

# ARTERIAL HYPERTENSION IN CHILDREN AND ADOLESCENTS



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# ARTERIAL HYPERTENSION IN CHILDREN AND ADOLESCENTS

**eBook**

1. Introduction



# Introduction

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Undiagnosed and untreated arterial hypertension in children is a severe, chronic disease with very serious health consequences. According to epidemiological data, it occurs in 2-4% of children, but is often not recognized. Awareness about hypertension, its diagnosis and treatment among specialists dealing with children seems to be still insufficient.

In 2016 The European Society of Hypertension published guidelines about the diagnosis and management of hypertension in youth. To date, this document constitutes the basis for good practice in the management of children diagnosed and treated for hypertension.

In 2023 HyperChildNet and the European Academy of Pediatrics revealed the joint statement about the diagnosis and management of hypertension in youth, based on the European Society of Hypertension Guidelines with the aim to improve its implementation.

We would like the HyperChildNet about pediatric hypertension eBook to expand on the problems and topics raised in these documents. We are aware that the rules of scientific publications and guidelines do not allow us to fully develop all topics and answer relevant questions. That's why we propose an eBook format, which we hope will reach a wide range of people interested in the topic of hypertension in children and adolescents.



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# ARTERIAL HYPERTENSION IN CHILDREN AND ADOLESCENTS

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2. General Remarks



# General remarks:

definition,  
epidemiology,  
risk factors of  
pediatric  
hypertension

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## Definition

Arterial hypertension in children is defined as systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) persistently at least 95th percentile for sex, age and height measured on at least three separate occasions.

Children with average SBP and/or DBP at least 90th, but less than 95th are classified as having high-normal BP.

For boys and girls aged 16 or older, the definition of arterial hypertension should no longer be based on the 95th percentile but on the absolute cutoff used for adults (arterial hypertension SBP 140-159 and/or DBP 90-99 mmHg, and high-normal BP SBP 130-139 and/or DBP 85-89 mmHg) [1,2].

Diagnostic criteria for elevated blood pressure (BP) in children are based on the concept that BP in children increases with age and body size. That makes impossible to utilize a single-BP level to define normal or abnormal values, as done in adults. Therefore contrary to adults, the definition of arterial hypertension in children is based on the normal distribution of blood pressure in healthy children and not on the cardiovascular morbidity and mortality associated with a certain level of BP [1].

However, differences in guidelines among various societies, as well as gaps in knowledge lead to ambiguity regarding office BP interpretation and management decisions.

Critically analyzing and reviewing the ESH 2016 definition, in 2023, HyperChildNet and European Academy of Pediatrics experts issued a joint position in which they emphasized the following issues:

There is an ongoing need to develop reference values in large groups of children, using oscillometric devices adapted to measure blood pressure in the pediatric population (The largest normative BP database (National High Blood Pressure Education Program or NHBPEP) is based on auscultatory measurements [3].

Validated devices and appropriate cuff sizes to fit the child's arm circumference especially for neonates and infants are limited [3].



There is a need to define a place in the diagnosis of hypertension for home measurements and for measurements using 24-hour blood pressure monitoring, which will be possible after developing appropriate, valuable reference standards based on large, reliable studies [3].



## Epidemiology of arterial hypertension in children

It is not easy to precisely determine the incidence of hypertension in children worldwide. Based on the mathematical interpretation of the definition that hypertension is diagnosed as systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) persistently at least 95th percentile for sex, age and height, it could be concluded that the problem affects 5% of each population. This rarely happens, however, probably because the normative values used are limited to the USA and may not exactly apply to other part of the world, or because the normative data are more than 20 years old, and the current epidemics of overweight and obesity may have changed the matter [1].



Epidemiological studies also do not always confirm these theoretical calculations regarding frequency. The results of the epidemiological analyzes are primarily influenced by the research methodology - starting from the devices and measurement techniques used, through the health and nutritional status of the child population, to the reference values used. In the era of the overweight and obesity epidemic, it is difficult to interpret the results of measurements at the population level as "made in a healthy population".

An attempt to overcome these difficulties is to compare the results of many studies in the form of meta-analyses. One of the largest and newest was published in 2019 by Song et al. Authors analyzed 47 articles. According to their results the prevalence of arterial hypertension was 4 % (95% CI, 3.29%-4.78%) and 9.67% (95% CI, 7.26%-12.38%) for prehypertension. The prevalence of childhood hypertension was higher when measured by aneroid sphygmomanometer (7.23% vs 4.59% by mercury sphygmomanometer vs 2.94% by oscillometric sphygmomanometer) and among overweight and obese children (15.27% and 4.99% vs 1.90% among normal-weight children) [4].

