An Analysis on the Relationship between Obesity and COVID-19 Mortality

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Abstract: Since 2020, obesity and coronavirus disease 2019 (COVID-19) have become two of the most globally challenged health and medical conditions, and the proportion of obese population and numbers of deaths for COVID-19 continue to grow. Obesity has been claimed as a possible risk factor of COVID-19 infection and mortality by the World Health Organization (WHO) and the World Obesity Federation. However, the mechanisms about why obesity worsens COVID-19 symptoms have not been extensively and thoroughly studied. So, literature research was performed in this study to propose the reason for declaring obesity as a risk factor of severe COVID-19 and COVID-19 mortality. In conclusion, obesity induces endoplasmic reticulum (ER) stress and vitamin D deficiency, which causes localized inflammation and impedes the immune responses to SARS-CoV-2 infections. As ER stress state prolongs, unfolded protein response (UPR) and apoptosis may be induced, which give rise to injury of tissues and organs. Although the obese population has increased lung surfactants to balance their increased chest wall restraints, SARS-Cov-2 infections strongly impair lung surfactants and enhance mechanical compression. These elements decrease lung compliance in obese COVID-19 patients; thus, the patients experience difficulties of breathing. Therefore, the susceptibility to the COVID-19 mortality increases. Further research is still needed to test these theoretical ideas and to explore more on relationships between obesity and COVID-19.

1 INTRODUCTION

SARS-CoV-2, a new strain of coronavirus caused COVID-19, has killed over 4 million deaths since the beginning of 2020. Researches on SARS-CoV-2 and COVID-19 are being carried out urgently in many laboratories. It has been discovered that obesity seems to be one of the risk factors for COVID-19 mortality (Cuschieri, and Grech 2020). A meta-analysis based on over three million cases has shown a significant increase in the COVID-19 mortality rate of the obese population (Wang, Xu, Wang, Hou, Feng, and Yang 2021). However, there is very little research studying why obese COVID-19 patients are more susceptible to death. Therefore, this study will discuss the relationship between obesity and COVID-19 mortality. Furthermore, brief descriptions of each potential cause will be outlined respectively. It is acknowledged that these three factors are not the only factors that push obesity as a risk factor of COVID-19 mortality, but this study will pay attention to the theoretical analysis of how these three factors become the main factors resulting in death in obese people. For further research, experiments are needed to confirm the proposed mechanisms and some potential physical activity interventions that could be taken to decrease COVID-19 mortality in the obese population.

Previous researches have shown that both obesity and virus infections induce ER stress in cells (Banerjee, Czinn, Reiter, and Blanchard 2020, Zhou, and Liu 2010). ER usually serves as a protein modifying and secretory site. However, under ER stress, unfolded and misfolded proteins are accumulated in ER, which exceed the normal protein concentration of 100 mg/ml and impede the functions of ER (Wu, and Kaufman 2006). The ER stress will activate unfolded protein response (UPR) to rapidly decrease protein translation rate and initiate ER-associated degradation (ERAD). Therefore, unfolded and misfolded proteins are eliminated and the survival rates of the cells are increased (Sureda, Alizadeh, Nabavi, Berindan-Neagoe, Cismaru, Jeandet, Łos, Clementi, Nabavi, and Ghavami 2020). However, if the condition of ER stress prolongs and the effort of survival fails, apoptosis will be activated

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Table 1. General information of included studies (Wang, Xu, Wang, Hou, Feng, and Yang 2021)

