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Combined Dyslipidemia in Children and Adolescents: a Proposed New Management Approach

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Abstract

Purpose of Review Combined dyslipidemia (CD), the predominant abnormal lipid pattern in children and adolescents, is characterized by moderate/severe triglyceride elevation with reduced high-density lipoprotein cholesterol. CD is prevalent, present in 30–50% of obese adolescents. Epidemiologic and lipid sub-population findings demonstrate CD to be highly atherogenic. In the short term, CD responds well to lifestyle change; long-term results are lacking.

Recent Findings Major longitudinal studies now confirm that CD in childhood predicts early cardiovascular disease events in adults. Targeted nutritional interventions can be safely and effectively introduced in young children. These findings support introduction of a new approach to CD management.

Summary New evidence supporting the atherosclerotic risk associated with CD and the effectiveness of lifelong diet interventions is reviewed and a new family-based primordial approach to CD beginning in infancy is proposed. Aligned with existing pediatric care recommendations, this has the potential to significantly decrease the development of CD.

Keywords Combined dyslipidemia · Atherogenic dyslipidemia · Mixed dyslipidemia · Obesity · Visceral adiposity · Premature cardiovascular disease

Introduction

Cardiovascular disease (CVD) remains the leading cause of death in the USA. Despite COVID's staggering death toll of 1.1 million Americans, diseases of the heart and circulation claim significantly more lives [1]. Key facts underlie this statistic: the underlying CVD pathology of atherosclerosis begins early in childhood when known risk factors (RFs) which exponentiate the process are also initiated. Dyslipidemia is an established RF and a growing body of evidence directly associates dyslipidemia in childhood with CVD in adult life [2•, 3].

Combined Dyslipidemia: the Problem

Dyslipidemia identifies disorders of lipoprotein metabolism resulting in one or more lipid profile abnormalities. Based on normative values from population data, childhood lipid values are designated as "acceptable," "borderline," and "abnormal," as shown in Table 1 [4]. National population data from 1999 to 2016 show that dyslipidemia is prevalent: 15.2% of children and 25.2% of adolescents have at least one adverse lipid level [5, 6].

Combined dyslipidemia (CD) is an abnormal lipid pattern characterized by moderate to severe elevation in triglycerides (TGs) with reduced high-density lipoprotein cholesterol (HDL-C), seen almost exclusively in youth with obesity. The ongoing pediatric obesity epidemic has resulted in a large population of children with CD, the most prevalent abnormal lipid pattern in youth, and in adults with CVD events. In typical CD in childhood, TG levels are between 150 and 400 mg/dL and HDL-C is less than 40 mg/dL.[4]

As body mass index (BMI) increases, CD prevalence increases, from 14% with normal weight to 22% with overweight (BMI 85th to 95th percentile), and 43% with obesity (BMI >95th percentile) [7]. National data from 2011 to 2020 show the overall prevalence of obesity among youth aged 2 to 19 years was 21.5%, up from 17.7%, with increases in all race and ethnicity groups [8]. Favorable trends have been observed in lipid levels but adverse TG and HDL-C levels persisted in those with obesity [6]. Since 85% of overweight

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Table 1 Acceptable, borderline, and high plasma lipid, lipoprotein and apolipoprotein concentrations (mg/dL) for children and adolescents* [1]. Note: Values given are in mg/dL; to convert to SI units, divide the results for TC, LDL-C, HDL-C, and non-HDL-C by 38.6; for TG, divide by 88.6

Category	Acceptable	Borderline	High
TC	< 170	170–199	> 200
LDL-C	< 110	110–129	> 130
Non-HDL-C	< 120	120–144	≥ 145
TG			
0–9 years	< 75	75–99	≥ 100
10–19 years	< 90	90–129	≥ 130
Category	Acceptable	Borderline	Low
HDL-C	> 45	40–45	< 40

*Values for plasma lipid and lipoprotein levels are from the 2011 NHLBI Expert Panel Guidelines [1] The cutpoints for high and borderline high represent the 95th and 75th percentiles, respectively. The low cutpoint for HDL-C represents the 10th percentile. www.nhlbi.nih.gov/guidelines/cvd_ped.index.htm

adolescents become obese adults, obesity and CD are important health problems.

Typical acquired CD is strongly familial, based on multiple polygenic traits expressed with the development of obesity. There is overlap between CD and "familial combined hyperlipidemia" (FCH), an older term which includes a heterogenous group of disorders. Next-generation genetic analysis confirms that FCH also has a polygenic basis, with contribution from the accumulation of small-to-moderate effect common single nucleotide polymorphisms throughout the genome [9].

Atherogenicity of CD

Analysis by nuclear magnetic resonance spectroscopy (NMR) shows that the CD lipid profile pattern is represented at subpopulation level as increased small, dense LDL-C and LDL particle number plus reduced total HDL-C and large HDL particles [10]. High LDL particle number, especially small, dense LDL particles, facilitates LDL entrapment in the arterial sub-endothelial matrix; reduced large HDL particles decreases cholesterol efflux. Thus, CD is highly atherogenic [11].

The impact of CD is increased by its association with other atherogenic RFs for CVD, particularly visceral adiposity and insulin resistance. Increased abdominal adipose tissue reflects an inability of the subcutaneous adipose tissue depot to expand, resulting in ectopic fat deposition, primarily in the viscera. Visceral fat contributes directly to CD by enhanced delivery of free fatty acids to the liver via the portal vein. Increasing visceral adiposity correlates directly with development of CD [12].