## Risk factors

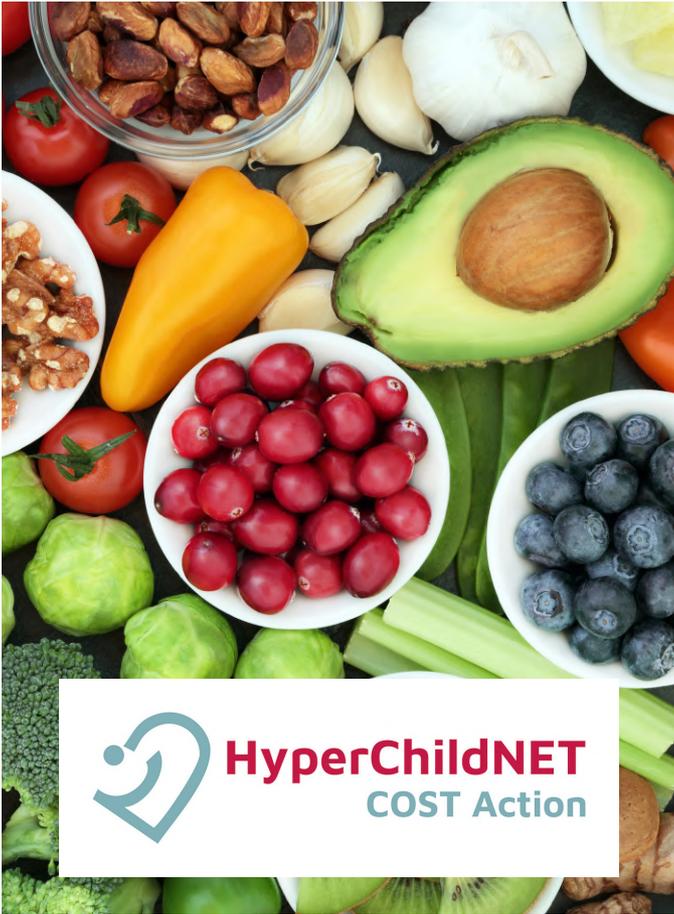
Risk factors for hypertension in children can be divided into non-modifiable and modifiable. The first group includes: family history of hypertension, congenital heart disease, chronic kidney disease, solid organ transplantation, the need for constant use of drugs increasing BP, elevated intracranial pressure, history of prematurity or small for gestational age, history of neonatal intensive care unit hospitalization, systemic diseases associated with high blood pressure (eg. neurofibromatosis type 1). The second group of risk factors includes primarily factors related to modern lifestyle: inadequate, high-calorie diet rich in sodium and sugar, low physical activity, lack of sleep, excessive exposure to screens, smoking and alcohol [1,3,5].



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# ARTERIAL HYPERTENSION IN CHILDREN AND ADOLESCENTS

**eBook**

Early Nutrition  
**3.1 Prevention Strategies**



# Prevention strategies

The role of nutritional programming in the prevention of obesity and high blood pressure

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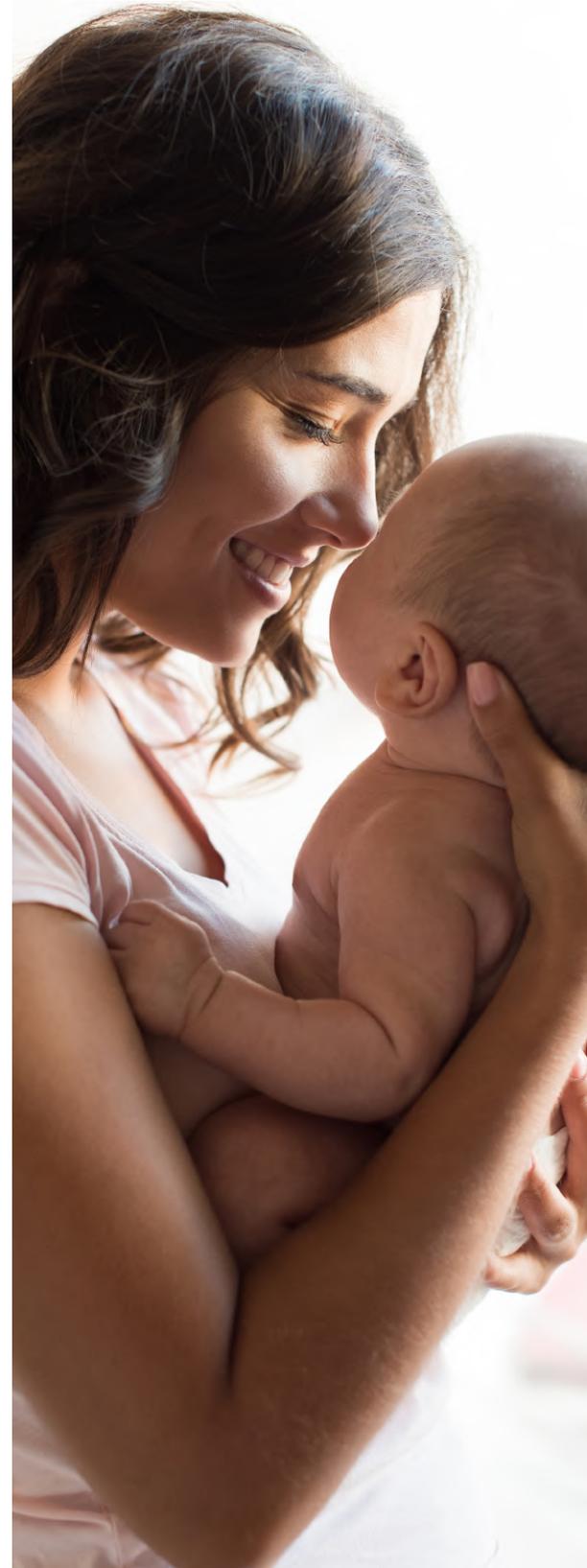
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## Breastfeeding as tool to prevent obesity and high blood pressure

