

REVIEW ARTICLE



Epidemiology and Population Health

Obesity and infectious diseases: pathophysiology and epidemiology of a double pandemic condition

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The current pandemic due to widespread SARS-CoV-19 infection has again highlighted the role of obesity, whose global prevalence increased up to 13%, as a risk factor for both susceptibility to infections and the occurrence of a more severe disease course. To date, this association has not been sufficiently explored. Obesity-related susceptibility to infectious diseases is mostly thought to be due to an impairment of both innate and adaptive immune responses and vitamin D deficiency. Several cofactors can indirectly favour the onset and/or worsening of infectious diseases, such as impairment of respiratory mechanics, skin and subcutaneous tissue homeostasis, obesity-related comorbidities and inappropriate antimicrobial therapy. Subjects with obesity have a higher incidence of cutaneous infections, probably due to changes in skin barrier functions and wound healing. Excess weight is also associated with an increased risk of urinary tract infection and its recurrence, as well as with a higher prevalence of both lower and higher respiratory tract infections. Moreover, patients with obesity appear to have an increased risk of surgical site infections when undergoing general, orthopaedic, gynaecological, and bariatric surgery. Data concerning the different infectious diseases related to obesity are rather limited since anthropometric parameters are usually poorly recorded. Furthermore, specific therapeutic protocols in subjects with obesity are lacking, especially regarding antibiotic therapy and further supplements. This review summarizes etiopathogenetic and epidemiological evidence and highlights areas of uncertainty in the field of infectious diseases and obesity, which require further research. It is important to raise public awareness of this additional risk related to obesity and to raise awareness among the scientific community to develop specific clinical protocols for subjects with obesity.

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INTRODUCTION

According to a recent estimate from the World Health Organization (WHO), at least 2.8 million of people die per year due to complications related to overweight or obesity (<https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>). Moreover, an estimated 35.8 million (2.3%) of global Disability-Adjusted Life Years (DALYs) are caused by overweight or obesity (<https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>). Worldwide, obesity has nearly tripled since 1975: currently, more than 1.9 billion adults are overweight, and more than 650 million of them are obese (39% of adults are overweight and 13% obese, according to the WHO) (<https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>), although obesity is defined as a real pandemic (<https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>).

In the era of a serious health crisis due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, emerging data have demonstrated that obesity is a risk factor for infections and worsens the course and prognosis of diseases,

leading to higher mortality rates [1]. Considering the above, an understanding of both mechanisms underlying the association between obesity and infectious diseases and the identification of more effective treatment strategies is urgently needed. By examining data on the incidence and prognosis of the most common infections in subjects with obesity, in regard to the flu, several meta-analyses and epidemiological studies disclosed an association between obesity and more severe prognosis, increased risk of admission to the intensive care unit (ICU) and death in subjects with H1N1 (Table 1); however, a higher incidence of infection in subjects with obesity has not been demonstrated [2–6]. Several other recent studies have shown an association between obesity and an increased risk of urinary tract infection (UTI), especially posttraumatic, ICU-acquired, pregnancy-related and postpartum [7–10]. Different cohort studies reported a close relation between obesity and the risk of nosocomial infections [11, 12], skin and surgical site infections (SSIs) [13–16], longer hospitalization and higher incidence rates of sepsis [17, 18]. Obesity is a risk factor for infectious pancreatitis [19], including its

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Table 1. Epidemiological studies on H1N1 respiratory infection and obesity.

Author	Experimental design	Country	No. of enrolled subjects	Age enrollment (years)	Infection	No. of obese subjects	Outcome
Fezeu et al. [2]	Systematic review and meta-analysis	Canada, USA, Ireland, France, Netherlands	3059 subjects from 6 cross-sectional studies.	0–92	H1N1	—	Obesity is associated with higher risks of intensive care unit (ICU) admission or death in patients with influenza A (H1N1) infection.
Van Kerkhove [3]	Global pooled analyses	19 countries	70,000 patients requiring hospitalization, 9700 patients admitted to ICU, and 2500 fatalities	—	H1N1	—	Morbid obesity is a risk factor for ICU admission and fatal outcome.
Murphy et al. [4]	Cross-sectional study	England	8407	48 (35–63)	H1N1	2159	Obesity was not associated with an increase in self-reported influenza-like illness (ILI) during the 2009 H1N1 influenza pandemic
Kim et al. [5]	Case–control	Korea	7448 school-aged children	12.9 ± 3.03	H1N1	—	BMI and waist circumference (WC) are associated with H1N1 infection in school-aged children.
Bijani et al. [6]	Observational study	Iran	55	25.67 ± 16.9	H1N1	28 overweight; 24 with metabolic syndrome (MS)	Metabolic syndrome (MS) is risk factors for hypoxaemia in influenza H1N1.
Louie et al. [116]	Cohort	California	534	46 (20–92)	H1N1	274	Extreme obesity increase odds of death.
Morgan et al. [117]	Case-cohort study	California	565	2–19 years old/ ≥20 years old	H1N1	2–19 years old: 41 ≥20 years old: 110	Morbid obesity is associated with hospitalization and possibly death due to H1N1 infection.
Diaz et al. [125]	Prospective, observational and multicentre study	Spain	416	43.9 ± 12.3	H1N1	150	Obesity increase the duration of mechanical ventilation, ICU length of stay, and hospitalization.
Viasus et al. [126]	Prospective, observational and multicentre study	Spain	585	39 (16–87)	H1N1	87	Chronic comorbid conditions, morbid obesity and bacterial coinfection are independent risk factors for severe H1N1 infection.







Immune system		<ul style="list-style-type: none"> ➤ Alteration of the innate and adaptive immune response ➤ Imbalanced cross-talk between immune system and adipose cells ➤ Impaired chemotaxis ➤ Increased pro-inflammatory M1 macrophages ➤ Dysregulated cytokine production
Hypovitaminosis D		<ul style="list-style-type: none"> ➤ Impairment of the immune response ➤ Possible increased predisposition to systemic infections
Respiratory tract		<ul style="list-style-type: none"> ➤ Decreased pulmonary volumes ➤ Decreased compliance ➤ Ventilation-perfusion mismatching ➤ Respiratory muscle inefficiency ➤ Critical care limitations
Skin, soft tissues		<ul style="list-style-type: none"> ➤ Disrupted micro- and macro circulation ➤ Delayed wound healing ➤ Lymphedema
Obesity-related Comorbidities		<ul style="list-style-type: none"> ➤ Diabetes mellitus ➤ Cardiovascular disease ➤ Hypertension ➤ Metabolic syndrome
Pharmacological issues		<ul style="list-style-type: none"> ➤ Limited data on the right dosing of antimicrobials in obesity ➤ Altered protein binding, metabolism and volume of distribution of antimicrobials

Fig. 1 Mechanisms involved in the increased susceptibility to infections in the subject with obesity. Various mechanisms (red) have been postulated to contribute to increased infectious susceptibility in subjects with obesity, including alterations in respiratory mechanics and vitamin D deficiency and some cofactors (green) as alterations in homeostasis of the skin and subcutaneous tissue, impairment of both innate and adaptive immune responses, the presence of obesity-related comorbidities and limitations relating to antimicrobial therapy.