Insulin resistance (IR) is the precursor to type 2 diabetes mellitus (T2DM), both more prevalent in specific racial/ethnic groups—Native-Americans, African-Americans, Latinos, and Asian-Pacific Islanders. Higher BMI is associated with higher fasting insulin levels in childhood and adolescence and higher fasting glucose levels in young adulthood [13]. Hyperinsulinemia enhances hepatic very-low-density lipoprotein synthesis, manifest as high TGs. At tissue level, IR promotes lipoprotein lipase dysfunction, further elevating TGs. In adolescents, IR and CD were seen only in obese subjects and dyslipidemia correlated with the severity of IR [14].

CD, IR/T2DM, and visceral adiposity are components of the metabolic syndrome (MS), an established high-risk constellation for CVD, reported in a third of American adults. Cross-sectional data show overall prevalence of the MS cluster among adolescents of ~10%; as obesity severity increased, the prevalence increased to 38.7% of moderately obese and 49.7% of severely obese adolescents [15]. Of major importance, presence of the MS cluster at a mean age of twelve was an independent predictor of CVD 25 years later [16].

Thus, there is strong evidence that CD alone and the combination of CD with obesity and insulin resistance are powerful predictors of atherosclerotic risk beginning in childhood.

Current Management of CD

The 2011 NHLBI pediatric guidelines were the first to recognize the importance of CD in childhood [4]. The guidelines recommend selective lipid screening when overweight or obesity is first identified (BMI > 85th%ile for age/sex); when any other major cardiovascular risk is present; and when there is a family history of early CVD or treated dyslipidemia. Intervention is recommended whether CD is identified by selective or universal screening. In this situation, obesity and CD are already established and a combination of diet and activity change is recommended. Implementation of a diet that is low in fat and simple carbohydrates and high in complex carbohydrates significantly decreases TG levels in children as does exercise training. Most importantly, even small amounts of weight loss are associated with significant decreases in TG level and increases in HDL-C. Only very rarely is any drug treatment indicated. Multiple reports describe and support this approach [4, 17, 18•, 19–21]. While the response to lifestyle change in clinical studies has been acceptable, long-term results in the real world are unknown.

Evidence for a New Approach

Since acquired CD appears overwhelmingly in obese youth in a shared family context, an alternate approach could be primordial prevention, beginning before either obesity or

dyslipidemia develop in children at increased risk because of their family setting. Such an approach would require strong evidence associating childhood obesity and dyslipidemia with adult CVD. That evidence is now available through the work of the International Childhood Cardiovascular Cohort Consortium (i3C), a collaboration of seven large, longitudinal studies which measured CV RFs in children who were followed into adulthood [22]. Created in 2009, i3C combines childhood data from these cohorts on blood pressure (BP), lipids, smoking history, and/or adiposity with adult results. Altogether, more than 40,000 children were followed in the 7 collaborating cohorts [23].

These remarkable studies provide critical information about the impact of RFs in childhood on adult CVD outcomes. Among the most relevant to a review of acquired CD are the findings related to obesity. Analysis of 12,142 individuals with BMI determined in childhood and adult life showed that Class II/III (moderate) adult obesity developed in 6% of normal weight children, 29% of overweight children, 56% of obese children, and 80% of severely obese children [24].

An important i3C cohort included 5195 adults with serial BMI and blood lipids measured from childhood to adulthood [25]. Participants with dyslipidemia (high TGs/low HDL-C/high LDL-C) had significantly higher BMI levels from childhood to adulthood compared to those with normal lipids. Even after adjusting for age, race, sex, and cohort, adult dyslipidemia was significantly associated with higher childhood and adulthood BMI, suggesting the impact of excess body weight originates in early life. Childhood BMI, fasting glucose, and insulin also predicted adult onset of diabetes beginning at 30 years of age [26].

Finally, an i3C analysis of BMI, systolic BP, total cholesterol [TC], TG level, and youth smoking at 3 to 19 years was performed in 319 participants with confirmed fatal CV events at a mean age of 46 years. Childhood RFs and the change in a combined-risk *z* score between childhood and adulthood were significantly associated with fatal cardiovascular events in midlife [2•]. In the CVD subjects, the hazard ratio for a fatal event increased by 2.71 (95% CI, 2.23 to 3.29) for each unit increase in the combined-risk *z* score [2•].

Thus, solid evidence from longitudinal studies associating childhood dyslipidemia and obesity with adult CVD provides the infrastructure for a primordial pediatric approach to this combination.

Evidence for Intervention in Early Childhood

Another remarkable study provides evidence that early childhood diet intervention is safe and effective. The Special Turku Coronary Risk Factor Intervention Project (STRIP) was a prospective, randomized trial which began in 1990 when subjects were 7 months of age and continued for 20 years [27•]. Intervention children (n=540) received individualized diet counseling biannually, aimed at achieving a fat intake of 30–35% of daily energy, a saturated to unsaturated fatty acid ratio of 1:2, and cholesterol intake less than 200 mg/day. Breast feeding or formula was advised during the first year with skim milk thereafter. High intake of vegetables, fruits, berries, and whole grains was specifically recommended beginning at 1 year. Control children (n=522) received diet recommendations routinely provided at Finnish well-child clinics, including cow's milk with 1.9% fat after 1 year of age. Intervention children were followed with serial evaluations including 4-day diet records, beginning at 13 months of age.

