Obesity Paradox in Patients Hospitalized with Community Acquired Sepsis: Does Age Make a Difference?

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ABSTRACT **Background:** Higher body mass index (BMI) has been shown to be a protective factor from mortality in sepsis patients. Yet, whether this effect is different in the very elderly is currently unknown.

Objectives: To investigate the relationship between BMI and sepsis outcomes in patients older and younger than 80 years of age.

Methods: A retrospective analysis of consecutive patients admitted with sepsis to Shamir Medical Center, Israel, was conducted. We compared patients older than and younger than 80 years of age with a BMI higher and lower than 25 kg/m² for hospitalization outcomes.

Results: Patients older than 80 years presented with multiple co-morbidities compared to younger patients, but with no difference between BMI groups. Similarly, hospitalization outcomes of functional deterioration, discharge to long-term care facilities, and readmission were not significantly different between BMI groups in the same age category. Mortality was significantly different between BMI groups in patients older than 80 years of age, with higher mortality in BMI < 25 kg/m²: in-hospital mortality (23.4% vs. 14.9%, $P < 0.001$), 30-day mortality (27.6% vs. 17.9%, $P < 0.001$), and 90-day mortality (43.4% vs. 28.9%, $P < 0.001$). This difference was not significant between the groups younger than 80 years old. On logistic regression, BMI over 25 kg/m² was protective in all mortality categories. Nevertheless, there was no significant interaction between age over 80 years to BMI over 25 kg/m² in all mortality outcomes.

Conclusions: Among patients hospitalized with sepsis, higher BMI is a protective factor against mortality in both elderly and younger patients.

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Sepsis might be hazardous for anyone at any age, but it can be particularly devastating for seniors. The incidence of sepsis increases with age, causing a sharp incline in people older than 80 years, and is associated with extremely high mortality rates [1,2]. In a recent meta-analysis reported by Haas et al. [1] in-hospital mortality from sepsis ranged from 31% to 84% in the very elderly (> 80 years), and one-year mortality ranged from 53% to 83%.

Although increasing numbers of very elderly patients are hospitalized with sepsis [2], few studies have investigated risk factors associated with morbidity and mortality in this patient population. In addition to standard risk factors, such as baselines co-morbidities and physiological indices [3,4], frailty and functional dependency are important predictors of short- and long-term prognosis in the elderly and have also been shown to increase the risk for mortality in sepsis [5,6].

Available evidence suggests that obesity is associated with increased mortality in the general population [7,8]. However, previous investigations have indicated that, counterintuitively, obesity and overweight might be associated with better outcomes in infectious disease and sepsis. This survival benefit has been termed the *obesity paradox*. Several large cohort studies revealed lower in-hospital mortality in overweight (25.0–29.9 kg/m²) and obese (> 30.0 kg/m²) patients compared to normal weight (18.5–24.9 kg/m²) patients [9-12].

The World Health Organization defines a healthy body weight range for adults as a body mass index (BMI) between 18.5 and 24.9 kg/m² based on reduced mortality risk [13]. However, this range has been based primarily on studies in younger adults and ideal BMI for the elderly may differ from the rest of the adult population. Previous studies have shown that older adults with overweight or obesity class BMI had reduced risk for all-cause mortality compared to normal BMI class [14-16].

It is currently unknown whether the obesity paradox in patients with sepsis is age dependent. In this study, we explored this question by comparing sepsis patients older and younger than 80 years of age with BMI groups over and under 25 kg/m².

PATIENTS AND METHODS

In this observational, retrospective cohort study, data of patients admitted to Shamir Medical Center, Israel, from August to December 2016, were collected. The study was approved by the local ethics (Helsinki) committee prior to its initiation.

Consecutive adult patients (> 18 years) with sepsis on admission (i.e., community-onset infection) were enrolled. The cohort consisted of patients from whom blood cultures were drawn in their first 2 calendar days of hospitalization (including visits to and immediate discharge from the emergency department) who concurrently had systemic inflammatory response syndrome and clinically suspected of having an infectious disease .Patients were excluded if they were directly transferred from another facility or if they were hospitalized in the past 7 days for any reason or in the past 30 days with the same infectious clinical syndrome.

