

REVIEW ARTICLE

Obesity in the COVID era: A global health challenge[☆]Miguel A. Rubio Herrera^{a,*}, Irene Bretón Lesmes^b

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KEYWORDS

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Abstract Obesity is a chronic disease that leads to an increased risk of mortality and morbidity, and the impact of the COVID-19 pandemic may create a new health challenge. There is clear evidence showing that some biological and social factors associated with obesity involve an increased risk of COVID-19 infection, hospitalization, and greater severity compared to people with normal weight. Undoubtedly, obesity involves a low-grade proinflammatory state that produces a dysregulation of the immune system that compromises its ability to respond to respiratory infection by COVID-19 and so produces a worsening of the disease. In this review, the main epidemiological and pathophysiological data that associate obesity with COVID-19 are described.

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PALABRAS CLAVE

Obesidad;
COVID-19;
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Obesidad grave

Obesidad en tiempos de COVID-19. Un desafío de salud global

Resumen La obesidad es una enfermedad crónica asociada a incremento de la morbimortalidad en el mundo, y el impacto con la pandemia de COVID-19 puede suponer un nuevo reto sanitario. Disponemos de evidencias que sugieren que algunos factores biológicos y sociales asociados con la obesidad confieren un mayor riesgo de infección por COVID-19, de hospitalización y de mayor gravedad respecto a las personas con normopeso. Sin duda, la obesidad comporta un estado proinflamatorio de bajo grado que produce una desregulación del sistema inmune que compromete su capacidad de respuesta ante la infección respiratoria por la COVID-19 y propicia un empeoramiento de la enfermedad. En esta revisión se exponen los principales datos epidemiológicos y fisiopatológicos que asocian obesidad con la COVID-19.

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Infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), designated by the World Health Organization (WHO) as COVID-19, was declared a pandemic on 11 March 2020. Although obesity is a chronic disorder associated with increased morbidity and mortality,¹ it was not considered a risk factor in the early stages of the pandemic²; as a result, there has been an uneven compilation of information for understanding the true impact of COVID-19 infection upon individuals with obesity.

The present review describes the key epidemiological and pathophysiological aspects associating obesity and COVID-19.

Obesity as a risk factor in COVID-19. The epidemiological evidence

Previous influenza epidemics have shown obesity and diabetes to be associated with a poorer prognosis of the infection.^{3,4} Preliminary data from Wuhan (China) on COVID-19 found that 88.24% of the critically ill patients who died had a body mass index (BMI) >25 kg/m², as compared to 18.95% of the survivors ($p < 0.001$).⁵ In another Chinese series, people with obesity (BMI ≥ 28 kg/m²) presented an increased risk of severe pneumonia (odds ratio [OR]: 3.40; 95%CI: 1.40–8.26; $p = 0.007$).⁶

In the North American COVID-NET registry, obesity was present in 48.3% of those affected, and was the main risk factor in people <65 years of age.⁷ In another series in New York ($n = 5700$), 41.7% of the patients were found to be obese, though those with severe obesity (BMI ≥ 35 kg/m²) had a greater risk of admission to the Intensive Care Unit (ICU) (OR: 6.16; 95%CI: 1.42–26.66).⁸ These obesity rates are similar to the population-based prevalence figures (obesity 42.4%; morbid obesity 9.2%).⁹ It was therefore concluded that these data largely reflected the situation in the country. Other parallel observations suggested that the greatest severity impact corresponded to obese individuals under 60 years of age: those with a BMI of 30–34 kg/m² were very likely to be admitted to the ICU (OR: 1.8; 95%CI: 1.2–2.7; $p = 0.006$), with a doubling of the risk in the case of severe obesity (OR: 3.6; 95%CI: 2.5–5.3; $p < 0.0001$).¹⁰ Another study in New York city reinforces this relationship, as morbid obesity (BMI ≥ 40 kg/m²) was found to be independently associated with mortality (adjusted OR: 5.1; 95%CI: 2.3–11.1) in people <50 years of age, with a decreased risk among older individuals.¹¹

In Europe, data from France (Lille and Lyon) confirmed the greater number of people with obesity requiring ICU admission (25% with respect to the 15.4% prevalence of obesity in the country),¹² with an up to 7-fold increased need for invasive mechanical ventilation (IMV) in subjects with a BMI ≥ 35 kg/m² (adjusted OR: 7.36; 95%CI: 1.63–33.14; $p = 0.021$). These data are very surprising, bearing in mind that the reported IMV rate is much higher than in other non-COVID pneumonia scenarios. Indeed, it has even been described as a “paradox” that obese individuals in general appear to exhibit lesser severity and mortality due to respiratory infection, since this is in clear contradiction to the current data referring to COVID-19.^{13,14}

