Original article

Obesity and COVID-19 in children and adolescents: a double pandemic

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Abstract. *Background and aim of the study.* The high prevalence of obesity and obesity-related comorbidities has reached pandemic proportions, particularly in Western countries. It has been recently recognized as a significant risk factor in severe cases of COVID-19 in children and adolescents. Here, we summarize the existing knowledge regarding the pathophysiology of COVID-19 and consider how its various components may be exacerbated by the presence of obesity to investigate the impact of obesity on disease severity among patients with COVID-19 and collaborate for better clinical care of these patients. *Methods.* The literature search was conducted from March 2020 to January 2022. A review of articles was performed via the online database PubMed, combining the terms "obesity," "weight gain," "COVID-19", "children." *Results*. Excessive adipose tissue, insulin resistance, dyslipidemia, hypertension, high levels of proinflammatory cytokines are factors that compromise the functioning of organs and systems in obese patients. In obese patients with COVID-19 these changes can increase the risk of death, need for ventilatory assistance, risk of thromboembolism, and perpetuation of inflammatory response. *Conclusions.* Obesity increases the risk for hospitalization, intensive care admission, mechanic ventilation requirement, and death among children and adolescents with COVID-19. These findings emphasize the need for effective actions by health professionals to increase awareness of the risks resulting from obesity and how these are heightened in the current global pandemic. (www.actabiomedica.it)

Key words: SARS-CoV-2 infection; Coronavirus disease-19 (COVID-19); Obesity; Children; Adolescents

Introduction

Since 2020 two pandemics have collided: the obesity pandemic, a chronic non-communicable disease, and the other hand, coronavirus disease 2019 (COVID-19) pandemic, characterized by severe pneumonia and substantial mortality and morbidity (1). Although most pediatric patients often experience mild symptoms, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is known to induce a rare but severe clinical manifestation, such as the multisystem inflammatory syndrome in children (MIS-C) (2-4). Children with comorbidities, such as chronic kidney and respiratory diseases, malignancies, diabetes, obesity, sickle cell anemia, immune disorders, chromosomal abnormalities, heart disease, and congenital malformations, are more likely to develop a severe form of COVID-19 (4-10). Recently, obesity has been recognized as a significant risk factor for coronavirus disease-related prognosis, contributing to worse outcomes in those with established COVID-19. Notably, emerging evidence suggests that people with obesity are associated with higher hospitalization rates in acute or intensive care units and a greater risk for invasive mechanical ventilation (IMV). However, the mechanisms underlying this association are poorly understood (11,12).

The present article aims to discuss how obesity might increase the risk of COVID-19, potentially affect its prognosis and its health consequences, and collaborate for pediatric patients' better clinical care.

Material and Methods

The literature search was conducted from March 2020 to January 2022. A review of articles was performed via the online database PubMed, combining the terms "obesity," "weight gain," "COVID-19", "children ." All articles that examined obesity or weight gain in children, adolescents, and young adults during the COVID-19 pandemic were considered eligible.

SARS-CoV-2 infection in children and adolescents

COVID-19 equally affects children and adults. The current incidence of COVID-19 among Italian children and adolescents is about 2-3% of confirmed cases (https://www.iss.it/documents/20126/0/csAggiornamento+EPI+e+valutazione+del+rischio_9+febbraio_2022.pdf/03a630de-5dd4-d992-c97b-fbc739d81ae7?t=1644598330553), with an extremely low mortality rate. Most children and adolescents affected by COVID-19 have mild to moderate symptoms, with a significant percentage of asymptomatic patients (13). A small percentage of children with severe symptoms require intensive care (14-15). The most common symptoms of SARS-CoV-2 infection among children and adolescents are cough, fever, sore throat, sneezing, myalgia, wheezing, fatigue, rhinorrhea, and nasal obstruction. Gastrointestinal symptoms, like diarrhea and vomiting, can also be observed. Hypoxia and dyspnea are uncommon findings (13-14). The reasons for the lower severity of COVID-19 in the pediatric age group remain unanswered, but some hypotheses have been raised. The less exposure to SARS-CoV-2 due to social isolation and school closures, lower frequency of comorbidities and tobacco smoke exposure, and a greater capacity for pulmonary regeneration are considered the most probable explanations of the clinical heterogeneity of COVID-19 according to age (15-16). Besides, children have a lover of angiotensin-converting enzyme 2 (ACE-2) expression than adults, making the process of internalizing the virus less efficient. Finally, they have more effective trained innate immunity, an immune response of medium duration, due to increased exposure to viruses and vaccines (15-16).

