



Global pandemics interconnected — obesity, impaired metabolic health and COVID-19

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Abstract | Obesity and impaired metabolic health are established risk factors for the non-communicable diseases (NCDs) type 2 diabetes mellitus, cardiovascular disease, neuro-degenerative diseases, cancer and nonalcoholic fatty liver disease, otherwise known as metabolic associated fatty liver disease (MAFLD). With the worldwide spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), obesity and impaired metabolic health also emerged as important determinants of severe coronavirus disease 2019 (COVID-19). Furthermore, novel findings indicate that specifically visceral obesity and characteristics of impaired metabolic health such as hyperglycaemia, hypertension and subclinical inflammation are associated with a high risk of severe COVID-19. In this Review, we highlight how obesity and impaired metabolic health increase complications and mortality in COVID-19. We also summarize the consequences of SARS-CoV-2 infection for organ function and risk of NCDs. In addition, we discuss data indicating that the COVID-19 pandemic could have serious consequences for the obesity epidemic. As obesity and impaired metabolic health are both accelerators and consequences of severe COVID-19, and might adversely influence the efficacy of COVID-19 vaccines, we propose strategies for the prevention and treatment of obesity and impaired metabolic health on a clinical and population level, particularly while the COVID-19 pandemic is present.

As of 20 December 2020, more than 75 million people have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and more than 1.6 million deaths worldwide were attributed to coronavirus disease 2019 (COVID-19)¹. On the basis of the infection to fatality ratio, the mortality of individuals with COVID-19 is ~2%¹. However, this widely used ratio is not the ideal measure of overall mortality as it only relates to confirmed infections and confirmed deaths. The infection to fatality ratio might be inaccurate owing to a delay of several weeks between symptom onset and death, and because surveillance-based case reports underestimate the total number of patients infected with SARS-CoV-2, as testing focuses on individuals with symptoms. In most instances, the symptomatic infection to fatality ratio and infection to fatality ratio show largely different numbers².

After infection with SARS-CoV-2, individuals can remain asymptomatic. By contrast, in symptomatic individuals the disease course can follow various stages: for example, mild symptoms in the initial 2 weeks after infection that can then progress to more complicated disease, defined by the severity of clinical symptoms and the potential for recovery. Patients who require hospital

treatment have a considerably increased risk of death due to COVID-19. For example, the mortality of hospitalized patients with COVID-19 ranges from 10% to 26% in the USA, the UK, Italy and Germany^{3–7}. Mortality increases further to 22–48% in patients with COVID-19 who were admitted to an intensive care unit (ICU)^{3–7}. Therefore, for risk stratification purposes it is crucial to understand the parameters that predispose patients with SARS-CoV-2 infection to a severe course of COVID-19.

Older age and male sex are well established as risk factors for severe COVID-19. The median age of hospitalized patients varies between 47 and 73 years, and in most cohort studies the percentage of men was ~60%⁸. Furthermore, although only ~25% of all patients infected with SARS-CoV-2 have comorbidities, 60–90% of hospitalized patients with COVID-19 have comorbidities⁸. The first studies reporting characteristics of hospitalized patients with COVID-19 showed that the most common comorbidities were hypertension, diabetes mellitus, cardiovascular disease (CVD), chronic pulmonary disease, chronic kidney disease, cancer and chronic liver disease^{8,9}. Only since mid-April 2020 has obesity been recognized as an important comorbidity^{10,11}. In addition, hyperglycaemia in the non-diabetic range (that is,

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Key points

- Obesity, particularly severe obesity, is a strong and independent determinant of severe coronavirus disease 2019 (COVID-19); novel studies also suggest that visceral obesity increases the risk of complications.
- Although diabetes mellitus is an established risk factor for severe COVID-19, evidence is increasing that hyperglycaemia in the non-diabetic and diabetic range also strongly predicts severe COVID-19.
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) targets organs and tissues that are relevant for cardiometabolic health; SARS-CoV-2-induced organ or tissue dysfunction could result in an increased incidence of cardiometabolic diseases.
- Targeted interventions for metabolic pathologies could improve management of COVID-19; the SARS-CoV-2 vaccination response should be carefully evaluated in patients with obesity and/or diabetes mellitus because of a potentially reduced response.
- Programmes resulting in weight loss and the improvement of metabolic health in people with metabolically unhealthy obesity should be implemented at the patient level and in the public health sector.
- Research to understand how diet and nutritional status modify the immune response could help explain some of the variability in COVID-19 morbidity and mortality and improve patient outcomes.

people with prediabetes, impaired glucose tolerance or isolated fasting glycaemia) is now recognized as an important determinant of severe COVID-19 (REFS^{12–14}). Furthermore, in patients with type 2 diabetes mellitus (T2DM) and COVID-19, good glucose control near the target range was associated with decreased mortality¹⁵. These data support the hypothesis that we proposed in April 2020 (REF.¹⁶), that obesity and impaired metabolic health might strongly, and independently of other comorbidities, associate with increased risk of severe COVID-19. We consider this aspect very important, as both obesity and impaired metabolic health are modifiable risk factors that can often be effectively treated by lifestyle intervention.

In this Review, we build upon this hypothesis. First, we summarize the data of the largest studies investigating the strength of the independent relationships of obesity, visceral obesity and impaired metabolic health with severe COVID-19. Second, we discuss the consequences of SARS-CoV-2 infection for organ function in infected patients and their risk of future cardiometabolic diseases; severely ill patients with COVID-19 can die of organ failure that is related to their underlying illness, such as CVD, diabetes mellitus, kidney disease, liver disease¹⁷ or obesity-related complications¹⁶. We consider this issue important, particularly because impaired organ function can persist even after patients have fully recovered from the viral infection. Third, we propose strategies to

prevent and treat obesity and impaired metabolic health on a clinical and population level, particularly while the COVID-19 pandemic is present.

Severity of COVID-19

Obesity and severity of COVID-19. Based on data from the WHO, last updated in 2018, globally, 13% of adults aged 18 years and older had obesity in 2016 (REF.¹⁸). The highest prevalence of obesity (>35%) was observed in the USA and in Saudi Arabia and a high prevalence of obesity (>20%) was also observed in Turkey, Egypt, Libya, Iran, Iraq, South Africa, Canada, Mexico, Australia and in most of the countries in South America and Europe. In addition, data from the WHO, last updated on 29 November 2020, show that in these countries with high obesity prevalence, a high cumulative number of confirmed COVID-19-related deaths per million people is being observed¹⁹. The question is whether there is a relationship between obesity and severe COVID-19. Furthermore, the risk of severe COVID-19 is high in older adults (aged >65 years), and obesity is thought to shift this increased risk of severe COVID-19 into younger age groups²⁰. However, because obesity²¹ and, more importantly, metabolically unhealthy obesity²² are associated with an increased risk of cardiometabolic diseases, which themselves correlate with severe COVID-19, it is unclear whether obesity is an independent determinant of COVID-19 severity (TABLE 1).

The first studies investigating the relationship between obesity and COVID-19 had fairly small sample sizes. For example, a study from a university hospital in Lille, France, reported data from 124 patients with COVID-19 admitted to the ICU, and saw that the odds ratio (OR) for invasive mechanical ventilation requirement in patients with a BMI of $\geq 35 \text{ kg/m}^2$ was 7.36 (95% CI 1.63–33.14), compared with patients with a BMI of $< 25 \text{ kg/m}^2$ (REF.¹⁰). This association was independent of age, sex and comorbidities (such as diabetes mellitus, hypertension or dyslipidaemia). Furthermore, a study from Shenzhen, China, among 383 hospitalized patients with COVID-19 found that overweight (BMI 24.0–27.9 kg/m^2) and obesity (BMI $\geq 28 \text{ kg/m}^2$) were associated with a multivariate adjusted OR of 1.84 (95% CI 0.99–3.43) and 3.40 (95% CI 1.40–2.86), respectively, for developing severe pneumonia, compared with patients of normal weight (BMI 18.5–23.9 kg/m^2) (REF.²³). In addition, a study examined 75 patients with obesity and COVID-19 in three hospitals in China, who were matched 1:1 by age and sex to 75 patients with COVID-19 but not obesity. In this study, obesity was associated with an approximately threefold increased risk of having severe COVID-19 (OR 3.00; 95% CI 1.22–7.38), after adjustment for age, sex, smoking status, hypertension, diabetes mellitus and dyslipidaemia²⁴.

