitamins, minerals, nutritional supplements, and essential oils are regulated as medicines. The TGA is equivalent to the FDA approval for pharmaceuticals. Although it sounds like alphabet soup—NPA, NSF, USP, and TGA—make sure the supplement manufacturers you use meet the standards of these organizations.

Besides coming from cGMP companies, ideally the supplements you take should be scientifically evaluated to verify effectiveness of constituents. Few supplement manufacturers conduct clinical trials on their formulas to document safety and effectiveness because research is very expensive to perform. However, purchasing supplements that have research supporting them is a better investment in your health.

In addition to safety, quality assurance, and effectiveness, look for bioavailable forms of nutrients and dosages. The supplements you take are as important as any prescribed medications. In fact, you may consider them to be more important than prescription drugs since they can help you prevent the "polypharmacy" that is standard of care for aging Americans.

Your heart requires a constant supply of oxygen and nutrients. The most important quality supplements or nutraceuticals to protect the heart, optimize cholesterol levels, lower inflammation and oxidative stress, improve mitochondrial function, decrease insulin resistance and high blood sugar, and enhance endothelial function include fish oil, red yeast rice, antioxidants or substance that boost antioxidant enzyme function (vitamin C, mixed tocopherols, lycopene, lutein, resveratrol, flavonoids, EGCG from green tea), vitamin K, vitamins B3, 6, 12, and active folate, magnesium, curcumin, alpha-lipoic acid, cinnamon, berberine, chromium, and coenzyme Q10.

The following nutraceuticals may help in optimizing lipids and glucose control, lowering oxidative stress and inflammation, and reducing cardiometabolic risk:

- **Metabolic Recovery Formula** is a fructose-free, hypoallergenic, high-protein formula that supports healthy blood sugar, lowers inflammation and unhealthy cholesterol, and enhances digestion and detoxification. It can also help with

weight loss if used as a meal replacement once or twice per day

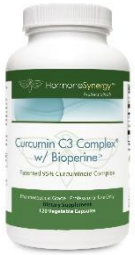
- **Berberine,** the bright yellow alkaloid found in Oregon grape, goldenseal, barberry, and other Chinese botanicals has extensive beneficial effects in reducing cardiovascular risk. Berberine improves glucose metabolism and insulin sensitivity and may be as effective as metformin in lowering blood sugar.[429,430] It has pleotropic effects in blood vessel and heart health by reducing inflammation, increasing nitric oxide production, and enhancing endothelial function.[431,432] Berberine also improves mobilization and function of endothelial progenitor cells (the cells that repair damaged blood vessels).[433,434] Berberine has been shown to reduce triglycerides and LDL-C through mechanism distinct from statins.[435,436] One small study showed that berberine can improve symptoms and extend life span in congestive heart failure patients.[437]

- **CholestProtect** contains citrus bergamot, berberine, and curcumin. These 3 ingredients effectively and safely improve lipid metabolism, cholesterol, and blood sugar levels. Supplementation of citrus bergamot (*Citrus bergamia*) inhibits HMG-CoA reductase, reducing LDL-C in addition to lowering triglycerides.[438] Bergamot decreases blood sugar, and small dense LDL, and improves HDL and fatty liver.[439] Berberine improves glucose metabolism and insulin sensitivity, and may be as effective as metformin in lowering blood sugar.[440,441] Berberine also has pleotropic effects in blood vessel and heart health by reducing inflammation and enhancing endothelial function.[442,443] Berberine lowers triglycerides and LDL-C through a unique mechanism distinct from statins.[444,445] By increasing nitric oxide production, berberine improves mobilization and function of endothelial progenitor cells that repair damaged blood vessels.[446,447] One small study showed symptom improvement and extended life span in congestive heart failure patients treated with berberine.[448] Curcumin can lower inflammation, prevent LDL oxidation, decrease blood clot risk, and improve endothelial function and possibly, HDL functionality.[449-451] Curcumin C3 Complex is the most clinically studied curcumin preparation. In patients with type 2 diabetes, 1000 mg of Curcumin C3 Complex reduces oxidative stress, increasing serum total antioxidant capacity and the activity of superoxide dismutase (SOD).[452] High-dose curcumin (4,000 mg of curcuminoids) has been shown to decrease heart attacks associated with coronary artery bypass.[453] Smaller dosages of a more bioavailable, absorbable form of curcumin have been shown to improve endothelial function similar to aerobic exercise.[454] Curcumin also improves intestinal hyperpermeability (“leaky gut”) and may help with inflammatory conditions.[455-458] Curcumin also improves brain function, minimizes inflammation and oxidation, and possibly decreases beta-amyloid deposition.[459-463]

- **Fish oil** significantly decreases triglycerides, improves LDL particle size, and reduces Lp-PLA_2 (blood vessel inflammation).[464-466] Fish oil also improves insulin resistance and lowers blood pressure.[467,468] Fish oil reduces inflammation and may lessen the risk for blood clots, heart disease, heart failure, arrhythmias, and stroke.[469–471] **SynergyPure EPA 1200** contains 1200 mg EPA per capsule. The addition of eicosapentaenoic acid (EPA) to statin therapy provides additional benefit in preventing major cardiovascular events, possibly through lipid-independent mechanisms. The Japan Eicospapentaenoic Acid Lipid Intervention Study (JELIS) tested long-term use of EPA 1800 mg/day in addition to statin therapy and found a decrease in major coronary events, fatal heart attacks, non-fatal heart attacks, unstable angina, and bypass and stent placement.[472] The recent REDUCT-IT trial showed 31% relative risk reduction in heart attack, 28% reduction in stroke, and 20% reduction in cardiovascular death risk in patients with heart disease and high triglycerides who took a statin plus 4,000 mg

of EPA per day compared to statin-only patients.[473]

- **Curcumin C3 Complex** contains bioavailable curcumin and flavonoids to lower inflammation, prevent LDL oxidation, decrease blood clot risk, and improve endothelial function and possibly, HDL functionality.[474-476] Curcumin C3 Complex is the most clinically studied curcumin preparation on the market. In patients with type 2 diabetes, 1000 mg of Curcumin C3 Complex reduces oxidative stress, increasing serum total antioxidant capacity and the activity of superoxide dismutase (SOD).[477] High-dose curcumin (4,000 mg of curcuminoids) has been shown to decrease heart attacks associated with coronary artery bypass.[478] Smaller dosages of a more bioiavailable, absorbable form of curcumin have been shown to improve endothelial function similar to aerobic exercise.[479] Curcumin also improves intestinal hyperpermeability ("leaky gut") and may help with inflammatory conditions.[480-483]Curcumin also improves brain function, minimizes inflammation and oxidation, and possibly decreases beta-amyloid deposition.[484-488]



- **UbiquiMax Q10** is a patented, standardized, highly absorbable form of CoQ10. Ubiquinone or Coenzyme Q10 is an enzyme used for ATP (energy) production in mitochondria. CoQ10 is also a potent antioxidant that prevents "internal rusting" of cells, and can prevent LDL oxidation.[489,490] Coenzyme Q10 levels decline with aging and can significantly decline, up to 40%, with the use of statins.[491] Supplementing with CoQ10 while on a statin can prevent CoQ10 depletion and possibly, statin side effects.[492] As little as 30 mg of CoQ10 improves endothelial function.[493] CoQ10 may also lower blood pressure and blood sugar, and improve arrhythmias.[494,495] In patients with heart failure, cardiovascular events and mortality may be reduced by taking higher dosages (300 mg) of CoQ10.[496]

- **Vitamin B3 (niacin)** has been used for lipid management for more than 40 years. It can decrease the incidence of heart attacks, reverse plaque, and reduce arrterial thickening (IMT) and carotid and coronary artery stenosis progression.[497-504] Niacin decreases total cholesterol, LDL-C and small dense LDL, apo B, triglycerides, and Lp(a).[505] Niacin also increases HDL-C, enhances reverse cholesterol transport, and endothelial function and nitric oxide synthesis.[506] In addition, niacin decreases inflammatory markers, namely levels of Lp-PLA_2 and C-reactive protein (CRP).[507] 2000 to 3000 mg is most effective; however, severe flushing can occur at these dosages so it's important to start with a lower dosage and work up. In addition, niacin can raise blood sugar, homocysteine, and liver enzymes—you must have your liver enzymes monitored if you take high dosages of niacin. HormoneSynergy Sustained-Release Niacin (made by Xymogen) or pharmaceutical Niaspan are least likely to cause flushing. Do not take Slo-Niacin, or encapsulated niacin. Taking an 81-mg aspirin or quercetin along with sustained-release niacin can minimize flushing.

- **Methyl B Synergy** contains active folate, B2, B6, B12, and trimethylglycine needed for healthy DNA methylation, synthesis, and repair, and to properly metabolize homocysteine. An optimally functioning homocysteine pathway provides methyl and sulfur groups for biochemical reactions such as detoxification, immune function, joint and cartilage structure, and brain and cardiovascular health. In excess amounts, homocysteine can damage the inner lining of arteries. Elevated homocysteine increases the risk for Alzheimer's,[508] osteoporosis and hip fracture,[509,510] heart disease,[511,512] stroke,[513] depression and anxiety,[514,515] and cognitive impairment.[516,517]

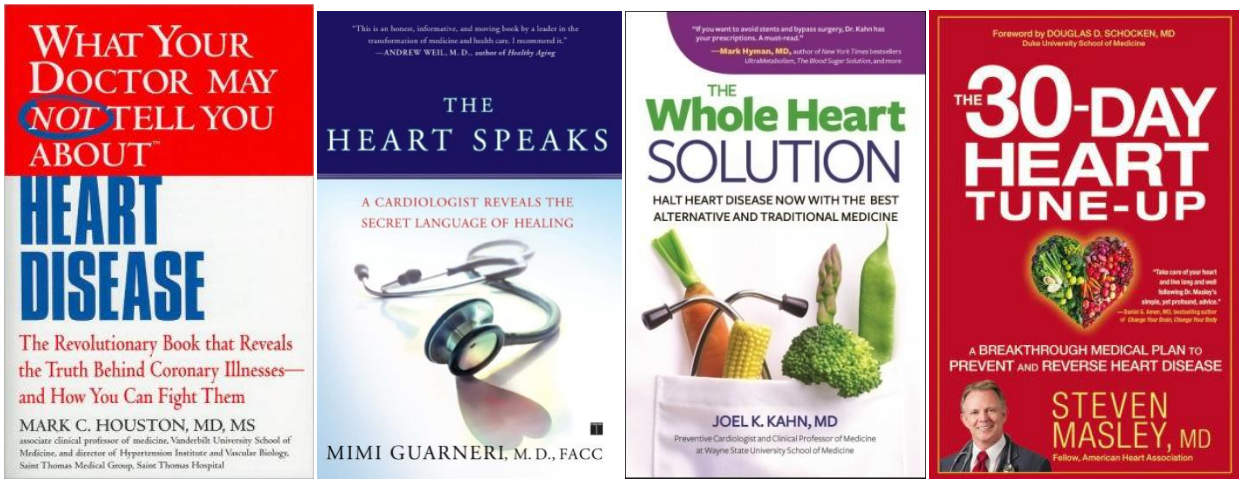
- **Red Yeast Rice** (*Monascus purpureus*) is a red-pigmented yeast grown on rice. A Chinese meta-analysis of 93 randomized trials including nearly 10,000 participants concluded that red yeast rice was comparable to, and in some studies, better than statin medications in lowering LDL-C and triglycerides and raising HDL.[518] Several naturally occurring statins (called "monacolins") are found in red yeast rice; monacolin K is identical to pharmaceutical Lovastatin®. Red yeast rice also contains phytosterols—beta-sitosterol, campesterol, and stigmasterol. Combined effects of these constituents may reduce atherosclerosis progression, CIMT, and improve plaque reversal. Red Yeast rice may also decrease blood clot risk, lower inflammation, and improve insulin resistance.[519-522] Dosage of red yeast rice ranges from 1,800 to 4,800 mg per day. It is critical not to use high-quality red yeast rice since many brands have been found to have contaminants and variability of monacolins.[523] High quality brands include HormoneSynergy (made by Xymogen), Thorne Research, Designs for Health, and Douglas Labs.

- **ArgiMax** contains high-potency L-arginine, citrulline, quercetin, cofactors, and antioxidants to increase nitric oxide (NO) production. NO improves endothelial function, enhancing blood flow and dilation of blood vessels. Improving endothelial function and health is critical for plaque prevention and stabilization, and to prevent blood clots. NO is needed to keep blood pressure low and for normal erectile function.

