

# Genetic Variation, Diet, Inflammation, and the Risk for COVID-19

## Keywords

Genetic variation · Diet · Omega-6 and omega-3 fatty acid balance · Inflammation · Obesity · COVID-19 risk

## Abstract

COVID-19, which is caused by SARS-CoV-2, is characterized by various symptoms, ranging from mild fatigue to life-threatening pneumonia, “cytokine storm,” and multiorgan failure. The manifestation of COVID-19 may lead to a cytokine storm, i.e., it facilitates viral replication that triggers a strong release of cytokines, which then modulates the immune system and results in hyperinflammation. Today’s diet is high in omega-6 fatty acids and deficient in omega-3 fatty acids; this, along with a high fructose intake, leads to obesity, which is a chronic state of low-grade inflammation. Omega-6 fatty acids are proinflammatory and prothrombotic whereas omega-3 fatty acids are less proinflammatory and thrombotic. Furthermore, omega-3 fatty acids make specialized lipid mediators, namely resolvins, protectins, and maresins, that are potent anti-inflammatory agents. Throughout evolution there was a balance between omega-6 and omega-3 fatty acids with a ratio of 1–2/1 omega-6/omega-3, but today this ratio is 16–20/1 omega-6/omega-3, leading to a proinflammatory state. In addition, genetic variants in FADS1, FADS2, ELOV-2, and ELOV-5 lead to a more efficient biosynthesis of long-chain polyunsaturated fatty acids (PUFAs), e.g., of linoleic acid (LA) to arachidonic acid (ARA), and (alpha-linolenic acid) (ALA) to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), leading to higher ARA lev-

els. Because the US diet is already high in omega-6 fatty acids, the increased biosynthesis of ARA in people with the derived FADS haplotype (haplotype D) leads to an increased production of leukotrienes, thromboxanes, C-reactive protein (CRP), and eventually elevated levels of cytokines, like interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF), which may increase susceptibility to COVID-19. About 80% of African Americans, 50% of Hispanics, and 45% of European Americans have the FADS haplotype D and are thus efficient metabolizers, which could account for the higher vulnerability of these populations to COVID-19. Therefore, another reason that African Americans and Hispanics are more susceptible to COVID-19 is that they have a higher frequency of haplotype D, which is no longer beneficial in today’s environment and diet. Genetic variation must be considered in all studies of disease development and therapy because it is important to the practice of precision nutrition by physicians and other health professionals. The objective of this commentary is to emphasize the importance of genetic variation within populations and its interaction with diet in the development of disease. Differences in the frequency of genes and their interactions with nutrients in various population groups must be considered among the factors contributing to health disparities in the development of COVID-19. A balanced omega-6/omega-3 ratio is essential to health. Physicians should measure their patients’ fatty acids and recommend decreasing the intake of foods rich in omega-6 fatty acids and increasing the intake of omega-3 fatty acids along with fruits and vegetables.

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## Genetic Variation, Diet, Inflammation, and the Risk for COVID-19

Coronavirus disease 2019 (COVID-19) is a pandemic that has been difficult to control. Patients who carry the virus may be asymptomatic, or have moderate to severe coughing, fever, or shortness of breath. In more severe cases, complications can include acute respiratory distress syndrome, septic shock, and death [1]. These complications are believed to be related to what has been described as the “cytokine storm,” in which viral replication triggers an abnormally strong release of cytokines and other immune-related stimuli, resulting in hyperinflammation [1, 2].

As the numbers testing positive for COVID-19 reached high proportions and the number of people being hospitalized and dying from the disease increased, it became apparent that there were higher proportions of African Americans, Hispanics, the Navajo nation, and some Asian minority groups that were at a higher risk for contracting COVID-19. When collecting the data, race and ethnicity were not included from the very beginning of the pandemic, meaning that data are not accurate in terms of the total number of deaths of the various ethnic groups across the USA [3, 4]. Some investigators began to consider and study the reasons for these health disparities. Studies appeared on the relationship of socioeconomic status (SES), geographic location, and other factors that were related to health disparities across the various racial groups [4, 5]. In fact, Chowkwanyun and Reed [6], in their paper “Racial Health Disparities and COVID-19 – Caution and Content,” outline at great length the danger of considering racial biology, behavioral explanations predicated on racial stereotypes, and territorial US stigmatization. Senator Elizabeth Warren (D-MA) and representative Ayanna Presley (D-MA) called for a more thorough collection of racial data, criticizing the government in an open letter for “currently failing to collect and publicly report on the racial and ethnic demographic information of patients tested for and affected by COVID-19” [6]. Soon after that, several states began to collect data incorporating demographic details.

