Obesity paradox, obesity orthodox, and the metabolic syndrome: An approach to unity

Obesity paradox and the metabolic syndrome.

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Abstract:

Obesity and the accompanying metabolic syndrome are strongly associated with heightened morbidity and mortality in older adults. In our review of more than 20 epidemiologic studies of major infectious diseases, including leaders such as tuberculosis, community-acquired pneumonia, and sepsis, obesity was associated with better outcomes. A cause-and-effect relationship between over-nutrition and survival with infection is suggested by results of two preliminary studies of infections in mice, where high fat feeding for 8-10 weeks provided much better outcomes. The better outcomes of infections with obesity are reminiscent of many recent studies of "sterile" non-infectious medical and surgical conditions where outcomes for obese patients are better than for their thinner counterparts --- and given the tag "obesity paradox". Turning to the history of medicine and biological evolution, we hypothesize that the metabolic syndrome has very ancient origins and is part of a lifelong metabolic program. While part of that program (the metabolic syndrome) promotes morbidity and mortality with aging, it helps infants and children as well as adults in their fight against infections and recovery from injuries, key roles in the hundreds of centuries before the public health advances of the 20th century. We conclude with speculation on how understanding the biological elements that protect obese patients with infections or injuries might be applied advantageously to thin patients with the same medical challenges.
(1) Introduction

(¶1) The continuing increase in the prevalence of obesity (and the tapering of tobacco abuse) lead experts to predict that obesity will shortly become the leading personal health problem worldwide. Obesity and the accompanying metabolic syndrome are typically associated with shortened life expectancy, premature disability, and heightened prevalence of cardiovascular disorders, cancer, diabetes, and Alzheimer disease as well as multiple other disorders linked to advancing age.

(¶2) In the jeremiads inspired by obesity, the modest but deeply rooted health advantages of obesity are typically neglected (Table 1). In this paper we add further to the list of advantages of obesity; we review over 20 epidemiology studies of six serious infectious diseases, including tuberculosis, pneumonia, and sepsis, where outcomes are inversely related to body mass index. The consistency of the obesity advantage is especially remarkable because the usual measurements to express adiposity i.e. body mass index (BMI; the weight in kilograms divided by the square of the height in meters) as well as waist circumference or neck circumference are such rough approximations of total body fat or of visceral fat or of metabolic syndrome. The connection between body mass index and the metabolic syndrome in epidemiology studies is further loosened by impressive ethnic differences (Figure 1) [1] and changes in individuals with aging. To support the idea that the inverse relationship between adiposity in patients and infection outcomes likely reflects cause-and-effect (rather than simply an association), we shall review preliminary experiments with two models of short term infections in mice where high fat feeding over a few weeks reproduced the advantage of obesity in overcoming infections.

(¶3) The obesity advantage recounted here with clinical and experimental infectious diseases are concordant with many publications in the last decade citing multiple (infection-free, i.e. "sterile") medical and surgical situations where obesity was associated with better outcomes (Table 1). That so many of these were tagged as an "obesity paradox" reflects the health community's puzzlement about obesity.

(¶4) In the concluding section, based on the history of medicine and biological evolution, we marshal evidence to propose a union of these ideas. We will posit that the metabolic syndrome does not arise de novo in middle life. Rather, it is part of a continuous lifelong metabolic program. This program in
early life (and probably its primary raison d'être for millions of years) provided an inflammatory defense that was vitally needed to help in the battle against the many infections that decimated youngsters before the 20th century introduction of clean water, vaccinations, insect control, and antibiotics. Those with better nutrition, more body fat and more highly activated immune functions, were favored to survive. The same program helped advance reproductive capacity (in females) and physical strength (in males and females) and helped both sexes to survive infections and sterile challenges, including wounds and injuries. In middle life, these same beneficial processes were subordinated to the damaging forces we associate with metabolic syndrome and premature death. (Tongue in cheek: adiposity shortens the individual’s life span but provides better "road service" on the way to the cemetery, e.g. resolving infections and healing fractures). To close, we initiate a discussion of how future research might yield insights whereby the positive elements of obesity that we catalog here might be applied to thin patients in the short term to better overcome infections and non-infectious challenges.

