Coronavirus Disease 2019 (COVID-19) and Nutritional Status: The Missing Link?

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is an emerging disease that has reached pandemic status by rapidly spreading worldwide. Elderly individuals and patients with comorbidities such as obesity, diabetes, and hypertension show a higher risk of hospitalization, severe disease, and mortality by acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. These patients frequently show exacerbated secretion of proinflammatory cytokines associated with an overreaction of the immune system, the so-called cytokine storm. Host nutritional status plays a pivotal role in the outcome of a variety of different infectious diseases. It is known that the immune system is highly affected by malnutrition, leading to decreased immune responses with consequent augmented risk of infection and disease severity. Body composition, especially low lean mass and high adiposity, has consistently been linked to worsened prognosis in many different diseases. In this review, evidence concerning the impact of nutritional status on viral infection outcomes is discussed. *Adv Nutr* 2021;12:682–692.

Keywords: COVID-19, SARS-CoV-2, BMI, obesity, undernutrition, sarcopenia, immune system

Introduction

The coronavirus disease 2019 (COVID-19) pandemic is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This disease has rapidly spread across the globe, and as of 1st June 2020, 6 million cases of COVID-19 have been reported worldwide, including >371,000 deaths (1).

Age, diabetes, cardiovascular disease, immunosuppression, and organ failure are risk factors related to illness severity (2). SARS-CoV-2 infection is associated with a broad clinical spectrum, ranging from asymptomatic to the development of serious pneumonia, acute respiratory distress syndrome, and death. Data from 72,314 patients with COVID-19 show that the prevalences of mild, severe, and critical cases were found to be 81%, 14%, and 5%, respectively (2). Fever, cough, fatigue, muscle pain, diarrhea, and

pneumonia are the most common manifestations of COVID-19, and may progress to acute respiratory distress syndrome, metabolic acidosis, septic shock, coagulation dysfunction, and organ failure, including liver, kidney, and heart (3–6).

COVID-19 patients usually present lymphocytopenia upon admission, and thrombocytopenia and leukopenia are frequent among those with serious illness (7). Furthermore, augmented concentrations of C-reactive protein and proinflammatory cytokines, such as IL-6, were also associated with severity (7, 8). The body's first reaction against viral infection is the triggering of rapid and synchronized innate immune responses. However, an excessive reaction may cause damage to human tissues (9, 10). It is postulated that hyperinflammatory aggression of the lungs, induced by disproportionate immune activation and coagulopathy, may be involved in disease progression and aggravation.

Nutritional status and diet modulate inflammation and immune function and may be adjusted to impact COVID-19 outcome. Herein, we will discuss the current available evidence concerning the role of nutritional status in COVID-19 patients, as well as the potential relevance of nutritional readjustment in the prevention and management of infection.

Nutritional Status and COVID-19

The unexpected and sudden appearance of new infectious diseases, such as HIV, severe acute respiratory syndrome, chikungunya virus, and now, the COVID-19 pandemic, has emphasized our vulnerability to newly emergent pathogenic agents. Host nutritional status has been accepted as a key factor in the outcome of a variety of different infectious diseases (11).

Obesity

A high prevalence of obesity is described among hospitalized patients with SARS-CoV-2 infection (12–16). In Spanish intensive care units (ICUs), 48% of the first patients admitted with COVID-19 were obese (14). Similarly, among 1482 of US hospitalized patients with COVID-19, 48.3% were obese (17). In the same way, a study from China showed that ∼43% of the hospitalized patients with COVID-19 were obese or overweight at admission (18). Obesity has also been associated with mortality and increased disease severity (12, 13, 15, 19). BMI of patients with cardiovascular disease and SARS-CoV-2 infection in the ICU is higher than that of patients without need for critical care (13). The same study also demonstrated higher overweight/obesity prevalence among nonsurvivors (13). Among the patients who died of COVID-19, obesity prevalence was found to range from 4.60% to 12.10% in Brazil and Italy, respectively (20).

Even though young individuals are at decreased risk of critical COVID-19, if obesity is a concomitant condition, patients are ∼2.0 times more likely to need critical care on admission (21). The association between younger patients with a BMI (kg/m^2) ≥25 and pneumonia at admission was also described, and low-flow supplemental oxygen and mechanical ventilation was necessary in such cases (22).

Thrombotic events potentially aggravate the course of COVID-19 (23), and obese patients are at increased risk (24). Obesity also inflicts detrimental consequences on lung physiology, such as reduced forced expiratory volume and forced vital capacity (25). Invasive mechanical ventilation in patients with COVID-19 has been reported to be positively correlated with obesity, independently of age and comorbidities (15).

Obesity is characterized by an excess of white adipose tissue, which is an extremely active organ with immunologic, endocrine, and metabolic functions (26). Adipose tissue–resident immune cells are important for tissue homeostasis and significant changes in their number and function are observed in obesity. Adipose tissue chronic low-grade inflammation in obesity is attributed to the expansion of effector T cells, including CD4$^+$ helper T (Th) cells and CD8$^+$ cytotoxic T lymphocytes, as well as to macrophage infiltration (27–32). Some studies also describe B-lymphocyte accumulation in animal models of obesity (33, 34), which, through interactions with T cells, increase inflammation (33). The preactivation of specific inflammatory cytokines in the expanded adipose tissue results in reduced antigen response and functional impairment of natural killer (NK) cells, dendritic cells, and macrophages (35, 36). One such immune dysfunction results in a dampened immune response to infections (37–39).

Remarkably increased concentrations of proinflammatory cytokines in patients with severe SARS-CoV-2 infection are considered to be among the most important causes of acute respiratory distress syndrome and multiple-organ failure (40). A balanced pro- and anti-inflammatory response is crucial for body homeostasis (41, 42). The loss or impaired function of one of the regulatory components can favor the "cytokine storm" phenomenon in tissues with exacerbated proinflammatory response, such as the lung and adipose tissue (43). As recently proposed by Ryan and Caplice (44), unbalanced local inflammation is associated with overreaction to viral spread, entry, and viral shedding, leading to amplification and maintenance of the immune response (44). The impaired inflammatory response contributes to the severity of lung lesions found in patients with influenza (45), and may play a key role in COVID-19 progression. We put forward the hypothesis that white adipose tissue acts as a relevant player in the disease, since SARS-CoV-2 enters human cells via angiotensin-converting enzyme 2 (ACE2), which is expressed not only in the lung and heart, kidney, liver, and blood vessels, but also abundantly in the white adipose tissue (46, 47), An additional interesting aspect is that there is adipose anatomical site–associated heterogeneity in the expression of ACE2, which is higher in the visceral depots (48). The enlarged visceral adipose pads in obese patients have been suggested to possibly act as reservoir for viruses, thereby increasing total virus load as a result of an "explosive systemic response of the angiotensin II and angiotensin II type 1 receptor axis" promoted by the tissue, and not perceived by the clinicians, who generally do not envisage white adipose tissue as a vital organ (47).

Obese individuals present additionally, a delayed capacity of IFN production, which allows higher viral RNA replication, consequently increasing the opportunity of the emergence of novel, more virulent viral strains (38, 49). Obesity is also associated with epithelial dysfunction and increased permeability, which could permit rapid virus shedding from the tissue and, consequently, faster spreading (50). Based on these data, it is possible to infer that obesity could have a potential role in the transmission of SARS-CoV-2 (51). In patients with influenza, obesity was related to virus shedding for an extended time (up to 104% longer) than that observed in lean individuals (52), whereas BMI was positively correlated with virus content in exhaled breath (53). Thus, apart from their increased susceptibility to infection, obese individuals could have a role in the augmentation of virus pathogenicity and transmission. Since 52% of the world's population are now obese or overweight (54), practical implications, such as a longer quarantine for obese people, should be considered (45).