severe forms, and it has been shown to predispose patients to local complications such as pancreatic pseudocysts, abscesses and necrosis [20]. Several studies have suggested that obesity is associated with a wide range of skin diseases, such as cellulitis and erysipelas [21, 22], and with recurrent soft-tissue infections or prolonged hospitalization. However, regarding the prognosis, there is limited evidence indicating that the outcomes of cellulitis are worse in subjects with morbid obesity [23]. Obesity also carries an increased risk of hepatic steatosis in patients with chronic hepatitis C virus (HCV) infection, and it has been shown to have an adverse effect on the progression of chronic HCV liver disease, with diminished response to antiviral therapy [24]. It is very interesting to note that body mass index (BMI) seems to influence susceptibility to infections following a U-shaped trend [25]. In a prospective Danish cohort, 75,001 middle-aged women were monitored over a median time period of 11.9 years to evaluate the association between BMI and hospitalization and/or treatment for acute infections. The results indicated that the risk of overall and respiratory and skin infections was U-shaped, showing that both underweight and obesity can favour community-acquired infections [25]. These data were supported by a meta-analysis of 25 studies investigating 2.5 million adults and children older than 12 years living in industrialized countries that also demonstrated a U-shaped relationship between BMI and the risk of flu-related pneumonia [26]. Additionally, in elderly patients already more prone to infections and factors weakening the immune system, an overall increased risk of infection in subjects aged >75 years, both underweight (BMI < 20 kg/m²) and overweight (BMI > 28 kg/m²), was found. This finding suggests that BMI is a predictor for infectious disease risk regardless of age [27]. Therefore, the purpose of this review is to identify the possible etiopathogenetic mechanisms underlying the association between obesity and infectious diseases and then analyse the role of obesity in the context of infections in different body regions.

SEARCH STRATEGIES

Articles were individually retrieved by each author up to February 2021 by searching PubMed (MEDLINE) using the following search

terms: ‘obesity’, ‘immune system’, ‘infectious diseases’, ‘COVID-19’, ‘respiratory tract infections’, ‘urinary tract infections’, ‘skin infections’, ‘surgical site infections’, ‘vitamin D deficiency’, ‘type 2 diabetes mellitus’, and ‘H1N1 flu’. The reference lists of relevant articles and reviews were also searched manually.

MECHANISMS INVOLVED IN THE INCREASED SUSCEPTIBILITY TO INFECTIONS IN OBESITY

The mechanisms underlying the increased susceptibility to different types of infections in patients with obesity are not well established; however, some potential risk factors may be directly involved, including obesity-related alterations of the immune system and vitamin D deficiency. There are also some cofactors often associated with obesity that, even without a clear cause–effect relationship, can indirectly favour the onset or worsening of infectious diseases. These cofactors include changes in respiratory physiology, alterations in skin and soft tissue, comorbidities such as type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), drug therapy, and, above all, the underdosing of antibiotics (Fig. 1).

Immune system

It has been shown that obesity has substantial effects on the immune system, probably because of the structural and functional similarity between immune system cells and adipocytes, both capable of producing mediators such as cytokines, chemokines and adipokines [28, 29]. Excess adipose tissue has been assimilated to a state of chronic inflammation, also known as ‘low-grade inflammation’, with consequences both locally on the adipose tissue itself—causing cell necrosis and dysfunction—and at the systemic level—altering the immune response [30]. In obesity, visceral adipose tissue produces an excess of cytokines such as tumour necrosis factor α (TNF α) and interleukin (IL) 6 and 1 β that could weaken the response of immune cells during an infectious stimulus [30, 31]. In addition, in a state of excess weight, a condition of hyperleptinemia is observed that can contribute to an immune imbalance. Indeed, most innate immune cells express the leptin receptor [32]. The monocyte line, for example, produces

greater amounts of IL-6, IL-12 and TNF α in response to leptin, while polymorphonuclear neutrophils pretreated with leptin produce twice as many reactive oxygen species (ROS) compared to those not treated [33, 34]. The adaptive immune system is also affected by leptin stimulation because leptin regulates both lymphopoiesis and myelopoiesis, as shown by a study in which ob/ob mice had fewer bone marrow cells than wild-type mice in response to leptin injection [35]. In particular, pre-B and immature B cells decreased by 21% and 12%, respectively, while there was a minor impact on myeloid cells [35]. Leptin also plays a role by stimulating activators of CD4 and CD8 T cells [36]. More recently, an effect on Treg proliferation and function was observed by De Rosa et al. who showed that Treg cells can increase their proliferation in the absence of leptin; thus, leptin resistance leads to an immunosuppressive phenotype. During excess weight, a leptin-resistant condition can develop, so its regulatory role in the immune system decreases, thus exposing the patient with obesity to a deficient immune response to infections. Obesity is also characterized by hyperinsulinaemia and insulin resistance. Monocytes express the insulin receptor; nevertheless, it is not clear how it affects their activity [37]. T cells do not express the insulin receptor under basal conditions, but once activated, they upregulate this receptor, showing insulin sensitivity [38]. Therefore, it is not yet clear how hyperinsulinaemia and insulin resistance influence the immune response.

Over the years, the effect of excess glucose and fatty acids, typical of obesity, on the immune balance has also been studied. Several immune cells express surface glucose transporters (GLUTs), such as GLUT1 and GLUT3, which are responsible for the internalization of glucose necessary for cellular metabolism. Excessive exposure to this energy source results in an increase in ROS synthesis and lipid peroxidation [39]. The influence of fatty acids on the immune system has been studied in reference to their similarity to lipopolysaccharide (LPS); therefore, the ability to stimulate the Toll-like receptors present on T cells has been investigated [40]. Unfortunately, there has not yet been unanimous consensus, and further studies are expected to analyse the role of fatty acids in regulating the immune response.

Considering the above, excess adipose tissue violates the well-balanced system of adipocytes and immune cells, with subsequent disturbances in the immune surveillance system, both innate and adaptive [28]. Regarding innate immunity, obesity is accompanied by altered neutrophil function, increased proinflammatory M1 macrophage activity, abnormal natural killer (NK) cell phenotypes, and an increased inflammatory response of dendritic cells, resulting in an overall altered first line of defence, increased inflammatory response, and abnormal T-cell response, as seen in a low-grade chronic systemic mechanism [41]. Under conditions of excess weight, the number of macrophages in the adipose tissue increases for both local proliferation of resident macrophages and the recruitment of peripheral monocytes. Furthermore, dysfunctional adipocytes in subjects with obesity produce proinflammatory cytokines that favour the activation of M1 macrophages despite M2 macrophages. Hyperglycaemia, frequently encountered in obesity, also appears to favour the proinflammatory polarization of macrophages [42].

Neutrophil function was studied in a case-control study in which 18 subjects with severe obesity (BMI: 35–68 kg/m²) were matched with 14 normal weight subjects. In the subjects with obesity, neutrophils retained phagocytosis ability and showed significant elevation in the release of basal superoxide ($P < 0.0001$) levels and chemotactic ($P < 0.0003$) and random ($P < 0.0001$) migration compared with lean controls. Therefore, the ability of neutrophils to fight infections was maintained in patients with excess weight, but oxidative stress associated with obesity was sustained by the overproduction of superoxide by neutrophils [43]. Furthermore, a

study conducted in mice showed that a high-fat diet induced the upregulation of ligands of the NK cell-activating receptor (NCR1) on adipocytes of visceral adipose tissue. The induced NK cell proliferation and interferon- γ (IFN- γ) production, which in turn triggered the differentiation of proinflammatory macrophages, was considered a further stimulus for the polarization of M1 macrophages [44]. The innate immune response represents the first line of defence and coordinates the adaptive immune response and is particularly important in the response process to viral and bacterial infections; therefore, the alterations occurring in subjects with obesity are claimed to be responsible for greater susceptibility to infections [41]. Additionally, the adaptive immune response is compromised in obesity, resulting in decreased $\gamma\delta$ T-cell functions, increased inflammatory T helper phenotypes, decreased regulatory T cells, and impaired B-cell functions, which inevitably leads to a less effective response against viral and fungal infectious agents and therefore causes a higher incidence and more severe disease course in subjects with obesity [41].

