Experimental evidence of complex routes to nucleation of organic molecular crystals via two-step nucleation comes from a phenomenon known as non-photochemical laser induced nucleation (NPLIN) (*11*). Supersaturated solutions of small organic molecules exposed to the laser nucleate much faster compared with control solutions. Different polymorphs of glycine can be obtained by changing the polarization state of the laser. Linear and circularly light appears to have different efficiencies in the alignment of the molecular building blocks of the two polymorphs. This lends further support to a mechanism in which noncrystalline clusters of molecules undergo rearrangement prior to nucleation.

Recent work in our laboratory has shown that both polymorphic form and crystal morphology can be controlled by nucleating organic crystals on either amorphous or crystalline surfaces of different materials. For example, amorphous polymers can be imprinted with different shapes that not only change the rate of nucleation but also can template different crystalline shapes (*12*). These results are indicative of a two-step nucleation process. Furthermore, they generalize the classical approach to templating crystallization. This approach is based on purely geometric considerations, yet in many systems, chemical interactions are important or even governing (*12*). Simple lattice matching is the basis behind the famous (though unproven) templating of water droplet nucleation in clouds via seeding with silver iodide. It is now clear that nucleation is much more complex than this kind of templating implies.

Molecular simulations offer the best possibility for studying these very complex processes, but face two major challenges: sampling nucleation processes that occur at much larger time scales than readily accessible by molecular simulations, and ensuring that the models used are accurate enough to elucidate real systems. Several methods are being developed that address the time scale problem via clever sampling. These include the replica-exchange molecular dynamics used by Wallace *et al*., metadynamics (*10*), transition-path sampling (*13*), and string methods (*14*). These methods typically fall into two categories: biased and unbiased. Biased methods use mathematical functions ("collective variables") that are proposed to be governing parameters of nucleation processes (*10*, *14*). These functions can be quite complex (*9*, *15*), and it is difficult to be sure that the hypothesized variables are the correct ones. Unbiased methods (*5*, *13*) [although the method in (*5*) can also be used with a bias] sample the systems without limiting their motion by imposing collective variables. However, these methods are limited in how complex a process they can sample.

Thus, the challenges of studying nucleation encompass both the intrinsic complexity of the process and the difficulty of sampling using molecular simulations. Nevertheless, the past decade has brought tremendous advances in both, and the next decade promises fascinating progress in elucidating the complexity of nucleation processes.

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PHYSIOLOGY

The Health Risk of Obesity—Better Metrics Imperative

The impact of a high BMI on mortality is in question, calling for a rethinking of how metabolic health is assessed.

Rexford S. Ahima and Mitchell A. Lazar

Obesity has increased worldwide; is a major risk factor for diabetes, cardiovascular disease, cancer, sleep apnea, nonalcoholic fatty liver disease, osteoarthritis, and other ailments; and has been associated with disability, mortality, and enormous health costs (*1*, *2*). Despite these clear adverse consequences of obesity, some studies have suggested that obesity as defined by body mass index (BMI) improves survival under certain conditions (*3*–*8*). Here, we discuss the controversies surrounding the "obesity-mortality paradox" and offer potential mechanisms to explain the effects of obesity on health.

The diagnosis of obesity is often based on BMI, calculated as weight in kilograms divided by height in meters squared (kg/m^2). Individuals with BMI 18.5 to 24.9 are considered as having normal weight, those with BMI 25 to 29.9 are considered overweight, and those with BMI >30 are considered obese (*1*–*3*). Obesity is further categorized into grade I (BMI 30 to 34.9), grade II (BMI 35 to 39.9) and grade III (BMI >40). Although these categories for defining overweight and obesity are widely used, it is noteworthy that the BMI values for overweight and obesity are different for Asians (*9*). A U-shaped relationship between BMI and mortality has been described (*1*, *2*). A BMI greater than 30 is associated with increased mortality from cardiovascular diseases, diabetes, cancer, and other diseases, whereas a BMI less than 18.5 is associated with increased mortality from chronic wasting diseases, smoking, and cancer (*1*, *2*).