Several larger studies have subsequently been published, investigating more than 1,000 patients each. According to two US studies, patients with SARS-CoV-2 infection were at increased risk of hospital admission if they had obesity^{11,25}. Furthermore, a BMI of $\geq 40 \text{ kg/m}^2$ was associated with a greater than twofold increase in risk of hospitalization compared with patients of normal weight (OR 2.45; 95% CI 1.78–3.36), independent

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Table 1 | Summary table of the independent association of obesity with COVID-19 severity

Author, ref.; study location	Participants	Outcome	Reference group	Relative risk (95% CI) associated with obesity	Adjustment
Anderson et al. ³¹ ; New York City, USA	2,466 hospitalized patients with COVID-19	Intubation or death ^a	BMI 25–29.9	BMI 30–34.9: 1.1 (0.9–1.4); BMI 35–39.9: 1.3 (0.98–1.7); BMI ≥40: 1.6 (1.1–2.1)	Age, sex, race or ethnicity, hypertension, asthma or COPD, CKD, pulmonary hypertension, smoking, cancer, diabetes mellitus
Bello-Chavolla et al. ³² ; Mexico	51,633 confirmed patients with COVID-19	COVID-19-related death	Without obesity	Clinician-defined obesity: 1.25 (1.17–1.34)	Age, diabetes mellitus, pneumonia, CKD, COPD, immunosuppression
Cunningham et al. ³⁶ ; USA	3,222 hospitalized patients with COVID-19 aged 18–35 years	Invasive mechanical ventilation or death	Without obesity	Morbid obesity: 2.30 (1.77–2.98)	Age, sex, race–ethnicity, region, month, asthma, hypertension, diabetes mellitus, smoking
Dennis et al. ³⁸ ; England, UK	19,256 patients with COVID-19 requiring admission to a high dependency unit or ICU	Death	BMI <30	BMI ≥30: 1.06 (0.99–1.15)	Age, sex, ethnicity, chronic respiratory disease, asthma, hypertension, heart disease, renal disease, liver disease, neurological disease, immunosuppressive disease
Docherty et al. ⁶ ; UK	20,133 hospitalized patients with COVID-19	ICU admission or death	Without obesity	Clinician-defined obesity: 1.33 (1.19–1.49) ^b	Age, sex, chronic cardiac disease, chronic pulmonary disease, CKD, diabetes mellitus, chronic neurological disorder, dementia, malignancy, moderate or severe liver disease
Hamer et al. ²⁶ ; England, UK (UKB)	387,109 adults	Hospital admission	BMI <25	BMI 25–29.9: 1.32 (1.09–1.60); BMI ≥30: 1.97 (1.61–2.42)	Age, sex, education, ethnicity, diabetes mellitus, hypertension, CVD (heart attack, angina or stroke)
Hippisley-Cox et al. ³³ ; England, UK	8,275,949 patients from GP	COVID-19 positivity	BMI 20–24.9	BMI 25–29.9: 1.04 (1.00–1.08); BMI 30–34.9: 1.20 (1.15–1.25); BMI ≥35: 1.54 (1.46–1.62)	Age, deprivation, ethnicity, geography, smoking, comorbidities (e.g. CVD, hypertension, diabetes mellitus, CKD, asthma, COPD) and long-term medication
		ICU admission		BMI 25–29.9: 1.64 (1.37–1.97); BMI 30–34.9: 2.59 (2.14–3.15); BMI ≥35: 4.35 (3.54–5.35)	
Kim et al. ²⁸ ; USA	2,491 hospitalized patients with COVID-19	ICU admission	BMI <30	BMI ≥30: 1.31 (1.16–1.47)	Age, sex, race–ethnicity, smoking status, hypertension, diabetes mellitus, chronic lung disease, CVD, neurological disease, renal disease, immunosuppression, use of an angiotensin receptor blocker
		Death		BMI ≥30: 1.09 (0.92–1.30)	
Kim et al. ³⁷ ; New York City, USA	10,861 hospitalized patients with COVID-19	Invasive mechanical ventilation	BMI 18.5–24.9	BMI 30–34.9: 1.48 (1.27–1.72); BMI 35–39.9: 1.89 (1.56–2.28); BMI ≥40: 2.31 (1.88–2.85)	Age, sex, race–ethnicity, hypertension, asthma, COPD, CKD, CAD, heart failure, hypertension, cancer, diabetes mellitus, smoking
		Death		BMI 30–34.9: 1.00 (0.87–1.16); BMI 35–39.9: 1.25 (1.03–1.52); BMI ≥40: 1.61 (1.30–2.00)	
Klang et al. ²⁹ ; New York City, USA	3,406 patients with COVID-19	Death	BMI <30	Age ≤50 years; BMI 30–39.9: 1.1 (0.5–2.3); BMI ≥40: 5.1 (2.3–11.1)	Age, sex, CAD, chronic heart failure, hypertension, diabetes mellitus, hyperlipidaemia, CKD, history of cancer, smoking, race
				Age >50 years; BMI 30–39.9: 1.1 (0.9–1.3); BMI ≥40: 1.6 (1.2–2.3)	
Petrilli et al. ¹¹ ; New York City and Long Island, USA	5,279 confirmed patients with COVID-19	Hospital admission	BMI <25	BMI 30–39.9: 1.8 (1.47–2.2); BMI ≥40: 2.45 (1.78–3.36)	Age, sex, race, smoking, CHD, heart failure, hyperlipidaemia, hypertension, diabetes mellitus, asthma or COPD, CKD, cancer
		Critical illness		BMI 30–39.9: 0.98 (0.77–1.2); BMI ≥40: 1.52 (1.04–2.2)	
		Death		BMI 30–39.9: 1.02 (0.82–1.27); BMI ≥40: 1.41 (0.98–2.01)	
Price-Haywood et al. ²⁵ ; Louisiana, USA	3,481 patients tested positive for SARS-CoV-2	Hospital admission	BMI <30	Diagnosed obesity or BMI ≥30: 1.43 (1.20–1.71)	Age, sex, race, Charlson comorbidity index score, residence, insurance
		In-hospital mortality		Diagnosed obesity or BMI ≥30: 1.05 (0.83–1.34)	
Sattar et al. ³⁴ ; England, UK (UKB)	374,922 adults	Positive SARS-CoV-2 test; COVID-19-related death	NA	BMI modelled continuously ^c ; effect size not reported	Age, socioeconomic status, ethnicity, smoking, alcohol intake, CVD and diabetes mellitus

Table 1 (cont.) | Summary table of the independent association of obesity with COVID-19 severity

Author, ref.; study location	Participants	Outcome	Reference group	Relative risk (95% CI) associated with obesity	Adjustment
Simonnet et al. ¹⁰ ; Lille, France	124 patients admitted in intensive care	Invasive mechanical ventilation	BMI <25	BMI 25–29.9: 1.69 (0.52–5.48); BMI 30–34.9: 3.45 (0.83–14.31); BMI ≥35: 7.36 (1.63–33.14)	Age, sex, diabetes mellitus, hypertension, dyslipidaemia
Soares et al. ²⁷ ; Espirito Santo state, Brazil	10,713 patients diagnosed with COVID-19	Hospital admission	Without obesity	Obesity: 1.74 (1.35–2.23) ^d	Age, sex, race, CVD, diabetes mellitus, kidney disease, pulmonary diseases, smoking, symptoms
Tartof et al. ³⁵ ; southern California, USA	6,916 patients diagnosed with COVID-19	Death ^e	BMI 18.5–24	BMI 25–29: 0.91 (0.62–1.35); BMI 30–34: 1.26 (0.82–1.95); BMI 35–39: 1.16 (0.63–2.17); BMI 40–44: 2.68 (1.43–5.04); BMI ≥45: 4.18 (2.12–8.26)	Age, sex, ethnicity, smoking, comorbidities (including hyperlipidaemia, hypertension, diabetes mellitus, myocardial infarction, stroke, chronic pulmonary disease, renal disease, among others), time of diagnosis
Williamson et al. ³⁰ ; England, UK	17,278,392 adult patients registered with GP EHR	COVID-19-related death	BMI <30	BMI 30–34.9: 1.05 (1.00–1.11); BMI 35–39.9: 1.40 (1.30–1.52); BMI ≥40: 1.92 (1.72–2.13)	Age, sex, smoking, ethnicity, IMD, blood pressure, respiratory disease, asthma, heart disease, diabetes mellitus, cancer, haematological malignancy, reduced kidney function, liver disease, stroke or dementia, other neurological disease, organ transplant, asplenia, rheumatoid arthritis or lupus or psoriasis, other immunosuppressive conditions

Units for BMI are kg/m². CAD, coronary artery disease; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; EHR, electronic health record; GP, general practice; ICU, intensive care unit; IMD, index of multiple deprivation; NA, not applicable; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UKB, UK biobank. ^aPositive association restricted to individuals aged <65 years. ^bSmoking and other comorbidities not independently associated. ^cBMI was associated strongly with positive test and risk of death related to COVID-19. Stronger associations in adults <70 years of age and those of non-white ethnicity. ^dNo association between obesity and death among those hospitalized. ^eStronger association of BMI with mortality with younger age (<60 years).

of age, sex, ethnicity and a variety of comorbidities¹¹. Similarly, in a study carried out in Louisiana, USA, patients with COVID-19 and obesity or with a recent (previous 12 months) BMI measurement ≥30 kg/m² had an adjusted OR of 1.43 for hospital admission, compared with patients who did not have obesity²⁵. Furthermore, increased risk of hospitalization for COVID-19 in individuals with obesity, independent of other determinants, has been reported from the UK Biobank²⁶ and a study in Brazil involving more than 10,000 patients²⁷. Moreover, several studies support that obesity is an important factor determining the severity of COVID-19 among hospitalized patients^{6,11,25,28–37}. End points in the aforementioned studies vary, and include ICU admission, intubation, mechanical ventilation and in-hospital death, as well as composite end points. Nevertheless, these studies uniformly observed increased risk of a more critical COVID-19 course among patients with obesity. For example, the multivariate adjusted OR for critical illness in patients with a BMI ≥40 kg/m² compared with patients of normal weight was 1.52 (95% CI 1.04–2.20) (REF.¹¹). Similarly, in a USA-wide study, patients with BMI ≥30 kg/m² were at 1.31-times higher risk of ICU admission than patients without obesity²⁸.