These data suggested the presence of a BMI cut-off point (≥ 35 kg/m²) beyond which excess weight resulted in greater

severity. It should be noted that most descriptive studies have limitations due to their usually retrospective design and the fact that body weight and height are not always available in the electronic medical records. Furthermore, the data typically reflect the situation only of hospital admissions, and in many publications patient follow-up is too short. Nevertheless, studies involving larger series and recent meta-analyses confirm that any degree of obesity confers an increased risk of both more severe disease and increased mortality due to COVID-19.^{15–18}

Up to that point, most studies analyzed what was happening in hospitals, but it was not really clear whether people with obesity had a higher risk of infection than those with normal weight. The debate focused on determining whether the greater prevalence of obesity in the North American and British series was due to the fact that a large percentage of the admitted patients were black, Hispanic and of other minority ethnic origins.^{19–22} These groups have a greater prevalence of obesity and its associated complications (arterial hypertension, diabetes mellitus or chronic kidney disease) than Caucasians. Moreover, they typically come from socially more depressed and economically disadvantaged urban areas with a low educational level, where less attention is paid to healthcare, and where social distancing measures are more difficult to maintain. Globally, these circumstances favour the spread of infection and result in higher admission rates due to COVID-19.

Large population-based studies allow us to examine and compare people with or without COVID-19, and to analyze cases with greater severity requiring hospitalization versus those with milder symptoms not requiring admission. For example, the OpenSAFELY database compiles socio-sanitary information from more than 17 million citizens in the United Kingdom, and this information was crossed with the over 10,000 deaths due to COVID-19.²³ In addition to known mortality risk factors associated with COVID-19 (including ethnic minorities), obesity is an independent mortality risk factor, proportional to the degree of obesity (HR: 1.92; 95%CI: 1.72–2.13, for BMI ≥ 40 kg/m²). Similar results were found in the British ISARC-WHO series involving over 20,000 patients (HR: 1.33; 95%CI: 1.19–1.49; $p < 0.001$),²⁴ and in Mexico, where a population-based analysis of 177,133 subjects showed obesity to be the only comorbid condition associated with an almost 5-fold higher mortality rate (HR: 4.989; 95%CI: 4.444–5.600).²⁵

It is of interest at this point to analyze the conditions under which some people with obesity suffer greater disease severity. People with severe obesity admitted to the ICU certainly pose greater management difficulties (hypventilation, a greater need for intubation, catheterization or placement in the prone position), though their cardiorespiratory condition is also worse. The amount of lean mass (skeletal muscle mass) clearly differentiates people with obesity who have a greater or a lesser cardiovascular risk, and this is a distinguishing fact in the recognized “obesity paradox”.^{26,27} Aerobic exercise results in improved physical performance, lesser visceral fat and greater lean mass (fitness versus fatness) that counteracts the proinflammatory state associated with excess body fat.²⁸ Therefore, also in situations of infectious respiratory disease such as COVID-19, the BMI alone does not tell the full story about the nature and type of obesity.

Likewise, nutritional status is an important mediator of complications in critical patients. It has been shown that people with obesity and energy-protein malnutrition admitted to the ICU due to any disease condition exhibit increased mortality as compared to well-nourished individuals in the same weight category (OR: 1.67; 95%CI: 1.29–2.15; $p < 0.0001$).²⁹ It is therefore feasible that when excess body weight is associated with sarcopenia and/or malnutrition, the medical respiratory complications prove much more serious.

The number of COVID-19 publications in PubMed at the time of this review exceeded 50,000 references. It is therefore necessary to resort to systematic reviews and meta-analyses in order to better understand the trends based on pooled data. In this scenario, a recent meta-analysis of 75 articles on obesity and COVID-19³⁰ has shown that: (1) the risk of COVID-19 positivity among obese individuals is 46% higher than in non-obese individuals (OR: 1.46; 95%CI: 1.30–1.65; $p > 0.0001$); (2) people with obesity have a two-fold higher risk of hospitalization (OR: 2.13; 95%CI: 1.74–2.60; $p < 0.0001$); (3) the risk of admission to the ICU, particularly when the BMI ≥ 35 kg/m², increases by 74% (OR: 1.74; 95%CI: 1.46–2.08; $p < 0.0001$). In addition, a large percentage of cases require the use of IMV (OR: 1.69; 95%CI: 1.38–1.99; $p < 0.001$); and (4), there is an excess mortality rate of 48% (OR: 1.48; 95%CI: 1.22–1.80; $p < 0.0001$).

