International Journal of Medical and All Body Health Research

International Journal of Medical and all body Health Research
ISSN: 2582-8940
Received: 18-11-2021; Accepted: 03-12-2021
www.allmedicaljournal.com
Volume 2; Issue 4; October-December 2021; Page No. 54-63

Unhealthy lifestyles and their deleterious relationship with infections: A Narrative Review

Shashi K Agarwal
US Highway 1, Suite 309, North Brunswick, NJ 08902, USA

Corresponding Author**: Shashi K Agarwal**

DOI: https://doi.org/10.54660/Ijmabhr.2021.2.4.2

Abstract
Infection morbidity and mortality generate a significant global health burden. Several pandemics throughout human history have caused considerable suffering and killed millions of people. The ongoing Covid-19 pandemic is one such example. Individual lifestyles, if healthy, have been shown to modulate immune function and help fight infection. The five most important lifestyles are diet, obesity, exercise, alcohol consumption, and smoking. A favorable lifestyle or a prudent change result in reducing the risk and severity of infections. These include several viral, bacterial, parasitic, and fungal infections. The medical scientific literature is loaded with large well-done studies that have focused on the individual role of these lifestyles. A direct connection has been identified and verified in most cases. This manuscript provides a narrative review of this lifestyle-infection relationship. The aim is to raise the awareness of health care providers on the significant impact healthy lifestyles can have on infectious diseases. It is hoped that disseminating this data will translate into improved healthcare.

Keywords: infections, smoking, lifestyles, exercise, alcohol, diet, obesity

Introduction
Infection is defined as 'the invasion of a host organism's bodily tissues by disease-causing organisms, their multiplication, and the reaction of host tissues to these organisms and the toxins they produce' [1]. Infections are caused by microorganisms such as viruses, bacteria, and larger organisms like parasites and fungi. It's been one hundred years since the "Spanish" flu - a global viral flu that was devastating, infected almost 500 million people, and killed more than 50 million [2]. Most deaths resulted from secondary bacterial bronchopneumonia. Smallpox, caused by variola virus, is estimated to have caused 300–500 million deaths in the 20th century alone [3]. Human immunodeficiency virus (HIV) has infected 75 million people and killed about 32 million to date [4]. There are 36 million persons living with HIV (PLHIV) and 1.9 million new HIV cases occur annually [5]. Over the last decade, the world has seen the emergence and re-emergence of several lethal viral infections, including those by Zika virus [6], the Ebola Influenza virus [7], and the Middle East Respiratory Syndrome coronavirus [8]. More recently, humans are facing the wrath of the COVID-19 virus, which has become a pandemic infection. As of this writing, there have been more than 250 million cases with 5 million deaths from COVID-19 worldwide [9]. -and the infections and fatalities continue to rise. COVID-19 was the 2nd leading cause of death in the U.S. in September 2021 [10]. During this period, it was the number 1 cause of death for people aged 35-54 [11]. These deaths are mainly due to pneumonia, progressing to respiratory failure, shock, and multiple organ failure [12]. Bacterial infections are no less prevalent. Globally, pneumonia is the most common infectious cause of death, the fourth most common cause of death overall, and the second leading cause of life years lost. In 2015, the Global Burden of Disease Study estimated that lower respiratory tract infection caused 2 million adult deaths and an estimated 37 million years of life lost [13]. Tuberculosis (TB) is another scourge, especially in low-income countries. TB incidence according to the World Health Organization (WHO) in the African and Southeast Asian regions is 275 and 246 cases per 100 000, respectively. It is estimated that 86% of global TB deaths occur in these regions [14]. Further, TB is the most common cause of death in people living with HIV (PLHIC) worldwide and accounted for one-third of all HIV-related deaths in 2018 [15]. Another infection, cryptococcal meningitis, accounts for 15% of acquired immunodeficiency syndrome-related deaths [16]. Fungi infect billions of people worldwide and kill more than 1.5 million per year. This death toll is on par with deaths caused by prominent bacterial and parasite pathogens, such as those causing tuberculosis and malaria [17]. Alarmingly, the incidence of invasive fungal infections is increasing, and multidrug-resistant pathogens are spreading across the globe [18]. Parasitic infections like Malaria also continue to thrive and kill. In 2019, an estimated 409,000 people died of malaria-most were young children in sub-Saharan Africa [19]. Intestinal infections like amoebiasis, ascariasis, hookworm infection and trichiniasis are among the ten most common infections in the world [20]. Despite the advent of modern anti-infectious agents, due to the development of drug resistance and the appearance of new mutants, humans continue to be highly vulnerable to infectious diseases.

Discussion

Hosts fight infections using their immune systems. The innate immune system is the first line of defense against infections. It is rapid and short-lived and is not characterized by long-term immunological memory. Encoded pattern-recognition receptors recognize evolutionarily conserved pathogenic structures and induce the macrophages to eliminate the invaders [21]. Adaptive immunity is lifelong and involves the action of long-lived T and B lymphocytes, which recognize specific pathogens and remember them [22]. They thus prime the body for any later attack by the same organism. T cells represent the main mediators of the cellular immune response while B cells are the mediators of the humoral immune response [23]. Vaccines utilize this innate process to provide future immunity. The main functions of the innate and adaptive immune systems are to recognize aggressor agents and to activate effector mechanisms, defending the organism against infections (and chronic inflammatory diseases). The innate response is associated with a rise in the acute phase protein called C-reactive protein (CRP) [24]. Normal CRP levels are typically below 3.0 mg/L. They are usually above 10 mg/L in acute infections. The hs-CRP test can detect lower levels of CRP in the bloodstream (0.5–10 mg/L). Levels between 3 mg/L and 10 mg/L are mildly elevated and usually result from chronic non-communicable diseases. Levels between 10 mg/L and 100 mg/L are moderately elevated and indicate a significant inflammation from an infectious or non-infectious cause. A severe infection will raise the CRP levels above 100 mg/L. Lower levels of CRP usually indicate a 'sterile' inflammation [25] and are found in approximately 10% of healthy individuals [26]. Sterile low-grade inflammation increases the susceptibility to infections. Unhealthy lifestyles are often associated with low-grade inflammation [27]. These include obesity [28], smoking [29], lack of physical activity [30], alcohol intake (in excess) [31], and an unhealthy diet [32]. Unhealthy lifestyles frequently co-exist with each other and produce a deleterious synergistic effect [33]. For example, the COVID-19 pandemic has been associated with a 28.6% increase in sedentary behavior and a significant rise in the consumption of less healthy food [34]. Healthy lifestyles decrease low-grade inflammation and not only protect the body against infection but also retard its progression [35, 36]. They also improve the response to vaccination [37]. These lifestyles and their relationship with infections is discussed below.

