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Editorial

Measuring Cardiovascular Risk Across the Lifespan: When Should We Start Checking and What Should We Do About It?

Michael Khoury, MD, FRCPC

Department of Pediatrics, University of Alberta, Stollery Children's Hospital, Edmonton, Alberta, Canada

See article by Fan et al., pages 1253–1262 of this issue.

Studies evaluating the impact of cardiovascular risk factors (CVRFs) in children have been limited by a relative difficulty to demonstrate causative links with manifest atherosclerotic cardiovascular disease (CVD). With the exception of children with genetic disorders resulting in marked CVRF abnormalities (for example, homozygous familial hypercholesterolemia), atherosclerotic burden is typically early and clinically silent in children, adolescents, and young adults. Thus, cross-sectional evaluations of CVRFs in youth are often dependent on surrogate measures of atherosclerosis and vascular disease, including the use of carotid intima media thickness (cIMT) for atherosclerotic burden and pulse-wave velocity (PWV) for an assessment of vascular stiffness. For children with marked CVRF abnormalities, these surrogate measures have proved to be useful in pediatric studies.[1] Despite this, the cross-sectional evaluation of CVRFs, and its direct linkage to current or future CVD risk, is of limited utility in the pediatric population.

Longitudinal Assessments of Cardiovascular Risk Throughout Childhood

Thankfully, numerous studies have undertaken the ambitious endeavour of following pediatric CVRFs in a longitudinal manner, with assessments throughout childhood and into adulthood. The Bogalusa Heart Study, perhaps the best known and most established undertaking to this end, was founded by the late Dr Gerald Berenson in 1973. It involved repeated assessments of CVRFs in children and adults from the ages of 4 to 58 years in a semirural and biracial (white and black) population in Bogalusa, Louisiana.[2] A number of adults also had assessments of arterial stiffness (via PWV) and atherosclerotic burden (via cIMT). The Bogalusa Heart Study has been instrumental in demonstrating the association between measured CVRFs and the presence and extent of atherosclerosis. For example, in a landmark study, Berenson et al. performed autopsies on 204 children and young adults (aged 2-39 years) who had died from various causes and demonstrated that the number and severity of antemortem CVRFs was associated with the presence and severity of atherosclerotic burden.[3]

Longitudinal evaluations such as the Bogalusa Heart Study have demonstrated that isolated CVRFs at single time point do not tell the full story regarding future CVD risk. Rather, trajectories of CVRFs seem to establish a better linkage with CVD risk in adulthood. For example, data from the International Childhood Cardiovascular Cohort (i3C) Consortium of long-term follow-up studies (including the Bogalusa Heart Study) demonstrated that higher blood pressure (including measurements categorised as "normal" but greater than the median) in both childhood and adolescence was associated with a higher frequency of self-reported hypertension in adulthood compared with those with elevated blood pressure measures at any time point in either childhood or adolescence.[4] Similar associations have been demonstrated between trajectories of childhood body mass index (BMI) and blood pressure with vascular stiffness in adulthood.[5]

What Is the Relative Impact of the Cumulative Burden of Various CVRFs on CVD Risk in Adulthood?

In this issue of the *Canadian Journal of Cardiology*, Fan et al. sought to characterise the cumulative burden of commonly evaluated traditional CVRFs (BMI, blood pressure, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides) from childhood to adulthood and their association with atherosclerotic burden (via cIMT) and arterial stiffness (via aortic-femoral PWV) in adulthood with the use of data from the Bogalusa Heart Study.[6] The authors identified 900 participants who had been examined at least twice in childhood and

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Corresponding author: Dr Michael Khoury, Assistant Professor, Pediatric Cardiology, Department of Pediatrics, Stollery Children's Hospital, 8440-112th St NW, Edmonton, Alberta T6G 2B7, Canada. Tel.: +1-780-407-8361; fax: +1-780-407-3954.

E-mail: khoury1@ualberta.ca

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adulthood (at least 4 examinations in total) with complete CVRF, PWV, and cIMT data. They undertook a complex and sophisticated statistical analysis, including generating an area under the curve for each individual CVRF to evaluate the long-term cumulative burden of each CVRF. Growth curve models for the CVRFs were generated with the use of a mixed-models approach with the Akaike information criterion used for model selection.

Using multivariable linear regression analyses, the authors found that in childhood, BMI was associated with both increased PWV and cIMT, though the strength of association was relatively week (β coefficients 0.088 (95% confidence interval [CI] 0.027-0.149) and 0.075 (0.011-0.139) for PWV and cIMT, respectively). Importantly, childhood LDL-C was associated with cIMT in adulthood, although the association was similarly weak as those seen with childhood BMI. This finding builds on existing literature that has shown atherosclerotic burden to be linked with the presence of atherogenic lipoproteins, such as LDL-C, and that LDL-C accumulation from childhood can have long-term implications.[7]

The strength and directionality of associations between CVRFs across the lifespan (from childhood to adulthood) and in adulthood alone with PWV and cIMT were similar, with systolic blood pressure demonstrating the strongest associations with both PWV and cIMT. Moreover, these associations were in general much stronger than those observed for childhood CVRFs alone with PWV and cIMT. For example, systolic blood pressure across the lifespan had β coefficients of 0.32 (95% CI 0.251-0.392) and 0.21 (0.130-0.282) for PWV and cIMT, respectively, compared with 0.028 (−0.038 to 0.095) and 0.033 (−0.036 to 0.102), respectively, for childhood systolic blood pressure alone.