With regard to mortality, the relationship with obesity seems slightly less clear. Most studies could not confirm statistically significant independent associations, although point estimates of the OR suggest an increased risk of death in people with obesity^{11,25,28,38}; however, in some studies, composite end points were investigated^{6,31,39}. Nevertheless, studies from southern

California³⁵, New York City³⁷ and the UK Biobank³⁴ support our hypothesis that obesity is associated with increased mortality in COVID-19. This association might be stronger in younger people than in older people^{29,35,36}. The largest study investigating relationships of comorbidities and mortality in patients with COVID-19 was published on behalf of the National Health Service England OpenSAFELY, a secure health analytics platform covering 40% of all patients in England. Within OpenSAFELY, primary care records of 17,278,392 adults were anonymously linked to 10,926 COVID-19-related deaths. Patients with obesity had a higher multivariate adjusted risk of mortality compared with individuals without obesity and the highest risk of death was observed in individuals with a BMI >40 kg/m² (fully adjusted HR 1.92; 95% CI 1.72–2.13) (REF.³⁰).

To better estimate how obesity compares with other established comorbidities in predicting the risk of COVID-19-associated death, we have summarized the data about age, sex, obesity, smoking, diabetes mellitus, reduced kidney function, chronic respiratory disease, chronic liver disease and stroke or dementia (FIG. 1). Increasing age was most strongly associated with mortality risk, with those aged ≥80 years having a >20-fold increased risk compared with those aged 50–59 years (fully adjusted HR 20.61; 95% CI 18.72–22.70). In agreement with most of the previously published studies, male sex was also associated with an increased mortality risk (fully adjusted HR 1.59; 95% CI 1.53–1.65) (REF.³⁰). Furthermore, non-white ethnicity, deprivation and most comorbidities were associated with an increased

risk of death³⁰. However, the excess mortality associated with obesity is similar to or higher than that of many comorbidities, including hypertension, diabetes mellitus, asthma and other respiratory diseases or cancer³⁰.

Visceral obesity and severity of COVID-19. In individuals with or without obesity, disproportionate adipose tissue distribution, and particularly increased visceral adipose mass^{40,41}, strongly and independently predict an increased risk of cardiometabolic diseases. The relationships of BMI and adipose tissue distribution with COVID-19-related hospitalization in the ICU and/or invasive mechanical ventilation was investigated in 30 patients with COVID-19 from a medical centre in Berlin, Germany⁴². In this study, each 10 cm² increase in visceral adipose area measured by CT was associated with an OR of 1.37 (95% CI 1.07–1.89) for ICU treatment and an OR of 1.32 (95% CI 1.04–1.91) for mechanical ventilation (both adjusted for age and sex).



Fig. 1 | Selected estimated and adjusted hazard ratios for risk factors for COVID-19 death in OpenSAFELY. The data derive from Williamson et al.³⁰, using OpenSAFELY, a new data analytics platform created to address urgent questions relating to the epidemiology and treatment of coronavirus disease 2019 (COVID-19) in England. Error bars represent limits of the 95% confidence interval for the hazard ratio. All hazard ratios are adjusted for all other factors listed in figure 3 of the original publication by Williamson et al.³⁰, other than ethnicity. Total $n = 17,278,392$. The different colours show different categories of risk factor. eGFR, estimated glomerular filtration rate; OCS, oral corticosteroid; Ref, reference group. Adapted from REF.³⁰, Springer Nature Limited.

Interestingly, BMI was not associated with the severity of COVID-19 (REF.⁴²). Furthermore, a study investigating 150 patients with COVID-19 from an emergency department in Rome, Italy, found that for each unit of increase in the visceral adipose tissue area, measured by chest CT, there was an OR of 2.47 (95% CI 1.02–6.02) for the need for intensive care, independently of age, sex, diabetes mellitus, CVD, hypertension, kidney failure, inflammatory markers, malignancies, pharmacological treatment, total adipose tissue area and subcutaneous adipose tissue area⁴³. Interestingly, in the same statistical model, total adipose tissue area was no longer an independent determinant of the need for intensive care⁴³. In addition, using similar parameters for adjustment, a study investigating 143 patients with COVID-19 in a hospital in Wuhan, China, found that a high (≥ 1.33 in men and ≥ 0.71 in women) visceral to subcutaneous adipose tissue area ratio measured by abdominal CT (OR 2.47; 95% CI 1.05–5.98) was an independent risk factor for critical illness, compared with those with values below this threshold⁴⁴. If replicated in larger studies, these findings might support the hypothesis that visceral obesity is superior to general obesity in predicting the outcome in patients with COVID-19.

Hyperglycaemia and severity of COVID-19. Hyperglycaemia is independently associated with an increased risk of cardiometabolic diseases and mortality, even when it occurs in the non-diabetic range^{45–47}. Studies also support the relevance of hyperglycaemia for COVID-19 outcomes. For example, among 605 patients with COVID-19 in two hospitals in Wuhan, China, patients with a fasting blood glucose (FBG) level during hospital admission of 6.1–6.9 mmol/l had an adjusted OR of 2.61 (95% CI 1.64–4.41) for 28-day in-hospital complications, compared with patients with a FBG level <6.1 mmol/l (REF.¹³). Furthermore, among 461 patients with COVID-19 treated in six hospitals in Guangdong, China, FBG on admission (OR per mmol/l 1.22; 95% CI 1.05–1.40) was independently associated with poor 30-day outcome (acute respiratory distress syndrome, multiple organ dysfunction, ICU admission, septic shock or death), even after adjustment for pre-existing diabetes mellitus. The area under the curve of FBG for predicting poor 30-day outcome was 0.817 (95% CI 0.765–0.868) and the optimal FBG cut-off was ≥ 6.23 mmol/l, with a sensitivity of 75.6% and specificity of 77.0% (REF.⁴⁸).

In a cohort of 339 patients with COVID-19 who were consecutively hospitalized at four sites in Wenzhou, China, the presence of diabetes mellitus was associated with an approximately fourfold increased risk of severe COVID-19 illness (unadjusted OR 3.83; 95% CI 2.06–7.13). This association remained statistically significant after adjustment for age, sex, obesity, hypertension and smoking history (adjusted OR 2.05; 95% CI 1.01–4.19) (REF.⁴⁹). Furthermore, in a whole-population study among all individuals registered with general practice centres in England ($n = 61,414,470$), the multivariate-adjusted risk for in-hospital COVID-19-related death was 2.86 (95% CI 2.58–3.18) for patients with type 1 diabetes mellitus (T1DM) ($n = 263,830$) and 1.80 (95% CI 1.75–1.86) for those with T2DM ($n = 2,864,670$) (REF.⁵⁰).

Mendelian randomization analysis

A research method that provides evidence about putative causal relationships between modifiable risk factors and disease, using genetic variants.

Moreover, in this population-based cohort, increased COVID-19-related mortality was independently associated with cardiovascular and renal complications of diabetes mellitus and with glycaemic control and BMI⁵¹.

In a study of 453 patients with COVID-19 admitted to Union Hospital in Wuhan, China, patients with newly diagnosed diabetes mellitus had the highest risk of ICU admission (11.7% were admitted to ICU) and were most likely to require invasive mechanical ventilation (11.7%), followed by patients with known diabetes mellitus (4.1% ICU; 9.2% mechanical ventilation) and patients with hyperglycaemia (FBG 5.6–6.9 mmol/l and/or HbA_{1c} 5.7–6.4%: 6.2% ICU; 4.7% mechanical ventilation), compared with patients with normal glucose levels (1.5% ICU; 2.3% mechanical ventilation). The multivariable-adjusted hazard ratios of mortality among COVID-19 patients with hyperglycaemia, newly diagnosed diabetes mellitus or known diabetes mellitus compared with patients with normal glucose levels were 3.29 (95% CI 0.65–16.6), 9.42 (95% CI 2.18–40.7) and 4.63 (95% CI 1.02–21.0), respectively⁵².