The information available in Spain on confirmed COVID-19 patients (21 May 2020)³¹ indicated that 87% of the deceased individuals were over 70 years of age (median: 83 years), and of these, 95% had some major comorbidity (60% cardiovascular diseases). Although no data on obesity are available in this official registry, we know that the prevalence of obesity in Spain among individuals over 65 years of age is 35%.³² The recently published case series in Spain include the SEMI COVID-19 registry, which contains a total of 15,111 patients from 150 hospitals.³³ This is a descriptive study indicating a 21.2% incidence of obesity among the admitted patients, with a mean age of 69.4 years. The frequency of obesity in the COVID-19@Spain Study was 13.8% among the 4035 subjects analyzed, with a mean age of 70 years and involving 127 centres.³⁴ In this study, obesity was identified as an independent mortality factor (HR: 1.21; 95%CI: 1.01–1.44; $p = 0.036$). Lastly, the evaluation of 1000 patients aged 62 years on average, included in the SIESTA research network comprising 61 hospital emergency care departments, reported a frequency of obesity of 14.3% among the admitted patients.³⁵ In the multivariate analysis, only age and obesity were associated with in-hospital mortality (adjusted OR for obesity: 2.53; 95%CI: 1.47–4.35) or combined events such as ICU admission, the need for IMV, and in-hospital mortality (adjusted OR: 2.38; 95%CI: 1.51–3.74). Although the obesity rates of the analyzed patients were lower than the prevalence of obesity in the Spanish population, it was again seen that people with obesity admitted due to COVID-19 were at a greater risk of complications and mortality.

Why may people with obesity be more vulnerable to infections and complications?

It is well known that obesity is associated with a low-grade proinflammatory state, characterized by increased levels

of cytokines (TNF- α , interleukin-6), that results in dysregulation of the innate and adaptive immune response. This immune condition in people with obesity leads to increased susceptibility to infections, a deficient response to treatment with antiviral agents, and the reduced efficacy of vaccines.^{36,37} In obese individuals, the poorer T cell (CD4+ and CD8+) response, together with lymphocytopenia secondary to infection and apoptosis induced by COVID-19,³⁸ favours a worsening of lung problems.^{39,40} In this situation, the presence of a higher proportion of macrophages contributes to the rapid release of inflammatory cytokines (''cytokine storm''), and this plays a prominent role in the multiorgan failure associated with COVID-19 infection.⁴¹

The host entry pathway of SARS-CoV-2 involves the interaction of the virus with the renin-angiotensin system (RAS), specifically the angiotensin-converting enzyme-2 (ACE-2) receptor, which is expressed in the alveolar epithelium of the lungs, heart, vascular endothelium, kidney, pancreas and intestine, causing lesions and dysfunction of the affected organs. After coming into contact with the virus, ACE-2 experiences down-regulation, generating the accumulation of angiotensin-2, which is believed to be responsible for lung tissue damage and respiratory distress syndrome, due to its vasoconstrictive and fibrotic properties.⁴²

Although there is no direct evidence of adipose tissue infection by SARS-CoV-2, it is known that ACE-2 is also expressed in this tissue. There is a possibility that intrathoracic (lung), perirenal (kidney), epicardial (heart) and mesenteric (bowel) fat may serve as a reservoir and dissemination target for the virus.⁴³ It has been argued that this peculiarity would cause people with obesity to have a greater viral load and longer dissemination time.

Obesity is also associated with medical complications (arterial hypertension, type 2 diabetes, cardiovascular diseases), the hypercoagulability state and thrombosis, which determine a poorer prognosis in relation to COVID-19.^{44–46} In addition, obese individuals have greater breathing difficulties due to airflow resistance, lesser lung expansion, and difficulties in mobilizing the chest (diaphragm and intercostal muscles). This, in turn, results in hypoventilation, pulmonary hypertension, and sleep apnea (Fig. 1).

Another common finding in people with obesity is vitamin D⁴⁷ deficiency. In addition to its recognized actions upon bone, vitamin D plays an important role in regulating innate and adaptive immunity,⁴⁸ both in inflammatory modulation, by reducing the expression of proinflammatory cytokines,⁴⁹ and in RAS control, by increasing ACE-2 expression. From the clinical perspective, vitamin D deficiency is associated with an increase in respiratory infections, respiratory distress and lung fibrosis,⁵⁰ while vitamin D treatment prevents these complications.^{51,52} An epidemiological association has been described between low vitamin D levels and the number of cases and mortality due to COVID-19 in countries such as Spain and Italy, in contrast to the northern European countries, with different vitamin D levels,⁵³ though no causal relationship has yet been confirmed.⁵⁴ Some publications have suggested the possibility of preventive and therapeutic treatment with vitamin D with a view to preventing and treating COVID-19.^{55,56} In a preliminary study conducted in Spain, the administration of high-dose calcifediol in patients admitted due to COVID-19⁵⁷ reduced the probability of ICU