(II) Infectious diseases

(¶5) (A) Tuberculosis as an unconquerable -- Tuberculosis is the epitome of what we have designated as an unconquerable infectious disease, one that is not curable without specific pharmacologic therapy [2,3]. (Another widespread unconquerable is American trypanosomiasis i.e. Chagas disease). Absent specific modern drugs, tuberculosis infection is lifelong, irrespective of whether the disease (i) is active, (ii) was active and now in remission, or (iii) never clinically active but latent and capable of progression to active disease, in the absence and presence of risk factors such as HIV/AIDS or TNF blockers [4,5,6].

(¶6) Classically, tuberculosis is associated with an acute or chronic diminution in body weight. The wasting is epitomized by phthisis and consumption, old-fashioned synonyms for active tuberculosis.

In Table 2, we present six narratives (of many) where rates of tuberculosis were inversely related to nutrition [7]. Several other studies show a similar trend [8,9]. In Figure 2A, six modern epidemiologic studies from four countries show a clear inverse relationship between body mass index and incidence of tuberculosis. Not widely appreciated, this relationship is continuous from quite low BMI's through to the
overweight and obese [10]. In the Hong Kong study (Figures 2A & 2B) over 40,000 patients over age 65 were followed for 5 years or more. The curve that is tracking morbidity (“cumulative hazard function”) showed a clear change in slope for each of five BMI categories from less than 18.5 to over 30 (Figure 2B) [11]. In a later larger study rooted within the NHANES I Health and Nutrition Survey in the USA, recruits followed for around a decade, showed a similar trend, although the rates of tuberculosis were much lower and the patients were younger (Figure 2C). Underweight patients were clearly at highest risk. Over the range from normal weight to obese, differences appeared to be continuous but less marked than in Hong Kong [12].

(¶7) Interestingly, before the introduction of streptomycin and other tuberculosis-targeted drugs in the mid-1950's, a long list of therapies were recommended. Osler, the leading physician in North America one hundred years ago, promulgated recommendations that are quite representative of these past therapies. "Make patient grow fat and strong …. The importance of rest must be always kept in mind and the amount of exertion allowed carefully ordered." For patients with fever, “absolute rest” is recommended. In retrospect, Osler et al. exhorted physicians to launch their patients with tuberculosis headlong into the metabolic syndrome and to sustain it as best as possible [13].

(¶8) (B) Community acquired pneumonia -- With tuberculosis presented as the lead example of unconquerable infections, we turn to community-acquired pneumonia as the model of an acute chance infection [2,3]. Community acquired pneumonia in most adult patients is likely to be the result of a new infection, where *Streptococcus pneumoniae* is the most frequent bacterium [14,15]. In a recent study, *S. pneumoniae*, was found in less than 5% of healthy adults [16]. Diagnosis of a respiratory infection on the screening day was the only significant risk factor for a positive culture (P<0.05) [16]. (This is in sharp contrast to children where typically carrier rates for *S. pneumoniae* were 10 times higher). In the pre-antibiotic, pre-vaccine era, a typical patient with pneumonia presented acutely, with a severe febrile course over a few days culminating in death or rapid recovery. Despite the lack of specific therapies, signs of the illness were markedly better in a few days and largely gone in a few months, leaving the patient with long term immunity to that subtype of the bacterium.
(¶9) Mortality with pneumonia appears to be inversely related to adiposity (Figure 3A) [17]. In another recent study with patients in one veteran’s hospital, the 30-day mortality with community-acquired bacterial pneumonia was four times higher in underweight patients (BMI < 18.5) than in those with obesity (BMI > 30) (Figure 3B) [18]. Those patients designated as normal weight and overweight showed intermediate values suggesting that these differences were not overly dependent on an accumulation of susceptibility factors in the underweight. In Figure 3B, the results of the Corrales-Medina study are compared to results with large studies by King et al. and by Singanayagam et al [19,20]. In two other studies (data not shown), one very large study of middle-age and elderly Japanese and a more recent study of 226 patients from Spain of older patients with community-acquired pneumonia, an elevated BMI was associated with better outcomes and a reduced BMI was linked to poorer outcomes. The better outcomes among the obese patients occurred in the face of a higher prevalence of co-morbidities that may affect susceptibility and outcomes with pneumonia (e.g. diabetes, gastro-esophageal reflux, reduced respiratory excursions, and less effective coughing).