Data were extracted from electronic patient charts regarding demographics, co-morbidities, hospitalization characteristics, 90-day readmission, and in-hospital mortality. The post-hospitalization mortality data were extracted from a national registry governed by the Israeli Ministry of Interior.

STATISTICAL ANALYSES

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA). All statistical tests were two sided, and $P < 0.05$ was considered statistically significant. Categorical data are expressed as frequencies and percentages. Continuous variables were evaluated for normal distribution using histogram and Q-Q plot and expressed as median and interquartile range (IQR).

Chi-square test and Fisher's exact test were applied to compare categorical variables and the Kruskal-Wallis test and Mann-Whitney test were used to compare continuous variables.

Multivariable logistic regression was used to study the association between age and BMI groups and the study outcomes while controlling for potential confounders including demographics, co-morbidities, acute medical characteristics, microbiology, and clinical syndromes. The regression included three blocks. In the first block, age and BMI categories were forced into the regression model. In the second block, all potential confounders were entered into the model and then a backward method was applied. Variables with a significance value above 0.1 at Wald test were excluded from the regression. In the last block, the interaction variable between age and BMI category was added.

RESULTS

Among 1527 patients admitted with community-onset sepsis, 1275 had a recorded BMI measurement. These patients were divided into four groups: group 1 age < 80 years and BMI < 25 kg/m2, group 2 age < 80 years and BMI ≥ 25 kg/m2, group 3 age ≥ 80 years and BMI < 25 kg/m2, and group 4 age years ≥ 80 with a BMI ≥ 25 kg/m2. Patients in the same age group but different BMI group were directly compared (groups 1 vs. 2 and groups 3 vs. 4). An additional comparison between all four groups was also conducted (data not shown). Demographics and co-morbidities by age and BMI group are reported in Table 1.

COMPARISON OF PATIENTS UNDER THE AGE OF 80 YEARS (GROUP 1 AND 2)

Generally, patients in the higher BMI group (group 2) were older and with more co-morbidities than in the lower BMI group (group 1). A higher percent of these patients had ischemic heart disease (18.8% vs. 11.9%, $P = 0.004$), heart failure (12.8% vs. 5.6%, $P \leq 0.001$), diabetes (40.8% vs. 16.7%, $P \leq 0.001$), chronic kidney disease (15.7% vs. 8.7%, $P = 0.001$), and a dependent functional status prior to the index hospitalization (23.0% vs. 16.5%, $P = 0.013$). Similarly, Charlson's score was also significantly higher in these patients (group 2 vs. group 1) 3 vs. 1, $P < 0.001$.

COMPARISON OF PATIENTS ABOVE THE AGE OF 80 YEARS (GROUP 3 AND 4)

The two groups had similar baseline characteristics apart from a higher percentage of diabetes in the higher BMI group (group 4 vs. group 3) 48.8% vs. 37.2%, $P = 0.033$ and a lower percentage of patients with malignancy 9.0% vs. 22.0%, $P = 0.001$.

Acute illness indices, clinical syndrome, and microbiology profile, by age and BMI group, are also reported in Table 1.

Generally, there was no difference between the BMI groups in both older and younger patients, except for a higher percentage of skin and soft tissue infections in group 2 vs. group 1 (20.5% vs. 11.9%, $P < 0.001$), and a higher percent of acute kidney injury also between these groups (20.4% vs. 15.0%, $P = 0.034$).

Hospitalization outcomes are reported in Table 2 and Figure 1. In the patient groups under 80 years, there was no significant difference in all outcomes comparing the lower and higher BMI groups (group 1 and 2), although a trend toward significance was seen in 90-day mortality with higher mortality, 9.4%, in group 1 vs. 6.2% in group 2, $P = 0.063$. In the patient groups above 80 years, patients in the higher BMI group (group 4 vs. group 3) had a significantly lower percent in all mortality outcomes, but no difference in functional deterioration, discharge to long-term care facilities, and 90-day readmission. In-hospital mortality was 14.9% vs. 23.4%, $P = 0.044$, 30-day mortality was 17.9% vs. 27.6%, $P = 0.032$, and 90-day mortality was 28.9% vs. 43.4%, $P = 0.005$.