Through 20 years of follow-up, there were no differences in growth or pubertal maturation between groups. Beginning at the 13 month assessment and extending to age 20 years, intervention children consumed significantly less total and saturated fat and more polyunsaturated fat than controls. From 13 months to 7 years, intervention children had significantly lower TC and LDL-C; after age 7, the difference was only significant in males. Longitudinal analyses showed that TC and LDL-C levels were consistently lower in intervention participants [28]. Repeated dietary counseling did not reduce the prevalence of overweight but it did reduce the clustering of overweight-related cardiometabolic risk factors [29].

At 7 years of age, a subsample of 200 children from each group underwent determination of serum glucose and insulin concentrations and calculation of HOMA-IR, Homeostatic Model Assessment for Insulin Resistance. From age 15 years onwards, all participants had annual glucose and insulin determinations. HOMA-IR was significantly lower in intervention children at 7 years of age and then repeatedly between 15 and 20 years [30–32].

Late follow-up occurred 6 years after the trial ended when participants averaged 26 years of age. Intervention subjects had lower intake of cholesterol and saturated fat, and higher polyunsaturated to saturated fat ratio, as well as higher consumption of fiber, vegetables, fruit, and berries [33]. Mean serum TC and LDL-C concentrations were lower in intervention participants than in controls, although differences were not significant. Longitudinal analyses showed consistently lower levels of TC and LDL-C in intervention participants through 6 years post study completion [34].

At the post-intervention evaluation, serum glucose and IR were significantly lower in intervention subjects; longitudinal analyses showed similar, consistently lower insulin concentration and HOMA-IR [35]. A greater proportion of intervention group participants had ideal TC and optimal LDL-C, and significantly more had the combination of three ideal factors (TC

<5·17 mmol/L [<200 mg/ml]; glucose <5·6 mmol/L [<101 mg/dL]; BP <120/<80 mm Hg) than did controls [36].

In summary, 6 years post a 20-year, infant-onset dietary intervention, cardiometabolic health benefits observed in the STRIP trial were preserved into young adulthood. Intervention subjects continued to have better overall dietary quality with sustained, better cardiometabolic risk profile indicated by lower serum TC, LDL-C, and glucose levels and better insulin sensitivity.

The STRIP trial showed convincingly that nutritional interventions can be safely introduced in youth and sustained throughout childhood with long-term beneficial results.

Management of CD: Limitations of Current Recommendations

Current guidelines recommend screening for lipid abnormalities only after 2 years of age if/when an established risk factor is identified or with universal screening at 9 to 11 and 17 to 19 years of age [4]. But CD with obesity most often emerges in the setting of a familial/genetic context and a shared environment, both present from birth. Diet habits and food preferences develop beginning in infancy and persist through life, and through generations in families [37]. Activity patterns also begin in childhood and are also shaped by family behaviors. This means that the lifestyle that promotes development of CD will typically be well established before identification by lipid testing. Changing established behaviors is difficult to accomplish and even harder to maintain. Results from longitudinal studies in the i3C Consortium provide convincing evidence that childhood obesity, dyslipidemia, and insulin resistance predict adult CVD and T2DM. The STRIP trial shows conclusively that beneficial nutrition behaviors can begin in infancy and be sustained into young adult life. This evidence provides the evidence infrastructure for a primordial approach to prevention of CD.

Prevention of Combined Dyslipidemia—a Primordial Approach

Identifying the High-Risk Infant

The primordial approach aims to prevent development of CD and obesity and the metabolic precursor that accompanies them, IR. The approach combines the proven method of repeated, focused nutrition counseling from the STRIP trial with routine care measures from the American Academy of Pediatrics (AAP) for all children, and the dyslipidemia detection and management algorithms from the NHLBI guidelines. Primordial prevention is embedded in routine pediatric care and begins with identification of a newborn in a high-risk family setting of obesity, diabetes or treated dyslipidemia in a parent or sibling, with/without a family history of premature CVD.

- **Family obesity** is a powerful predictor of obesity in a child, reflecting the impact of genetic and environmental factors. A child with one obese parent has a 50% chance of being obese. When both parents are obese, their children have an 80% risk of obesity. In two-child families, having an obese sibling is associated with five times greater risk of obesity than if the sibling were not obese [38].
- **Insulin resistance** as a precursor to type 2 diabetes also has a strong familial basis with a 40% risk of developing T2DM if present in one parent, increasing to 70% if present in both [39, 40].
- **Family history of dyslipidemia** of any type significantly increases the risk for abnormal lipids in a child, with the magnitude of risk varying with the lipid diagnosis. Parents are often not aware of a specific dyslipidemia diagnosis so knowledge of any lipid disorder in a parent is considered an important risk magnifier for the development of dyslipidemia in a child.
- **Family history of premature CVD** encompasses the net effect of the unique combination of predisposing genetic and environmental factors in a particular family. For adults, a positive family history is defined as a parent and/or sibling with a history of treated angina, myocardial infarction, percutaneous coronary catheter intervention or coronary artery bypass before 55 years in men or 65 years in women. Because parents and siblings of children and adolescents are young themselves, history in pediatrics is expanded to include premature CVD in grandparents, aunts, and uncles: an expanded first-degree pedigree. In adults, a positive family history of premature CVD doubles baseline risk for CVD, with offspring risk inversely related to age at the index event [41]. In young subjects, autopsy findings and vascular abnormalities correlate with a family history of premature CVD [42]. Family history cannot be modified or prevented but knowledge of its presence is important risk information.