Smoking

Smoking increases the risk of several infections, including acute upper respiratory tract infection and community-acquired pneumonia (CAP) [38]. Baik *et al*. reported that the risk of CAP in smokers is approximately 1.5 times that of non-smokers [39]. Nuorti *et al*. found that the morbidity of CAP in smokers was 4.1 times that of non-smokers [40]. A more recent study by Almirall *et al*. found that this risk increase with smoking more cigarettes-and estimated that it increased by 3.89 in persons who smoked more than 20 cigarettes a day [41]. Passive smokers are also affected [42]. Smoking cessation helps. Quitting more than 4 years ago significantly decreased the risk of CAP when compared to individuals who quit smoking for less than 1 year (Odds Ratio-0.39) [43]. It is estimated that the risk reduces to that of non-smokers if smoking cessation exceeds 5 years [44]. Smoking increases the risk of meningitis (especially cryptococcal meningitis) in PLHIV [45]. Secondhand smoke increases the risk of developing an invasive meningococcal disease in children [46]. Smoking is associated with excessive destruction of the supporting periodontal tissues, bone loss, pocket formation, and premature tooth loss [47]. Smoking also increases the risk of H. pylori (HP) infection [48]. One study found that the HP infection rate in the smoking group (51.01%) was significantly higher than that in the non-smoking group (38.27%) [49]. Smoking also makes the anti-HP treatment less effective [50]. Smoking increases the susceptibility to tuberculosis (TB) by 2-2.5 times [51]. Smoking enhances TB progression, decreases the effectiveness of treatment, increases relapse, and raises mortality [52]. Smokers with TB are also more likely to be treatment non-compliant [53]. Smoking also increases the risk of oral candidiasis in PLHIV [54]. Besides the diminished immune status and direct damage by the smoke-related chemicals in these patients, tobacco may be contaminated with fungal spores [55]. Superficial fungal infections can become invasive in smokers and result in increased morbidity and mortality [56]. Since PLHIV are immunocompromised and smoke more [57], they are at a higher risk of invasive fungal infection. Smoking results in detrimental alteration of the structural, functional, and immunologic host defenses [58].

Alcohol

The increased risk for infections with alcohol consumption was recognized as early as 1785 by Benjamin Rush [59]. It is now well established that alcoholics have chronic low-grade inflammation and increased susceptibility to viral and bacterial infections [60]. A systematic review and meta-analysis found a 6% increase in the risk of pneumonia per standard drink of 12 g of pure alcohol per day [61]. Another study estimated that consuming drinks that contain 10–20 g of alcohol per day results in an 8% increased risk of acquiring CAP [62]. Alcohol use also increases the risk for developing incident TB by 35% [63]. Alcohol use results in poor TB outcomes, including treatment failure, increased mortality, and treatment non-compliance [64-67]. Alcohol has also been implicated in facilitating transmission of TB, via interactions in bars, prisons, and among homeless populations [68, 69]. Alcohol also adversely affects hepatitis C virus and hepatitis B virus infections [70, 71]. Both acute and chronic alcohol consumption increase host susceptibility to HIV infection [72, 73]. Alcohol consumption also renders PLHIV more susceptible to TB [74]. Alcohol intake may increase susceptibility to COVID-19 infection [75]. Gauthier *et al*. reported that maternal alcohol use increases the risk of infection in newborns [76]. Acute and chronic alcohol use leads to a dysregulated inflammatory state and an impaired immune response, and these effects contribute to a markedly increased risk of infections [60, 77].

Obesity

Obesity and its related non-communicable diseases have substantial effects on the global burden of infectious diseases [78]. Obese individuals are more likely to develop nosocomial [79] and postoperative infections [80]. These are more likely to progress to serious complications in these individuals. Obesity is also a risk factor for periodontitis [81], and skin and soft tissue infections [82]. There is an association between obesity and poor outcome in pandemic H1N1 influenza infection. Obese patients with H1N1 infection are more likely to be admitted to the intensive care unit, have a longer duration of mechanical ventilation, have a longer hospital

stay, and are more likely to die compared with non-obese patients [83]. Obesity also seems to worsen COVID-19 infections [84] resulting in more hospitalizations and more deaths [85]. In general, people with larger BMI have more severe infections and a reduced response to antimicrobial drugs [86]. They may also have a reduced response to vaccinations [87]. Adipocytes are actively involved in the regulation of inflammation and immunity [88, 89].

Exercise

Physical activity refers to activities undertaken during leisure time, at home, as part of employment, or for transport purposes. "Exercise" is a component of physical activity within the leisure time domain and refers to physical activities that are planned, structured, repetitive, and undertaken to improve or maintain components of physical fitness and/or sporting performance [90]. Regular physical activity is associated with a reduction in the risk of non-communicable diseases such as diabetes mellitus, cancer, cardiovascular disease, and many other disorders [91]. It also helps in reducing the risk of contracting infections [92-96]. Exercise helps improve immunosurveillance, thereby reducing the risk of contracting infections and related morbidity and mortality [97]. An inverse relationship exists between moderate exercise training and incidence of acute viral respiratory infections including the common cold, influenza, pneumonia, and Covid-19 [98]. Barret *et al*, in a randomized controlled trial, reported that participants in the exercise group had fewer episodes of illness compared to participants leading sedentary lifestyles [99]. Neiman and colleagues found that a daily brisk walk cut the number of sickness days by half (monitored for a 12- to 15-week period), when compared to inactivity [100]. In another study, aerobic exercise 5 days or more per week resulted in 43% lower episodes of acute respiratory illness when compared with those who were largely inactive (after adjusting for several confounders) [101]. In a meta-analysis, Chastin and colleagues found that a higher level of habitual physical activity not only decreases the risk of acquiring community based infectious diseases - a 31% risk reduction (hazard ratio 0.69; N = 557,487 individuals) but is also associated with a 37% risk reduction (hazard ratio 0.64, 4 studies, N = 422,813 individuals) of infection-related mortality [102]. The mortality benefits of regular moderate-intensity exercise had been noted earlier in a large epidemiological study of 97,844 adults from England and Scotland. In this study, mortality due to bacterial and viral infections were reduced by more than 50% over a 9-year period with exercise [103]. Regular exercise also beneficially impacts COVID-19 infections [104-106]. In one review, physical inactivity was related to a 32% increased risk for COVID-19 hospitalizations [107]. Physical exercise has also been noted to influence HIV infections. In PLHIV, regular physical exercise (aerobic combined with strengthening exercise) helps mitigate pre-sarcopenia, sarcopenia, myalgia, and low bone mineral density [108]. It helps improve cardiorespiratory fitness, body composition, mental health, and the overall quality of life in these patients [108]. Physical exercise also helps patients with TB. In 2016, the American Thoracic Society recommended exercise rehabilitation in patients with tuberculosis109. Moderate exercise may also help control infections caused by intracellular parasites such as Listeria monocytogenis, Toxoplasma gondii, Trypanosoma cruzi, and Leishmania protozoa [110]. Exercise can also increase the risk of infections. Intense exercise has been associated with greater morbidity and mortality from infectious diseases [111-113]. There appears to be an open window (3-72 hours) of altered immunity following intense exercise, where there is a higher incidence of subclinical and clinical infection [114]. Further, exercising in gyms during periods of peak occupancy and poor ventilation may increase the risk of infections such as influenza and tuberculosis [115]. Also, fungi and germs may thrive at the gym (warm moist places such as sweaty exercise equipment and locker room showers), exposing exercising individuals to a variety of common skin infections, including ringworm, plantar warts, or impetigo [116]. Swimming in fresh or saltwater for sports or exercise can result in cercarial dermatitis, a parasitic disease [117]. It appears that the current guidelines for physical exercise recommended by most major professional associations (150 min per week of moderate to vigorous physical activity, combining aerobic and strengthening activity) for the prevention of chronic disease can also reduce the risk of infectious diseases and infectious disease mortality [118]. Regular moderate exercisers also have a better response to vaccination [119]. Physical activity helps improve several chronic conditions such as diabetes or obesity and reduces stress, and this may also help reduce the risk of complications and mortality due to infectious disease [120]. Exercise enhances innate and adaptive immune systems, as evidenced by an increased in CD4 cell counts and salivary immunoglobulin IgA concentration, decreased neutrophil counts, and higher antibody concentration after vaccinations [102].