Author	Cases	Obesity (%)	Age (years)	Male (%)	Study type	Country/region	Definition of obesity	Effect size (95% CI)
Klang E*	3406	1231 (36.1)	66 ± 12.2	75.6	Retrospective study	USA	BMI ≥ 30	1.63 (1.0–2.65)
Rottoli M	482	104 (21.6)	66.2 ± 16.8	62.7	Retrospective study	Italy	BMI ≥ 30	2.35 (1.17–4.75)
Antwi-Amoabeng D	172	89 (51.7)	53 (33.5–68)	55.8	Retrospective study	USA	BMI ≥ 30	10.55 (1.07–104.45)
Deiana G	1223	NA	NA	40.8	Retrospective study	Italy	BMI ≥ 30	1.1 (0.4–2.9)
Hashemi N	363	NA	63.34 ± 16.5	55.4	Retrospective study	USA	BMI ≥ 30	1.03 (0.51–2.09)
Pettit NN	238	146 (61.3)	58.5 ± 17	47.5	Retrospective study	USA	BMI ≥ 30	1.7 (1.1–2.8)
Shah P*	522	347 (66.5)	63 (50–72)	41.8	Retrospective study	USA	BMI ≥ 30	1.79 (1.12–2.88)
Aeshad S	2541	1250 (52.3)	63.7 ± 16.5	51.1	Retrospective study	USA	BMI ≥ 30	0.775 (0.624–0.962)
Gupta S*	2215	NA	60.5 ± 14.5	64.8	Multicenter cohort study	USA	BMI ≥ 30	1.2 (0.92–1.56)
Nakeshbandi M	504	215 (43)	68 ± 15	52	Retrospective study	USA	BMI ≥ 30	1.3 (1–1.7)
Hernandez-Galdamez DR	211,003	41,344 (19.59)	45.7 ± 16.3	54.71	Cross-sectional study	Mexico	BMI ≥ 30	1.42 (1.37–1.47)
Berenguer J	4035	497 (13.8)	70 (56–80)	61	Retrospective study	Spain	BMI ≥ 30	1.21 (1.01–1.44)
Almazeedi S	1096	44 (4)	47 ± 31.11	81	Retrospective study	Kuwait	BMI ≥ 30	0.223 (0.033–1.513)
Posso M	834	55 (6.6)	78.2 ± 9.8	46.5	Retrospective study	Spain	BMI ≥ 30	1.21 (0.6–2.45)
Tartof SY*	6916	3171 (45.9)	49.1 ± 16.6	45	Retrospective study	USA	BMI ≥ 30	1.95 (1.09–3.50)
Parra-Bracamonte GM	142,690	28,432 (20)	45 (34.0–57.0)	56	Dataset	Mexico	BMI ≥ 30	1.264 (1.207–1.323)
Yehia BR	7139	2044 (28.6)	68 (56–79)	51.3	Retrospective study	USA	Obesity	0.97 (0.81–1.16)
Ng JH*	10,482	NA	65.38 ± 15.2	59.5	Retrospective study	USA	BMI ≥ 30	1.05 (0.91–1.22)
Czernichow S*	5795	1264 (21.8)	59.7	65.4	Prospective study	France	BMI ≥ 30	2.3 (1.78–2.98)
Nimkar A	327	113 (34.6)	71 (59–82)	55.7	Retrospective study	USA	BMI ≥ 30	1.3 (0.1–14.9)
Biran N	764	276 (36.1)	65.29 ± 14	65.7	Retrospective study	USA	BMI ≥ 30	1.06 (0.85–1.32)
Giorgi Rossi P	2653	65 (2.7)	63.2	50.1	Prospective study	Italy	Obesity	1.3 (0.6–2.9)
Seiglie J	450	191 (42.4)	63.3	57.6	NA	USA	Obesity	1.1 (0.5–2.45)
Fried MW	11,721	1891 (16.1)	62	53.4	Retrospective study	USA	Obesity	1.07 (0.93–1.24)
Mukherjee V	137	104 (77.6)	59.0 (51.0–70.0)	72.3	Retrospective study	USA	BMI ≥ 30	0.7 (0.5–1.2)
Carrillo-Vega MF	9946	2053 (20.82)	48.15 ± 14.35	57.84	Dataset	Mexico	Obesity	1.74 (1.35–2.26)
Morgenthau AS	7337	1993 (27.2)	61.5 ± 18.85	55.2	Retrospective study	USA	Obesity	1.5 (1.3–1.7)
Lauriola M	377	30 (8.0)	71.8 ± 13.4	65.8	Retrospective study	Italy	Obesity	1.329 (0.779–2.268)
Miller J	3633	1758 (51.8)	58.4 ± 18.1	46.2	Retrospective study	USA	Obesity	0.94 (0.71–1.24)
Ioannou GN	10,131	78 (0.8)	63.6 ± 16.2	91	Longitudinal cohort study	USA	Obesity	1.66 (0.99–2.77)

to respond to irreversible ER stress (Sureda, Alizadeh, Nabavi, Berindan-Neagoe, Cismaru, Jeandet, Łos, Clementi, Nabavi, and Ghavami 2020).