In the primordial prevention approach, the first step is a baseline evaluation of these RFs in a family, identifying a newborn at significant risk to develop CD, obesity, and IR in childhood and manifest CVD in adult life. A baseline family history of premature CVD in an expanded first-degree pedigree is obtained for every newborn, to be updated every 3–5 years. A specific family history of obesity, dyslipidemia, and/or T2DM in parents or siblings is established as part of the baseline risk evaluation. More than 40% of Americans are obese, 60% of obese individuals have dyslipidemia, typically CD, and 89% of individuals with type 2 diabetes are overweight or obese—thus, this RF pattern is extremely prevalent [43–45]. Identifying any of these RFs alone or in

combination in a family alerts the child care provider to the importance of preventing their development beginning in infancy. The intervention itself is simple—focused attention on specific recommendations that are already part of routine care measures from the AAP for care of all children [46].

Identification of the high-risk setting is followed by introduction of this concept to the baby's parent(s), framed as an opportunity to improve future health outcomes. The pediatric care provider initiates the intervention with a brief educational discussion of the cardiometabolic risk in the family based on their combination of a positive family history of premature CVD, obesity, lipid abnormalities, and/or diabetes—a simple family history diagram can be very helpful in educating a family about their newborn's risk for development of future CVD. If unavailable, lipid profile evaluation of parents is recommended. A heart symbol on the health care record is suggested, identifying the baby to the family and the practice as receiving special care. This newborn period discussion initiates the primordial intervention linked to recommendations made by AAP/Bright Futures for preventive health care from birth to 20 years of age [46].

Diet and Nutrition

Birth to 2 years:

Changes in weight status in infancy influence risk of obesity significantly, with more rapid increases in weight for length in the first 6 months of life associated with sharply increased risk of obesity at 3 years of age [47]. Such findings mark diet and nutrition guidance in the first year of life as critical for the high-risk newborn. AAP Guidelines address multiple nutrition topics in the first 2 years of life and pediatric care providers can use these interactions in a high-risk baby to focus on appropriate nutrition to optimize normal growth with matched weight-for-height proportions. Specific intervention steps include:

- Encourage exclusive breastfeeding for as long as possible – longer breastfeeding duration reduces overnutrition later in life by influencing the type and timing of introduction of complementary foods.
- Delay introduction of solid foods to 4 months – for a child at high risk of obesity, the pediatric health care provider can emphasize this delay in the introduction of cereal and the need for this to be spoon fed, never added to bottle feeds.
- Chart height and weight at each visit and share findings with the family – this is an effective way to educate parents about matching velocities for height and weight gain over time.
- Delay introduction of juice – AAP guidelines recommend that juice should never be introduced to infants before 12 months of age and should be limited to maximally 4 ounces/day in toddlers, 1 through 3 years of age, and 4 to 6 ounces/day through 6 years of age. For the infant at risk of obesity, this limit should be emphasized and parents instructed to never give juice by bottle.
- As more solid foods are introduced in the second half of the first year, focus on self-feeding of fruits and vegetables rather than spoon feeding of sweets and processed grains. Teach parents that this early period of diet transition shapes subsequent food selection and improves diet quality.
- At a year of age when children are transitioning from breast or bottle feeding, recommend skim milk by cup.
- Offer no sugar-sweetened beverages (SSBs) – children less than 1 year of age should not be given beverages with any added sugars.
- Use repeated review of growth chart information with parents to emphasize the primordial prevention focus on healthy growth of their baby.

Throughout, these special efforts represent safe and effective obesity prevention steps, in a period when food habits are first established [37, 48]. The rationale for and the importance of these recommendations are repeatedly reinforced with the family.

>2–11 years of age:

As children grow, questions continue to arise about growth, food choices, portion size, and eating patterns. This is a time when healthy diet education by the pediatric care provider is critical.

- A simple, straightforward approach comes from Bright Futures: 5 servings of fruits and/or vegetables/day and no intake of sugar-sweetened beverages.
- Excessive weight gain is a specific issue in these high-risk children so calculation of appropriate energy intake for age, gender, and activity is important and often revealing. Daily energy (calorie) estimates for age, sex, and activity level determined by the Institute of Medicine are provided in the NHLBI guidelines [4].
- While special diet recommendations can be introduced and maintained in infancy, children over 2 usually eat with other family members so an appropriate diet for the whole family needs to be in place. As part of the NHLBI guidelines, a DASH eating plan was adapted for children and adolescents. Recommendations are for all children and are suitable for family use. They reflect appropriate diet composition for children at risk for CD and obesity. Available in the NHLBI guidelines, the plan is organized for daily calorie intake and by servings/day/food group [4].
- Consultation with a registered dietitian can guide a family towards this optimal eating plan.

- Beginning at 2 years of age, BMI is calculated at each periodic health visit and charted for age with BMI ≥ 95th percentile defined as obese and between the 85th and 95th percentiles as overweight.
- Growth over time should be followed very carefully in these high-risk children. A child or adolescent with a consistently high BMI percentile is at high risk of sustained obesity and CD in adult life [25, 49].
- Accelerated weight gain with weight increase crossing growth chart percentiles while height percentile is stable is a health care emergency for the high-risk child. The physician should step in as soon as possible, identifying the problem for the family. Sharing the growth chart findings is a useful way to introduce a focused plan to address excessive weight gain. Estimation of current caloric intake using a food diary and calculation of appropriate intake for age, sex, and activity allows development of a plan to gradually decrease calories towards the appropriate level over several weeks.
- Take-home diet recommendations and/or growth chart findings can be very helpful.

