I began my formal introduction to cardiovascular epidemiology when I enrolled in the University of North Carolina Chapel Hill School of Public Health; my informal introduction began when I was 6 years old. My father, David Kritchevsky, was a biochemist and expert in animal models of atherosclerosis. Growing up, our dinner table conversations routinely included discussions about studies like the Ni-Hon-San study\(^1\) and the Irish-Brothers Study.\(^2\) Being an émigré himself, my father was interested in the immigrant health experience. The pattern seen for cardiovascular and many other diseases was that disease rates approached those of the destination country with the length of time in the new country, indicating that acculturation and early life experiences shape adult chronic disease risk.

The ‘Relationship of childhood weight status to morbidity in adults’\(^3\) buttresses the concept that early life experiences shape cardiovascular risk. The authors report on 717 men (mean age 48 years) from Hagerstown, Maryland, examined between 1961 and 1963 and who had height and weight information in their elementary school records from between 1923 and 1928 when they were 9–13 years old. In this sample, being ‘markedly overweight’ as an adult—defined by measured weight relative to ‘ideal weight’—was associated with blood glucose, beta-lipoprotein levels (a precursor to LDL cholesterol determinations) and blood pressure. For the most part, childhood weight status was not associated with adult risk factor status, with one notable exception. Risk factor levels were most adverse in those who were underweight as children but more than 20% heavier than ideal weight as adults. This observation is ominous. What is it about being underweight when young that makes lifelong weight gain deleterious? Would it have made a difference if the weight status was assessed at 5 years of age or at 1 year or at birth? Is this generalizable to women? On the other end of the life-span, would it make a difference if weight was assessed at 60 years or 80 years? Does this phenomenon obtain to more than just cardiovascular disease risk?

Data relevant to many of these questions have appeared since the publication of ‘Relationship of childhood weight status to morbidity in adults’.
status to morbidity in adults’. There is considerable evidence that in utero development influences the development of middle-aged metabolic disease. In the early 1990s David Barker articulated the fetal origins of adult disease hypothesis, presenting data showing that low birthweight and body size at birth are associated with the increased prevalence of metabolic disease in middle-aged men. The finding extends to women. The explanation proposed by Barker and his co-authors was that metabolic pathways are in some way ‘entrained’ in utero to prepare the infant’s metabolism for the environment they are likely to be born into. The hypothesis holds that disease can result when the adult environment differs from that for which the person’s metabolism is prepared. A small baby would be at risk for metabolic disease as an adult if exposed to a calorie-rich environment. There are biological mechanisms which could give rise to these observations. Nutritional influences can affect the epigenetic marking during development, having long-lasting influences on gene expression and physiological function. For example, choline insufficiency during fetal development has permanent post-natal effects on neurological function, an effect thought to be mediated through epigenetic pathways involved in gene methylation. Allometric mismatch between organ size and overall body size can also lead to adult disease. Depending on the tissue, much of organ development takes place from during fetal development through the first year of life. With respect to the kidney, for example, the number of nephrons is set very early on. Having relatively few nephrons in a large body can put the kidneys under stress. In studies of kidney transplant patients, allograft survival is shorter and adverse metabolic effects are accentuated when a kidney from a small individual is transplanted into a large one. Thus, hypertension might result if a person born with smaller kidneys grows into a large person. Beyond fetal biology, there are certainly socioeconomic correlates of low birthweight and undernutrition during childhood reflected in disease at middle age. Underweight status may well be a marker for poverty and stress. Rapid weight gain may have been a reaction to a period of deprivation. Anxiety generated by the experience of deprivation may never entirely wane. Even in non-human primate models, social stress is linked to accelerated rates of cardiometabolic disease onset. To the body mass changes is relevant. Typically bone mass peaks in the third decade of life and skeletal muscle mass peaks in the fifth. Weight gain from age 40 onwards is mostly due to the accumulation of fat. The pattern of fat accumulation also changes with age. Early in life, much of the fat is deposited subcutaneously. With age, fat accumulation is more central, with deposition in and around organs. Social stress also promotes central fat deposition, and pre-term infants tend to deposit fat more centrally. Later in the life-course there is a generalized loss of mass from all compartments. The timing varies, but it appears to begin during the eighth decade of life in well-functioning adults. Unintentional weight loss in older adults is a sign of subclinical and overt disease. Thus, excess body weight in very old adults is typically associated with better health outcomes, and current body weight in an older adult may not reflect relative weight across the life-course.