- **Alpha Lipoic Acid Controlled Release**is a patented, controlled-release, high dose (600 mg) form of alpha-lipoic acid (ALA). ALA is a whole-body antioxidant that neutralizes free radicals in both water and the lipid portion of cells. ALA helps the body synthesize glutathione, and "recharges" other antioxidants such as vitamins C and E, and CoQ10, giving them the ability to fight free radicals for extended periods of time. Data from a 12-week clinical study indicates that supplementation with ALAmax CR™ (1200 mg per day, divided doses) may support healthy C-peptide levels (C-peptide is used as an indication of insulin sensitivity).[524,525] ALA is a potent, safe antioxidant that may help decrease oxidized LDL and improve nitric oxide production and healthy endothelial function.[526-529]

- **Mitochondrial Synergy** contains three active, orally bioavailable formulas that stimulate SIRT1 mimicking the protective benefits of exercise and calorie restriction on mitochondrial biogenesis, metabolic fitness, and aging. These ingredients promote effecient use of insulin and glucose, increase exercise performance, and impove antioxidant status including glutathione synthesis. In addition, key constituents increase nitric oxide production, enhancing vasodilation and endothelial function

Recommended Reading



[1] Benjamin, et al. (2019). AHA Statistical Update. Heart disease and stroke statistics—2019 update. A report from the American Heart Associaton. *Circulation*. 139:e56-e528.
[2] Yusuf S, et al. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 364(9438):937-52.
[3] Ilic M, et al. (2018). Myocardial infarction and alcohol consumption: a case-control study. *PLoS One*. 13(6):e098129.
[4] Houston M. (2018). The role of noninvasive cardiovascular testing, applied clinical nutrition and nutritional supplements in the prevention and treatment of coronary heart disease. *Ther Adv Cardiovasc Dis*.12(3):85-108.
[5] Verma S, et al. (2003). Endothelial function testing as a biomarker of vascular disease. *Circulation*. 108:2054-9.
[6] Lerman A, Zeiher A. (2005). Endothelial function, cardiac events. *Circulation.*111:363-8.
[7] Matsuzawa Y, et al. (2013). Peripheral endothelial function and cardiovascular events in high-risk patients. *J Am Heart Assoc*. 2(6):e000426.
[8] Csiba L. (2006). Endothelial function testing. *Front Neurol Neurosci.* 21:27-35.
[9] Kuvin J, Karas R. (2003). Clinical utility of endothelial function testing: Ready for prime time? *Circulation.*107:3242-7.
[10]Corrado E, et al. (2008). Endothelial dysfunction and carotid lesions are strong predictors of clinical events in patients with early stages of atherosclerosis: a 24-month follow-up study. *Coron Artery Dis*.19(3):139-44.
[11]Smith S, et al. (2000). AHA Conference Proceedings. Prevention conference V. Beyond secondary prevention: identifying the high-risk patients for primary prevention. Executive summary. *Circulation.* 101:111–6.
[12]Modena M, et al. (2002). Prognostic role of reversible endothelial dysfunction in hypertensive postmenopausal women. *J Am Coll Cardiol.* 40:505–10.
[13] de la Sierra A, et al. (2014). Nocturnal hypertension or nondipping: which is better associated with the cardiovascular risk profile? *Am J Hypertens*. 27(5):680-7.
[14]Ishizu T, et al. (2002). The correlation of irregularities in carotid arterial intima-media thickness with coronary artery disease. *Heart Vessels.* 17(1):1-6.
[15] Moon JH, et al. (2015). Carotid intima-media thickness is associated with the progression of cognitive impairment in older adults. *Stroke*. 46(4):1024-30.
[16]Valenti V, et al. (2015). A 15-year warranty period for asymptomatic individuals without coronary artery calcium: a prospective follow-up of 9,715 individuals. *JACC: Cardiovasc Imaging.*8(8):900-9.
[17]Rosenberg S, et al. (2010). Multicenter validation of the diagnostic accuracy of a blood-based gene expression test for assessing obstructive coronary artery disease in nondiabetic patients. *Ann Intern Med*. 153:425-34.
[18]Thomas GS, et al. (2013). A blood-based gene expression test for obstructive coronary artery disease tested in symptomatic nondiabetic patients referred for myocardial perfusion imaging: The COMPASS Study. *Circulation: Cardiovascular Genetics*.6(2):154-62.
[19]Voros S, et al. (2014). A peripheral blood gene expression score is associated with atherosclerotic Plaque Burden and Stenosis by cardiovascular CT-angiography: results from the PREDICT and COMPASS studies. *Atherosclerosis.* 233(1):284-90.
[20] Centers for Disease Control and Prevention: http://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/effects_cig_smoking/
[21] Johnson H, et al. (2010). Effects of smoking and smoking cessation on endothelial function. 1-year outcomes from a randomized clinical trial. *J Am Coll Cardiol*. 55(18):1988-95.

[22] Morgan CJ, et al. (2013). Cannabidiol reduces cigarette consumption in tobacco smokers: preliminary findings. *Addict Behav.* 38(9):2433-6.
[23]Holyrod J. (1980). Hypnosis treatment for smoking: an evaluative review. *Int J Clin Experimental Hypnosis*. 28(4):341-57.
[24]Weiss EP,et al. (2008). Endothelial function after high-sugar-food ingestion improves with endurance exercise performed on the previous day. *Am J ClinNutr.*88(1):51-7.
[25] Iwata N, et al. (2011). Trans fatty acids induce vascular inflammation and reduce nitric oxide production in endothelial cells. *PLoS One*. 6(12):e29600.
[26] Lambert E, et al. (2017). Endothelial function in healthy young individuals is associated with dietary consumption of saturated fat. *Front Physiol.* 8:876.
[27] Nicholls SJ, et al. (2006). Consumption of saturated fat impairs the anti-inflammatory properties of high-density lipoproteins and endothelial function. *J Am Coll Cardiol.* 15;48(4):715-20.
[28]Plotnick G, et al. (1997). Effect of antioxidant vitamins on the transient impairment of endothelium—dependent brachial artery vasoactivity following a single high-fat meal. *JAMA*. 278(20):1682-6
[29] Fisher ND, et al. (2012). Habitual flavonoid intake and endothelial function in healthy humans. *J Am Coll Nutr*. 31(4):275-9.
[30] Vita J. (2005). Polyphenols and cardiovascular disease: effects on endothelial and platelet function. *Am J Clin Nutr*. 81(1):292S-297S.
[31] Varadharaj S, et al. (2017). Role of dietary antioxidants in the preservation of vascular function and the modulation of health and disease. *Front Cardiovasc Med*. 4:64.
[32] Brown A, Hu F. (2001). Dietary modulation of endothelial function: implications for cardiovascular disease. *Am J Clin Nutr*. 73(4):673-86.
[33]Papamichael C, et al. (2004). Red wine's antioxidants counteract acute endothelial dysfunction caused by cigarette smoking in healthy nonsmokers. *Am Heart J.* 147(2):E5.
[34] Gilchrist M, et al. (2013). Effect of dietary nitrate on blood pressure, endothelial function, and insulin sensitivity in type 2 diabetes. *Free Radic Biol Med*. 60:89-97.
[35] SPRINT Research Group (2015). A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 373(22):2103-6.
[36] Modena MG, et al. (2002). Prognostic role of reversible endothelial dysfunction in hypertensive postmenopausal women. *J Am Coll Cardiol*. 40(3):505-10.
[37] Law MR, et al. (2009). Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 338:b1665.
[38] Kjeldsen SE, et al. (2018). Intensive blood pressure lowering prevents mild cognitive impairment and possible dementia and slows development of white matter lesions in brain: the SPRINT Memory and Cognition IN Decreased Hypertension (SPRINT MIND) study. *Blood Press*. 27(5):247-8.
[39] SPRINT Research Group. (2019). Effect of intensive vs standard blood pressure control on probable dementia. *JAMA.* 321(6):553-61.
[40] Takagi H, Umemoto T. (2014). A meta-analysis of randomized controlled trials of telmisartan for flow-mediated dilatation. *Hypertens Res*. 37(9):845-51.
[41] Ghiadoni L, et al. (2012). Hypertension and endothelial dysfunction: therapeutic approach. *Curr Vasc Pharmacol*. 10(1):42-60.
[42]Javanmard SH, et al. (2011). Enalapril improves endothelial function in patients with migraine: a randomized, double-blind, placebo-controlled trial. *J Res Med Sci.* 16(1):26-32.
[43]Tzemos N, et al. (2009). Valsartan improves endothelial dysfunction in hypertension: a randomized, double-blind study. *Cardiovasc Ther*. 27(3):151-8.
[44] Shiota A, et al. (2012). Telmisartan ameliorates insulin sensitivity by activating the AMPK/SIRT1 pathway in skeletal muscle of obese db/db mice. *Cardiovasc Diabetol*. 11:139.
[45] He H, et al. (2010). Telmisartan prevents weight gain and obesity through activation of peroxisome proliferator-activated receptor-delta-dependent pathways. *Hypertension*.55(4):869-79.
[46] Sugimoto K, et al. (2016). Telmisartan but not valsartan increases caloric expenditure and protects against weight gain and hepatic steatosis. *Hypertension*. 47(5):1003-9.
[47] Ghebremariam Y, et al. (2014). Proton pump inhibitors and cardiovascular risk. *Circul.* 129(13):e428.
[48] Sibal L, et al. (2010). The role of asymmetric dimethylarginine (ADMA) in endothelial dysfunction and cardiovascular disease. *Curr Cardiol Rev.* 6(2):82-90.
[49] Lazaro A, et al. (2017). Use of proton-pump inhibitors predicts heart failure and death in patients with coronary artery disease. *PLoS One*. 2017;12(1):e0169826.
[50] Shah N, et al. (2015). Proton pump inhibitor usage and the risk of myocardial infarction in the general population. *PLoS One*. 10(6): e0124653.
[51] Malhotra K, et al. (2018). Cerebrovascular outcomes with proton pump inhibitors and thienopyridines: a systematic review and meta-analysis. *Stroke.* 49:312-8.

[52]Lazarus B, et al. (2016). Proton pump inhibitor use and risk of chronic kidney disease. *JAMA Intern Med*. 176(2):238-46.
[53]Ghiadoni L, et al. (2000). Mental stress induces transient endothelial dysfunction in humans. *Circulation*. 102:2473-8.
[54]Toda N, Nakanishi-Toda M. (2011). How mental stress affects endothelial function. *Pflugers Arch.* 462(6):779-94.
[55]Hambrecht R, et al. (2000). Effect of exercise on coronary endothelial function in patients with coronary artery disease. *N Engl J Med*. 342(7):454-60.
[56]Clarkson P, et al. (1999). Exercise training enhances endothelial function in young men. *J Am Coll Cardiol*. 33(5):1379-85.
[57] Higashi Y, Yoshizumi M. (2004). Exercise and endothelial function: Role of endothelium-derived nitric oxide and oxidative stress in healthy subjects and hypertensive patients. *PharmacolTher.*102(1):87-96.
[58] Rehman J, et al. (2004). Exercise acutely increases circulating endothelial progenitor cells and monocyte-/macrophage-derived angiogenic cells. *J Am Coll Cardiol.*43(12):2314-8.
[59] Gradinaru D, et al. (2015). Oxidized LDL and NO synthesis—biomarkers of endothelial dysfunction and ageing. *Mech Ageing Dev.* 151:101-13..
[60]Balligand J. (2002). New mechanisms of LDL-cholesterol induced endothelial dysfunction; correction by statins. Bull Mem Acad R Med Belg. 157(10-12)427-31.
[61]Laufs U. (2003). Beyond lipid-lowering: effects of statins on endothelial nitric oxide. *Eur J Clin Pharmacol*. 58(11):719-31.
[62]Davignon J. (2004). Beneficial cardiovascular pleiotropic effects of statins. *Circulation.* 109(23 Suppl 1):11139-43.
[63] Temple ME, et al. (2000). Homocysteine as a risk factor for atherosclerosis. *Ann Pharmacother.* 34(1):57-65.
[64]McDowell IF, Lang D. (2000). Homocysteine and endothelial dysfunction: a link with cardiovascular disease.*J Nutr*. 130(2S Suppl):369S-372S.
[65] Pushpakumar S, et al. (2014). Endothelial dysfunction: the link between homocysteine and hydrogen sulfide. *Curr Med Chem*. 21(32):3662-72.
[66] Cheng Z, et al. (2009). Hyperhomocysteinemia and endothelial dysfunction. *Curr Hypertens Rev*. 5(2):158-65.
[67] Moat SJ, et al. (2004). Folate, homocysteine, endothelial function and cardiovascular disease. *J NutrBiochem*. 15(2):64-79.
[68]Solenkova N, et al. (2014). Metal pollutants and cardiovascular disease: mechanisms and consequences of exposure. *Am Heart J.* 168(6):812-22.
[69] Houston MC. (2007). The role of mercury and cadmium heavy metals in vascular disease, hypertension, coronary heart disease, and myocardial infarction. *AlternTher Health Med.* 13(2):S128-33.
[70] Wolf MB, Baynes JW. (2007). Cadmium and mercury cause an oxidative stress-induced endothelial dysfunction. *Biometals*. 20(1):73-81.
[71] Lamas GA, et al. (2016). Heavy metals, cardiovascular disease, and the unexpected benefits of chelation therapy. *J AM Coll Cardiol.* 67(20):2411-18.
[72] Houston M, Hays L. (2014). Acute effects of an oral nitric oxide supplement on blood pressure, endothelial function, and vascular compliance in hypertensive patients. *J Clin Hypertens (Greenwich).* 16(7):524-9.
[73]Ashor AW, et al. (2014). Effect of vitamin C on endothelial function in health and disease: a systematic review and meta-analysis of randomized controlled trials. *Atherosclerosis*. 235(1):9-20.
[74]Tarcin O, et al. (2009). Effect of vitamin D deficiency and replacement on endothelial function in asymptomatic subjects. *J Clin Endocrinol Metab*.94(10):4023-30.
[75] Gao L, et al. (2012). Effects of coenzyme Q10 on vascular endothelial function in humans: a meta-analysis of randomized controlled trials. *Atherosclerosis*. 221(2):311-6.
[76]Armoza A, et al. (2013). Tomato extract and the carotenoids lycopene and lutein improve endothelial function and attenuate inflammatory NF-κB signaling in endothelial cells. *J Hypertens.* 31(3):521-9.
[77] Vita JA. (2005). Polyphenols and cardiovascular disease: effects on endothelial and platelet function. *Am J ClinNutr.* 81(1 Suppl):292S-297S.
[78] Williams MJ, et al. (2005). Aged garlic extract improves endothelial function in men with coronary artery disease. *Phytother Res*. 19(4):314-9.
[79] Shechter M, et al. (2000). Oral magnesium therapy improves endothelial function in patients with coronary artery disease. *Circulation*. 102(19):2353-8.
[80]Larinjani VM, et al. (2013). Beneficial effects of aged garlic extract and coenzyme Q10 on vascular elasticity and endothelial function: the FAITH randomized clinical trial.*Nutrition*. 29(1):71-5.
[81]Goodfellow J, et al. (2000). Dietary supplementation with marine omega-3 fatty acids improve systemic large artery endothelial function in subjects with hypercholesterolemia. *J Am Coll Cardiol*. 35(2):265-70.
[82] Brown A, Hu F. (2001). Dietary modulation of endothelial function: implications for cardiovascular disease. Am *J ClinNutr*. 73(4):673-86.
[83] Arora S, et al. (1998). Estrogen improves endothelial function. *J Vasc Surg.* 27(6): 1141-6.
[84] Moreau K, et al. (2013). Essential role of estrogen for improvements in vascular endothelial function with endurance exercise in postmenopausal women. *J Clin Endocrinol Metab.* 98(11):4507-15.