In a recent study, BMI was found to be inversely related to the number of $\gamma\delta$ T cells [45]. These cells play a crucial function in wound repair, so their dysfunction can lead to delays in wound healing and infectious complications. A proinflammatory state in individuals with obesity is also due to the increase in Th17 and Th22 lymphocytes [46]; although the evidence is still limited, this process boosts the cascade process that can lead to a worsening of chronic systemic inflammation and worsening of the host response to infections. Moreover, Tregs seem to be decreased in patients with obesity, as observed by Wagner et al., who demonstrated reduced circulating Treg cell numbers in the blood of the obese group (BMI ≥ 27 kg/m²) compared with the nonobese group (BMI < 27 kg/m²) [47]. This subpopulation of T lymphocytes is specialized in suppressing the activation of the immune system towards autoantigens and thus in maintaining tolerance to self, thus excess weight could also affect the regulation of autoimmunity. An interesting aspect in support of the obesity-related nature of these alterations is that some of them can be reversed following bariatric surgery, suggesting the role of weight loss in the homeostasis of the immune system [48].

In the context of alterations in immune system cells, although there is very limited evidence, differences between the conditions of metabolically healthy and metabolically unhealthy obesity have been detected. In particular, in a recent study, ten metabolically healthy subjects with obesity (Edmonton Obesity Staging System (EOSS) stage 0) and nine subjects with obesity and T2DM (EOSS stage 2) matched for BMI were evaluated. Subjects with stage 2 obesity had higher proportions of cytotoxic T cells, activated helper T cells (CD4+CD278+), and inflammatory monocytes (CD14+CRTh2+) and increased production of ROS by activated neutrophils than metabolically healthy subjects with obesity [49]. This finding suggested that metabolically unhealthy individuals with obesity and T2DM have impaired neutrophil function and T-cell responses, which may be partly responsible for the increased prevalence of infection susceptibility. Another study showed that the absolute count of proinflammatory monocytes (Mon2A, Mon3A) was lower in metabolically healthy obese individuals than in metabolically unhealthy individuals, although it was higher than that in healthy lean controls. Again, this suggests that some immune alterations, i.e., the presence of low-grade inflammation, even if not clinically apparent, is present in cases of obesity without metabolic complications and cannot be considered a benign condition in any case [50]. Differences in the immune response between metabolically healthy or unhealthy obese individuals could lead to a different susceptibility to infection or to different severity degrees of prognosis; however, in the literature, there are not yet adequate epidemiological studies comparing the two populations in this regard.

Vitamin D deficiency

Another common condition in obesity, which is potentially linked to infection susceptibility, is the deficiency of vitamins and, in particular, vitamin D; it has been reported that vitamin D deficiency increases the predisposition to systemic infections and impairs the immune response [51–54]. Both the National Health and Nutrition Examination Survey III (<https://www.cdc.gov/nchs/nhanes/index.htm>) and the Framingham study (<https://framinghamheartstudy.org/>) demonstrated a linear correlation between BMI and vitamin D values. A recent meta-analysis revealed that the prevalence of hypovitaminosis D in the population with obesity, regardless of age, latitude, cut-offs used to define the vitamin status and socioeconomic development index of the analysed geographical area, was 35% greater than normal weight and 24% higher than overweight [55]. One possible explanation for this phenomenon is that receptors for vitamin D are expressed in a conspicuous number of organs and tissues, including visceral and subcutaneous adipose tissue, both in human differentiated adipocytes (white and brown) and in cell cultures of preadipocytes [52]. Thus, once absorbed, vitamin D is seized and stored in different tissues, mainly in adipose tissue, as well as muscle tissue [56]. Additionally, the cells of both the innate and acquired immune systems express the vitamin D receptor (VDR) [52]. In vitro studies have observed that CYP27B1, an enzyme that activates vitamin D, is expressed within both monocytes/macrophages and dendritic cells (DCs) [52]. The immunomodulatory activity of vitamin D takes place within monocytes/macrophages by stimulating the synthesis of cathelicidine, a protein with antibacterial activity, and other cytokines, such as IL-1 β and IL-8 [57], while in DCs, it inhibits their maturation and therefore their ability to present the antigen in an infectious process [57]. Kuo et al. observed that there was no increase in TNF α levels when monocytes pretreated with 1,25(OH)2D3 were exposed to LPS [58]; likewise, another in vitro study demonstrated that preactivated human monocytes with LPS, once exposed to 1,25(OH)2D3, did not produce IL1 α , IL6 and TNF- α in a dose-dependent fashion [59].

Moreover, vitamin D is also involved in the regulation of the adaptive immune system. In particular, it has been observed that the expression of VDR on T and B lymphocytes in resting conditions is low, while in conditions of activation and proliferation, these cells upregulate the expression of VDR, which, in turn, regulates the downstream transcription of more than 500 genes involved in the differentiation and proliferation of T and B lymphocytes [60]. Several in vitro studies have observed that calcitriol stimulation results in an anti-inflammatory polarization of lymphocytes, inhibiting the Th1 response in favour of a Th2 response: the production of IL2, IL6 and IL17 decreases in favour of the production of IL10 when CD4 T cells are treated with 1,25(OH)2D3 [61, 62].

Since vitamin D acts to suppress T-cell-driven inflammation and enhance the effects of suppressive Treg cells, its deficiency could be crucial in the pathogenesis of both infectious and autoimmune diseases [57]. In contrast, vitamin D supplementation can prevent respiratory infections through several immunoregulatory functions, including the reduced production of proinflammatory cytokines by the innate immune system [63]. For upper respiratory tract infections (RTIs), in the National Health and Nutrition Examination Survey, in a cohort study of 18,883 participants, it was observed that concentrations of 25(OH) vitamin D were independently and inversely associated with recent infections: subjects with circulating levels <10 ng/L presented a 1.4 times higher likelihood of developing infectious diseases than those with 25(OH) vitamin D levels >30 ng/L [64].

Cofactors

Pulmonary physiology is significantly modified by excess weight, which provokes reduced lung volumes, decreased compliance,

abnormal ventilation and perfusion relationships, and respiratory muscle inefficiency [65]. Obesity causes a reduction in functional residual capacity (FRC) and expiratory reserve volume (ERV), with an inverse relationship between BMI and FRC [65]. In addition, excess weight also determines a reduction in lung and chest wall compliance, which has been shown to be exponentially related to BMI [65]. This depends both on decreased volumes, causing collapse and atelectasis of the smaller airways and an increase in alveolar surface tension, and on chest wall overload linked to adipose accumulation around the ribs, diaphragm, and abdomen, which can worsen respiratory mechanics, especially in the supine position [65]. Obesity has also been associated with ventilation/perfusion (V/Q) mismatching [66]. In fact, unlike healthy subjects, patients with obesity might present hypoventilation in the lower zones [66]. This depends on both small airway closure caused by lower ERV and reduced chest wall compliance, which can induce V/Q mismatching and hypoxaemia. Moreover, excess weight leads to greater fatigue of the respiratory muscles and increased oxygen consumption by those muscles, further worsening respiration [67]. Patients with obesity also have additional critical care limitations to consider, including difficulty in intubation, extubation, mask ventilation, prone positioning, and higher ventilatory pressures required [68]. Thus, alterations in respiratory mechanics and physiology can be responsible for an increased risk of pulmonary infection and contribute to a worse prognosis [69]. Pulmonary consolidation during pneumonia can cause an intrapulmonary shunt and a varying degree of V/Q mismatch, which can cause V/Q alterations, as reported in subjects with obesity, and can exacerbate hypoxemic respiratory failure [70]. Although no skin infection is specifically linked to obesity, some, including candidiasis, intertrigo, folliculitis, furunculosis, erythrasma, tinea cruris and erysipelas, have a higher incidence in subjects with obesity [71, 72]. Excess weight predisposes patients to lymphedema, alterations in micro- and macrocirculation with essential development of obesity-related micro- and macroangiopathy [73] and delayed wound healing [69, 74, 75]. Obesity worsens lymphatic flow, involving a collection of protein-rich lymphatic fluid in the subcutaneous tissue, which can lead to lymphedema [76]. Obesity also causes impaired capillary recruitment and a significant reduction in the cutaneous vasomotor response to autonomic activation [73]. This progressive accumulation of fluid results in reduced tissue oxygenation, which can cause fibrosis and a chronic inflammatory state over time [76]. Furthermore, lymphedema's disruption of immune cell trafficking leads to localized immune suppression, with the development of chronic inflammation and infections such as cellulitis and verrucosis [74], contributing to secondary complications in the lower extremities, such as foot infections and ulcerations [77]. In an observational study, two cohorts of patients with lymphedema confirmed by lymphoscintigraphy were compared: Group 1, normal weight patients (BMI \leq 25 kg/m²) and Group 2, patients with obesity (BMI \geq 30 kg/m²) [41]. Group 2 was more likely to undergo infection (59%, $P < 0.001$) and hospitalization (47%, $P < 0.001$) than Group 1 [75]. The presence of infection can cause delayed wound healing, increased hospitalization, increased health-care costs and reduced patient quality of life [78], which boosts the vicious circle of obesity, skin infections and delayed wound healing.