Screening for dyslipidemia

- The NHLBI guidelines recommend universal lipid screening at 9–11 years of age. If a child is shown to have CD, the NHLBI algorithm for management of CD should be implemented [4].
- Specific diet recommendations include referral to a registered dietitian for counseling on the CD-recommended diet.

Screening for insulin resistance (IR)/T2DM

- Screening for IR/T2DM is controversial with no recommendations addressing this in the AAP guidelines. By contrast, the American Diabetic Association recommends screening with a fasting glucose beginning at 10 years of age and every 2 years thereafter in children with BMI above the 85th percentile plus 2 of the following: positive family history of T2DM; presence of acanthosis nigricans, CD, or polycystic ovary syndrome; high-risk race/ethnicity. The NHLBI guidelines recommend this approach and given the strong association between CD, obesity, and IR/T2DM, these recommendations are appropriate for the high-risk child [4].

Adolescence (>12–20 years):

Adolescence is characterized by growing independence and separation from family authority; in the context of primordial prevention, this shift requires the health care provider to foster an independent relationship with the emerging young adult. Continued periodic health supervision during adolescence is important for anticipatory guidance and reinforcement of the nutritional behaviors that began in infancy.

- Energy requirements increase disproportionately with the growth spurt of adolescence, also a time when nutritional needs are less likely to be met at home. An independent meeting with the adolescent allows the health care provider to review the "high risk" identification and the association of RFs with premature CVD.
- A straightforward description of the nutrition intervention that began in infancy allows the provider to present the most critical elements: matching activity needs to energy intake; daily intake of at least 5 servings of fruits and vegetables; and no intake of sugar-sweetened beverages (SSBs).
- Particular attention is needed to SSBs which contribute 10 to 15% of caloric intake and are the primary source of added sugar in the diets of youth [50, 51]. From the NHLBI Dash diet with recommendations for sugar intake based on age, sex, and activity level, the high concentration of sugars in SSBs essentially eliminates them in the diet of a healthy adolescent. In a high-risk child who has been managed from infancy, this will always have been the case but reinforcement of the recommendations with the adolescent him/herself at this stage is important, especially since sports drinks are often very high in sugar.
- A disproportionate increase in weight for height on an adolescent's growth chart is a critical red flag since approximately 80% of obese adolescents will be obese in adulthood [24, 49, 52]. The onset of accelerated weight gain is a critical time for referral of the teenager her/himself to a registered dietitian for diet counseling.
- Lipid screening should be repeated at 17–19 years of age and followed as outlined in the NHLBI algorithm [4].

Activity Recommendations

Activity is the second important area for specific attention in children identified as high risk. Aerobic activity facilitates the hydrolysis and utilization of TGs in skeletal muscle, reducing deposition as adipose tissue. In multiple trials in youth with CD, aerobic exercise interventions significantly decreased TG levels and increased HDL-C, proportionate to activity intensity and duration. The Bright Futures and NHLBI guidelines and the Guidelines for Healthy Activity in Americans outline activity recommendations beginning in infancy [4, 46, 53].

Infancy:

- Before 2 years of age, the primary recommendation is complete avoidance of screen time.

- Parents are encouraged to create an environment that models an active lifestyle with moderate sedentary time.

2–4 years of age:

- For toddlers 2 to 4 years of age, unlimited active playtime is encouraged and screen time of any kind is limited to maximally 1–2 h per day.
- Television in a child's bedroom is explicitly excluded.
- Ask parents to model an active lifestyle with a family activity at least once a week.

5 to 10 years of age:

- All children should participate in moderate-to-vigorous activity every day with simultaneous limitation of leisure screen time to less than 2 h per day.
- Involvement in school or community sports is one way to achieve this but the pediatrician often needs to work with busy families to find a way to start and maintain a child's activity.
- Given the ubiquity of access to personal screens in even the youngest children, addressing those limitations is as important as recommending activity.
- Family activity at least once a week is again encouraged.
- Educating children and families on the appropriate intensity level with aerobic activity is important to achieve maximum exercise benefits. If doing nothing is 0 and the highest level is 10, then moderate intensity is 5 or 6, associated with a perceptible increase in heart and breathing rates. Vigorous intensity begins at a level of 7 or 8 with much faster heart and breathing rates. To achieve activity benefits, youth aged 5 to 18 years require a minimum of 60 min of at least moderate intensity activity every day with aerobic activities as the majority and vigorous intensity whenever possible [54]. This level and duration of exercise is even more important for high-risk children.
- The pediatric health care provider explicitly reinforces the activity recommendations by taking an activity/screen time history at least once a year with the child and parent.

Adolescents (12–18 years of age):

- Activity guidelines for teenagers extend the recommendations for younger children—adolescents need 1 h every day of moderate activity and vigorous activity at least 3 days/week.
- Families should discourage leisure screen time in an adolescent's bedroom and when possible, limit total daily screen time. This is a significant challenge given the importance of all forms of screen time (including educational) for most teenagers.
- To reinforce the recommendations, the pediatric care provider takes a personal history of activity and screen time directly from the adolescent at health supervision visits. Review of the specific health care benefits of activity can be motivating [54, 55].
- There are current efforts to develop public health–based activity interventions for youth but until these are achieved, the pediatrician needs to help the adolescent and family find an activity schedule that works for that individual [56, 57].