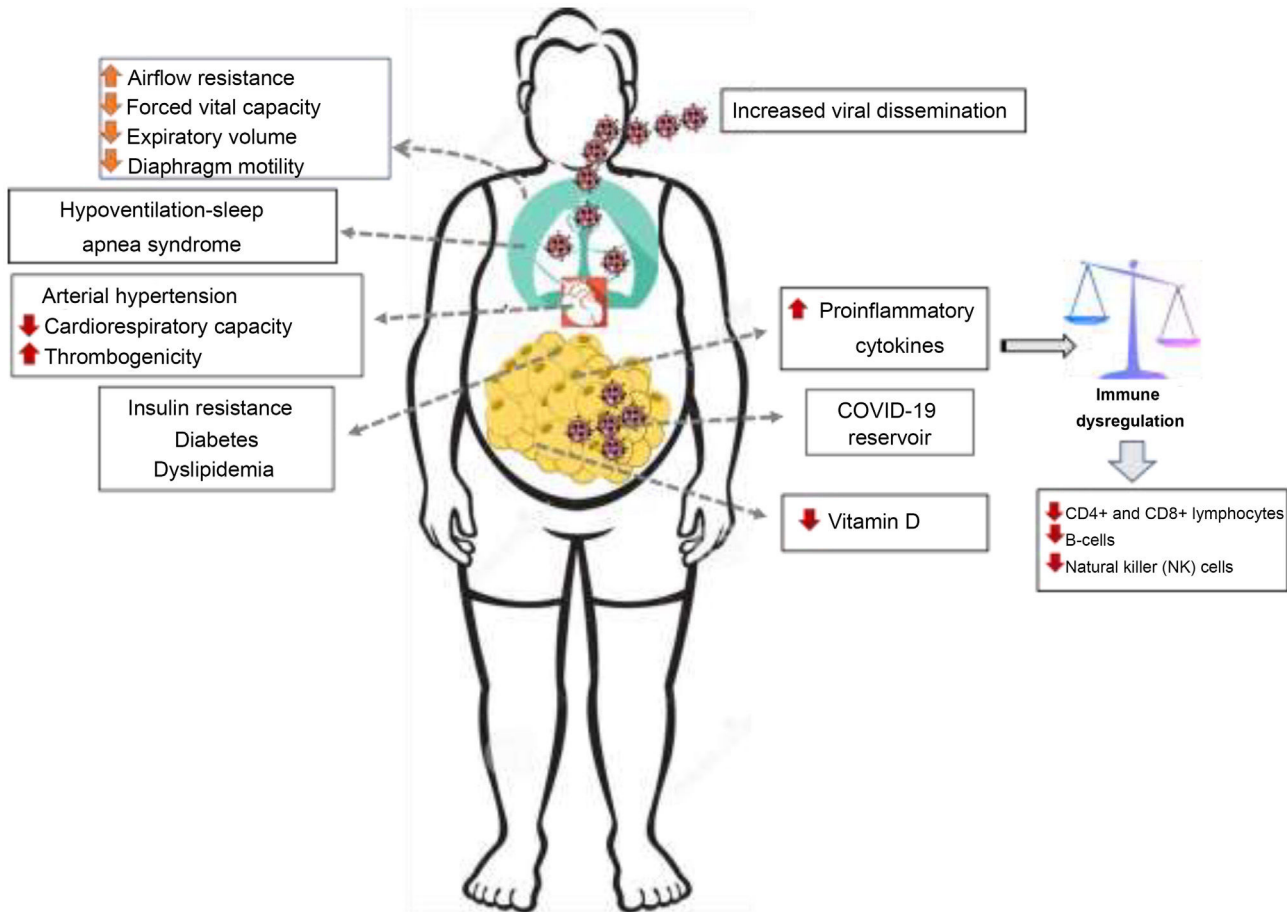


Figure 1 Potential pathogenic mechanisms of COVID-19 in people with obesity.

admission by 98%. Although these findings are very encouraging, more robust results are needed from the many ongoing clinical trials.

