EDITORIAL

Childhood Risk Factors and Prediction of Adult Cardiovascular End Points

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Children almost never have myocardial infarctions or other adverse cardiovascular (CV) events, yet there has long been evidence that atherosclerosis may be found on postmortem examination of youths who have died accidently.[1-3] Indeed, cohort studies such as the Cardiovascular Risk in Young Finns Study, the Bogalusa Heart Study, and the Muscatine Study have shown increased coronary-artery calcification[4,5] and increased carotid-artery intima–media thickness among adolescents.[6-8] But direct evidence that CV risk factors in childhood are linked to hard CV disease (CVD) outcomes in adulthood has been elusive.

And no wonder! Given the length of each human generation, studies that aim to demonstrate directly how and whether hypotheses are correct, when viewed from a clinical investigator's standpoint, are daunting and often outstrip the working life of investigators. However, increasingly sophisticated biostatistical methods and ever-growing surrogate markers of the risk of disease seemingly promise that hard data could be realized, if only the right questions are asked.

Fortunately, a number of robust clinical cohorts have come of age, thereby permitting comparisons and association studies with hard end points that occur in adult life.[9,10] Take, for example, risk factors for CVD: the association of childhood risk factors with subsequent adverse CV events has been based on biomarkers or cross-sectional data. Now, multiple-cohort studies, with carefully collected data plus the aging of participants assessed longitudinally, have reached a point at which cardiovascular outcomes — major cardiac adverse events — occur as expected. The results of the International Childhood Cardiovascular Cohorts (i3C) Consortium Outcomes Study, which includes seven cohorts from the United States, Finland, and Australia, are now reported in the *Journal*[9]; the data were prospectively obtained from early childhood through adolescence and, subsequently, during adult life. In this study, cardiac events in adult life were documented and adjudicated so that the long-held, well-known hypothesis that childhood CV risk factors are associated with the subsequent development of adult CVD events could be assessed in many persons — 38,589 participants (of the 42,324 originally enrolled in the seven cohorts) with information for follow-up were included in the analysis sample. Because different protocols were used for each participating cohort, the CV risk data were harmonized and then incorporated into a single database.

The i3C Consortium investigators concentrated on five risk factors (body-mass index, systolic blood pressure, total cholesterol level, triglyceride level, and smoking during youth), which were recorded as repeated measures with data from physical examinations and laboratory studies and analyzed with the use of i3C-derived age- and sex-specific z scores and with a five-factor combined-risk z score. A comparable adult combined-risk z score (preceding any cardiovascular event) was analyzed jointly with the childhood risk factors. The outcomes were obtained through the Heart Health Survey that vigorously solicited adult CV end points through mail, email, telephone calls, and clinic visits.

The findings are compelling: among participants with a mean age of 46 years, there were 319 CVD-related deaths and a total of 776 fatal or

nonfatal CVD events; these events were positively associated with the childhood risk factors and z scores in an incremental, stepwise fashion. However, the questions about the importance of childhood risk factors themselves pose several problems, the most obvious of which is that it is hard to know whether such risk factors observed during childhood and adolescence track simply into adulthood in the prediction of CVD events, whether those childhood risk factors might constitute early evidence of adult risk factors, and whether independent, additional risk factors later modify adult CVD risk factors, which would also influence the hard outcomes. For example, do prenatal and perinatal events have an effect on the outcomes? How much do adverse childhood experiences influence risk-taking behavior? What do adult exposures contribute to the risk of CVD?

There are additional concerns, despite the best efforts by the investigators. Whereas the findings for fatal CV events were clear, with vital status or cause of death having been verified in 96% of all the participants, nonfatal CV events posed a problem, because 46% of the sample could not be contacted. Thus, nonfatal CV events were imputed. It is reassuring that multiple methods produced similar results, so the authors suggested that loss-to-follow-up was not a major bias.

Can these findings be generalized? As the investigators note, the cohorts involved were predominantly White — with Blacks representing 21% of the U.S. participants, which is actually a greater percentage than that in the U.S. population, and 15% of the participants from other locations; there were few Latinx and Asian participants. In addition, the countries involved were relatively high-income countries. However, the risk-score components were clear and straightforward, and the analyses were carefully performed.

Despite these limitations and questions, this longitudinal study showed clear associations between an elevated risk-factor score and the presence of documented CVD later in life. What does this mean for practice? If CV risk factors can be identified early in life, we as clinicians have opportunities to address health issues early and might uncouple risk from an inexorable march toward CVD and death. We have been waiting for hard data showing that risk factors seen in childhood forecast future disease, and now we have a good start concerning CVD.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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