(¶10) (C) Sepsis -- For patients with severe sepsis (including those with septic shock), mortality was reduced as a function of increased BMI. In a retrospective study of 1404 adults over 65 with severe sepsis, there was a dose response relationship between one-year mortality and BMI in patients from normal weight through severe obesity [21]. Underweight patients were excluded. Wacharasint et al., analyzing a drug study cohort retrospectively, found in 713 patients with septic shock that 28 day mortality was inversely related to body mass index; every one unit increase in BMI was associated with an adjusted mortality decrease of 2% (Figure 4A) [22]. Using a multivariate logistic regression model on 301 patients, Wurzinger et al. found that overweight and obese patients in intensive care units with septic shock had a better survival rate than those with normal or reduced BMI [23].

(¶11) Trivedi et al. in their comprehensive systematic review, selected seven studies for detailed analysis (out of 183 published studies of obesity and sepsis mortality) [24]. They agreed with the validity of the conclusions in the three studies we reviewed in the previous paragraph i.e. better outcomes in obese patients with sepsis. In the four other studies that met their validation criteria, three studies failed to show
a significant correlation after multivariate analysis. In the seventh study, obesity with sepsis was
associated with a poorer outcome. We cautiously agree that the overweight and obese patients do better
than those of normal or reduced weight but extreme heterogeneity of the patients is a barrier to
unambiguous conclusions.

(D) American trypanosomiasis -- Trypanosoma cruzi, an insect-borne protozoa, causes
American trypanosomiasis, or Chagas Disease, a chronic “unconquerable” infection very widespread in
Latin America that results in debilitating cardiac disease, mega-syndromes of the viscera, disability, and
shortened life-span [25]. Successes in Chagas disease prevention and therapy are improving. Among
Chagas patients with heart disease followed for 10 years, obese patients survived longer (despite the
burdens that obesity places on cardiovascular function). Also, in patients with Chagas disease who were
free of heart disease, the long-term outcome with obesity was also clearly superior (Figure 4B) [26].

(E) Gall bladder disease -- Among 427 patients with acute cholecystitis, the obese patients
had milder disease. Most infected patients had a BMI within the normal range. BMI inversely correlated
with the presence of biliary bacteria, bacteremia, pigmented (more bacteria-friendly) stones, and severity
of illness (Figure 4C) [27]. In another retrospective study of 139 patients post-cholecystectomy, BMI was
also inversely related to bacteremia and bactibilia [28].

(F) Surgical peritonitis -- Among 253 consecutive patients with severe secondary surgical
peritonitis (with sepsis) who needed intensive care for over 2 days, the mortality rate at 28 days fell
progressively from 73% to 31% in those with BMI < 21 vs those with BMI > 30 (Figure 4D) [29]. This
obesity advantage held, despite the finding that those in the obese quartile had modestly more diabetes,
coronary artery disease and heart failure than observed in the other three groups. The mortality advantage
observed in the obese patients with infection was in the short term. By 5 years, the negative consequences
of obesity were manifest [29]. These findings suggest that with serious infection, obesity provides an
advantage over the short term. Absent infection, over the longer term, the well-recognized detrimental
effects of obesity dominate.

(G) Evidence from Animal Studies -- To distinguish an association from a cause-and-
effect relationship, we turned to experiments in mice. With T. cruzi infections, we and our colleagues raised survival from 40% to 80% by administering a standard high fat diet (Figure 5A and 5B) [30]. That diet, initiated weeks, days, or even one day before infection and carried through several weeks of the acute infectious process, rapidly promoted obesity and the metabolic syndrome, along with the increased survival. In addition, the high fat diet protected mice from T. cruzi infection-induced myocardial damage [31].