Pathophysiology of obesity and its relationship with COVID-19

Obesity is a chronic disease resulting from a breakdown of the body energy regulatory system (ERS), impacted by genetic, environmental, and psychosocial factors. Currently, obesity affects over 337 million children globally, of whom 213 million are overweight, and 124 million are obese and severely obese. The adipose tissue is an active endocrine organ that plays a critical role in maintaining energy balance (17). When excessive nutrients enter the adipocyte, a cellular stress response initiates, resulting in a sustained increase in cortisol production and chronic inflammation. This phenomenon is marked by the over-expression of inflammatory mediators and decreased adiponectin (an anti-inflammatory adipokine) production (18). Unchecked, chronic inflammation leads to ERS dysfunction manifesting as cardiovascular disease, metabolic abnormalities, immunodepression, and other metabolic conditions, all main risk factors that link obesity to COVID-19. The inflammation resulting from obesity combined with the COVID-19 hyperinflammation and a weakened immune response increases the risk of developing sepsis and organ failure (19). These mechanisms include several aspects related to obesity itself and its comorbidities (20). It should be emphasized that the risks may be present even in the mildest cases of obesity. Figure 1 shows the relationship between these two pandemics.

Insulin resistance and dyslipidemia

An increase in circulating insulin levels in both fasting and postprandial states is one of the earliest metabolic disturbances associated with obesity, and it is due to impaired insulin action, principally in the liver and skeletal muscle (21). The entire pathophysiological process leads to several health repercussions, such as dyslipidemia, arterial hypertension, non-alcoholic stea-

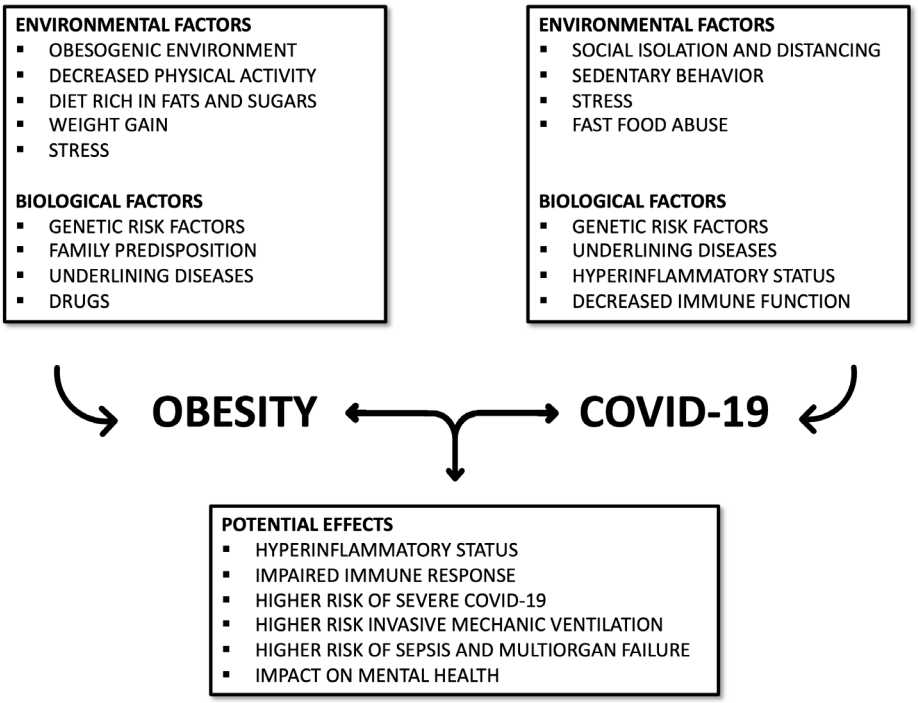

Figure 1. Relationships between obesity and COVID-19 and their potential effects on patient's health.

