In the United States, approximately 70% of adults and 33% of children and adolescents are overweight or obese. Although it is widely accepted that there are a variety of genetic, behavioral, and environmental determinants, the strength of the associations of individual risk factors with obesity is only small to moderate. Other than bariatric surgery, no pharmacologic or behavioral weight loss treatments have been found to consistently result in large sustained weight losses. One reason for the lack of stronger associations with risk factors or more consistently successful treatment is that all types of overweight and obesity are often grouped together. This approach potentially obscures strong associations between risk factors and specific subtypes of obesity.

Many other diseases are more finely classified and treatment may vary by subtype. For example, asthma can be classified into multiple subtypes including allergic vs nonallergic asthma, occupational asthma, and exercise-induced asthma. Although all types of asthma have similar symptoms, there are important differences in the causes and treatments for the various subtypes. Within the obesity field there has been increasing recognition that prevention and treatment programs should be culturally sensitive and that the prevalence of risk factors and obesity may vary by race or ethnicity, but the same basic recommendations for prevention and treatment are given in all settings. An important question is whether this is one reason for not achieving better treatment outcomes.

Molecular pathological epidemiology is an emerging interdisciplinary field conceptually defined as the epidemiology of molecular heterogeneity of disease. By subtyping a disease based on pathogenic mechanisms, the molecular pathological epidemiology approach has yielded important findings, demonstrating that risk factors for and treatment responses to a disease may vary by subtype. For example, Liao et al found that patients with mutated-PIK3CA colorectal cancer who regularly took aspirin after their diagnosis had a longer survival, whereas, patients with wild-type PIK3CA colorectal cancer who did not benefit from taking aspirin. This is consistent with the emerging field of personalized or precision medicine.

To date, much molecular pathological epidemiology research has been conducted on cancers, but this approach may also be important for obesity. Currently many obesity treatment studies have overall small effects, but substantial variability in results, with some individuals having a large amount of weight loss and others gaining weight. The focus on mean overall effects may preclude identifying an effective treatment program for a specific subtype of obesity, but not others. Although data are limited, with little research on subtypes of obesity, some evidence suggests that subtypes exist. For example, high insulin secretion; low responsiveness to internal satiety signals; high responsiveness to external food cues; learned patterns and preference for foods high in calories, fat, sugar, and salt; binge eating or food addiction; and low reinforcing value of activity or high reinforcing value of being sedentary. However, these are only several possible subtypes but others may exist.

For example, Chaput et al found that high insulin secretion modifies the association between dietary intake patterns and weight gain. Thus, including all obese patients in 1 disease category will mask or weaken the association with these specific dietary patterns because of mixing of individuals with high vs low susceptibility. When subtypes based on disease heterogeneity are not considered, study findings can be substantially influenced by subtype distribution in a given sample. Thus, inconsistent results across studies may be partially due to differences in distribution of subtypes across studies.

Currently, major advances are being made in statistical methods to understand the development of obesity, the neuroscience of eating behaviors, use of sensors to better measure exposures, and exploration into the functional role of genetic polymorphisms associated with obesity. Additional advances are needed in how to conceptualize and phenotype the outcome of obesity. The one-size-fits-all approach is yielding small average weight losses. Clinicians, researchers, and patients need and want larger and more sustained weight losses. Bariatric surgery is not an appropriate treatment for the majority of overweight and obese adolescents and adults.

Perhaps one reason for the inconsistent findings about the effects of the built environment on obesity is that only a subset of individuals are susceptible to external stimuli to eat. There is a higher reinforcing value of food among overweight compared with leaner children. Thus, environments in which large quantities of highly palatable foods and beverages are found may be the most enticing to those most susceptible to weight gain and obesity; studying this group of individuals could help to better understand the pathophysiological mechanism.

Taste preferences are developed early in life and some individuals become overweight or obese due to overconsumption of highly palatable, highly processed foods, usually served in large portions. These individuals have adopted this eating pattern early in life and some pattern may be present in multiple generations. Education about reducing intake of sugar-sweetened beverages, fast food, and other processed foods may be some-
what useful for this subgroup. But education is unlikely to be sufficient to change behavior. For individuals who are extremely influenced by the sights and smells of highly palatable foods, education is likely to be much less effective.

Numerous genes and their variants are associated with obesity, but the strength of the association for each individual gene is relatively weak. Recent and ongoing research is examining how the reinforcing value of food, binge eating, and other types eating for reasons other than hunger may be the mechanisms through which a variety of genes increase the risk of obesity. Genetics likely play a larger role in obesity for an adult who has been obese since age 2 years than a person who gained 5 pounds each year and gradually became obese. However, the latter group is more prevalent.

The molecular pathological epidemiology model has recently emerged to help address the heterogeneity of disease. Obesity is a heterogeneous and complex disease influenced by exogenous and endogenous exposures. Stratifying obesity into meaningful subtypes could provide a better understanding its causes and enable the design and delivery of more effective prevention and treatment interventions.

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REFERENCES