Breastfeeding represents an early nutritional strategy to prevent obesity, inflammation and hypertension later in life. Data on breastfeeding show its key role in the modulation of metabolic responses; meta-analysis on 25 studies (226,508 participants), highlights that breastfeeding protects children from obesity [1]. An inverse correlation between breastfeeding duration (from 2 to 12 months of breastfeeding) and the incidence of overweight/obesity in children at 6 y.o. was observed [2]. Besides, a similar correlation has been observed for the proinflammatory biomarkers; longer is breastfeeding lower is the level of C Reactive Protein (CRP) in young adult.

High CRP was observed in young adults that had a low birth weight at born and received short breastfeeding (<2 months) [3]. Breastfeeding resulted able to contrast the increase of body mass index (BMI) in early infancy and in childhood, as well as the prevalence of type 2 diabetes [4]. A positive effect of breastfeeding has been observed on the control of blood pressure; a reduced risk of maternal hypertension and diabetes has been observed in Chinese women who did not breastfeed [5]. A decrease of blood pressure has been measured in breastfeed children (mean systolic/diastolic 99/58 mm Hg) at 3 years of age compared to who did not received breastfeeding (103/60 mm Hg) [6]. Furthermore, mother by breastfeeding can transfer to the new-born some flavours of healthy food (i.e. vegetables), ameliorating the acceptance of vegetables during childhood [7].

In conclusion, breastfeeding represents a key tool within the preventive strategies to maintain health; longer is breastfeeding (>3 months) more is the positive impact on BMI, control of diabetes, inflammation and blood pressure in children and mothers.



## The role of selected macronutrients in the prevention of obesity and high blood pressure



### Protein

Early nutrition or metabolic programming assumes that nutritional experience during critical periods in early life, both pre- and post-natal, can program the developmental trajectories of individuals with respect to metabolism and health. One of the components of the diet, which is attributed an epigenetic role in shaping the risk of developing obesity is protein [8]. The Childhood Obesity Project (CHOP) conducted in 5 European and involving 1678 healthy infants born on time with birth weight appropriate for gestational age, revealed that a high intake of protein with baby formula, increases the concentration of insulinogenic amino acids in plasma and tissues, which are mediators of insulin growth and insulin growth factor 1 (IGF-1) inducing greater weight gain and fat deposition and causing an increase in the risk of obesity at the age of 2 years. Consumption of lower-protein infant formula in infancy reduced the risk of obesity at early school age by 2.43-fold (unadjusted relative risk) or 2.87-fold (adjusted relative risk), respectively [9].

In the European Union countries, the composition of products for special nutritional purposes is regulated by the European Commission Directive (2013/46/EU of 28.08.2013). In the latest EFSA opinion (2017), it is recommended to reduce the minimum amount of protein in infant formula for further infant nutrition to 1.8 g / 100 kcal. [10]. However, the evidence for the role that dietary protein plays in programming obesity after infancy is inconsistent.

SYSTEMATIC REVIEW	AUTHORS OUTCOMES
Pearce & Langley-Evans 2013 [11]	Some association was found between high protein intakes at 2- 12 months of age and higher body mass index (bmi) or body fatness in childhood, but was not the case in all studies.
Hornell et al. 2013 [12]	The evidence was described by the authors as “limited-inconclusive (grade 4)” considering the conflicting results of the identified studies with respect to the effects of protein intake in early childhood on later body fat.
Patro-Gołąb et al. 2016[13]	There is inconsistent evidence of an association between a higher dietary protein intake in early childhood beyond infancy and later childhood overweight or obesity.

In summary, lowering the protein content of infant formula is a promising intervention to reduce the risk of later overweight and obesity in children, but more studies replicating the effects on long-term health outcomes are needed. The effect of protein intake on the risk of obesity in older children is ambiguous.

## Fat

The “early fat programming hypothesis” was proposed in the ELANCE prospective study. It was showed that early low fat intake was associated with high adult body fat and serum leptin concentration. Authors suggested that adult leptin resistance may have been programmed in early childhood as a result of early dietary fat reduction. Limiting fat intake in young children can activate adaptive metabolism mechanism to prevent underweight, thus increasing susceptibility to the development of overweight and metabolic diseases in the future, in a situation where there is an increased energy intake [14]. On the other hand a Cochrane review (2014) and later Patro-Gołąb et al. 2016 review indicate that there is no clear association between lower total fat intake in children and later BMI and/or body composition [13,15]. A review by Voortman et al. 2015, assessed the influence of the intake and status of LCPUFA in infancy on later obesity (including effects on BMI and body fat). The authors concluded that there was insufficient evidence to suggest an effect of polyunsaturated fatty acid intake in early childhood on later overweight or obesity [16].