With a standard model of severe sepsis in mice (polymicrobial sepsis following perforated appendix i.e. cecal ligation & puncture), animals pre-fed a high fat diet to produce obesity showed markedly enhanced survival (Figure 6A and 6B) [32]. In another study, a high fat diet inaugurated 12 weeks before surgery, raised survival from sepsis from approx. 10% to 65% (Figure 6B) [33].

(H) Potential sources of confusion -- Overfed animals with obesity have elevated levels of circulating leptin. Leptin is a robust broadly acting promoter of immune activation, e.g. as with metabolic syndrome. Humans and rodents lacking leptin (ob/ob, Zucker, other) or lacking leptin receptors (db/db) are very obese but have deficiencies in immunity [34,35]. In interpreting experiments, it is vital that hyperleptinemic obesity, which is similar to the common condition in obese humans, be distinguished from hypoleptinemic obesity, a very uncommon condition in humans and rodents, but widely used in laboratory experiments. Hyperglycemia and diabetes are also sources of confusion (Figure 7C). As adiposity increases, metabolic syndrome intensifies, raising level of immune protection (Figure 7A and 7B). Simultaneously, groundwork is paved for dysglycemia and diabetes with serious undermining of multiple components of immune protection (Figure 7C).

I) Exceptions -- We have suggested that infections in general are associated with better survival in overweight patients, but also recognize that outcomes in some individual infections may be worse with obesity [36,37]. These infections include H1N1 influenza A [38,39,40,41] and hepatitis B and C [42,43,44,45]. The influence of obesity on additional individual infectious diseases does warrant further study.

(III) Sterile (non-infectious) Diseases
(¶19) **(A) Infectious processes and sterile injury** – More than twenty epidemiology studies of six major infectious diseases -- including leaders like tuberculosis, community-acquired pneumonia, sepsis, and American trypanosomiasis --- all show that elevated adiposity is associated with a significant survival advantage. A similar advantage with adiposity has been noted widely among patients with non-infectious disorders, including those designated as "sterile injury" (Table 1). Because the obese and overweight patients often fare better than their normal weight counterparts, "obesity paradox" has often been applied as a tag. As shown in Figure 8A and 8B, patients with obesity who have uninfected fractures of the hip or of other bones show better outcomes that are reminiscent of those observed with so-called unconquerable infections [46]. Valentijn et al. compiled a collection of published reports of surgical entities and a similar collection of non-surgical entities where patients with above normal adiposity show better outcomes [47,48]. Finally, we were unable to measure the effects of publication bias; publications with results that are statistically significant are much more likely to overcome the multiple barriers that line the road to publication.

(¶20) **(B) Overlaps of body responses to sterile and infectious processes**— The local and systemic responses to sterile injury, including ischemia and inflammation, resemble in many ways the body's responses to infection. The old (no longer favored) idea that the response to infections involves two sets of sensing pathways, PAMPs (pathogen associated molecular patterns) and DAMPs (damage associated molecular patterns), while sterile inflammation involves only the DAMPS has been replaced by recognition that both conditions involve both clusters of endogenous response elements [49]. As research advances, more overlaps between the two pathways (PAMPs and DAMPs) are being recognized. Recent data suggest that products of commensal organisms from the gut microbiota supply PAMP activators during so-called "sterile" events, heightening our appreciation of the overlaps of the two pathways. That would be consistent with the widespread view that death with most infections is not due directly to the microbe but due to endogenous processes, immunologic and other, inaugurated by the infection but have a sustaining momentum of their own, as occurs with so-called "sterile" events. Given the similarities, the favorable therapeutic response in mice from activating elements of the metabolic
syndrome observed in preliminary experiments with trypanosomiasis and polymicrobial sepsis raises our optimism that similar tools possibly may also be effective in many of the so-called "sterile" conditions [50,51,52,53,54,55].