In addition to a dichotomous comparison of high vs. low BMI with a cutoff of 25 kg/m^2, we also performed an additional comparison of patient mortality outcomes above and below 80 years of age, divided into the standardized BMI groups: underweight patients (BMI < 18.5 kg/m^2), healthy weight patients (BMI 18.5–24.9 kg/m^2), overweight patients (BMI 25–29.9 kg/m^2), and obese patients (BMI > 30 kg/m^2, Data not shown). In

Table 1. Demographics, co-morbidities, and acute illness indices by age and BMI group

	Age < 80 years			Age ≥ 80 years		
	Group 1	Group 2	*P*-value	Group 3	Group 4	*P*-value
	BMI < 25 kg/m² (n=413)	BMI ≥ 25 kg/m² (n=517)		BMI < 25 kg/m² (n=145)	BMI ≥ 25 kg/m² (n=201)	
Age, years (IQR)	52 (32–67)	64 (49–71)		85 (82–89)	85 (83–88)	
Female sex (%)	226 (54.7)	257 (49.7)	0.129	74 (51.0)	118 (58.7)	0.157
LTCF (%)	107 (25.9)	144 (27.9)	0.507	74 (51.0)	92 (45.8)	0.334
Background medical status and co-morbidities						
Dependent functional status	68 (16.5)	119 (23)	**0.013**	111 (76.6)	141 (70.1)	0.187
Altered consciousness at base	37 (9)	31 (6)	0.085	61 (42.1)	71 (35.3)	0.202
IHD (%)	49 (11.9)	97 (18.8)	**0.004**	59 (40.7)	80 (39.8)	0.868
CHF (%)	23 (5.6)	66 (12.8)	**< 0.001**	34 (23.4)	62 (30.8)	0.129
PVD (%)	23 (5.6)	41 (7.9)	0.158	16 (11)	15 (7.5)	0.251
DM (%)	69 (16.7)	211 (40.8)	**< 0.001**	54 (37.2)	98 (48.8)	**0.033**
CKD (%)	36 (8.7)	81 (15.7)	**0.001**	41 (28.3)	66 (32.8)	0.365
CLD (%)	64 (15.5)	106 (20.5)	**0.050**	27 (18.6)	55 (27.4)	0.059
Cerebral vascular disease (TIA, CVA) (%)	36 (8.7)	55 (10.6)	0.327	35 (24.1)	41 (20.4)	0.407
Dementia (%)	34 (8.2)	29 (5.6)	0.114	58 (40)	72 (35.8)	0.428
Chronic pressure ulcer (%)	14 (3.4)	11 (2.1)	0.237	20 (13.8)	19 (9.5)	0.208
Permanent devices (%)	33 (8)	50 (9.7)	0.372	30 (20.7)	36 (17.9)	0.516
Active malignancy (%)	43 (10.4)	38 (7.4)	0.100	32 (22)	18 (9)	**0.001**
Recent hospitalization	90 (21.8)	126 (24.4)	0.355	57 (39.3)	79 (39.3)	0.999
Charlson's combined condition score (IQR)	1 (0-5)	3 (1-6)	**< 0.001**	7 (6-10)	7 (6-8)	0.076
Acute medical indices						
Severe sepsis/ septic shock/ MOF (%)	85 (20.6)	116 (22.4)	0.494	74 (51)	96 (47.8)	0.548
ICU stay (%)	15 (3.6)	17 (3.3)	0.775	14 (9.7)	16 (8)	0.580
Ventilated (%)	28 (6.8)	25 (4.8)	0.204	25 (11.7)	20 (10)	0.598
AKI (%)	60 (15)	101 (20.4)	**0.034**	42 (30.4)	79 (40.3)	0.065
Altered consciousness during illness (%)	62 (15)	58 (11.2)	0.086	74 (51)	92 (45.8)	0.334
Clinical syndrome						
Pneumonia (%)	151 (36.6)	172 (33.3)	0.295	64 (44.1)	91 (45.3)	0.834
UTI (%)	93 (22.5)	114 (22.1)	0.865	40 (27.6)	58 (28.9)	0.796
SSTI (%)	49 (11.9)	106 (20.5)	**< 0.001**	17 (11.7)	27 (13.4)	0.638
Other (%)	120 (29.1)	125 (24.2)	0.093	24 (16.6)	25 (12.4)	0.279
Microbiology						
Positive blood cultures	66 (16.0)	81 (15.7)	0.896	48 (33.1)	49 (24.4)	0.075
Staphylococcus aureus BSI (%)	4 (1)	8 (1.5)	0.437	3 (2.1)	2 (1)	0.409
Klebsiella pneumoniae BSI (%)	3 (0.7)	6 (1.2)	0.502	3 (2.1)	2 (1)	0.409
Escherichia coli BSI (%)	9 (2.2)	14 (2.7)	0.606	14 (9.7)	13 (6.5)	0.275
MDR infection (%)	29 (7)	42 (8.1)	0.529	24 (16.6)	41 (20.4)	0.366

