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NHLBI integrated pediatric guidelines: battle for a future free of cardiovascular disease

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Abstract

The report of the National Heart, Lung and Blood Institute Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents collects into one document atherosclerotic disease prevention in pediatric age groups. The guidelines summarize the evidence base and make recommendations that encourage universal adoption of healthier lifestyles, identification of children with cardiovascular disease risk factors, and treatment of those risk factors using targeted lifestyle modification and rarely pharmacotherapy. These recommendations highlight childhood as a frontier for cardiovascular disease prevention. The guideline recommendations are controversial and not universally embraced, but at the very least, they suggest directions for important research. This article explores key facets of the guidelines, controversies and future directions in preventive cardiology for children.

Keywords

cardiovascular; child; cholesterol; risk; screening; treatment

Contrary to Admiral Ross McIntire's declaration, in the modern era cardiovascular disease (CVD) events can no longer be considered a 'bolt from the sky', but instead are eminently preventable. While improvements in CVD risk factor treatment have reduced CVD mortality in adults, an alarming countervailing trend dominates the future of CVD – obesity and obesity-related diabetes [1–6] – one that is the focus of national healthcare organization priorities [7,8,101]. A focus on children offers a prime opportunity to address national priorities to both reduce the occurrence and improve the treatment of CVD risk factors. Childhood is a key time for progress because children that are affected by CVD risk factors may already have evidence of atherosclerotic changes and seem to be malleable enough to change lifestyle habits to avoid developing CVD risk factors. The National Heart, Lung and Blood Institute (NHLBI) Expert Panel Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, released in November 2011, responds directly to these goals by extending CVD prevention to America's children [9]. The guidelines unify previously disparate streams of CVD prevention including diet, activity, inactivity, blood pressure (BP), lipids, obesity and tobacco use under a single aegis and update these domains

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with a comprehensive data review. In compiling these recommendations, the NHLBI integrated guidelines extend the reach of CVD prevention to an earlier, more malleable life stage.

The guidelines: conceptual framework & synopsis

CVD risk factor modification can be conceptualized as secondary prevention, primary prevention and primordial prevention [10]. If secondary prevention is the avoidance of recurrent CVD events in those with a history of CVD, and primary prevention is the treatment of CVD risk factors in order to avoid the first CVD event, primordial prevention is intervention to prevent the occurrence of CVD risk factors themselves [11]. The NHLBI Expert Panel Integrated Guidelines make specific, developmentally appropriate recommendations interdigitating CVD risk factor prevention into general pediatric practice for every child. These recommendations can be divided into CVD risk factor prevention, detection and risk factor treatment guidelines that help justify detection during childhood. The identification and treatment sections are centered on the premise that the child's aggregate CVD risk is the overarching concept, rather than the risk attributable to any specific risk factor. Therefore, treatment guidelines are influenced by the totality of the risk picture instead of focusing on 'normal' versus 'abnormal' CVD risk factors.

It is well established that subclinical atherosclerotic abnormalities occur in childhood, that these changes are related to CVD risk factor presence and that risk factors in adults are related to CVD events in a continuous fashion [12–16]. But what to do when, as Geoffrey Rose portrayed the problem, the population is 'sick'? [17]. The striking increase in pediatric overweight and obesity and the presence of risk factors in a large proportion of normal weight children suggests that a population approach to risk factor reduction and prevention is essential [18]. National data shows that while overweight and obesity increase the relative risk of high LDL cholesterol (LDL-C), approximately 45% of all high LDL-C adolescents are normal weight, hinting that CVD risk factors are prevalent across the broad distribution of children. Given this, the proposed solutions must be scaled to the population-level. The population approach to risk factor reduction should be attempted based on the previous success in population-wide tobacco use reduction in the USA, which occurred in the absence of widely effective individual-level therapy for tobacco cessation. Instead, it has been achieved through mobilizing public sentiment, broad-based economic disincentives, and restrictions on advertisement, procurement and use of tobacco products. Parallel efforts to reduce causes of hyperlipidemia, hypertension or obesity meet entrenched opposition due to the lack of demonstrated second-hand harm from lifestyle behaviors and concerns about freedom of personal choice. However, protecting children from adverse influences leading to CVD risk factors may be more easily accepted because their lifestyle choices are frequently appropriately constrained by their parents, and because they may be less able to make healthy choices on their own.