(IV) History and Evolution

(¶21) (A) History may provide intellectual unity – Evolutionary history rationalizes the coexistence of obesity’s positive and negative contributions. The metabolic syndrome with its continually growing list of negative consequences has caused the bio-medical community to be resistant to recognizing benefits to patients that might accrue from obesity. This reticence is reflected in the growing use of “obesity paradox” when benefits are uncovered, especially those associated with sterile injury. Our reports here of benefits from obesity with infectious diseases join this list. Reflections on possible evolutionary origins will lead us to suggest that the help with infections appeared very early in evolution and contributes benefits very early in the lives of individuals. We hypothesize that the benefits with sterile injury arose later in evolution and typically matter more during later life. Metabolic syndrome not only becomes prominent late in the life of the individual but historically rose to prominence only in recent times.

(¶22) (B) Evolution -- In contrast to deaths in 2000, causes and demographics of mortality in 1900 were probably much closer to the mortality scene in the first 150,000 years of Homo sapiens on this planet or of the millions of years for our hominid ancestors. Infections (along with trauma) dominated while the degenerative diseases of old age were uncommon causes of death. From an evolutionary point of view, it is remarkable that the metabolic syndromes in mice and rats are so similar to one another and to the syndrome in humans, although the two rodent lines separated evolutionarily over one million years ago and we shared a common ancestor with rodents over 10 million years ago [2,3]. The durability of the program over time across species supports our proposal of its vital role, particularly in youngsters.

(¶23) “One of the most remarkable transformations in the history of mankind” -- Rothstein reminds us that “The twentieth century has witnessed the greatest and most rapid changes in both death rates and causes of death in recorded history. At the beginning of the century, infectious diseases were
the paramount cause of death in all societies, killing millions of infants, children, and young adults.

After 1900, death rates from these diseases declined rapidly in advanced countries, enabling many more people to live to old age” (Figure 9) [3,56]. In 1900, only 2% of people in USA were over 65. By 2000, that percentage had multiplied six-fold. In contemporary Japan, Germany and Italy, the over 65 constitute 20% of the population. The demographic shift is mirrored in the causes of death. In 1900, pneumonia was a leader and affected all ages. Tuberculosis, a close second, accounted for more than 10% of all deaths in USA (Figure 9). Tuberculosis affected all ages “from the newborn to the octogenarian but ages 18-35 were hardest hit” [13]. The ferocity of tuberculosis was reflected in its nicknames, "The Captain of the Men of Death" and "The White Plague".

(¶24) At present, with the decline in infectious diseases and 12% of the U.S. population older than 65, heart disease and cancer are the leading causes of death and most of those affected are well along in years (Figure 9). Deaths from pneumonia are in the single digits (and typically affect the very old, the very young, and those already ill). Tuberculosis deaths are so few that we artificially inflated the marking in the column for tuberculosis 2000 in the figure so it was just visible. Worldwide, tuberculosis is still a major infectious disease killer, ranking #1 or #2 depending on criteria for calculation. We estimate that in the time it takes to read this article, 50 - 100 humans will die of tuberculosis [57].

(¶25) The standard 21st century view of the metabolic syndrome as a herald and bearer of the major pathology associated with diseases of aging derives from the brilliant pioneer work of Reaven et al., brought to full flowering by him and his successors [58]. One major weakness of the current definition that has emerged is the use of a final declaration "yes" or "no" -- the individual has or does not have the metabolic syndrome. It is treated as a diagnostic entity (yes/no) rather than as a continuous pathophysiologic process. We envision the metabolic syndrome to be a continuous process, controlled in a rheostat-like fashion (like the volume dial on the car radio) that affects all of us all of the time. More important, each of the myriad components that characterize excess adiposity and the metabolic syndrome represent an individual process, each with its own rheostat-like continuum. A future hypothetical desirable goal would be to harness one or more of these processes for magnification in normal weight or
under-weight patients with infectious diseases (or sterile injury) to re-create the therapeutic benefits of obesity without the adiposity.