Obesity is associated with a number of comorbidities constituting metabolic syndrome, such as T2DM, hypertension and CVD, already known as predictive factors of susceptibility to infections [79–81]. It has been observed that The Middle East respiratory syndrome coronavirus (MERS-CoV) is associated with life-threatening severe illnesses and a mortality rate of approximately 35%, especially in patients with these underlying comorbidities [79]. In particular, the presence of T2DM leads to an increase in the incidence of respiratory infections and is often identified as an independent risk factor for developing lower RTIs [80]. While

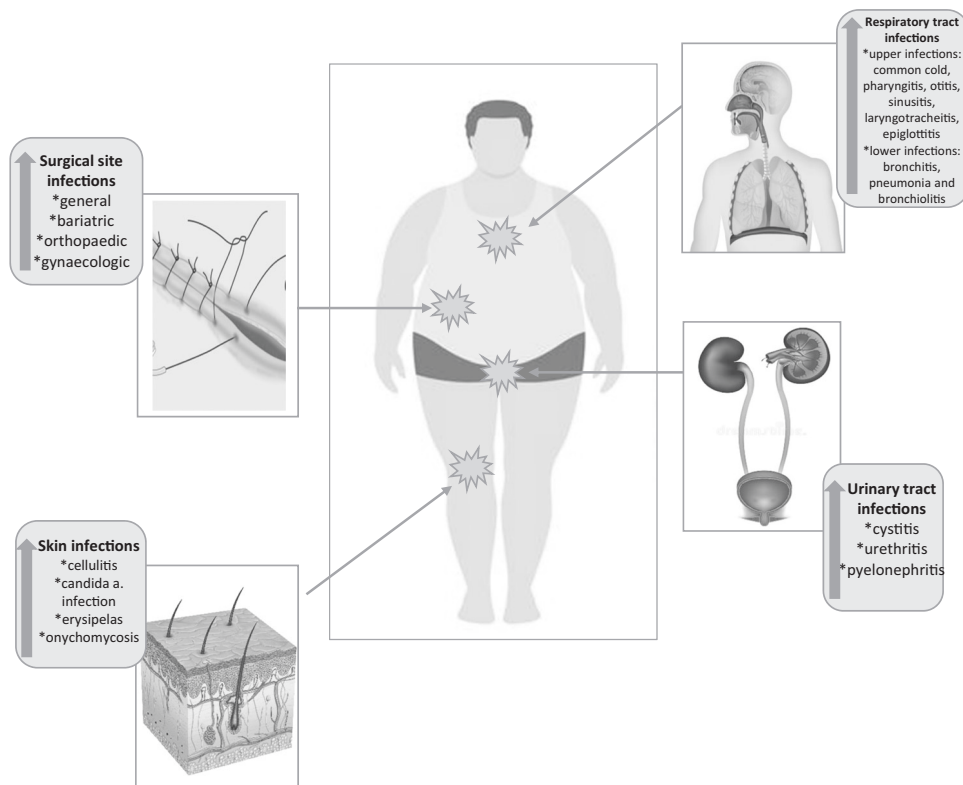


Fig. 2 Excess weight has been assessed as a risk factor for infections divided by body district. Several epidemiological studies have demonstrated that overweight and obesity are associated with a higher prevalence of respiratory tract infections (RTIs), characterized by a longer duration of disease and higher mortality. Upper infections (common cold, pharyngitis, otitis, sinusitis, laryngotracheitis and epiglottitis) and lower infections (bronchitis, pneumonia and bronchiolitis) have a higher prevalence among subjects with obesity and weight gain would seem to increase the risk of RTIs. Excess weight has been identified as a risk factor and recurrence factor for skin infections, in particular the incidence of onychomycosis and cellulitis increases in proportion to BMI. *Candida Albicans* infections are more prevalent among the population with obesity and also more complicated than normal weight populations. Erythrasma would seem to be complicated by the condition of overweight, probably, due to skin folds. Moreover, obesity is associated with a significantly increased risk of skin and soft-tissue infection when undergoing general, orthopaedic, gynaecological and bariatric surgery. Finally, several studies have identified obesity as risk factor for urinary tract infections, also in specific conditions such as admission in intensive care or moderate or major surgery, or after traumatic injury.

respiratory infections by *Mycobacterium tuberculosis*, *Staphylococcus aureus*, gram-negative bacteria and fungi are more common in the general population, those from *Streptococcus* and the flu virus may be more associated with increased morbidity and mortality in subjects with T2DM [80]. Hospitalization due to the flu virus or flu-like infections is up to six times more likely to occur in patients with T2DM than in the healthy population, and diabetic patients are hospitalized after infection complications more frequently [80]. Furthermore, a meta-analysis on more than 30 million subjects highlighted not only that having a higher BMI significantly increased the risk of postoperative sepsis but also that several comorbidities, including T2DM, chronic kidney disease, heart failure, cerebrovascular disease and CVD, further augmented the risk of postoperative sepsis [81].

Another aspect that is often underestimated and can affect the prognosis of subjects with obesity and infections is the inappropriate treatment per weight [82]. The condition of obesity can modify the pharmacokinetics of drugs, depending on multiple factors, including the degree of obesity, organ functions and drug characteristics [82]. The drug distribution phase results are severely different because of both alteration of plasma protein binding and volume of distribution (VD) of drugs: VD of lipophilic drugs (fluoroquinolones) increases while that of hydrophilic drugs (amikacin and tobramycin) lows [82]. In a review board-approved retrospective study at the American Society of Metabolic and Bariatric Surgery Center of Excellence, data from the emergency

department (ED) evaluating adherence to hospital guidelines in the first prescription of cefepime, ceftazidime or ciprofloxacin to patients with obesity were collected, and it was observed that the adherence rates for the first dose of these drugs administered were 8.0%, 3.0%, and 1.2%, respectively; therefore, these antimicrobials were frequently underdosed in subjects with obesity [83].

In the following sections, infections will be analysed according to body region and the role of excess weight will be discussed (Fig. 2).

SKIN INFECTIONS

A higher incidence of cutaneous infections has been reported in patients with obesity than in nonobese patients (Table 2), which is probably due to changes in skin barrier function, lymphatic system, collagen structure and function, the latter being also responsible for wound-healing difficulties.