Diet

Certain foods and food ingredients have anti-inflammatory and antioxidant properties and provide better immunity [121, 122]. A well-functioning immune system helps prevent and control pathogenic infections [123, 124]. However, certain states may hamper this. A poor nutritional status resulting in under nutrition can impair immunity to an infection due to micronutrient deficiencies [125, 126]. On the other hand, over nutrition induces low-grade chronic inflammation caused by excess adiposity [88, 89]. The harmful effects of excess body weight on infectious diseases have been discussed under obesity. Finally, malnutrition, where the diet is unbalanced or is lacking in certain nutrients, induces low-grade inflammation and a reduction in T- and B-cells [127, 128]. This results in leucopenia and impairment in the immune response. A proper diet is therefore extremely important to ward off and fight infections [129-131]. The Western diet is extremely unbalanced. It is characterized by a high intake of saturated fats and omega-6 fatty acids, reduced omega-3 fat intake, and a high intake of refined sugar and salt [132]. This dietary pattern is associated with elevated serum markers of inflammation [133]. Saturated fats enhance prostaglandin E2, which has pro-inflammatory actions. It increases Interleukin 17 (IL-17) production and macrophage activation [134]. IL-17 is a pro-inflammatory cytokine and is responsible for the development of inflammation in many disorders135. Dietary fats alter the lipids in the membranes of immune cells [136, 137]. Several other mechanisms also come into play to induce inflammation [138, 139]. Omega-6 polyunsaturated fats, found in most cooking oils, also alter the immune response [140-142]. Simple sugars reduce white blood cell phagocytosis and increase inflammatory cytokine markers in the blood [143, 144]. High amount of salt in the diet increases IL-17 mediated inflammation [145, 146]. On the other hand, plant-based diets are

rich in immune-boosting nutraceuticals, polyphenols, terpenoids, flavonoids, alkaloids, sterols, pigments, and unsaturated fatty acids [147]. They are also rich in complex fiber and several micronutrients, which help reduce inflammation and play a vital role in human immune surveillance and defense [148]. The Mediterranean diet (MedD) is primarily a plant-based diet, abundant in vegetables, fruits, cereals, minimally processed legumes, and extra virgin olive oil, honey, dairy products, poultry, fish in moderate amounts, red meat in small quantities, and includes consumption of moderate quantities of wine [149, 150]. There is a paucity of ultra-processed foods, refined sugars, and saturated fats. The EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) in oily fish is converted to resolvins, protectins, and maresins, which help in the resolution of inflammation and help the healing process [151, 152]. Fermented food products, like yogurt in the MedD also help improve the gut microbiome [153, 154]. Overall, MedD reduces inflammation, increases immunity, and decreases infections [150, 155]. Micronutrients that play a vital role in immunity protection are vitamins A, C, D, E, B6 and B12, folic acid, and metals like iron, copper, selenium, and zinc [156, 157]. Vitamin A is involved in maintaining the structural and functional integrity of the mucosal cells. This vitamin is important for the normal function of both innate (macrophages, neutrophils) and adaptive (T and B lymphocytes) immune cells [158]. Vitamin D plays affects the maturation and differentiation of various immune cells, inducing the production of antiviral peptide cathelicidins and defensins, and reducing the production of pro-inflammatory cytokines. Its insufficiency and deficiency have been associated with increased susceptibility to COVID-19 and a poor prognosis [159-161]. Vitamin C is an important antioxidant and stimulates the production, function, and movement of leukocytes (e.g., neutrophils, lymphocytes, phagocytes) [162, 163]. Vitamin E improves immunity by protecting the integrity of cell membranes from damage caused by reactive oxygen species (ROS). It also increases IL-2 production and T-mediated cell functions [164, 165]. Vitamins B6 and B12 play an important role in the production of antibodies, cytokines, and in the proliferation and differentiation of lymphocytes [157, 164, 165]. Folic acid supports Th1-mediated immune response [165, 166]. Metals (iron, zinc, selenium, copper)-are important in the differentiation and proliferation of T lymphocytes and in the production of antibodies [158, 167]. In a recent report, a significant difference in mean ferritin levels was found between survivor and non-survivor COVID-19 patients [168]. Low zinc level has been shown to double pneumonia-related mortality rate in the elderly [158]. Glutamine and arginine, two amino acids, also beneficially modulate the immune cells [169, 170]. A prudent diet is therefore important for immuno-protection. There is some indication that a healthy diet, along with supplemental antioxidant intake, is beneficial to COVID-19 patients [171]. A poor diet is associated with a higher risk of non-communicable diseases (such as diabetes mellitus), and the latter further increase susceptibility to infections [172]. On the other hand, chronic infections may decrease appetite, resulting in a poor intake of nutrients, and thereby further worsening the immune function and increasing the risk of infections [173].

Conclusion

Healthy lifestyles have a significant effect on preventing and improving the prognosis of several infectious diseases. They also help mitigate chronic non-communicable diseases. The combined benefit results in an improvement in survival. Li Yanping *et al*., recently estimated that the life expectancy at age 50 years was 29.0 years for women and 25.5 years for men who had zero low-risk lifestyle factors. The life expectancy increased at age 50 years to 43.1 years for women and 37.6 years for men, if all five healthy lifestyles were adopted. This meant an increase in projected life expectancy at age 50 years by 14.0 years among females and 12.2 years in men. This major increase in lifespan has also been reported in other countries. A healthy lifestyle was associated with an estimated increase of 7.4–17.9 years in life expectancy in several countries, including Japan, UK, Canada, Denmark, Norway, and Germany. This increased lifespan with healthy lifestyles is accompanied by a decrease in infections and non-communicable diseases.

Author Contributions

SKA. Performed all parts of this work including concept, design, literature scoping and synthesis, and writing all parts of the manuscript. The author have read and agreed to the published version of the manuscript.

Acknowledgement: None
Funding: None
Conflict of Interest: None

References

1. Signore A. About inflammation and infection. EJNMMI Res. 2013; 3(1):8. Published 2013 Feb 1. Doi: 10.1186/2191-219X-3-8.
2. https://www.cdc.gov/flu/pandemic-resources/1918-pandemic-h1n1.html.
3. Thèves C., Biagini P., Crubézy E. The rediscovery of smallpox. Clin. Microbiol. Infect. 2014; 20:210-218. 10.1111/1469-0691.12536.
4. https://www.who.int/gho/hiv/en/.
5. WHO, Global Health Observatory (GHO) Data. World Health Organization Geneva; Switzerland, 2016.
6. Hu T, Li J, Carr M.J, Duchene S, Shi W. The Asian lineage of Zika virus: transmission and evolution in Asia and the Americas. Virol Sin, 2019.
7. To KK, Chan JF, Tsang AK, Cheng VC, Yuen KY. Ebola virus disease: A highly fatal infectious disease reemerging in West Africa. Microbes Infect. 2015; 17 (2):84-97.
8. Dawson P, Malik MR, Parvez F, Morse SS. What have we learned about Middle East respiratory syndrome coronavirus emergence in humans? A systematic literature review. Vector Borne Zoonotic Dis. 2019; 19(3):174-192.
9. https://www.worldometers.info/coronavirus/.
10. https://www.healthsystemtracker.org/brief/covid19-and-other-leading-causes-of-death-in-the-us.
11. Elezukurtaj S, Greuel S, Ihlow J, *et al*. Causes of death and comorbidities in hospitalized patients with COVID-19. Sci Rep. 2021; 11:4263. https://doi.org/10.1038/s41598-021-82862-5.
12. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020; 323(13):1239-1242.
13. Murray CJL, Lopez AD, Naghavi M, Wang H. GBD