Conclusion

In youth, CD—the combination of high TGs and reduced HDL-C—is a prevalent, highly atherogenic lipid disorder, almost always associated with obesity and frequently with insulin resistance/T2DM. New findings from international longitudinal studies provide convincing evidence that these childhood RFs predict CVD in adult life. Randomized trial results show that diet interventions begun in infancy are safe and effective. For established CD, primary therapy is lifestyle change focused on weight loss, diet composition change, and increased activity, usually very effective in the short term. This paper proposes a new concept: primordial prevention of CD beginning in the newborn identified as having high familial risk for premature CVD, using a focused version of recommended diet/nutrition and activity guidelines for all children. Optimizing diet and activity beginning in infancy and extending these benefits through adolescence have the potential to prevent RF development and thereby reduce progressive atherosclerosis and clinical CVD.

Declarations

Conflict of Interest Rae-Ellen W. Kavey has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Shiels MS, Haque AT, Berrington de González A, et al. Leading causes of death in the US during the COVID-19 pandemic, March 2020 to October 2021. JAMA Intern Med. 2022;182(8):883–6. https://doi.org/10.1001/jamainternmed.2022.2476.
2.• Jacobs DR, Woo JG, Sinaiko AR, et al. Childhood cardiovascular risk factors and adult cardiovascular events. N Engl J Med. 2022;386(20):1877–88. https://doi.org/10.1056/NEJMoa2109

191. **The International Childhood Cardiovascular Cohort Consortium (i3C) is a collaboration of seven large, longitudinal studies which measured CV RFs in children who were then followed into adulthood. Analyses from this collaboration now provide strong evidence associating childhood dyslipidemia and obesity with CVD events in adult life.**