Primordial prevention recommendations

The guidelines seek to implement population-level primary prevention interventions through each child. Some of the specific recommendations include counseling to make the home environment a source of healthy diet, healthy activity and minimal inactivity, and tobacco-free. Tobacco abolition is recommended beginning in infancy and continuing throughout childhood and adolescence. Dietary recommendations include breastfeeding for the first 12 months, limiting calories from milk fat and fruit juice, and adherence to the CHILD-1 diet after 2 years of age. The CHILD-1 diet is tested to be safe and consists of limiting total calories from fat to 30%, from saturated fat to less than 10%, from carbohydrate to less than 55% and from protein to less than 20%, along with restricting dietary cholesterol to 300 mg per day, limiting sugar sweetened beverage intake, avoiding excessive calories, encouraging

plant-based foods and encouraging fiber intake. Inactive screen time is completely discouraged prior to 2 years of age and restricted to no more than 2 h per day in older children, while active play in toddlerhood and 1 h per day of moderate-to-vigorous activity in older children and adolescents is universally recommended. The guidelines endorse, stress and advance this population-level approach to CVD risk factor prevention as the 'new norm' for American children.

Enhanced detection is an important element of the guideline recommendations owing to the high prevalence of CVD risk factors. Some key recommendations include: inquiring about family history of early CVD events; assessing tobacco exposure, either personal or second hand; screening for obesity; identifying high-risk medical conditions such as renal disease, heart or kidney transplant, or inflammatory syndromes; selective screening for diabetes in obese children with family history, high-risk race/ethnicity, clinical signs or insulin resistance; universal measurement of BP annually; and universal screening for lipid disorders. The integrated guidelines combine, refine and extend previous guidelines from the 4th report of the High Blood Pressure in Children and Adolescents Working group as well as the American Academy of Pediatrics (AAP) 2008 guidelines on Lipid Screening and Cardiovascular Health in Childhood among other reports [19,20]. These previous efforts advocated for screening high BP at every pediatric patient encounter and screening for lipid disorders in individuals with high-risk medical conditions or concerning family histories, and for lifestyle and pharmacological management of pediatric lipid disorders. The NHLBI guidelines extend the previous AAP cholesterol guidelines to endorse universal screening to enhance detection of young individuals with familial hypercholesterolemia (FH) who are at very high risk of early atherosclerosis.

Primary prevention recommendations

CVD risk factor treatment is an important part of the NHLBI guidelines that has prompted some controversy. Treatment is advised owing to the links between those risk factors in adolescence and pathological evidence of atherosclerosis, the stability of CVD risk factors from childhood to adulthood, and the ability of those childhood risk factors to predict subclinical atherosclerotic changes and CVD events, even after adjustment for adult CVD risk factor levels [14,15,21–25]. It is also clear that CVD risk factors are modifiable. Temporal trends show that tobacco smoking rates have generally decreased in adults, and cholesterol levels in American children appear to be decreasing over time [26,27]. Furthermore, modifiable risk factors play an essential role in CVD. Adult cohorts such as MONICA, INTERHEART and INTERSTROKE demonstrated that 90% of stroke and coronary heart disease incidents were attributable to potentially modifiable risk factors [28–31]. Recent randomized controlled trials in adult patients with chronic stable angina, Type 2 diabetes and coronary disease with systolic heart failure demonstrated that aggressive CVD risk factor modification appeared to be as effective as invasive revascularization in averting CVD events and death [32–34]. On the other hand, temporal trends show that obesity is on the rise and cholesterol levels are worsening all over the world [35,36]. Therefore, we can be sure that CVD risk factors are modifiable in positive or negative directions.