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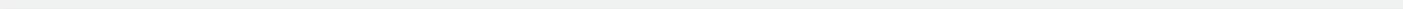


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# ARTERIAL HYPERTENSION IN CHILDREN AND ADOLESCENTS

**eBook**

Sleep & Screen use  
**3.2 Prevention Strategies**





# Prevention strategies: Sleep & Screen use

by Julio Alvarez-Pitti

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## Introduction

In the last 100 years, technological progress has decreased the overall need for human movement, giving rise to a new behavior called sedentary behavior or physical inactivity, which goes against our own nature. Sedentary behavior has extraordinarily reduced daily energy expenditure in children and adolescents in Western countries and has decreased by about 600 kcal in the last 50 years (1). This is due to a significant reduction in their movement: remote control for the television, mobile digital devices, escalators, elevators, automatic revolving doors, occupations that involve sitting, leisure time spent watching television, Internet, etc. Voluntary and recreational physical activity has acquired fundamental importance to satisfy movement needs, but, unfortunately, voluntary physical activity is not very popular.



On the other hand, a sedentary lifestyle, defined as any waking behavior characterized by energy expenditure  $\leq 1.5$  metabolic equivalents (METs) such as sitting, reclining, or lying down (2) has become an epidemic among children and adolescents in the world. The most recent global comparative estimates available (those for 2010), indicate that worldwide 23% of adults (3) and 81% of adolescents (aged 11-17 years) (4) do not meet the World Health Organization (WHO) global recommendations for physical activity to improve health.

The consequence of this situation, which goes against the very nature of childhood, is that contemporary youths are more familiar with controlling a cell phone than throwing a ball.

The "product" of this cultural behavior makes today's children weaker, slower, and heavier than in the past, leading to an enormous burden of present and future diseases. This makes the call for action to address this phenomenon never more urgent.

Healthy sleep habits in children are crucial as sleep promotes healthy physical and mental child development. Moreover, sleep disorders have been linked to various cognitive, behavioral, emotional, and physical health problems (5,6).

The American Academy of Sleep Medicine (AASM) published in 2016 a consensus statement on the amount of sleep for pediatric populations (7). These recommendations are summarized in table 1.

Table 1: Healthy Sleep Duration (AASM Consensus)

AGE	Sleep duration
Infants* 4 months to 12 months	12 to 16 hours per 24 hours (including naps)
Children 1 to 2 years	11 to 14 hours per 24 hours (including naps)
Children 3 to 5 years	10 to 13 hours per 24 hours (including naps)
Children 6 to 12 years	9 to 12 hours per 24 hours
Teenagers 13 to 18 years	8 to 10 hours per 24 hours

Findings from studies that used complementary research methods have converged to strongly suggest that inadequate sleep quality and quantity are causally linked to sleepiness, inattention, and probably other cognitive and behavioral deficits that affect daytime functioning, with potential implications for long-term development (6). But also, studies show that increased sleep variability and irregularity are associated with obesity, decreased physical activity, dysregulated eating and inadequate diet, metabolic dysfunction, impaired cardiac autonomic balance, and elevated blood pressure in adolescents (8).

It is therefore alarming that sleep duration has decreased, while the frequency of sleep problems has increased in recent decades (9–11). Prevalence rates of sleep problems range from 15 to 44 % (12); in Germany and the United States, 20–25 % have been previously reported (13).



## Screen-time benefits and risks on development and mental health

“Digital media” refers to content transmitted over the Internet or computer networks on all devices. In contrast “Screen time” refers to time spent with any screen, including smartphones, tablets, television, video games, computers, or wearable technology.

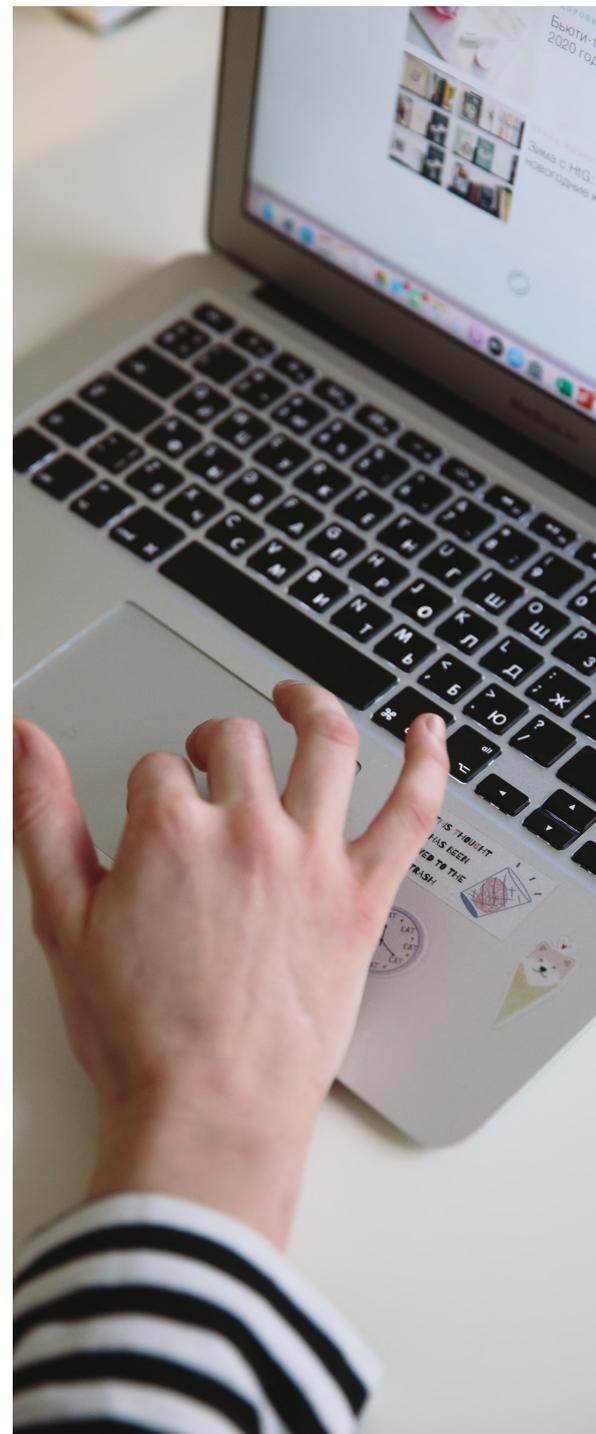
Digital media are integrated into the everyday lives of children and adolescents, and healthcare providers are often asked about the effects of screen use on mental and physical health, and on family life. Current evidence shows that digital media differ in their impacts on cognition, psychosocial function, and physical health and that benefits and risks are nuanced. And even the effect varies by age (school-age children Vs. adolescents).