2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016; 388:1459-544.
14. World Health Organization. Global tuberculosis report. Geneva: World Health Organization, 2016.
15. World Health Organization. Global tuberculosis report 2019. Geneva: World Health Organization, 2019.
16. Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM, *et al*. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis. 2017; 17(8):873-881.
17. Brown GD, Denning DW, Levitz SM. Tackling human fungal infections. Science. 2012a; 336:647. 10.1126/science.1222236.
18. Fisher MC, Gow NAR, Gurr SJ. Tackling emerging fungal threats to animal health, food security and ecosystem resilience. Philos. Trans. R. Soc. B Biol. Sci. 2016; 371:20160332.
19. https://www.cdc.gov/malaria/malaria_worldwide/impact.html.
20. https://www.who.int/publications/i/item/WHO-TRS-749.
21. Charles A, Janeway J, Medzhitov R. Innate immune recognition.Ann Rev Immunol. 2002; 20:197-216. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell. 2010; 140:805-820. Doi: 10.1016/j.cell.2010.01.022.
22. Boehm T. Design principles of adaptive immune systems.Nat Rev Immunol. 2011; 11:307-317. Doi: 10.1038/nri2944.
23. Ruggieri A, Anticoli S, D'Ambrosio A, Giordani L, Viora M. The influence of sex and gender on immunity, infection and vaccination. Ann Ist Super Sanita. 2016; 52(2):198-204. Doi: 10.4415/ANN_16_02_11.
24. Pepys MB, Hirschfield GM. C-reactive protein: A critical update. J Clin Invest. 2003; 111(12):1805-12. 10.1172/jci200318921.
25. Calder PC, *et al*. A consideration of biomarkers to be used for evaluation of inflammation in human nutritional studies. Br. J Nutr. 2013; 109:S1-S34.
26. Imhof A, Fröhlich M, Loewel H, Helbecque N, Woodward M, Amouyel P, *et al*. Distributions of C-reactive protein measured by high-sensitivity assays in apparently healthy men and women from different populations in Europe. Clin Chem. 2003; 49(4):669-72. 10.1373/49.4.669,
27. Villegas R, Xiang YB, Cai H, Elasy T, Cai Q, Zhang X, *et al*. Lifestyle determinants of C-reactive protein in middle-aged, urban Chinese men. Nutr Metab Cardiovasc Dis NMCD. 2012; 22(3):223-30. 10.1016/j.numecd.2010.07.007.
28. Mraz M, Haluzik M. The role of adipose tissue immune cells in obesity and low-grade inflammation. J Endocrinol. 2014. 10.1530/JOE-14-0283.
29. Darabseh MZ, Maden-Wilkinson TM, Welbourne G, *et al*. Fourteen days of smoking cessation improves muscle fatigue resistance and reverses markers of systemic inflammation. Sci Rep. 2021; 11(1):12286. Doi: 10.1038/s41598-021-91510-x.
30. Della Guardia L, Codella R. Exercise tolls the bell for key mediators of low-grade inflammation in dysmetabolic conditions. Cytokine Growth Factor Rev. 2021; 21:S1359-6101(21)00070-8. Doi: 10.1016/j.cytogfr.2021.09.003.
31. Volpato S, Pahor M, Ferrucci L, *et al*. Relationship of Alcohol Intake With Inflammatory Markers and Plasminogen Activator Inhibitior-1 in Well-Functioning Older Adults. The Health, Aging, and Body Composition Study. Originally published10 Feb Circulation. 2004; 109:607-612. https://doi.org/10.1161/01.CIR.0000109503.13955.00.
32. Power Guerra N, Müller L, Pilz K, Glatzel A, Jenderny D, Janowitz D, *et al*. Dietary-Induced Low-Grade Inflammation in the Liver. Biomedicines. 2020; 98(12):587. Doi: 10.3390/biomedicines8120587.
33. Xiao Q, Keadle SK, Hollenbeck AR, Matthews CE. Sleep duration and total and cause-specific mortality in a large US cohort: Interrelationships with physical activity, sedentary behavior, and body mass index. Am. J Epidemiol. 2014; 180:997-1006. Doi: 10.1093/aje/kwu222.
34. Ammar A, Brach M, Trabelsi K, Chtourou H, Boukhris O, Masmoudi L, *et al*. Effects of COVID-19 home confinement on eating behaviour and physical activity: Results of the ECLB-COVID19 international online survey. Nutrients. 2020; 12:1583. Doi: 10.3390/nu12061583.
35. Almirall J, Bolíbar I, Serra-Prat M, Roig J, Hospital I, Carandell E, *et al*. Community-Acquired Pneumonia in Catalan Countries (PACAP) Study Group. New evidence of risk factors for community-acquired pneumonia: a population-based study. Eur Respir J. 2008; 31(6):1274-84. doi: 10.1183/09031936.00095807.
36. Hamer M, O'Donovan G, Stamatakis E. Lifestyle risk factors, obesity and infectious disease mortality in the general population: Linkage study of 97,844 adults from England and Scotland. Prev. Med. (Baltim) 2019; 123:65-70. Doi: 10.1016/j.ypmed.2019.03.002.
37. Fourati S, *et al*. Pre-vaccination inflammation and B-cell signalling predict age-related hyporesponse to hepatitis B vaccination. Nat. Commun. 2016; 7:10369.
38. Nuorti JP, Butler JC, Farley MM, *et al*. Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. N Engl J Med. 2000; 342:681-9. Gold R. Epidemiology of bacterial meningitis. Infect Dis Clin North Am 1999; 13:515-25 v.
39. Baik I, Curhan GC, Rimm EB, Bendich A, Willett WC, Fawzi WW. A prospective study of age and lifestyle factors in relation to community-acquired pneumonia in US men and women. Arch Intern Med. 2000; 160(20):3082-3088. Doi: 10.1001/archinte.160.20.3082.
40. Nuorti JP, Butler JC, Farley MM, *et al*. Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. N Engl J Med. 2000; 342(10):681-689. doi: 10.1056/nejm200003093421002.
41. Almirall J, Serra-Prat M, Bolibar I, Balasso V. Risk Factors for Community-Acquired Pneumonia in Adults: A Systematic Review of Observational Studies. Respiration. 2017; 94(3):299-311. Doi: 10.1159/000479089.
42. Sismanlar Eyuboglu T, Aslan AT, Kose M, *et al*. Passive Smoking and Disease Severity in Childhood Pneumonia Under 5 Years of Age. J Trop Pediatr. 2020; 66(4):412-418. Doi: 10.1093/tropej/fmz081.
43. Almirall J, Bolibar I, Serra-Prat M, *et al*. New evidence