tohepatitis, micronutrients deficiencies, increased oxidative stress, and hyperuricemia. In situations of intense metabolic activity, such as during immune response to SARS-CoV-2 infection, pancreatic beta cells produce a high amount of insulin, which may not be achieved when they are already working at their limit. It was also reported that SARS-CoV-2 could infect and kill the pancreatic beta cells through the interaction with the ACE-2 receptor, further aggravating this process (22). In addition, insulin resistance leads to a reduction in phosphoinositide 3-kinase, impairing nitric oxide's protective and anti-inflammatory effects (23).

In addition, dyslipidemia is highly prevalent among obese children and adolescents. Low concentrations of high-density lipoprotein (HDL) cholesterol and increased low-density lipoprotein (LDL) cholesterol levels are proven risk factors of progressive endothelial dysfunction and atherosclerosis (24). Insulin resistance is one of the critical links between obesity and poor COVID-19 outcomes. Therefore, even short-term low-calorie diets combined with physical activity could be essential to improve insulin sensitivity within days and provide a way of reducing the risk of death for a large number of obese individuals (24).

Respiratory and cardiovascular systems

Normal respiratory physiology is usually impaired in obese patients (25). As the lung is one of the main targets and leads to more significant risks for patients with COVID-19, this aspect must always be considered. The hematosis (blood oxygenation) is generally impaired in obese patients and worsens when the exchange areas are reduced because of viral interstitial pneumonia (26). The pressure exerted by abdominal adiposity on the lungs through the diaphragm also limits the movement of respiratory muscles, with less oxygen saturation and worsening clinical presentation due to the lower lung volume of obese patients. In addition, some comorbidities linked to obesity may contribute to a higher risk of lung infections, such as asthma, which is highly prevalent among obese children. Finally, obese children have a low exercise tolerance, which closes this vicious circle (27-29). The critical functional unit of the lung is the alveolar-capillary unit. Pivotal cells include type 1 pneumocytes (AT1) separated from capillary endothelial cells by a fused basement membrane and type 2 pneumocytes (AT2) that produce surfactant and serve as alveolar progeni-

tors. ACE2 is the receptor of SARS-CoV-2 and is expressed predominantly by AT2 in the alveolus (30). Obesity may affect the integrity of the alveolus. Recent studies suggested that in states of overnutrition, the ectopic lipid can appear in cells of the pulmonary alveolus, resulting in ultrastructural abnormalities and altered surfactant production (31). The "fatty lung" could be a common causal pathway where obesity worsens COVID-19 pathology.

Cardiac anatomy changes linked are recognized even in very young obese children, in whom hypertrophy of the left ventricle (related to the degree of obesity and blood pressure) is observed, among other structural changes (32). Obese children and adolescents have higher blood pressure levels, which increases potential endothelial injury, one of the bases of COVID-19 pathophysiology (33). Hypertensive children treated with antihypertensive drugs that inhibit angiotensin-converting enzymes or block angiotensin receptors have increased expression of ACE-2 receptors, increasing their susceptibility to coronavirus infection. The intima layer of arteries is thickened in obese children, foreshadowing the onset of atherosclerosis, which occurs very early (34). Hardening of the arteries, associated with impaired nitrogen performance and chronic oxidative stress, has been implicated in changes linked to the severity of COVID-19, such as inflammation of endothelium, myocarditis, multiple organ failure, severe acute respiratory syndrome, and venous thromboembolism (23). Leptin, usually elevated among obese people, damages endothelium leading to less nitric oxide production and increased expression of monocyte chemoattractant protein 1, contributing to the inflammatory infiltrate in vascular cells (23). Perivascular adipose tissue contributes to vasoconstriction and endothelial dysfunction through the production of inflammatory mediators, oxidative stress, and reduction in nitric oxide production (23).