Finally, the largest study addressing the relationship of blood levels of glucose at the point of hospital admission with the course of COVID-19 was an analysis that included 2,041 consecutive hospitalized patients with COVID-19 from Wuhan, China. This study showed that higher median glucose level during hospital stay or after critical diagnosis (≥ 6.1 mmol/l) was independently associated with increased risk of progression to critical disease or death among non-critical patients, as well as in-hospital mortality in patients with critical illness. Interestingly, in the same statistical model, diabetes mellitus, hypertension, chronic kidney disease, chronic obstructive pulmonary disease or cancer were not independent determinants of critical illness¹². Furthermore, data from Hubei, China, shows that mortality was much lower (adjusted HR 0.14; 95% CI 0.03–0.60) in hospitalized patients with COVID-19 and diabetes mellitus, with well-controlled glucose levels (glycaemic variability within 3.9–10.0 mmol/l) compared with patients with diabetes mellitus and poorly controlled glucose levels (upper limit of glycaemic variability exceeding 10.0 mmol/l) (REF.¹⁵). Taken together, these data indicate that good glucose control should be a critical target in patients with hyperglycaemia and COVID-19.

Of note, it cannot be excluded that hyperglycaemia during hospital admission for COVID-19 might simply be a marker of disease severity and not a modifiable risk factor that can alter outcome. In this respect, dexamethasone⁵³ was found to improve clinical outcomes in COVID-19 in the RECOVERY trial, despite the fact that it might precipitate hyperglycaemia in some individuals. However, because large studies^{30,51} found an independent relationship of increased HbA_{1c} with severe COVID-19, it is reasonable to assume that good glucose control could improve the clinical outcomes in COVID-19.

Mendelian randomization analyses. Findings from observational studies investigating the independent relationships of obesity and parameters of impaired metabolic health with COVID-19 are partly supported

by the genetically based approach of Mendelian randomization analysis. A study investigated, with Mendelian randomization, whether there is a causal effect of cardiometabolic traits on risk of severe COVID-19 (REF.⁵⁴). Genome-wide association study summary data were used from a study with 1,610 patients with severe COVID-19 with respiratory failure and 2,205 control individuals with no or mild COVID-19 symptoms⁵⁵. A higher genetically proxied (based on genetic variants) BMI was associated with increased risk of severe COVID-19 (OR 1.75; 95% CI 1.20–2.57). Interestingly, in that study, limited evidence was provided to support associations of genetically proxied lipid traits (that is, HDL-cholesterol, LDL-cholesterol or triglycerides), systolic blood pressure or T2DM susceptibility with risk of severe COVID-19. A limitation of this approach is that a Mendelian randomization study considers the lifelong effect of genetic variants that contribute to cardiometabolic traits, which is different from short-term measurement of specific parameters that might also strongly affect the outcome⁵⁴. Although the authors explored the association of genetically proxied T2DM susceptibility with risk of sepsis, they were not able to explore genetically proxied T2DM itself, as this is a binary trait. Thus, they cannot exclude that a causal relationship between T2DM (or glycaemic control) and sepsis risk might exist.

Cardiometabolic damage

To clarify why some patients experience severe COVID-19, it is important to better understand viral–host interactions and, more specifically, which human tissues and organs are most strongly affected by SARS-CoV-2 infection. SARS-CoV-2 enters target cells by the coronavirus spike protein, which engages angiotensin-converting enzyme 2 (ACE2) as an entry receptor. Cell entry also requires priming of the spike protein by the cellular serine protease TMPRSS2 (REFS^{56–59}). Quantification of the SARS-CoV-2 viral load of different human tissue samples revealed multiorgan tropism, and particularly high viral loads were found in the respiratory tract, and in myocardial, renal, neurological and gastrointestinal tissues^{60–65}. Furthermore, expression of ACE2 and TMPRSS2 is found in human lung alveolar epithelial cells, nasal goblet secretory cells, cholangiocytes, colonocytes, oesophageal keratinocytes, gastrointestinal epithelial cells, pancreatic β -cells and renal proximal tubules and podocytes^{60–65}. The mechanisms of interaction of SARS-CoV-2 with host cells and extrapulmonary manifestation of COVID-19 have been elegantly summarized and discussed^{8,65,66}. Here we summarize the effect of SARS-CoV-2 infection on cardiometabolic relevant tissues and organs, particularly in obesity (FIG. 2).

Endotheliitis and hypercoagulopathy in COVID-19.

Obesity is associated with hypercoagulability of the blood and an increased risk of thromboembolism. Mechanisms explaining this relationship involve chronic inflammation activating prothrombotic signalling pathways in platelets and other vascular cells and impaired fibrinolysis, mediated largely by increased production of plasminogen activator inhibitor 1 (PAI1)⁶⁷. In obesity, expression of PAI1 is predominantly upregulated

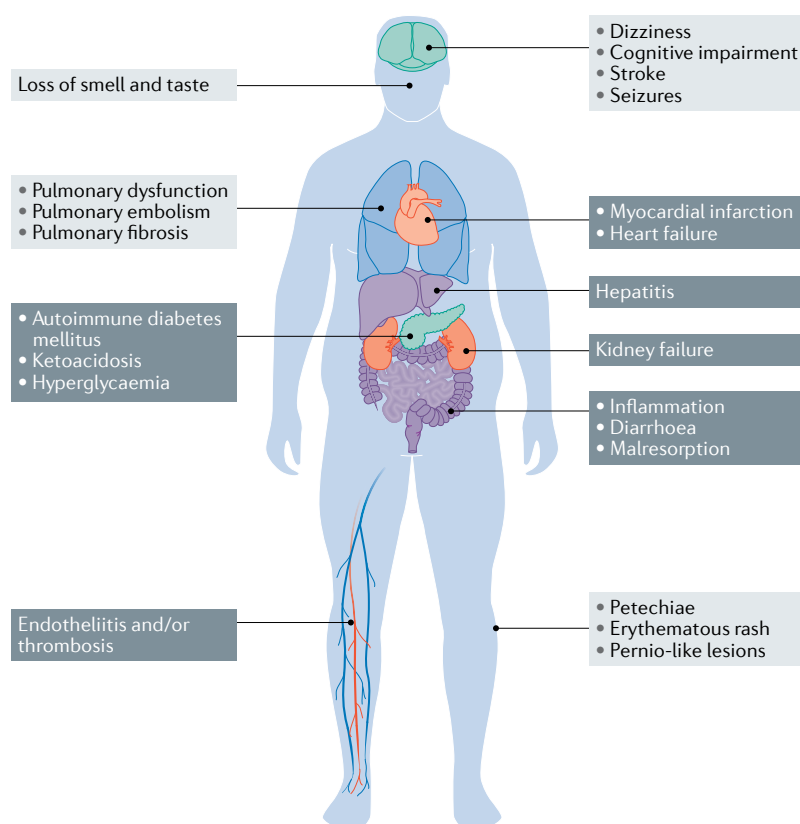


Fig. 2 | Pulmonary and extrapulmonary pathologies of COVID-19 and cardiometabolically relevant complications in patients with obesity. The pulmonary manifestations of coronavirus disease 2019 (COVID-19) caused by infection with severe acute respiratory syndrome coronavirus 2, including pneumonia and acute respiratory distress syndrome, are well recognized^{3–5}. Furthermore, neurological, gastrointestinal, dermatological and ophthalmological manifestations are being observed⁶⁵. The cardiometabolic complications that can occur in patients with COVID-19 are highlighted in darker grey.

in visceral adipose tissue, and plasma levels of PAI1 are elevated in patients with obesity or the metabolic syndrome^{68,69}. SARS-CoV-2 enters endothelial cells via ACE2 and induces endotheliitis and potentially thrombosis, not only in the lungs⁷⁰, but also across vascular beds of different organs, thereby increasing the risk of thrombosis⁷¹. In COVID-19, microthrombi formation and microvascular dysfunction are observed, which might be particularly critical in obesity, visceral adiposity and impaired metabolic health, phenotypes that are generally considered as being characterized by a prothrombotic state.

Myocardial injury in COVID-19. SARS-CoV-2-induced endotheliitis and microvascular dysfunction are also relevant for the myocardium. The cytokine storm that is observed in severe COVID-19 (REF.⁷²) is thought to result in vascular inflammation and atherosclerotic plaque instability, as well as in myocardial inflammation^{73–78}. An acute COVID-19 cardiovascular syndrome can occur, which is characterized by an acute cardiac injury with cardiomyopathy, ventricular arrhythmias and haemodynamic instability in the absence of obstructive coronary artery disease⁷⁵. The cause of this injury is uncertain but is suspected to be related to myocarditis, microvascular

injury, systemic cytokine-mediated injury or stress-related cardiomyopathy. ACE2 is highly expressed in arterial and venous endothelial cells, pericytes and also in cardiomyocytes. Therefore, acute cellular injury of cardiomyocytes caused by SARS-CoV-2 through ACE2-mediated entry and subsequent viral replication is considered important^{76–78}. These pathologies can result in clinical manifestation in patients with COVID-19, such as acute coronary syndrome, acute myocardial injury without obstructive coronary artery disease, arrhythmias, heart failure with or without cardiogenic shock, pericardial effusion and thromboembolic complications⁷⁵. Whether COVID-19 primarily induces CVD or whether cardiovascular complications are predominantly a consequence of severe COVID-19 is still unsolved⁷⁷. Most probably, both pathogenic courses are relevant for COVID-19.