The results of several studies suggest that adolescents are less susceptible to the negative effects of high screen time (more than 6 hours per day) in cognition and physiological function than younger children(14).

### I.-School-age children:

The use of digital media has shown some benefits in school-age children as improvements in children’s academic performance if the contents are guided and co-viewed with family(15,16)□; cooperative or competitive videogames played with family or friends can function as traditional play (17), allowing many children to socialize through them connecting with peers even online; and finally, digital technology can help children keep in touch with family and friends(18).

On the other hand, some important risks of inadequate use of digital media have been also identified. Exposure to age-inappropriate content, excessive exposure to screens (digital devices, TV in the bedroom, and background TV), can negatively affect development and behavior. Also, what is known as “media multitasking” (dividing attention between two or more devices simultaneously) has a negative impact on both concurrent learning (in class or at home) and academic outcomes in children aged 12 years and younger.





## 2-Adolescents:

In adolescents, both no or excessive use of screens is associated with negative effects, while moderate use (typically between 2 and 4 hours per day) is associated with some cognitive and psychosocial benefits (19).

Friendship, is the main motivator for adolescents' "online life". Connecting with each other through mobile communication systems or social networks seems to improve their self-concept by increasing the perceived quality of friendship(20). The positive effects appear to be greater in adolescents who have less social support or who feel more uncomfortable socializing face-to-face (21).

As for the positive effects of action video games in older children and adolescents, they have revealed specific short-term increases in some cognitive skills, such as attention, visual and representational processing (22), but also, above all, in executive function and visual and spatial working memory (23).

But also have been described several "side effects". Many teenagers are aware that they spend "too much" time connected. Thus, half of the teenagers in a survey conducted in the United States reported feeling "addicted" to their mobile devices (64).

The type and “tone” of online communication use also have an influence. Being the recipient (or sender) of instant messages with negative content correlates with the presence of anxiety or depressive disorders (65). There is also a small but significant association between excessive screen time (more than 6 hours/day) and feelings of depression in adolescents (17,21,38).

More than 50% of U.S. students report that they often or sometimes use social networking sites while doing homework (17,21,38). Some studies suggested that adolescents who are more prone to multitasking may be the least able to learn effectively (60).

In terms of time spent playing video games, undesirable effects have only been found at very high levels. Spending more than 50% of their daily free time playing games has been shown in studies to have slight negative effects on general well-being, as well as behavioral problems, hyperactivity, peer problems, and emotional problems (17,19).

Adolescents may be developmentally predisposed to online risk-taking (69,70). Above all, those who are socially anxious or depressed communicate online more often with strangers (46,53,54) and tend to take fewer precautions (44).

Finally, parents do report a decrease in family time and closeness in homes where many devices are used, and too much technology can erode family connection (49).



## Screen time and its Impact on Physical Health

In terms of physical health screen use and digital media have shown also benefits. Some screen activities promote PA. Studies have associated exergaming (e.g., Wii boxing) with increasing PA levels(24,25), mainly when part of a comprehensive weight control program and played as a team (25–27). But in the majority of the studies, excessive use of digital devices is linked to sedentarism, the risk of increasing weight, and decrease time and quality of sleep (19). However, there has been criticism of professional guidelines as non-evidenced-based,<sup>7</sup> as evidence for an impact of screentime on health is inconsistent, with systematic reviews showing inconsistent findings (8–11).



It has been recently published a systematic review of published systematic reviews, reporting methods, and findings using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist. The main results of this systematic review which included 13 reviews on the physical health aspects of children and adolescents are summarized:

**-Body composition:** the authors conclude that a greater amount of television viewing is moderately strongly associated with greater adiposity. However, there is insufficient evidence of an association with total screen time of any type or with screen time other than television. There is moderate evidence of a dose-response association with either total screen time or TV time. But a specific threshold of hours of screen time is not identified.