Coagulation

Obese people, including children and adolescents, with COVID-19, are at increased risk of developing coagulopathy associated with poor clinical outcomes. Chronic inflammation leads to negative regulation of anticoagulant proteins (tissue factor pathway inhibitor, antithrombin, and the protein C anticoagulation system). However, this leads to positive regulation of procoagulant factors and adhesion molecules (P-selectin), in addition to increases in thrombin generation and enhanced platelet activation, increasing the risk of thrombosis. Venous thromboembolism rates are much higher in severe COVID-19 and obesity (23, 35).

Chronic inflammation and immune system

One of the most relevant aspects for understanding the severity of COVID-19 among obese patients is related to inflammatory issues (36). Obese patients have chronic subclinical inflammation, characterized by a permanent inflammatory state, which can start early. It is believed that this process is due to cytokines, particularly adipokines with inflammatory properties, produced by adipose tissue (22) and the drop in adiponectin, which has anti-inflammatory properties (37). In adipose tissue biopsies from obese, insulin-resistant people, one frequently sees an excess of dead and dying adipocytes, often accompanied by an excess of infiltrating macrophages. These are activated and contribute to the production of a systemic proinflammatory state, characterized by increases in circulating levels of cytokines, such as tumor necrosis factor a (TNFa), IL-6, and IL-1b (37,38). In obesity, macrophages cells constitute about 40% - 60% of immune cells derived from visceral adipose tissue (39). Lipotoxic damage to other cells such as hepatocytes can also contribute to the enhanced inflammatory state. Adipose tissue expansion in obesity results in the elaboration of inflammatory cytokines and changes the profile of secreted hormones. It is associated with higher circulating leptin and lower circulating adiponectin.

Some evidence associates high leptin levels with pulmonary inflammation, but this is not compelling (40). There is, however, a growing body of evidence more securely implicating adiponectin as an anti-inflammatory agent (41). Hypoadiponectinemia frequently seen in obesity could facilitate an exaggerated inflammatory response directed to pulmonary capillaries. Adipocytes are also a significant source of several of the components of the complement system. Levels of some complement components (C3, C3a, CFD, properdin) increase with the rising adiposity. Circulating levels of C3 are posi-

tively associated with insulin resistance, independently from adiposity status (42 - 46). Given the existence of amplification loops in the complement pathway, it is conceivable that modest elevations of complement components in obesity could serve as a nidus for microthrombosis and pathological inflammation (44). In COVID-19, the imbalance of the immune system observed in obesity may contribute to a worse clinical outcome evolving into an intense and severe systemic inflammatory reaction called "cytokine storm" (47).

Psychosocial impact of COVID-19 on childhood obesity

The COVID-19 pandemic introduced potentially traumatic events into everyone's lives, especially in children (48,49). The pandemic has led to socioeconomic changes that may impact childhood obesity. These stress triggers favor activating our body's stress response system, leading to chronic health issues, including obesity (50). According to several studies, children, adolescents, and young adults have increased their food intake, gained weight, and increased consumption of fried foods, sweets, sugar-added drinks, and dairy products during the lockdown period (51-53). Worse family financial status was associated with more weight gain. The restrictions imposed by lockdown include social distancing and reducing physical activity out of the house. Parents reported that children physical activity decreased, whereas sedentary behavior increased (54). As COVID-19 spread globally, many countries employed school closure as a part of their social distancing policies. School closure affected children and their ability to maintain a healthy weight in many ways, including the exacerbation of food insecurity, change in availability of healthy foods in physical activity, regression in academic progress (55). Isolation from peers and disruption of everyday routines may also affect children's mental health and wellbeing. COVID-19 restrictions disrupted the everyday routine of children, adolescents, and young adults and elicited changes in their eating behaviors and physical activity (Table 1). To protect them, health care providers should highlight the risk of obesity and provide preventive strategies, also ensuring parental participation. Worldwide policies, guidelines, and precautionary measures should ideally be established (56).