of risk factors for community-acquired pneumonia: a population-based study. Eur Respir J. 2008; 31(6):1274-1284. Doi: 10.1183/09031936.00095807.
44. Almirall J, Gonzalez CA, Balanzo X, Bolibar I. Proportion of community-acquired pneumonia cases attributable to tobacco smoking. Chest. 1999; 116(2):375-379. doi: 10.1378/chest.116.2.375.
45. Hajjeh RA, Conn LA, Stephens DS, *et al*. Cryptococcosis: population-based multistate active surveillance and risk factors in human immunodeficiency virus-infected persons. Cryptococcal Active Surveillance Group. J Infect Dis. 1999; 179:449-54.
46. Murray RL, Britton J, Leonardi-Bee J. Secondhand smoke exposure and the risk of invasive meningococcal disease in children: systematic review and meta-analysis. BMC Public Health. 2012; 12:1062.
47. Bergström J. Tobacco smoking and chronic destructive periodontal disease. Odontology. 2004; 92(1):1-8. Doi: 10.1007/s10266-004-0043-4.
48. Ozaydin N, Turkyilmaz SA, Cali S. Prevalence and risk factors of Helicobacter pylori in Turkey: a nationally representative, cross-sectional, screening with the C-Urea breath test. BMC Public Health. 2013; 13:1215. doi: 10.1186/1471-2458-13-1215.
49. Zhang X, Chen H, Yang G. [Analysis of Helicobacter pylori infection in healthy people] Chinese Journal of Social Medicine. 2017; 34(3):313-315. Doi: 10.3969/j.issn.1673-5625.2017.03.032.
50. Chen L, Jia X, Wang S. [Analysis of current status and risk factors of Helicobacter pylori infection in medical examination population in Miyun District, Beijing] Clinical Medicine of China. 2017; 33(10):891-894. Doi: 10.3760/cma.j.issn.1008-6315.2017.10.007.
51. Jeyashree K, Kathirvel S, Hd S, Kaur H, Goel S. Smoking cessation interventions for pulmonary tuberculosis treatment outcomes (Review) Cochrane Database Syst Rev. 2016; 1:CD011125. Doi: 10.1002/14651858.CD011125.pub2.
52. Leung CC, Yew WW, Chan CK, Chang KC, law WS, Lee SN, *et al*. Smoking adversely affects treatment response, outcome and relapse in tuberculosis. Eur Respir J. 2015; 45:583-5.
53. Wang EY, Arrazola RA, Mathema B, Ahluwalia IB, Mase SR. The impact of smoking on tuberculosis treatment outcomes: a meta-analysis. Int J Tuberc Lung Dis. 2020; 24(2):170-175. Doi: 10.5588/ijtld.19.0002.
54. Barr C, Friedmann P, Desjarlais D. Smoking is a significant factor in HIV-related oral candidiasis. J Dent Res. 1998; 77:155.
55. Verweij PE, Kerremans JJ, Voss A, Meis JF. Fungal contamination of tobacco and marijuana. JAMA. 2000; 284:2875.
56. Pourbaix A, Lafont Rapnouil B, Guéry R, Lanternier F, Lortholary O, Cohen JF. Smoking as a Risk Factor of Invasive Fungal Disease: Systematic Review and Meta-Analysis. Clin Infect Dis. 2020; 71(4):1106-1119.
57. Mdege ND, Shah S, Ayo-Yusuf OA, Hakim J, Siddiqi K. Tobacco use among people living with HIV: analysis of data from demographic and health surveys from 28 low-income and middle-income countries. Lancet Glob Health. 2017; 5:e578-92.
58. Feldman C, Anderson R. Cigarette smoking and mechanisms of susceptibility to infections of the respiratory tract and other organ systems. J Infect. 2013; 67:169-84.
59. Rush B. An Inquiry into the Effects of Ardent Spirits upon the Human Body and Mind: With an Account of the Means of Preventing, and of the Remedies for Curing Them. 6th ed. Cornelius Davis; New York, NY, USA: 1811. (Originally published 1785).
60. Szabo G, Saha B. Alcohol's Effect on Host Defense. Alcohol Res. 2015; 37(2):159-70.
61. Samokhvalov AV, Irving HM, Rehm J. Alcohol consumption as a risk factor for pneumonia: a systematic review and meta-analysis. Epidemiol Infect 2010; 138:1789-95. 10.1017/S0950268810000774.
62. Simou E, Britton J, Leonardi-Bee J. Alcohol and the risk of pneumonia: a systematic review and meta-analysis. BMJ Open. 2018; 8(8):e022344. Published 2018 Aug 22. Doi: 10.1136/bmjopen-2018-022344.
63. Imtiaz S, Shield KD, Roerecke M, Samokhvalov AV, Lönnroth K, Rehm J. Alcohol consumption as a risk factor for tuberculosis: Meta-analyses and burden of disease. Eur. Respir. J. 2017; 50:1700216. Doi: 10.1183/13993003.00216-2017.
64. Ragan EJ, Kleinman MB, Sweigart B, *et al*. The impact of alcohol use on tuberculosis treatment outcomes: A systematic review and meta-analysis. Int. J Tuberc. Lung. Dis. 2020; 24:73-82. Doi: 10.5588/ijtld.19.0080.
65. GBD. 2016 Lower Respiratory Infections Collaborators Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect. Dis. 2018; 18:1191-1210. Doi: 10.1016/S1473-3099(18)30310-4.
66. Dos Santos DT, Arroyo LH, Alves YM, Alves LS, Berra TZ, Crispim JA, *et al*. Survival time among patients who were diagnosed with tuberculosis, the precocious deaths and associated factors in southern Brazil. Trop. Med. Health. 2021; 49:31. Doi: 10.1186/s41182-021-00320-4.
67. Workie MG, Aycheh MW, Birhanu MY, Tsegaye TB. Treatment interruption among drug-susceptible pulmonary tuberculosis patients in Southern Ethiopia. Patient Prefer. Adherence. 2021; 15:1143-1151. Doi: 10.2147/PPA.S307091.
68. Cords O, Martinez L, Warren JL, *et al*. Incidence and prevalence of tuberculosis in incarcerated populations: A systematic review and meta-analysis. Lancet Public Health. 2021; 6:e300-e308. Doi: 10.1016/S2468-2667(21)00025-6.
69. Friedman LN, Sullivan GM, Bevilaqua RP, Loscos R. Tuberculosis screening in alcoholics and drug addicts. Am. Rev. Respir. Dis. 1987; 136:1188-1192. Doi: 10.1164/ajrccm/136.5.1188.
70. Bhattacharya R, Shuhart MC. Hepatitis C. and alcohol: interactions, outcomes, and implications. J Clin Gastroenterol. 2003; 36(3):242-52. Doi: 10.1097/00004836-200303000-00012.
71. Gitto S, Micco L, Conti F, Andreone P, Bernardi M. Alcohol and viral hepatitis: a mini-review. Dig Liver Dis. 2009; 41(1):67-70. doi: 10.1016/j.dld.2008.05.009.
72. Szabo G. Consequences of alcohol consumption on host defence. Alcohol Alcohol. 1999; 34:830-841. Doi: 10.1093/alcalc/34.6.830.
73. Neuman MG. Cytokines-central factors in alcoholic liver disease. Alcohol Res. Health. 2003; 27:307-316.
74. Happel KI, Nelson S. Alcohol, immunosuppression, and