The immune response is essential for defending against viral infections. Nevertheless, the previous study has shown that obesity will chronically attenuate immune response by impeding the synthesis of vitamin D, which is required for the functions of the immune system (Banerjee, Czinn, Reiter, and Blanchard 2020). Additionally, obesity causes a decrease in lung compliance by lipid accumulation, increasing chest wall compression, and relative surfactant deficiency (Inselman, Chander, and Spitzer 2004). The decreased lung compliance requires more forces during lung inflation and deflation. All these factors contribute to COVID-mortality.

2 OBESITY, COVID-19, AND ER STRESS

ER stress and its following mechanisms contribute to COVID-19 mortality in the obese population by causing organ damage. Both obesity and SARS-CoV-2 infections cause ER stress, activating the UPR, and triggering adaptive programs. The accumulation of misfolded and unfolded proteins is detected by an ER-specific chaperone called binding immunoglobin protein (BiP, 78kDa), which then activates the three ER stress sensors: protein kinase-like ER kinase (PERK), the inositol-requiring ER-to-nucleus signal kinase 1 (IRE1), and activating transcription factor 6 (ATF6) (Zhou, and Liu 2010). These three routes will contribute to solving the problem of ER stress by increasing ER folding efficiency, degrading unfolded and misfolded protein by ubiquitin-proteasome pathway or autophagy-dependent pathway, and producing apoptotic signals if necessary (Zhou, and Liu 2010).

It has been observed that many tissues like adipose tissues, the liver, and the pancreas undergo ER stress because the homeostasis is not balanced in obese patients (Zhou, and Liu 2010). The inflammatory responses can be augmented by reducing adiponectin gene expression; however, adiponectin plays an important role in autophagy-mediated degradation (Zhou, and Liu 2010). The decrease in adiponectin is observed in both of obese and COVID-19 patients. COVID-19 patients with a higher body mass index (BMI, 32.8 ± 9.5) have a lower survival rate (75%) than non-COVID-19 patients (BMI, 30.2 ± 5.4; survival rate, 82%). Also, nearly 4 times lower adiponectin level was discovered in COVID-19 patients with respiratory failure compared to non-COVID-19 respiratory failure (Kearns, Ahern, Patrie, Horton, Harris, and Kadl 2021). The decreased adiponectin level results in the ineffectiveness of degrading misfolded and unfolded proteins and a prolonged the chronic inflammatory condition, which is harmful to the human body and causes many other systematic problems.

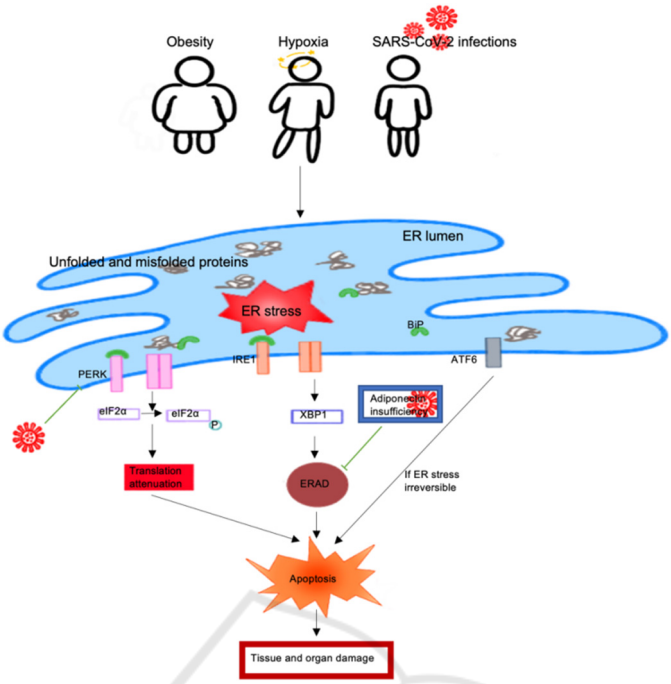

Figure 1. Schematic representation of how obesity increases COVID-19 mortality by activating ER stress and apoptosis. SARS-CoV-2 causes inhibition of translational attenuation and adiponectin transcription, leading to prolonged ER stress and tissue and organ damage.