Table 1. Common sources of stress that may exacerbate childhood obesity

Source of stress
• Quarantine for COVID-19
• Lockdown measures and social isolation
• School closure
• Imposed lifestyle changes
• Parental stress
• Less group activities
• Increased junk food consuption
• Reduced physical activity

Conclusion

Childhood obesity and COVID-19 are global pandemics. The clashing of the two diseases and subsequent changes in the bioecological environment have placed children and adolescents at increased risk of developing obesity and exacerbating its severity. Obesity is a risk factor for a greater susceptibility and severity of COVID-19 and is associated with nutritional, cardiac, respiratory, and immunological alterations, which may potentiate the complications of SARS-CoV-2 infection. The impact of stress on both diseases, characterized by inflammation and weakened immune response, and exacerbated by disparities, affects health, economic, and social outcomes. The need for social isolation can have the effect of causing or worsening obesity and its comorbidities, and pediatricians need to be aware of this issue. As the pandemic is still ongoing, to protect the age mentioned above groups, health care providers should highlight the risk of obesity and provide prevention strategies, with a systematic assessment of their health and biopsychosocial needs that is critical to reducing the negative impact of obesity and COVID-19.

Conflict of Interest: Authors declare that they do not have any commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article

References

1. Cava E, Neri B, Carbonelli MG, et al. Obesity pandemic during COVID-19 outbreak: Narrative review and future considerations. Clin Nutr. 2021; 40(4):1637-43.
2. Brambilla I, Castagnoli R, Caimmi S, et al. COVID-19