A dysfunction in the production process of senile adipocytes in the dermis is most likely the reason for the increased risk of infections in obesity. In a recent study, it was observed that a high-fat dietary regimen promotes hyperplastic growth of adipocytes, which complete their maturation process off dermal progenitors. These progenitors feature stronger capabilities of secretive antimicrobial peptides, and this peculiar function is lost in the maturation process [84]. The decrease in adipocyte progenitors in

Table 2. Epidemiological studies on skin infections and obesity.

Author	Experimental design	Country	No. of enrolled subjects	Age enrollment (years)	Infection	No. of obese subjects	Outcome
Karpelin et al. [21]	Case–control study	Finland	Cases: 90 Controls: 90	58 (21–90)	Cellulitis	Cases: 37 Controls: 15	Obesity was an independent risk factor for acute non-necrotizing cellulitis leading to hospitalization.
Carratalà et al. [23]	Cohort	Spain	332	59.7 ± 16.7	Cellulitis	23	Morbid obesity was indicated as a factor associated with mortality in adult patients hospitalized for cellulitis.
Cheong et al. [71]	Cohort	Korea	171,322	37.9 ± 8	Cellulitis	5069	Increased body mass index was associated with an increased risk of cellulitis and hospitalization for cellulitis.
Dupuy et al. [72]	Case–control study	France	Cases: 167 Controls: 294	Cases: 56.5 ± 1.8 Controls: 56.6 ± 1.1	Erysipelas	Overweight cases: 68 Controls: 97	Overweight was the only general risk factor associated with erysipelas of the leg.
Kozłowska et al. [86]	Retrospective study	Poland	223	61	Erysipelas	—	Recurrent erysipelas was more often diagnosed in patients with comorbidities, including overweight.
Rob et al. [87]	Retrospective study	Czech Republic	132	60.2 ± 12.3	Erysipelas	68	Benzathine penicillin G 1.2 MU once every 3 weeks is an effective prophylaxis of recurrent erysipelas, but obesity is a risk factor for recurrent erysipelas.
Döner et al. [90]	Cohort	Turkey	500	43.6 ± 12.8	Obesity-associated dermatoses	250	Total dermatoses was higher in subjects with obesity than in controls. There were significant differences between two groups with regard to tinea pedis, onychomycosis and intertrigo.
Chan et al. [91]	Prospective epidemiologic survey	China	877	42.5 (1–93)	Fungal foot disease	—	In adults, obesity appeared to be the most frequently occurring factor coexisting with fungal foot disease.
Mirmirani et al. [92]	Retrospective population-based study	California	248,775 children and adolescents	11.3	Bacterial and fungal skin infections	47,501	Childhood obesity was observed to be associated with a higher prevalence of bacterial and fungal skin infections.

diet-induced obese (DIO) mice was explained by the expression of transforming growth factor- β (TGF β) by mature adipocytes that then inhibited adipocyte progenitors and the production of cathelicidin, a powerful antimicrobial agent, in vitro [84]. It was also observed that administration of a TGF β receptor inhibitor reversed this inhibition in both cultured adipocyte progenitors and in mice and subsequently restored the capacity of obese mice to defend against *S. aureus* skin infection [84]. Therefore, the increase in dermal mature adipocytes associated with obesity seems to weaken the immune response towards skin infections. Cellulitis has a high incidence in subjects with obesity. In particular, in a large cohort of 171,322 Korean adults followed from 2011 to 2016, increased BMI was associated with an increased risk of cellulitis and hospitalization in both metabolically healthy and unhealthy individuals, suggesting that obesity can be an independent risk factor for cellulitis regardless of the metabolic phenotype [71]. In addition, severe cellulitis tends to occur more commonly in the legs of patients with coexisting lymphedema, a condition frequently encountered in subjects with obesity [85].

Several studies have indicated that obesity predisposes individuals to erysipelas independently of potential confounders [21, 72], and it is a known risk factor for its complications [86, 87]. In a retrospective chart review of patients hospitalized for primary and recurrent erysipelas, it was found that obesity prolongs the time of hospitalization [86, 87], while another study showed that obesity is associated with erysipela recurrence notwithstanding prophylactic treatment with benzathine penicillin G [87]. *Candida albicans* infection is also more prevalent in patients with obesity and might cause folliculitis, intertrigo, furunculosis, or paronychia of the hands or feet [88]. The presence of skin folds such as inframammary, genitocrural, axillary and abdominal folds, which favour macerated erythematous plaques along with eventual poor local hygiene, are predisposing factors for the onset of cutaneous mycosis, especially recurrent *Candida* intertrigo [89].

Obesity is also one of the most important risk factors for onychomycosis [90, 91]. Significant increases in the incidence of onychomycosis have also been observed in inpatient clinic attendees with obesity [90]. A Chinese study conducted on 877 adult patients revealed that obesity is one of the three most prevalent predisposing factors (vascular disease and diabetes are the other two) for fungal nail disease [91]. Furthermore, skin infections appear to be associated with excess weight even in children [92]. In a retrospective, population-based study at the Kaiser Permanente Northern California Managed Health care System, the presence of skin disorders in 248,775 children was assessed, and childhood obesity was observed to be associated with a higher prevalence of bacterial and fungal skin infections [92].

URINARY TRACT INFECTIONS

UTIs are one of the most commonly acquired bacterial infections in outpatient and hospitalized populations; its prevalence is approximately 11% in the overall population [93]. Women are more affected than men [94], and they also present a greater risk of recurrence [95]. Several studies have identified an association between UTIs and obesity (Table 3). In a descriptive study on 95,598 subjects, Semins et al. demonstrated an association between obesity and both UTIs and pyelonephritis, with a higher prevalence in female patients [96]. In line with these observations, in a prospective cohort study on 457 patients with T2DM, obesity was found to be a risk factor for UTIs in a male population [97]. Some studies have shown that obesity can be a risk factor for UTIs in specific conditions, such as admission to intensive care, moderate or major surgery, or after traumatic injury [3, 4, 98]. In a prospective study on 1105 patients admitted to the ICU over a 2-year period, mostly due to trauma, a twofold increase in the relative risk of acquiring a UTI was observed in patients with

obesity [7]. Furthermore, a high BMI was independently associated with a higher rate of ICU-acquired UTIs ($P = 0.02$) in a retrospective study on 301 patients affected by septic shock [8]. Patients with obesity had a significantly higher risk of UTIs than nonobese patients, and obesity was found to be an overall independent risk factor for perioperative morbidity [98]. It was also observed that obesity was associated with UTIs regardless of the presence of comorbidities such as type T2DM or vitamin D deficiency [99]. Regarding the gender difference in UTIs, the recent Danish Donor Blood study has shown that UTIs are not only more common in females [100] but also specifically during pregnancy and the postpartum period [9, 10]. Obesity was a risk factor for UTI in 767 pregnant women [9] and in 8350 postpartum women in a population-based observational study [10], and again, it determined a worse prognosis and course of UTI [9, 10]. A case-control study on premenopausal non-pregnant women with recurrent UTI (RUTI), defined as symptomatic UTI that follows the resolution of a previous UTI or three or more symptomatic episodes over a 12-month period, demonstrated that the mean BMI among women with RUTIs was significantly higher than controls [101], suggesting that obesity may also have a role in recurrent forms, which are frequent in women. Several paediatric studies have analysed the association between obesity and UTIs [102, 103]. In a retrospective case-control study on 41,819 patients aged 2–20 years, obesity was strongly associated with the presence of UTIs in the female paediatric hospitalized population, and the risk of UTIs was increased by 45% in females with obesity [102]. Therefore, also in paediatric patients with obesity, the management of body excess weight and urinalysis should be considered as early as possible, considering the higher incidence of UTIs in overweight and obese children <2 years of age presenting with fever compared to normal weight febrile children [103]. Moreover, the negative prognostic value of obesity was also confirmed in subjects with UTIs aged <18 years [104].