Renal injury in COVID-19. Related to impaired metabolic health, chronic kidney disease is both a cause for increased morbidity and mortality in cardiometabolic diseases, and a consequence (for example, resulting from hypertension, hyperglycaemia, insulin resistance and subclinical inflammation)^{79,80}. Thus, renal injury in COVID-19 could be very important, particularly for patients with obesity and impaired metabolic health. In patients with COVID-19, acute renal injury is often observed and is associated with increased mortality^{65,81–83}. In the kidney, ACE2 is expressed in podocytes, mesangial cells, parietal epithelium of Bowman's capsule, proximal cell brush border and collecting ducts⁸³. Furthermore, ACE2 is implicated in the kidneys in reducing glomerular and tubular damage and fibrosis⁸³. Thus, increased entry of SARS-CoV-2 into renal cells, which results in infection and possibly reduced availability of the ACE2 receptor, together with SARS-CoV-2-induced microthrombi formation and microvascular dysfunction and pro-inflammatory cytokine expression, might explain the acute renal injury that is frequently observed in patients with COVID-19.

Hepatic injury in COVID-19. Liver dysfunction, particularly nonalcoholic fatty liver disease (NAFLD), is now accepted as a cause of impaired glucose and lipid metabolism, and as a consequence of obesity and impaired metabolic health^{84,85}. Moreover, this close relationship of NAFLD with impaired glucose and lipid metabolism resulted in experts advocating a new definition for NAFLD, that is, metabolic associated fatty liver disease (MAFLD)⁸⁶. The new definition more strongly supports hepatic steatosis being an important non-communicable disease. In a small study from Wenzhou, China, 55 patients with COVID-19 aged <60 years with MAFLD were 1:1 matched by age, sex and obesity status to patients infected with SARS-CoV-2 without MAFLD; in this study, MAFLD was associated with a fourfold (OR 4.07; 95% CI 1.20–13.79) increased risk of severe COVID-19 (REF.⁸⁷). Furthermore, in a cohort of 310 patients with COVID-19 in Zhejiang Province, China, the fibrosis-4 index (adjusted OR 1.90; 95% CI 1.33–2.72) and the NAFLD fibrosis score (adjusted OR 2.57; 95% CI 1.73–3.82) were significantly associated

Endotheliitis

An inflammatory immune response within the endothelium of blood vessels.

Cytokine storm

A proinflammatory state characterized by release of multiple proinflammatory cytokines and chemokines.

with greater severity of COVID-19, independently of sex, obesity, diabetes mellitus and presence or absence of MAFLD⁸⁸.

Thus, knowledge about the susceptibility of patients with liver disease to severe COVID-19 and any consequent hepatic injury is very important for patients with obesity and impaired metabolic health. In critically ill and hospitalized patients with COVID-19, markers of hepatocellular injury are frequently observed (14–53% of patients)^{66,89}. Although several studies investigated the prognostic value of abnormal liver function test in patients with COVID-19 (for example, for disease progression, ICU admission, length of hospital stay and mortality), the results are inconclusive⁸⁹. Single-cell RNA-sequencing studies in human liver identified *ACE2* mRNA expressed in a subpopulation of cholangiocytes and only very limited or no expression in hepatocytes; expression was not observed in any other liver cell type^{90,91}. Furthermore, single-cell RNA-sequencing analysis in human liver samples did not predict hepatocyte infection by SARS-CoV-2 (REF.⁹¹). In addition, data from a US clinical study including 1,827 hospitalized patients with COVID-19 indicated that any liver damage was predominantly hepatocellular, rather than cholestatic, which suggests no direct cytopathic effects by SARS-CoV-2 in the liver⁹².

Of note, in whole liver samples, *ACE2* and *TM6SS2* mRNA expression was increased in patients with T2DM and increased liver fat content⁹³. Furthermore, cytokine storm and hypoxia-induced organ damage^{66,94} might be very important in the liver. In this respect, endotheliitis has also been observed in the liver of patients with COVID-19 (REFS^{71,95,96}). Furthermore, fibrin microthrombi were found in liver sinusoids. In addition, in liver biopsy samples taken at autopsy from individuals who died of COVID-19, massive dilation of portal vein branches, luminal thrombosis, portal tract fibrosis and microthrombi in the sinusoids was observed^{71,95,96}.

Gastrointestinal injury in COVID-19. Compared with several other human tissues, by far the highest expression of *ACE2* was found in the small intestine, followed by the colon and the duodenum⁹⁰. Furthermore, in small intestinal organoids, enterocytes were readily infected by SARS-CoV (the virus that causes severe acute respiratory syndrome, SARS) and SARS-CoV-2, and these enterocytes produced infectious viral particles⁹⁷. In addition, gastrointestinal symptoms are observed in a subset of patients with COVID-19 (REF.⁹⁸).

The gut has a well-established and important role in the regulation of adipose tissue mass and of glucose and lipid metabolism. A Western diet induces dysregulation of the intestinal microbiome composition, resulting in disruption of the intestinal barrier and translocation of gut microbiota, metabolites and activated immune cells into the circulation^{99,100}. Predominantly via such a leaky gut, bacteria-derived products are considered to contribute to the pathogenesis of metabolic diseases, inducing adipose tissue inflammation, hepatic steatosis and hepatic inflammation^{100,101}. In mice, feeding of a high-fat diet was found to induce a proinflammatory condition in the gut, which was associated with an increase in

IL-17-producing cells, an increase in IFN γ -producing T helper 1 (T_H1) cells and CD8⁺ T cells, and a concomitant reduction in regulatory T cells¹⁰². In patients with COVID-19, an increase in IL-17-producing T_H17 cells and high cytotoxicity of CD8⁺ T cells are observed in the peripheral blood¹⁰³, which are thought to have important roles in the cytokine storm of COVID-19 (REFS^{104–106}). Thus, very similar proinflammatory characteristics seem to be present in the gut of patients with severe COVID-19 and individuals with metabolically unhealthy obesity who consume a Western diet.

Pancreatic injury in COVID-19. Finally, among the cardiometabolically relevant organs, the pancreas is a crucial target of SARS-CoV-2. Applying two single-cell RNA-sequencing data sets, a study found that *ACE2* was expressed in both the exocrine glands and the islets¹⁰⁷. In addition, in that study few patients (1.85%) with mild COVID-19 had increased levels of amylase and lipase. However, in patients with severe COVID-19, 17.91% of the patients had increased levels of amylase and 16.41% had increased levels of lipase¹⁰⁷. CT scans of patients with severe COVID-19 showed changes in the pancreas, mainly focal enlargement of the pancreas or dilation of the pancreatic duct, without acute necrosis, and some patients had symptoms of acute pancreatitis¹⁰⁷.

In respect of endocrinological complications of severe COVID-19, islet cell damage is critical. A 2010 study found that *ACE2* protein was strongly expressed in the pancreatic islets¹⁰⁸. Furthermore, in a study of patients with SARS, SARS-CoV-associated damage occurred in the kidney, heart, lung and endocrine part of the pancreas. In addition, during a 3-year follow-up period, a higher incidence of diabetes mellitus was found in patients who recovered from SARS (who were not treated with glucocorticoids), compared with uninfected control individuals¹⁰⁸.

The risk of β -cell damage induced by SARS-CoV and SARS-CoV-2 might also result in acute complications. In this respect, several cases of newly diagnosed diabetes mellitus were reported in patients with COVID-19, with and without pre-existing comorbidities, which were often accompanied by ketoacidosis¹⁰⁹. In a Chinese study, SARS-CoV-2 infection was associated with ketoacidosis. Furthermore, from a total of 42 patients in this study with COVID-19-associated ketosis and ketoacidosis, 27 patients had ketoacidosis without a diagnosis of diabetes mellitus¹¹⁰. Furthermore, a London study identified 35 patients with COVID-19 who presented with diabetic ketoacidosis (DKA) (31.4%), mixed DKA and hyperosmolar hyperglycaemic state (HHS) (37.1%), HHS (5.7%) or hyperglycaemic ketosis (25.7%). In that study a very high prevalence (80%) of patients with T2DM presented with DKA, which indicates acute insulinopenia in patients with COVID-19 and T2DM. Furthermore, 5.7% of the 35 patients with COVID-19 had newly diagnosed diabetes mellitus¹¹¹. Thus, insulin resistance and insulinopenia in a subset of critically ill patients with COVID-19 might result in an increased incidence of diabetes mellitus and a complicated course in patients with diagnosed diabetes mellitus^{112,113}. This issue is currently under intense investigation¹¹⁴.

Western diet

A diet that is rich in processed foods, saturated fat and sugar.