the lung. Proc. Am. Thorac. Soc. 2005; 2:428-432. Doi: 10.1513/pats.200507-065JS.
75. Tu Testino G. Are Patients With Alcohol Use Disorders at Increased Risk for Covid-19 Infection? Alcohol Alcohol. 2020; 55(4):344-346. Doi: 10.1093/alcalc/agaa037.
76. Gauthier TW, Drews-Botsch C, Falek A, Coles C, Brown LA. Maternal alcohol abuse and neonatal infection. Alcohol Clin Exp Res. 2005; 29(6):1035-43. Doi: 10.1097/01.alc.0000167956.28160.5e.
77. Szabo G, Mandrekar P. A recent perspective on alcohol, immunity, and host defense. Alcohol. Clin. Exp. Res. 2009; 33:220-232. Doi: 10.1111/j.1530-0277.2008.00842.x.
78. Huttunen R, Syrjänen J. Obesity and the risk and outcome of infection. Int J Obes (Lond). 2013; 37(3):333-40. Doi: 10.1038/ijo.2012.62.
79. Huttunen R, Karppelin M, Syrjänen J. Obesity and nosocomial infections. J Hosp Infect. 2013; 85(1):8-16. Doi: 10.1016/j.jhin.2013.06.012.
80. Słabuszewska-Jóźwiak A, Szymański JK, Jóźwiak Ł, Sarecka-Hujar B. A Systematic Review and Meta-Analysis of Wound Complications after a Caesarean Section in Obese Women. J Clin Med. 2021; 10(4):675. Doi: 10.3390/jcm10040675.
81. Chen TP, Yu HC, Lin TH, Wang YH, Chang YC. Association between obesity and chronic periodontitis: A nationwide population-based cohort study in Taiwan. Medicine (Baltimore). 2021; 100(41):e27506. Doi: 10.1097/MD.0000000000027506.
82. Grupper M, Nicolau DP. Obesity and skin and soft tissue infections: how to optimize antimicrobial usage for prevention and treatment? Curr Opin Infect Dis. 2017; 30(2):180-191. Doi: 10.1097/QCO.0000000000000356.
83. Albashir AAD. The potential impacts of obesity on COVID-19. Clin Med (Lond). 2020; 20(4):e109-e113. Doi: 10.7861/clinmed.2020-0239.
84. Yang J, Hu J, Zhu C. Obesity aggravates COVID-19: A systematic review and meta-analysis. J Med Virol. 2021; 93(1):257-261. Doi: 10.1002/jmv.26237.
85. Townsend MJ, Kyle TK, Stanford FC. Commentary: COVID-19 and obesity: exploring biologic vulnerabilities, structural disparities, and weight stigma. Metabolism 2020; 110:154316. doi:10.1016/j.metabol.2020.154316.
86. Dhurandhar NV, Bailey D, Thomas D. Interaction of obesity and infections. Obes Rev. 2015; 16(12):1017-29. Doi: 10.1111/obr.12320.
87. Popkin BM, Du S, Green WD, *et al*. Individuals with obesity and COVID-19: A global perspective on the epidemiology and biological relationships. Obes Rev 2020; 21:e13128. doi:10.1111/obr.13128.
88. Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol. 2005; 115(5):911-9. Quiz 920. doi: 10.1016/j.jaci.2005.02.023.
89. Mikhailova SV, Ivanoshchuk DE. Innate-Immunity Genes in Obesity. J Pers Med. 2021; 11(11):1201. Doi: 10.3390/jpm11111201.
90. https://healthyliving.azcentral.com/acsm-definition-cardiovascular-exercise-18723.html.
91. Warburton DER, Bredin SSD. Health benefits of physical activity: a systematic review of current systematic reviews. Curr Opin Cardiol 2017; 32(5):541-56.10.1097/HCO.0000000000000437).
92. Pape K, Ryttergaard L, Rotevatn TA, Nielsen BJ, Torp-Pedersen C, Overgaard C, *et al*. Leisure-time physical activity and the risk of suspected bacterial infections. Med Sci Sports Exerc 2016; 48(9):1737-44.10.1249/MSS.0000000000000953.
93. Kostka T, Berthouze SE, Lacour J, Bonnefoy M. The symptomatology of upper respiratory tract infections and exercise in elderly people. Med Sci Sports Exerc. 2000; 32(1):46-51.10.1097/00005768-200001000-00008.
94. Leveille SG, Gray S, LaCroix AZ, Ferrucci L, Black DJ, Guralnik JM. Physical inactivity and smoking increase risk for serious infections in older women. J Am Geriatr Soc. 2000; 48(12):1582-8.10.1111/j.1532-5415.2000.tb03867.x.
95. Romaniszyn D, Pobiega M, Wojkowska-Mach J, Chmielarczyk A, Gryglewska B, Adamski P, *et al*. The general status of patients and limited physical activity as risk factors of methicillin-resistant Staphylococcus aureus occurrence in long-term care facilities residents in Krakow, Poland. BMC Infect Dis. 2014; 14:271.10.1186/1471-2334-14-271.
96. Baik I, Curhan GC, Rimm EB, Bendich A, Willett WC, Fawzi WW. A prospective study of age and lifestyle factors in relation to community-acquired pneumonia in US men and women. Arch Intern Med. 2000; 160(20):3082-8.10.1001/archinte.160.20.3082,
97. Nieman DC, Pedersen BK. Exercise and immune function. Recent developments. Sports Med. 1999; 27(2):73-80. doi: 10.2165/00007256-199927020-00001.
98. Calabrese L, Neiman DC. Exercise, infection and rheumatic diseases: what do we know?. RMD Open. 2021; 7(2):e001644. Doi: 10.1136/rmdopen-2021-001644.
99. Barrett B, Hayney MS, Muller D, Rakel D, Brown R, Zgierska AE. Meditation or exercise for preventing acute respiratory infection (MEPARI-2): A randomized controlled trial. PLoS ONE. 2018; 13(6):1-20.
100. Nieman DC, Pedersen BK. Exercise and immune function. Recent developments. Sports Med. 1999; 27(2):73-80. doi: 10.2165/00007256-199927020-00001.
101. Nieman DC, Henson DA, Austin MD, *et al*. Upper respiratory tract infection is reduced in physically fit and active adults. Br J Sports Med 2011; 45:987-92. 10.1136/bjsm.2010.077875.
102. Chastin SFM, Abaraogu U, Bourgois JG, *et al*. Effects of Regular Physical Activity on the Immune System, Vaccination and Risk of Community-Acquired Infectious Disease in the General Population: Systematic Review and Meta-Analysis. Sports Med. 2021; 51(8):1673-1686. Doi: 10.1007/s40279-021-01466-1.
103. Hamer M, O'Donovan G, Stamatakis E. Lifestyle risk factors, obesity and infectious disease mortality in the general population: linkage study of 97,844 adults from England and Scotland. Prev Med. 2019; 123:65-70. 10.1016/j.ypmed.2019.03.002.
104. Simpson RJ, Campbell JP, Gleeson M, *et al*. Can exercise affect immune function to increase susceptibility to infection? Exerc Immunol Rev. 2020; 26:8-22.
105. Filgueira TO, Castoldi A, Santos LER, *et al*. The relevance of a physical active lifestyle and physical fitness on immune defense: mitigating disease burden, with focus on COVID-19 consequences. Front Immunol. 2021; 12:587146. 10.3389/fimmu.2021.587146.
106. Valenzuela PL, Simpson RJ, Castillo-García A, *et al*.