Regarding the pathophysiological mechanisms, a common unanimous consensus has not yet been achieved. For example, glycosuria represents a predisposing factor for UTIs in subjects with diabetes. However, not all diabetic subjects have glycosuria, which does not explain the increased incidence of UTIs in nondiabetic subjects with obesity, suggesting the existence of other mechanisms. The urinary tract constitutively expresses antimicrobial agents such as several nonenzymatic ribonucleases (RNases), lipocalin 2 (Lcn2), defensins and cathelicidin LL-37, whose secretion can also be induced by higher levels of bacteria in the urine [105]. These act mainly by preventing microbes from adhering to the epithelium or by preventing their replication. It has been shown that the expression of some antimicrobial peptides, particularly RNase7, by the uroepithelium could be induced by insulin via the classical insulin signalling pathway. In particular, using primary human urothelial cells, it was demonstrated that insulin induces RNase 7 production via the phosphatidylinositol 3-kinase signalling pathway (PI3K/AKT) to shield urothelial cells from uropathogenic *E. coli* [106]. Evaluating obese hyperglycaemic db/db mice, which exhibit a T2DM phenotype, an increased susceptibility to uropathogenic *E. coli* inoculation was observed [107]. Moreover, insulin-resistant normoglycaemic TALLYHO mice had increased UTI susceptibility, independent of hyperglycaemia or glucosuria, suggesting a role for insulin resistance more than glycosuria in this process [107]. Furthermore, using murine and human primary renal epithelial cells, Murtha et al. demonstrated that RNase4 and Lcn2 from both sources were induced by the presence of insulin and that the response could be suppressed by administration of a PI3K inhibitor, wortmannin, supporting the role of classical insulin signalling in the induction of antimicrobial agents and the plausible role of insulin resistance in increased susceptibility to UTIs [107]. On the other hand, it is not yet known whether the link between insulin resistance and UTIs can be mediated by an excess

Table 3. Epidemiological studies on urinary tract infections and obesity.

Author	Experimental design	Country	No. of enrolled subjects	Age enrollment (years)	Infection	No. of obese subjects	Outcome
Bohicchio et al. [7]	Prospective cohort study	USA	1105	42 ± 21	Bloodstream, urinary tract, or respiratory infections	62	Patients with obesity had a more than twofold increase in relative risk of acquiring a bloodstream, urinary tract, or respiratory infection, or being admitted to the intensive care unit (ICU).
Basu et al. [9]	Cross-sectional study	South Africa	767	—	UTIs	337	Urinary tract infection (UTIs) were significantly more common among women with morbid obesity.
Semins et al. [96]	Descriptive study	USA	95,598	—	UTIs and pyelonephritis	30,051	Obesity is a significant risk factor for being diagnosed with UTI as well as pyelonephritis.
Bamgbade et al. [98]	Retrospective cohort study	USA	6773	—	Wound infections and UTIs	2232	Subjects with obesity have a significantly higher risk of wound infection, and urinary infection. Morbid obesity is a risk factor for mortality.
Saliba et al. [99]	Retrospective cohort study	Israel	153,439	≥ 18	UTIs	43,884	In males, obesity was independently associated with UTI while, in females, there was a non-significant tendency to increased risk of UTI for body mass index (BMI) ≥ 50 kg/m ²
Kaspersen et al. [100]	Retrospective cohort study	Denmark	37,808	—	Abscesses, infections of the skin and subcutaneous tissue, respiratory tract infections, gastrointestinal infections, UTIs and pelvic inflammatory diseases	16,509	Obesity was associated with increased risk of abscesses (both sexes), infections of the skin and subcutaneous tissue (men), and respiratory tract infections and cystitis (women).
Nseir et al. [101]	Retrospective case – control study	Israel	Case: 122 Control: 122	20–55	UTIs	—	Obesity has been associated with recurrence of UTIs in premenopausal women
Grier et al. [102]	Retrospective cohort study	USA	41,819	2–20	UTIs	41,819	There is a 41% increased risk of UTIs in the patients with obesity compared with the nonobese cohort.
Hsu and Chen [103]	Retrospective case – control study	Taiwan	Case: 212 Control: 260	< 2	Lower UTIs and acute pyelonephritis	Case: 42 Control: 23	The percentage of obesity and underweight were significantly greater in UTIs patients compared to non-UTIs controls.
Okubo et al. [104]	Retrospective cohort study	USA	51,918	< 18	UTIs	1488	In hospitalized patients with UTIs, obesity was associated with higher total hospitalization costs, longer length of hospital stays, and increased risk for hypertension.

of generalized or predominantly kidney-localized visceral adipose tissue. One study has shown that the presence of perinephric fat stranding is an independent predictive factor for febrile UTIs after ureteroscopic lithotripsy [108], suggesting a role of perirenal fat in the onset of UTIs.

RESPIRATORY TRACT INFECTIONS

It is well known that obesity is associated with an increased risk of RTIs (Tables 1 and 4) [100]. As mentioned before, a chronic proinflammatory state in association with an excessive oxidative stress response and impaired immunity (typical of overweight/obese patients) could explain this relationship [28, 29, 73]. Obesity could be considered either a risk factor for the onset of RTIs or as a risk factor for poor prognosis [67]. There is no evidence that excess adipose tissue at the level of the lungs can be a determinant for the risk of respiratory infections. The accumulation of fat at the abdominal visceral level seems to be a negative prognostic factor for patients suffering from severe pulmonary deficiency, as in SARS-CoV-2 disease (COVID-19). It has been observed that for every 1-cm increase in abdominal circumference in COVID-19 patients, the risk of intensive care admission increased by 1.13 and for mechanical ventilation by 1.25 [109]. Similarly, excess fat at the level of the neck is related to a worse prognosis: a neck circumference greater than 42.5 cm in men/37.5 cm in women was associated with early intubation in COVID-19 patients compared to patients with smaller circumferences [110]. These observations could be justified both by mechanical reasons, causing a reduction in airflow in the upper airways or a reduction in the expansion of the rib cage, and by paracrine proinflammatory mechanisms of adipose tissue that could modify the immune response. Moreover, the correlation between the risk of infection and severe course of COVID-19 and obesity has been investigated in relation to the expression of angiotensin converting enzyme-2 (ACE2), considering that SARS-CoV-2 interacts with ACE2 to enter alveolar cells involving the serine protease TMPRSS2. Ai Heiely et al. showed that in obese mice, there was an upregulation of ACE2 and TMPRSS2 PMC [111]; this observation, however, has not been confirmed by studies conducted in humans, in which there would be no significant variations in the expression of ACE2 in adipose tissue of obese vs. nonobese patients [112]. Human studies have also evaluated the change in ACE2 expression following weight reduction, and while some studies have found a reduction in ACE2 expression, others have not identified any significant difference, so there are no consistent results in the literature to link obesity-ACE2 expression and the risk of SARS-CoV-2 infection [113, 114]. Therefore, in subjects with obesity, the role of ACE2 in the pathophysiology of COVID-19 remains controversial. It is important to consider that excess weight is associated with an environment that favours vascular damage, inflammation, remodelling of membranes and subsequent alteration of vascular flow with risk of hypoxia and development of thrombosis [115]. Several epidemiological studies have demonstrated that overweight and obesity are associated with a higher prevalence of RTIs, characterized by a longer duration of disease and higher mortality [3, 4, 116–124]. Obesity impairs the immune response to flu and flu vaccination through alterations of the cellular immune system, probably due to hyperinsulinaemia or hyperleptinemia that could dysregulate T-cell metabolism [48]. During the first pandemic influenza 2009/H1N1 swine flu, obesity was identified as an independent risk factor for increased morbidity and mortality based on public health surveillance data of hospitalized California residents [116]. A case–control study has shown that morbid obesity (BMI \geq 40) was an independent risk factor for hospitalization among 564 hospitalized adult patients with H1N1 flu, with or without recognized chronic conditions (cardiovascular disease, pulmonary disease, liver disease, cancer, and diabetes) [117]; in contrast, underweight patients 2–19 years