[85]Worboys S, et al. (2001). Evidence that parenteral testosterone therapy may improve endothelium-dependent and -independent vasodilation in postmenopausal women already receiving estrogen. *J Clin Endocrinol Metab.* 86(1):158-61.
[86] Chistiakov DA, et al. (2018). Role of androgens in cardiovascular pathology. *Vasc Health Risk Manag.* 14:283-90.
[87]Empen K, et al. (2012). Association of testosterone levels with endothelial function in men: results from a population-based study. *Arterioscler Thromb Vasc Biol*. 32(2):481-6.
[88]Akishita M, et al. (2007). Low testosterone level is an independent determinant of endothelial dysfunction in men. *Hypertens Res*. 2007;30(11):1029-34
[89] Sader MA, et al. (2001). Oestradiol improves arterial endothelial function in healthy men receiving testosterone. *Clin Endocrinol (Oxf).* 54(2):175-81.
[90] Bernini G, et al. (2006). Vascular reactivity in congenital hypogonadal men before and after testosterone replacement therapy. *J Clin Endocrinol Metab*. 91(5):1691-7.
[91] Harada A, et al. (2017). Cholesterol uptake capacity: a new measure of HDL functionality for coronary risk assessment. *J Appl Lab Med.* 2(2):186-200.
[92] Barter PJ, et al. (2007). Effects of Torcetrapib in patients at high risk for coronary events. *N Engl J Med*. 357(21):2109–22.
[93] AIM-HIGH Investigators. (2011). Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med.* 365(24):2255–67.
[94] Otvos JD, et al. (2006). Low-density lipoprotein and high-density lipoprotein particles subclasses predict coronary events and are favorably changed by gemfibrozil therapy in the Veterans Affairs High-Density Lipoprotein Intervention Trial. *Circulation.* 113(12):1556-63.
[95] Mora S, et al. (2013). High-density lipoprotein cholesterol, size, particle number, and residual vascular risk after potent statin therapy. *Circulation.* 128(11):1189-97.
[96] Tabas I, et al. (2007). Subendothelial lipoprotein retention as the initiating process in atherosclerosis: update and therapeutic implications. *Circulation*. 116(16):1832-44.
[97] Han R. (2010). Plasma lipoproteins are important components of the immune system. *Microbiol Immunol*. 54(4):246-53.
[98] Vreugdenhil A, et al. (2001). LPS-binding protein circulates in association with apo-containing lipoproteins and enhances endotoxin-LDL/VLDL interaction. *J Clin Invest*. 107(2):225-34.
[99] deFerranti S, et al. (2015). Prevalence of familial hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). *Circulation*. 122:1067-72.
[100] Akioyamen L, et al. (2017). Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. *BMJ Open*. 7(9):e016461.
[101] Ference BA, et al. (2017). Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 38(32):2459-72.
[102] Otvos JD, et al. (2011). Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. *J Clin Lipidol.* 5(2):105-13.
[103] Fernandez ML, Calle M. (2010). Revisiting dietary cholesterol recommendations: does the evidence support a limit of 300 mg/d? *Curr Atheroscler Rep*. 12(6):377-83.
[104] Blesso C,N, Fernandez ML. (2018). Dietary cholesterol, serum lipids, and heart disease: are eggs working for or against you? *Nutrients*. 10(4):426.
[105] Berger S, et al. (2015). Dietary cholesterol and cardiovascular disease: a systematic review and meta-analysis. *Am J Clin Nutr.* 102(2):276-94.
[106] Jones PJ, et al. (1996). Dietary cholesterol feeding suppresses human cholesterol synthesis measured by deuterium incorporation and urinary mevalonic acid levels. *Arterioscler Thromb Vasc Biol*. 1996;16(10):1222-8.
[107] Forouhi NG, et al. (2018). Dietary fat and cardiometabolic health: evidence, controversies, and consensus for guidance. *BMJ.* 361:k2139.
[108] Katan M, et al. (1995). Trans fatty acids and their effects on lipoproteins in humans. *Annu Rev Nutr.* 473-93.
[109] de Souza RJ, et al. (2015). Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. *BMJ.* 351:h3978.
[110] Houston M. (2018). The relationship of saturated fats and coronary heart disease: fa(c)t or fiction? A commentary. *Ther Adv Cardiovasc Dis.* 12(2):33-7.
[111] Fernandez ML, West KL. (2005). Mechanisms by which dietary fatty acids modulate plasma lipids. *J Nutr.* 135(9):2075-8.
[112] Han JR, et al. (2007). Effects of dietary medium-chain triglyceride on weight loss and insulin sensitivity in a group of moderately overweight free-living type 2 diabetic Chinese subjects. *Metabolism.* 56(7):985-91.
[113] Nettleton J, et al. (2017). Saturated fat consumption and risk of coronary heart disease and ischemic stroke: a science update. *Ann Nutr Metab.* 70(1):26-33.
[114] Siri-Tarino PW, et al. (2010). Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *Am J Clin Nutr.* 91(3):535-46.

[115] Dehghan M, et al. (2017). Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. *Lancet.* 390(10107):2050-62.
[116] Bogani P, et al. (2007). Postprandial anti-inflammatory and antioxidant effects of extra virgin olive oil. *Atherosclerosis.* 190(1):181-6.
[117] Pérez-Jiménez F, et al. (2002). Protective effect of dietary monounsaturated fat on arteriosclerosis: beyond cholesterol. *Atherosclerosis.* 163(2):385-98.
[118] Mozaffarian D, et al. (2010). Effects of coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med.* 7(3):e1000252.
[119] Hu T, et al. (2012). Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors: a meta-analysis of randomized controlled clinical trials. *Am J Epidemiol*. 176(Suppl 7):S44-54.
[120] Gjuladin-Hellon T, et al. (2019). Effects of carbohydrate-restricted diets on low-density lipoprotein cholesterol levels in overweight and obese adults: a systematic review and meta-analysis. *Nutr Rev.* 77(3):161-80.
[121] Monsoor N, et al. (2016). Effects of low-carbohydrate diets v. low-fat diets on body weight and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Br J Nutr.* 115(3):466-79.
[122] Snorgaard O, et al. (2017). Systematic review and meta-analysis of dietary carbohydrate restriction in patients with type 2 diabetes. *BMJ Open Diab Res Care.* 5:e000354.
[123] Andronescu CI, et al. (2018). Nonalcoholic fatty liver disease: epidemiology, pathogenesis and therapeutic implications. *J Med Life.* 11(1):20-3.
[124] Ahmed M. (2015). Non-alcoholic fatty liver disease in 2015. *World J Hepatol.* 7(11):1450-9.
[125] Jacobs DR, et al. (2009). Food synergy: an operational concept for understanding nutrition. *Am J Clin Nutr.* 89(5):1543S-1548S.
[126] Widmer RJ, et al. (2015). The Mediterranean Diet, its components, and cardiovascular disease. *Am J Med.* 128(3):229-38.
[127] Martínez-González MA, et al. (2019). The Mediterranean diet and cardiovascular health. *Circ Res.* 124(5):779-798.
[128] Estruch R, et al. (2018). Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med.* 378(25):e34.
[129] Giugliano R, et al. (2018). Benefits of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus. *Circulation.* 137(15):1571-82.
[130] Berneis K, et al. (2010). Ezetimibe alone or in combination with simvastatin increases small dense low-density lipoproteins in healthy men: a randomized trial. *Eur Heart J.* 31(13):1633-9.
[131] Rubins HB, et al. (1999). Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med.* 341(6):410-8.
[132] Elam M, et al. (2011). Role of fibrates in cardiovascular disease prevention, the ACCORD-Lipid perspective. *Curr Opin Lipidol.* 22(1):55-61.
[133] Ansquer JC, et al. (2009). Fibrates and microvascular complications in diabetics—insight from the FIELD study. *Curr Pharm Des.* 15(5):537-52.
[134] Wasserman D. (2008). Four grams of glucose. *Am J Physiol Endocrinol Metab.* 296(1):E11-21.
[135] National Diabetes Statistics Report, 2017: http://www.diabetes.org/assets/pdfs/basics/cdc-statistics-report-2017.pdf accessed 04/18/2019
[136] American Diabetes Association. (2018). Economic costs of diabetes in the U.S. in 2017. *Diabetes Care.* 41(5): 917-28.
[137] DeFronzo R, Tripathy D. (2009). Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. *Diabetes Care.* 32(suppl 2):S157-63.
[138] Hirata Y, et al. (2019). Hyperglycemia induces skeletal muscle atrophy via a WWP1/KLF15 axis. *JCI Insight*. 4(4):e124952.
[139] Gast KB, et al. (2012). Insulin resistance and risk of incident cardiovascular events in adults without diabetes: meta-analysis. *PLoS One*. 7(12):e52306.
[140] Ginsberg HN, et al. (2006). Metabolic syndrome: focus on dyslipidemia. *Obesity (Silver Spring).* Suppl 1:41S-49S.
[141] Cersosimo E, DeFronzo RA. (2006). Insulin resistance and endothelial dysfunction: the road map to cardiovascular diseases. *Diabetes Metab Res Rev. 22(6):423-36.*
[142] Stanley WC, et al. (2005). Myocardial substrate metabolism in the normal and failing heart. *Physiol Rev.* 85(3):1093-129.
[143] D'Souza K, et al. (2016). Lipid metabolism and signaling in cardiac lipotoxicity. *Biochim Biophys Acta.* 1861(10):1513-24.
[144] Ormazabal V, et al. (2018). Association between insulin resistance and the development of cardiovascular disease. *Cardiovasc Diabetol.* 17(1):122.
[145] Hu F, et al. (2001). Diet, Lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med.* 345(11):790-7.
[146] Lijnen HR. (2008). Angiogenesis and obesity. *Cardiovasc Res.* 78(2):286-93.
[147] https://www.obesityaction.org/community/article-library/hypertension-and-obesity-how-weight-loss-affects-hypertension/ accessed 07/20/2019
[148] Fantuzzi G. (2005). Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol*. 115(5):911-9.

