Cardiovascular risk factor investigation: a pediatric issue

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Objectives: To correlate cardiovascular risk factors (e.g., hypertension, obesity, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, sedentariness) in childhood and adolescence with the occurrence of cardiovascular disease.


Summary of findings: Risk factors for atherosclerosis are present in childhood, although cardiovascular disease arises during adulthood. This article presents the main studies that describe the importance of investigating the risk factors for cardiovascular diseases in childhood and their associations. Significant rates of hypertension, obesity, dyslipidemia, and sedentariness occur in children and adolescents. Blood pressure needs to be measured in childhood. An increase in arterial blood pressure in young people predicts hypertension in adulthood. The death rate from cardiovascular disease is lowest in children with lower cholesterol levels and in individuals who exercise regularly. In addition, there is a high prevalence of sedentariness in children and adolescents.

Conclusions: Studies involving the analysis of cardiovascular risk factors should always report the prevalence of these factors and their correlations during childhood because these factors are indispensable for identifying an at-risk population. The identification of risk factors in asymptomatic children could contribute to a decrease in cardiovascular disease, preventing such diseases as hypertension, obesity, and dyslipidemia from becoming the epidemics of this century.

Keywords: Cardiovascular risk, Children, Hypertension, Obesity, Dyslipidemia, Sedentariness, Metabolic syndrome.
risk factors identified in adults, and minimizing or reducing these known risk factors is prudent.\textsuperscript{7,8} Therefore, investigating risk factors for that stage of life is fundamentally important, because these risk factors can have profound implications for disease manifestations in adulthood.\textsuperscript{9–12}

Sources

In this systematic review, we analyze the main cardiovascular risk factors present in childhood and their prevalence. Electronic searches were conducted for selected articles from PubMed, SciELO, and Cochrane from 1992 to 2012 using the following terms: physical activity, cardiovascular risk factors, obesity in childhood, children and adolescents, hypertension in childhood, and atherosclerotic disease. Searches for books, dissertations, and theses were performed using the Google Scholar search tool. There was no language restriction. Four researchers independently evaluated the titles that were identified in the initial search. Two authors independently reviewed the articles selected from the initial search for methodological quality, number of subjects studied, and results demonstrated. Studies with dubious methodologies or with very low numbers of assessed individuals and studies that repeated information that was available in other studies were excluded. In the latter case, preference was given to the most recent study and to the study with the greatest number of individuals assessed, respectively. Disagreements were resolved by consensus. The identification of risk factors in children in combination with cooperative action by public agencies and medical professionals, especially pediatricians and cardiologists, can produce positive effects for one of the world’s major public health problems. Table 1 shows the distribution of the references according to continent and country.

### Cardiovascular risk factors

#### Overview of associated factors

The finding that AD begins at an early stage of life reveals childhood and adolescence as critical periods for the detection of risk factors for cardiovascular disease and the prevention of future complications. Monitoring these factors would help identify early signs that when modified can mitigate or even reverse the progression of those dysfunctions. A range of risk factors, including genetic factors, hypertension, dyslipidemia, obesity, metabolic syndrome (MS), an atherogenic diet, and physical inactivity, is associated with cardiovascular disease, and the prevalence of these factors is increasing among children and adolescents.\textsuperscript{13–17}

Lifestyle and eating habits are fundamentally important for protection against the manifestation and progression of AD risk factors. AD is considered the main causal factor for cardiovascular disease,\textsuperscript{18,19} and therefore should be a key target of heart disease-prevention programs.\textsuperscript{20} The emphasis is on hypercholesterolemia, hypertriglyceridemia, overweight, hyperglycemia, hypertension, and physical inactivity.\textsuperscript{21} Correlations between the plasma levels of cholesterol and a decrease or delay in AD progression by means of diet and lifestyle changes have been documented,\textsuperscript{22} with the hypothesis that for each 1% reduction in total cholesterol, a decrease of 2% in the occurrence of coronary artery disease was observed. Studies have also reported that the degree of atherosclerosis in children and young adults can be correlated with the same risk factors that have been identified in adults. Therefore, an increase in the incidence of cardiovascular disease is likely to occur when current teens enter adulthood. Thus, as in other age-groups, it is prudent to minimize or reduce risk factors in youth.\textsuperscript{7}