old had a higher hospitalization rate than patients with obesity [117]. This negative role of obesity was confirmed by two Spanish prospective, observational, multicentric studies that identified a longer hospitalization and a more frequent and longer use of mechanical ventilation among H1N1 patients with obesity, albeit similar death rates [125, 126]. In addition, the WHO conducted a study to evaluate risk factors associated with H1N1 prognosis among 20 countries, and it was found that obesity, asthma and pregnancy were related to disease severity [3]. Some studies did not identify the same association: obesity was not related to any flu viruses among adults \geq 20 years with a medical encounter for acute respiratory illness [4, 127]. These contrasting results make it difficult to understand the actual effect of obesity on susceptibility to influenza and the utility of starting an antiviral therapy protocol sooner than nonobese patients. Nevertheless, the association between obesity and RTIs may not be limited to the flu season [118]: a retrospective cohort study of 13 years on 104,665 individuals in Ontario demonstrated that subjects with obesity were at an increased risk of outpatient visits for RTIs during both flu and nonflu periods [118]. This might occur as a consequence of obesity-related enhanced susceptibility to any viral and bacterial respiratory pathogens [118]. BMI has also been evaluated as a risk factor for other respiratory infections: a recent prospective study conducted on a large cohort of 1455 patients showed that patients who were overweight and obese had a higher prevalence of RTIs, considering both upper infections (common cold, pharyngitis, otitis, sinusitis, laryngotracheitis, epiglottitis) and lower infections (bronchitis, pneumonia and bronchiolitis) [122]. In particular, lower infections were more common among obesity-affected patients, and the association between pneumonia and bronchitis was statistically significant [122]. In the Canadian Healthy Project, BMI was related to an increase in the self-report diagnosis rate of chronic bronchitis after exposure to a second risk factor, such as smoking [124]. Additionally, in the paediatric population (6–17 years), obesity has been identified as a risk factor for chronic bronchitis [120, 121]. The association between BMI and RTIs suggests that their incidence could be possibly decreased by lifestyle interventions [119]. A study found that weight gain in the male population had a twofold increase in the likelihood of community-acquired pneumonia (CAP) compared with those who maintained their weight, but a linear correlation was not found between BMI and CAP in women [119]. More data are needed to understand sex differences in the relation between obesity and the risk of pneumonia [119]. A recent retrospective study conducted on paediatric inpatients aged between 2 and 20 years with pneumonia or bronchitis showed that obesity was significantly associated with the use of both noninvasive and invasive mechanical ventilation and with the development of septicaemia/bacteremia [123]. Although the relationship between obesity and RTIs appears cogent, further studies are needed to confirm it.

SURGICAL SITE INFECTIONS

SSIs are postoperative infections that occur within 30 days of a surgical procedure (or within 1 year for permanent implants) and constitute up to 19.6% of hospital-acquired infections (HAIs), as was revealed in a survey of health-care-associated infections and antimicrobial use in European acute care hospitals. SSIs negatively impact patient health by increasing both morbidity and mortality [128] and decreasing overall patient quality of life [129] as well as the public health economy, causing prolonged hospitalization with an additional cost of management [130]. Previous prospective cohort studies have indicated that obesity is associated with a significantly increased risk of skin and soft-tissue infections after surgery [14–16].

T2DM has been shown to be an independent risk factor for SSIs, and considering its frequency in patients with obesity, it should be

Table 4. Epidemiological studies on respiratory tract infections and obesity.

Author	Experimental design	Country	No. of enrolled subjects	Age enrollment (years)	Infection	No. of obese subjects	Outcome
Campitelli et al. [118]	Cohort	Canada	104,665	18–64	Acute RTIs (acute nasopharyngitis, sinusitis, tonsillitis, laryngitis, bronchitis, pneumonia, influenza, and other viral diseases)	Overweight: 32,260 Obese subjects: 24,073	Higher rates of outpatient visits for acute respiratory infections were observed during influenza season periods for overweight individuals, compared with normal weight ones.
Baik et al. [119]	Cohort	USA	104,491	—	Community-acquired pneumonia	—	Excessive weight gain during adulthood were associated with increased risk of community-acquired pneumonia.
Karunanayake et al. [120]	Cross-sectional study	Canada	351	6–17	Chronic bronchitis	71	Obesity was identified as modifiable risk factor for chronic bronchitis in children.
Lee et al. [121]	Prospective cohort study	Taiwan	3634	12–15	Chronic bronchitis	650	Obesity would significantly increase the risk of incident bronchitis among adolescents between 12 and 15 years of age.
Maccioni et al. [122]	Cross-sectional study	German	1455	18–70	Upper (common cold, pharyngitis, otitis, sinusitis, laryngotracheitis, epiglottitis) and lower (bronchitis, pneumonia and bronchiolitis) RTIs	187	Patients with overweight and obesity have a higher prevalence of respiratory tract infections (RTIs), considering both upper and lower infections.
Okubo et al. [123]	Retrospective cohort study	USA	133,602	2–20	Bronchitis and pneumonia	1510	Paediatric obesity is an independent risk factor for severity and morbidity for lower RTIs.
Pahwa et al. [124]	Cohort	Canada	720	34.83 ± 14.47	Chronic bronchitis	255	Obesity was identified as modifiable risk factor for chronic bronchitis.

ICU intensive care unit, SARS-CoV-2 severe acute respiratory syndrome coronavirus-2, COVID-19 coronavirus disease 2019.

Table 5. Epidemiological studies on surgical site infections and obesity.

Author	Experimental design	Country	No. of enrolled subjects	Age enrollment (years)	Infection	No. of obese subjects	Outcome
Waisbren et al. [14]	Prospective cohort study	USA	591	18–64	SSIs (superficial infection, deep incisional infection and organ/space infection) 30-day postoperative data	409	Patients with surgical site infections (SSIs) had a significantly higher percent body fat (%BF) than those without SSI. More patients in the SSI group than in the non-SSI group were obese by percent body fat (%BF).
Di Leo et al. [15]	Prospective cohort study	Italy	1281	8–97	SSIs (superficial infection, deep incisional infection and organ/space infection)	73	Obesity, diabetes mellitus, and emergency surgery were associated with a higher risk of SSIs.
Beldi et al. [16]	Prospective cohort study	Switzerland	1032	5–94	SSIs (superficial infection, deep incisional infection and organ/space infection)	—	Body mass index (BMI) > 30 kg/m ² was a significant independent risk factors for SSIs after general surgical procedures.
Ferraz et al. [136]	Prospective cohort study	Brazil	1596	18–65	SSIs	1596	The increase in BMI was related to a higher incidence of SSIs using both laparotomy and laparoscopic approach.
Wahl et al. [139]	Retrospective cohort study	USA	74,891	52–72	30-day postoperative SSIs	25,236	The incidence of SSIs increased progressively with BMI class from overweight to severe obesity after colorectal surgery
Merkow et al. [140]	Retrospective cohort study	USA	3202	Mean 67	SSIs	1003	Compared with normal weight patients, subjects with morbid obesity had a higher risk of surgical site infection, dehiscence, pulmonary embolism, and renal failure after colectomy for cancer.
Healy et al. [141]	Retrospective cohort study	Ireland	414	—	SSIs	—	There was no difference in the incidence of major and minor complications in patients with or without obesity, including wound complications.
Okabayashi et al. [142]	Retrospective study	Japan	152	30–86	SSIs	—	BMI > 23.6 kg/m ² , estimated blood loss volume >810 mL, presence of postoperative bile leakage of organ/space, SSIs and use of the sliding scale, spotted insulin method for postoperative glucose control were independent risks factors for SSIs after hepatic resection.
Gervaz et al. [143]	Prospective case –control study	Denmark	Case: 114 Control: 420	Mean 68	SSIs (superficial infection, deep incisional infection and organ/space infection)	Case: 34 Control: 51	Obesity, contamination class 3–4, American Society of Anesthesiologists grade III–IV and open surgery correlated with an increased risk of SSIs.
Greenblatt et al. [144]	Retrospective cohort study	USA	4945	—	SSIs	—	Patients with age, morbid obesity, and hypoalbuminemia, are at significantly increased risk for adverse outcomes (sepsis, surgical site infection and respiratory complications) after pancreaticoduodenectomy.
	Prospective cohort study	Spain	1557	>18		78	Obesity, diabetes mellitus, operative time and reoperation for bleeding were

