In this issue of Circulation, Juhola et al from the International Childhood Cardiovascular Cohort Consortium (i3C) address the effect of changing blood pressure (BP) in children on carotid intima-media thickness (CIMT) in adulthood. In 4210 children in 4 cohorts around the globe followed for an average of 23 years, children with elevated BP that resolved by adulthood had lower CIMT in comparison with children whose high BP persisted into adulthood. Although i3C is relatively large for a combined pediatric cohort, the study had marginal power to determine whether the small residual risk of resolved BP elevation in comparison with never-elevated BP was significant. These results represent decades of foresight and diligent effort in presaging the future of cardiovascular disease (CVD) risk. The findings can be contextualized in 3 domains: in relation to previous data on the long-term consequences of elevated BP in youth, the utility of CIMT in youth, and the role of suboptimal data types in clinical decision making.

Longitudinal cohort studies demonstrate that elevated adolescent BP predicts CVD and mortality in adulthood. BP in adolescent male military enlistees and male college students predicts future CVD events and mortality in a graded fashion. These relations appear robust to adjustment for the association between young-adult BP and middle-age BP, suggesting a specific role for young-adult BP in the risk assessment of future CVD. Few data exist on the relation between childhood elevated BP per se and later events. One study from Native American communities detailed an association between a physician diagnosis of hypertension, but not study-measured BP, and early mortality. Importantly, despite the inordinately high prevalence of CVD risk factors, CVD was not the leading cause of mortality in this cohort. Additional focus is needed to examine the longitudinal relation between CVD risk factors and other metabolic diseases in children. Early-life BP does appear to predict life-threatening events, although the picture in young children is murky.

The challenges of demonstrating the association between childhood BP and events deserve enumeration here. First, very long term follow-up is logistically challenging. Following enough children to discern a statistically and clinically relevant increase in CVD events 30 to 50 years hence requires extensive resources, funding agency commitments, and institutional memory with teamwork to span decades. Very few are capable of such a feat, which in turn highlights the relevance of the i3C cohort and the boon it offers to preventive medicine in the coming years. Despite the number of open questions, one wonders whether such longitudinal studies can ever happen again in our current scientific-funding milieu. As an approximation, a recent publication drawn from administrative databases demonstrates a temporal decrease in stroke incidence in all age groups, with the exception of youth where stroke incidence has increased dramatically. Although the total event rate in this group was small, the proportion with CVD risk factors is on the rise. Whether this increase is the tip of the iceberg is not yet known. The second challenge is that children change. This same i3C consortium has underscored the problem with risk factor assessments in children: young children are different than older children. BP tracks moderately over early life at best. In this study, 41% of children with normal BP developed elevated BP as adults, whereas 59% of kids with elevated BP persisted. Yet, this group and others have demonstrated that single point-in-time measurements of CVD risk factors in childhood do predict subclinical atherosclerotic changes, with adolescent assessments being superior in general. So if kids are changing, but single measurements are relevant, how do we catalog the accumulated CVD insults? Adult data suggest that subclinical atherosclerosis is now assayable and predicts CVD events. Among these, CIMT plays an intriguing role. The presence of internal carotid plaque adds to discrimination over classic CV risk factors, whereas common CIMT does not increase prediction over CVD risk factors alone. Unfortunately, the present study used a single measurement of the left common carotid far wall as the common measurement most frequently present in the separate cohorts. Ideally, more measurements would be assessed and averaged. But, to borrow a phrase, where you stand depends on where you sit: although adult providers may find common CIMT disappointing given its lack of additional explanatory ability, pediatric-focused investigators may find CIMT useful as a summary index of the accumulated fluctuating CVD risk factors. That common CIMT captures classic CVD risk factors is actually an advantage to pediatric studies and perhaps even future providers. More data are needed linking early adult CIMT to future CVD events. We may look to the i3C group to provide those answers.

The literature is converging on what constitutes gold-standard data to inform such answers. Borrowing from principles enumerated by Hill’s criteria on causation and bolstered by
studies demonstrating how intuitively satisfying cardiac interventions can be wrong or even dangerous, the scientific community is realizing that the right answer is sometimes irrational.11,12 Therefore, truth is derived from rigorous randomized, blinded, controlled trials (RCTs), and clinical action should only transpire following these verdicts. No doubt, there is a strong role for the RCT, but what to do when it is not forthcoming? For example, which RCT addresses children eating vegetables to prevent adult CVD? Will such a study ever transpire? Do children have free license to eat cake at will in the absence of RCT data to the contrary? Substituting vegetables in this absurd example with other interventions illustrates the difficulties in testing primordial and primary CVD prevention strategies. Simply focusing on obesity lacks credibility in a population where nearly 1 in 20 children have elevated BP, nearly 1 in 5 have elevated cholesterol, and close to 50% of both subsets have normal weight.13 CVD risk factors in children deserve attention too, because emerging data support the rational conjecture that lifelong CVD risk reduction may be superior to pharmacological CVD risk reduction.14 So, in the absence of an RCT testing BP-lowering interventions over a 25-year frame, the present study offers specific evidence for the utility of improving BP in children. The physiology of the improvement in this study may relate to obesity, because the mean body mass index decreased significantly in the resolution group. Other explanations may include white-coat hypertension, which is particularly problematic in children and complicates the epidemiological assessment of outcomes.

Although the data presented by Juhola and colleagues are compelling, we must not infer the effect of pharmacological BP lowering from these data as mechanisms of improvement, side-effect profiles in developing bodies over a 20+ year frame likely differ, and current children may or may not be similar to the i3C cohort who were children 20 years ago. The present data do extend the atherosclerotic benefits of BP lowering down to the pediatric age group. We can hope that more data on long-term outcomes and biological mechanisms are forthcoming.

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None.

References


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