Karaca-Mandic et al. [7] examined the racial/ethnic prevalence of cumulative COVID-19 hospitalizations in the 12 states that report such data and compared how this prevalence differs from the racial/ethnic composition of each state’s population. Their data show disproportionately high COVID-19 hospitalizations for Blacks, Hispanics, American Indians, and the Alaskan native populations. A new analysis by the Centers for Disease Control

and Prevention (CDC) of >114,000 Americans who died of COVID-19 between May and August 2020 found that 24% were Hispanic or Latino, even though only about 18% of Americans are of Hispanic descent. Just 12.5% of Americans are Black, but Blacks accounted for almost 19% of all COVID-19 deaths in those 4 months [8]. In Africa, fewer cases and deaths [9] have been reported, despite similar genetic variation to African Americans, possibly due to the fact that a larger proportion of the population is younger than that in the USA and the diet is not as high in omega-6 fatty acids and ultra-processed foods.

In the 5th century BC, Hippocrates pointed out that overall health depends on the interaction of genes with a number of environmental factors. Nutrition or diet is the most important environmental factor that interacts with genes. There is enormous genetic variation in humans around the world [10]. It is this genetic variation that makes each one of us unique. Recognizing that genetics deals with variation, a fundamental aspect of the genetics approach to disease is an appreciation of human variation, its nature and extent, its origin and maintenance, its distribution in families and populations, its interaction with environmental factors (especially diet), and its consequences for normal development and homeostasis.

The issues focused on in this commentary are: (1) the interaction of genetic variation and the evolutionary aspects of diet in the development of a proinflammatory state that may increase susceptibility to COVID-19, and (2) obesity as a chronic state of low-grade inflammation that may account for the increased susceptibility to COVID-19 of African Americans and Hispanics, possibly due to their genetic predisposition and high intake of omega-6 fatty acids and fructose.

### Evolutionary Aspects of Diet and the Omega-6/Omega-3 Fatty Acid Balance

Although our genes have not changed over the past 10,000 years, major changes have taken place in our food supply, which began 75 years ago in the wake of World War II, with a major increase in the intake of oils rich in omega-6 fatty acids, which led to omega-3 deficiency worldwide [11], and simple sugars, especially fructose. Animals are now grain-fed (vs. grass-fed), mostly on corn, to gain weight faster. Corn is high in linoleic acid (LA), i.e., omega-6 fatty acids, whereas grass is high in alpha-LA (ALA), i.e., omega-3 fatty acids. This dietary change for animals affected the composition of meat, dairy products, and the eggs of chickens fed corn, and led

to a high omega-6/omega-3 ratio and a proinflammatory state in humans [12]. This could increase susceptibility to COVID-19 [13], particularly in the presence of genetic variants that increase the biosynthesis of arachidonic acid (ARA) from LA and lower docosahexaenoic acid (DHA). Schwarz et al. [13] showed that the risk factors for COVID-19 associated with severe disease and increased mortality (such as advanced age, hypertension, diabetes, and obesity) pathologically disrupt the lipidome. This disruption may be a unifying feature of severe COVID-19.

During human evolution, there was a balance in the intake of LA and ALA in a ratio of about 1/1. Both LA and ALA are essential for human health and must be obtained from the diet. Furthermore, our genes are programmed to respond to this balanced ratio for health. In addition to changes in meat composition, the food supply in the USA has come to have a high omega-6/omega-3 ratio of approximately 16/1, due to the increased production of oils high in LA, e.g., corn oil 63%, sunflower oil (74%), safflower oil (70%), and soybean oil (53%). Studies on the biosynthetic pathway of LA and ALA in humans show the presence of genetic variants in FADS1, FADS2, ELOV-2, and ELOV-5 that determine the efficiency of the synthesis of ARA from LA, and eicosapentaenoic acid (EPA) and DHA from ALA, further increasing the levels of ARA [14, 15]. The eicosanoid metabolic products of ARA, leukotrienes, and thromboxanes are proinflammatory and prothrombotic, leading to a proinflammatory state that activates the immune system and the replication of COVID-19 [2, 13, 16], but those derived from EPA and DHA are less thrombotic and less inflammatory. Omega-6 and omega-3 fatty acids and their metabolites have opposing properties, so a balanced ratio is important for health. In fact, EPA and DHA produce specialized proresolving lipid autacoid mediators (SPMs), such as resolvins, which are being used to resolve inflammation and could be used as antiviral agents along with other agents in the management of COVID-19 which is characterized by an inflammatory state referred to as cytokine storm [17]. LA and ARA increase inflammation and fat cell proliferation. The current US diet which is high in LA leads to higher rates of chronic low-grade inflammation and obesity with its comorbidities like type 2 diabetes, hypertension, cardiovascular disease, some forms of cancer, and to arthritis and asthma, all of which have been found to influence the severity of COVID-19 [18]. The world today is fighting two pandemics, one of chronic low-grade inflammation, i.e., obesity, and one of acute inflammation, i.e., COVID-19.