(V) Scoping the Future --- Research Prospectus

(¶26) How can the select better outcomes in obese patients be reproduced in thin patients (especially the vulnerable elderly) with these conditions, e.g. tuberculosis, pneumonia, sepsis, or hip fracture? Weight gain for thin patients (i) can be difficult; (ii) is likely to bring both desirable and undesirable elements; and (iii) hard to undo once the need is over.

(¶27) The medical profession's longstanding fight against obesity may have a useful lesson; efforts to control body weight (short of by-pass surgery) continue to have limited success. Greater health benefits have been derived by identification and treatment of individual health-harming components of obesity, e.g. hypercholesterolemia, hypertension, hyperglycemia, and sleep apnea. We can envision researchers identifying elements that are providing the benefit to obese patients showing the "obesity paradox" and then re-create in thin patients one or a few of these elements over the short term. Possibly one menu will fit all conditions that manifest the "obesity paradox", or more likely, multiple menus will be devised. Our optimism is fueled by (i) therapeutic successes achieved (in the opposite direction) by altering single elements, e.g. TNF or IL-1 in complex inflammatory disorders; (ii) deep knowledge and availability of hormone-like agents e.g. leptin, resistin, and adiponectin whose circulating levels differ in thin and obese subjects; and (iii) animal models (see earlier) that promise to be in the vanguard in this search.

(VI) Conclusion

(¶28) Excess adiposity and its companion, the metabolic syndrome, have well deserved reputations as major detriments to health and longevity. Unexpected was the inverse relationship between adiposity and mortality that we derived from over 20 epidemiology studies of six infectious diseases of broadly different etiologies (and a score of "sterile" medical and surgical "obesity paradoxes" from other published literature). Recall that the body mass index (BMI) and waist circumference are very inexact
measures of visceral fat deposits and of the associated metabolic syndrome. Further smudging of the
relationship between BMI and metabolic syndrome comes from the sizeable ethnic variations and from
distortions from aging, other diseases, and medications. It is remarkable that the tightness of the linkages
survive the many uncontrollable variables.

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Disclosure

The authors declare they have no competing interests as defined by Molecular Medicine, or other interests
that might be perceived to influence the results and discussion reported in this paper.
References:


Table 1: Obesity and its benefits.

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<th>Benefits of obesity in surgical conditions</th>
<th>Benefits of obesity in non-surgical conditions</th>
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<td>Increased mass of skeletal muscle</td>
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Figure 1: The relationship between body mass index and incidence of diabetes in four ethnic groups in Canada

Figure 1: In Ontario, Canada, approximately 60,000 non-diabetic men and women, ages 30 and up were followed for up to 12.8 years for diabetes incidence. The median duration of follow-up was six years. The incidence of diabetes increased with increased body mass index in each ethnic group, as expected. South Asians became diabetic at BMI values that were the lowest followed by the Chinese, the Black, and the White. The graph shows the incidence rate of diabetes per 1,000 person-years at each level of BMI [1].
Table 2

Summary of selected reports relating nutrition to TB (Adapted from Cegielski & McMurray, 2003)[7]

- During World War I, Denmark, a non-combatant, became a very heavy exporter of meats and dairy products to the U.K. The resulting food shortage in Denmark was associated with a clear uptick in active TB. Cessation of exports, due to the German blockade in 1918, led to the restoration of domestic food supplies and restored TB rates to normal.

- Sailors-in-training in Norway had an unexpectedly high rate of active TB. Physical improvements in housing produced no change but marked upgrade in diet reduced incidence of TB and other infections.

- In a prisoner-of-war camp in World War II, British and Russian prisoners were treated similarly by the Germans, but the British were better nourished because of weekly Red Cross food packages. The Russians, with their reduced level of nutrition, showed a high rate of TB while the British TB rate stayed at the usual level for British civilians.

- Among US Navy World War II recruits, tuberculin test results on recruitment were independent of nutrition status (based on body height and weight) but TB incidence following recruitment did correlate inversely with nutrition.