Table 5. continued

Author	Experimental design	Country	No. of enrolled subjects	Age enrollment (years)	Infection	No. of obese subjects	Outcome
Figuerola-Tejerina et al. [146]					SSIs (superficial infection, deep incisional infection and organ/space infection)		independent risk factors for SSIs in valve surgery.
Ashley et al. [147]	Case–case –control study	USA	Case: MRSA 64 MSSA 79 Control: 80	≥ 18	Postoperative mediastinitis (<i>S. aureus</i>)	Case: MRSA 40 MSSA 49 Control: 36	Obesity was a risk factor for postoperative mediastinitis due to methicillin-susceptible <i>S. aureus</i> (MSSA) but not for postoperative mediastinitis due to methicillin-resistant <i>S. aureus</i> (MRSA) among patients who underwent median sternotomy.
Lu et al. [148]	Retrospective cohort study	China	724	16–74	SSIs	214	Open fracture, current smoking, obesity, and diabetes mellitus were identified to be significantly associated with the increased risk of SSI.
Dias et al. [149]	Retrospective cohort study	UK	453	—	SSIs	—	SSIs rates were high in women with severe obesity following caesarean section, regardless of location of skin incision.

DSWI deep sternal wound infection, IABP intra-aortic balloon pump.

carefully investigated and treated before any surgical procedure [15]. One of the reasons for the greater risk of surgical site infections in patients with obesity is difficulties in wound healing, which promote the entrance and proliferation of microorganisms. It is known that the pathological expansion of white adipose tissue in conditions of excess weight modifies blood flow; indeed, there is cross-talk between endothelial cells and adipocytes that regulates the production of nitric oxide and therefore vasodilation [131]. Several studies have shown less endothelium-induced vasodilation in association with excess weight [132]; hence, decreased blood flow could cause unfavourable wound healing. In addition, the influence of adipose tissue on $\gamma\delta$ T-cell activity alters their auxiliary function in tissue repair [45].

Waisbren et al. carried out a prospective study that included 591 adult elective surgical patients evaluated during preoperative, operative, and 30-day postoperative periods, and they found that patients with obesity, defined by body fat percentage (%BF) > 25% in men and >31% in women, at a bioelectrical impedance analysis were five times more likely to have SSIs after surgery [14]. In contrast, using BMI > 30 kg/m² as a diagnostic parameter of obesity, there was no significant difference in the incidence of SSIs between subjects with or without obesity [14]. Given these results, they concluded that BF% was a more sensitive and precise measurement than BMI in determining the association between obesity and the risk of postoperative SSIs [14]. Hence, more studies should be conducted using %BF instead of BMI, although it is more difficult to calculate. The main studies on SSIs and obesity are summarized in Table 5.

Bariatric surgery

Bariatric surgery has become a very effective option to treat obesity, providing adequate and effective weight loss, improving quality of life and reducing morbidity and mortality [133], albeit it requires appropriate pre- and postsurgical adherence to dietary attitudes and eventual medical treatment [134]. Particular attention is necessary to manage the complications of surgery in patients with obesity, especially the risk of SSIs. A retrospective study that compared two different groups with obesity, a morbidly obese group (BMI 35–49 kg/m²) and a superobese group (BMI ≥ 50 kg/m²), showed that the latter had a significantly greater incidence of postoperative complications, including superficial and deep wound infections, sepsis, septic shock and increased 30-day mortality [135]. A recent study that analysed 334 patients who underwent open bariatric surgery and 262 patients who underwent video-laparoscopic bariatric surgery from July 2008 to January 2018 showed that a higher body mass index was associated with a higher incidence of SSIs, despite the use of a dedicated preventive strategy to correct risk factors [136]. Moreover, the laparotomy approach and the presence of T2DM increased the rate of SSIs [136]. Accordingly, in patients undergoing bariatric surgery, it is recommended to reduce the modifiable risk factors for SSIs (weight excess and T2DM) and adopt a laparoscopic approach.

General surgery

The association between SSIs and obesity results in the decreased oxygen tension of the relatively avascular adipose tissue, differences in wound healing, greater wound size, or technical difficulties [35–38]. SSIs are the most common complication after colectomy, and obesity can increase this risk by 2.5–5 times [137]. Obesity is an established risk factor for the development of colorectal cancer; hence, many studies can be found regarding the risk stratification of colorectal cancer surgery complications [138]. A recent retrospective study on a population of 74,891 subjects with colorectal cancer stratified according to BMI showed that patients with obesity experienced incremental odds of SSIs after elective colorectal surgery as BMI increased [139]. Similarly, an observational study on 3202 patients who underwent colectomy

for cancer showed that patients with morbid obesity (BMI > 35 kg/m²) had a higher risk of surgical site infection than normal weight patients, confirming a linear association between BMI and SSI incidence after colectomy for colorectal cancer [140]. In a retrospective study on 414 patients with colorectal cancer who underwent surgery, it was observed that postoperative pelvic abscesses were more common in patients with obesity than in nonobese patients [141]. Furthermore, even after liver resection surgery, obesity was found to be a risk factor with predictive value for SSI [142]. Gervaz et al. defined risk factors in the so-called COLA score (contamination, obesity, laparotomy and American Society of Anaesthesiologists grade—ASA). They demonstrated that obesity, contamination class 3–4, ASA grade III–IV and open surgery significantly increased the risk for SSIs [143]. BMI was found to be an independent factor for the occurrence of serious postoperative infectious complications in patients who underwent pancreatoduodenectomy [144, 145]. Furthermore, a prospective 6-year cohort study showed that obesity is a risk factor for SSIs in cardiac surgery, especially in valve surgery [146], in which sternal wound infection, mediastinitis and bacteremia are the most common infectious complications [146, 147]. Obesity has also been linked with other types of surgery, such as orthopaedic [148] and gynaecologic (caesarean) surgery [116, 149], showing a strong relationship between excess adiposity and SSIs.

CONCLUSIONS

Subjects with obesity definitively present a higher risk of contracting different infectious diseases, as well as experiencing a more severe course with increased mortality rates. Considering the increasing rate of obesity worldwide, it is necessary to investigate possible mechanisms and processes that underlie this association to improve preventive and therapeutic strategies. Furthermore, it is expected that this higher infectious risk along with cardiovascular mortality can provide a strong incentive for weight loss in subjects with obesity. Campaigns for the prevention of excess weight can be useful tools to promote a healthy lifestyle with a goal to decrease the rates of obesity and related complications.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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