The relatively weak associations between childhood CVRF measures and PWV and cIMT, combined with the finding that associations observed for adulthood and full lifespan CVRFs were quite similar might imply that childhood CVRF assessment is of relatively low importance compared with assessments in adulthood. However, CVRFs do not exist in isolation. Rather, they cluster and track from childhood to adulthood.[8] Rather than treating CVRFs in adulthood, our patients are better served by preventing the occurrence of the CVRFs in the first place through primordial prevention. Specifically, many CVRFs cluster within the metabolic milieu of obesity. For example, childhood obesity tracks strongly to adulthood,[9] and obesity is a central modifiable risk factor for hypertension development.[10] Thus, a lifelong cumulative burden of obesity starting from childhood may contribute to hypertension development in adulthood. Therefore, the early identification and management of obesity (or better yet, the prevention of obesity development entirely) is likely to reduce the incidence of hypertension across the lifespan, which in turn can lead to reductions in CVD risk.

One of the fundamental challenges of longitudinal assessments such as the present analysis is that CVRFs do not exist in isolation; rather, numerous contributing factors arise across the lifespan that may contribute to an individual's CVD risk. The authors attempted to account for this as best as they could by adjusting for covariates such as age, race, sex, smoking, alcohol consumption, and the presence of lipid-lowering or antihypertensive treatments in their multivariable linear regression analysis. Nonetheless, unidentified confounding or contributing factors must be considered when interpreting longitudinal analyses such as these. Moreover, although the authors undertook a rigourous statistical approach, it is difficult to appreciate the mediation effects of various CVRFs on individual associations with PWV or cIMT. For example, in a different analysis of data from the Bogalusa Heart Study, this same group previously demonstrated that the association between BMI with PWV was largely mediated by elevated blood pressure.[5]

There are other limitations that must also be considered when interpreting the study results, some of which were acknowledged by the authors. For example, in the generation of the growth curves, the absolute values of childhood BMI and systolic blood pressure were used, rather than percentiles. This is an important consideration because the normative values for both BMI and blood pressure are not static throughout childhood. Rather, they change with time, with normative BMI values decreasing from age 2 to about age 5 years old and then increasing throughout childhood[11] and blood pressure gradually increasing throughout childhood.[12] The lack of incorporating indexing to normative values for BMI and blood pressure may have significantly affected the area under the curve (ie, life-course burden) assessments of these CVRFs and their resultant associations with PWV and cIMT. However, the use of percentiles for children and absolute values for adults would make continuous modelling throughout the lifespan difficult or not at all possible.

Where Do We Go From Here?

This study emphasises a fundamental point that, regardless of the strength of associations between CVRFs in childhood with CVD risk in adulthood, each clinical encounter throughout childhood represents an opportunity to decrease the cumulative burden of CVRFs and alter an individual's CVD risk trajectory. However, for treatment to occur, at-risk children must first be identified. Unfortunately, there remains significant room for improvement in the detection of CVRFs in youth, both in Canada and abroad.[13,14] Thus, systematic strategies are necessary to allow for the identification and management of youth at increased CVD risk.

Demonstrating associations between CVRFs from childhood into young to middle adulthood with subclinical CVD in adulthood reinforces the notion that atherosclerosis begins in youth and that its progression is linked with the presence and severity of CVRFs across the lifespan. Moreover, as the populations from these longitudinal cohorts age, demonstrating associations with manifest CVD is becoming increasingly possible. For example, data from the i3C Consortium recently identified associations between CVRFs in childhood and adulthood, as well as changes in the severity of these risk factors from childhood to adulthood, with fatal and nonfatal CVD.[15] These findings support and expand on the already important work by Fan et al. and reinforce the importance of surrogate measures of CVD such as PWV and cIMT, despite their infrequent use in routine clinical care (particularly in pediatric care). Early detection of subclinical CVD risk before manifest disease facilitates primary prevention strategies. In addition, these surrogate measures may serve as short- or long-term treatment targets for children at increased CVD risk. For example, in a randomised controlled

trial of children with familial hypercholesterolemia, 2-year statin treatment was associated with a reduction in cIMT compared with children who had received a placebo.[1] Moreover, 20-year follow-up data of this cohort demonstrated that long-term statin treatment resulted in a cIMT that was not significantly different from these participants' unaffected siblings (ie, did not have familial hypercholesterolemia).[7]

The study from Fan et al.[6] in the current issue of *CJC* contributes to an increasingly robust evidence basis that has accumulated over recent decades supporting CVD primary prevention strategies beginning from childhood. These findings should inspire pediatric specialists to redouble our efforts to improve the systematic detection and management of CVRFs in Canadian youth so that we may slowly bend the arc of future CVD development. To quote the late Dr Berenson, when speaking of the Bogalusa Heart Study, "The message of this study is that adult heart disease begins in childhood, and lifestyle changes have to begin then, too."[16]

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