- Among 1.7 million Norwegians (age 14 and older) followed for 8-19 years, the incidence of pulmonary TB (smear positive and smear negative) was inversely related to BMI for both males and females, with a five-fold difference between the highest and lowest weight group.

- The inaugural NHANES study (started 1971 and followed up 1982-1992) found that low nutrition was associated with a 6-12 fold higher risk of TB than those with normal values. The population in the upper 40% of adiposity had markedly reduced incidence of TB, compared to those with normal adiposity.
Figure 2

(A) The authors describe “a remarkably consistent inverse logarithmic relationship between TB incidence and BMI, across studies that had been carried out over the past 50 years in diverse study populations with a large variation in average TB incidence, and which had controlled for various sets of confounders” [10]. (B) Obesity reduces risk of tuberculosis. Hazard function curves illustrating morbidity with active tuberculosis for different body mass index categories. Individuals with a low body mass index have an increased risk of active tuberculosis. The opposite is true for individuals with high body mass index, illustrating the protective effect of obesity. These data were reformulated for the Hong Kong curve in figure 2A [11]. (C) This figure depicts the probability of individuals in the inaugural NHANES study remaining free of tuberculosis from 1971-1992 (stratified by initial BMI into 4 groups) [12].
Figure 3

**A** Obesity and outcomes in patients hospitalized with pneumonia.

**B** 30 Day Mortality and BMI in Community Acquired Pneumonia

- CORRALES-MEDINA et al, Retrospective (n=266)
- KING et al, Retrospective (n=18746)
- SINGANAYAGAM et al, Prospective (n=1079)
Figure 3: (A) Among the 907 patients with community acquired pneumonia in this prospective study, admitted to six hospitals in Edmonton, Canada, the in-hospital mortality rate was inversely related to BMI ($p<0.001$). The nadir in the mortality rate was at BMI = 40 with only a shallow slope upward at BMI over 40 levels that we associate with extreme obesity [17].

(B) 1) In this retrospective study of 266 patients with proven pneumococcal (or Hemophilus) community-acquired pneumonia, the mortality at day 30 of admission is plotted as a function of body mass index. The inverse relationship between mortality and body mass index was significant at $p<0.01$ in univariate and multivariate logistic regression analyses [18].
2) From this retrospective study of 18,746 patients with a discharge diagnosis of pneumonia (using data from Department of Veterans Affairs), 30-day post admission mortality is plotted as a function of body mass index. On the univariate model, there was an inverse relationship between mortality and body mass index ($p<0.001$). This relationship persisted after adjusting for potential confounders in regression models as obesity was associated with decreased mortality (or 0.86, 95% CI 0.74-0.99) and underweight patients had increased mortality (or 1.40, 95% CI 1.14-1.73) [19].
3) The results of a prospective observational study from U.K. (Edinburgh). The 30-day mortality is plotted against body mass index for 1,079 patients diagnosed with community-acquired pneumonia. After Cox proportional hazards regression analysis, obesity was independently associated with decreased 30-day mortality (HR 0.53, 95% CI 0.29-.98) [20].
Figure 4

A. One size does not fit all in severe infection: obesity alters outcome, susceptibility, treatment, and inflammatory response. (Wacharasint P. et al. 2013)

B. The "obesity paradox" in an elderly population with a high prevalence of Chagas disease: The 10-year follow-up of the Bambui (Brazil) Cohort Study of Aging. (Belegoli AM et al.)