Long-term effects of the pandemic

Data are just emerging regarding the effect of the COVID-19 pandemic on the prevalence and incidence of obesity and cardiometabolic diseases during a long-term follow-up (FIG. 3). Direct effects might include organ dysfunction in affected patients. However, indirect effects could also occur, such as effects on health care for patients without COVID-19 or effects on health-related behaviour, which is strongly dependent on regional lockdown measures and public perception and/or fear of infection.

Effects of the COVID-19 pandemic on the obesity pandemic. When investigating the long-term effects of the COVID-19 pandemic, it is important to separate the health consequences of SARS-CoV-2 infection from the effect of the COVID-19 pandemic on behaviour and lifestyle of non-infected people. After the SARS pandemic in 2003, physicians observed a high rate of patients with SARS who continued to have clinical symptoms weeks and months after they recovered from the acute infection. For example, one study investigated health-care workers from Toronto, Canada, who remained unable to return to their former occupation

after a mean 19.8 months (range 13–36 months) following SARS. In these patients, a very high rate of a chronic post-SARS syndrome was observed, which was characterized by chronic fatigue, pain, weakness, depression and sleep disturbance¹¹⁵. Furthermore, in a multicentre prospective follow-up study of 52 survivors of Middle East respiratory syndrome (MERS, caused by the related MERS-CoV) in the Republic of Korea, 48% and 33% of the patients had clinically relevant chronic fatigue after 12 (referred to as T1) and 18 (referred to as T2) months of follow-up, respectively. Post-traumatic stress symptoms were found in 42% of patients at T1 and 27% at T2, and clinically relevant depressive symptoms were found in 27% of patients at T1 and 17% at T2. Among these patients, chronic fatigue was found to induce post-traumatic stress symptoms partly through provoking depression¹¹⁶. A meta-analysis of 28 studies, which included 2,820 patients with SARS or MERS, examined long-term outcomes and reported high rates of post-traumatic stress disorder (38%), depression (33%) and anxiety (30%) at 6 months following illness, as well as pulmonary dysfunction, reduced exercise tolerance and reduced health-related quality of life^{117,118}.

In patients who had recovered from COVID-19 after having been hospitalized in Rome, Italy, 87.4% reported persistence of at least one symptom, particularly fatigue and dyspnoea, when assessed after a mean of 60.3 (s.d. 13.6) days after symptom onset¹¹⁹. Of note, in young healthy men, a decrease in daily physical activity for only 2 weeks results in a loss of muscle mass and an increase in visceral adipose mass, insulin resistance and increased plasma levels of triglyceride¹²⁰. Therefore, physical deconditioning and sarcopenia from bed rest and physical inactivity during COVID-19 might strongly impair metabolism in many patients. Finally, because there is a bidirectional relationship of anxiety and depression with obesity¹²¹, post-COVID-19 depression, chronic fatigue and post-traumatic stress symptoms might induce weight gain.

COVID-19 could also influence obesity development in people who are not infected by SARS-CoV-2. For example, among 123 patients with obesity from a clinic in Texas, two patients tested positive for SARS-CoV-2 and 14.6% reported symptoms. However, a total of 72.8% of patients reported increased anxiety and 83.6% reported increased depression since stay-at-home orders were initiated. Furthermore, 69.6% of the patients reported more difficulty in achieving weight-loss goals. More specifically, during lockdown conditions, patients spent less time exercising (47.9%) and at a decreased intensity (55.8%), increased their stockpiling of food (49.6%) and reported increased stress eating (61.2%)¹²².

A decrease in physical activity in particular is being observed during the COVID-19 pandemic. For example, based on estimates of step counts in more than 30 million people in Europe, a reduction in physical activity ranging between 7% and 38% is being assumed during the pandemic^{123,124}. The complex of physical, emotional, social and financial challenges that individuals face during the pandemic also affects food purchasing and consumption habits. Positive experiences in terms of household food behaviours (for example, home-cooking,

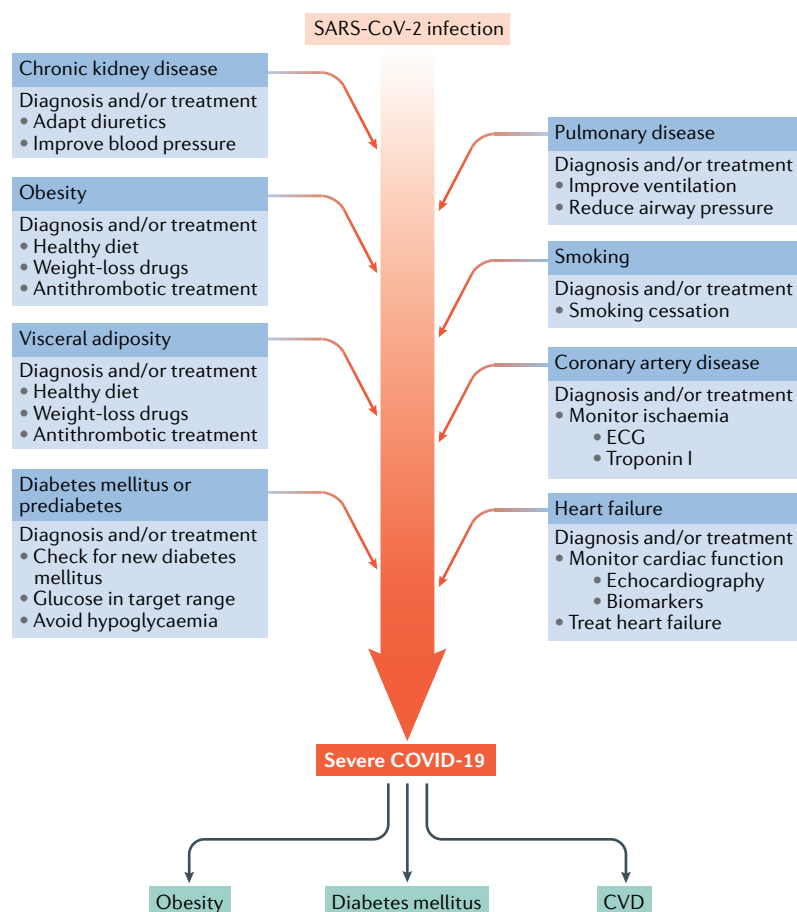


Fig. 3 | **Selected causes, consequences and treatment of severe COVID-19.**

Important risk factors for a severe course of coronavirus disease 2019 (COVID-19) and suggestions for their treatment during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are depicted. Furthermore, the figure highlights that obesity and cardiometabolic diseases could be a consequence of a severe course of COVID-19. CVD, cardiovascular disease; ECG, electrocardiogram.

food sharing and increased attention to diet) during lockdowns are contrasted by exacerbated food insecurity and decreased affordability, particularly among vulnerable groups¹²⁵. Persistent food insecurity is associated with a sustained diet of cheap and energy-dense foods, which could lead to a rise in rates of obesity¹²⁶. In addition to changes in lifestyle, the COVID-19 pandemic could also considerably affect the treatment of obesity. For example, a delay in bariatric surgery for patients with morbid obesity has been observed¹²⁷. In Italy, elective bariatric and metabolic surgery was cancelled on 21 February 2020 and it was gradually restarted on 4 May 2020 (REF.¹²⁸). These data suggest that the COVID-19 pandemic considerably affects patients with obesity, regardless of infection status^{129,130}.

Effects of the COVID-19 pandemic on cardiometabolic health. Novel data suggest that persistent myocardial injury might occur in patients who have recently recovered from COVID-19. A study from Germany investigated the characteristics, cardiac blood markers and cardiovascular MRI data of 100 patients who had recovered from COVID-19, as well as an age-matched and sex-matched control group of 50 healthy volunteers and 57 cardiometabolic risk factor-matched individuals¹³¹. In that study, cardiovascular MRI revealed cardiac involvement in 78% and ongoing myocardial inflammation in 60% of the patients who had recovered from COVID-19, independent of pre-existing conditions, or the severity and overall course of the acute illness, or time from the original diagnosis¹³¹. These data support the need for further investigation of the long-term CVD consequences of COVID-19.

With respect to diabetes mellitus, an increase in its prevalence and a worsening of glucose control is expected. A study from India analysed demographic and clinical data from 100 apparently healthy household members (related or unrelated) of patients with T2DM, which were collected for 49 days of lockdown. In that study, a trend for weight gain was observed in 40% of the cohort, with 16% of the population experiencing a 2.1–5.0 kg increase in weight. Furthermore, an increase in the American Diabetes Association risk score occurred in 7% of the population¹³². A second study by the same authors investigated the effect of lockdown duration on glycaemic control and complications related to diabetes mellitus. A simulation model was generated using glycaemic data from previous disasters (taken as similar in effect to the current lockdown) on baseline HbA_{1c} and complications related to diabetes mellitus from an India-specific database. The researchers found that the predicted relative increment in HbA_{1c} from baseline to the end of 30 days and 45 days of lockdown was projected as 2.26% and 3.68%, respectively. Furthermore, they estimated that the percentage increase in rates of diabetic complications at the end of a 30-day lockdown amounted to 2.8% for non-proliferative diabetic retinopathy, 2.9% for proliferative diabetic retinopathy, 1.5% for retinal photocoagulation, 9.3% for microalbuminuria, 14.2% for proteinuria, 2.9% for peripheral neuropathy, 10.5% for lower extremity amputation, 0.9% for myocardial infarction, 0.5% for stroke and 0.5% for infections¹³³.

