

Prevention of Cardiovascular Disease Must Start in Children

Written by Mary Mosley

The well-known and stark statistics on the worldwide incidence of cardiovascular disease (CVD) and its complications clearly suggest that current approaches to prevention and control are insufficient. These approaches miss the mark because they focus on later stages of prevention, stated Brian W. McCrindle, MD, MPH, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada. In his Maureen Andrew Plenary Address, Prof McCrindle advocated for a shift to primordial and early-stage prevention—namely, preventing the development of chronic disease in adulthood by focusing efforts on youth.

THE GROWING BURDEN OF CVD

CVD accounts for 31% of all deaths worldwide, according to data compiled by the World Health Organization. By 2030, the number of deaths annually is projected to increase to 23.3 million. Of the 17.5 million deaths in 2012, 7.4 million were from ischemic heart disease; men and women were affected equally. Deficiencies in health care delivery and a high prevalence of comorbidities and cardiovascular risk factors (CVRFs), especially obesity and smoking, have translated into a high incidence of CVD in low- and middle-income countries, which account for 80% of ischemic heart disease globally.

The human and financial costs of CVD are equally bleak. Of the 151 million annual disability-adjusted life-years, 63 million are from CVD in men. Forecasts by the American Heart Association project that 41% of the US population will have some form of CVD by 2030, with a concomitant increase in total direct costs to \$818 billion and real indirect costs to \$276 billion [Heidenreich PA et al. *Circulation*. 2011].

CURING ATHEROSCLEROSIS: THE CASE FOR EARLIER INTERVENTION

Prevention is not given its fair due, stated Prof McCrindle, with proportionally more (and increasing) health care dollars spent on care of acute and chronic illnesses rather than their prevention. Currently, intervention occurs late in the atherosclerotic process, where disease is less reversible and salvageable [Wiegman A et al. *Eur Heart J*. 2015].

Tertiary prevention (treating symptomatic disease to ameliorate its effects or delay/prevent progression) or secondary prevention (early detection of disease or prevention of events in asymptomatic disease) is too late. Prof McCrindle stated that some effort is made on primary prevention (reduction of CVRFs before disease onset), but there is very little primordial prevention of developing CVRFs.

Curing atherosclerosis must become the focus, with earlier or more aggressive intervention to lower low-density lipoprotein cholesterol (LDL-C) levels and other CVRFs to reset the vascular aging clock [Robinson JG, Gidding SS. *J Am Coll Cardiol*. 2014]. The atherosclerotic process begins in youth, with autopsy studies showing the presence of CVRFs and early atherosclerosis in the aorta and coronary arteries. The Bogalusa Heart Study showed a linear relation between higher LDL-C levels measured during childhood and a greater degree of aortic fatty streak involvement at autopsy for subjects who died during follow-up.

The study also found a relation between an increasing number of CVRFs in children and young adults and an exponential increase in the extent of fibrous plaques in the aorta and coronary arteries at autopsy. Of those children who were obese, 58% had ≥ 1 CVRFs. These data also suggested that screening of those who are overweight or obese could identify 50% of children with multiple CVRFs (ie, a higher risk of accelerated atherosclerosis [AS]) noted Prof McCrindle. The associations of CVRFs to overweight were similar to adults, and 77% of the children remained obese in adulthood.

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IMPACT OF EARLIER INTERVENTION

Indirect evidence from pediatric studies using established disease surrogates provides support for early population-based prevention aimed at achieving ideal cardiovascular (CV) health that is maintained across the lifetime and for a high-risk individual approach starting in youth, stated Prof McCrindle. Noninvasive measures of subclinical AS established that endothelial function, arterial stiffness, carotid intima-media thickness (CIMT), and coronary artery calcium have proven to be useful disease surrogates that can be measured and tracked in youth.