3. Morrison JA, Glueck CJ, Horn PS, et al. Pediatric triglycerides predict cardiovascular disease events in the fourth to fifth decade of life. Metabolism. 2009;58(9):1277–84.
4. National Heart, Lung and Blood Institute Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Pediatrics. 2011;128(Suppl 5):S213–56. www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm.
5. Kit BK, Kuklina E, Carroll MD, et al. Prevalence of and trends in dyslipidemia and blood pressure among US children and adolescents, 1999-2012. JAMA Pediatr. 2015;169:272.
6. Perak AM, Ning H, Kit BK, et al. Trends in levels of lipids and apolipoprotein B in US youths aged 6 to 19 years, 1999-2016. JAMA. 2019;321(19):1895–905. https://doi.org/10.1001/jama.2019.4984.
7. Centers for Disease Control and Prevention (CDC). Prevalence of abnormal lipid levels among youths —United States, 1999–2006. Morb Mortal Wkly Rep. 2010;59(2) http://www.cdc.gov/nchs/nhanes.htm
8. Hu K, Staino AE. Trends in obesity prevalence among children and adolescents aged 2 to 19 years in the US from 2011 to 2020. JAMA Pediatr. 2022;176(10):1037–9.
9. Gill PK, Hegele RA. Familial combined hyperlipidemia is a polygenic trait. Curr Opin Lipidol. 2022;33(2):126–32. https://doi.org/10.1097/MOL.0000000000000796.
10. Burns SF, Lee SJ, Arslanian SA. Surrogate lipid markers for small dense low-density lipoprotein particles in overweight youth. J Pediatr. 2012;161(6):991–6.
11. Cromwell WC, Otvos JD, Keyes MJ, et al. LDL particle number and risk of future cardiovascular disease in the Framingham Offspring Study – implications for LDL management. J Clin Lipidol. 2007;1(6):583–92.
12. Turer CB, Brady TM, de Ferranti SD. Obesity, hypertension, and dyslipidemia in childhood are key modifiable antecedents of adult cardiovascular disease. Circulation. 2018;137:1256–9. https://doi.org/10.1161/CIRCULATIONAHA.118.032531.
13. Bao W, Srinivasan SR, Berenson GS. Persistent elevation of plasma insulin levels is associated with increased cardiovascular risk in children and young adults. The Bogalusa Heart Study. Circulation. 1996;93(1):54–9. PMID: 8616941. https://doi.org/10.1161/01.cir.93.1.54.
14. Hannon TS, Bacha F, Lee SJ, et al. Use of markers of dyslipidemia to identify overweight youth with insulin resistance. Pediatr Diabetes. 2006;7:260–6.
15. De Ferranti SD, Gauvreau K, Ludwig DS, et al. Prevalence of the metabolic syndrome in American adolescents: findings from the third national health and nutrition survey. Circulation. 2004;110:2494–7.
16. Morrison JA, Friedman LA, Gray-McGuire C. Metabolic syndrome in childhood predicts adult cardiovascular disease 25 years later: the Princeton Lipid Research Clinics Follow-up Study. Pediatrics. 2007;120:340–5.
17. Ferranti SD, Newburger JW. Dyslipidemia in children: management. Waltham, MA, USA: UpToDate; 2020.
18.• Kavey RE. Combined dyslipidemia in children and adolescents. In: Endotext [Internet]. South Dartmouth(MA): MD Text.com, Inc.; 2000–2020. www.endotext.org. **This review describes the contemporary approach to a diagnosis of combined dyslipidemia in childhood**.
19. Valaiyapathi B, Sunil B, Ashraf AP. Approach to hypertriglyceridemia in the pediatric population. Pediatr Rev. 2017;38(9):424–34. https://doi.org/10.1542/pir.2016-0138.
20. Pratt RE, Kavey RE, Quinzi D. Combined dyslipidemia in obese children: response to a focused lifestyle approach. J Clin Lipidol. 2014;8:181–6. https://doi.org/10.1016/j.jacl.2014.01.003.
21. Jacobson TA, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 2. J Clin Lipidol. 2015;9:S1–S122. https://doi.org/10.1016/j.jacl.2015.09.002.
22. Dwyer T, Sun C, Magnussen CG, et al. Cohort Profile: the International Childhood Cardiovascular Cohort (i3C) consortium. Int J Epidemiol. 2013;42(1):86–96. https://doi.org/10.1093/ije/dys004. Epub 2012 Mar 20. PMID: 22434861 PMCID: PMC3600617
23. Sinaiko AR, Jacobs DR, Wee JG, et al. The International Childhood Cardiovascular Cohort (i3C) consortium outcomes study of childhood cardiovascular risk factors and adult cardiovascular morbidity and mortality: Design and recruitment. Contemp Clin Trials. 2018;69:55–64. https://doi.org/10.1016/j.cct.2018.04.009. Epub 2018 Apr 22
24. Woo JG, Zhang N, Fenchel M, et al. Prediction of adult class II/III obesity from childhood BMI: the i3C consortium. Int J Obes (Lond). 2019;44 https://doi.org/10.1038/s41366-019-0461-6.
25. Yan Y, Bazzano LA, Juonala M, et al. Long-term burden of increased body mass index from childhood on adult dyslipidemia: the i3C consortium study. J Clin Med. 2019;8(10) pii: E1725 https://doi.org/10.3390/jcm8101725.
26. Hu T, Jacobs DR Jr, Sinaiko AR, et al. Childhood BMI and fasting glucose and insulin predict adult type 2 diabetes: The International Childhood Cardiovascular Cohort (i3C) Consortium. Diabetes Care. 2020;43(11):2821–9. https://doi.org/10.2337/dc20-0822.
27.• Lapinleimu H, Viikari J, Jokinen E, et al. Prospective randomized trial in 1062 infants of diet low in saturated fat and cholesterol. Lancet. 1995;345:471–6. https://doi.org/10.2337/dc18-0869. **The Special Turku Coronary Risk Factor Intervention Project (STRIP) was a prospective, randomized trial which began in 1990 when subjects were 7 months of age and continued for 20 years. Intervention children received individualized diet counseling, aimed at achieving a low fat, low saturated fat, and low cholesterol diet. Throughout the study and at 6-year post evaluation, intervention subjects had lower fat and saturated fat intake. Longitudinal analyses showed consistently lower levels of TC and LDL-C in intervention participants. At the post evaluation, serum glucose and IR were also significantly lower in intervention subjects. The STRIP trial showed convincingly that nutritional interventions can be safely introduced in youth and sustained throughout childhood with long-term beneficial results.**
28. Niinikoski H, Pahkala K, Ala-Korpela M, et al. Effect of repeated dietary counseling on serum lipoproteins from infancy to adulthood. Pediatrics. 2012;129:e704–13. https://doi.org/10.1542/peds.2011-1503.
29. Kahanen M, Lagstrom H, Pahkala K, et al. Dietary and lifestyle counselling reduces the clustering of overweight-related cardiometabolic risk factors in adolescents. Acta Paediatr. 2010;99(6):888–95. PMID: 20002624. https://doi.org/10.1111/j.1651-2227.2009.01636.
30. Oranta O, Pahkala K, Ruottinen S, et al. Infancy-onset dietary counseling of low-saturated-fat diet improves insulin sensitivity in healthy adolescents 15-20 years of age: the Special Turku Coronary Risk Factor Intervention Project (STRIP) study. Diabetes Care. 2013;36:2952–9. https://doi.org/10.2337/dc13-0361.
31. Niinikoski H, Jula A, Viikari J, et al. Blood pressure is lower in children and adolescents with a low-saturated-fat diet since