**-Diet and energy intake:** this study identifies moderate evidence of an association between screen time, particularly television, and higher energy intake and less healthy diet quality. TV watching can suppress satiety signals (82), while fast food, sweetened beverages, and restaurant ads contribute to intake (78). Thus, diet and sedentary behavior in young people may better explain associations between screen time and weight gain than the displacement of PA (41,82).



**-Sleep:** Although the number of televisions in bedrooms has decreased in recent years, the presence of other portable screens has increased (74,78,88-90). In 2014, 39% of Canadian students with cell phones reported sleeping with them (5). There is increasing evidence that new technologies, along with television, are displacing sleep time, causing emotional arousal, inhibiting melatonin release, and disrupting sleep rhythms (44).

However, in the previously described systematic review, there is weak evidence that screen time is associated with decreased sleep quality, including delayed sleep onset, reduced total time, and daytime fatigue. One of the included reviews demonstrates that this association is observed across all forms of TV, computer, video, and cell phone time.

**-Physical Activity:** in the review, they do not specifically analyze the relationship between screen time and physical activity. However, they study its relationship with Physical Fitness and they found weak and inconsistent evidence for an association between screentime or television screentime and cardiorespiratory fitness, with weak evidence for a 2-hour daily screentime threshold.

Despite the widespread perception, there is no firm evidence that screen use alone directly decreases PA. However, studies seem to indicate that already inactive adolescents spend more time using screens (17,41,71). Current evidence also suggests that screen time affects health more than sedentary time in general, but while a relationship is observed between increased screen and TV time, poorer body composition, and physical fitness (41,72), this relationship is not necessarily causal or consistent (41,73) and appears to be much more complex than the simple relationship, screen use Vs physical activity time.

**Cardiovascular risk:** Associations between screentime and cardiovascular risk were examined by one high-quality and three medium-quality reviews. The authors report a weak association between screen time and TV time with metabolic syndrome. They found no clear evidence of an association with any individual cardiovascular risk factor.



## Evidence based Recommendations

Because of these concerns, expert groups have suggested controlling screen time for children and adolescents. In 2016, The American Academy of Pediatrics recommended limiting screentime for children aged 2–5 years to 1 hour/day of high-quality programs and for parents to limit screentime in agreement with children and young people's 6 years and older (16). The Canadian Paediatric Society issued similar guidelines in 2017 (28).

But the latest studies tell us that the unfavorable relationship between the use of screens and the health of children and adolescents is not so much linked to the time of use but to the way they are used. For this reason, the latest recommendations focus more on the healthy use of screens, not only for children and adolescents but also for the whole family.

Some examples of this are the recommendations published in 2019 by the Canadian Pediatric Society the "Digital Health Task Force" (29), summarized in the four essential 'Ms' (Minimize, mitigate, be mindful, model), the recently published Canadian Guidelines for preschool children, or the American Academy of Pediatrics Family Digital Plan, updated in 2022.



## The general recommendations for parents can be summarized as:

**1. Monitor what kind of devices and tools your children are using.**

**2. Promote “screen-free times”. Keep in mind that:**

- It is recommended not to sleep with electronic devices and to remove them one hour before going to bed.
- It is not recommended to use media during the hours dedicated to study.
- Remember that there are times of the day for family communication (meals,...) when the screen should not be present.
- Promote family activities (sports, excursions, etc.).

**3. Recommended time of use by age (from AAP Guidelines):**

- For children under 18 months, media consumption should be avoided except for video chats. Parents of children between 18 to 24 months of age who want to introduce digital content should choose high-quality programs and watch them in the company of their children to help them discern what they are watching.

- For children between the ages of 2 to 5 years, use should be limited to 1 hour per day of high-quality programs. Parents should watch media content with their children to help them understand what they are watching and apply it to the world around them.
- For children ages 6 and older, parents should set consistent limits on the time and type of content they use, and ensure that their consumption does not take time away from adequate sleep, physical activity, and other essential health behaviors.



4. **Encourage healthy lifestyle habits:** 1 hour of exercise per day and 8-12 hours of sleep per day is recommended, depending on the child's age.
5. **Use the media together with your children and take advantage of them to teach appropriate behaviors.**
6. **Educate on the responsible use of technology and the risks involved.**

7. Educate your children in civic behavior in all areas of life against cyberbullying.
8. Teach your children how to protect their privacy and in which situations they should ask for help.
9. Watch out for signs of technology abuse (low interest in offline relationships, difficulties in leaving the Internet,...) or that your child could be being harassed or blackmailed on the Internet.
10. Do not forget to do everything possible - know and be protected - against the "big bad wolf trilogy" on the Internet: cyberbullying, sexting and grooming.