The guidelines recommend vigorously counseling children to stop smoking through direct appeal, telephone helplines, communal cessation programs and pharmacotherapy. The guidelines also advocate treating obesity in children older than 6 years of age by negative energy balance through diet change and exercise coupled with behavioral change counseling. Diabetes treatment per American Diabetes Association guidelines is endorsed [37]. For children following a CHILD-1 diet with elevated BP, recommendations include the CHILD-1 diet as a Dietary Approaches to Stop Hypertension (DASH)-style option, lowering sodium intake, weight loss if appropriate, and using pharmacological modification and therapeutic adjuncts, all while acknowledging that hypertension persists in 33% of boys and

25% of girls over 2 years of age. Finally, the child with identified lipid disorders should partake in the CHILD-2 LDL or CHILD-2 triglyceride diets, depending on the lipid abnormality, reduce obesity if appropriate, and if lifestyle modification is ineffective for an extended period, use lipid-lowering medications at thresholds predicated on family history of early atherosclerosis and personal risk factors. Critics may charge that the goal of the NHLBI Expert Panel is to increase the market for lipid and BP-lowering medications to children, while ignoring the real societal problem around healthy lifestyles, however, this criticism is contradicted by the actual guidelines. The guidelines include recommendations that are intended to alter the population propensity to develop CVD risk factors (primordial prevention), as well as primary prevention recommendations to enhance screening and treat risk factors with lifestyle modification, and adjunctive pharmacotherapy when needed. However, the well-intentioned guidelines are not without controversy.

Controversies

Universal screening to detect genetic dyslipidemias

The most controversial topic raised by the Expert Panel has been the new mandate for universal lipid screening, which aims to enhance identification of genetic lipid disorders, such as heterozygous FH. FH appears to fulfill all 1968 WHO criteria for screening in that it occurs in approximately 1 in 500 births, silently leads to highly elevated LDL-C over the life-course, manifests as life-threatening CVD events in young adulthood, and appears to be eminently treatable with the combination of lifestyle modification and lipid-lowering drugs [38]. Without treatment, approximately 50% of boys and 20% of girls with heterozygous FH will have a coronary event before 50 years of age [39–41]. Studies show that reliance on family history of high lipid or CVD events may miss 30–60% of affected children due to a lack of understanding about lipid levels, lack of knowledge about family history, refusal of parents to have their own cholesterol levels checked and the ability of lipid-lowering medications currently available to profoundly delay or prevent CVD events in affected adults [42–46]. Focusing on children treats them as individuals worthy of care, independent of the reliability of his/her parents, and this focus may actually enhance identification of other family members with FH who may not have been detected otherwise. However, the downsides of universal screening are considerable and should not be ignored [47–49]. Children could be falsely labeled as ‘abnormal’ by a nonfasting lipid screening. This phenomenon is not unique to children; CVD risk factors also fluctuate in adults. Similar to adults, single measurements of lipids in childhood predict atherosclerotic changes in adulthood [14,15,21]. The guidelines recommend averaging multiple lipid values and using fairly high thresholds to designate abnormal, to help reduce errors of random misclassification and regression to the mean. It is likely that a very small number will be falsely labeled as FH after two more fasting lipid profiles, the follow-on testing advocated by the guidelines. More data is required to assess the effects of this screening approach, in terms of both the negative and positive effects [18]. Attention to CVD risk factors may offer powerful motivation to improve overall CVD health. Further research is needed to better understand and quantify the harms as well as the benefits for universal pediatric lipid screening.

Lifestyle dyslipidemias

As noted above, the purpose of the guidelines is to identify genetic dyslipidemias. To their credit, the expert panel acknowledges the probability of detecting primarily lifestyle-driven dyslipidemias and argues that such children are also worthy of medical attention. Critics are concerned that because both lipid values and weight are variable – making for a potentially unstable phenotype – weight loss should be the only approach. It is vital to disentangle abnormal weight from abnormal lipid values; the two are not synonymous. While obesity

increases the risk of lifestyle dyslipidemias, a substantial proportion of dyslipidemia patients are normal weight, and not all abnormal weight patients have dyslipidemia [18]. While the roots of both lie in disordered diet, activity and inactivity, the precise details make all the difference. It is possible to affect CVD risk factors through lifestyle modification, especially diet quality change, without immediately affecting weight. The treatment of lifestyle dyslipidemias may depend on the specific dyslipidemia [50–53]. For example, as described in the guidelines, avoidance of simple carbohydrates is not expected to markedly change LDL-C, but may be quite useful in attacking high triglyceride levels. These facts are critical to providers and to policymakers, because identifying and treating abnormal weight with the hopes of modifying the causal CVD risk factor pathways may not be a cost-effective means of preventing CVD events [54]. Identifying those with risk factors farther down the causal chain may allow for more targeted therapy, and lead to more success. In our experience, children who hear the same weight-loss advice from pediatric providers, on top of advice from family and peers, may tune out the critical message. But when confronted with the possibility that they may need lipid-lowering therapy and given specific tools to avoid medicine, they may become more engaged. The rest of the conversation may be a message identical to the weight-centered approach, but taking a different approach can allow providers to forge a uniquely therapeutic relationship with an at-risk child.