BMI = body mass index, IQR = interquartile range, LTCF = long-term care facilities, IHD = ischemic heart disease, CHF = congestive heart failure, PVD = peripheral vascular disease, DM = diabetes mellitus, CKD = chronic kidney disease, CLD = chronic lung disease, TIA = transient ischemic attack, CVA = cerebrovascular accident, UTI = urinary tract infection, SSTI = skin and soft tissue infections, BSI = bloodstream infection, MDR = multi-drug resistant (including any *Staphylococcus aureus* resistant to oxacillin such as MRSA), ampicillin and/or vancomycin-resistant enterococcus genus, penicillin or ceftriaxone non-susceptible *Streptococcus pneumoniae*, *A. baumannii* (regardless susceptibilities), *P. aeruginosa*, or *Achromobacter xylosoxidans* (regardless susceptibilities), any Enterobacteriaceae that is resistant to any 3rd or 4th generation cephalosporin, any Enterobacteriaceae with meropenem MIC > 1, metronidazole non-susceptible anaerobic bacteria, fluconazole non-susceptible Candida species, *Stenotrophomonas maltophilia*

Table 2. Hospitalization outcomes by age and BMI groups

	Age < 80 years		*P*-value	Age ≥ 80 years		*P*-value
	Group 1	Group 2		Group 3	Group 4	
	BMI < 25 kg/m²	BMI ≥ 25 kg/m²		BMI < 25 kg/m²	BMI ≥ 25 kg/m²	
	(n=413)	(n=517)		(n=145)	(n=201)	
Functional deterioration (%)	27 (6.9)	34 (6.8)	0.954	22 (19.8)	38 (22.2)	0.630
Discharge to LTCF (%)	11 (2.9)	13 (2.7)	0.841	9 (9.6)	18 (12.2)	0.533
Readmission (%)	85 (25.2)	116 (26.5)	0.691	44 (44.0)	67 (44.1)	0.990
In-hospital mortality (%)	24 (5.8)	20 (3.9)	0.168	34 (23.4)	30 (14.9)	**0.044**
Mortality 30 days (%)	24 (5.8)	20 (3.9)	0.168	40 (27.6)	36 (17.9)	**0.032**
Mortality 90 days (%)	39 (9.4)	32 (6.2)	0.063	63 (43.4)	58 (28.9)	**0.005**