However, some studies have described an inverse relationship of obesity and mortality in heart failure, coronary vascular disease, kidney failure, and other chronic diseases (*4*, *5*). Recently, Flegal *et al*. studied the association of BMI and mortality in a sample of more than 2.88 million people and 270,000 deaths (*3*). In comparison with nor-

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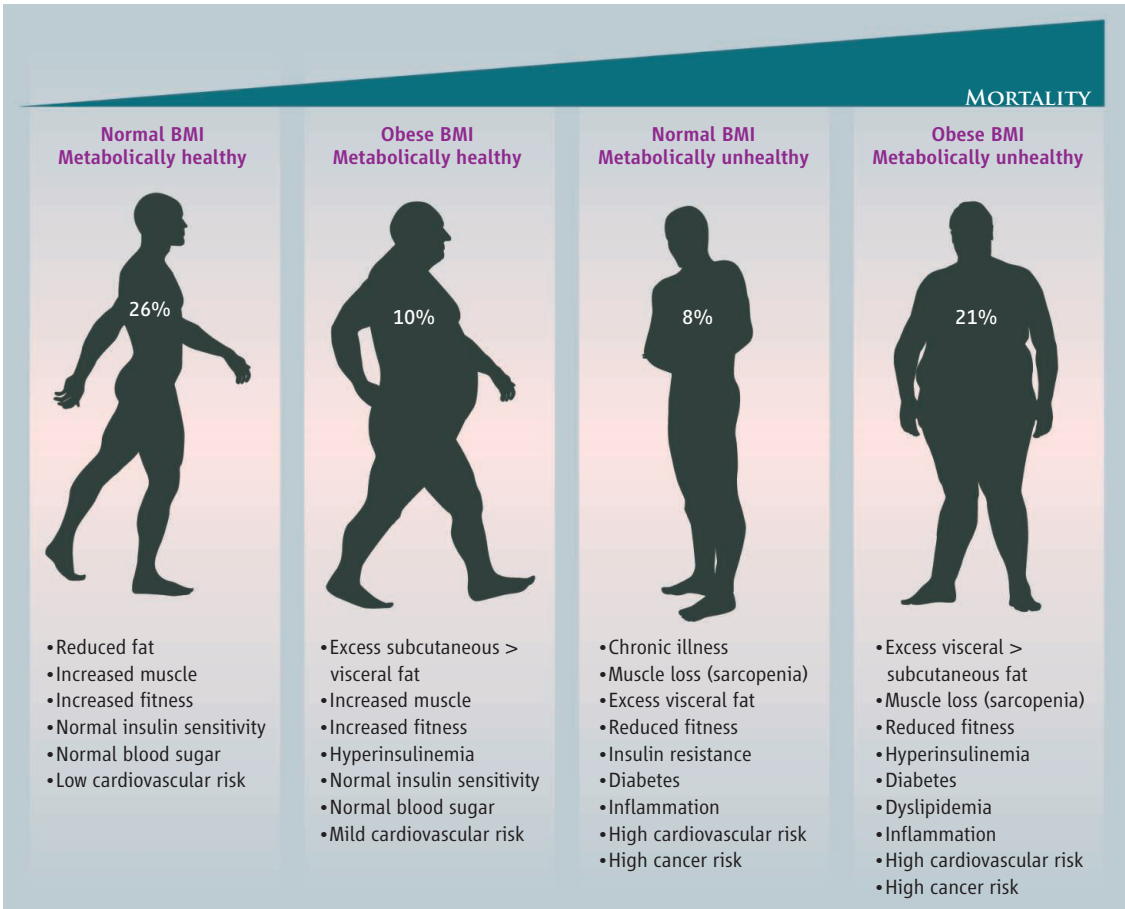

Two faces of obesity and mortality? Obesity, defined by a high BMI, substantially increases the risk of developing diabetes, cardiovascular diseases, cancer, and other chronic diseases, leading to higher mortality. However, it has been estimated that about 10% of adults in the United States have obese BMI and are metabolically healthy, compared with 8% who have a normal BMI and are metabolically unhealthy. In contrast, 26% of adults have normal BMI and are healthy, whereas 21% have obese BMI and are unhealthy (*13*).