It is also important to highlight that obese people may not benefit from a vaccine against SARS-CoV-2 to the same extent as healthy-weight individuals. An association between higher BMI and a greater decline in influenza antibody

titers 1-y post vaccination (55), as well as lower concentrations of vaccine-induced H1N1-specific antibodies in obese mice (56), were reported. Additionally, vaccinated obese individuals show double the risk of developing influenza (and influenza-like illness) compared with normal weight individuals (57). If the same is observed in COVID-19 patients, vaccination may not be an effective method for ensuring protection of the overweight population.

Anthropometric (i.e., BMI, waist and hip circumferences) and metabolic parameters (i.e., plasma glucose and insulin) have been used to evaluate the risk of COVID-19 complications (58). Assessment of insulin resistance, a robust indicator of altered metabolic health, impaired cardiovascular function, and cardiovascular disease–related mortality, is recommended (59) both in primary care, as well as in the evaluation of the potential risk and prognosis in patients with a positive SARS-CoV-2 test result.

It is worth noting that obese patients are at higher risk of the development of comorbidities, such as type 2 diabetes, hypertension, and cardiovascular disease (60). These comorbidities are increasingly associated with disease progression and poor COVID-19 outcome (61). In a meta-analysis with data from 76,993 patients, the prevalence of hypertension, cardiovascular disease, and diabetes in patients with COVID-19 was ∼16%, 12%, and 7%, respectively (62). The incidence of comorbidities was also determined in a meta-analysis of 6 studies: diabetes, hypertension, and cardio-cerebrovascular diseases were found to be 2- to 3-fold more prevalent in ICU/critical patients than in noncritical cases. These results highlight the susceptibility for worsened outcome among individuals with obesity-related comorbidities (63). In addition to increased propensity and worsened outcome in patients with previous cardiovascular metabolic disease, COVID-19 infection can, per se, induce cardiovascular complications, including heart failure, myocarditis, pericarditis, vasculitis, and cardiac arrhythmias (64, 65). Diabetic individuals show an increased susceptibility to infectious diseases, especially influenza and pneumonia (65–67), and experience the disease with greater severity when infected with respiratory viruses (68–70).

At present, the reason why individuals with obesity-related comorbidities are at increased risk of severe COVID-19 infection is unrecognized; however, it may be associated with the ACE2 expression in adipose pads and adipose tissue capacity to induce systemic inflammation. ACE inhibitors and angiotensin II type I receptor blockers increase considerably the expression of ACE2, and these drugs are very commonly used for the treatment of patients with diabetes and cardiovascular diseases (71, 72). Thus, the higher ACE2 content could help internalization of the virus by cells, thereby increasing the severity of COVID-19 (73).

Serum concentrations of inflammation-related biomarkers are also considerably higher in patients with diabetes (74). Thus, such patients, when infected, may be at higher risk of developing the "cytokine storm," and consequently of worsened prognosis. In type 2 diabetes there is an imbalance between coagulation and fibrinolysis, leading to increased concentration of clotting factors and relative inhibition of the fibrinolytic system. Additionally, endothelial dysfunction with enhanced platelet aggregation and activation is observed in insulin resistance and type 2 diabetes, favoring the emergence of a hypercoagulable prothrombotic state (75).

Distancing measures aimed at the reduction of social interaction have been adopted in several countries as a measure to reduce the spread of SARS-CoV-2 infection (76). Given the potential risk of developing severe COVID-19, individuals with comorbidities should firmly adhere to protective measures. To decrease the risk of infection and severe disease, diabetic individuals should maintain strict glycemic control. Inadequate glycemic control is associated with several infections, such as pneumonia, endocarditis, and tuberculosis (77). Frequent monitoring of glycemia is even more important for obese individuals with type 2 diabetes, since medication adjustment to maintain blood glucose concentrations may be necessary to adapt to the new caloric requirements of reduced physical activity and energy intake imposed by quarantines (78). In addition, diabetic patients with heart disease or kidney disease may require specific care to stabilize cardiac/renal status (77).

Undernutrition

Undernutrition, a pathologic state in which dietary intake fails to meet the body's energy or nutritional requirements, can arise from inadequate intake of macronutrients or micronutrients, abnormally increased energy expenditure, defective absorption of nutrients, or any combination of these (79). Worldwide, there were an estimated 821 million undernourished individuals in 2017 (80), a condition widely prevalent in developing countries (81). Protein–energy malnutrition, as well as deficiencies in specific single nutrients, are largely related to increased risk of mainly occuring infectious diseases (82–85).

Immune cells show high energy expenditure (86), and energetic and nutritional demand is increased during periods of infection. For example, basal metabolic rate is significantly higher during a fever due to the activation of the immune response (87). Because immune cells have no substantial reserve of nutrients, glucose and amino acid uptake is required for immune system activation (88). Indeed, malnutrition induces a reduction in immune cell number, especially of T cells (81, 85, 89, 90). For instance, lower CD4$^+$ and CD8$^+$ T-cell numbers have been described in malnourished children (91). Moreover, malnutrition induces atrophy of primary lymphoid organs, reducing T- and B-cell numbers, leading to leukopenia (92). This reduced number of immune cells contributes to the impairment of the immune response in malnutrition (93).

Both under- and overnutrition have a great impact on adipose tissue mass, modulating the factors secreted by this tissue, such as hormones and cytokines. During starvation, the activation of immune cells is limited by adipokine signaling, which reduces nutrient consumption, and consequently, the body becomes more susceptible to infection (94). Leptin plays a pivotal role in reporting nutritional status to

immune cells by increasing glucose metabolism in T cells (93). Leptin concentrations are inversely modified in both extremes of body weight, being reduced in malnourished and increased in obese individuals. Experimental studies show that leptin receptor–deficient mice, as well as malnourished animals, present reduced viral clearance, diminished lung IFN-γ concentration, and lower survival during influenza-A pneumonia infection (95). It is known that body adiposity is extremely affected by protein–energy malnutrition, leading to reduced systemic leptin concentrations (96). Therefore, the impaired immune response in malnutrition may be related to poor nutrient intake and dysfunction in leptin signaling, critical factors for the activity and proliferation of immune cells (93). These findings suggest a crucial role of adipose tissue in the maintenance of immune defense in viral infections.

As described previously for obesity, undernutrition may also impact viral replication and pathogenicity. Increased oxidative stress in animal models was associated with virulence and incidence of reproducible genome mutations observed for coxsackievirus and influenza (97). Since this phenomenon was described for 2 distinct viral RNA families, it is possible to infer that malnutrition may affect the outcome of other virus-induced diseases (97).

ACE2, the receptor crucial to the SARS-CoV-2 entry into the host cells, is widely expressed in gastrointestinal cells, such as those of the intestinal epithelium. Therefore, the digestive system may also be affected by SARS-CoV-2 infection, leading to gastrointestinal disorders and impairment of the nutritional status of patients (98). Indeed, anorexia, diarrhea, vomiting, nausea, and mild abdominal pain were reported in COVID-19 patients (7). Anorexia is the most common among the digestive system–related symptoms, and it could be related to inflammation, hypoxia, dysregulated hepatic function, or represent the side effects of therapeutic drugs. Diarrhea is yet another common gastrointestinal symptom, affecting ∼2% to 50% of patients (99). The particular mechanism related to the pathogenesis of diarrhea in patients with COVID-19 is not fully elucidated; however, some possible causes are described: direct aggression to the digestive epithelium by the virus, side effects of antiviral drugs, or dysbiosis of the intestinal microbiota induced by antibiotics (99). Anorexia along with diarrhea could contribute to nutritional imbalance, and consequently to a delay in recovery (100, 101). Moreover, patients with COVID-19 and digestive symptoms were more prone to complications of acute respiratory distress syndrome (7). Clearly, the gastrointestinal symptoms of COVID-19 may be even more harmful in malnourished patients. This aspect could be of even more importance for the elderly, since a reduction in mobility along with a depletion of muscle mass and poor nutrient intake are frequently present in older adults (102).