Better ideal CV health in childhood is associated with decreased risk of measures of subclinical disease and CVRFs in adulthood. The number of high-level CVRFs at ages 12 to 18 years was associated with higher CIMT at ages 33 to 39 years in the Cardiovascular Risk in Young Finns study. A relation between the number of CVRFs during ages 12 to 18 years and the risk of cardiometabolic outcomes in adulthood was shown in a recent analysis from this study (Table 1) [Laitinen TT et al. *Circulation*. 2012]. Pooled data from longitudinal studies found an association between lifetime ideal CV health and vascular risk in middle age; improvement in CV health scores improved vascular markers, suggesting the possibility of altering outcomes with intervention [Laitinen TT et al. *Int J Cardiol*. 2013]. Improvement in healthy lifestyle factors was also shown to improve disease markers (CIMT, coronary calcium) in the CARDIA study [Spring B et al. *Circulation*. 2014].

Table 1. Relation Between AHA Ideal CV Health Index in Childhood and Cardiometabolic Outcomes in Adulthood

	OR	95% CI	P
Hypertension	0.66	0.54–0.80	<0.001
Metabolic syndrome	0.63	0.52–0.77	<0.001
Type 2 diabetes mellitus	0.70	0.32–1.52	0.37
High LDL cholesterol	0.66	0.52–0.85	0.001
Low HDL cholesterol	0.94	0.79–1.13	0.54
High triglycerides	0.80	0.65–0.99	0.04
High-risk IMT	0.75	0.60–0.94	0.01

AHA indicates American Heart Association; OR, odds ratio; CI, confidence interval; LDL, low-density lipoprotein; HDL, high-density lipoprotein; and IMT, intima-media thickness. Odds ratios are for a 1-unit increase in ideal cardiovascular health index.

Laitinen TT et al. Ideal cardiovascular health in childhood and cardiometabolic outcomes in adulthood: the Cardiovascular Risk in Young Finns Study. *Circulation*, 2012, Vol 125, Issue 16, Pages 1971–8A, with permission from American Heart Association, Inc.

The case is the strongest for the relation between elevated LDL-C in youth and subsequent disease, stated Prof McCrindle. Pooled data show that CIMT was significantly thicker at age 35 years in persons who were overweight/obese and had dyslipidemia at age 15 years [Magnussen CG et al. *J Am Coll Cardiol*. 2009]. Along with evidence showing the impact of LDL-C on CVD, there is evidence that lowering LDL-C with statin therapy reduces this risk—and that the greatest benefit appeared to be achieved at the lowest levels of risk [Cholesterol Treatment Trialists' Collaborators. *Lancet*. 2012].

Early statin therapy normalized brachial artery reactivity in a study of children with familial hypercholesterolemia (FH) [Braamskamp MJ et al. *J Pediatr*. 2015; Avis HJ et al. *Curr Opin Lipidol*. 2009; Versmissen J et al. *BMJ*. 2008; McCrindle BW et al. *J Pediatr*. 2003]. Brachial artery reactivity is a measure of endothelial function, and dysfunction is a pivotal step in the initiation of AS. Statin therapy regressed CIMT in these patients in another study, despite a high mean LDL-C >180 mg/dL after 2 years of therapy. Further follow-up to 10 years showed that CIMT progression was normalized when compared with the patients' normocholesterolemic siblings [Kusters DM et al. *JAMA*. 2014]. The impact of earlier treatment to lower LDL-C and delay the age of onset of coronary heart disease has been modeled for patients with FH; without statin treatment, this threshold is met at age 35 years, while initiating statin treatment at age 10 years delays this to age 53 years and initiating statins at age 18 years delays the age of onset to 48 years [Nordestgaard BG et al. *Eur Heart J*. 2013].

This evidence and thinking is leading to a new paradigm for the treatment of FH in youth, with early comprehensive treatment including statins starting early in the AS process and later intensification to achieve LDL-C targets to maintain lower risk across the life span [Wiegman A et al. *Eur Heart J*. 2015].

EARLY PREVENTION IN CLINICAL PRACTICE

Prof McCrindle suggested that health care providers should be personal role models for a healthy lifestyle, work to counter mixed messages from the media that are aimed at today's youth, advocate for policy and environmental change, and address inequities. They should also learn and practice more effective lifestyle behavioral counseling strategies, such as motivational interviewing. In clinical practice, they should implement existing pediatric guidelines for CV health and risk reduction [Kavey RE W et al. *Pediatrics*. 2011], assessing and intervening on CVRFs in children with a focus on ideal CV health across the life span.