C. Body Mass Index (Mean ± SEM)

D. Cumulative Survival

- 28 Days
- 5 Years

BMI: High Yes, Normal No

Severity Grade

- Non-Obese
- Overweight
- Obese

28 Days

<21.0 21.0-26.0 26.0-30.0 >30.0
**Figure 4:** (A) Survival with septic shock. Among 730 patients with septic shock, mortality recorded in the initial 28 hospital days was inversely related to BMI \( (p < 0.02) \) [22]. (B) This longitudinal study is from a small city in Brazil where longstanding endemic Chagas was stopped by 1970 through the use of insecticides. Residents over 60 years of age \( (n=1271) \) who acquired Chagas in their youth were followed from 1997 - 2007 with normal BMI = 18.5 - 24.9 and high BMI >25. Heart disease was defined by EKG and B-type natriuretic peptide measurements. The Kaplan-Meier survival curves show that among patients without heart disease, 10-year survival of obese patients was better than among their thinner normal weight counterpart. Patients with heart disease showed much lower survival (than those free of heart disease) but heart disease with elevated BMI did better than patients with heart disease who were of normal weight [26]. (C) Biliary Tract Infection. All patients in this figure had biliary bacteria. Association of BMI and illness severity was significant \( (p <0.02) \). Group 1 – jaundice but no evidence of infection or inflammation. Group 2 – fever, leukocytosis, tachypnea, & tachycardia. Group 3 – cholangitis, empyema of gall bladder, gangrenous cholecystitis or abscess. Grade 4 -- bacteremia, hypotension, organ dysfunction [27]. (D) Peritonitis with sepsis. The graph depicts the short-term mortality (28 day – black bar) and long-term mortality (5 year – striped bar) in 253 consecutive patients with peritonitis and sepsis who needed intensive care for more than 2 days postoperatively. Patients were severely ill with high APACHE II scores, which correlated well with the mortality rate. Excluded were patients with acute pancreatitis or primary spontaneous bacterial peritonitis [29].
**Figure 5:** Effect of diet on survival post infection with *Trypanosomiasis cruzi*.

**Figure 5A:** Mice were fed a regular diet until day 56 pre-infection when half were switched to a high fat diet for the duration of the experiment. At day zero, half of the mice in each of the two diet groups were infected with *T. cruzi*. With the high fat diet, about 80% of the mice survived while around 40% of the regular diet mice survived [30]. **Figure 5B:** Similar results were observed when the high fat diet was started 56 days, 28 days, and 1 day before infection and continued for 42 days post infection [31].
Figure 6: Experimental Peritonitis with Sepsis. In 6A, peritonitis and sepsis were produced in mice by cecal ligation and puncture (CLP). Mice fed a high fat diet (upper curve) displayed enhanced survival [32]. The same data are summarized in Figure 6A, for comparison with Figure 6B. In 6B, survival after cecal ligation and puncture of C57BL/6 mice that were fed a high fat diet for 12 weeks were compared to those on a regular diet. Survival of un-operated controls was 100% [33].
Figure 7: (A) The link between body weight and inflammation. The curved line is a schematic representation of the baseline relationship between inflammatory processes and body weight in one hypothetical individual. As the body mass index in an individual increases or decreases, inflammation typically follows along. (B) The dashed-curved line represents the relationship between body weight and inflammation in a hypothetical individual (equivalent to the solid line in previous graph). When the body weight is unchanging, changes in inflammation can still occur. The box at lower right catalogs agents that are anti-inflammatory. The box at the upper left has agents that are pro-inflammatory. (C) Typically with body weight increases, the defenses against infection increase. The dashed line with an arrow points to conditions that diminish the immune responses below the level expected for that body mass index.
Figure 8: Survival following hip (8A) and non-hip fractures (8B). This figure records the association of adiposity with mortality after hip fractures (left) and non-hip fractures (right) in men and women over 40 years of age who were registered in a nationwide electronic database in Spain. The numbers at the right of each curve represents body mass index obtained at time = 0. Among the 6,988 hip fracture patients, early survival (6 months) and long term survival (3 yrs.) were highest in the top two body weight categories (BMI 25 and above). In 3,768 patients with non-hip fractures, survival was progressively better in the heavier weight categories, especially notable by the 3 year follow-up [46].
Figure 9: Comparison of causes of death in 1900 versus 2000. The percentage of all deaths due to four classes of diseases are shown for the years 1900 (light blue bars) and 2000 (dark blue bars). The dark blue bar for tuberculosis in the year 2000 in actuality should have been invisible. However, for this figure, we falsely increased the height of the bar so as to make it just visible [57].