In a recent study, researchers have discussed how coronavirus causes ER stress and interrupts the UPR (Banerjee, Czinn, Reiter, and Blanchard 2020). In the cases of COVID-19, hypoxia, another factor causing ER stress, has been observed (Sureda, Alizadeh, Nabavi, Berindan-Neagoe, Cismaru, Jeandet, Łos, Clementi, Nabavi, and Ghavami 2020). The levels of reactive oxygen species and Ca^{2+} are disrupted in the infected cells (Banerjee, Czinn, Reiter, and Blanchard 2020). These disturbances are activated by ER stress and lead to signal transductions and activations of the UPR. However, the researchers also suggested that coronavirus can interrupt the host UPR by interacting with the host's UPR pathways (Banerjee, Czinn, Reiter, and Blanchard 2020). The route of PERK, which has antiviral activities, could be disrupted by the virus via constant eukaryotic translation initiation factor 2 alpha (eIF2α) phosphorylation. This phosphorylation also blocks the translation of the X-box binding protein 1 (XBP1) transcriptional factor, which can attenuate the ERAD quality control mechanism and lead to prolonged ER stress and inflammation state. Apoptosis is activated by the UPR and inflammatory signals are increased dramatically if obese patients are invaded by SARS-CoV-2. Obesity accelerates this process as the apoptosis continues in inflammatory tissues and damages organs (Sureda, Alizadeh, Nabavi, Berindan-Neagoe, Cismaru, Jeandet, Łos, Clementi, Nabavi, and Ghavami 2020). As a one of the leading causes of death, organ damages have been observed in many deaths of obese COVID-19 patients.

3 OBESITY, COVID-19, AND IMMUNE RESPONSE

Obesity gives rise to the hindrance and attenuation of immune response to SARS-CoV-2, which increases the risk of COVID-19 mortality. If obese patients stay in chronic inflammation for a long time, the inflammation will spread from local to systematic inflammation and from adipose cells to mass cells such as pulmonary epithelial and endothelial cells (Cuschieri, and Grech 2020). The inflammation in the airway increases the susceptibility to be infected by SARS-CoV-2 and have airway diseases. Besides, systematic inflammation can disrupt blood flow, thus inducing hypoxia and impairing immune cell functions and responses (Cuschieri, and Grech 2020). The chronic and systematic inflammation condition also delays immune responses, which gives SARS-

CoV-2 viruses more time to replicate and spread. Besides, the severe medical issue called cytokine storm occurs and causes fatal problems in the human body (Hammock, Wang, Gilligan, and Panigrahy 2020). The quick multiplication of the virus and cytokine storm augments the therapeutic difficulties.

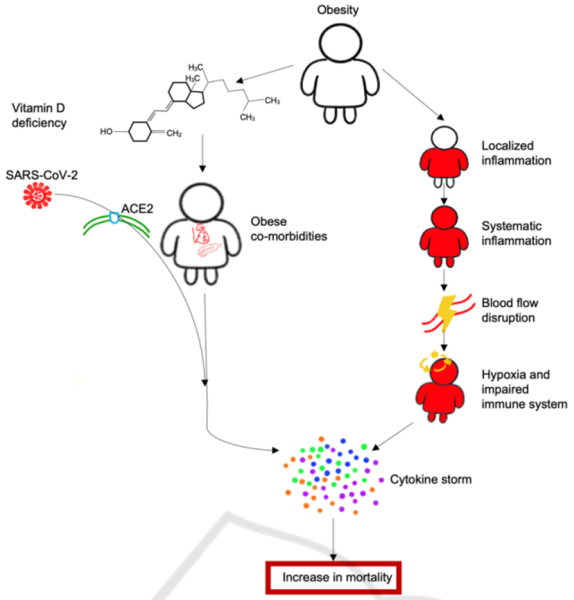

Figure 2. Schematic representation of how obesity increases COVID-19 mortality by the combination of vitamin D deficiency and delayed immune responses. This combination gives more possibility of cytokine storm occurrence and increases in COVID-19 mortality.

It has been reported that vitamin D deficiency was shown in most of the obese patients. This deficiency may be caused by co-morbidities of obesity like liver steatosis and hyperparathyroidism (Cuschieri, and Grech 2020). Vitamin D takes an important role in the "modulation of both the innate and the adaptive immune responses" (Cuschieri, and Grech 2020). Therefore, if the vitamin D is deficient, the immune responses cannot be efficient, the susceptibility of the spread of SARS-CoV-2 in the body is increased, and cytokine storm are induced. Obese patients themself have delayed immune responses additionally with vitamin D deficiency further worsens the symptoms of COVID-19.