[149]Mattu HS, Randeva HS. (2013). Role of adipokines in cardiovascular disease. *J Endocrinol*. 216(1):T17-36.
[150]Rabkin SW. (2007). Epicardial fat: properties, function and relationship to obesity. *Obes Rev*. 8(3):253-61.
[151]Janssen I, Ross R. (2005). Linking age-related changes in skeletal muscle mass and composition with metabolism and disease. *J Nutr Health Aging*. 9(6):408-19.
[152] Flegal KM, Troiano RP. (2000). Changes in the distribution of body mass index of adults and children in the US population. *Int J Obes Rela tMetab Disord*. 24(7):807-18.
[153] Van Pelt RE, et al. (1997). Regular exercise and the age-related decline in resting metabolic rate in women. *J Clin Endocrinol Metab.* 82(10):3208-12.
[154] Van Pelt RE, et al. (2001). Age-related decline in RMR in physically active men: relation to exercise volume and energy intake. *Am J Physiol Endocrinol Metab*. 281(3):E633-9.
[155] Willcox DC, et al. (2006). Caloric restriction and human longevity: What can we learn from the Okinawans? *Biogerontology.* 7:173-7.
[156] Masoro E. (2005). Overview of caloric restriction and aging. *Mech Ageing Develop*. 126(9):913-22.
[157] Fontana L, Klein S. (2007). Aging, adiposity, and calorie restriction. *JAMA*. 297:986-94.
[158] Balasubramanian P, et al. (2017). Aging and caloric restriction research: a biological perspective with translational potential. *EBioMedicine.* 21:37-44.
[159] Sacks FM, et al. (2009). Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med* 360(9):859-73.
[160] Thomas DE, et al. (2007). Low glycaemic index or low glycaemic load diets for overweight and obesity. *Cochrane Database Syst Rev.* 18(3):CD005105.
[161] Brehm BJ, et al. (2003). A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. *J Clin Endocrinol Metab.* 88(4):1617-23.
[162] Bazzano L, et al. (2014). Effects of low-carbohydrate and low-fat diets: a randomized trial. *Ann Intern Med.* 161(5):309-18.
[163] Lindeberg S, et al. (2007). A Palaeolithic diet improves glucose tolerance more than a Mediterranean-like diet in individuals with ischaemic heart disease. *Diabetologia.* 50(9):1795-1807.
[164] Osterdahl M, et al. (2008). Effects of a short-term intervention with a paleolithic diet in healthy volunteers. *Eur J Clin Nutr.* 62(5):682-5.
[165] Jönsson T, et L. (2009). Beneficial effects of a Paleolithic diet on cardiovascular risk factors in type 2 diabetes: a randomized cross-over pilot study. *Cardiovasc Diabetol.* 8:35.
[166] Ryberg M, et al. (2013). A Palaeolithic-type diet causes strong tissue-specific effects on ectopic fat deposition in obese postmenopausal women. *J Intern Med.* 274(1):67-76.
[167] Masharani U, et al. (2015). Metabolic and physiologic effects from consuming a hunter-gatherer (Paleolithic)-type diet in type 2 diabetes. *Eur J Clin Nutr.* 69(8):944-8.
[168] Manheimer EW, et al. (2015). Paleolithic nutrition for metabolic syndrome: systematic review and meta-analysis. *Am J Clin Nutr.* 102(4):922-32.
[169] Westman E, et al. (2008). The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. *Nutr Metab (Lond).* 5:36.
[170] Yancy WS Jr, et al. (2005). A low-carbohydrate, ketogenic diet to treat type 2 diabetes. *Nutr Metab (Lond).* 2:34.
[171] Boden G, et al. (2005). Effect of a low-carbohydrate diet on appetite, blood glucose levels, and insulin resistance in obese patients with type 2 diabetes. *Ann Intern Med.* 142(6):403-11.
[172] Johnstone AM, et al. (2008). Effects of a high-protein ketogenic diet on hunger, appetite, and weight loss in obese men feeding ad libitum. *Am J Clin Nutr.* 87(1):44-55.
[173] Sumithran P, et al. (2013). Ketosis and appetite-mediating nutrients and hormones after weight loss. *Eur J Clin Nutr.* 67(7):759-64.
[174] Bueno NB, et al. (2013). Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomized controlled trials. *Br J Nutr.* 110(7):1178-87.
[175] Dahsti HM, et al. (2004). Long-term effects of a ketogenic diet in obese patients. *Exp Clin Cardiol.* 9(3):200-5.
[176] Volek JS,et al. (2005). Modification of lipoproteins by very low-carbohydrate diets. *J Nutr.* 135(6):1339-42.
[177] Creighton B, et al. (2018). Paradox of hypercholesterolaemia in highly trained, keto-adapted athletes. *BMJ Open Sport & Exercise Med.* 4e000429.
[178] Saris W. (2001). Very-low-calorie diets and sustained weight loss. *Obesity Research.* Suppl 4:295S-301S.
[179]Wadden TA, et al. (2009). One year weight losses in the Look AHEAD study: factors associated with success. *Obesity.* 17(4):713-22.
[180]Bellisle F, et al. (1997). Meal frequency and energy balance. *Br J Nutr*: 77 (Suppl 1):S57-70.
[181]Verboeket-van de Venne WP, et al. (1993). Effect of the pattern of food intake on human energy metabolism. *Br J Nutr.* 70(1):103-15.
[182] Cameron JD, et al. (2010). Increased meal frequency does not promote greater weight loss in subjects who were prescribed an 8-week equi-energetic energy-restricted diet. *Br J Nutr.* 103(8):1098-101.
[183] See: Geneen Roth: Women Food and God, When Food is Love, Breaking Free from Emotional Eating, Feeding the Hungry Heart, When You Eat at the Refrigerator, Pull Up a Chair, Appetites, and Why Weight?.

[184] Colman RJ, et al. (2009). Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science.* 325(5937):201-4.
[185] Mattison JA, et al. (2012). Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study. *Nature.* 489(7415):318-21.
[186] Mattison JA, et al. (2017). Caloric restriction improves health and survival of rhesus monkeys. *Nat Commun.* 8:14063.
[187] Vidacek NS, et al. (2017). Telomeres, nutrition, and longevity: can we really navigate our aging? *J Gerontol A Biol Sci Med Sci.* 73(1):39-47.
[188]Heilbronn L, et al. (2006). Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. *JAMA*. 295(13):1539-48.
[189]Civitarese AE, et al. (2007). Calorie restriction increases muscle mitochondrial biogenesis in healthy humans. *PLoS Med*. 4(3):e76
[190] Kraus W, et al. (2019). 2 years of calorie restriction and cardiometabolic risk (CALERIE): exploratory outcomes of a multicenter, phase 2, randomised controlled trial. *The Lancet Diabetes Endocrinol.*
[191] Panda S. (2016). Circadian physiology of metabolism. *Science.* 354(6315):1008-1015.
[192] Chaix A, et al. (2019). Time-restricted eating to prevent and mange chronic metabolic diseases. *Annu Rev Nutr.* [Epub ahead of print].
[193] Gabel K, et al. (2018). Effects of 8-hour time restricted feeding on body weight and metabolic disease risk factors in obese adults: A pilot study. *Nutr Healthy Aging.* 4(4):345-53.
[194] Sutton E, et al. (2018). Early time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes. *Cell Metab.* 27(6):1212-21.
[195] Patterson R, Sears D. (2017). Metabolic effects of intermittent fasting. *Ann Rev Nutr*. 37:371-93.
[196] Hutchinson AT, et al. (2019). Time-restricted feeding improves glucose tolerance in men at risk for type 2 diabetes: a randomized crossover trial. *Obesity (Silver Spring).* 27(5):724-32.
[197] Golia E, et al. (2014). Inflammation and cardiovascular disease: from pathogenesis to therapeutic target. *Curr Atheroscler Rep*. 16(9):435.
[198] www.sott.net/article/242516-Heart-surgeon-speaks-out-on-what-really-causes-heart-disease accessed 06/03/2019
[199] Fontana L, et al. (2007). Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes*. 56(4):1010-3.
[200] Nakamura K, et al. (2014). Adipokines: a link between obesity and cardiovascular disease. *J Cardiol.* 63(4):250-9.
[201] O'Keefe JH, et al. (2008). Dietary strategies for improving post-prandial glucose, lipids, inflammation, and cardiovascular health. *J Am Coll Cardiol.* 51(3):249-55.
[202] Chai W, et al. (2017). Dietary red and processed meat intake and markers of adiposity and inflammation: the multiethnic cohort study. *J Am Coll Nutr.* 36(5):378-85.
[203] Mozaffarian D, et al. (2004). Dietary intake of trans fatty acids and systemic inflammation in women. *Am J Clin Nutr.* 79(4):606-12.
[204] Baer DJ, et al. (2004). Dietary fatty acids affect plasma markers of inflammation in healthy men fed controlled diets: a randomized crossover study. *Am J Clin Nutr.* 79(6):969-73.
[205] DiNicolantonio JJ, O'Keefe JH. (2018). Omega-6 vegetable oils as a driver of coronary heart disease: the oxidized linoleic acid hypothesis. *Open Heart.* 5(2):e000898.
[206] Johnson GH, Fritsche K. (2012). Effect of dietary linoleic acid on markers of inflammation in healthy persons: a systematic review of randomized controlled trials. *J Acad Nutr Diet.* 112(7):1029-41.
[207] Simopoulos AP. (2002). The importance of the ratio of omega-6/omega-3 essential fatty acids. *Biomed Pharmacother.* 56(8):365-79.
[208] Simopoulos AP. (2006). Evolutionary aspects of diet, the omega-6/omega-3 ratio and genetic variation: nutritional implications for chronic diseases. *Biomed Pharmacother.* 60(9):502-7.
[209] Buchowski M, et al. (2012). Effect of modest calorie restriction on oxidative stress in women, a randomized trial. *PLoS One.* 7(10):e47079.
[210] Redman LM, et al. (2018). Metabolic slowing and reduced oxidative damage with sustained calorie restriction support the rate of living and oxidative damage theories of aging. *Cell Metab.* 3;27(4):805-15.
[211] Shinmura K. (2013). Effects of caloric restriction on cardiac oxidative stress and mitochondrial bioenergetics: potential role of cardiac sirtuins. *Oxid Med Cell Longev.* 2013:528935.
[212] Meydani SN, et al. (2016). Long-term moderate calorie restriction inhibits inflammation without impairing cell-mediated immunity: a randomized controlled trial in non-obese humans. *Aging (Albany NY).* 8(7):1416-31.
[213] Bouzid MA, et al. (2018). Lifelong voluntary exercise modulates age-related changes in oxidative stress. *Int J Sports Med.* 39(1):21-8.
[214] Margonis K, et al. (2007). Oxidative stress biomarkers responses to physical overtraining: implications for diagnosis. *Free Radic Biol Med.* 43(6):901-10.
[215] Fukui H. (2016). Increased intestinal permeability and decreased barrier function: does it really influence the risk of inflammation? *Inflamm Intest Dis.* 1(3):135-45.
[216] Bischoff SC, et al. (2014). Intestinal permeability—a new target for disease prevention and therapy. *BMC Gastroenterol*. 14:189.