Aging and Nutrition and COVID-19

Elderly persons are more susceptible to SARS-CoV-2 infection and experience a poorer outcome when compared with younger patients (7, 103, 104). Aging is associated with alterations in both the innate and the adaptive immune response, a process known as immunosenescence (105). Hematopoietic tissue (106, 107), lymphocyte number (108), proliferative and functional capacity of effector lymphocytes (107), and activity of NK cells (109) are all reduced in the elderly. These alterations induce a basal systemic inflammatory state, or "inflammaging" (110), and are associated with an augmented susceptibility to viral infection (111). High morbidity and mortality are observed in elderly patients with infections, especially those of the respiratory tract (112–114). This situation could be prevented through vaccination; however, vaccine efficacy in this population is greatly reduced in comparison to that in younger adults (115–119). Immunosenescence-related alterations, such as reduced concentrations of naive T and B cells, decreased B-cell diversity, and impaired antibody response to new antigens, result in diminished response to vaccination or new infection (108, 120, 121).

Nutritional deficiencies of micro- and/or macronutrients are frequent in older adults, as stated (122). Although there are few data regarding malnutrition in patients with SARS-CoV-2 infection, given the prevalence of severe disease among elderly patients it is likely that a significant proportion of these patients were undernourished at the time of hospitalization (123). In agreement with this hypothesis, the risk of malnutrition and malnutrition in individuals >65 y of age was 27.5% and 52.7%, respectively, in a cross-sectional study in patients with COVID-19 (124). Many reasons may be related to the higher prevalence of compromised nutritional status in older patients with COVID-19. First, a catabolic state induced by the inflammatory response to SARS-CoV-2 infection may induce skeletal muscle wasting. The concentrations of proinflammatory markers, such as C-reactive protein, TNF-α, and ferritin are usually augmented in these patients (125), and the utilization of albumin and even muscle protein may be needed to synthesize the acute-phase proteins (125). This is consistent with the hypoalbuminemia and low calf circumference observed in these patients (126, 127). Second, in addition to respiratory symptoms, gastrointestinal symptoms have been reported as being most prevalent in elderly patients with COVID-19 (7). Thus, digestive tract malfunction can exacerbate the poor nutritional status in older patients with COVID-19. Last, immunosenescence per se may contribute to potentialize all alterations in COVID-19 (128).

Sarcopenia

Sarcopenia is defined by impaired muscle strength, reduced muscle quantity/quality, and poor physical performance (129). The pathogenesis of sarcopenia is associated with proinflammatory cytokines (130, 131), and muscle mass and strength are inversely proportional to IL-6 and TNF-α plasma concentrations in healthy older individuals (131). Loss of muscle mass and function is a usual condition in the elderly, as well as in younger individuals with acute and chronic muscle-wasting diseases, such as cancer, chronic

heart failure, liver cirrhosis, and chronic infection (132). Studies have described that sarcopenia is a predictor of the risk of pneumonia in the elderly (132), and it is associated with mechanical ventilation, hospitalization time, and mortality in ICU patients (130, 132–134).

Sarcopenia may affect normal weight healthy and overweight/obese individuals, being different from weight loss or cachexia (135–137). Augmented fat mass associated with low muscle mass or high fat mass together with low muscle strength are known as sarcopenic obesity (138). Ectopic fat accumulation in skeletal muscle and other tissues is a characteristic of obesity (139). The increased fat content leads to mitochondrial dysfunction and induces the production of reactive oxygen species (134). This microenvironment is related to enhanced secretion of proinflammatory myokines capable of inducing muscle dysfunction (134). In turn, adipose tissue inflammation may be exacerbated by these proinflammatory myokines, supporting the condition of chronic low-grade systemic inflammation. This sets up a vicious cycle supporting inflammation of both skeletal muscle and adipose tissue, hence stimulating and maintaining sarcopenic obesity (134). As obesity has been related to a poor prognosis in patients with COVID-19, it cannot be discarded that sarcopenic obesity is an even more harmful scenario (133).

The sarcopenic phenotype is also associated with decreased physical activity (129). This is extremely relevant in terms of the COVID-19 pandemic, since many people are staying at home and are currently physically inactive (spending a long time sitting or lying down). Prolonged immobility is associated with muscle mass wasting within the first week of bed rest, which is even worse in individuals with the severe form of the disease (140). The duration of hospital stay of COVID-19 patients is, on average, between 11 and 15 d (141); thus, patients may be prone to developing sarcopenia.

Bearing in mind that sarcopenia may play a relevant role in COVID-19 outcome, Krznaric and colleagues (142) recently proposed the utilization of 2 clinical tools to assess nutritional risk and loss of muscle mass and function remotely by incorporating them into telemedicine processes and digital platforms. For a simple, preliminary diagnosis of sarcopenia, the Strength, Assistance with walking, Rise from a chair, Climb stairs and Falls (SARC-F) questionnaire, which evaluates muscle strength, assistance with walking, rise from a chair, climbing stairs, and falls, may be adopted (143). The prescription of personalized nutrition care and support is recommended for patients whose questionnaire results are predictive of sarcopenia and poor outcome (142, 144, 145).

Concluding Remarks
The COVID-19 outbreak has brought a great challenge for all communities and health care systems worldwide. Considering the absence of specific therapeutic treatment and of an effective vaccine, countries are taking strong measures to contain the spread of COVID-19, ranging from increasing social distancing to community-wide quarantine.

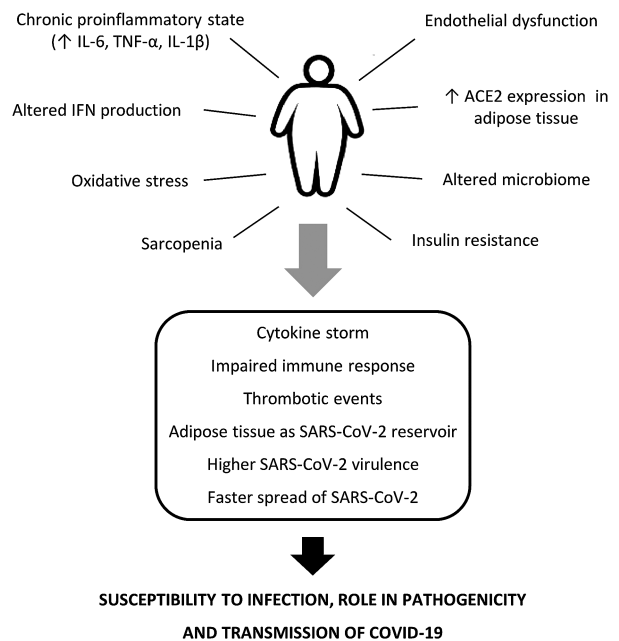**Obesity and related comorbidities**

FIGURE 1 Obesity and related comorbidities are associated with physiological alterations leading to higher susceptibility to infection and pathogenicity and transmission of COVID-19. ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Changes in dietary habits and lifestyle parameters, due to quarantine and social isolation, may lead to an impaired nutritional status. Obesity and related comorbidities are associated with physiological alterations leading to higher susceptibility to infection and pathogenicity and transmission of COVID-19 (**Figure 1**). Moreover, with no imminent end to the pandemic , people should be encouraged to improve their lifestyle to lessen the risks both in the current and likely subsequent waves of COVID-19. Healthy habits are important not only to ensure optimal immune response but also to prevent and/or treat undernutrition, obesity, and obesity-related comorbidities in COVID-19 patients. Therefore, clear advice on the impact of the nutritional status in COVID-19 outcomes should be provided to alert the population. Finally, it should be emphasized that nutritional status must be considered also in health policies designed to diminish the impact of COVID-19.