It is commonly known that obese patients have various co-morbidities such as type 2 diabetes mellitus, hypertension, respiratory muscle function impairment, and cardiovascular diseases. These co-morbidities are linked with cell dysfunctions, impaired immune system, and increased risk of COVID-19 mortality. SARS-CoV-2 can easily enter pancreatic and myocardial cells through angiotensin-converting enzyme 2 (ACE2) receptors, which are commonly found in many cell types and "responsible for anti-inflammatory responses" (Cuschieri, and Grech 2020). The disruption of ACE2 signaling pathways results in acute metabolic dysfunctions like hyperglycemia and acute cell injury. For this reason, COVID-19 patients with obesity and its co-morbidities have a 2 to 3 times higher rate of being in intensive care unit (Cuschieri, and Grech 2020) and thus an augmented risk of mortality.

4 OBESITY, COVID-19, AND LUNG COMPLIANCE

Decreased lung compliance in obese patients by increased chest wall compression and surfactant deficiency conduce to augmented COVID-19 mortality. It has often been seen that obese patients have faster and shallower breaths. This symptom is due to the stiff chest wall caused by mechanical compression, accumulated lipid around the diaphragm and in the abdomen, and increased work of respiratory muscles (Cuschieri, and Grech 2020, Inselman, Chander, and Spitzer 2004) A 33% increase of respiratory rates (RR) and 29% and 44% decreases of dynamic and specific lung compliance were observed in obese rat models with a 31% increase in weights (Inselman, Chander, and Spitzer 2004). The respiratory muscles try to adapt and compromise the decreased lung compliance and "the

increased mechanical and metabolic requirements for chest wall expansion" (Inselman, Chander, and Spitzer 2004, Mahadev, Salome, Berend, and King, 2013). However, the respiratory muscles adaptions are not enough to compromise the increased mechanical compression. Adding to the problem, the stiffness of respiratory muscles is increased and consequently further narrows the airway by 42.6 ± 8.6% (Inselman, Chander, and Spitzer 2004) (Inselman, Chander, and Spitzer 2004, Mahadev, Salome, Berend, and King 2013). The narrower airway is fatal for COVID-19 patients as they have acute respiratory distress syndrome (ARDS), which can further decrease blood oxygen levels and deteriorate the symptoms of hypoxia. The reduced chest wall compliance can increase dead space during breathing and increase ventilation heterogeneity, which may result in more severe pulmonary dysfunctions. Besides, the continued airway inflammation and airway narrowing are associated with surfactant dysfunction (Mahadev, Salome, Berend, and King 2013).

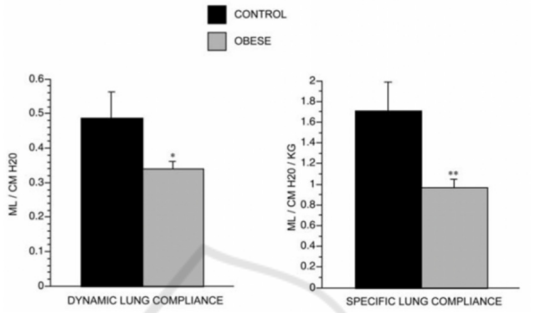

Figure 3. Dynamic and specific compliance in control and obese rats at age 8 weeks. Values are means ± SE. *p < 0.05; ** p < 0.001. Both dynamic and specific lung compliance are reduced in obese rats (n = 16) when compared with control rats (n = 14) (Inselman, Chander, and Spitzer 2004).

To compromise increased chest wall compressions, a slight increase in lung surfactant levels of large aggregates (14%) and small aggregates (35%) has been observed in obese rat models (Inselman, Chander, and Spitzer 2004). However, these changes can result in a deficiency of lung surfactants and impairment of lung functions. As COVID-19 may result in lung injury, the surfactant can progressively aggregate and lead to "a loss of overall surface activity in the lung" (Inselman, Chander, and Spitzer 2004) and lung instability (Schousboe, Wiese, Heiring, Verder, Poorisrisak, Verder, and Nielsen 2020)]. The lung surfactant deficiency can be fatal because it increases the difficulty of breathing in obese COVID-19 patients and further augments COVID-19 severity. It has been monitored that if COVID-19 patients' lung compliances further decrease to 42 ± 3 mL/cmH2O and the breaths become shallower, it is likely to cause hyperinflation that gives rise to more severe diseases and deaths (Roesthuis, van den Berg, and van der Hoeven 2020).