[217] Vreugdenhil A, et al. (2001). LPS-binding protein circulates in association with apoB-containing lipoproteins and enhances endotoxin-LDL/VLDL interaction. *J Clin Invest.* 107(2):225-134.
[218] Dimitrov S, et al. (2017). Inflammation and exercise: inhibition of monocytic intracellular TNF production by acute exercise via β_2-adrenergic activation. *Brain Behav Immun.* 61:60-8.
[219] Rosenkranz MA, et al. (2013). A comparison of mindfulness-based stress reduction and an active control in modulation of neurogenic inflammation. *Brain Behav Immun.* 27(1):174-84.
[220] Tolahunase M, et al. (2017). Impact of yoga and meditation on cellular aging in apparently healthy individuals: a prospective, open-label single-arm exploratory study. *Oxid Med Cell Longev.* 2017:2784153.
[221] Williams D, et al. (2019). Heart rate variability and inflammation: a meta-analysis of human studies. *Brain, Behav Immun*. pii: S0889-1591(18)30466-5. [Epub ahead of print]
[222] Martínez-Huélamo M, et al. (2017). Modulation of Nrf2 by olive oil and wine polyphenols and neuroprotection. *Antioxidants*. 6(4):73.
[223] Kou X, et al. (2013). Natural products for cancer prevention associated with Nrf2-ARE pathway. *Food Sci Human Wellness.* 2(1):22-8.
[224] Houghton CA, et al. (2016). Sulforaphane and other nutrigenomic Nrf2 activators: can the clinician's expectation be matched by reality? *Oxid Med Cell Longev.* 2016:7857186.
[225] Lee BJ, et al. (2012). Coenzyme Q10 supplementation reduces oxidative stress and increases antioxidant enzyme activity in patients with coronary artery disease. *Nutrition.* 28(3):25-5.
[226] Sinha R, et al. (2018). Oral supplementation with liposomal glutathione elevates body stores of glutathione and markers of immune function. *Eur J Clin Nutr*. 72(1):105-11.
[227] Bruggeman BK, et al. (2019). The absorptive effects of orobuccal non-liposomal nano-sized glutathione on blood glutathione parameters in healthy individuals: a pilot study. *PLoS One.* 14(4):e0215815.
[228] Richie JP Jr, et al. (2015). Randomized controlled trial of oral glutathione supplementation on body stores of glutathione. *Eur J Nutr*. 54(2):251-63.
[229] Vogel JU, et al. (2005). Effects of S-acetylglutathione in cell and animal model of herpes simplex virus type 1 infection. *Med Microbiol Immunol.* 194(1-2):55-9.
[230] Panahi Y, et al. (2016). Effects of curcumin on serum cytokine concentrations in subjects with metabolic syndrome: a post-hoc analysis of a randomized controlled trial. *Biomed Pharmacother*. 82:578-82.
[231] Calder PC. (2010). Omega-3 fatty acids and inflammatory processes. *Nutrients.* 2(3):355-74.
[232] Mashhadi NS, et al. (2013). Anti-oxidative and anti-inflammatory effects of ginger in health and physical activity: review of current evidence. *Int J Prev Med.* 4(Suppl 1):S36-42.
[233] Kinlay S. (2007). Low-density lipoprotein-dependent and -independent effects of cholesterol-lowering therapies on C-reactive protein: a meta-analysis. *J Am Coll Cardiol.* 2007;49(20):2003–9.
[234] Nissen SE, et al. (2005). Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med*. 352(1):29–38.
[235] Ridker PM, et al. (2005). C-reactive protein levels and outcomes after statin therapy. *N Engl J Med*. 352(1):20–8.]
[236] Epstein S, et al. (2000). Infection and atherosclerosis: potential roles of pathogenic burden and molecular mimicry. *Arterioscler Throm Vasc Biol.* 20(6):1417-20.
[237] Kahlenberg JM, Kaplan M. (2013). Mechanisms of premature atherosclerosis in rheumatoid arthritis and lupus. *Ann Rev Med*. 64: 249-63.
[238] Lockhart PB, et al. (2012). Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: a scientific statement from the American Heart Association. *Circulation.* 125(20):2520-44.
[239] Bahekar AA, et al. (2007). The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis. *Am Heart J.* 154(5):830-7.
[240] Haraszthy VI, et al. (2000). Identification of periodontal pathogens in atheromatous plaques. *J Periodontol.* 71(10):1554-60.
[241] Koren O, et al. (2011). Human oral, gut, and plaque microbiota in patients with atherosclerosis. *Proc Natl Acad Sci U S A.* 108 Suppl 1:4592-8.
[242] Eke PI, et al. (2015). Update on prevalence of periodontitis in adults in the United States: NHANES 2009 to 2012. *J Periodontol.* 86(5):611-22.
[243] Rupprecht HJ, et al. (2001). Impact of viral and bacterial infectious burden on long-term prognosis in patients with coronary artery disease. *Circulation.* 103(1):25-31.
[244] Rosenfeld ME, Campbell LA. (2011). Pathogens and atherosclerosis: update on the potential contribution of multiple infectious organisms to the pathogenesis of atherosclerosis. *Thromb Haemost.* 106(5):858-67.
[245] Ott SJ, et al. (2006). Detection of diverse bacterial signatures in atherosclerotic lesions of patients with coronary heart disease. *Circulation.* 113(7):929-37.
[246] Zhu J, et al. (2000). Effects of total pathogen burden on coronary artery disease risk and C-reactive protein levels. *Am J Cardiol.* 85(2):140-6.
[247] Han R. (2010). Plasma lipoproteins are important components of the immune system. *Microbiol Immunol.* 54(4):246-53.
[248] Forkosh E, Ilan Y. (2019). The heart-gut axis: new target for atherosclerosis and congestive heart failure therapy. *Open Heart.* 6:e000993.

[249] Sender R, et al. (2016). Revised estimates for the number of human and bacteria cells n the body. *PLoS Biol.* 14(8):e1002533.
[250] Xuan Li, et al. (2017). Gut microbiota dysbiosis drives and implies novel therapeutic strategies for diabetes mellitus and related metabolic diseases. *Front Immunol.* 8:1882.
[251] Henao-Mejia J, et al. (2012). Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. *Nature.* 482(7384):179-85.
[252] Sun L, et al. (2018). Insights into the role of gut microbiota in obesity: pathogenesis, mechanisms, and therapeutic perspectives. *Protein Cell.* 9(5):397-403.
[253] Ma J, Li H. (2018). The role of gut microbiota in atherosclerosis and hypertension. *Front Pharmacol.* 9:1082.
[254] Tang WH, et al. (2017). Gut microbiota in cardiovascular health and disease. *Circ Res.* 120(7):1183-96.
[255] Molinero N, et al. (2019). Intestinal bacteria interplay with bile and cholesterol metabolism: implications on host physiology. *Front Physiol.* 10:185.
[256] Fu J, et al. (2015). The gut microbiome contributes to a substantial proportion of the variation in blood lipids. *Circ Res*. 117(9):817-24.
[257] Le Chantelier E, et al. (2013). Richness of human gut microbiome correlates with metabolic markers. *Nature.* 500(7464):541-6.
[258] Ley RE, et al. (2006). Microbial ecology: human gut microbes associated with obesity. *Nature.* 444(7122):1022-3.
[259] Turnbaugh PJ, et al. (2006). An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature.* 444(7122):1027-31.
[260] Wiedermann C, et al. (1999). Association of endotoxemia with carotid atherosclerosis and cardiovascular disease: prospective results from the Bruneck Study. *J Am Coll Cardiol.* 34(7):1975-81.
[261] Bjarnason I, et al. (2018). Mechanisms of damage to the gastrointestinal tract from non-steroidal anti-inflammatory drugs. *Gastroenterology.* 154:500-14.
[262] Coxib and traditional NSAID Trialists' (CNT) Collaboration. (2013). Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomized trials. *Lancet.* 382(9894):769-79.
[263] Bjarnason I, Takeuchi K. (2009). Intestinal permeability in the pathogenesis of NSAID-induced enteropathy. *J Gastroenterology*. 44(Suppl 19):23-9.
[264] Utzeri E, Usai P. (2017). Role of non-steroidal anti-inflammatory drugs on intestinal permeability and nonalcoholic fatty liver disease. *World J Gastroenterol.* 23(22):3954-63.
[265] Panda S, et al. (2014). Short-term effect of antibiotics on human gut microbiota. *PLoS One*. 9(4):e95476.
[266] Jernberg C, et al. (2010). Long-term impacts of antibiotic exposure on the human intestinal microbiota. *Microbiology.* 156(Pt 11):3216-23.
[267] Jackson MA, et al. (2016). Proton pump inhibitors alter the composition of the gut microbiota. *Gut.* 65(5):749-56.
[268] Kwok CS, et al. (2012). Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis. *Am J Gastroenterol*. 107(7):1011-9.
[269] Hollon J, et al. (2015). Effect of gliadin on permeability of intestinal biopsy explants from celiac disease patients and patients with non-celiac gluten sensitivity. *Nutrients.* 7(3):1565-76.
[270] Uhde M, et al. (2016). Intestinal cell damage and systemic immune activation in individuals reporting sensitivity to wheat in the absence of coeliac disease. *Gut.* 65:1930-7.
[271] Ventura MT, et al. (2006). Intestinal permeability in patients with adverse reactions to food. *Dig Liver Dis*. 38(10):732-6.
[272] Groschwitz KR, Hogan SP. (2009). Intestinal barrier function: molecular regulation and disease pathogenesis. *J Allergy Clin Immunol.* 124(1):3-22.
[273] Dunne C, et al. (2009). Mechanisms of adherence of a probiotic Lactobacillus strain during and after in vivo assessment in ulcerative colitis patients. *Microbial Ecology Health Dis.* 16(2-3): 96-104.
[274] Miyauchi E, et al. (2012). Mechanism of protection of transepithelial barrier function by Lactobacillus salvarius: strain dependence and attenuation by bacteriocin production. *Am J Physiol Gastrointest Liver Physiol.* 303(9):G1029-41.
[275] Khalesi S, et al. (2014). Effect of probiotics on blood pressure: a systematic review and meta-analysis of randomized controlled trials. *Hypertension.* 64(4):897-903.
[276] Wang L, et al. (2018). The effects of probiotics on total cholesterol: a meta-analysis of randomized controlled trials. *Medicine (Baltimore).* 97(5):e9679.
[277] Wu Y, et al. (2017). Effect of probiotic Lactobacillus on lipid profile: A systematic review and meta-analysis of randomized, controlled trials. *PLoS One.* 12(6):e0178868.
[278] Jones ML, et al. (2012). Cholesterol lowering and inhibition of sterol absorption by Lactobacillus reuteri NCIMB 30242: a randomized controlled trial. *Eur J Clin Nutr.* 66(11):1234-41.
[279] Mekkes MC, et al. (2014). The development of probiotic treatment in obesity: a review. *Benef Microbes.* 5(1):19-28.
[280] Stenman L, et al. (2016). Probiotic with or without fiber controls body fat mass, associated with serum zonulin, in overweight and obese adults—randomized controlled trial. *EBioMedicine*. 13:190-200.
[281] Duntas LH. (2002). Thyroid disease and lipids. *Thyroid*. 12(4):287-293.
[282] Taddei S, et al. (2003). Impaired endothelium-dependent vasodilatation in subclinical hypothyroidism: beneficial effect of levothyroxine therapy. *J Clin Endocrinol Metab.* 88(8):3731-7**.**

[283] Danzi S, Klein I. (2003). Thyroid hormone and blood pressure regulation. *Curr Hypertens Rep.* 5(6):513-20.
[284]Hak AE, et al. (2000). Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: The Rotterdam Study. *Ann Int Med*. 132 (4):270-8.
[285] Qureshi Al, et al. (2006). Free thyroxine index and risk of stroke: results from the National Health and Nutrition Examination Survey Follow-up Study. *Med Sci Monit.* 12(12):CR501-506.
[286] Biondi B, Klein I. (2004). Hypothyroidism as a risk factor for cardiovascular disease. *Endocrine.* 24(1):1-13.
[287] Klein I, Danzi S. (2007). Thyroid disease and the heart. *Circulation.* 116(15):1725-35.
[288] Kim SK, et al. (2009). Regression of the increased common carotid artery-intima media thickness in subclinical hypothyroidism after thyroid hormone replacement. *Endocr J*. 56:743.
[289]Riedel M, et al. (1995). Vascular responses to 17 beta-oestradiol in postmenopausal women. *Eur J Clin Invest.* 25(1):44-7.
[290] Kawano H, et al. (2003). Effects of transdermal and oral estrogen supplementation on endothelial function, inflammation and cellular redox state. *Int J Clin Pharmacol Ther.* 41(8):346-53.
[291]Zegura B, et al. (2003). Orally and transdermally replaced estradiol improves endothelial function equally in middle-aged women after surgical menopause. *Am J Obstet Gynecol*. 188(5):1291-6.
[292] Lee S, et al. (2001). Effect of estrogen on endothelial dysfunction in postmenopausal women with diabetes. *Diabetes Research Clin Practice*. 54(2):S81-S92.
[293] Higashi Y, et al. (2001). Effect of estrogen replacement therapy on endothelial function in peripheral resistance arteries in normotensive and hypertensive postmenopausal women. *Hypertension*. 37(2 pt. 2):651-7.
[294]Sanada M. (2002). Hormone replacement effects on endothelial function measured in the forearm resistance artery in normocholesterolemic and hypercholesterolemic postmenopausal women. *J Clin Endocrinol Metab*. 87(10):4634-41.
[295]Worboys S, et al. (2001). Evidence that parenteral testosterone therapy may improve endothelium-dependent and -independent vasodilation in postmenopausal women already receiving estrogen. *J Clin Endocrinol Metab.* 86(1):158-61.
[296] Iellamo F, et al. (2010). Testosterone therapy in women with chronic heart failure: a pilot double-blind, randomized, placebo-controlled study. *J Am Coll Cardiol.* 56(16):1310-16.
[297]Budoff M, et al.(2005). Effects of hormone replacement on progression of coronary calcium as measured by electron beam tomography. *J Womens Health.*14(5):410-17
[298] Manson JE, et al. (2008). Estrogen therapy and coronary-artery calcification. *N Eng J Med*. 2007;356:2591-2602.
[299] Karim R, et al. Relationship between serum levels of sex hormones and progression of subclinical atherosclerosis in postmenopausal women. *J Clin Endocrinol Metab*. 93(1):131-8.
[300] Sendag F, et al. (2002). Effects of sequential combined transdermal and oral hormone replacement therapies on serum lipid and lipoproteins in postmenopausal woman. *Arch Gynecol Obstet*. 266(1):38-43.
[301] Vehkavaara S, et al. (2001). Effects of oral and transdermal estrogen replacement therapy on markers of coagulation, fibrinolysis, inflammation and serum lipids and lipoproteins in postmenopausal woman. *Thromb Haemost*. 85(4):619-25.
[302]Canonico M, et al. (2007). Hormone therapy and venous thromboembolism among postmenopausal women: impact of route of administration and progestogens: the ESTHER study. *Circulation*. 115:840-5.
[303] Zegura B, et al. (2006). The effect of various menopausal hormone therapies on markers of inflammation, coagulation, fibrinolysis, lipids, and lipoproteins in healthy postmenopausal women. *Menopause.*13(4):643050.
[304]Zegura B, et al. (2003). Double blind, randomized study of estradiol replacement therapy on markers of inflammation, coagulation and fibrinolysis. *Atherosclerosis*. 168(1):123-9.
[305]Mueck AO. (2012). Postmenopausal hormone replacement therapy and cardiovascular disease: the value of transdermal estradiol and micronized progesterone. *Climacteric*. 15 Suppl 1:11-7.
[306] Rossi R, et al. (2004). Transdermal 17-β-estradiol and risk of developing type 2 diabetes in a population of healthy, nonobese postmenopausal women. *Diabetes Care*. 27(3):645-9.
[307] Bernini GP, et al. (1999). Endogenous androgens and carotid intima-medial thickness in women. *J Clin Endocrinol Metab*. 84(6):2008-12.
[308] Williams MR, et al. (2004). Dehydroepiandrosterone increases endothelial cell proliferation in vitro and improves endothelial function in vivo by mechanisms independent of androgen and estrogen receptors. *J Clin Endocrino Metab.* 89(9):4708-15.
[309]Sievers C, et al. (2010). Low testosterone levels predict all-cause mortality and cardiovascular events in women: a prospective cohort study in German primary care patients. *Eur J Endocrinol*. 163(4):699-708.
[310]Araujo AB, et al. (2011). Endogenous testosterone and mortality in men: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 96:3007–19.
[311]Vigen R, et al. (2013). Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA.* 310(17):1829-36.
[312]Finkle WD, et al. (2014). Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS ONE.* 9(1):e85805.
[313] Morgentaler A, Luenfeld B. (2014). Testosterone and cardiovascular risk: world's experts take unprecedented action to correct misinformation. *Aging Male.* 17(2):63-5.
[314] Baillargeon J, et al. (2014). Risk of myocardial infarction in older men receiving testosterone therapy. *Ann Pharmacother*. 48(9):1138-44.