**This information is summarized for parents in Hyperchildnet's Fact Sheet: [click this link.](#)**



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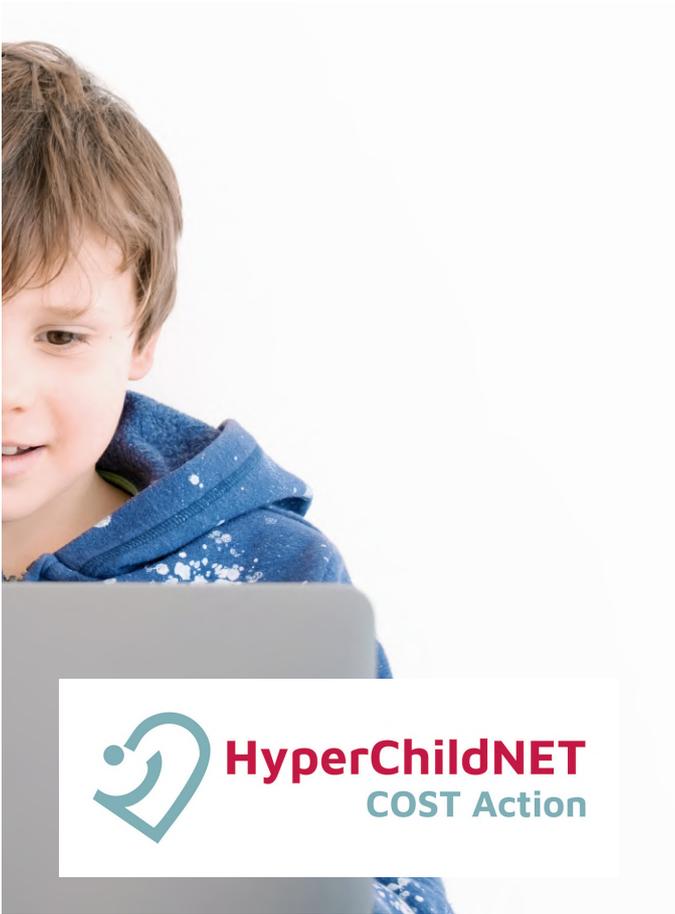
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# ARTERIAL HYPERTENSION IN CHILDREN AND ADOLESCENTS

eBook

Nutrigenomics  
& Nutri-epigenetics  
4.1 Biology

# Biology

## Nutrigenomics & nutri-epigenetics

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## Nutrigenomics as a tool to address healthy gene expression

Nutrigenomics is the study of interaction between dietary components and the genome; it defines the molecular mechanisms that modulate gene expression and finally protein synthesis with a noteworthy impact on cell metabolism (1) The diseases like obesity, metabolic syndromes, type 2 diabetes, cardiovascular disease (CVD), and some types of cancers are polygenic and multifactorial and their onset and progression are related to multiple genes and their variants as well as to several environmental factors, especially the diet (2) □ Nutrients are regularly ingested and are involved indirectly and directly in the regulation of gene expression, it follows that a subset of genes regulated by diet must be involved in disease initiation, progression, and severity.

Transcription factors (TFs) are one of the key molecules act as nutrient sensors by changing the level of DNA transcription of specific genes in response to nutrients changes. Approximately 40 micronutrients are needed in the human diet. Inappropriate intakes of specific micronutrients have been associated with diseases inter alia: CVD, cancer, neural tube defects, and bone mass(3) For instance, B6, B12 and folate deficiencies, are associated with increased serum homocysteine levels which is a risk factor and marker for coronary artery disease. Deficiency of vitamin B12, B6, folic acid, niacin, vitamin C, E and iron or zinc appears to imitate radiation in damaging DNA by causing single and double-strand breaks, oxidative lesions, or both (4) Furthermore, macronutrients (i.e. fat, proteins and carbohydrates) are able to exert a different nutrigenomic impact; dietary lipid composition, (saturated and unsaturated fatty acids) and simple carbohydrates (i.e. fructose, glucose) stimulated different genes switch on/off gene associated to pro-inflammatory responses(5). Vegetables and fruits contain polyphenols able to promote anti-inflammatory, antioxidant and detoxifying responses; moreover, fibers contained in plant-based food products can be used by gut microbiota to produce short chain fatty acids with a key anti-inflammatory activity.

In conclusion what we eat can modulate molecular responses toward health or unhealth status.



## Epigenetics: how can be programmed adult health?

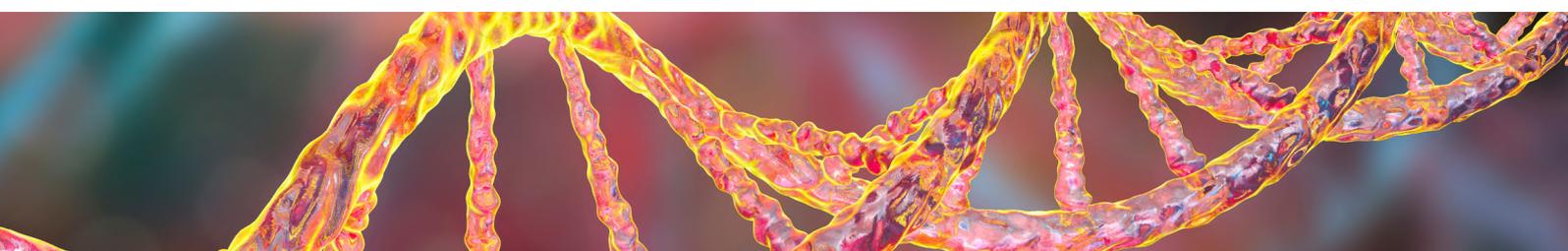
Epigenetics studies the change in gene expression that are not associated with modifications of DNA sequence; it has been defined “on top of” or “in addition to” genetics to highlight that epigenetics works by functional groups added on top of chromatin structure (DNA + histones). These groups (i.e., methyl, acetyl, phosphate groups) are synthesized through metabolic pathways in our cells; methyl groups are used for DNA methylation which consists of the methylation at the carbon 5 of cytosine near guanine (CpG sites) by DNA methyltransferases (DNMTs). This methylation can occur at the gene promoter, or at the gene core, or in intragenic regions with a different impact on gene expression.