Future opportunities

The advent of the new healthcare models based on telemedicine will have an impact upon obesity as a disease. In addition to a dramatic decrease in face-to-face visits,⁵⁸ these patients suffer a lack of funding for pharmacological treatments, difficulties in accessing educational, psychological or nutritional aids, and long waiting lists for bariatric surgery. The stigmatization of people with obesity may also result in further delays in their seeking help to lose weight.⁵⁹

Despite the difficulties, however, we have useful tools for curbing the potential susceptibility of obese individuals to COVID-19. Firstly, we can control the comorbidities that lead to the accumulation of risk factors for vulnerability to infection and poorer disease outcomes. Secondly, we can implement active therapeutic measures to promote lifestyle changes that help reduce the proinflammatory state and restore the immune balance. We should promote a low-calorie diet based on the Mediterranean diet, containing a variety of nutrients with high antioxidant capacity.⁶⁰ We also need to encourage aerobic exercise, which has clear immune modulating and antiinflammatory actions, reducing proin-

flammatory cytokines and improving insulin sensitivity.^{61,62} Both treatment measures require a comprehensive and multidisciplinary approach to ensure long-term success.⁶³ Here in Spain, most of these therapeutic measures should form part of a consensus-based collaboration between specialists and primary care. Scientific bodies, such as the SEEN, and others involved in the management of obesity, are seeking to quickly generate healthcare intervention protocols based on telemedicine to adapt to the new healthcare reality, without forgetting the need to reactivate bariatric surgery^{64,65} as a further therapeutic tool that could help reduce the impact of obesity upon COVID-19.

Obesity is a public health problem that poses a very important economic and social burden. Despite the limitations of retrospective studies and insufficient information regarding the phenotypic characteristics of obesity, we have sufficient data to suggest that obesity is an independent risk factor in COVID-19, being associated with an increased likelihood of disease severity and mortality. It is therefore time to strengthen actions aimed at preventing and treating obesity on an equal footing with other chronic diseases.

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Conflicts of interest

The authors declare that they have no conflicts of interest related to this publication.