### Atherosclerosis

Although AD becomes symptomatic later in life, the early identification and modification of risk factors can reduce its later incidence.\textsuperscript{1} These diseases are currently the most common causes of death. Studies suggest that the AD process is as old as the human species.\textsuperscript{3,22} AD begins in childhood; therefore, its prevention should begin early, because at this stage it is considered reversible, with high levels of blood lipoproteins playing a fundamental role in its manifestation.\textsuperscript{24} In children, fatty streaks in the aorta, although reversible,
arise at around 3 years of age and already compromise 15% of this artery by 15 years of age. Several studies cited by Françoso and Coates present evidence of fatty streaks and fibrous plaques in the coronary arteries of adolescents between 10 and 14 years of age and thickening of the inner layer (intima) of the coronary arteries in children less than 5 years of age. Researchers have demonstrated that a fatty diet and other traditional vascular risk factors begin to influence blood lipid levels during the early years of life.6,23

Due to the variety of criteria used to define optimal lipid levels in adolescents, it is difficult to compare results from across the world. However, studies have shown, for example, the presence of atheromatosis in aortic intima with cholesterol levels between 140 and 170 mg/dL. Thus, the epidemiological goals for plasma cholesterol in children would be an average of 150 mg/dL.8

In a review of studies conducted in 26 countries (from 1975 to 1996) involving 60,494 children and adolescents aged 2–19 years, Brotons et al24 found an average of 165 mg/dL for cholesterol, 60 mg/dL for HDL-cholesterol, and 67 mg/dL for triglycerides. Table 2 demonstrates the lipid levels recommended in adolescents up to 19 years of age.26

Studies conducted in Brazil revealed higher levels of cholesterol in adolescents attending private schools compared to those attending public school.11,27 This trend was confirmed by other studies that showed that adolescents with lower family income and those that attend public schools have lower cholesterol levels than adolescents from higher-income families and private schools. These data support Guimarães’s and Guimarães’s proposition that families with higher socioeconomic levels do not necessarily have a better and healthier lifestyle. The lower household income in developing countries may prevent these children from consuming high levels of calories in diets heavy in saturated fats and cholesterol. In addition, students of public schools tend to expend more energy in their daily lives because they need to walk to school or use public transportation.

Despite methodological limitations for calculating low-density lipoprotein cholesterol as part of the lipid profile, its measurement is widely regarded as the gold standard for both risk assessment and intervention programs for cardiovascular diseases.8 Because triglycerides are deposited on the vessel wall and initiate the process of low-density lipoprotein accumulation, they are strongly associated with the risk of developing AD.30,31

Whether breastfeeding during the first year of life confers protection against future increases in the levels of plasma

<table>
<thead>
<tr>
<th>Lipids</th>
<th>Desired (mg/dL)</th>
<th>Borderline (mg/dL)</th>
<th>Elevated (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/dL)</td>
<td>&lt;150</td>
<td>150–169</td>
<td>≥170</td>
</tr>
<tr>
<td>LDL-c (mg/dL)</td>
<td>&lt;100</td>
<td>100–129</td>
<td>≥130</td>
</tr>
<tr>
<td>HDL-c (mg/dL)</td>
<td>≥45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGs (mg/dL)</td>
<td>&lt;100</td>
<td>100–129</td>
<td>≥130</td>
</tr>
</tbody>
</table>

**Abbreviations:** TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; TGs, triglycerides.

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**Figure 1** Relationship between cholesterol levels in adolescents and mortality from circulatory diseases in Brazil’s cities.