References
1. World Health Organization. Coronavirus disease (COVID-19). Situation report—120[Internet]. [cited May 19, 2020]. Available from:

https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200519-covid-19-sitrep-120.pdf?sfvrsn=515cabfb_2.

2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. JAMA[Internet]. 2020;323:1239. [cited Apr 23, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32091533.

3. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet[Internet]. 2020[cited Aug 4, 2020];395:507–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32007143.

4. Zhu J, Ji P, Pang J, Zhong Z, Li H, He C, Zhang J, Zhao C. Clinical characteristics of 3062 COVID-19 patients: a meta-analysis. J Med Virol[Internet]. 2020;jmv.25884. [cited Aug 4, 2020]. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25884.

5. Yang W, Cao Q, Qin L, Wang X, Cheng Z, Pan A, Dai J, Sun Q, Zhao F, Qu J, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multi-center study in Wenzhou city, Zhejiang, China. J Infect[Internet]. 2020;80:388–93. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32112884.

6. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest[Internet]. 2020;130:2620–9. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32217835.

7. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, Liu L, Shan H, Lei C, Hui DSC, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med[Internet]. 2020.[cited Apr 27, 2020]. Available from: http://www.nejm.org/doi/10.1056/NEJMoa2002032.

8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet[Internet]. 2020;395:1054–62. [cited Apr 29, 2020]. Available from: https://www.sciencedirect.com/science/article/pii/S0140673620305663.

9. Channappanavar R, Fehr AR, Vijay R, Mack M, Zhao J, Meyerholz DK, Perlman S. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host Microbe[Internet]. 2016;19:181–93. [cited Apr 29, 2020]. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1931312816300063.

10. Shaw AC, Goldstein DR, Montgomery RR. Age-dependent dysregulation of innate immunity. Nat Rev Immunol[Internet]. 2013;13:875–87. [cited Apr 27, 2020]. Available from: http://www.nature.com/articles/nri3547.

11. 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[Internet]. 2020;12:1181. [cited May 19, 2020]. Available from: https://www.mdpi.com/2072-6643/12/4/1181.

12. Sun X, Wang T, Cai D, Hu Z, Chen J, Liao H, Zhi L, Wei H, Zhang Z, Qiu Y, et al. Cytokine storm intervention in the early stages of COVID-19 pneumonia. Cytokine Growth Factor Rev 2020;53:38–42.

13. Peng YD, Meng K, Guan HQ, Leng L, Zhu RR, Wang BY, He MA, Cheng LX, Huang K, Zeng QT. [Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV.] Zhonghua Xin Xue Guan Bing Za Zhi[Internet]. 2020;48:E004. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32120458.

14. Barrasa H, Rello J, Tejada S, Martín A, Balziskueta G, Vinuesa C, Fernández-Miret B, Villagra A, Vallejo A, San Sebastián A, et al. SARS-CoV-2 in Spanish intensive care units: early experience with 15-day survival in Vitoria. Anaesthesia Crit Care Pain Med[Internet]. 2020.[cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32278670.

15. Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, Labreuche J, Mathieu D, Pattou F, Jourdain M, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity (Silver Spring)[Internet]. 2020;28:1195–9. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32271993.

16. Garg M, Al-Ani A, Mitchell H, Hendy P, Christensen B. Editorial: low population mortality from COVID-19 in countries south of latitude 35 degrees north-supports vitamin D as a factor determining severity. Authors' reply. Aliment Pharmacol Ther[Internet]. 2020;51:1438–9. [cited Aug 4, 2020]. Available from: http://doi.wiley.com/10.1111/apt.15796.

17. Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, Prill M, Chai SJ, Kirley PD, Alden NB, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019—COVID-NET, 14 states, March 1–30, 2020. MMWR Morb Mortal Wkly Rep[Internet]. 2020;69:458–64. [cited Apr 18, 2020]. Available from: http://www.cdc.gov/mmwr/volumes/69/wr/mm6915e3.htm?s_cid=mm6915e3_w.

18. Cai Q, Chen F, Wang T, Luo F, Liu X, Wu Q, He Q, Wang Z, Liu Y, Liu L, et al. Obesity and COVID-19 severity in a designated hospital in Shenzhen, China. 2020. [cited May 20, 2020]. [Internet]. Available from: https://pubmed.ncbi.nlm.nih.gov/32409502/?from_term=wu+COVID-19+obesity&from_pos=1.

19. Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, Southern WN, Mantzoros CS. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism[Internet]. 2020;108:154262. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32422233.

20. de Oliveira MHS, Wong J, Lippi G, Henry BM. Analysis of clinical and demographic heterogeneity of patients dying from COVID-19 in Brazil versus China and Italy. Brazilian J Infect Dis[Internet]. 2020.[cited Jun 6, 2020]. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1413867020300568.

21. Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, Stachel A. Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission. Clin Infect Dis[Internet]. 2020.[cited Apr 20, 2020]. Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa415/5818333.

22. Ong SWX, Young BE, Leo Y-S, Lye DC. Association of higher body mass index (BMI) with severe coronavirus disease 2019 (COVID-19) in younger patients. Clin Infect Dis[Internet]. 2020.[cited May 20, 2020]. Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa548/5831985.

23. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost[Internet]. 2020;18:844–7. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32073213.

24. Movahed MR, Khoubyari R, Hashemzadeh M, Hashemzadeh M. Obesity is strongly and independently associated with a higher prevalence of pulmonary embolism. Respiratory Investigation [Internet]. 2019;57:376–9. [cited May 14, 2020]. Available from: https://linkinghub.elsevier.com/retrieve/pii/S221253451830282X.

25. Sattar N, McInnes IB, McMurray JJV. Obesity is a risk factor for severe COVID-19 infection: multiple potential mechanisms. Circulation[Internet]. 2020;142:4–6. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32320270.

26. Mraz M, Haluzik M. The role of adipose tissue immune cells in obesity and low-grade inflammation. J Endocrinol[Internet]. 2014;222:R113–27. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25006217.

27. McLaughlin T, Liu L-F, Lamendola C, Shen L, Morton J, Rivas H, Winer D, Tolentino L, Choi O, Zhang H, et al.T-cell profile in adipose tissue is associated with insulin resistance and systemic inflammation in humans. Arterioscler Thromb Vasc Biol[Internet]. 2014;34:2637–43. [cited May 1, 2020]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4445971/.

28. Kintscher U, Hartge M, Hess K, Anna Foryst-Ludwig MC, Wabitsch M, Pamela Fischer-Posovszky T, Dragun D, Skurk T, Hauner H, Blüher M, et al. T-lymphocyte infiltration in visceral adipose tissue: a primary event in adipose tissue inflammation and the development of obesity-mediated insulin resistance. Aterioscler Thromb Vasc Biol. 2008;28:1304–10.

29. Oh DY, Morinaga H, Talukdar S, Bae EJ, Olefsky JM. Increased macrophage migration into adipose tissue in obese mice. Diabetes[Internet]. 2008;28:346–54. [cited Aug 9, 2020]. Available from: https://pubmed.ncbi.nlm.nih.gov/22190646/

30. Khan IM, Perrard X-YD, Perrard JL, Mansoori A, Smith CW, Wu H, Ballantyne CM. Attenuated adipose tissue and skeletal muscle inflammation in obese mice with combined CD4+ and CD8+ T cell deficiency. Atherosclerosis[Internet]. 2014;233:419. [cited Aug 9, 2020]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4094239/.