References

- GBD 2015 Obesity Collaborators Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377:13–27, <http://dx.doi.org/10.1056/NEJMoa1614362>.
- Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. *Aging (Albany NY)*. 2020;12:6049–57, <http://dx.doi.org/10.18632/aging.103000>.
- Louie JK, Acosta M, Winter K, Gavali S, Schechter R, Vugia D, et al. Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. *JAMA*. 2009;302:1896–902, <http://dx.doi.org/10.1001/jama.2009.1583>.
- Morgan OW, Bramley A, Fowlkes A, Freedman DS, Taylor TH, Gargiullo P, et al. Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A(H1N1) disease. *PLoS ONE*. 2010;5:e9694, <http://dx.doi.org/10.1371/journal.pone.0009694>.
- Peng YD, Meng K, Guan HQ, Leng L, Zhu RR, Wang BY, et al. Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV. *Zhonghua Xin Xue Guan Bing Za Zhi*. 2020;48:450–5, <http://dx.doi.org/10.3760/cma.j.cn112148-20200220-00105>.
- Cai Q, Chen F, Wang T, Luo F, Liu X, Wu Q, et al. Obesity and COVID-19 severity in a designated hospital in Shenzhen, China. *Diabetes Care*. 2020;43:1392–8, <http://dx.doi.org/10.2337/dc20-0576>.
- Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, 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*. 2020;69:458–64, <http://dx.doi.org/10.15585/mmwr.mm6915e3>.
- Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020;323:2052–9, <http://dx.doi.org/10.1001/jama.2020.6775>.
- Hales K, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. *NCHS Data Brief*. 2020;360. Available from: <https://www.cdc.gov/nchs/products/databriefs/db360.htm> [accessed 24.05.20].
- Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, et al. Obesity in patients younger than 60 years is a risk factor for COVID-19 hospital admission. *Clin Infect Dis*. 2020;71:896–7, <http://dx.doi.org/10.1093/cid/ciaa415>.
- Klang E, Kassim G, Soffer S, Freeman R, Levin MA, Reich DL. Morbid obesity as an independent risk factor for COVID-19 mortality in hospitalized patients younger than 50. *Obesity (Silver Spring)*. 2020;28:1595–9, <http://dx.doi.org/10.1002/oby.22913>.
- Caussy C, Pattou F, Wallet F, Simon C, Chalopin S, Telliam C, et al. Prevalence of obesity among adult inpatients with COVID-19 in France. *Lancet Diabetes Endocrinol*. 2020;8:562–4, [http://dx.doi.org/10.1016/S2213-8587\(20\)30160-1](http://dx.doi.org/10.1016/S2213-8587(20)30160-1).
- Nie W, Zhang Y, Jee SH, Jung KJ, Li B, Xiu Q. Obesity survival paradox in pneumonia: a meta-analysis. *BMC Med*. 2014;12:61, <http://dx.doi.org/10.1186/1741-7015-12-61>.
- Ni YN, Luo J, Yu H, Wang YW, Hu YH, Liu D, et al. Can body mass index predict clinical outcomes for patients with acute lung injury/acute respiratory distress syndrome? A meta-analysis. *Crit Care*. 2017;21:36, <http://dx.doi.org/10.1186/s13054-017-1615-3>.
- Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ*. 2020;369:m1966, <http://dx.doi.org/10.1136/bmj.m1966>.
- Hussain A, Mahawar K, Xia Z, Yang W, el-Hasani S. Obesity and mortality of COVID-19. *Meta-analysis. Obes Res Clin Pract*. 2020;14:295–300, <http://dx.doi.org/10.1016/j.orcp.2020.07.002>.
- Pranata R, Lim MA, Yonas E, Vania R, Lukito AA, Siswanto BB, et al. Body mass index and outcome in patients with COVID-19: a dose–response meta-analysis. *Diabetes Metab*. 2020;S1262-3636:30097–105, <http://dx.doi.org/10.1016/j.diabet.2020.07.005>.
- Földi M, Farkas N, Kiss S, Zadóri N, Váncsa S, Szakó L, et al. Obesity is a risk factor for developing critical condition in COVID-19 patients: a systematic review and meta-analysis. *Obes Rev*. 2020;21:e13095, <http://dx.doi.org/10.1111/obr.13095>.
- Gold JAW, Wong KK, Szablewski CM, Patel PR, Rossow J, da Silva J, et al. Characteristics and clinical outcomes of adult patients hospitalized with COVID-19 — Georgia, March 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:545–50, <http://dx.doi.org/10.15585/mmwr.mm6918e1>.
- Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among black patients and white patients with Covid-19. *N Engl J Med*. 2020;382:2534–43, <http://dx.doi.org/10.1056/NEJMsa2011686>.
- Suleyman G, Fadel RA, Malette KM, Hammond C, Abdulla H, Entz A, et al. Clinical characteristics and morbidity associated with coronavirus disease 2019 in a series of patients in Metropolitan Detroit. *JAMA Netw Open*. 2020;3:e2012270, <http://dx.doi.org/10.1001/jamanetworkopen.2020.12270>.
- De Lusignan S, Dorward J, Correa A, Jones N, Akinyemi O, Amirthalingam G, et al. Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study. *Lancet Infect Dis*. 2020;20:1034–42, [http://dx.doi.org/10.1016/S1473-3099\(20\)30371-6](http://dx.doi.org/10.1016/S1473-3099(20)30371-6).
- Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature*. 2020;584:430–6, <http://dx.doi.org/10.1038/s41586-020-2521-4>.
- Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with Covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ*. 2020;369:m1985, <http://dx.doi.org/10.1136/bmj.m1985>.
- Bello-Chavolla OY, Bahena-López JP, Antonio-Villa NE, Vargas-Vázquez A, González-Díaz A, Márquez-Salinas A, et al. Predicting mortality due to SARS-CoV-2: a mechanistic score relating obesity and diabetes to COVID-19 outcomes in Mexico. *J Clin Endocrinol Metab*. 2020;105:dga346, <http://dx.doi.org/10.1210/clinem/dgaa346>.
- McAuley PA, Artero EG, Sui X, Lee DC, Church TS, Lavie CJ, et al. The obesity paradox, cardiorespiratory fitness, and coronary heart disease. *Mayo Clin Proc*. 2012;87:443–51, <http://dx.doi.org/10.1016/j.mayocp.2012.01.013>.
- Barry VW, Baruth M, Beets MW, Durstine JL, Liu J, Blair SN. Fitness vs. fatness on all-cause mortality: a meta-analysis. *Prog Cardiovasc Dis*. 2014;56:382–90, <http://dx.doi.org/10.1016/j.pcad.2013.09.002>.

