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EDITORIAL COMMENT

Before Metabolic Syndrome

Moving Cardiovascular Prevention Earlier

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Cardiometabolic disease does not begin when a patient first meets the criteria for metabolic syndrome, diabetes, or hypertension. These diagnoses are often the visible consequence of abnormalities that have been developing for years. Yet cardiovascular prevention remains disproportionately concentrated in middle age, after excess adiposity, hyperglycemia, elevated blood pressure, and dyslipidemia have already clustered and become clinically recognizable. By then, much of the cardiometabolic trajectory we hope to alter may already be established.

Young adulthood represents a particularly important and underused window for prevention. Low short-term event rates can create false reassurance and encourage deferral of attention to metabolic abnormalities. However, low short-term event risk is not equivalent to low lifetime risk. The relevant question is not simply whether a 25-year-old is likely to experience myocardial infarction during the next decade. It is whether the metabolic trajectory present at age 25 is laying the foundation for disease decades later. Young adulthood is therefore not a cardiovascular waiting room; it is a period when cardiometabolic trajectories are being established.

In this issue of *JACC: Advances*, Wu et al[1] provide important longitudinal evidence supporting this life-course perspective. Using data from 3,622 participants in the CARDIA (Coronary Artery Risk Development in Young Adults) study, the investigators examined insulin resistance in young adulthood, metabolic syndrome (MetS) approximately 20 years later, and subsequent atherosclerotic cardiovascular disease (ASCVD). Young-adulthood insulin resistance was associated with a 51% higher cumulative risk of ASCVD at the end of follow-up. More importantly, approximately two-thirds of this association was estimated to operate through midlife MetS.[1] Rather than evaluating insulin resistance and MetS as isolated risk factors, Wu et al place them along a temporal continuum: early metabolic dysfunction, subsequent clustering of conventional cardiometabolic abnormalities, and ultimately clinical cardiovascular disease.

A growing body of evidence has made it increasingly difficult to view childhood and young adulthood as periods free of cardiovascular risk. In the International Childhood Cardiovascular Cohort Consortium, childhood body mass index, blood pressure, cholesterol, triglycerides, and smoking were associated with cardiovascular events decades later.[2] Elevated blood pressure and low-density lipoprotein cholesterol during young adulthood are likewise associated with later cardiovascular events independent of measurements obtained later in life.[3] More recently, the Global Cardiovascular Risk Consortium demonstrated striking differences in cardiovascular disease-free life expectancy according to the burden of major risk factors by midlife. The absence of 5 classic risk factors at 50 years of age was associated with more than a decade longer cardiovascular disease-free life expectancy than the presence of all 5 risk factors.[4] Recent baseline imaging data from REACT provide a complementary perspective: subclinical atherosclerosis was detected in 8.7% of men and 6.7% of women aged 18 to 29 years.[5] REACT demonstrates that atherosclerosis can already be detected in early adulthood, whereas Wu et al link an early metabolic abnormality to subsequent clinical events. Together, these observations

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strengthen the rationale for recognizing cardiovascular vulnerability before clinical disease becomes apparent.

Importantly, trajectory is not destiny. In longitudinal childhood cohorts, individuals whose nonhigh-density lipoprotein cholesterol dyslipidemia resolved by adulthood did not demonstrate the excess cardiovascular risk observed among those with persistent dyslipidemia.[6] Early identification should not be used to assign young people a fixed prognosis but rather to identify a period during which an unfavorable trajectory may still be altered.

The findings from Wu et al extend this principle into metabolic health. MetS identifies an important clustering of central adiposity, elevated blood pressure, hyperglycemia, and lipid abnormalities. But its diagnostic threshold should not become the threshold for preventive care. A young adult with progressively increasing abdominal adiposity, worsening blood pressure, rising triglycerides, and deteriorating glycemic measures should not need to accumulate multiple abnormalities before clinicians recognize the direction of travel.