Treatment

Excessive use of pharmacologic treatment is often raised as a concern, even though this is not the major focus of the guidelines. In fact, the NHLBI guidelines do not substantially extend recent recommendations regarding BP and lipid therapy in children, and a more aggressive therapy recommendation (younger age) was previously made in the AAP 2008 guidelines. The critic's focus on pharmacological treatment distracts from the main messages of lifestyle modification and identification and treatment of genetic dyslipidemias. The NHLBI guidelines encourage those who have FH as determined by a very high LDL-C threshold to be treated with the CHILD-2 LDL diet, which adds to the general CHILD-1 diet more restriction on saturated fat and dietary cholesterol intake, and consideration of increased plant stanol/sterol intake. If this fails, lipid-lowering medications (statins and HMG-CoA reductase inhibitors) in children older than 10 years of age is recommended.

The main criticisms of the treatment approach relate to a lack of perceived urgency due to the long latency between risk factor exposure and CVD events, the lack of data on the risks and benefits of childhood treatment, and the unintended consequences engendered by universal screening. The application of the Framingham 10-year risk calculators to these children with genetic dyslipidemia is incorrect. The Framingham calculator is derived from and intended for a general population cohort, not a high-risk diagnosis like FH. For example, entering a total cholesterol value above 320 mg/dl into the online risk calculator results in an error message requesting a lower value. A more appropriate risk assessment is natural history data in FH patients showing a 50% risk of incident coronary events in men less than 50 years of age and a 20% risk in women.

Second, the criticism regarding lack of data is well placed. Important knowledge gaps include the relative risks of treatment side effects versus benefits of primary prevention. While the concept of treating CVD risk factors in childhood is attractive, the current treatment modalities and even the current risk factor characterizations temper enthusiasm. The guidelines detail the extant data regarding the tolerability and efficacy of statins in lowering LDL-C. However, no longer term studies exist on the ability of statin therapy started in youth to reduce CVD events, or on long-term safety. Critics cite unforeseen side effects from other medications in the past as a reason to be skeptical about statin use, and thereby avoid some hypothetical pediatric-specific adverse events. On the other hand, the volume of patient data from statin use in adults is staggering and convincingly argues

against additional adverse events beyond well-described myotoxicity, possible risk of hepatotoxicity and emerging risks regarding incident diabetes mellitus [55–58]. While this gestalt opinion is generally concordant with adult recommendations, the math is slightly different depending on the patient's age [59]. Using back-of-the-envelope calculations assuming a constant risk rate of 1 in 255 over 4 years, the cumulative risk of incident diabetes alone in a 10-year-old FH patient over 30 years is approximately 2.9%. This estimate is relatively large, but is dwarfed by the risk of CVD combined with the widely accepted causal role of LDL-C in incident coronary disease, CVD event prevention related to the degree of LDL-C lowering, and demonstrated efficacy of LDL-C lowering in children. When the family history involves severe and early CVD in a parent, the discussion about pharmacologic treatment takes on a greater urgency. Potential as yet undescribed risks are important to consider, but the preponderance of evidence supports the use of lipid-lowering medication therapy in children significantly affected by FH. Of course, the decision to actually treat an affected child with a medication is always a collaborative one between parent, provider and child.