[315]Hak AE, et al. (2002). Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam study. *J Clin Endocrinol Metab*. 87(8):3632-39.
[316] Corona G, et al. (2011). Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. *Eur J Endocrinol*. 165(5):687-701.
[317]Khaw KT, et al. (2007). Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. *Circulation*. 116(23):2694-701.
[318]Yeap BB, et al. (2009). Lower testosterone levels predict incident stroke and transient ischemic attack in older men. *J Clin Endocrinol Metab*. 94:2353–9
[319]English KM, et al. (2000). Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms*. Eur Heart J.* 21(11):890-4..
[320] Hyde Z, et al. (2012). Low free testosterone predicts mortality from cardiovascular disease but not other causes: the health in men study. *J Clin Endocrinol Metab*. 97(1):179-89.
[321] Soisson V, et al. (2012). Low plasma testosterone and elevated carotid intima-media thickness: importance of low-grade inflammation in elderly men. *Atherosclerosis.*223(1):244-9.
[322] Vodo S, et al. (2013). Testosterone-induced effects on lipids and inflammation. *Mediators Inflamm.* 2013:183041.
[323] Ding EL, (2006). Sex differences of endogenous sex hormones and risk of type 2 diabetes. *JAMA*. 295:1288–99.
[324] Svartberg J, et al. (2006). Low testosterone levels are associated with carotid atherosclerosis in men. *J Intern Med*. 259(6):576-82.
[325] Maggio M, et al. (2005). The relationship between testosterone and molecular markers of inflammation in older men. *J Endocrinol Invest*. 28(11 Suppl Proceedings):116-9.
[326] Mäkinen JI, et al. (2008). Endogenous testosterone and serum lipids in middle-aged men. *Atherosclerosis*. 197(2): 688–93.
[327] Wang Ch, et al. (2011). Low testosterone associated with obesity and the metabolic syndrome contributes to sexual dysfunction and cardiovascular disease risk in men with type 2 diabetes. *Diabetes Care*. 34(7):1669-75.
[328] Fukui M, et al. (2003). Association between serum testosterone concentration and carotid atherosclerosis in men with type 2 diabetes. *Diabetes Care*. 26(6):1869-73.
[329] Shimshi M, Potenza M. (2008). Male hypogonadism: The unrecognized cardiovascular risk factor. *J Clin Lipidol.* 2(2):71-8.
[330] Traish AM, et al. (2009). The dark side of testosterone deficiency: III. Cardiovascular disease. *J Androl*. 30(5):477-94.
[331] Malkin CJ, et al. (2010). Low serum testosterone and increased mortality in men with coronary heart disease. *Heart.* 96(22):1821-5.
[332] Sharma R, et al. (2015). Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. *Eur Heart J*. 36(40):2706-15.
[333] Shores MM, et al. (2012). Testosterone treatment and mortality in men with low testosterone levels. *J Clin Endocrinol Metab*. 97(6):2050-8
[334] Traish AM, et al. (2014). Long-term testosterone therapy in hypogonadal men ameliorates elements of the metabolic syndrome: an observational, long-term registry study*. Int J Clin Practice*. 68(3):314-29.
[335] Stellato RK, et al. (2000). Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: prospective results from the Massachusetts male aging study. *Diabetes Care*. 23(4):490-4.
[336] Aversa A, et al. (2010). Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. *J Sex Med*. 7(10):3495-503.
[337] Jones TH, et al. (2011). Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). *Diabetes Care.* 34(4):828-37.
[338] Kapoor D, et al. (2006). Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. *Eur J Endocrinol*. 154(6):899-906.
[339] Muraleedharan V, et al. (2013). Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. *Eur J Endocrinol.* 169(6):725-33.
[340] Zgliczynski S, et al. (1996). Effect of testosterone replacement therapy on lipids and lipoproteins in hypogonadal and elderly men. *Atherosclerosis*. 121(1):35-43.
[341] Malkin C, et al. (2004). The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. *J Clin Endocrinol Metab*. 89(7):3313-18.
[342] Goglia L, et al (2010). Endothelial regulation of eNOS, PAI-1 and t-PA by testosterone and dihydrotestosterone in vitro and in vivo. *Mol Hum Reprod*. 16(10):761-9.
[343] Yu J, et al. (2010). Androgen receptor-dependent activation of endothelial cels: role of phospatidylinositol 3-kinase/akt pathway. *Endocrinol.* 151(4):1822-8.
[344] Steidle C, et al.(2003). AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. *J Clin Endocrinol Metab.* 88(6):2673-81.
[345] Bhasin S. (2003). Effects of testosterone administration on fat distribution, insulin sensitivity, and atherosclerosis progression. *Clin Infect Dis*. 37 Suppl 2:S142-9.

[346] Isidori AM, Giannetta E, Greco EA, et al. (2005). Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis.*Clin Endocrinol (Oxf*). 63(3):280-93.
[347] English K, et al. (2000). Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina. *Circulation*. 102(16):1906-11.
[348] Malkin CJ, et al. (2004). Testosterone replacement in hypogonadal men with angina improves ischaemic threshold and quality of life. *Heart.* 90(8): 871–876.
[349] Webb CM, et al. (1999). Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. *Circulation*. 100(16):1690-6.
[350] Webb CM, et al (1999). Effect of acute testosterone on myocardial ischemia in men with coronary artery disease. *Am J Cardiol*. 83(3): 437-9.
[351] Toma M, et al. (2012). Testosterone supplementation in heart failure: a meta-analysis. *Circ. Heart Failure.* 5(3):315-321.
[352] Carminiti, G. et al. (2009). Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. *J Am Coll Cardiol*. 54(10):919-27.
[353]Kromhout D, et al. (2002). Prevention of coronary heart disease by diet and lifestyle: evidence from prospective, cross-cultural, cohort, and intervention studies. *Circulation.* 105:893-8.
[354]Erridge C, et al. (2007). A high fat meal induces low-grade endotoxemia: evidence of a novel mechanism of portprandial inflammation. *Am J ClinNutr*. 86:1286-92.
Am J ClinNutr. 2007; 86(5):1286-92.
[355] Snowdon DA, Phillips RL. (1985). Does a vegetarian diet reduce the ocurrence of diabetes? *Am J Public Health.* 75(5):507-12.
[356] Barnard ND, et al. (2005). The effects of a low-fat, plant-based dietary intervention on body weight, metabolism, and insulin sensitivity. *Am J Med*. 118(9):991-7.
[357] Nicholson AS, et al. (1999). Toward improved management of NIDDM: a randomized, controlled, pilot intervention using a lowfat, vegetarian diet. *Prev Med*. 29(2):87-91.
[358] Ornish D, et al. (1998). Intensive lifestyle hanges for reversal of coronary heart disease. *J Am Med Assoc.* 280(23):2001-7.
[359]Esselstyn CB JR. (2001). Resolving the coronary artery disease epidemic through plant-based nutrition. *Prev Cardiol.* 4(4):171-77.
[360]Siervo M, et al. (2013). Inorganic nitrate and beetroot juice supplementation reduces blood pressure in adults: a systematic review and meta-analysis. *J Nutr.* 143(6):818-26.
[361]Hord N, et al. (2009). Food sources of nitrates and nitrites: the physiologic context for potential health benefits. *Am J ClinNutr*. 90(1):1-10.
[362] Hobbs DA, et al. (2013). The effects of dietary nitrate on blood pressure and endothelial function: a review of human intervention studies. *Nutr Res Rev*. 26(2):210-22.
[363]Fuhrman B, et al. (2005). Pomegranate juice inhibits oxidized LDL uptake and cholesterol biosynthesis in macrophages. *J Nutr Biochem*. 16(9):570-6.
[364]Aviram M, et al. (2004). Pomegranate juice consumption for 3 years by patients with carotid artery stenosis reduces common carotid intima-media thickness, blood pressure and LDL oxidation. *Clin Nutr.* 23(3):423-33.
[365]Ignarro LJ, et al. (2006). Pomegranate juice protects nitric oxide against oxidative destruction and enhances the biological actions of nitric oxide. *Nitric Oxide*. 15(2):93-102.
[366] Stowe CB. (2011). The effects of pomegranate juice consumption on blood pressure and cardiovascular health. *Complement Ther Clin Pract.* 17(2):113-5
[367] Rodriguez-Mateos A, et al. (2013). Inake and time dependence of blueberry-favonoid—induced improvements in vascular function: a randomized, controlled, double-blind, crossover, intervention study with mechanistic insights into biological activity. *Am J ClinNutr*. 98(5):1179-91.
[368]Hamley S. (2017). Effect of replacing saturated fat with mostly n-6 polyunsaturated fat on coronary heart disease: a meta-analysis of randomized controlled trials. *Nutrition J.* 16(1):30.
[369] De Souza RJ, et al. (2015). Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: a systematic review and meta-analysis of observational studies. *BMJ.* 351:h3978.
[370]Uribarri J, et al. (2010). Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J Am Diet Assoc*. 110(6):911-16.
[371]Bray GA, et al. (2004). Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am J Clin Nutr.* 79:537–43.
[372] Adamowicz J, Drewa T. (2011). Is there a link between soft drinks and erectile dysfunction? *Cent European J Urol.* 64(3):140-3.
[373] Li Z, et al. (2013). Decrease of postprandial endothelial dysfunction by spice mix added to high-fat hamburger meat in men with type 2 diabetes mellitus. *Diabet Med*. 30;590-5.
[374] West S, Skulas-Ray A. (2014). Spices and herbs may improve cardiovascular risk factors. *Nutrition Today.* 49(5):S8-S9.