**Note:** Mortality per 100,000 inhabitants.
Obesity

Obesity (more specifically, excessive adiposity), which is defined as an excessive accumulation of body fat, is a heterogeneous disorder with a common final pathway in which energy intake chronically exceeds energy expenditure. Obesity features a combination of genetic and environmental factors. The energy imbalance often begins in childhood, and when this imbalance occurs the likelihood of obesity in adulthood increases. Among young people, the prevalence of obesity has greatly increased in recent years and represents the most common chronic disorder. Excessive adiposity in childhood represents a greater risk to adult health than obesity starting in adulthood. Adults who were overweight as adolescents have an increased risk of diseases compared with adults who were of normal weight as adolescents. Obesity is the result of a complex interaction of factors, including metabolic, physiological, environmental, genetic, behavioral, and social influences. The Bogalusa Heart Study in Louisiana (USA), which was conducted among children and adolescents, suggested significant correlations between obesity and both lipoprotein levels (low-density lipoprotein in particular) and insulinenia, which were correlated with the risk of cardiovascular diseases.

Although it is unclear if childhood obesity is an independent risk factor for cardiovascular disease, studies show a clear association between severe obesity and increased mortality. The importance of childhood obesity as a risk factor for cardiovascular disease is increasingly evident. Obesity deserves particular attention because it is usually accompanied by two notorious and significant risk factors: diabetes and arterial hypertension. Therefore, controlling obesity during childhood is important because the obesity acquired during this period of life tends to persist into adulthood.

Studies have reported a substantial increase in the number of overweight children and adolescents in recent decades, and this increase is associated with an increased risk of hypertension, lipid abnormalities, type II diabetes, early atherosclerotic lesions, adult obesity, and mortality in young adulthood. Preventing childhood obesity is the best opportunity to introduce changes in lifestyle and thus reduce cardiovascular morbidity and mortality. The diagnosis of overweight and obesity still presents difficulties, because the best criteria to determine these categories in this age-group remain unclear. One of the contested methods is the “cutoff point” for their identification. However, the body mass index, based on international standards, is useful, inexpensive, and replicable. Recently, the term “obesity” has been used to identify body mass index ≥ P95 in children and adolescents.

Data on childhood and adolescent obesity around the world are still limited, and the lack of uniformity among definitions and studied age-ranges complicates comparisons of prevalence. Obesity in children and adolescents is increasing significantly, including in developing countries. A national study, Nutre Brasil Infância (Nourish Brazil Childhood),
indicated that 23% of Brazilian children up to 5 years of age exhibit excess weight,\textsuperscript{56} while in developed countries, obesity mainly affects the lower-income social classes; in Brazil, for example, the most favored social classes are still the most affected, although there is a tendency toward change. The most recent studies conducted in Brazil reveal that the prevalence of overweight in children and adolescents ranges from 8.4% to 19%, while that of obesity ranges from 3.1% to 18%.\textsuperscript{54,57} Furthermore, the prevalence of overweight and obesity is greater in higher-income households.\textsuperscript{58,59} The National Health and Nutrition Examination Survey estimated a prevalence of 30% for overweight and obesity \( \geq P85 \) and a prevalence of 15% for obesity \( \geq P95 \) for the age-group between 6 and 19 years of age.\textsuperscript{60} In Brazil, studies stress the physical inactivity of children as one of the most important factors associated with obesity.\textsuperscript{60–54}

**Metabolic syndrome**

MS is currently characterized as the combination of a number of risk factors for cardiovascular disease, including dyslipidemia, hypertension, carbohydrate-metabolism disorders, and obesity, especially abdominal obesity.\textsuperscript{61} In children, the global consensus regarding MS is still a matter of discussion.\textsuperscript{26} A direct association between obesity and insulin-resistance syndrome has been demonstrated in children, and was recently recognized as a major precursor of atherosclerotic cardiovascular disease and type II diabetes.\textsuperscript{7,62}

Although we do not have a global consensus to define and diagnose MS in adults and children, MS is associated with a 1.5-fold increase in overall mortality and a 2.5-fold increase in cardiovascular mortality.\textsuperscript{63} Given its importance, various organizations, including the World Health Organization,\textsuperscript{64} the National Cholesterol Education Program Adult Treatment Panel III,\textsuperscript{55} the European Group for the Study of Insulin Resistance,\textsuperscript{66} and the International Diabetes Federation, have proposed criteria to define and treat MS.