28. Zbinden-Foncea H, Francaux M, Deldicque L, Hawley JA. Does high cardiorespiratory fitness confer some protection against pro-inflammatory responses after infection by SARS-CoV-2? *Obesity* (Silver Spring). 2020;28:1378–81, <http://dx.doi.org/10.1002/oby.22849>.
29. Robinson MK, Mogensen KM, Casey JD, McKane CK, Moromizato T, Rawn JD, et al. The relationship among obesity, nutritional status, and mortality in the critically ill. *Crit Care Med*. 2015;43:87–100, <http://dx.doi.org/10.1097/CCM.0000000000000602>.
30. Popkin BM, Du S, Green WD, Beck MA, Algaith T, Herbst CH, et al. Individuals with obesity and COVID-19: a global perspective on the epidemiology and biological relationships. *Obes Rev*. 2020;21:e13128, <http://dx.doi.org/10.1111/obr.13128>.
31. Informe n.º 32. Situación de COVID-19 en España a 21 de mayo de 2020. Informes COVID-19. Ministerio de Ciencia e Innovación. Available from: <https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Paginas/InformesCOVID-19.aspx> [accessed 24.05.20].
32. Gutiérrez-Fisac JL, Guallar-Castillón P, León-Muñoz LM, Graciani A, Banegas JR, Rodríguez-Artalejo F. Prevalence of general and abdominal obesity in the adult population of Spain, 2008–2010: the ENRICA study. *Obes Rev*. 2012;13:388–92, <http://dx.doi.org/10.1111/j.1467-789X.2011.00964.x>.
33. Casas-Rojo JM, Antón-Santos JM, Millán-Núñez-Cortés J, Lumbrales-Bermejo C, Ramos-Rincón JM, Roy-Vallejo E, et al. Características clínicas de los pacientes hospitalizados con COVID-19 en España: resultados del Registro SEMI-COVID-19. *Rev Clin Esp*. 2020;S0014-2565:30206-X, <http://dx.doi.org/10.1016/j.rce.2020.07.003>.
34. Berenguer J, Ryan P, Rodríguez-Baño J, Jarrín I, Carratalán J, Pachón J, et al. Characteristics and predictors of death among 4,035 consecutively hospitalized patients with COVID-19 in Spain. *Clin Microbiol Infect*. 2020;S1198-743X:30431-6, <http://dx.doi.org/10.1016/j.cmi.2020.07.024>.
35. Gil-Rodrigo A, Miró O, Piñera P, Burillo-Putze G, Jiménez S, Martín A, et al. Evaluación de las características clínicas y evolución de pacientes con COVID-19 a partir de una serie de 1000 pacientes atendidos en servicios de urgencias españoles. *Emergencias*. 2020;32:233–41.
36. Richard C, Wadowski M, Goruk S, Cameron L, Sharma AM, Field CJ. Individuals with obesity and type 2 diabetes have additional immune dysfunction compared with obese individuals who are metabolically healthy. *BMJ Open Diabetes Res Care*. 2017;5:e000379, <http://dx.doi.org/10.1136/bmjdr-2016-000379>.
37. Dhurandhar NV, Bailey D, Thomas D. Interaction of obesity and infections. *Obes Rev*. 2015;16:1017–29.
38. Cao X. COVID-19: immunopathology and its implications for therapy. *Nat Rev Immunol*. 2020;20:269–70, <http://dx.doi.org/10.1038/s41577-020-0308-3>.
39. Liu J, Li S, Liu J, Liang B, Wang X, Wang H. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *EBioMedicine*. 2020;55:102763, <http://dx.doi.org/10.1016/j.ebiom.2020.102763>.
40. Liu PP, Blet A, Smyth D, Li H. The science underlying COVID-19: implications for the cardiovascular system. *Circulation*. 2020;142:68–78.
41. Muniyappa R, Sriram Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. *Am J Physiol Endocrinol Metab*. 2020;318:E736–41, <http://dx.doi.org/10.1152/ajpendo.00124.2020>.
42. Cheng H, Wang Y, Wang GQ. Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. *J Med Virol*. 2020;92:726–30, <http://dx.doi.org/10.1002/jmv.25785>.
43. Ryan PM, Caplice NM. Is adipose tissue a reservoir for viral spread immune activation and cytokine amplification in Coronavirus disease 2019? *Obesity* (Silver Spring). 2020;28:1191–4, <http://dx.doi.org/10.1002/oby.22843>.
44. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of Coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708–20, <http://dx.doi.org/10.1056/NEJMoa2002032>.
45. Stefan N, Birkenfeld AL, Schulze MB, Ludwig DS. Obesity and impaired metabolic health in patients with COVID-19. *Nat Rev Endocrinol*. 2020;16:341–2, <http://dx.doi.org/10.1038/s41574-020-0364-6>.
46. Sanchis-Gomar F, Lavie CJ, Mehra MR, Henry BM, Lippi G. Obesity and outcomes in COVID-19: when an epidemic and pandemic collide. *Mayo Clin Proc*. 2020;95:1445–53, <http://dx.doi.org/10.1016/j.mayocp.2020.05.006>.
47. Pereira-Santos M, Costa PR, Assis AM, Santos CA, Santos DB. Obesity and vitamin D deficiency: a systematic review and meta-analysis. *Obes Rev*. 2015;16:341–9, <http://dx.doi.org/10.1111/obr.12239>.
48. Gombart AF, Pierre A, Maggini S. A Review of micronutrients and the immune system-working in harmony to reduce the risk of infection. *Nutrients*. 2020;12:236, <http://dx.doi.org/10.3390/nu12010236>.
49. Fabbri A, Infante M, Ricordi C. Editorial — Vitamin D status: a key modulator of innate immunity and natural defense from acute viral respiratory infections. *Eur Rev Med Pharmacol Sci*. 2020;24:4048–52, <http://dx.doi.org/10.26355/eurrev.202004.20876>.
50. Shi Y, Liu T, Yao L, Xing Y, Zhao X, Fu J, et al. Chronic vitamin D deficiency induces lung fibrosis through activation of the renin-angiotensin system. *Sci Rep*. 2017;7:3312, <http://dx.doi.org/10.1038/s41598-017-03474-6>.
51. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ*. 2017;356:i6583, <http://dx.doi.org/10.1136/bmj.i6583>.
52. Quesada-Gómez JM, Entrenas-Castillo M, Bouillon R. Vitamin D receptor stimulation to reduce acute respiratory distress syndrome (ARDS) in patients with coronavirus SARS-CoV-2 infections: revised Ms SBMB 2020.166. *J Steroid Biochem Mol Biol*. 2020;202:105719, <http://dx.doi.org/10.1016/j.jsbmb.2020.105719>.
53. Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging Clin Exp Res*. 2020;32:1195–8, <http://dx.doi.org/10.1007/s40520-020-01570-8>.
54. Hastie CE, Mackay DF, Ho F, Celis-Morales CA, Katikireddi SV, Niedzwiedz CL, et al. Vitamin D concentrations and COVID-19 infection in UK Biobank. *Diabetes Metab Syndr*. 2020;14:561–5, <http://dx.doi.org/10.1016/j.dsx.2020.04.050>.
55. Ebadi M, Montano-Loza AJ. Perspective: Improving vitamin D status in the management of COVID-19. *Eur J Clin Nutr*. 2020;74:856–9, <http://dx.doi.org/10.1038/s41430-020-0661-0>.
56. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients*. 2020;12:988, <http://dx.doi.org/10.3390/nu12040988>.
57. Castillo ME, Entrenas Costa LM, Vaquero Barrios JM, Alcalá-Díaz JM, López Miranda J, Bouillon R, et al. Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: a pilot randomized clinical study. *J Steroid Biochem Mol Biol*. 2020, <http://dx.doi.org/10.1016/j.jsbmb.2020.105751>.