[375] Davis PA, Yokoyama W. (2011). Cinnamon intake lowers fasting blood glucose: meta-analysis. *J Med Food*. 14(9):884-9.
[376] Allen RW, et al. (2013). Cinnamon use in type 2 diabetes: an updated systematic review and meta-analysis. *Ann Fam Med*. 11(5):452-9.
[377] Engler MB, et al. (2004). Flavonoid-rich dark chocolate improves endothelial function and increases plasma epicatechin concentrations in healthy adults. *J Am Coll Nutr.* 23(3):197-204.
[378] Mursu J, et al. (2004). Dark chocolate consumption increases HDL cholesterol concentration and chocolate fatty acids may inhibit lipid peroxidation in healthy humans. *FRBM.* 37:1351-9.
[379]Taubert. (2003). Chocolate and blood pressure in elderly individuals with isolated systolic hypertension. *JAMA*290:1029-30.
[380]Grassi D, et al. (2005). Short-term administration of dark chocolate is followed by a significant increase in insulin sensitivity and a decrease in blood pressure in healthy persons. *Am J ClinNutr.* 81:611-14.
[381] GrassiD, et al. (2005). Cocoa reduces blood pressure and insulin resistance and improves endothelium-dependent vasodilation in hypertensives. *Hypertension.* 46:398-405.
[382] Ried K, et al. (2017). Effect of cocoa on blood pressure. Cochrane Database of Systematic Reviews. 4: CD008893.
[383]Alexopoulos N, et al. (2008). The acute effect of green tea consumption on endothelial function in healthy individuals. *Eur J CardiovasPrevRehabil*. 15(3):300-5.
[384] Duffy S, et al. (2001). Short- and long-term black tea consumption reverses endothelial dysfunction in patients with coronary artery disease. *Circulation*. 104:151-6.
[385]Bogdanski P, et al. (2010). Green tea extract reduces blood pressure, inflammatory biomarkers, and oxidative stress and improves parameters associated with insulin resistance in obese, hypertensive patients. *Nutr Res.* 32(6):421-7.
[386]Landberg R, et al. Diet and endothelial function: from individual components to dietary patterns. *Cur Opin Lipidol.* 23(2):147-55.
[387]Wang ZM, et al. (2011). Black and green tea consumption and the risk of coronary artery disease: a meta-analysis. *Am J Clin Nutr*. 93(3):506-15.
[388]Arab L, et al. (2009). Green and black tea consumption and risk of stroke: a meta-analysis.*Stroke.* 40(5):1786-92.
[389]Sano J, et al. (2004). Effects of green tea intake on the development of coronary artery disease. *Circ J*. 68(7):665-70.
[390]Klangjareonchai T, et al. (2012). The effect of egg consumption in hyperlipemic subjects during treatment with lipid-lowering drugs. *J Lipids*. 2012:672720.
[391]Scrafford CG, et al. (2011). Egg consumption and CHD and stroke mortality: a prospective study of US adults. *Public Health Nutr*. 14(2):261-70.
[392]Rong Y, et al. (2013). Egg consumption and risk of coronary heart disease and stroke: dose-response meta-analysis of prospective cohort studies. *BMJ.* 346:e8539.
[393]Bazzano LA, et al. (2014). Effects of low-carbohydrate and low-fat diets: a randomized trial. *Ann Intern Med*. 161:309-18.
[394]Dickinson KM, et al. (2011). Endothelial function is impaired after a high-salt meal in healthy subjects. *Am J Clin Nutr.* 93(3):500-5.
[395]Bragulat E, Sierra A. (2002). Salt intake, endothelial dysfunction, and salt-sensitive hypertension. *J Clin Hypertens.* (4):41-6.
[396] Kong YW, et al. (2016). Sodium and its role in cardiovascular disease—the debate continues. *Front Endocrinol (Lausanne).* 7:164.
[397]Ronksley P, et al. (2011). Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. *BMJ*. 342:d671.
[398] Patra J, et al. (2010). Alcohol consumption and the risk of morbidity and mortality for different stroke types—a systematic review and meta-analysis. *BMC Public Health*. 10:258
[399]Slentz CA, et al. (2007). Inactivity, exercise training and detraining, and plasma lipoproteins. STRRIDE: a randomized, controlled study of exercise intensity and amount. *J Appl Physiol.* 103(2):417-8.
[400]Di Francescomarino S, et al. (2009). The effect f physical exercise on endothelial function. *Sports Med.* 39(10):797-812.
[401] Walther C, et al. (2004). The effect of exercise training on endothelial function in cardiovascular disease in humans. *Exer Sport Sci Rev*. 32(4):129-34.
[402]Fuchsjager-Mayrl G, et al. (2002). Exercise training improves vascular endothelial function in patients with type 1 diabetes. *Diabetes Care*. 25:1795-1801.
[403]Vina J, et al. (2012). Exercise acts a drug; the pharmacological benefits of exercise. *B J Pharmacol*. 167(1):1-12
[404] Ross R, et al. (2004). Exercise-induced reduction in obesity and insulin resistance in women: a randomized controlled trial. *Obesity Res*. 12(5): 789-98.
[405]Rehman J, et al. (2004). Exercise acutely increases circulating endothelial progenitor cells and monocyte/macrophage-derived angiogenic cells. *J Am Coll Cardiol*. 43(12):2314-8.

[406]Ross MD, et al. (2014). Resistance exercise increases endothelial progenitor cells and angiogenic factors. *Med Sci Sports Exerc*. 46(1):16-23.
[407] Hill JM, et al. (2003). Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. *N Engl J Med*. 348(7):593-600.
[408]Tjonna A, et al. (2008). Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome. Exercise Physiology. *Circulation*. 118(4):346-54.
[409]Rosengren A, et al. (2004). Association of psychosocial risk factors with risk of acute myocardial infarction in 11,119 cases and 13,648 controls from 52 countries (the INTERHEARTT study): case-control study. *Lancet.* 364(9438):953-62.
[410] Yusuf S, et al. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 364(9438):937-52.
[411]Ghiadoni L, et al. (2000). Mental stress induces transient endothelial dysfunction in humans. *Circulation*. 102:2473-78.
[412]Toda N, Nakanishi-Toda M. (20110. How mental stress affects endothelial function. *Pflugers Arch.* 462(6):779-94.
[413] Schneider R, et al. (2012). Stress reduction in the secondary prevention of cardiovascular disease. Randomized, controlled trial of transcendental meditation and health education in Blacks. *Circulation: Cardiovascular Quality and Outcomes*. 5:750-8.
[414] Somers V, et al. (2008). Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation scientific statement from the American Heart Association council for high blood pressure research professional education committee council on clinical cardiology, stroke council and council on cardiovascular nursing in collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation.* 118:1080-11.
[415] Silverberg DS, et al. (1998). Sleep-related breathing disorders as a major cause of essential hypertension: fact or fiction? *CurrOpinNephrol Hypertens*. 7:353–7.
[416] Schafer H, et al. (1999). Obstructive sleep apnea as a risk marker in coronary artery disease. *Cardiology*.92(2):79-84.
[417] Sin DD, et al. (1999). Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. *Am J RespirCrit Care Med*. 160:1101–6.
[418] Calhoun D, Harding S. (2010). Sleep and hypertension. 2010;139(2):434-43.
[419]Yaggi HK, et al. (2006). Sleep duration as a risk factor for the development of type 2 diabetes. *Diabetes Care*. 29(3):657-61.
[420] Knutson KL, Van Cauter E. (2008). Associations between sleep loss and increased risk of obesity and diabetes. *Ann N Y Acad Sci*. 1129:287-304.
[421]Sabanayagam Ch, Shankar A. (2010). Sleep duration and cardiovascular disease: results from the National Health Interview Survey. *Sleep*. 33(8):1037-42.
[422]Ruiter Petrov ME, et al. (2014). Self-reported sleep duration in relation to incident stroke symptoms: nuances by body mass and race from the REGARDS study. *J Stroke Cerebrovasc Dis*. 23(2):e123-32.
[423]Goldberg IJ, et al. (2001). AHA Science Advisory: Wine and your heart: a science advisory for healthcare professionals from the Nutrition Committee, Council on Epidemiology and Prevention, and Council on Cardiovascular Nursing of the American Heart Association. *Circulation.* 103:472–5.
[424]Koppes LL, et al. (2005). Moderate alcohol consumption lowers the risk of type 2 diabetes: a meta–analysis of prospective observational studies. *Diabetes Care*. 28:719–25.
[425]Mukamal KJ, et al. (2006). Alcohol consumption and risk of coronary heart disease in older adults: the Cardiovascular Health Study. *J Am Geriatr Soc*. 54:1965-70.
[426] Reynolds K, et al. (2003). Alcohol consumption and risk of stroke: a meta-analysis. *JAMA*. 289(5):79-58.
[427] Murray R, et al. (2002). Alcohol volume, drinking pattern, and cardiovascular disease morbidity and mortality: is there a U-shaped function. *Am J Epidemiol*. 155(3):242-248.
[428] Interlandi J. Supplements can make you sick. *Consumer Reports*. July, 2016.
[429] Zhang Q, et al. (2011). Berberine moderates glucose and lipid metabolism through mulitpathway mechanisms. *Evid Based Complement Alternat Med.* 2011. pii:924851.
[430] Yin J, et al. (2008). Efficacy of berberine in patients with type 2 diabetes. *Metabolism*. 57(5): 712-7.
[431]Affuso F, et al. (2010). Cardiovascular and metabolic effects of berberine. *World J of Cardiol.*2(4):71-7.
[432] Wu M, et al. (2010). Advance of studies on anti-atherosclerosis mechanism of berberine. *Chin J Integr Med*. 16(2):188-92.
[433] Xu MG, et al. (2009). Berberine-induced upregulation of circulating endothelial progenitor cells is related to nitric oxide production in healthy subjects. *Cardiology.* 112:279-86.
[434]Xy MG, et al. (2008). Berberine-induced mobilization of circulating endothelial progenitor cells improves human small artery elasticity. *J Hum Hypertens*. 22(6):389-93.
[435] Brusq JM, et al. (2006). Inhibition of lipid synthesis through activation of AMP kinase: an additional mechanism for the hypolipidemic effects of berberine. *J Lipid Res*.47(6):1281-8.
[436] Kong W, et al. (2004). Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. *Nat Med*. 10(12):1344-51.
[437]Zeng XH, et al. (2003). Efficacy and safety of berberine for congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 15;92(2):173-6.

[438] Mollace V, et al. (2011). Hypolipemic and hypoglycaemic activity of bergamot polyphenols: From animal models to human studies. *Fitoterapia*. 82(3):309–16.
[439] Gliozzi M, et al. (2014). The effect of bergamot-derived polyphenolic fraction on LDL small dense particles and non alcoholic fatty liver disease in patients with metabolic syndrome. *Advances in Biological Chemistry*. 4:129-37.
[440]Zhang Q, e t al. (2011). Berberine moderates glucose and lipid metabolism through mulitpathway mechanisms. *Evid Based Complement Alternat Med.* 2011. pii:924851.
[441]Yin J, et al. (2008). Efficacy of berberine in patients with type 2 diabetes. *Metabolism*. 208;57(5):712-7.
[442]Affuso F, et al. (2010). Cardiovascular and metabolic effects of berberine. *World J of Cardiol.* 2(4):71-7.
[443]Wu M, et al (2010). Advance of studies on anti-atherosclerosis mechanism of berberine. *Chin J Integr Med*. 16(2):188-92.
[444]Brusq JM, et al. (2006). Inhibition of lipid synthesis through activation of AMP kinase: an additional mechanism for the hypolipidemic effects of berberine. *J Lipid Res*. 47(6):1281-8.
[445] Kong W, et al. (2004). Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. *Nat Med*. 10(12):1344-51.
[446] Xu MG, et al. (2009). Berberine-induced upregulation of circulating endothelial progenitor cells is related to nitric oxide production in healthy subjects. *Cardiology*. 112:279-86.
[447] Xu MG, et al. (2008). Berberine-induced mobilization of circulating endothelial progenitor cells improves human small artery elasticity. *J Hum Hypertens.* 22(6):389-93.
[448]Zeng XH, et al. (2003). Efficacy and safety of berberine for congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 15;92(2):173-6.
[449] Wongcharoen W, Phrommintikul A. (2009). The protective role of curcumin in cardiovascular diseases. *Int J Cardiol*.133(2):145-51.
[450] Ramirez-Tortosa MC, et al. (1999). Oral administration of a turmeric extract inhibits LDL oxidation and has hypocholesterolemic effects in rabbits with experimental atherosclerosis. *Atherosclerosis.* 147:371-8.
[451] Ganjali S, et al. (2017). Effects of curcumin on HDL functionality. *Pharmacol. Res*. 119:208-18.
[452] Panahi Y, et al. (2017). Antioxidant effects of curcuminoids in patients with type 2 diabetes mellitus: a randomized controlled trial. *Inflammopharmacology*. 25(1):25-31.
[453] Wongcharoen W, et al. (2012). Effects of curcuminoids on frequency of acute myocardial infarction after coronary artery bypass grafting. *Am J Cardiol*. 110(1):40-4.
[454] Akazawa N, et al. (2012). Curcumin ingestion and exercise training improve vascular endothelial function in postmenopausal women. *Nutr Res/* 32(10):795-9.
[455] Ghosh SS, et al. (2014). Oral supplementation with non-absorbable antibiotics or curcumin attenuates western diet-induced atherosclerosis and glucose intolerance in LDLR-/- mice—role of intestinal permeability and macrophage activation. *PLoS One*. 9(9):e108577.
[456] Antiga, et al. (2015). Oral curcumin (Meriva) is effective as an adjuvant treatment and is able to reduce IL-22 serum levels in patients with psoriasis vulgaris. *Biomed Res Int*. 2015:283634.
[457] Thangapazham RL, et al. (2007). Beneficial role of curcumin in skin diseases. *Adv Exp Med Biol*. 595:343-57.
[458] Thangapazham RL, et al. (2013). Skin regenerative potentials of curcumin. *Biofactors.* 39(1):141-9.
[459] DiSilvestro R, et al. (2012). Diverse effects of a low-dose supplement of lipidated curcumin (as Longvida®) in healthy middle-aged people. *Nutr. J*. 26;11:79.
[460] Reddy PH, et al. (2018). Protective effects of Indian spice curcumin against amyloid beta in Alzheimer's disease. *J Alzheimers Dis.* 61(3):843-66.
[461] Reddy PH, et al. (2016). Protective effects of a natural product, curcumin, against amyloid β induced mitochondrial and synaptic toxicities in Alzheimer's disease. *J Investig Med.* 64(8):1220-34.
[462] Begum AN, et al. (2008). Curcumin structure-function, bioavailability, and efficacy in models of neuroinflammation and Alzheimer's disease. *J Pharmacol Exp Ther*. 326(1):196-208.
[463] Ono K, et al (2004). Curcumin has potent anti-amyloidogenic effects for Alzheimer's beta-amyloid fibrils in vitro. *J Neurosci Res*. 75(6):742-50.
[464]Eslick G, et al. (2009). Benefits of fish oil supplementation in hyperlipidemia: a systematic review and meta-analysis. *Int J Cardiol*. 136(1):4-16.
[465]Suzukawa M, et al. 1995). Effects of fish oil fatty acids on low density lipoprotein size, oxidizability, and uptake by macrophages. *J Lipid Res*. 36(3):473-84.
[466]Gajos G, et al. (2014). Polyunsaturated omega-3 fatty acids reduce lipoprotein-associated phospholipase A(2) in patients with stable angina. *Nutr Metab Cardiovasc Dis*. 24(4):439-9.
[467] Puglisi MJ, et al. (2011). The role of adipose tissue in mediating the beneficial effects of dietary fish oil. *J Nutr Biochem*. 22(2):101-8.
[468] Morris MC, et al. (1993). Does fish oil lower blood pressure? A meta-analysis of controlled trials. *Circulation*. 88(2):523-33.
[469] Kang JX, Weylandt KH. (2008). Modulation of inflammatory cytokines by omega-3 fatty acids. *Subcell Biochem*. 49:133-43.
[470]Djoussé L, et al. (2012). Fish oil consumption, omega-3 fatty acids and risk of heart failure: a meta-analysis. *ClinNutr*. 31(6):846-53.