Physical activity: a coadjuvant treatment to COVID-19 vaccination? Brain Behav Immun. 2021; 94:00105-7. 10.1016/j.bbi.2021.03.003.
107. Hamer M, Kivimäki M, Gale CR, *et al*. Lifestyle risk factors, inflammatory mechanisms, and COVID-19 hospitalization: a community-based cohort study of 387,109 adults in UK. Brain Behav Immun. 2020; 87:184-7. 10.1016/j.bbi.2020.05.059.
108. O'Brien K, Tynan Anne-Marie, Nixon S, Glazier RH. Effectiveness of aerobic exercise for adults living with HIV: systematic review and meta-analysis using the Cochrane Collaboration Protocol, 2016. Doi: 10.1186/s12879-016-1478-2.
109. Muñoz-Torrico M, Rendon A, Centis R, *et al*. Is there a rationale for pulmonary rehabilitation following Victoria M. Ruta *et al*. 16 successful chemotherapy for tuberculosis? J Bras Pneumol. 2016; 42(5):374-85. DOI: 10.1590/S1806- 37562016000000226.
110. Gleeson M. Exercise and immune function. J. Appl. Physiol. 2007; 103:693-699. 10.1152/japplphysiol.00008.2007.
111. Ekblom B, Ekblom O, Malm C. Infectious episodes before and after a marathon race. Scand J Med Sci. Sports. 2006; 16(4):287-93.
112. Heath GW, Ford ES, Craven TE, Macera CA, Jackson KL, Pate RR. Exercise and the incidence of upper respiratory tract infections. Med Sci Sports Exerc. 1991; 23(2):152-7.
113. Nieman DC, Johanssen LM, Lee JW, Arabatzis K. Infectious episodes in runners before and after the Los Angeles Marathon. J Sports Med Phys Fitness. 1990; 30(3):316-28.
114. Nieman DC, Pedersen BK. Exercise and immune function. Recent developments. Sports Med. 1999; 27(2):73-80. Doi: 10.2165/00007256-199927020-00001.
115. Andrade A, Dominski FH, Pereira ML, de Liz CM, Buonanno G. Infection risk in gyms during physical exercise. Environ Sci Pollut Res Int. 2018; 25(20):19675-19686. doi: 10.1007/s11356-018-1822-8.
116. aad.org
117. Hoeffler DF. Swimmers' itch (cercarial dermatitis). Cutis. 1977; 19(4):461-5, 467.
118. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, *et al*. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med. 2020; 54:1451-1462. Doi: 10.1136/bjsports-2020-102955.
119. Barrett B, Hayney MS, Muller D, Rakel D, Brown R, Zgierska AE. Meditation or exercise for preventing acute respiratory infection (MEPARI-2): A randomized controlled trial. PLoS ONE. 2018; 13(6):1-20.
120. Lee DH, de Rezende LFM, Eluf-Neto J, Wu K, Tabung FK, Giovannucci EL. Association of type and intensity of physical activity with plasma biomarkers of inflammation and insulin response. Int J Cancer. 2019; 145:360-369. Doi: 10.1002/ijc.32111.
121. Beck MA, Levander OA. Dietary oxidative stress and the potentiation of viral infection. Annu Rev Nutr. 1998; 18(1):93-116.; Beck MA. The influence of antioxidant nutrients on viral infection. Nutr Rev. 2009; 56(1):S140-6.
122. Caccialanza R, Laviano A, Lobascio F, *et al*. Early nutritional supplementation in non-critically ill patients hospitalized for the 2019 novel coronavirus disease (COVID-19): rationale and feasibility of a shared pragmatic protocol. Nutrition. 2020; 74:110835.
123. Alkhatib A, Tuomilehto J. Lifestyle Diabetes Prevention. In: Huhtaniemi I, Martini L, editors. Encyclopaedia of Endocrine Diseases. Volume 1. Elsevier; Amsterdam, the Netherlands, 2019, 148-159.
124. López-Varela S, González-Gross M, Marcos A. Functional foods and the immune system: A review. Eur. J Clin. Nutr. 2002; 56(Suppl. 3):S29-S33. Doi: 10.1038/sj.ejcn.1601481.
125. Childs CE, Calder PC, Miles EA. Diet and Immune Function. Nutrients. 2019; 11:1933. Doi: 10.3390/nu11081933.
126. Silverio R, Caetano Gonçalves D, Andrade MF, Seelaender M. Coronavirus Disease 2019 (COVID-19) and Nutritional Status: The Missing Link? Adv. Nutr. 2020, 1-11. doi: 10.1093/advances/nmaa125.
127. Childs CE, Calder PC, Miles EA. Diet and Immune Function. Nutrients. 2019; 11:1933. Doi: 10.3390/nu11081933.
128. Silverio R, Caetano Gonçalves D, Andrade MF, Seelaender M. Coronavirus Disease 2019 (COVID-19) and Nutritional Status: The Missing Link? Adv. Nutr, 2020, 1-11. doi: 10.1093/advances/nmaa125.
129. Morais AHA, Aquino JS, da Silva-Maia JK, Vale SHL, Maciel BLL, Passos TS. Nutritional status, diet and viral respiratory infections: perspectives for severe acute respiratory syndrome coronavirus 2. Br J Nutr. 2021; 125(8):851-862. Doi: 10.1017/S0007114520003311.
130. Shivappa N., Bonaccio M, Hebert JR, *et al*. Moli-sani study Investigators. Association of proinflammatory diet with low-grade inflammation: Results from the Moli-sani study. Nutrition. 2018; 54:182-188. Doi: 10.1016/j.nut.2018.04.004.
131. Cena H, Chieppa M. Coronavirus Disease (COVID-19-SARS-CoV-2) and Nutrition: Is Infection in Italy Suggesting a Connection? Front. Immunol, 2020 Doi: 10.3389/fimmu.2020.00944.
132. USDA USDoA. Profiling Food Consumption in America. Washington, DC: Book AF, 2002.
133. Lopez-Garcia E, Schulze MB, Fung TT, Meigs JB, Rifai N, Manson JE. Major dietary patterns are related to plasma concentrations of markers of inflammation and endothelial dysfunction. Am J Clin Nutr 80:1029-1035.
134. Kalinski P. Regulation of immune responses by prostaglandin E2. J Immunol. 2012; 188:21-28.
135. Tabarkiewicz J, Pogoda K, Karczmarczyk A, Pozarowski P, Giannopoulos K. The Role of IL-17 and Th17 Lymphocytes in Autoimmune Diseases. Arch Immunol Ther Exp (Warsz). 2015; 63(6):435-449. Doi: 10.1007/s00005-015-0344-z.
136. Calder PC. Fatty acids and inflammation: the cutting edge between food and pharma. Eur J Pharmacol. 2011; 668(Suppl 1):S50-S58.
137. Kim K, Jung N, Lee K, Choi J, Kim S, Jun J, *et al*. Dietary omega-3 polyunsaturated fatty acids attenuate hepatic ischemia/reperfusion injury in rats by modulating toll-like receptor recruitment into lipid rafts. Clin Nutr. 2013; 32:855-862.
138. Liu J, Hu S, Cui Y, Sun MK, Xie F, Zhang Q, *et al*. Saturated fatty acids up-regulate COX-2 expression in prostate epithelial cells via toll-like receptor 4/NF-kappa B signaling. Inflammation. 2013; 37(2):467-477.
139. Frommer KW, Schaffler A, Rehart S, Lehr A, Muller-