31. Surmi BK, Hasty AH. Macrophage infiltration into adipose tissue: initiation, propagation and remodeling. Future Lipidology[Internet]. 2008;3:545–56. [cited Aug 9, 2020]. Available from: https://www.futuremedicine.com/doi/10.2217/17460875.3.5.545.

32. Surmi BK, Hasty AH. The role of chemokines in recruitment of immune cells to the artery wall and adipose tissue. Vasc Pharmacol[Internet]. 2010;52:27–36. [cited May 2, 2020]. Av ailable from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2823842/.

33. Winer DA, Winer S, Shen L, Wadia PP, Yantha J, Paltser G, Tsui H, Wu P, Davidson MG, Alonso MN, et al. B cells promote insulin resistance through modulation of T cells and production of pathogenic IgG antibodies. Nat Med[Internet]. 2011;17:610–7. [cited Aug 9, 2020], Available from: http://www.ncbi.nlm.nih.gov/pubmed/21499269,

34. Duffaut C, Galitzky J, Lafontan M, Bouloumié A. Unexpected trafficking of immune cells within the adipose tissue during the onset of obesity. Biochem Biophys Res Commun[Internet]. 2009;384:482–5. [cited Aug 9, 2020]. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0006291X09008948?via%3Dihub.

35. O'Shea D, Hogan AE. Dysregulation of natural killer cells in obesity. Cancers (Basel)[Internet]. 2019;11. [cited Apr 18, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31018563.

36. Wang T, He C. Cytokinesok: The link between obesity and osteoarthritis. Cytokine Growth Factor Rev[Internet]. 2018;44:38–50. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30340925.

37. Andersen CJ, Murphy KE, Fernandez ML. Impact of obesity and metabolic syndrome on immunity. Adv Nutr[Internet]. 2016;7:66. [cited Apr 23, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26773015.

38. Honce R, Karlsson EA, Wohlgemuth N, Estrada LD, Meliopoulos VA, Yao J, Schultz-Cherry S. Obesity-related microenvironment promotes emergence of virulent influenza virus strains. MBio[Internet]. 2020;11. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32127459.

39. Mancuso P. Obesity and respiratory infections: does excess adiposity weigh down host defense? Pulmonary Pharmacol Therapeutics[Internet]. 2013;26:412–9. [cited Aug 5, 2020]. Available from: https://www.sciencedirect.com/science/article/pii/S1094553912000703?via%3Dihub.

40. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, Wang J, Qin Y, Zhang X, Yan X, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The perspectives of clinical immunologists from China. Clin Immunol[Internet]. 2020;214:108393. [cited May 20, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32222466.

41. Trahtemberg U, Mevorach D. Apoptotic cells induced signaling for immune homeostasis in macrophages and dendritic cells. Front Immunol[Internet]. 2017;8:1356. [cited May 11, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29118755.

42. Elenkov IJ, Iezzoni DG, Daly A, Harris AG, Chrousos GP. Cytokine dysregulation, inflammation and well-being. Neuroimmunomodulation[Internet]. 2005;12:255–69. [cited May 11, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16166805.

43. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the "cytokine storm" in COVID-19. J Infect 2020;80:607–13.

44. Ryan PM, Caplice NM. Is adipose tissue a reservoir for viral spread, immune activation and cytokine amplification in COVID-19. Obesity[Internet]. 2020;oby.22843. [cited Apr 22, 2020]. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/oby.22843.

45. Luzi L, Radaelli MG. Influenza and obesity: its odd relationship and the lessons for COVID-19 pandemic. Acta Diabetol[Internet]. 2020.[cited Apr 23, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32249357.

46. Aleksova A, Ferro F, Gagno G, Cappelletto C, Santon D, Rossi M, Ippolito G, Zumla A, Beltrami AP, Sinagra G. COVID-19 and renin-angiotensin system inhibition—role of angiotensin converting enzyme 2 (ACE2)—is there any scientific evidence for controversy? J Intern Med[Internet]. 2020.[cited Jun 5,2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32459372.

47. Iannelli A, Favre G, Frey S, Esnault V, Gugenheim J, Bouam S, Schiavo L, Tran A, Alifano M. Obesity and COVID-19: ACE 2, the missing tile. Obes Surg[Internet]. 2020.[cited Jun 5, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32451913.

48. Zhang Y, Somers KR, Becari C, Polonis K, Pfeifer MA, Allen AM, Kellogg TA, Covassin N, Singh P. Comparative expression of renin-angiotensin pathway proteins in visceral versus subcutaneous fat. Front Physiol[Internet]. 2018;9:1370. [cited Jun 5, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30364113.

49. Klinkhammer J, Schnepf D, Ye L, Schwaderlapp M, Gad HH, Hartmann R, Garcin D, Mahlakõiv T, Staeheli P. IFN-λ prevents influenza virus spread from the upper airways to the lungs and limits virus transmission. Elife[Internet]. 2018;7. [cited Apr 20, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29651984.

50. Weger-Lucarelli J, Carrau L, Levi LI, Rezelj V, Vallet T, Blanc H, Boussier J, Megrian D, Coutermarsh-Ott S, LeRoith T, et al. Host nutritional status affects alphavirus virulence, transmission, and evolution. PLoS Pathog[Internet]. 2019;15:e1008089. [cited Apr 18, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31710653.

51. Kassir R. Risk of COVID-19 for patients with obesity. Obes Rev[Internet]. 2020;21. [cited May 14, 2020]. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/obr.13034.

52. Maier HE, Lopez R, Sanchez N, Ng S, Gresh L, Ojeda S, Burger-Calderon R, Kuan G, Harris E, Balmaseda A, et al. Obesity increases the duration of influenza A virus shedding in adults. J Infect Dis[Internet]. 2018;218:1378–82. [cited Apr 20, 2020]. Available from: https://academic.oup.com/jid/article/218/9/1378/5051913.

53. Yan J, Grantham M, Pantelic J, Bueno de Mesquita PJ, Albert B, Liu F, Ehrman S, Milton DK. Infectious virus in exhaled breath of symptomatic seasonal influenza cases from a college community. Proc Natl Acad Sci USA[Internet]. 2018;115:1081–6. [cited Apr 202020]. Available from: http://www.pnas.org/lookup/doi/10.1073/pnas.1716561115.

54. World Health Organization. Obesity and overweight [Internet]. 2020. [cited May 19, 2020]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.

55. Sheridan PA, Paich HA, Handy J, Karlsson EA, Hudgens MG, Sammon AB, Holland LA, Weir S, Noah TL, Beck MA. Obesity is associated with impaired immune response to influenza vaccination in humans. Int J Obes[Internet]. 2012;36:1072–7. [cited Aug 9, 2020]. Available from: http://www.nature.com/articles/ijo2011208.

56. Kim Y-H, Kim J-K, Kim D-J, Nam J-H, Shim S-M, Choi Y-K, Lee C-H, Poo H. Diet-Induced obesity dramatically reduces the efficacy of a 2009 pandemic H1N1 vaccine in a mouse model. J Infect Dis[Internet]. 2012;205:244–51. [cited Aug 5, 2020]. Available from: https://academic.oup.com/jid/article-lookup/doi/10.1093/infdis/jir731.

57. Neidich SD, Green WD, Rebeles J, Karlsson EA, Schultz-Cherry S, Noah TL, Chakladar S, Hudgens MG, Weir SS, Beck MA. Increased risk of influenza among vaccinated adults who are obese. Int J

Obes[Internet]. 2017;41:1324–30. [cited Aug 9, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28584297.

58. Carter SJ, Baranauskas MN, Fly AD. Considerations for obesity, vitamin D, and physical activity amidst the COVID-19 pandemic. Obesity (Silver Spring)[Internet]. 2020[cited Apr 22, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32299148.