[471] Kris-Etherton K, et al. (2002). AHA Scientific Statement: fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation*. 106:2747-57.
[472] Yokoyama M, et al. (2017). Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomized open-label, blinded endpoint analysis. *Lancet.* 369(9567):1090-98.
[473] Bhatt D, et al. (2019). Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 380:11-22.
[474]Wongcharoen W, Phrommintikul A. (2009). The protective role of curcumin in cardiovascular diseases. *Int J Cardiol*. 133(2):145-51.
[475] Ramirez-Tortosa MC, et al. (1999). Oral administration of a turmeric extract inhibits LDL oxidation and has hypocholesterolemic effects in rabbits with experimental atherosclerosis. *Atherosclerosis.* 147:371-8.
[476]Ganjali S, et al. (2017). Effects of curcumin on HDL functionality. *Pharmacol. Res*. 119:208-18.
[477] Panahi Y, et al. (2017). Antioxidant effects of curcuminoids in patients with type 2 diabetes mellitus: a randomized controlled trial. *Inflammopharmacology*. 25(1):25-31.
[478]Wongcharoen W, et al. (2012). Effects of curcuminoids on frequency of acute myocardial infarction after coronary artery bypass grafting. *Am J Cardiol*. 110(1):40-4.
[479]Akazawa N, et al. (2012). Curcumin ingestion and exercise training improve vascular endothelial function in postmenopausal women. *Nutr Res*. 32(10):795-9.
[480] Ghosh SS, et al. (2014). Oral supplementation with non-absorbable antibiotics or curcumin attenuates western diet-induced atherosclerosis and glucose intolerance in LDLR-/- mice—role of intestinal permeability and macrophage activation. *PLoS One*. 9(9):e108577.
[481]Antiga, et al. (2015). Oral curcumin (Meriva) is effective as an adjuvant treatment and is able to reduce IL-22 serum levels in patients with psoriasis vulgaris. *Biomed Res Int*. 2015:283634.
[482]Thangapazham RL, et al. (2007). Beneficial role of curcumin in skin diseases. *Adv Exp Med Biol*. 595:343-57.
[483]Thangapazham RL, et al. (2013). Skin regenerative potentials of curcumin. *Biofactors.* 39(1):141-9.
[484]DiSilvestro R, et al. (2012). Diverse effects of a low-dose supplement of lipidated curcumin (as Longvida®) in healthy middle-aged people. *Nutr J*. 26:11:79.
[485] Reddy PH, et al. (2018). Protective effects of Indian spice curcumin against amyloid beta in Alzheimer's disease. *J Alzheimers Dis.* 61(3):843-66.
[486] Reddy PH, et al. (2016). Protective effects of a natural product, curcumin, against amyloid β induced mitochondrial and synaptic toxicities in Alzheimer's disease. *J Investig Med.* 64(8):1220-34.
[487] Begum AN, et al. Curcumin structure-function, bioavailability, and efficacy in models of neuroinflammation and Alzheimer's disease. *J PharmacolExpTher*. 2008;326(1):196-208.
[488] Ono K, et al. (2004). Curcumin has potent anti-amyloidogenic effects for Alzheimer's beta-amyloid fibrils in vitro. *J Neurosci Res*. 75(6):742-50.
[489] Crane FL. (2013). Discovery of ubiquinone (coenzyme Q) and an overview of function. *Mitochondrion*. Suppl:S2-7.
[490]Ahmadvand H, et al. Effects of coenzyme Q10 on LDL oxidation in vitro. *Acta Med Iran*. 2013;51(10):12-8.
[491]Ghirlanda G, et al. (1993). Evidence of plasma CoQ10-lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study. *J Clin Pharmacol.*33(3):226-9
[492]Zlatohlavek L, et al. (2012). The effect of coenzyme Q10 in statin myopathy. *Neuro Endocrinol Lett.* 33 Suppl 2:98-101.
[493]Larijani V, et al. (2013). Beneficial effects of aged garlic extract and coenzyme Q10 on vascular elasticity and endothelial function: the FAITH randomized clinical trial. *Nutrition.* 29:71-5.
[494]Langsjoen P, et al. (1994). Treatment of essential hypertension with coenzyme Q10. *Mol Aspects Med*. 15 Suppl: S265-72.
[495] Hodgson JM, et al. (2002). Coenzyme Q10 improves blood pressure and glycaemic control: a controlled trial in subjects with type 2 diabetes. *Eur J ClinNutr.* 56(11):1137-42.
[496] Mortensen S, et al. (2014). The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. *JACC Heart Fail.* 2(6):641-9.
[497] Lee JM, et al. (2009). Effects of high-dose modified-release nicotinic acid on atherosclerosis and vascular function: a randomized, placebo-controlled, magnetic resonance imaging study. *J Am Coll Cardiol.* 54(19):1787-94.
[498] Brown G, et al. (1990). Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N. Engl. J. Med.* 323:1289–98.
[499]Taylor AJ, et al. (2009). Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med.* 361(22):2113-22.
[500] Berge KG, Canner PL. (1991). Coronary drug project: experience with niacin. *Eur J ClinPharmacol.* 40 Suppl1:S49-51.
[501] Brown G, et al. (2001). Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N. Engl. J. Med.* 345:1583–1592.
[502] Taylor AJ, et al. (2004). Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation* 110: 3512–17.

[503] Taylor AJ, et al. (2006). The effect of 24 months of combination statin and extended-release niacin on carotid intima-media thickness: ARBITER 3. *Curr. Med. Res. Opin.* 22:2243–50.
[504] Phan BA, et al. (2013). Effects of niacin on glucose levels, coronary stenosis progression, and clinical events in subjects with normal baseline glucose levels (<100 mg/dl): a combined analysis of the Familial Atherosclerosis Treatment Study (FATS), HDL-Atherosclerosis Treatment Study (HATS), Armed Forces Regression Study (AFREGS), and Carotid Plaque Composition by MRI during lipid-lowering (CPC) study. *Am J Cardiol*. 111(3):352-5.
[505]Gangi SH, et al. (2006). Effect of niacin on lipoproteins and atherosclerosis. *Future Lipidol.* 1:549–557.
[506]Kuvin JT, et al. (2002). *A* novel mechanism for the beneficial vascular effects of high-density lipoprotein cholesterol: enhanced vasorelaxation and increased endothelial nitric oxide synthase expression. *Am. Heart J.* 144(1):165–72.
[507]Kuvin JT, et al. (2006). Effects of extended-release niacin on lipoprotein particle size, distribution, and inflammatory markers in patients with coronary artery disease. *Am. J. Cardiol.* 98:743–74.
[508]Religa D, et al. (2003). Homocysteine, apolipoprotein E and methylenetetrahydrofolate reductase in Alzheimer's disease and mild cognitive impairment. *Dement Geriatr Cogn Disord*. 16(2):64-70.
[509] van Meurs JB, et al. (2004). Homocysteine levels and the risk of osteoporotic fracture. *N Engl J Med*. 350(20):2033-41.
[510] McLean RR, et al. (2004). Homocysteine as a predictive factor for hip fracture in older persons. *N Engl J Med.* 350(20):2042-9.
[511]Kazemi MB, et al. (2006). Homocysteine level and coronary artery disease. *Angiology*. 57(1):9-14.
[512] Sarwar AB, et al. (2007). Measuring subclinical atherosclerosis: is homocysteine relevant? C*lin Chem Lab Med*. 45(12):1667-77.
[513] McIlroy SP, et al. (2002). Moderately elevated plasma homocysteine, methylenetetrahydrofolate reductase genotype, and risk for stroke, vascular dementia, and Alzheimer disease in Northern Ireland. *Stroke*. 33(10):2351-6.
[514]Bjelland I, et al. (2003). Folate, vitamin B12, homocysteine, and the MTHFR 677C->T polymorphism in anxiety and depression: the Hordaland Homocysteine Study. *Arch Gen Psychiatry*. 60(6):618-26.
[515] Almeida OP, et al. (2008). Homocysteine and depression in later life. *Arch Gen Psychiatry*. 65(11):1286-94.
[516] Kim JM, et al. (2008). Folate, vitamin B12, and homocysteine as risk factors for cognitive decline in the elderly. *Psychiatry Investig.*;5(1):36-40.
[517] Ravaglia G, et al. (2003). Homocysteine and cognitive function in healthy elderly community dwellers in Italy. *Am J ClinNutr.* 77(3):668-73.
[518] Liu J, et al. (2006). Chinese red yeast rice (*Monascuspurpureus*) for primary hyperlipidemia: a meta-analysis of randomized controlled trials. *Chin Med*. 1:4.
[519] Fujimoto M, et al. (2012). Study of the effects of monacolin K and other constituents of red yeast rice on obesity, insulin-resistance, hyperlipidemia, and nonalcoholic steatohepatitis using a mouse model of metabolic syndrome. *Evidence-Based Compl Alt Med*. 2012:892697.
[520] Patrick L, Uzick M. (2001). Cardiovascular disease: C-reactive protein and the inflammatory disease paradigm: HMG-CoA reductase inhibitors, alpha-tocopherol, red yeast rice, and olive oil polyphenols. A review of the literature. *Altern Med Rev.* 6(3):248-71.
[521]Zhu X-Y, et al. (2013) Xuezhikang, extract of red yeast rice, improved abnormal hemorheology, suppressed caveolin-1 and increased eNOS expression in atherosclerotic rats. PLoS ONE. 2013;8(5):e62731.
[522]Li P, et al. Xuezhikang. (2011). Extract of red yeast rice, inhibited tissue factor and hypercoagulable state through suppressing nicotinamide adenine dinucleotide phosphate oxidase and extracellular signal-regulated kinase activation. *J Cardiovasc Pharmacol.* 58(3):307-18.
[523]Gordon RY, et al. (2010). Marked variability of monacolin levels in commercial red yeast rice products: buyer beware! *Arch Intern Med.* 170(19):1722-27.
[524] Evans JL, Goldfi ID. (2000). Alpha-lipoic acid: a multi-functional antioxidant that improves insulin sensitivity in patients with type 2 diabetes. *Diabetes Technol* 2(3):401-13.
[525] Jacob S, et al. (1999). Oral administration of RAC-alpha-lipoic acid modulates insulin sensitivity in patients with type 2 diabetes mellitus: a placebo-controlled pilot trial. *Free RadicBiol Med*. 27:309-14.
[526] Harding SV, et al. (2012). Evidence for using alpha-lipoic acid in reducing lipoprotein and inflammatory related atherosclerotic risk. *J Diet Suppl*. 9(2):116-27
[527] Wollin S, Jones P. (2003). α-lipoic acid and cardiovascular disease. *J Nutr.* 133(11):3327-30.
[528] Sabharwal AK, May JM. (2008). Alpha-Lipoic acid and ascorbate prevent LDL oxidation and oxidant stress in endothelial cells. *Mol Cell Biochem*. 309(1-2):125-32.
[529] Bojunga J, et al. (2004). Antioxidative treatment reverses imbalances of nitric oxide synthase isoform expression and attenuates tissue-cGMP activation in diabetic rats. *Biochem Biophys Res Commun*. 316(3):771-80