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mal weight (defined as BMI 18.5 to <25), the combined grades 1, 2, 3 obesity, and grades 2 and 3 obesity, were associated with significantly higher all-cause mortality (*3*). In contrast, grade 1 obesity alone was not associated with higher mortality, and overweight was associated with significantly reduced mortality (*3*). These findings suggesting a protective influence of overweight and mild obesity have garnered a lot of publicity and controversy (*10*). There are concerns that the sampling methods used by Flegal *et al*. did not adequately adjust for weight loss and higher mortality from chronic illness, smoking, and aging (*10*). Furthermore, the classification of "normal weight" within a broad BMI range of 18.5 to 25 may have masked differences between people with BMI 18.5 to 22 and highest mortality, and those with BMI 22 to 25 and lowest mortality (*1*–*3*).

Nevertheless, recent studies have also challenged assumptions about the relationship between obesity and mortality in diabetes (*6*–*8*). Carnethon *et al*. analyzed the association of BMI and mortality in newly diagnosed diabetic patients in the United States (*6*). Deaths from all causes, cardiovascular, and other diseases were higher for normal BMI than for overweight or obese BMI. This inverse relationship between mortality and BMI was maintained even after adjusting the results for ethnicity, cardiovascular risk factors, waist circumference, and smoking (*6*). In another study involving 12 years follow-up of Taiwanese with type 2 diabetes, higher mortality was associated with older age, male gender, longer duration of diabetes, insulin therapy, hypertension, and smoking (*7*). Yet, a high BMI at the time of enrollment into the study was associated with fewer deaths compared with normal BMI (*7*). Furthermore, in a 15-year study of African-American and Caucasian male veterans with diabetes, BMI was inversely associated with mortality in both groups (*8*). Importantly, the mortality rate was lowered by increased physical activity independently of BMI and race (*8*).

Given the vast evidence of adverse effects of obesity on morbidity and mortality, how could overweight or obesity promote survival? Ultimately, this counterintuitive notion of health benefits of obesity requires careful examination of epidemiological data supported by mechanisms establishing causality. Although it is widely used, the BMI does not accurately measure fat content, reflect the proportions of muscle and fat, or account for sex and racial differences in fat content and distribution of intra-abdominal (visceral) and subcutaneous fat (*11*). Indeed, the body shape index (ABSI), a new index that quantifies abdominal adiposity relative to BMI and height is thought to be a better predictor of mortality than BMI (*11*). Excessive visceral fat in obesity predisposes to the "metabolic syndrome," associated with insulin resistance, diabetes, hyperlipidemia, and cardiovascular diseases (*12*) (see the figure). In contrast, massive fat storage in peripheral adipose tissue has been shown to be metabolically inert in certain mouse models (*12*). Likewise, it is possible that subcutaneous depots provide a safe harbor for potentially toxic lipids in obese individuals, thereby improving metabolic and cardiovascular health (*12*). The latter scenario may occur in some obese individuals with a healthy metabolic status, associated with a preponderance of subcutaneous fat, normal insulin sensitivity, absence of diabetes, and reduced risk of cardiovascular diseases (*13*). It is also possible that adipose tissue provides crucial energy reserves to meet metabolic demands during chronic illness, potentially decreasing mortality in obese patients. It must also be considered whether health care providers have increasingly adopted aggressive diagnostic and treatment strategies such as diet and exercise for obese diabetic patients, leading to better health outcomes and reduction in mortality.