It remains to be seen whether such increases will be observed after the COVID-19 pandemic.

Importantly, the COVID-19 pandemic is thought to affect the behaviour of patients and their health-care providers^{134,135}. For example, in children and adolescents with T1DM that was newly diagnosed during the COVID-19 pandemic in Germany, an alarming increase in the incidence of DKA was observed. The researchers found a higher incidence of DKA compared with the previous 2 years (44.7% in 2020 versus 24.5% in 2019; adjusted risk ratio 1.84 (95% CI 1.54–2.21) versus 24.1% in 2018; adjusted risk ratio 1.85 (95% CI 1.54–2.24))¹³⁶. The underlying causes were hypothesized to be multifactorial, including reduced access to medical services, fear of approaching the health-care system and more complex psychosocial factors¹³⁶.

During the first months of the COVID-19 pandemic, the numbers of deaths unrelated to COVID-19 increased¹³⁷. This change could partly be explained by a substantial increase in the number of avoidable cancer deaths; for example, as suggested for the UK, an increase in cancer-related death is to be expected as a result of diagnostic delays due to the COVID-19 pandemic¹³⁸. Moreover, CVD-associated morbidity and mortality are expected to increase. For example, a UK study reported a statistically significantly lower admission rate for acute heart failure during a study period between 2 March and 19 April 2020, when compared with a pre-COVID-19 cohort or the corresponding time periods in 2017–2019 (REF.¹³⁹). Whether the incidence of acute heart failure has actually declined is unclear; however, observations of a decline in acute coronary syndrome admissions in Austria since the outbreak of COVID-19 support the suggestion that patients showed a reluctance to attend hospitals when the symptoms of cardiac dysfunction occurred¹⁴⁰. It remains to be investigated whether such delays in seeking medical care will be associated with worse long-term outcomes. Finally, during the COVID-19 pandemic, a large decline in the level of habitual physical activity was observed in patients with heart failure¹⁴¹, which could also considerably affect heart health in patients with heart disease.

Treating obesity in the COVID-19 pandemic

Considering the strong effects of overweight, obesity and impaired metabolic health on the course of COVID-19, achieving reductions in adipose tissue mass and improvements in metabolic health is crucial. Here, two questions are relevant. First, how should we manage patients who are infected with SARS-CoV-2 to achieve this goal? Second, what are the best strategies for this purpose in people who have recovered from COVID-19 or who have not been infected yet?

Treatment of patients with metabolically unhealthy obesity and COVID-19. Supportive and intensive care treatment of patients with COVID-19 is well established⁸. Furthermore, encouraging new results from clinical trials with antiviral drugs (remdesivir)¹⁴² and immunomodulatory drugs (dexamethasone)⁵³ in patients with severe COVID-19 have been published. However, as discussed by Clifford Lane and Anthony S. Fauci¹⁴³, despite the

Mediterranean diet

A diet characterized by fairly high consumption of olive oil, legumes, unrefined cereals, fruits, vegetables and fish and moderate consumption of dairy products.

expected reduction in morbidity and mortality that might occur when these drugs are more often used, many people with COVID-19 will still die. Thus, there is hope that new therapeutic agents, such as monoclonal antibodies, more selective immunosuppressive agents and vaccines against this disease^{8,143}, will help to lower the number of complications and mortality in patients with COVID-19.

In patients with metabolically unhealthy obesity, close monitoring of the clinical development of COVID-19 is necessary during the acute phase of infection, owing to the increased risk of a complicated course. Furthermore, biomarkers of pulmonary, cardiac, liver and renal function, as well as of glycaemic control, should be used early in the disease course to assess the progression of the disease^{75,112,113}. In general, the acute COVID-19 cardiovascular syndrome should be managed by a multidisciplinary team that includes infectious disease consultation to help guide therapy selection⁷⁵. For diabetes mellitus, treatment should aim for reduction of hyperglycaemia into the target range, using, wherever possible, drugs that have a low risk of hypoglycaemia, lactic acidosis and ketoacidosis, and fluid retention^{112,113}.

Treatment of people with metabolically unhealthy obesity without COVID-19. Owing to the striking resemblance between the mechanisms by which obesity and impaired metabolic health affect the risk of cardiometabolic diseases and severe COVID-19 (REFS^{16,22,40,41,65,66}), preventive measures taken to reduce the risk of cardiometabolic diseases could also decrease the risk of severe COVID-19. Furthermore, obesity and impaired metabolic health might adversely influence the efficacy of vaccines against SARS-CoV-2 (REFS^{144–147}). For example, patients with obesity and/or T2DM show immune senescence and accelerated ageing of the immune system, particularly of the CD4⁺ and CD8⁺ T cell compartments^{148,149}. In addition, reduced influenza vaccine efficacy has been observed in people with obesity^{150–153}. One study reported that although people with obesity do not have an impaired initial response to influenza vaccination, the percentage of influenza-activated CD8⁺ T cells (which kill virus-infected cells) and two markers of functional CD8⁺ T cell activity (IFN γ and granzyme B) were found to decrease substantially 12 months after vaccination in people with obesity, compared with individuals with normal weight¹⁵¹. Furthermore, in 7 patients with T1DM and 41 patients with T2DM, a higher HbA_{1c} tended to be associated with a lower immune response to an influenza A (H1N1) vaccine, independently of age, sex and BMI¹⁵⁴. Therefore, in the efficacy analyses of the results of the ongoing vaccine trials, measures of obesity and hyperglycaemia need to be carefully taken into account.

Altogether, preventive measures for obesity and cardiometabolic diseases need to be taken at patient level and in the public health sector. When targeting obesity and visceral obesity, most clinical guidelines recommend an initial loss of 5–8% of total body weight for individuals with overweight or obesity, to prevent cardiometabolic diseases^{155,156}. However, increased weight loss might be necessary to decrease this risk, particularly for people with more severe obesity (class II (BMI 35.0–39.9 kg/m²)

and III (BMI ≥ 40 kg/m²))¹⁵⁷. In people with obesity, lifestyle intervention, including a reduction in caloric intake and an increase in physical activity, is effective in decreasing adipose tissue mass and the risk of cardiometabolic diseases^{155,156}. The PREDIMED trial demonstrated that an adapted ad libitum Mediterranean diet over a median follow-up of 4.8 years reduced the risk of cardiovascular events by ~30% in people who were at high cardiovascular risk, but with no cardiovascular disease at enrolment, compared with a control diet, despite having little effect on body weight^{158,159}. Therefore, people with metabolically unhealthy obesity might be advised to switch to a Mediterranean diet to reduce their cardiometabolic risk.

Evidence is accumulating about the beneficial cardiometabolic effects of a ketogenic (that is, high-fat and very-low-carbohydrate) diet. Ketones have very well-documented neuroprotective, hepatoprotective and cardioprotective effects^{160,161}. Moreover, ketogenic diets were found to alter the human and mouse gut microbiome, distinct from a high-fat diet. Importantly, the ketogenic diet decreased the levels of intestinal pro-inflammatory T_H17 cells in mice¹⁶², the cell type that is thought to largely contribute to the proinflammatory response observed in COVID-19 (REFS^{104–106}). Thus, it is worth investigating whether a ketogenic diet as a weight-loss strategy might be superior to other weight-loss strategies in the context of COVID-19. However, as a ketogenic diet might increase the risk of DKA¹⁶³, it should not be continued in patients with diabetes mellitus who are infected with SARS-CoV-2.

At the patient level, the first steps to reduce body adipose tissue mass and improve metabolic health are lifestyle counselling to implement an energy deficit, healthy nutrition and to increase physical activity¹⁶⁴. If these measures are not effective, pharmacological treatment should be started as an adjunct to the aforementioned lifestyle intervention. Medications can be considered in adults who have a BMI ≥ 30 kg/m² or a BMI of 27–29 kg/m² with at least one weight-related coexisting condition^{165–167}. In patients without T2DM, approved medications to reduce elevated body weight include orlistat, phentermine, phentermine–topiramate, naltrexone–bupropion and liraglutide^{165–167}. In patients with obesity and T2DM, glucagon-like peptide 1 receptor agonists and sodium–glucose cotransporter 2 inhibitors should preferentially be used, because they were shown to have cardiovascular and heart failure benefits that were also associated with weight loss¹⁶⁸. For patients with severe obesity or for patients with obesity who cannot achieve the recommended amount of weight loss and/or the improvement in metabolic health, bariatric surgery should be considered. In patients with obesity, bariatric surgery is very effective in reducing adipose tissue mass and lowering the long-term risk of cardiometabolic diseases and all-cause mortality, compared with weight-matched non-surgical patients. Thus, bariatric surgery could be an important therapeutic option in many people with severe obesity, particularly during the COVID-19 pandemic¹²⁹ (FIG. 4).