## Genetic Variation

Studies over the past 15 years show that genetic variants in FADS1, FADS2, ELOV-2, and ELOV-5 involved in the biosynthesis of LA to ARA, and ALA to EPA and DHA, are distributed differently in populations in various parts of the world [15, 19, 20]. The results of these studies challenged the concept that the biosynthesis of long-chain polyunsaturated fatty acids (LC-PUFAs) from 18C-PUFA is the same across individuals and populations [15, 19, 20]. They showed that there are marked differences in the frequency of genetic variance in FADS1, FADS2, ELOV-2, and ELOV-5 between populations of African and European ancestry due to the circulating levels of omega-6 and omega-3 LC-PUFAs. About 80% of African Americans carry 2 copies of FADS alleles that more efficiently biosynthesize LC-PUFAs from 18-C PUFA, versus only 45% of European Americans; this genetic difference explains a large proportion of the variability of the levels of LC-PUFAs in the circulation between African and European Americans, and the (up to 28%) higher levels of ARA can increase the production of proinflammatory cytokines, which may increase the COVID-19 risk [15, 19, 20]. People of Arctic and Native American ancestry and about 45% of European and Asian populations have less efficient LC-PUFA biosynthetic pathways [21].

Studies by Ameur et al. [22] and Chilton et al. [23] on the evolutionary aspects of fatty acid biosynthesis and metabolism showed that, in different populations around the globe, there are major differences in the frequency of the FADS ancestral (A) haplotype (haplotype A) and FADS-derived (D) haplotype (haplotype D) and thus in the efficiency of LC-PUFA biosynthesis. For example, haplotype A, which is less efficient, is found in 97% of people of Native American ancestry and is virtually absent in Africa, indicating that Native Americans have a more limited capacity than Africans to synthesize LC-PUFA from LA and ALA. The frequency of haplotype D varies from 80–85% in African Americans to 25–50% in Europe and East Asia [22, 24]. Extensive evolution of the FADS cluster led to changes in the efficiency of LC-PUFA biosynthesis, as early humans adapted to local environments as they moved from Africa to the Americas. Individuals with haplotype D have higher levels of ARA and produce more inflammatory and prothrombotic metabolites, that further increase the production of leukotrienes, interleukin (IL)-2, IL-8, tumor necrosis factor (TNF)- $\alpha$ , IL-6, and other cytokines, leading to a chronic inflammatory state which supports the replication of the virus that

causes COVID-19 [2, 16]. Because of the higher frequency of haplotype D in African Americans, more African Americans and Hispanics are in a proinflammatory state than European Americans (as well as the African American admixture in the Hispanic populations); this may indeed account for the higher susceptibility of these populations to COVID-19 [25].

## Obesity

In the USA, 42.4% of adults are obese (BMI  $\geq 30$ ), and 50% of these are Black and female; however, the prevalence of obesity differs across populations of different ancestry [15, 17, 20, 25–27]. The majority are African Americans (approx. 48.4%), followed by Hispanics/Latinos (approx. 40%). European Americans account for 36.4%. Women show greater differences than men across all ancestries. Studies on the causes of these differences across groups include environmental factors, lifestyle, and cultural and social practices. However, these types of studies partly explain health disparities across ancestries. Differences in genetic ancestry have also been considered that may also predispose certain populations to obesity more than others [28, 29]. In addition to genetic variations, differences exist in the type of food intake of different ethnic groups. Recent data from the NHANES survey [30] showed that the fast-food intake of adolescents varies enormously among Whites (with 15% of their calorie intake being from fast food), Hispanics (18.5%), and African Americans (21.5%). The diets of African American and Hispanics are generally lacking in fish, fruits, and vegetables, and characterized by high amounts of ultra-processed foods (high in omega-6 fatty acids) that are proinflammatory. Ultra-processed diets lead to obesity and an inflammatory state with an omega-6/omega-3 ratio of 11.1:1 (vs. the 1–2:1 during human evolution) [31, 12]. The combination of obesity, high omega-6 fatty acid intake, and haplotype D frequency enhances the inflammatory status of these population groups and makes them more prone to vasculitis and the catastrophic effects of COVID-19 [12, 18].