infancy: the special Turku coronary risk factor intervention project. Hypertension. 2009;53:918–24. https://doi.org/10.1161/HYPERTENSIONAHA.109.130146.
32. Pahkala K, Hietalampi H, Laitinen TT, et al. Ideal cardiovascular health in adolescence: effect of lifestyle intervention and association with vascular intima-media thickness and elasticity (the Special Turku Coronary Risk Factor Intervention Project for Children [STRIP] study). Circulation. 2013;127:2088–96. https://doi.org/10.1161/CIRCULATIONAHA.112.000761.
33. Lehtovirta M, Matthews LA, Laitinen TT, et al. Achievement of the targets of the 20-year infancy-onset dietary intervention-association with metabolic profile from childhood to adulthood. Nutrients. 2021;13(2):533. PMID: 33562015 PMCID: PMC7915301. https://doi.org/10.3390/nu13020533.
34. Pahkala K, Laitinen TT, Niinikoski H, et al. Effects of 20-year infancy-onset dietary counselling on cardiometabolic risk factors in the Special Turku Coronary Risk Factor Intervention Project (STRIP): 6-year post-intervention follow-up. Lancet Child Adolesc Health. 2020;4(5):359–69. https://doi.org/10.1016/S2352-4642(20)30059-6.
35. Nupponen M, Pahkala K, Juonala M, et al. Metabolic syndrome from adolescence to early adulthood: effect of infancy-onset dietary counseling of low saturated fat: the Special Turku Coronary Risk Factor Intervention Project (STRIP). Circulation. 2015;131(7):605–13. https://doi.org/10.1161/CIRCULATIONAHA.114.010532. Epub 2015 Jan 20
36. Laitinen TT, Nuotio J, Juonola H, et al. Success in achieving the targets of the 20-year infancy-onset dietary intervention: association with insulin sensitivity and serum lipids. Diabetes Care. 2018;41(10):2236–44. https://doi.org/10.2337/dc18-0869.
37. Patrick H, Nicklas TA. A review of family and social determinants of children's eating patterns and diet quality. J Amer Coll Nutrition. 2005;24(2):83–92. https://doi.org/10.1080/07315724.2005.10719448.
38. Pachuki MC, Lovenheim M, Harding M. Within-family obesity associations: evaluation of parent, child, and sibling relationships. Amer J Prev Med. 2014;47(4):382–91. https://doi.org/10.1016/j.amepre.2014.05.018.
39. Marateb HR, MohebbianR KR, et al. Prediction of dyslipidemia using gene mutations, family history of diseases and anthropometric indicators in children and adolescents: the CASPIAN-III study. Comput Struct Biotechnol J. 2016;(Suppl. 5) https://doi.org/10.1016/j.csbj.2018.02.009.
40. Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: the Framingham offspring study. Diabetes. 2000;49:2201–7. https://doi.org/10.2337/diabetes.49.12.2201.
41. Lloyd-Jones DM, Nam BH, D'Agostino RB Sr, et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. JAMA. 2004;291(18):2204–11.
42. Gaeta G, De Michele M, Cuomo S, et al. Arterial abnormalities in the offspring of patients with premature myocardial infarction. N Engl J Med. 2000;343(12):840–6.
43. Adult Obesity Facts. Centers for Disease Control and Prevention. 2021; https://www.cdc.gov/obesity/data/adult.html
44. Obesity and Dyslipidemia. Edited by Feingold KR, Anawalt B, Boyce A, et al. South Dartmouth (MA): MDText.com, Inc.; 2020. www.endotext.org.
45. National Diabetes Statistics Report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2020.
46. Bright Futures. Guidelines for Health Supervision of Infants, Children and Adolescents. Fourth edition. American Academy of Pediatrics. Edited by Hagen JF, Shaw JS, Duncan PM. Publication Date: February 21, 2018. https://www.aap.org/en/practice-management/bright-futures/bright-futures-materials-and-tools/bright-futures-guidelines-and-pocket-guide/.
47. Taveras EM, Rifas-Shiman SL, Belfort MB, et al. Weight status in the first 6 months of life and obesity at 3 years of age. Pediatrics. 2009;123(4):1177–83. https://doi.org/10.1542/peds.2008-1149. PMID: 19336378; PMCID: PMC2761645
48. Birch LL, Anzman-Frascaa PIM. Starting early: obesity prevention during infancy. In: Drewnowski A, Rolls BJ, editors. Obesity treatment and prevention: new directions. Nestlé Nutr Inst Workshop Ser, vol. 73; 2012. p. 81–94. Nestec Ltd., Vevey/S. Karger AG. Basel, ©.
49. Guo SS, Wu W, Chumlea WC, Roche AF. Predicting overweight and obesity in adulthood from body mass index values in childhood and adolescence. Am J Clin Nutr. 2002;76(3):653–8. https://doi.org/10.1093/ajcn/76.3.653.
50. Keller A, Bucher Della Torre S. Sugar-sweetened beverages and obesity among children and adolescents: a review of systematic literature reviews. Child Obes. 2015;11(4):338–46. https://doi.org/10.1089/chi.2014.0117. PMID: 26258560; PMCID: PMC4529053
51. Field AE, Sonneville KR, Falbe J, et al. Association of sports drinks with weight gain among adolescents and young adults. Obesity (Silver Spring). 2014;22(10):2238–43. https://doi.org/10.1002/oby.20845. PMID: 25044989; PMCID: PMC4180814
52. Simmonds M, Llewellyn A, Owen CG, Woolacott N. Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. Obes Rev. 2016;17(2):95–107. https://doi.org/10.1111/obr.12334. Epub 2015 Dec 23
53. Guidelines for Physical Activity in Americans. U.S. Department of Health and Human Services. Centers for Disease Control and Prevention. Division of Nutrition, Physical Activity, and Obesity. Office of Disease Prevention and Health Promotion; 2020. HealthyPeople.gov website. https://www.healthypeople.gov/2020/topics
54. Janssen I, LeBlanc AG. Systematic review of the health benefits of physical activity and fitness in school-aged children and youth. Int J Beh Nutr Phys Activity. 2010;7:40–56.
55. Davis CL, Pollock NK, Waller JL, et al. Exercise dose and diabetes risk in overweight and obese children A randomized controlled trial. JAMA. 2012;308(11):1103–12.
56. Bustamante EE, Ramer JD, Santiago-Rodríguez ME, et al. The S.P.A.C.E hypothesis: physical activity as medium — not medicine — for public health impact. Exerc Sport Sci Rev. 2021;49(2):133–45. https://doi.org/10.1249/JES.0000000000000248.
57. Pate RR, Dowda M. Raising an active and healthy generation: a comprehensive public health initiative. Exerc Sport Sci Rev. 2019;47(1):3–14. https://doi.org/10.1249/jes.0000000000000171. PMID: 30334849

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