Ladner U, Neumann E. Free fatty acids: potential proinflammatory mediators in rheumatic diseases. Ann Rheum Dis. 2013; 0:1-8.
140. Calder PC. Fatty acids and immune function: relevance to inflammatory bowel diseases. Int Rev Immunol. 2009; 28:506-534.
141. Innis SM. Dietary lipids in early development: relevance to obesity, immune and inflammatory disorders. Curr Opin Endocrinol Diabetes Obes. 2007; 14:359-364.
142. Kuhnt K, Wagner A, Kraft J, Basu S, Jahreis G. Dietary supplementation with 11trans- and 12trans-18:1 and oxidative stress in humans. Am J Clin Nutr. 2006; 84:981-988.
143. Sanchez A, Reeser JL, Lau HS, *et al*. Role of sugars in human neutrophilic phagocytosis. Am J Clin Nutr. 1973; 26:1180-1184.
144. Sorensen LB, Raben A, Stender S, Astrup A. Effect of sucrose on inflammatory markers in overweight humans. Am J Clin Nutr. 2005; 82:421-427.
145. Kleinewietfeld M, Manzel A, Titze J, *et al*. Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. Nature. 2013; 496:518-522.
146. Wu C, Yosef N, Thalhamer T, *et al*. Induction of pathogenic TH17 cells by inducible salt-sensing kinase SGK1. Nature. 2013; 496:513-517.
147. Maggini S, Pierre A, Calder PC. Immune Function and Micronutrient Requirements Change over the Life Course. Nutrients. 2018; 10:1531. Doi: 10.3390/nu10101531
148. Kuo SM. The interplay between fiber and the intestinal microbiome in the inflammatory response. Adv Nutr. 2013; 4:16-28.
149. D'Alessandro A, Lampignano L, De Pergola G. Mediterranean diet pyramid: a proposal for Italian people. A systematic review of prospective studies to derive serving sizes. Nutrients. 2019; 11(6):1296.
150. Davis C, Bryan J, Hodgson J, Murphy K. Definition of the Mediterranean diet: a literature review. Nutrients. 2015; 7(11):9139-53.
151. Weylandt KH, Chiu CY, Gomolka B, Waechter SF, Wiedenmann B. Omega-3 fatty acids and their lipid mediators: towards an understanding of resolvin and protectin formation. Prostaglandins Other Lipid Mediat. 2012; 97:73-82.
152. Calder PC, Carr AC, Gombart AF, Eggersdorfer M. Optimal Nutritional Status for a Well-Functioning Immune System Is an Important Factor to Protect against Viral Infections. Nutrients. 2020; 12:1181. Doi: 10.3390/nu12041181.
153. García-Burgos M, Moreno-Fernández J, Alférez MJM, Díaz-Castro J, López-Aliaga I. New perspectives in fermented dairy products and their health relevance. J. Funct. Foods. 2020; 72:104059.
154. Calder PC. Nutrition, immunity and COVID-19. BMJ Nutr. Prev. Health. 2020; 3:e000085. Doi: 10.1136/bmjnph-2020-000085.
155. Ahluwalia N, Andreeva VA, Kesse-Guyot E, Hercberg S. Dietary patterns, inflammation and the metabolic syndrome. Diabetes Metab. 2013; 39(2):99-110. Doi: 10.1016/j.diabet.2012.08.007.
156. Jayawardena R. Enhancing immunity in viral infections, with special emphasis on COVID-19: a review. Diabetes, Metab Syndrome: Clin Res Rev. 2020; 14(4):367-382.
157. Maggini S, Pierre A, Calder PC. Immune Function and Micronutrient Requirements Change over the Life Course. Nutrients. 2018; 10:1531. Doi: 10.3390/nu10101531.
158. Iddir M, Brito A, Dingeo G, *et al*. Strengthening the Immune System and Reducing Inflammation and Oxidative Stress through Diet and Nutrition: Considerations during the COVID-19 Crisis. Nutrients. 2020; 12:1562. Doi: 10.3390/nu12061562.
159. Vanherwegen AS, Gysemans C, Mathieu C. Regulation of Immune Function by Vitamin D and Its Use in Diseases of Immunity. Endocrinol Metab Clin North Am 2017; 46(4):1061-94. 10.1016/j.ecl.2017.07.010.
160. Pilz S, Zitterman A, Trummer C, Schwetz V, Lerchbaum E, Keppel M, *et al*. Vitamin D Testing and Treatment: A Narrative Review of Current Evidence. Endocr Connect. 2019; 8(2):R27-43. 10.1530/EC-18-0432.
161. Akbar MR, Wibowo A, Pranata R, Setiabudiawan B. Low Serum 25-Hydroxyvitamin D (Vitamin D) Level Is Associated With Susceptibility to COVID-19, Severity, and Mortality: A Systematic Review and Meta-Analysis. Front Nutr 2021; 8:660420. 10.3389/fnut.2021.660420.
162. Mrityunjaya M, Pavithra V, Neelam R, Janhavi P, Halami PM, Ravindra PV. Immune-Boosting, Antioxidant and Anti-inflammatory Food Supplements Targeting Pathogenesis of COVID-19. Front Immunol. 2020; 11:570122. Doi: 10.3389/fimmu.2020.570122.
163. Van Driel ML, Beller EM, Thielemans E, Deckx L, Price-Haywood E, Clark J, De Sutter AI. Oral vitamin C supplements to prevent and treat acuteupper respiratory tract infections. Cochrane Database Syst Rev. 2019: CD013292. Doi: 10.1002/14651858.CD013292.
164. Micronutrient Information Center Immunity in Depth. [(Accessed on 17 April 2018)]; Available online: http://lpi.oregonstate.edu/mic/health-disease/immunity.
165. Haryanto B, Suksmasari T, Wintergerst E, Maggini S. Multivitamin supplementation supports immune function and ameliorates conditions triggered by reduced air quality. Vitam. Miner. 2015; 4:1-15.
166. Saeed F, Nadeem M, Ahmed R, Nadeem M, Arshad M, Ullah A. Studying the impact of nutritional immunology underlying the modulation of immune responses by nutritional compounds- review. Food Agric. Immunol. 2016; 27:205-229. Doi: 10.1080/09540105.2015.1079600.
167. Alpert P. The role of vitamins and minerals on the immune system. Home Health Care Manag. Pract. 2017; 29:199-202. Doi: 10.1177/1084822317713300.
168. Taneri PE, Gómez-Ochoa SA, Llanaj E, *et al*. Anemia and iron metabolism in COVID-19: A systematic review and meta-analysis. Eur. J Epidemiol. 2020; 35:763-773. doi: 10.1007/s10654-020-00678-5,
169. Cruza V, Macedo Rogero M, Noel Keane K, Curi R, Newsholme P. Glutamine: Metabolism and Immune Function, Supplementation and Clinical Translation. Nutrients. 2018; 10:1564. Doi: 10.3390/nu10111564.
170. McCarthy MS, Martindale RG. Immunonutrition in Critical Illness: What Is the Role? Nutr. Clin. Pract. 2018: 33. Doi: 10.1002/ncp.10102.
171. Trujillo-Mayol I, Guerra-Valle M, Casas-Forero N, *et al*. Western Dietary Pattern Antioxidant Intakes and Oxidative Stress: Importance during the SARS-CoV-2/COVID-19 Pandemic. Adv Nutr. 2021; 12(3):670-681. Doi: 10.1093/advances/nmaa171.

172. Zhou K, Lansang MC. Diabetes Mellitus and Infections. 2021 Mar 16. In: Feingold KR, Anawalt B, Boyce A, *et al*., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000.
173. Rook GA. 99th Dahlem conference on infection, inflammation and chronic inflammatory disorders: darwinian medicine and the 'hygiene' or 'old friends' hypothesis. Clin Exp Immunol. 2010; 160:70-79.