The US population is a melting pot of nationalities, ethnicities, and cultures, as migrants have been arriving from all over the world since the 17th century. These migrant populations have undergone a more recent genetic admixture, e.g., African Americans have up to 20% European ancestry and Hispanics in New York City have up to 50% African ancestry [32]. In a recent study, Vishnu et al. [33] evaluated the role played by the country of birth and

genetic ancestry, and found that the former was the most significant contributor to variations in BMI and the risk of obesity in both men and women. Being born in the USA increased the risk of obesity 1.5-fold compared with being born outside the USA. Genetic ancestry determined by the proportion of African American ancestry was associated with a higher BMI in both African American and Hispanics. The authors concluded, “Overall, our results, together with the results from previous studies, provide evidence that genetic ancestry contributes to the variation in BMI and obesity risk, particularly among women” [33].

Obesity is the result of excess energy intake and decreased energy expenditure, but not all calories are the same in their contribution to obesity. A high omega-6/omega-3 ratio increases the risk of obesity by increasing appetite via the endocannabinoids from the high intake of LA and the increased production of fat cells [34]. High fructose intake also increases appetite. A chronic inflammatory state is induced by the metabolic surplus, which impacts the number and size of metabolic cells like white adipocytes which initiate the inflammatory process [35].

In the last few years, large-scale genome-wide association studies (GWAS) have identified multiple loci associated with BMI. These loci consist of commonly distributed variants that determine overall susceptibility to obesity [36]. A meta-analysis of GWAS identified 32 loci that are associated with BMI at a genome-wide significance level [37, 38]. During the past 40 years, the intake of sugar-sweetened beverages (SSBs) that are high in fructose has increased [39]. The composition of soft drinks (fructose) has been associated with the activation of different mechanisms that promote inflammation. Fructose promotes oxidative stress and the activation of NF- $\kappa$ B, inducing a stress response by the liver and lipid metabolic dysregulation. Studies have shown an association between the intake of SSBs and the risk of obesity [39–44]. In a longitudinal study, the interaction between SSBs and genetic predisposition score, calculated as based on the 32 loci that have an established association with BMI, were evaluated [45]. The results indicated that genetic effects on adiposity are stronger in individuals with a higher intake of sugars than those with a lower intake [45].

## Conclusions and Recommendations

It is evident that changes in the food supply over a relatively short period of time since World War II have had dire consequences worldwide. Our genes are programmed to respond to a diet consistent with our diet during hu-

man evolution. The enormous increase in the intake of omega-6 fatty acids, the decrease in omega-3 fatty acid intake, and the increase in the intake of fructose and ultra-processed foods have led to the prevalence of metabolic disease of the brain [46], obesity [47], and a chronic pro-inflammatory [48] state that may increase the susceptibility to and severity of COVID-19 infection [15]. Genetic variation must be considered in all studies of disease development and therapy. Precision nutrition will usher in the golden age of nutrition, with nutrigenetics/nutrigenomics leading the way. Today's diet is prothrombotic and proinflammatory; it is therefore dangerous to the homeostasis of populations with a high frequency of genes that were beneficial during evolution but are detrimental in today's environment and with the current food supply. It is essential that the food supply is balanced in omega-6 and omega-3 fatty acids by (1) lowering the intake of oils rich in omega-6 fatty acids (e.g., corn oil, sunflower oil, safflower oil, and soybean oil), (2) increasing the intake of oils rich in omega-3 fatty acids (e.g., canola, flaxseed, perilla, and chia), (3) increasing the intake of monounsaturated oils (olive oil, hazelnut oil, and macadamia nut oil), and (4) decreasing the consumption of ultra-processed foods that have an omega-6/omega-3 ratio >4:1. It

is essential that physicians and other health professionals measure the omega-6 and omega-3 fatty acids in their patients' red blood cell membrane phospholipids to ensure a healthy omega-6/omega-3 ratio, in order to decrease chronic low inflammation and maintain a normal/less inflammatory immune system that would decrease the risk for contracting COVID-19.

Healthy nutrition, i.e., balanced in omega-6 and omega-3 fatty acids and rich in fruits, vegetables, seeds, nuts, grains, fish, and lean meat, provides adequate protein, vitamins, minerals, and antioxidants. A proper diet (with a balanced omega-6/omega-3 fatty acid intake) and exercise, along with drugs, and eventually vaccines, should be able to conquer the pandemic of COVID-19.

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### Conflict of Interest Statement

The author has no conflicts of interest to declare.

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