To determine the prevalence of MS in children and adolescents, either the adult criteria are modified for pediatric reference values,\textsuperscript{67} or specific cutoff points are used.\textsuperscript{68,69} Some studies suggest cutoff points corresponding to the 95th percentiles of each variable by sex and age and the height percentile when including blood pressure (BP).\textsuperscript{70,71} However, the lack of consensus means that the prevalence of this syndrome is markedly different in different studies.\textsuperscript{72} Table 3 demonstrates the definition considered most suitable for MS, according to the Department of Metabolic Syndrome of the Brazilian Society of Diabetes.\textsuperscript{26}

Prospective studies have shown that obesity looms as the most important risk factor for MS and precedes the onset of insulin resistance by several years.\textsuperscript{62,73} Insulin resistance is the leading cause of the hemodynamic and metabolic disorders of MS.\textsuperscript{74} MS is caused by a combination of genetic and environmental factors in which obesity plays a primary role and leads to excessive production of insulin, which is associated with an increase in BP and dyslipidemia.\textsuperscript{50} An estimated 1 million US adolescents already meet the criteria for MS,\textsuperscript{50} with a prevalence of 4% between 12 and 19 years of age. In addition, MS is present in 30%–50% of overweight children.\textsuperscript{67,75}

**Hypertension**

Identified as one of the most common precursors of coronary artery disease, hypertension is usually asymptomatic, and prevention is the most efficient way to fight it and avoid the high social cost of its treatment and complications. Therefore, the need to measure hypertension levels and identify those individuals with high BP is mandatory. The worldwide

**Table 3** Classification of metabolic syndrome in children and adolescents

<table>
<thead>
<tr>
<th>Criteria/components</th>
<th>Age</th>
</tr>
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<tbody>
<tr>
<td>Definition of adiposity</td>
<td>From 6 to 10 years</td>
</tr>
<tr>
<td>Glucose metabolism</td>
<td>WC ( \geq P90 )</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>No defined cutoff value for the diagnosis of metabolic syndrome</td>
</tr>
<tr>
<td>Hypertension</td>
<td>No defined cutoff value for the diagnosis of metabolic syndrome</td>
</tr>
</tbody>
</table>

Abbreviations: WC, waist circumference; TGs, triglycerides; HDL-C, high-density lipoprotein cholesterol; ALD, antilipidemic drug; DBP, diastolic blood pressure; SBP, systolic blood pressure; AHD, antihypertensive drug.
The prevalence of hypertension in children is highly variable (2%–13%), depending on the methodology employed. In Brazil, for example, it is estimated that the prevalence of hypertension in children and adolescents is 4%.76 and the need for BP measurement is considered imperative from 3 years of age. Arterial BP commonly rises with age, and its elevation in children is a prediction of hypertension in adulthood that may have started in childhood or adolescence.7,77–80

BP should be interpreted as a result of the impact of environmental influences on the expression of several genes that in turn regulate other genes. It is influenced by angiotensin-converting enzyme gene expression and for endothelial NO synthase gene expression.81,82 Several known factors related to hypertension in adults, such as sex, age, family history, and the presence of increased body weight or obesity, are also observed in children and adolescents.83 High BP contributes to the development of cardiovascular complications. Its association with multiple risk factors has a multiplier effect on the risk of cardiovascular events.84–86

Hypertension is diagnosed when the values of systolic BP and/or diastolic BP are greater than or equal to the 95th percentile for sex, age, and height, plus 5 mmHg, on three separate occasions. A prehypertensive group should also be defined and identified with the purpose of adopting stringent preventive measures. BP values ≥ 90th percentile and <95th percentile characterize prehypertension; values that are included in this range and exceed the limits of 120/80 mmHg should also be considered as prehypertensive and follow the same recommendations proposed by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)85 for adults. Table 4 summarizes the classification of BP for children and adolescents.87