The importance of body composition trajectories certainly extends beyond cardiometabolic disease. In older adults, muscle mass and strength predict the development of age-related physical disability and death. However, it is not only strength measured in old age that predicts these outcomes. In the Honolulu Heart Program/Honolulu Asia Aging Study, grip strength measured at middle age was associated with disability-free survival up to 40 years later. This association probably reflects that better grip strength indicates a larger muscle reserve being brought into old age. Humans progressively lose both muscle mass and strength from middle age onward. Those with the greatest strength in middle-age can afford to lose more absolute strength before reaching a strength threshold beyond which normal functioning becomes difficult. A portion of adult strength also has its origins in development. In the National Survey of Health and Development, Kuh and colleagues found that a 1-kg difference in birthweight was associated with an adjusted difference in grip strength at age 53 of 1.83 kg (95% confidence interval (CI): 0.66, 3.01) in men and 1.27 kg (95% CI: 0.45, 2.10) in women. In the Hagerstown cohort, one is struck by the 40% prevalence of diagnosed ‘cardiovascular renal disease’ in this group of middle-aged men. For those entering the field of epidemiology today, it is difficult to appreciate the sense of urgency surrounding the cardiovascular disease (CVD) epidemic when it was unfolding. In the USA, before 1940 coronary heart disease was considered a rare disease, only to emerge as the leading cause of death in middle-aged men some 20 years later. Death from cardiovascular disease peaked around 1966. Before hitting this peak, it was not clear when the increase would end. CVD’s major risk
factors were fairly well established when Abraham, Collins and Nordsieck published their paper in 1971, including: smoking, high blood pressure, high blood glucose, high cholesterol and obesity.

The denomination of these entities with the single categorical term ‘risk factor’ obscures distinctions that have implications relative to their management and control. Most obviously, smoking is entirely an environmental exposure. Control of this risk factor is through limiting the exposure to cigarettes. Blood pressure, glucose and cholesterol levels reflect physiological steady states at the time they are measured. For example, fasting serum glucose represents a steady state between glucose production and clearance, and blood pressure is a function of current cardiac output and arterial resistance. They are not environmental risk factors, though the environment can influence the steady state. Interventions are aimed at modulating the physiological systems that determine the steady state. Body mass and obesity are neither strictly environmental nor reflect a physiological steady state. Body mass is the integrated net caloric balance of an individual throughout their life until the moment it is measured by the investigator.

A single measure does not tell you if the individual is in the process of losing weight, weight stable or in the process of gaining weight. The article by Abraham, Collins and Nordsieck highlights the question: what part of a risk relationship is due to excess body weight per se, and what part of the risk is due to the weight trajectory? In the extreme case, gastric bypass patients show rapid normalization of many metabolic measures very shortly after surgery despite very little absolute weight loss. In studies of older persons, we see that those with relatively low body mass indexes (BMIs) usually have lost from their peak BMI and are continuing on a downward trajectory. Conversely, those on the high end of the BMI distribution gained from middle age and are continuing on an upward trajectory. For older individuals, the trajectory is critical in the prediction of future disability risk. The Hagerstown study suggests that the trajectory is very important at younger ages as well. Public health approaches for dealing with the health consequences of obesity may not need to push obese persons to attain an ‘ideal’ normal weight. It may be more practical to target weight trajectories to moderate the tendency towards weight gain with age. A recent meta-analysis of randomized weight loss trials suggests that even moderate weight loss interventions over relatively short durations can reduce long-term mortality risk.

Clinical medicine tends to focus on the status of a person at the time of their clinical encounter. Much of the early history of cardiovascular epidemiology mirrored this thought pattern, focusing on one-time risk factor measurements and their relationship to future disease onset. ‘Relationship of childhood weight status to morbidity in adults’ is an early study revealing the limitations of this view. It suggests that late life disease is the consequence of complicated interactions between exposures across the entire life-course. The clear implication of this expanded view is that to have the greatest effect on cardiovascular disease, public health measures must similarly address exposures across the entire life-course.

References