5 CONCLUSIONS

This study has discussed the relationship between obesity and COVID-19 mortality and proposed three possible mechanisms of how obesity deteriorate the symptoms of COVID-19 symptoms. Obese individuals are more susceptible to death from COVID-19 because of ER stress-mediated apoptoses, defective immune responses, and decreased lung compliances. These three factors accelerate the process and severity of COVID-19. Obesity causes prolonged inflammation and ER stress. These two conditions expedite the action of driving degradation machinery UPR to activate apoptotic mechanisms. Along with SARS-CoV-2 infections, acute organ damage will be induced in the obese population. Also, obese people have dysfunctional immune systems due to vitamin D deficiency, cytokine storms, and disrupted ACE2 signal pathways. These hindered immune responses increase therapeutic difficulties. Lastly, obesity results in a decreased lung compliance and lung volume by increasing chest wall compression and lung surfactant dysfunction. COVID-19 patients may have lung injury which accelerates the aggregation of lung surfactants, leading to lung instability and dysfunctions, and then

contributing to COVID-19 mortality. These factors should be noticed when treating obese COVID-19 patients. Obesity, a chronic and metabolic disease, should be put more attention on because it not only causes a wide range of co-morbidities but may be fatal especially when people are invaded by viruses. This study may have important implications regarding to the development of valuable approaches to reduce COVID-19 mortality in the obese population. Future studies and experiments are needed to test whether these three reasons primarily cause increased COVID-19 mortality in the obese population. Also, efficient treatments and interventions can be considered based on these three factors.

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REFERENCES

Banerjee, A., Czinn, S. J., Reiter, R.J., and Blanchard, T. G. (2020). Crosstalk between endoplasmic reticulum stress and anti-viral activities: A novel therapeutic target for COVID-19. Life Sciences, 255, 117842.

Cuschieri, S., and Grech, S. (2020). Obesity population at risk of COVID-19 complications. Global Health, Epidemiology and Genomics, 5.

Hammock, B. D., Wang, W., Gilligan, M. M., and Panigrahy, D. (2020). Eicosanoids: The Overlooked Storm in Coronavirus Disease 2019 (COVID-19)? The American Journal of Pathology, 190(9), 1782–1788.

Inselman, L. S., Chander, A., and Spitzer, A. R. (2004). Diminished Lung Compliance and Elevated Surfactant Lipids and Proteins in Nutritionally Obese Young Rats. Lung, 182(2), 101–117.

Kearns, S. M., Ahern, K. W., Patrie, J. T., Horton, W. B., Harris, T. E., and Kadl, A. (2021). Reduced adiponectin levels in patients with COVID-19 acute respiratory failure: A case-control study. Physiological Reports, 9(7).

Mahadev, S., Salome, C. M., Berend, N., and King, G. G. (2013). The effect of low lung volume on airway function in obesity. Respiratory Physiology & Neurobiology. 188(2), 192–199.

Roesthuis, L., van den Berg, M., and van der Hoeven, H. (2020). Advanced respiratory monitoring in COVID-19 patients: use less PEEP! Critical Care, 24(1), 230–230.

Schousboe, P., Wiese, L., Heiring, C., Verder, H., Poorisrisak, P., Verder, P., and Nielsen, H. B. (2020). Assessment of pulmonary surfactant in COVID-19 patients. Critical Care, 24(1), 552–552.

Sureda, A., Alizadeh, J., Nabavi, S. F., Berindan-Neagoe, I., Cismaru, C. A., Jeandet, P., Łos, M. J., Clementi, E., Nabavi, S. M., and Ghavami, S. (2020). Endoplasmic reticulum as a potential therapeutic target for covid-19 infection management? European Journal of Pharmacology, 882, 173288.

Wang, Y., Xu, J., Wang, Y., Hou, H., Feng, H., and Yang, H. (2021). An updated meta-analysis on the relationship between obesity and COVID-19 mortality. Metabolism, 122, 154820.

Wu, J., and Kaufman, R. J. (2006). From acute ER stress to physiological roles of the Unfolded Protein Response. Cell Death & Differentiation, 13(3), 374–384.

Zhou, L., and Liu, F. (2010). Autophagy: Roles in obesity-induced ER stress and adiponectin downregulation in adipocytes. Autophagy, 6 (8), 1196–1197.