<table>
<thead>
<tr>
<th>Classification</th>
<th>Percentile for SBP and DBP</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>BP &lt; P90</td>
</tr>
<tr>
<td>Borderline</td>
<td>BP between P90 and P95 or if PA exceeds</td>
</tr>
<tr>
<td></td>
<td>120/80 mmHg, always &gt;90 and &lt; P95</td>
</tr>
<tr>
<td>Hypertension stage 1</td>
<td>P95 to P99 plus 5 mmHg</td>
</tr>
<tr>
<td>Hypertension stage 2</td>
<td>BP &gt; P99 plus 5 mmHg</td>
</tr>
<tr>
<td>White-coat hypertension</td>
<td>BP &gt; P95 in outpatient clinic or ambulatory</td>
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<tr>
<td></td>
<td>and normal BP in environments nonrelated to</td>
</tr>
<tr>
<td></td>
<td>clinical practice</td>
</tr>
</tbody>
</table>

Note: 8For age, sex, and height percentile.
Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

It is estimated that 30% of children and adolescents with overweight/obesity have hypertension.88 Thus, the presence of overweight/obesity appears to be one of the most important factors related to hypertension in children and adolescents worldwide.85,87–90 Several studies have shown that the presence of overweight/obesity is positively correlated with the occurrence of prehypertension in children and adolescents, and this combination increases the risk of developing adult hypertension.91–94 Certain conditions are strongly associated with hypertension in teens, including smoking and the use of contraceptives, alcohol, cocaine, amphetamines, anabolic steroids, phenylpropanolamine, and pseudoephedrine (nasal decongestants).

Therefore, changes in lifestyle, such as weight control, reduction in sodium intake, and exercise, are fundamental for the prevention of hypertension. Although threshold pressure levels are not yet well defined, BP most likely affects target organs in children, as in adults. Dietary intervention, maintaining an ideal weight, and engaging in regular physical activity could be encouraged at this stage as a method of primary prevention.24 In a study on the stiffness of large arterial vessels, which is attributed to aging, the only studied factor that could explain the group with vessels that did not show signs of age was the lowest BP level presented.95

### Sedentary behavior
The death rate from cardiovascular disease is lower in individuals who exercise regularly, and there are no doubts about the improvement in quality of life that is achieved through a physical conditioning program. However, this improvement depends on a proper prescription, and intensity, duration, and modality have an important role for a satisfactory result. In adults, the recommended physical conditioning activities lie between the ventilatory threshold and the respiratory compensation point; that range is most recommended for its beneficial effects on cardiopulmonary capacity.96 In children, the beneficial effects associated with physical activity include weight control, effects on cholesterol levels and insulin resistance, low BP, psychological well-being, and an increased predisposition for physical activity in young adulthood.7,97 Adolescents should engage in physical activities of moderate to vigorous intensity for at least 60 minutes a day, 5 days a week; this activity can be in or outside school and can be structured.97

A major challenge for public health authorities has been to increase the cardiorespiratory fitness of the population. Childhood and adolescence appear to be periods for promoting good physical activity habits and preventing sedentary
behavior in adulthood. Therefore, the prevention of cardiovascular disease is also a pediatric problem. In recent decades, children have become less physically active, with energy expenditure approximately 600 kcal/day lower than their contemporaries 50 years ago. Physical inactivity is recognized as an important determinant of chronic diseases, and an increase in the prevalence of these diseases during childhood has been documented.

Attention has been drawn to the need for physical education programs in schools and for community recreation facilities. However, few empirical studies have been conducted to determine the impact of such facilities and programs on physical activity and the level of inactivity in adolescents. Among adolescents, there is a trend to engage less in school physical education activities and vigorous activities and to spend more time watching television. These behaviors can affect future health problems, whereas greater physical fitness has been linked to a lower cardiovascular risk profile in children and adolescents.