in the Pediatric Population Admitted to a Tertiary Referral Hospital in Northern Italy: Preliminary Clinical Data. Pediatr Infect Dis J. 2020;39(7):e160.
3. Manti S, Licari A, Montagna L, et al. SARS-CoV-2 infection in pediatric population. Acta Biomed. 2020;91(11-S):e2020003.
4. Preston LE, Chevinsky JR, Kompaniyets L, et al. Characteristics and Disease Severity of US Children and Adolescents Diagnosed With COVID-19. Jama Netw Open. 2021;4(4): e215298.
5. Gotzinger F, Santiago-Garcia B, Noguera-Julian A, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health. 2020; 4(9):653-61.
6. Cianferoni A, Votto M. COVID-19 and allergy: How to take care of allergic patients during a pandemic? Pediatr Allergy Immunol. 2020;31 Suppl 26(Suppl 26):96-101.
7. Oualha M, Bendavid M, Berteloot L, et al. Severe and fatal forms of COVID-19 in children. Arch Pediatr. 2020; 27(5):235-8.
8. Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. JAMA Pediatr. 2020; 174(9):868-73.
9. Licari A, Votto M, Brambilla I, et al. Allergy and asthma in children and adolescents during the COVID outbreak: What we know and how we could prevent allergy and asthma flares. Allergy. 2020;75(9):2402-5.
10. De Filippo M, Votto M, Brambilla I, et al. Allergy and COVID-19. Acta Biomed. 2021;92(S7):e2021522.
11. Lockhart SM, O'Rahilly S. When Two Pandemics Meet: Why Is Obesity Associated with Increased COVID-19 Mortality? Med (NY). 2020;1(1):33-42.
12. Brambilla I, Tosca MA, De Filippo M, et al. Special Issues for Coronavirus Disease 2019 in Children and Adolescents. Obesity (Silver Spring). 2020;28(8):1369.
13. Castagnoli R, Votto M, Licari A, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review. JAMA Pediatr. 2020;174(9):882-9.
14. Zimmermann P, Curtis N. COVID-19 in Children, Pregnancy and Neonates: A Review of Epidemiologic and Clinical Features. Pediatr Infect Dis J. 2020;39(6):469-77.
15. Mantovani A, Rinaldi E, Zusi C, et al. Coronavirus disease 2019 (COVID-19) in children and/or adolescents: a meta-analysis. Pediatr Res. 2021;89(4):733-7.
16. Balasubramanian S, Rao NM, Goenka A, et al. Coronavirus Disease 2019 (COVID-19) in Children - What We Know So Far and What We Do Not. Indian Pediatr. 2020;57(5):435-42.
17. Dhochak N, Singhal T, Kabra SK, et al. Pathophysiology of COVID-19: Why Children Fare Better than Adults? Indian J Pediatr. 2020;87(7):537-46.
18. Reilly SM, Saltiel AR. Adapting to obesity with adipose tissue inflammation. Nat Rev Endocrinol. 2017;13(11):633-43.
19. Ellulu MS, Patimah I, Khaza'ai H, et al. Obesity and inflammation: the linking mechanism and the complications. Arch Med Sci. 2017;13(4):851-63.
20. Frydrych LM, Bian G, O'Lone DE, et al. Obesity and type 2 diabetes mellitus drive immune dysfunction, infection development, and sepsis mortality. J Leukoc Biol. 2018;104(3):525-34.
21. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988;37(12):1595-607.
22. Sattar N, McInnes IB, McMurray JJ. Obesity is a risk factor for severe COVID-19 infection: multiple potential mechanisms. Circulation. 2020;142(1):4-6.
23. Korakas E, Ikonomidis I, Kousathana F, et al. Obesity and COVID-19: immune and metabolic derangement as a possible link to adverse clinical outcomes. Am J Physiol Endocrinol Metab. 2020; 319(1):E105-9.
24. Bendor CD, Bardugo A, Pinhas-Hamiel O, et al. Cardiovascular morbidity, diabetes and cancer risk among children and adolescents with severe obesity. Cardiovasc Diabetol. 2020; 19(1):79.
25. Kirk E, Reeds DN, Finck BN, et al. Dietary fat and carbohydrates differentially alter insulin sensitivity during caloric restriction. Gastroenterology. 2009;136(5):1552-60.
26. Köchli S, Endes K, Bartenstein T, et al. Lung function, obesity and physical fitness in young children: The EXAMIN YOUTH study. Respir Med. 2019;159:105813.
27. Umbrello M, Fumagalli J, Pesenti A, et al. Pathophysiology and Management of Acute Respiratory Distress Syndrome in Obese Patients. Semin Respir Crit Care Med. 2019;40(1):40-56.
28. Fearnbach SN, Johannsen NM, Martin CK, et al. A pilot study of cardiorespiratory fitness, adiposity, and cardiometabolic health in youth with overweight and obesity. Pediatr Exerc Sci. 2020; 32(3):124-31.
29. Rychter AM, Zawada A, Ratajczak AE, et al. Should patients with obesity be more afraid of COVID-19? Obes Rev. 2020; 21(9):e13083.
30. De A, Rastogi D. Association of pediatric obesity and asthma, pulmonary physiology, metabolic dysregulation, and atopy; and the role of weight management. Expert Rev Endocrinol Metab. 2019; 14(5):335-49.
31. He L, Mäe MA, Muhl L, et al. Pericyte-specific vascular expression of SARS-CoV-2 receptor ACE2 – implications for microvascular inflammation and hypercoagulopathy in COVID-19. bioRxiv; 2020. doi: 10.1101/2020.05.11.088500.
32. Foster DJ, Ravikumar P, Bellotto DJ, et al. Fatty diabetic lung: altered alveolar structure and surfactant protein expression. Am J Physiol Lung Cell Mol Physiol. 2010;298(3):L392-403.
33. Lo MH, Lin IC, Lu PC, et al. Evaluation of endothelial dysfunction, endothelial plasma markers, and traditional metabolic parameters in children with adiposity. J Formos Med Assoc. 2019;118(1):83-91.
34. Kassir R. Risk of COVID-19 for patients with obesity.