How can a normal BMI be deleterious to health? Humans with genetic or acquired

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defects that prevent fat storage in adipose tissue are thin and yet develop severe fatty liver, insulin resistance, and diabetes (*12*). Furthermore, it is estimated that about 24% of adults in the United States with normal BMI have unhealthy metabolic profiles, even in the absence of major intercurrent illness (*13*). This "metabolically unhealthy/normal BMI" phenotype manifested by hyperinsulinemia, insulin resistance, hyperlipidemia, and increased risk of cardiovascular diseases is of greater concern for Asians, who have increased body fat at normal BMI values and are highly susceptible to developing diabetes (*14*). A low BMI may mask poor nutritional status and fail to detect crucial differences in fat and skeletal muscle content. Because skeletal muscle accounts for the majority of glucose disposal, loss of skeletal muscle mass (sarcopenia) owing to aging or physical inactivity, despite a normal BMI, can impair insulin sensitivity and negatively affect cardiovascular health and mortality (*15*). Relative insulin deficiency or poor control of blood sugar in diabetes also lead to sarcopenia, visceral adiposity, oxidative stress, and inflammation. These, as well as other factors, may plausibly predispose to morbidity and mortality in individuals with apparently normal BMI.

Another limitation of the epidemiology leading to the obesity-diabetes-mortality paradox is that these studies are generally cross-sectional or longitudinal, without intervention. Since obesity is linked to diabetes, cardiovascular diseases, and other illnesses, weight loss remains a logical strategy for prevention and treatment. Recently, however, the Look AHEAD (Action For Health in Diabetes) study found that weight loss from an intensive diet and exercise program improved metabolic outcomes yet failed to reduce heart attack and stroke in participants with type 2 diabetes, possibly because the study was underpowered for cardiovascular outcomes (*16*). Furthermore, in the prospective pioglitazone clinical trial in macrovascular events (PROactive) study population, obese BMI patients treated with the antidiabetic drug pioglitazone, which induces weight gain, had a lower mortality compared to normal weight patients, and weight loss was associated with increased mortality and morbidity (*17*). Additional studies are needed to clarify the specific roles of weight intervention in normal versus obese BMI individuals who are metabolically normal or abnormal, and the optimal weight associated with reduced mortality in obese patients with diabetes and cardiovascular disease.

The optimal weight that is predictive of health status and mortality is likely to be dependent on age, sex, genetics, cardiometabolic fitness, pre-existing diseases, and other factors. To quote Galileo, "Measure what can be measured, and make measurable what cannot be measured." Clearly, there is an urgent need for accurate, practical, and affordable tools for assessing body composition, adipose hormones, myokines, cytokines, and other biomarkers to serve as predictive tools for phenotyping obesity and related metabolic disorders and assessing the risk of mortality. Advances in these areas will allow the examination of biological mechanisms and provide insights into the causal role of obesity in health and disease.

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MATERIALS SCIENCE

Functional Ion Defects in Transition Metal Oxides

Dynamically tuning the concentration and profile of ions and vacancies in transition metal oxides provides a route to control of new functionalities.

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Transition metal oxides exhibit an astonishing array of functionalities that result from a combination of the strongly polarizable metal-oxygen bond and the so-called strong correlations between the localized transition metal valence electrons. The polarizability of transition metal oxides causes a heightened sensitivity to external electric fields, which can be exploited in applications such as highly insulating dielectrics in microcapacitors. Strong electron correlations, which cause each valence electron to explicitly affect the response of all other valence electrons in the system, are believed to underlie exotic phenomena such as high-temperature superconductivity. The coexistence and cross-couplings between these functionalities (see the figure, panel A) enables materials properties that have led to the widespread use of oxides—for example, as piezoelectric transducers that convert mechanical energy to electrical energy—and may form the basis of new device paradigms, such as the control of magnetism with electric fields.

In addition to these intrinsic physical functionalities, ionic defects can play a crucial role in enabling or enhancing functionality in transition metal oxides. The importance of defects is familiar from semiconductor physics, where defects (usually in the form of atoms of different chemistry) transform chemically inert, covalently bonded semiconductors such as silicon and gallium arsenide into the efficient carriers of electronic charge on which the entire information age is based. In transition metal oxides, defects play perhaps an even more important role in that they can lead to entirely new properties. For example, the parent compounds of the high-temperature cuprate supercon-

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