Cardiovascular disease is a major killer in the US and worldwide. Although many of the major factors contributing to atherosclerosis have been described over the past half-century, highly sophisticated investigations into its causes are ongoing. Family history is an important predictor of future heart disease, but the findings of recent genome-wide association studies have not demonstrated effect sizes that are large enough to explain the observed familial trends. We are left to suppose that the strong family-history effect in large part represents an effect of lifestyle. This hypothesis is strengthened by a recently published manuscript by Koskinen and coworkers regarding the effects of recovery from metabolic syndrome on arterial structure and function (1).

The study of Koskinen et al. (1) was based on data from the Cardiovascular Risk in Young Finns Study, an ongoing epidemiologic survey of Finnish males and females first examined in childhood (age 3–18 years) in 1980. There have been 2 subsequent examinations in 2001 and 2007, both of which have included anthropometric and lipid and vascular measures, including carotid intima–media thickness (IMT)2 and distensibility, as well as brachial flow–mediated dilation (FMD) in response to ischemia induced with a blood pressure cuff. This 2010 publication (1) reports on members of the original cohort who both participated in follow-up examinations and provided data for comparison. The follow-up examinations also included information on nutrition (food frequency questionnaires) and physical activity (“metabolic equivalent index”), as well as a panel of testing that allows a designation of metabolic syndrome at both time points. Thus, the authors were able to correlate changes in metabolic abnormalities over time and the presence of metabolic syndrome to several vascular findings. These changes are most likely attributable to alterations in lifestyle that occurred over the course of the 6-year follow-up period.

Results of the carotid distensibility and thickness (IMT) tests supported the presence of abnormal vasculature in young adults with metabolic syndrome. At the baseline measurement (2001), although carotid IMTs were similar regardless of metabolic syndrome status, carotid distensibility was better in participants without metabolic syndrome than in those with metabolic syndrome (P = 0.0002). At follow-up, the authors found that carotid distensibility and IMT had worsened in all groups, regardless of status of metabolic syndrome. Moreover, recovery from metabolic syndrome was associated with a reduced thickness of arteries (i.e., IMT) and reduced progression of IMT, compared with the group with persistent metabolic syndrome, as defined by the International Diabetes Federation criteria for adults.

The Young Finns data on brachial FMD, another measure of arterial responsiveness, less clearly supports a picture of vascular dysfunction associated with metabolic syndrome. In 2001, the mean FMD in the group with metabolic syndrome and that in the group without metabolic syndrome were statistically equivalent (P = 0.09). At the 2007 follow-up, the group that never had metabolic syndrome had a mean FMD percentage significantly lower than that of the group of participants who had recovered from metabolic syndrome, a finding that persisted despite adjustment for multiple traditional cardiovascular risk factors. Furthermore, those with persistent or incident metabolic syndrome had higher FMD values than the control group. Compared with 2001, all groups had an increase in FMD in 2007, regardless of metabolic syndrome status. FMD improved in the groups that never had metabolic syndrome (control) and in individuals who had persistent metabolic syndrome. The latter result was unexpected on biological grounds. This apparent discrepancy with the expected outcomes may reflect the variability of FMD measurements, the effect of multiple sonographers (although a single blinded reader analyzed all the studies), or other confounders not accounted for in the analysis.

In addition to the unexpected results related to FMD described above, other factors about the Young Finns data should be noted. The authors reported large intraperson variation in the vascular test results, particularly brachial artery reactivity (26.0%) and carotid distensibility (14.3%). The reproducibility testing,
however, was performed 3 months apart, a period of time over which lifestyle changes can substantially affect metabolic factors, particularly vascular reactivity, a measure that is already sensitive to small changes in the testing environment or to other effects. The rate of metabolic syndrome in the 2001 measurement period was somewhat higher in the group lost to follow-up than in those included in the analysis, although the difference did not reach statistical significance (17.3% vs 14.5%, \( P = 0.14 \)). The nutrition data in 2001 was of poorer quality than in 2007, because the food frequency questionnaire was greatly expanded for the later measurement. The physical-activity data were self-reported. The participants were white Europeans, and the results may not be generalizable to all populations.

Of note, between 2001 and 2007 there were some interesting shifts in lipid profiles and anthropometrics in the study cohort. Total cholesterol and LDL concentrations went down in all groups, including the participants who developed metabolic syndrome and those who recovered, as well as the participants who remained free of metabolic syndrome. In contrast, fasting glucose concentrations went up in all groups, even in participants who metabolically improved, and insulin increased in all participants except those who recovered from metabolic syndrome. One wonders whether this change might have been related to a society-wide shift toward a diet of lower fat and higher carbohydrate. Unfortunately, the dietary information for 2001 and 2007 could not be compared easily, owing to the different questionnaires that were used, so we are unable to explore whether there was a dietary etiology for this change. Furthermore, the authors were unable to assess total calorie intake over that period, something that would have been important to account for in the analysis. Consistent with the worldwide increases in obesity rates, weight, body mass index, and blood pressure went up in all groups except the participants who recovered from metabolic syndrome. Waist circumference increased in all groups over the course of the study as the participants aged.

The Young Finns report of Koskinen et al. (1) has a message that is perhaps more important than defining the relationship between metabolic syndrome and vascular change. Their report gives insight into the natural history of metabolic syndrome. At the first measurement-collection point, the Young Finns cohort already had a fairly substantial rate of metabolic syndrome. Of the 1673 participants, 237 had already had a fairly substantial rate of metabolic syndrome, yielding a prevalence estimate in the 2001 examination of 14.2%. This prevalence is higher than most of the published prevalence estimates obtained from National Health and Nutrition Examination Survey (NHANES) data, although many estimates use different definitions of metabolic syndrome (2). Of the 1436 young Finnish adults who did not have metabolic syndrome in 2001, quite a high number (194, 13.5%) went on to develop it over the course of 6 years; however, of the 237 participants who began with metabolic syndrome, 71 (30.0%) recovered. This relatively promising rate of recovery from metabolic syndrome has been less well described in the literature. If confirmed, the recovery rate of one-third during young adulthood gives us hope, for 2 reasons: (a) These recoveries were likely accomplished individually in some way, because this research study made no standardized intervention to reduce the prevalence of metabolic syndrome (although public health efforts over this period may have had an impact on risk factors for cardiovascular disease); and (b) some vascular improvements were seen in concert with the change in metabolic syndrome status, suggesting that the change in status has some clinical relevance. It is unfortunate that the prevalence of metabolic syndrome and the rates of various metabolic derangements from the original childhood testing date were not reported, because such data might have provided more information about the natural history of metabolic syndrome. Additionally, had there been interim visits between 2001 and 2007, such visits might have provided better information about the factors contributing to incident or persistent metabolic syndrome, as well as the factors important for recovery from metabolic syndrome.

In summary, the report of Koskinen and coworkers (1) makes 2 important contributions to the field of cardiometabolic risk. First, it describes a level of carotid IMT progression in participants who recovered from metabolic syndrome as being equal to that of the participants who never had metabolic syndrome, a finding that has not been reported previously. Such evidence supports the possibility that atherosclerosis is reversible. Second, the report describes a relatively high rate of recovery from metabolic syndrome, approximately one-third of individuals. Although we as a society have yet to make substantial inroads into the obesity epidemic at the pediatric or adult level, these data support the hypothesis that reversing metabolic syndrome is both possible and beneficial at the vascular level. The means for achieving this reversal may not yet be clear, but any success in this regard is certain to have a substantial payoff.

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References