59. Stefan N, Schick F, Häring H-U. Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. Cell Metab[Internet]. 2017;26:292–300. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28768170.

60. Khaodhiar L, McCowen KC, Blackburn GL. Obesity and its comorbid conditions. Clin Cornerstone[Internet]. 1999;2:17–31. [cited May 18, 2020]. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1098359799900029.

61. Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: prevalence, pathophysiology, prognosis and practical considerations. Diabetes Metab Syndr[Internet]. 2020;14:303–10. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32298981.

62. Emami A, Javanmardi F, Pirbonyeh N, Akbari A. Prevalence of underlying diseases in hospitalized patients with COVID-19: a systematic review and meta-analysis. Arch Acad Emerg Med[Internet]. 2020;8:e35. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32232218.

63. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, B Z, Zhao Y. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol[Internet]. 2020;109:531–38. [cited May 1, 2020]. Available from: https://link.springer.com/article/10.1007/s00392-020-01626-9.

64. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol[Internet]. 2020.[cited May 2, 2020]. Available from: https://jamanetwork.com/journals/jamacardiology/fullarticle/2763845.

65. Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: a review of pathogenesis. Indian J Endocrinol Metab[Internet]. 2012;16(Suppl 1):S27–36. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22701840.

66. Kornum JB, Thomsen RW, Riis A, Lervang H-H, Schønheyder HC, Sørensen HT. Type 2 diabetes and pneumonia outcomes: a population-based cohort study. Diabetes Care[Internet]. 2007;30:2251–7. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17595354.

67. Peleg AY, Weerarathna T, McCarthy JS, Davis TME. Common infections in diabetes: pathogenesis, management and relationship to glycaemic control. Diabetes Metab Res Rev[Internet]. 2007;23:3–13. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16960917.

68. Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, Sun GZ, Yang GR, Zhang XL, Wang L, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med[Internet]. 2006;23:623–8. [cited May 2, 2020]. Available from: http://doi.wiley.com/10.1111/j.1464-5491.2006.01861.x.

69. Schoen K, Horvat N, Guerreiro NFC, de Castro I, de Giassi KS. Spectrum of clinical and radiographic findings in patients with diagnosis of H1N1 and correlation with clinical severity. BMC Infect Dis[Internet]. 2019;19:964. [cited May 2,2020]. Available from: https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-019-4592-0.

70. Song Z, Xu Y, Bao L, Zhang L, Yu P, Qu Y, Zhu H, Zhao W, Han Y, Qin C. From SARS to MERS, thrusting coronaviruses into the spotlight. Viruses[Internet]. 2019;11:59. [cited May 2, 2020]. Available from: http://www.mdpi.com/1999-4915/11/1/59.

71. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol[Internet]. 2020;94. [cited May 2, 2020]. Available from: https://jvi.asm.org/content/94/7/e00127-20.

72. Li XC, Zhang J, Zhuo JL. The vasoprotective axes of the renin-angiotensin system: physiological relevance and therapeutic implications in cardiovascular, hypertensive and kidney diseases. Pharmacol Res[Internet]. 2017;125:21–38. [cited May 2, 2020]. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1043661817301780.

73. Ma RCW, Holt RIG. COVID-19 and diabetes. Diabet Med[Internet]. 2020;37:723–5. [cited May 1, 2020]. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/dme.14300.

74. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, Qin R, Wang H, Shen Y, Du K, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev[Internet]. 2020;e3319. [cited May 1, 2020]. Available from: https://pubmed.ncbi.nlm.nih.gov/32233013/.

75. Dunn E, Grant P. Type 2 diabetes: an atherothrombotic syndrome. Curr Mol Med [Internet]. 2005;5:323–32. [cited May 1, 2020]. Available from: http://www.eurekaselect.com/openurl/content.php?genre=article&issn=1566-5240&volume=5&issue=3&spage=323.

76. Wilder-Smith A, Freedman DO. Isolation, quarantine, social distancing and community containment: pivotal role for old-style public health measures in the novel coronavirus (2019-nCoV) outbreak. J Travel Med[Internet]. 2020;27. [cited Jun 5, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32052841.

77. Gupta R, Ghosh A, Singh AK, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. Diabetes Metab Syndr[Internet]. 2020;14:211–2. [cited Aug 4, 2020]. Available from: https://pubmed.ncbi.nlm.nih.gov/32172175/.

78. Frühbeck G, Baker JL, Busetto L, Dicker D, Goossens GH, Halford JCG, Handjieva-Darlenska T, Hassapidou M, Holm J-C, Lehtinen-Jacks S, et al. European Association for the Study of Obesity position statement on the global COVID-19 pandemic. Obes Facts[Internet]. 2020;13:292–6. [cited May 11, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32340020.

79. Velly H, Britton RA, Preidis GA. Mechanisms of cross-talk between the diet, the intestinal microbiome, and the undernourished host. Gut Microbes[Internet]. 2017;8:98. [cited Apr 29, 2020]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5390823/.

80. FAO of the United Nations. The state of food security and nutrition in the word [Internet]. 2019[cited Jun 2, 2020]. Available from: http://www.fao.org/state-of-food-security-nutrition.

81. Taylor AK, Cao W, Vora KP, La C JD, Shieh W-J, Zaki SR, Katz JM, Sambhara S, Gangappa S. Protein energy malnutrition decreases immunity and increases susceptibility to influenza infection in mice. J Infect Dis[Internet]. 2013;207:501–10. [cited May 16, 2020]. Available from: https://academic.oup.com/jid/article-lookup/doi/10.1093/infdis/jis527.

82. Scrimshaw NS, SanGiovanni JP. Synergism of nutrition, infection, and immunity: an overview. Am J Clin Nutr[Internet]. 1997;66:464S–77S. [cited Apr 27, 2020]. Available from: https://academic.oup.com/ajcn/article/66/2/464S/4655772.

83. Ambrus JL. Nutrition and infectious diseases in developing countries and problems of acquired immunodeficiency syndrome. Exp Biol Med (Maywood)[Internet]. 2004;229:464–72. [cited May 16, 2020]. Available from: http://journals.sagepub.com/doi/10.1177/153537020422900603.

84. Schaible UE, Kaufmann SHE. Malnutrition and infection: complex mechanisms and global impacts.PLoS Med [Internet]. 2007;4. [cited May 16, 2020]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1858706/.

85. Gerriets VA, MacIver NJ. Role of T cells in malnutrition and obesity. Front Immunol[Internet]. 2014;5:379. [cited May 16, 2020]. Available from: http://journal.frontiersin.org/article/10.3389/fimmu.2014.00379/abstract.

86. Cutrera AP, Zenuto RR, Luna F, Antenucci CD. Mounting a specific immune response increases energy expenditure of the subterranean rodent Ctenomys talarum (tuco-tuco): implications for intraspecific and interspecific variation in immunological traits. J Exp

Biol[Internet]. 2010;213:715–24. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20154186.

87. Childs CE, Calder PC, Miles EA. Diet and immune function. Nutrients [Internet]. 2019;11. [cited May 20, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31426423.

88. Ganeshan K, Chawla A. Metabolic regulation of immune responses. Annu Rev Immunol[Internet]. 2014;32:609–34. [cited May 16, 2020]. Available from: http://www.annualreviews.org/doi/10.1146/annurev-immunol-032713-120236.

89. Saucillo DC, Gerriets VA, Sheng J, Rathmell JC, MacIver NJ. Leptin metabolically licenses T cells for activation to link nutrition and immunity. J Immunol[Internet]. 2014 192:136–44. [cited May 16, 2020]. Available from: http://www.jimmunol.org/lookup/doi/10.4049/jimmunol.1301158.