To combat the obesity pandemic, strong measures should also be taken in the public health sector,

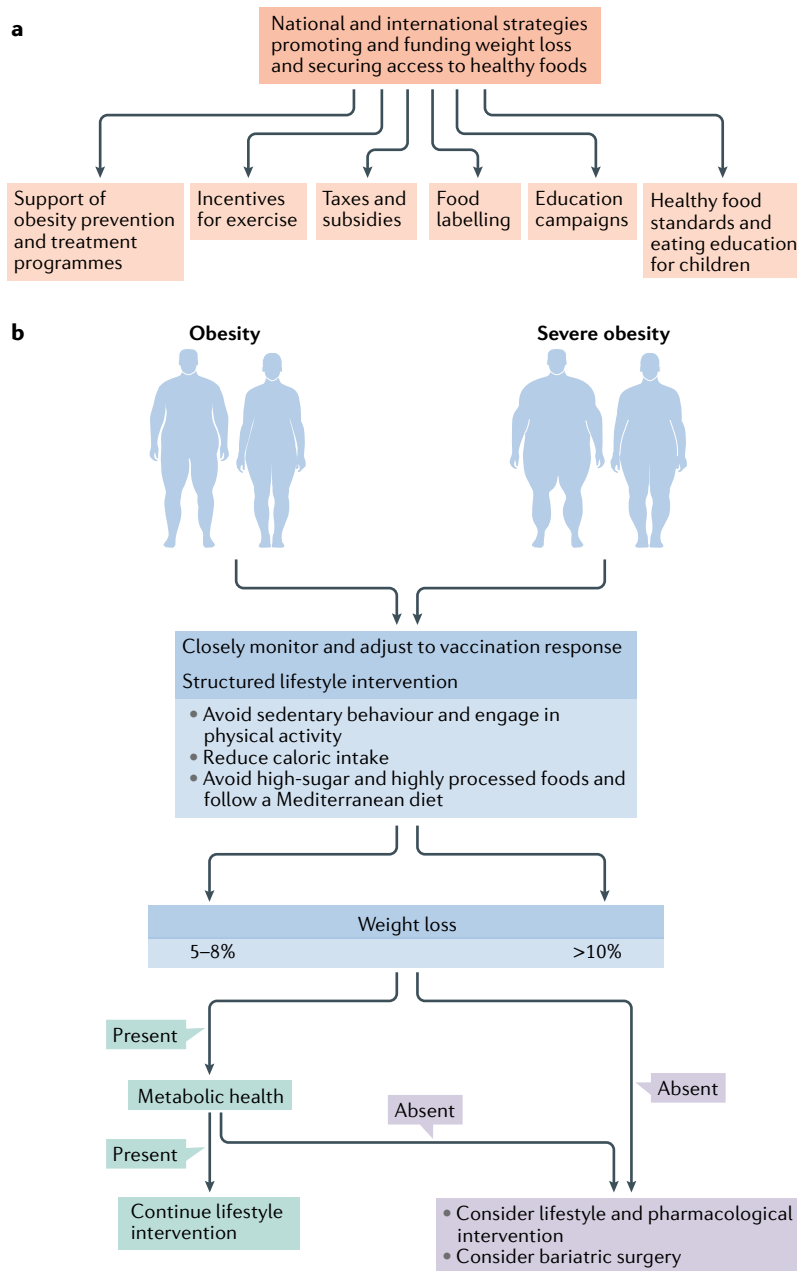


Fig. 4 | Political and patient level measures to prevent and treat obesity and impaired metabolic health. **a** | Political measures to promote weight loss and access to healthy foods should include different instruments, for example, related to nutrition education, food quality standards in schools, economic instruments and nutrition labelling. **b** | Patient-level measures to treat obesity and impaired metabolic health should define different targets of weight loss by lifestyle intervention depending on the degree of obesity. If these measures are not effective in reducing body weight and/or bringing about metabolic health, pharmacological treatment should be started as an adjunct to the aforementioned lifestyle intervention, and bariatric surgery might be necessary in some patients.

to reduce adipose tissue mass and improve metabolic health in the population. In this respect, health professionals and politicians should now, more than ever, promote the health benefits of physical activity and support efforts to implement programmes and policies to facilitate increased physical activity (FIG. 4). These measures could include support of sports federations, sports clubs,

schools and employers to implement safety measures during the COVID-19 pandemic. Furthermore, governments should help organizations that provide physical activity programmes and schools to find new ways to ensure that physical activity levels can be maintained and increased. In addition, governments should supply incentives to support an active lifestyle. Importantly, the prevalence of obesity and impaired metabolic health is particularly elevated in people with low socioeconomic status and in some ethnic groups¹⁶⁹. As such, politicians and health-care providers should use diverse ways of communication specifically to reach out to these communities, and should consider policies that increase access to sport and leisure facilities, and healthy foods, for all.

Examples of how food policies could be implemented to more effectively prevent obesity at the population level were suggested in a 2015 article¹⁷⁰. A range of disciplines need to be integrated (for example, politics, psychology, economics and public health nutrition) to develop a theory of change to understand how food policies work. Here the interaction between human food preferences and the environment in which those preferences are learned, framed and re-evaluated is critical. Such food policies involve school settings, economic instruments and nutrition labelling. Furthermore, they need to be accompanied by incentives for an increase in physical activity (FIG. 4).

As an example of such a coordinated effort on the political level, the UK government initiated a national campaign to encourage millions of adults to kick start their health and reduce their risk of serious illness, including COVID-19 (REF. ¹⁷¹). This campaign is based on the observation that people with obesity are considerably more likely to become seriously ill and be admitted to intensive care with COVID-19 compared with those with a healthy BMI. The campaign provides access to several apps and tools to help people stay in shape and make healthier food choices to prevent future weight gain. Furthermore, it includes TV advertisements, digital, print, radio and out of home advertising, and content across social media. In addition, press release and partnership activity will take place to motivate people to get active, eat better, drink less alcohol and quit smoking¹⁷¹. Finally, public communication of the increased risk of a severe COVID-19 that is brought about by obesity, such as is being done by the British Prime Minister Boris Johnson¹⁷², might be very effective in reaching many people and motivating them to lose weight.

Besides such educational efforts, governments should clearly admit their responsibility to implement comprehensive food policies to effectively reduce overweight and obesity in the general population, including necessary legislative measures¹⁷³. Using the UK example, the campaign mentioned above is part of a national strategy including several other measures, for example banning advertisements for unhealthy foods, restriction on price incentives for such foods and clear food labelling; however, this strategy has still been criticized for its strong focus on individual responsibility^{174,175}. Evidence-based public health nutrition interventions to fight the obesity pandemic exist¹⁶⁹, and more than ever it is time to take this issue seriously.

Importantly, further research is needed to better understand the variability in the health response to diet, particularly during the COVID-19 pandemic. To this end, Griffin P. Rodgers and Francis S. Collins from the National Institutes of Health (NIH) highlighted the 2020–2030 Strategic Plan for NIH Nutrition Research. They discussed that it is important to explore and understand how diet and nutritional status modify the immune response. Furthermore, this knowledge could help explain some of the variability in COVID-19 morbidity and mortality¹⁷⁶. Funding within this programme includes research that helps to better understand the role of nutrition in improving health and reducing the burden of disease throughout life and across generations. For example, interactions of nutrition with other potentially modifiable exposures such as the microbiome will be investigated as well as how to use this holistic knowledge to develop and implement actionable recommendations¹⁷⁷.

Conclusions

Based on data from large studies that investigated relationships of comorbidities with the course of COVID-19 using multivariate adjustment, obesity emerged as a strong and independent determinant of increased risk

of morbidity and mortality in patients infected with SARS-CoV-2. Furthermore, novel data suggest that visceral obesity and hyperglycaemia in the non-diabetic and diabetic range could also be important independent risk factors for severe COVID-19. In addition, as obesity and diabetes mellitus have been found to impair the development of immunological memory (for example, after influenza vaccination), it cannot be excluded that obesity and hyperglycaemia might also negatively affect the efficiency of a SARS-CoV-2 vaccine. These relationships, as well as the knowledge that metabolic processes largely determine the course of COVID-19, suggest that treating obesity and cardiometabolic complications might be very effective in overcoming acute SARS-CoV-2 infection, and also in reducing the risk of post-COVID-19 cardiometabolic diseases and obesity. Weight loss and improvement of metabolic health in people with obesity and/or those who are metabolically unhealthy might help them to better cope with COVID-19. Newly launched national and international programmes at the political level and in the public health sector, as well as projected novel research funding are more than welcome to help achieve this important goal.

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