This perspective is consistent with the contemporary cardiovascular-kidney-metabolic framework, which emphasizes the interconnected progression of adiposity, metabolic risk factors, kidney disease, and cardiovascular disease.[7] Wu et al[1] provide longitudinal support for this framework: insulin resistance may represent an early signal of an adverse cardiometabolic trajectory, whereas MetS may mark a subsequent stage of risk-factor clustering. The clinical implication is clear: individual abnormalities should be recognized and addressed before they accumulate into a syndrome.

Adolescence and emerging adulthood are periods of rapid behavioral, social, and physiologic change during which patterns of diet, physical activity, sleep, tobacco exposure, and weight gain become more firmly established. The American Heart Association has identified the transition from adolescence to emerging adulthood as a critical period for cardiovascular health promotion, emphasizing primordial prevention, early intervention, and developmentally tailored approaches.[8] These years therefore represent important preventive opportunities and reinforce a life-course approach to cardiovascular prevention.

The clinical implications require nuance. Wu et al[1] should not be interpreted as establishing a rationale for universal measurement of fasting insulin or homeostatic model assessment of insulin resistance (HOMA-IR). HOMA-IR is an indirect estimate of insulin resistance, fasting insulin is not routinely measured in clinical practice, and the cutoff used in this analysis was a cohort-specific percentile rather than a universally validated clinical threshold.[1] Whether HOMA-IR provides meaningful incremental prediction beyond routinely available measures remains unknown. Likewise, the mediation estimate should not be interpreted to mean that preventing MetS would necessarily prevent two-thirds of the ASCVD associated with early insulin resistance. Mediation analyses depend on assumptions regarding confounding and model specification; MetS was measured at a single midlife examination, and the analytic population was restricted to participants who remained under observation and ASCVD-free through year 20.[1] These limitations temper causal interpretation but do not diminish the broader observation that clinically recognizable cardiometabolic disease in midlife may reflect dysfunction present much earlier.

Similarly, the minimal mediated pathway through observed midlife diet and physical activity should not be mistaken for evidence that lifestyle intervention is ineffective. These measurements reflected naturally occurring behaviors, not a structured intervention designed to modify these behaviors over time. Randomized evidence from the Diabetes Prevention Program demonstrated that intensive lifestyle modification substantially reduced the development of MetS in high-risk adults.[9] The unanswered question is whether intervention initiated earlier, before multiple metabolic abnormalities have accumulated, can alter progression toward ASCVD.

For current practice, the most important implication is therefore not a new laboratory test. It is a new sense of urgency. The priority should be comprehensive assessment and sustained follow-up. Blood pressure, lipids, glycemia, adiposity, family history, and health behaviors should be considered together. Serial measurements, direction, and duration matter. Clinicians caring for adolescents and young adults should recognize worsening trajectories in these factors as components of lifetime risk rather than isolated abnormalities to “watch” until middle age. Prevention should focus on altering that trajectory through high-quality nutrition, regular physical activity, tobacco avoidance, adequate sleep, and evidence-based treatment of obesity, hypertension, dyslipidemia, and diabetes when indicated.

The health system must also make such prevention possible. The transition between pediatric and adult care can fragment longitudinal risk information precisely when individuals are assuming greater responsibility for their own health. Prevention cannot

depend on isolated counseling during a single visit. Families, schools, clinicians, communities, and health systems all influence whether young adults have access to nutritious food, safe opportunities for physical activity, continuity of care, and effective treatment. Identifying risk without providing realistic opportunities to modify it is not prevention.

Future studies should determine which early metabolic trajectories matter most, whether repeated assessment of insulin resistance adds meaningful information beyond routinely available risk factors, and which interventions can alter progression from early metabolic dysfunction to MetS and ultimately ASCVD. The central question is not simply whether insulin resistance predicts ASCVD, but whether identifying it earlier improves prevention beyond assessment of routinely measured risk factors alone. Wu et al have identified an important interval between early metabolic dysfunction and later cardiovascular disease. Cardiovascular prevention should make use of that interval rather than merely observe it.

MetS should signal the need to intensify prevention, rather than serve as the trigger to initiate it.

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