Identifying population values of maximal oxygen consumption (VO$_{2max}$) is important in studies that attempt to relate physical fitness to cardiovascular risk. VO$_{2max}$ is a measurement that is used to guide the prescription of exercise and analyze the effect of training programs. Aerobic capacity measured through VO$_{2max}$ depends on cardiovascular, respiratory, and hematological components, and the oxidative mechanisms of muscle in exercise. This value is determined by means of cardiopulmonary exercise testing, which allows the simultaneous assessment of the cardiovascular and respiratory systems’ ability to perform their main functions, such as gas exchange. Measurements of gas exchange are fundamental to understand the limitations of exercise. However, multiple paths (direct or indirect) have been used to determine cardiorespiratory fitness. The differences in the methods used may be responsible for the differences found in the predictive power of this important physiological variable and whether cardiorespiratory fitness can serve as a predictor of blood lipids in children. However, the expected increase in BP with age is lower in children with better physical fitness.

Adolescence is the period of transition to adulthood, during which many structural, hormonal, and biochemical changes occur in physiological systems that affect VO$_{2max}$. Thus, it is necessary to establish specific VO$_{2max}$ values for this population. The international literature offers benchmarks for healthy children and adolescents. Described as a behavior, physical activity includes many types of muscular activity that significantly increase energy expenditure. Physical fitness is described as an attribute, and generally refers to the ability to perform physical work; in addition, physical fitness is considered an adaptive state and is partly genetically determined. Physical fitness measurements are preferred over physical activity measurements because they are more objective and less error-prone. In addition, aerobic fitness and physical activity correlate better with cardiovascular diseases. Thus, efforts should be intensified to identify the starting point for daily physical activity to increase physical fitness in youth. However, determining this variable is not yet a global reality, and empirical evaluations have been performed. The use of cardiopulmonary exercise testing makes it possible to assess metabolic and cardiopulmonary capacity accurately through direct measurements of VO$_{2max}$. This value is the most important physiological measurement for determining aerobic capacity, the accurate level of physical fitness, and therefore the correct intensity of exercise to obtain the health benefits of a fitness program.

**Conclusion**

Although the manifestation of coronary heart disease occurs in adulthood, detecting risk factors during childhood is crucial for establishing a prognosis and preventing damage to target organs in adults. Thus, detection and prevention should begin during childhood, when changes in lifestyle can reduce the incidence and severity of heart disease. School seems to be the key to achieving this goal.

Studies of cardiovascular risk factors in a region, city, or country should always report the prevalence and its correlations in childhood as a fundamental step in identifying a population at risk.

The studies reviewed here note the gravity of the public health problem represented by coronary heart disease. It is imperative to discuss the issues of health promotion and the prevention of future diseases that arise from the risk factors mentioned in this review.

Autopsy studies clearly indicate that atherosclerotic lesions appear during childhood. Therefore, if the risk factors for cardiovascular diseases begin in childhood, they should be addressed at this stage. This timing reinforces the need for rigorous pediatric care in this age-group for an early diagnosis, particularly counseling regarding preventive measures. For example, dyslipidemia, which is the major known risk factor, can be modified by a moderate fat restriction without impairing the growth and development of children older than 2 years of age. Thus, it is possible to achieve a great impact on cardiovascular disease through research on evaluation of risk factors in asymptomatic children.
Therefore, it would be beneficial to identify those children and adolescents with the highest risk as early in life as possible, so that interventions to reduce cardiovascular risk could be targeted. Indeed, there are existing guidelines on screening of dyslipidemia, elevated BP, and obesity in childhood; however, there is a shortage of data on the optimal age for screening of cardiovascular disease risk factors in childhood.

It is necessary to raise social awareness at all levels and develop studies to plan programs and actions to control dyslipidemia, obesity, high BP, and a sedentary lifestyle at an early age so that they do not become the epidemics of this new century.

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Disclosure

The authors have nothing to declare.

References