Obes Rev. 2020; 21(6):e13034.
35. Nogueira-de-Almeida CA, Ciampo LA, Ferraz IS, et al. COVID-19 and obesity in childhood and adolescence: a clinical review. J Pediatr (Rio J). 2020; 96(5):546-58
36. Belančić A, Kresović A, Rački V. Potential pathophysiological mechanisms leading to increased COVID-19 susceptibility and severity in obesity. Obes Med. 2020;19:100259.
37. Luzi L, Radaelli MG. Influenza and obesity: its odd relationship and the lessons for COVID-19 pandemic. Acta Diabetol. 2020; 57(6):759-64.
38. Marques-Vidal P, Bastardot F, von Känel R, et al. Association between circulating cytokine levels, diabetes and insulin resistance in a population-based sample (CoLaus study). Clin Endocrinol (Oxf). 2013;78(2):232-41.
39. Um JY, Chung HS, Song MY, et al. Association of interleukin-1beta gene polymorphism with body mass index in women. Clin Chem. 2004;50(3):647-50.
40. Umano GR, Pistone C, Tondina E, et al. Pediatric Obesity and the Immune System. Front Pediatr. 2019;7:487.
41. Foster DJ, Ravikumar P, Bellotto DJ, et al. Fatty diabetic lung: altered alveolar structure and surfactant protein expression. Am J Physiol Lung Cell Mol Physiol. 2010;298(3):L392-403.
42. Scherer PE. The many secret lives of adipocytes: implications for diabetes. Diabetologia. 2019;62(2):223-32.
43. Vlaicu SI, Tatomir A, Boodhoo D, et al. The role of complement system in adipose tissue-related inflammation. Immunol Res. 2016;64(3):653-64.
44. Xin Y, Hertle E, van der Kallen CJH, et al. Longitudinal associations of the alternative and terminal pathways of complement activation with adiposity: The CODAM study. Obes Res Clin Pract. 2018;12(3):286-92.
45. Wlazlo N, van Greevenbroek MM, Ferreira I, et al. Complement factor 3 is associated with insulin resistance and with incident type 2 diabetes over a 7-year follow-up period: the CODAM Study. Diabetes Care. 2014;37(7):1900-9.
46. Gavriilaki E, Brodsky RA. Severe COVID-19 infection and thrombotic microangiopathy: success does not come easily. Br J Haematol. 2020;189(6):e227-30.
47. Kim J, Nam JH. Insight into the relationship between obesity-induced low-level chronic inflammation and COVID-19 infection. Int J Obes (Lond). 2020; 44(7):1541-2.
48. Fegert JM, Vitiello B, Plener PL, et al. Challenges and burden of the Coronavirus 2019 (COVID-19) pandemic for child and adolescent mental health: a narrative review to highlight clinical and research needs in the acute phase and the long return to normality. Child Adolesc Psychiatry Ment Health. 2020;14:20.
49. Votto M, De Filippo M; Pediatric Residents of the University of Pavia, Italy. How pediatric resident's life has changed during the COVID-19 pandemic. Ital J Pediatr. 2020;46(1):156.
50. Condon EM, Sadler LS, Mayes LC. Toxic stress and protective factors in multi-ethnic school age children: A research protocol. Res Nurs Health. 2018;41(2):97-106.
51. Adams EL, Caccavale LJ, Smith D, et al. Food Insecurity, the Home Food Environment, and Parent Feeding Practices in the Era of COVID-19. Obesity (Silver Spring). 2020;28(11):2056-63.
52. An R. Projecting the impact of the coronavirus disease-2019 pandemic on childhood obesity in the United States: A microsimulation model. J Sport Health Sci. 2020;9(4):302-12.
53. Buzzi C, Tucci M, Ciprandi R, et al. The psycho-social effects of COVID-19 on Italian adolescents' attitudes and behaviors. Ital J Pediatr. 2020;46(1):69.
54. Dunton GF, Do B, Wang SD. Early effects of the COVID-19 pandemic on physical activity and sedentary behavior in children living in the U.S. BMC Public Health. 2020;20(1):1351.
55. Van Lancker W, Parolin Z. COVID-19, school closures, and child poverty: a social crisis in the making. Lancet Public Health. 2020;5(5):e243-4.
56. Hoffman JA, Miller EA. Addressing the Consequences of School Closure Due to COVID-19 on Children's Physical and Mental Well-Being. World Med Health Policy. 2020 Aug:10.1002/wmh3.365.

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