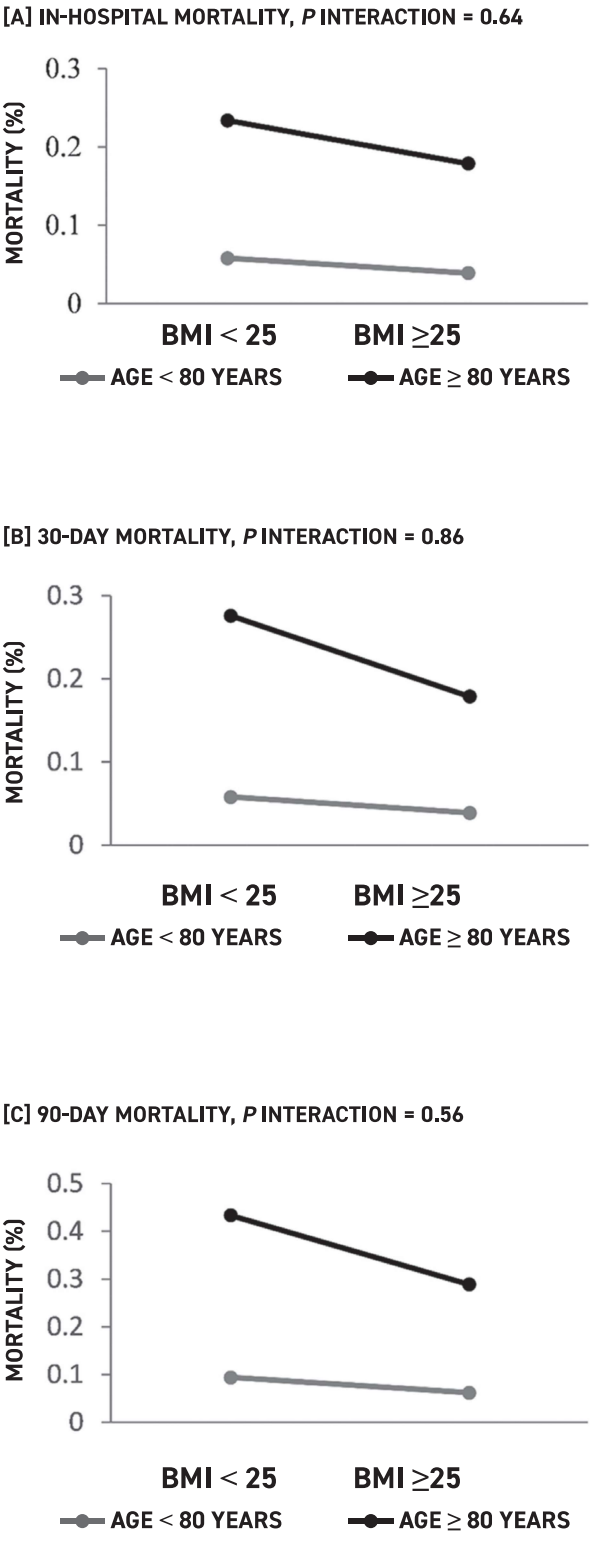
BMI = body mass index, LTCF = long-term care facilities
Bold indicates significance

Table 3. Risk factors for mortality among patients hospitalized with sepsis as determined by stepwise logistic regression analysis

	In-hospital mortality		30-day mortality		90-day mortality	
	aOR (95%CI)	*P*-value	aOR (95%CI)	*P*-value	aOR (95%CI)	*P*-value
Demographic and medical characteristics						
Age ≥ 80 years	1.30 (0.74–2.28)	0.355	1.73 (1.01–2.96)	**0.044**	1.96(1.24–3.10)	**0.004**
BMI ≥ 25 kg/m²	0.51 (0.30–0.86)	**0.012**	0.711 (0.42–1.2)	0.199	0.57 (0.36–0.89)	**0.015**
Recent LTCF stay	2.39 (1.39–4.12)	**0.002**	2.13 (1.25–3.63)	**0.006**	2.65 (1.69–4.14)	**< 0.001**
Dependent functional status	4.46 (2.25–8.83)	**< 0.001**	3.29 (1.61–6.74)	**0.001**	3.96(2.25–6.99)	**< 0.001**
Active malignancy	1.81(0.92–3.56)	0.086	2.14 (1.09–4.04)	**0.027**	4.05 (2.26–7.24)	**< 0.001**
CHF	1.86 (1.05–3.30)	**0.035**			2.24 (1.33–3.76)	**0.002**
Acute medical characteristics						
Severe sepsis	7.34(3.56–15.1)	**< 0.001**	3.26 (1.66–6.38)	**0.001**	2.12 (1.24–3.60)	**0.006**
AKI	2.65(1.48–4.74)	**0.001**	2.32 (1.31–4.09)	**0.004**	2.12 (1.27–3.53)	**0.004**
Decreased consciousness			2.06 (1.22–3.78)	**0.006**	2.09 (1.25–3.51)	**0.005**
Clinical syndrome						
Pneumonia	1.93 (1.14–3.27)	**0.015**	2.11 (1.25–3.54)	**0.005**	1.99(1.27–3.14)	**0.003**
Laboratory measurements						
Albumin			0.92 (0.88–0.97)	**0.004**	0.93 (0.89–0.97)	**0.004**