90. Peña-Cruz V, Reiss C, McIntosh K. Effect of respiratory syncytial virus infection on mice with protein malnutrition. J Med Virol[Internet]. 1991;33:219–23. [cited Apr 25, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1906929.

91. Na´jera O, Gonza´lez C, Toledo G, Lo´pez L, Ortiz R. Flow cytometry study of lymphocyte subsets in malnourished and well-nourished children with bacterial infections. Clin Diagn Lab Immunol[Internet]. 2004;11:577–80. [cited May 16, 2020]. Available from: https://cvi.asm.org/content/11/3/577.

92. Savino W, Dardenne M, Velloso LA, Dayse Silva-Barbosa S. The thymus is a common target in malnutrition and infection. Br J Nutr[Internet]. 2007;98:S11–6. [cited May 16, 2020]. Available from: https://www.cambridge.org/core/product/identifier/S0007114507832880/type/journal_article.

93. Alwarawrah Y, Kiernan K, MacIver NJ. Changes in nutritional status impact immune cell metabolism and function. Front Immunol[Internet]. 2018;9. [cited May 19, 2020]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5968375/.

94. Wensveen FM, Valentić S, Šestan M, Wensveen TT, Polić B. Interactions between adipose tissue and the immune system in health and malnutrition. Semin Immunol[Internet]. 2015;27:322–33. [cited May 20, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26603491.

95. Radigan KA, Morales-Nebreda L, Soberanes S, Nicholson T, Nigdelioglu R, Cho T, Chi M, Hamanaka RB, Misharin AV, Perlman H, et al. Impaired clearance of influenza A virus in obese, leptin receptor deficient mice is independent of leptin signaling in the lung epithelium and macrophages. PLoS One[Internet]. 2014;9. [cited May 19, 2020]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4169489/.

96. Maurya R, Bhattacharya P, Dey R, Nakhasi HL. Leptin functions in infectious diseases. Front Immunol[Internet]. 2018;9. [cited May 19, 2020]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6275238/.

97. Beck MA, Handy J, Levander OA. Host nutritional status: the neglected virulence factor. Trends Microbiol[Internet]. 2004;12:417–23. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15337163.

98. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet North Am Ed[Internet]. 2020;395:497–506. [cited May 20, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31986264.

99. D'Amico F, Baumgart DC, Danese S, Peyrin-Biroulet L. Diarrhea during COVID-19 infection: pathogenesis, epidemiology, prevention and management. Clin Gastroenterol Hepatol[Internet]. 2020. [cited Apr 29, 2020]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7141637/.

100. Mobarhan S, DeMeo M. Diarrhea induced by enteral feeding. Nutr Rev[Internet]. 2009;53:67–70. [cited Aug 4, 2020]. Available from: https://academic.oup.com/nutritionreviews/article-lookup/doi/10.1111/j.1753-4887.1995.tb01504.x.

101. Lee JSW, Auyeung TW. A comparison of two feeding methods in the alleviation of diarrhoea in older tube-fed patients: a randomised controlled trial. Age Ageing[Internet]. 2003;32:388–93. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12851181.

102. Graf CE, Pichard C, Herrmann FR, Sieber CC, Zekry D, Genton L. Prevalence of low muscle mass according to body mass index in older adults. Nutrition[Internet]. 2017;34:124–9. [cited 2020 Apr 29]. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0899900716302234.

103. Kunz R, Minder M. COVID-19 pandemic: palliative care for elderly and frail patients at home and in residential and nursing homes. Swiss Med Wkly[Internet]. 2020;150:w20235. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32208497.

104. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun[Internet]. 2020;109:102433. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32113704.

105. Pawelec G. Age and immunity: what is "immunosenescence"? Exp Gerontol[Internet]. 2018;105:4–9. [cited Aug 9, 2020]. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0531556517306599?via%3Dihub.

106. Ventura MT, Casciaro M, Gangemi S, Buquicchio R. Immunosenescence in aging: between immune cells depletion and cytokines up-regulation. Clin Mol Allergy[Internet]. 2017;15:21. [cited Aug 9, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29259496.

107. Montecino-Rodriguez E, Berent-Maoz B, Dorshkind K. Causes, consequences, and reversal of immune system aging. J Clin Invest[Internet]. 2013;123:958–65. [cited Aug 9, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23454758.

108. Goronzy JJ, Weyand CM. Aging, autoimmunity and arthritis: T-cell senescence and contraction of T-cell repertoire diversity—catalysts of autoimmunity and chronic inflammation. Arthritis Res Ther[Internet]. 2003;5:225–34. [cited Aug 9, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12932282.

109. Trzonkowski P, Szmit E, Myśliwska J, Myśliwski A. CD4+CD25+ T regulatory cells inhibit cytotoxic activity of CTL and NK cells in humans-impact of immunosenescence. Clin Immunol[Internet]. 2006;119:307–16. [cited Aug 6, 2020]. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1521-6616(06)00049-0.

110. Fulop T, Larbi A, Dupuis G, Le Page A, Frost EH, Cohen AA, Witkowski JM, Franceschi C. Immunosenescence and inflamm-aging as two sides of the same coin: friends or foes? Front Immunol[Internet]. 2018;8:1960. [cited Aug 9, 2020]. Available from: http://journal.frontiersin.org/article/10.3389/fimmu.2017.01960/full.

111. Crooke SN, Ovsyannikova IG, Poland GA, Kennedy RB. Immunosenescence and human vaccine immune responses. Immun Ageing[Internet]. 2019;16:25. [cited Aug 9, 2020]. Available from: https://immunityageing.biomedcentral.com/articles/10.1186/s12979-019-0164-9.

112. Heijl I, Schweitzer VA, Zhang L, Linden PD , Werkhoven CH, Postma DF. Inappropriate use of antimicrobials for lower respiratory tract infections in elderly patients: patient- and community-related implications and possible interventions. Drugs Aging [Internet]. 2018;35:389–98. [cited Aug 5, 2020]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5956067/.

113. Dang TT, Majumdar SR, Marrie TJ, Eurich DT. Recurrent pneumonia: a review with focus on clinical epidemiology and modifiable risk factors in elderly patients. Drugs Aging [Internet]. 2015;32:13–9. [cited Aug 4, 2020]. Available from: https://pubmed.ncbi.nlm.nih.gov/25491559/.

114. Millett ERC, Quint JK, Smeeth L, Daniel RM, Thomas SL. Incidence of community-acquired lower respiratory tract infections and pneumonia among older adults in the United Kingdom: a population-based study. PLoS One[Internet]. 2013;8:e75131. [cited Aug 5, 2020]. Available from: https://pubmed.ncbi.nlm.nih.gov/24040394/.

115. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis[Internet]. 2012;12:36–44. [cited Aug 5, 2020]. Available from: https://pubmed.ncbi.nlm.nih.gov/22032844/.

116. Thomas RE, Jefferson T, Lasserson TJ. Influenza vaccination for healthcare workers who care for people aged 60 or older living in long-term care institutions. Cochrane Database Syst Rev[Internet]. 2016;2:CD005187. [cited Aug 4, 2020]. Available from: https://pubmed.ncbi.nlm.nih.gov/27251461/.

117. Jefferson T, Di P C, Al-Ansary LA, Ferroni E, Thorning S, Thomas RE. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev[Internet]. 2010;17:CD004876. [cited Aug 4, 2020]. Available from: https://doi.org/10.1002/14651858.CD004876.pub3.

118. Ciabattini A, Nardini C, Santoro F, Garagnani P, Franceschi C, Medaglini D. Vaccination in the elderly: the challenge of immune changes with aging. Semin Immunol[Internet]. 2018;40:83–94. [cited Aug 9, 2020]. Available from: https://pubmed.ncbi.nlm.nih.gov/30501873/.