Obesity & lipid-lowering therapy

The most feared consequence of the new guidelines is that children with lifestyle-related dyslipidemias will receive pharmacological treatment. However, the guidelines should not be construed as advocating for lipid-lowering therapy as the response to the CVD risk of obesity. A contrarian might point out that no intervention to reduce lifestyle-related CVD risk factors has ever been proven widely effective in office-based or population-level interventions in children over long periods of time. Even in adults, while multiple lifestyle modification plans have been shown to be effective in CVD risk factor modification, few have ever been demonstrated to prevent CVD events. On the other hand, the contrarian might argue, statins are well demonstrated to effectively prevent CVD events, and are well tolerated across the life course, including in childhood. Therefore, when confronted in a clinic by an adolescent patient with CVD risk factors, the choice between an unproven lifestyle intervention with unknown efficacy versus an unproven pharmacological intervention likely to be effective might lead some rational contrarian providers to choose the drug option. The NHLBI expert panel does not condone the contrarian's choice. Instead the guidelines mandate lifestyle modification as the primary response. Only when lifestyle modification has been assiduously exhausted and other CVD risks are also present can pharmacotherapy even be prudently considered, and preferably under the guidance of a lipid specialist. This is distinctly at odds with prescribing patterns among adult providers. Indeed the most recent data on lipid-lowering therapies indicate that the number of children being treated is grossly inadequate [60,61]. Without diminishing the role of obesity as the crux of multiple CVD risks, the guidelines draw upon strong data linking the CVD risk factors in childhood to CVD phenotypes/events in adulthood to advocate for both identification and promotion of lifestyle modification for CVD risk factors. The guidelines, contrary to popular fears, advocate against the indiscriminate disbursement of statins to obese children.

Burdens of implementation

Undoubtedly, these recommendations will be a burden to healthcare providers and payers and, by implication, the insured/taxpayers. Critics point out that since the rate of CVD events is so low in childhood (nearly zero), is all this effort justified in any particular child? Is a decision on this point affected by the fact that primordial prevention is not designed to help an individual in the near term, but instead to produce benefits decades later? Conversely, the consequences of patients erroneously interpreting a normal cholesterol or BP level as a 'seal of approval' for an actually unhealthy diet and activity pattern may also have unintended consequences if a trained provider does not point out the lifestyle concerns. Certainly, retraining pediatric providers to deliver these prevention efforts will be costly in

time and money. This is of substantial concern as the most recent data point out that lipid-lowering therapies are prescribed at 10% of what would be expected to treat FH patients, much less than other high-risk patients [60,61]. Keeping in mind the direct costs of CVD in 2010 was US\$272.5 billion and is projected to increase to US\$818.1 billion by 2030, ignoring childhood CVD risk factors assuming someone else will fix the problem later is also costly [4]. From an ethical perspective, a strong argument can be made that CVD, which is morbid and mortal and has prevalent and modifiable risk factors, is as worthy as many other diseases we screen for during childhood. Population-level risk factor prevention techniques in children are modeled to be the most cost effective because of the variability in CVD risk factor stability [54]; however, analyses should consider the effects of lifestyle change on rates of cancer [62,63], diabetes, liver disease, psychological morbidity and other lifestyle-related diseases [24,64–66]. Additional benefits of risk factor identification and treatment may include benefits to other family members and members of the social network [67]. We should not underestimate the motivation of a parent trying to avoid having a 14-year-old on cholesterol or lowering medication. More research is needed on cost–benefit and cost–effectiveness of CVD prevention in childhood.

Criticisms & future directions

Policy approaches to prevention

While certainly an important step forward, the integrated guidelines are not a primordial prevention panacea. Important areas were left unresolved. First, the guidelines are relatively quiet on primordial prevention health policies aimed at lifestyle change. Certainly, voluntary adoption of healthier behaviors is uncontroversial, but involuntary policy-based disincentives to unhealthy behaviors are proven effective tools (e.g., seatbelts). The tension is evident as the full NHLBI expert panel report mentions the utility of taxing tobacco and the need to enhance affordability of healthy foods while these themes, and indeed the words ‘policy’, ‘tax’ and ‘disincentive’, are completely absent from the more widely read summary report. This was a missed opportunity to advocate for proven population-level prevention tools.

Lack of medium-term safety & effectiveness data

Supporters and critics alike are uncomfortable with the misapplication of the guidelines to place children on lipid-lowering medications inappropriately, whether through over- or underuse. Both sides lack data and definitive longitudinal CVD outcomes trial data are not forthcoming due to extended observation periods and a possible lack of equipoise toward statin treatment. One remedy to this data gap may be a comprehensive, registry-type surveillance of children treated with lipid-lowering medications recording CVD event rates, especially in high-risk conditions, as well as medication-related adverse events.