95%CI = confidence interval, AKI = acute kidney injury, aOR = adjusted odds ratio, BMI = body mass index, CHF = congestive heart failure, LTCF = long-term care facilities, UTI = urinary tract infection

Figure 1. Comparison of the effect of BMI group on mortality above the age of 80 (black line) and under the age of 80 (grey line). Interaction was computed using multivariable logistic regression



the group of patients under 80 years, mortality was only significantly higher in the underweight patients compared to all other BMI groups. In-hospital mortality was 13.5% vs. 3.1–5.1%, P = 0.044, 30-day mortality was 13.5% vs. 3.1–4.9%, P = 0.043, and 90-day mortality was 21.6% vs. 4.8–8.4%, P = 0.003. In patients above 80 years, generally, mortality was gradually decreased in consecutively higher BMI groups, but this was only significant in 30-day mortality when comparing patients with normal BMI to obese patients 27.7% vs. 15.4%, P = 0.016, and in 90-day mortality when comparing patients with normal BMI to overweight and obese patients, 44.6% vs. 31.–24.4%, P = 0.003.

To assess which risk factors were associated with mortality and whether there was an interaction between age and BMI groups, we conducted a stepwise logistic regression. Results are shown in Table 3. Age over 80 was a risk factor for 30-day and 90-day mortality (aOR [adjusted odds ratio] 1.73, 95% confidence interval [95%CI] 1.01–2.96, P = 0.044 and aOR 1.96, 95%CI 1.24–3.10, P = 0.004) BMI over 25 kg/m^2 was protective for in-hospital and 90-day mortality (aOR 0.51, 95%CI 0.30–0.86, P = 0.012, and aOR 0.57, 95%CI 0.36–0.89, P = 0.015). Nevertheless, there was no significant interaction between age over 80 years and BMI over 25 kg/m^2 in all mortality outcomes [Figure 1]. Additional risk factors included background medical status and co-morbidities such as recent long-term care facilities stay, dependent functional status, active malignancy, and heart failure. Acute medical characteristics included severe sepsis, acute kidney injury, decreased consciousness, and pneumonia. Last, serum albumin was slightly protective for 30-day and 90-day mortality (aOR 0.92, 95%CI 0.88–0.97, P = 0.004, and aOR 0.93, 95%CI 0.89–0.97, P = 0.004).

DISCUSSION

Obesity is considered a risk factor for morbidity and mortality in many longitudinal studies and serves as a risk factor for a wide variety of diseases, including cardiovascular disease, malignancies, and infections. However, cumulating data show that obesity is associated with reduced hospitalization mortality in patients with critical illness and congestive heart failure and after elective or urgent surgeries. This phenomenon is known as the obesity paradox [17-19]. In this retrospective hospital-based study, BMI over 25 kg/m^2 was a protective factor against mortality in patients admitted with community-acquired sepsis. These results compare with previous studies evaluating the protective effect of obesity on septic patients [9-12].

We compared outcomes between octogenarians and younger patients each in a low and high BMI group. Although only octogenarians had a significant mortality difference between BMI groups, on logistic regression, we found no significant interaction between age and BMI

groups, meaning that BMI does not have a different effect on mortality outcomes in the age over 80 group and the age under 80 group [Figure 1]. This finding suggests that overweight and obesity have a protective effect in all age groups and not only in the elderly. The lack of significant effects in patients younger than 80 years might be explained by a lower rate of mortality in these patients, concealing the true protective effect of higher BMI. This conclusion is supported by the trend to significant difference in 90-day mortality in the patient groups younger than 80 years (9.4% vs. 6.2%, $P = 0.063$), and by the general protective effect of BMI over 25 kg/m^2 evident in the results of the logistic regression [Table 3].