58. Dicker D, Bettini S, Farpour-Lambert N, Frühbeck G, Golan R, Goossens G, et al. Obesity and COVID-19: the two sides of the coin. *Obes Facts*. 2020, <http://dx.doi.org/10.1159/000510005>.
59. The Lancet Diabetes Endocrinology. Obesity-related stigmahiding in plain sight. *Lancet Diabetes Endocrinol*. 2020, [http://dx.doi.org/10.1016/S2213-8587\(20\)30123-6](http://dx.doi.org/10.1016/S2213-8587(20)30123-6).
60. Lecube A, Monereo S, Rubio MA, Martínez-de-Icaya P, Martí A, Salvador J, et al. Prevención, diagnóstico y tratamiento de la obesidad. Posicionamiento de la Sociedad Española para el Estudio de la Obesidad de 2016. *Endocrinol Diabetes Nutr*. 2017;64 Supl 1:15–22, <http://dx.doi.org/10.1016/j.endonu.2016.07.002>.
61. Luzi L, Radaelli MG. Influenza and obesity: its odd relationship and the lessons for COVID-19 pandemic. *Acta Diabetol*. 2020;57:759–64, <http://dx.doi.org/10.1007/s00592-020-01522-8>.
62. Codella R, Luzi L, Inverardi L, Ricordi C. The anti-inflammatory effects of exercise in the syndromic thread of diabetes and autoimmunity. *Eur Rev Med Pharmacol Sci*. 2015;19:3709–22.
63. Durrer Schutz D, Busetto L, Dicker D, Farpour-Lambert N, Pryke R, Toplak H, et al. European practical and patient-centred guidelines for adult obesity management in primary care. *Obes Facts*. 2019;12:40–66, <http://dx.doi.org/10.1159/000496183>.
64. Rubino F, Cohen RV, Mingrone G, le Roux CW, Mechanick JI, Arterburn DE, et al. Bariatric and metabolic surgery during and after the COVID-19 pandemic: DSS recommendations for management of surgical candidates and postoperative patients and prioritisation of access to surgery. *Lancet Diabetes Endocrinol*. 2020;8:640–8, [http://dx.doi.org/10.1016/S2213-8587\(20\)30157-1](http://dx.doi.org/10.1016/S2213-8587(20)30157-1).
65. Sánchez-Santos R, García Ruiz de Gordejuela A, Bretón Lesmes I, Lecube Torelló A, Moizé Arconé V, Arroyo Martín JJ, et al. Obesidad y SARS-CoV-2: Consideraciones sobre la cirugía bariátrica y recomendaciones para el inicio de la actividad quirúrgica. *Cir Esp*. 2020, <http://dx.doi.org/10.1016/j.ciresp.2020.06.005>.