Disparities

Discussions of disparities predicated on race, ethnicity, sex/gender, immigrant status, socioeconomics or healthcare access are found in the full NHLBI report but are notably de-emphasized or absent for the summary report. Indeed, certain racial/ethnic subgroups may be more prone to certain dyslipidemias either on the basis of intrinsic biological variability, dietary patterns or cultural practices [68,69]. Better understanding of the relationships between sociocultural factors and CVD risk factors may illuminate promising pathways to solutions, or at least deserve attention. This is a notable omission from the guideline summary.

The value of interim CVD outcomes

The guidelines are silent on how to measure short-term effectiveness of screening, lifestyle modification and pharmacotherapy. Because of the long latency between exposures and CVD events, better interim metrics are required to assess the ongoing impact of the guidelines. Measures of subclinical atherosclerosis would have been a significant contribution to move forward research, identify goals for pediatric provider expertise and illuminate the importance of CVD risk factor reduction. The expert panel was in a great position to recommend process metrics, and by so doing would have enhanced enthusiasm for guideline implementation by giving a more attainable target. Unfortunately, methods used in adults to measure subclinical disease will have to suffice for now.

Utility of assaying stable subclinical phenotypes

The inconstancy of classic CVD risk factors is a profound concern. The guidelines have built-in repeat assessments as an attempt to combat this problem (repeat BPs and repeat fasting lipid profiles). Would the effects of BP treatment be enhanced by detection and treatment of BP using ambulatory BP monitoring as suggested by adult and pediatric models? [70,71]. As noninvasive assessment of CVD subclinical phenotypes emerges, would therapy, especially pharmacotherapy, be better applied to children with evidence of left ventricular hypertrophy, carotid intimal medial thickening or arterial stiffening rather than transient CVD risk factor elevations? These subclinical phenotypes may reflect both classic CVD risk factor exposure as well as emerging risks, such as air pollution [72]. Is a staged approach most appropriate, considering risk factors and then subclinical cardiovascular findings? While the guidelines do endorse left ventricular hypertrophy as the *sine qua non* of hypertensive target end organ damage, the utility of other testing modalities may need to be revisited.

Focus on illness versus wellness

The guidelines were developed prior to the rollout of the American Heart Association Health Impact 2020 goals, which have emphasized promoting ideal cardiovascular health rather than just treating CVD risk factors [7]. The guidelines do not yet include the laudable goals enumerated in the Ideal Cardiovascular Health framework as ends in themselves, although in practice following the NHLBI guidelines may result in ideal cardiovascular health.

Developmental origins of CVD risk

The expert panel gives short shrift to extending the prevention umbrella to the prenatal period beyond tobacco smoking cessation. The expert panel chose to leave this area without recommendation owing to lack of evidence on maternal obesity in a pediatric care setting. Hopefully, the next iteration will draw on sufficient subsequent data to make firm recommendations in this regard.

Conclusion

Overall, the NHLBI Expert Panel Integrated Guidelines advocate for the prevention of CVD risk factor development through healthy behaviors in all children, identification and treatment of children with genetic dyslipidemias, use of specific lifestyle modifications for children with particular CVD risk factors, and restricted use of lipid pharmacotherapy in children with elevated CVD risk. These recommendations expose children as a hidden population of smoldering CVD risks, placing children in the center of the battle against future CVD. The controversies around the guidelines serve to highlight important gaps in the literature and misconceptions about familial disorders and obesity-related risk. With

perseverance, pediatric providers may be positioned to shift the CVD prevention focus from trimming off CVD events to cutting CVD out at the root.

Future perspective

Over the next 5–10 years, pediatric providers and training programs will become more attuned to the public health imperative in becoming more comfortable with screening for and treating CVD risk factors in children. More intermediate outcome data linking childhood and adolescent CVD risk factors to incident CVD events in adulthood will arise from ongoing longitudinal cohorts around the world. Simultaneously, additional data will accumulate in very high-risk pediatric populations that CVD risk factor modification does prevent early CVD events and mortality. Population-level risk factor modification will become better understood and embraced by medical providers and the general public alike when confronted by accumulating evidence of its effectiveness. The combination of these streams will develop childhood as the prime window for CVD treatment before it even has a chance to start.

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