Several explanations have been offered for the obesity paradox in patients with sepsis, including the protective effect of nutritional reserves in the increased catabolic state of sepsis, adipose tissue regulation of immune and anti-inflammatory responses, and adipose tissue acting as a functional storage depot for potentially toxic metabolites [20,21]. Nevertheless, this paradox may have additional and more straightforward explanations in the elderly population.

Average body weight gradually increases during most of adulthood and levels-off around 60 years of age after which mean body weight tends to decrease. This decrease is mostly attributed to the accelerated rate of muscle loss as people age [22]. Sarcopenia is a progressive and generalized skeletal muscle disorder, of which incidence increases with age. It is defined by low muscle strength and low muscle quantity or quality that may lead to low physical performance [23]. Sarcopenia is associated with an increased likelihood of adverse outcomes, physical disability, and mortality [24]. Furthermore, in a recent meta-analysis by Zhang et al. [25] sarcopenia was associated with an increased risk of mortality in critically ill patients.

In addition, lower BMI, especially from unintentional weight loss, may be indicative of underlying disease and may explain the worse prognosis in these patients. In our current study patients above the age of 80 years with a BMI lower than 25 kg/m^2 had a significantly higher percentage of active malignancy (22% vs. 9%, $P = 0.001$).

This study has several limitations. The retrospective, chart-review-based, single-center design impose multiple inherent confounders. In addition, the single BMI and age cutoffs may simplify the reciprocal effects of BMI and age on sepsis outcomes. Last, BMI, although a commonly used indicator, does not discriminate between different body compositions, which may have an important role, especially in elderly patients.

CONCLUSIONS

Overweight and obesity have a similar protective effect on outcomes of sepsis across different age groups. Further research is needed to advance our knowledge on specific factors, which may drive this effect and the possible contribution of different body compositions.

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The common idea that success spoils people by making them vain, egotistic and self-complacent is erroneous; on the contrary it makes them, for the most part, humble, tolerant, and kind.

William Somerset Maugham (1874–1965), English playwright, novelist, and short-story writer

Capsule

Lingering immune changes after obesity

A past period of obesity caused by a high-fat diet in mice produced persistent changes in innate immunity even after weight loss and normalization of metabolism. **Hata** and colleagues found that such diet-induced obesity in mice, even after it was resolved, led to persistent epigenetic changes in chromatin in macrophages associated with increased expression of genes that function in inflammatory responses. Experiments with transplants of adipose tissue or bone marrow implicated alterations of myeloid cells in exacerbating inflammatory responses to experimentally induced injury in the eye. If similar processes occur in humans, then the authors proposed that such changes could contribute to predisposition to age-related macular degeneration associated with obesity.

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Eitan Israeli

Capsule

Cold exposure impairs extracellular vesicle swarm-mediated nasal antiviral immunity

Seasonal variation in respiratory viral infections and the importance of ambient temperature in modulating immune responses to infections have been well recognized; however, the underlying biological mechanisms remain understudied. **Huang** et al. investigated the role of nasal epithelium-derived extracellular vesicles (EVs) in innate Toll-like receptor 3 (TLR3)-dependent antiviral immunity. The authors found that polyinosinic:polycytidylic acid, aka poly(I:C), exposure induced a swarm-like increase in the secretion of nasal epithelial EVs via the TLR3 signaling. EVs participated in TLR3-dependent antiviral immunity, protecting the host from viral infections through both EV-mediated functional delivery of miR-17 and direct virion neutralization after binding to virus ligands via surface receptors, including LDLR and ICAM-1. These potent antiviral immune defense functions mediated by TLR3-stimulated EVs were impaired by cold exposure via a decrease in total EV secretion as well as diminished microRNA packaging and antiviral binding affinity of individual EV. TLR3-dependent nasal epithelial EVs exhibit multiple innate antiviral mechanisms to suppress respiratory viral infections. Furthermore, this study provides a direct quantitative mechanistic explanation for seasonal variation in upper respiratory tract infection prevalence.

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