119. Oh S-J, Lee JK, Shin OS. Aging and the immune system: the impact of immunosenescence on viral infection, immunity and vaccine immunogenicity. Immune Netw[Internet]. 2019;19:e37. [cited Aug 9, 2020]. Available from: https://pubmed.ncbi.nlm.nih.gov/31921467/.

120. Goronzy JJ, Fulbright JW, Crowson CS, Poland GA, O'Fallon WM, Weyand CM. Value of immunological markers in predicting responsiveness to influenza vaccination in elderly individuals. J Virol[Internet]. 2001;75:12182–7. [cited Aug 4, 2020]. Available from: https://pubmed.ncbi.nlm.nih.gov/11711609/.

121. Gibson KL, Wu Y-C, Barnett Y, Duggan O, Vaughan R, Kondeatis E, Nilsson B-O, Wikby A, Kipling D, Dunn-Walters DK. B-cell diversity decreases in old age and is correlated with poor health status. Aging Cell[Internet]. 2009;8:18–25. [cited Aug 4, 2020]. Available from: https://pubmed.ncbi.nlm.nih.gov/18986373/.

122. de Morais C, Oliveira B, Afonso C, Lumbers M, Raats M, de Almeida MDV. Nutritional risk of European elderly. Eur J Clin Nutr[Internet]. 2013;67:1215–9. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/24065060.

123. Mehta S. Nutritional status and COVID-19: an opportunity for lasting change? Clin Med[Internet]. 2020;20:270–3. [cited May 18, 2020]. Available from: https://www.rcpjournals.org/content/clinmedicine/20/3/270.

124. Li T, Zhang Y, Gong C, Wang J, Liu B, Shi L, Duan J. Prevalence of malnutrition and analysis of related factors in elderly patients with COVID-19 in Wuhan, China. Eur J Clin Nutr[Internet]. 2020;1–5. [cited 2020 Apr 27]. Available from: http://www.nature.com/articles/s41430-020-0642-3.

125. Jia H. Pulmonary angiotensin-converting enzyme 2 (ACE2) and inflammatory lung disease. Shock[Internet]. 2016;46:239–48. [cited Apr 27, 2020]. Available from: https://insights.ovid.com/?an=00024382-201609000-00003.

126. Ohwada H, Nakayama T, Kanaya Y, Tanaka Y. Serum albumin levels and their correlates among individuals with motor disorders at five institutions in Japan. Nutr Res Pract[Internet]. 2017;11:57. [cited Apr 27, 2020]. Available from: https://synapse.koreamed.org/DOIx.php?id=10.4162/nrp.2017.11.1.57.

127. Maeda K, Akagi J. Muscle mass loss is a potential predictor of 90-day mortality in older adults with aspiration pneumonia. J Am Geriatr Soc[Internet]. 2017;65:e18–22. [cited Jun 1, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27858956.

128. Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, Pirlich M, Singer P. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. Clin Nutr[Internet]. [cited May 20, 2020]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7138149/.

129. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing[Internet]. 2019;48:16–31. [cited Jun 1, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30312372.

130. Cesari M, Kritchevsky SB, Baumgartner RN, Atkinson HH, Penninx B, Lenchik L, Palla SL, Ambrosius WT, Tracy RP, Pahor M. Sarcopenia, obesity, and inflammation—results from the Trial of Angiotensin Converting Enzyme Inhibition and Novel Cardiovascular Risk Factors Study. Am J Clin Nutr[Internet]. 2005;82:428–34. [cited Jun 2, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16087989.

131. Visser M, Pahor M, Taaffe DR, Goodpaster BH, Simonsick EM, Newman AB, Nevitt M, Harris TB. Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: the Health ABC Study. J Gerontol A Biol Sci Med Sci[Internet]. 2002;57:M326–32. [cited Jun 2, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11983728.

132. Anker SD, Coats AJS, Morley JE, Rosano G, Bernabei R, von Haehling S, Kalantar-Zadeh K. Muscle wasting disease: a proposal for a new disease classification. J Cachexia Sarcopenia Muscle[Internet]. 2014;5:1–3. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24595459.

133. Laviano A, Koverech A, Zanetti M. Nutrition support in the time of SARS-CoV-2 (COVID-19). Nutrition[Internet]. 2020;74:110834. [cited Aug 4, 2020]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7132492/.

134. Kalinkovich A, Livshits G. Sarcopenic obesity or obese sarcopenia: a cross talk between age-associated adipose tissue and skeletal muscle inflammation as a main mechanism of the pathogenesis. Ageing Res Rev[Internet]. 2017;35:200–21. [cited Aug 4, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27702700.

135. Prado CMM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, Baracos VE. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol[Internet]. 2008;9:629–35. [cited Jun 1, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18539529.

136. Reisinger KW, van Vugt JLA, Tegels JJW, Snijders C, Hulsewé KWE, Hoofwijk AGM, Stoot JH, Von Meyenfeldt MF, Beets GL, Derikx JPM, et al. Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. Ann Surg[Internet]. 2015;261:345–52. [cited Jun 1, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24651133.

137. de Hoogt PA, Reisinger KW, Tegels JJW, Bosmans J, Tijssen F, Stoot J. Functional Compromise Cohort Study (FCCS): sarcopenia is a strong predictor of mortality in the intensive care unit. World J Surg[Internet]. 2018;42:1733–41. [cited Jun 1, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29285609.

138. Rubio-Ruiz ME, Guarner-Lans V, Pérez-Torres I, Soto ME. Mechanisms underlying metabolic syndrome-related sarcopenia and possible therapeutic measures. Int J Mol Sci[Internet]. 2019;20. [cited Jun 1, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30717377.

139. Pieńkowska J, Brzeska B, Kaszubowski M, Kozak O, Jankowska A, Szurowska E. MRI assessment of ectopic fat accumulation in pancreas, liver and skeletal muscle in patients with obesity, overweight and normal BMI in correlation with the presence of central obesity and metabolic syndrom e. DMSO[Internet]. 2019;12:623–36. [cited May 1, 2020]. Available from: https://pubmed.ncbi.nlm.nih.gov/31118724/.

140. Parry SM, Puthucheary ZA. The impact of extended bed rest on the musculoskeletal system in the critical care environment. Extrem Physiol Med[Internet]. 2015;4:16. [cited Jun 1, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26457181.

141. Lewnard JA, Liu VX, Jackson ML, Schmidt MA, Jewell BL, Flores JP, Jentz C, Northrup GR, Mahmud A, Reingold AL, et al. Incidence, clinical outcomes, and transmission dynamics of severe coronavirus disease 2019 in California and Washington: prospective cohort study. BMJ[Internet]. 2020;369:m1923. [cited Jun 1, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32444358.

142. Krznaric Ž, BBender DV, Laviano A, Cuerda C, Landi F, Monteiro R, Pirlich M, Barazzoni R. A simple remote nutritional screening tool and practical guidance for nutritional care in primary practice during the COVID-19 pandemic. Clin Nutr[Internet]. 2020.[cited Jun 1, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32425292.

143. Biolo G, Cederholm T, Muscaritoli M. Muscle contractile and metabolic dysfunction is a common feature of sarcopenia of aging and chronic diseases: from sarcopenic obesity to cachexia. Clin Nutr[Internet]. 2014;33:737–48. [cited Jun 1, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24785098.

144. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, Compher C, Correia I, Higashiguchi T, Holst M, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr[Internet]. 2017;36:49–64. [cited Jun 1, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27642056.

145. Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, Baptista G, Barazzoni R, Blaauw R, Coats A, et al. GLIM criteria for the diagnosis of malnutrition—a consensus report from the global clinical nutrition community. Clin Nutr[Internet]. 2019;38:1–9. [cited Jun 1, 2020]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30181091.