Epigenetic modulation can regulate gene expression also by histone modifications; it changes chromatin condensation by adding acetyl, methyl or phosphate groups to histones of chromatin. The last epigenetic mechanism which occurs in the cytosol, is a post-transcriptional gene regulation that interferes with protein synthesis by non-coding RNAs (i.e., miRNAs). These three epigenetic mechanisms depend to the exposure to environmental stimuli like nutrition, physical activity, chemicals, stress, etc; nutrition has a significant role because it guarantees the substrates need to synthesize functional groups; for example, to produce methyl groups by one carbon cycle, is necessary the correct intake of folic acid, vitamin B2, B6, B12, choline and betaine. Epigenetics works across all our life but its impact on human health can be modulated according to the period of the exposure; during early life (prenatal and postnatal life) epigenetics works to promote cell differentiation; only genes necessary in an organ for its specific functions are on, the other genes are switched off by DNA methylation and histone modifications.

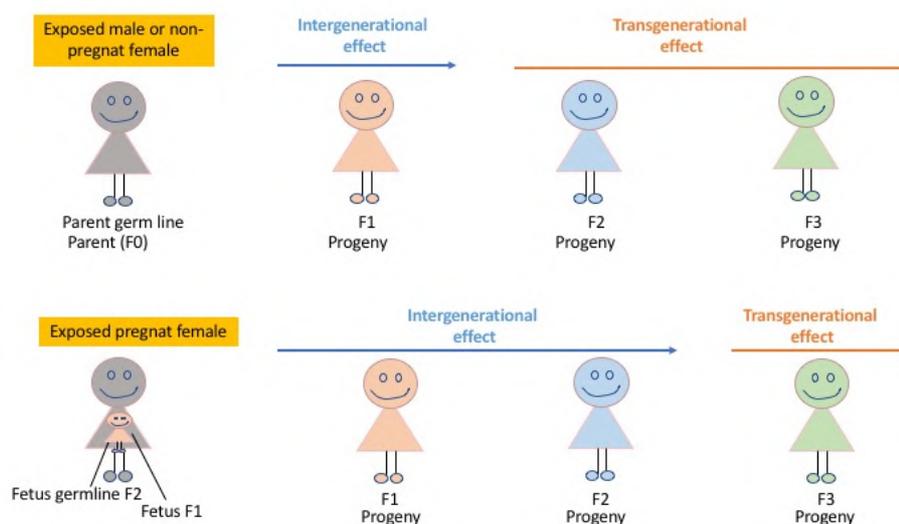
On the same time, if the mother receives during pregnancy and lactation unbalanced diet (i.e., high protein/lipid, low protein) the new-born epigenome can be modified with long term effect of health. Epigenetics shows its impact on phenotype later in life because cells acquire an epigenetic memory of the early life exposure. Studies on siblings born from malnourished mothers during pregnancy (i.e., Dutch famine), demonstrated that the period of malnutrition (all trimesters or the last trimester) changes DNA methylation and phenotype, differently (six or three genes have different DNA methylation, respectively) (6) Female developed glucose intolerance, while male became obese, in adult age; male obesity started at age 19(7) A positive correlation between prenatal maternal famine and adult type 2 diabetes/cardiovascular risk has been observed following Chinese famine of 1959-1961 (8,9). Studies on animal models show that high/low protein intake in early life can perturb pancreas development, leptin resistance and promote obesity. Furthermore, metabolic disturbances due to high dietary fats during prenatal and postnatal life can be alleviated by cotreatment with resveratrol which can counterbalance leptin resistance by epigenetic regulation (10) Adult health can be modulated also by early-life exposure to endocrine disrupting chemicals, contained in lotions, cosmetics, perfumes, etc.; neonatal exposure to bisphenol A, phthalates and perfluoroalkyl substance has been negatively associated to childhood overweight/obesity and adverse neurobehavioral disorders(11). Preclinical and clinical studies report that in utero exposure to environmental stress, increases maternal and fetus cortisol level, and leads to long term alterations in the epigenome with negative outcome on adaptation and development (12)



In conclusion, health can be programmed during early life by lifestyle choices; several factors can modulate the infant epigenome with phenotype effects in childhood and/or adulthood; nutrition, chemicals, stress and physical activity are all environmental factors that should be under control to prevent unhealthy life.

## Parental epigenetic inheritance

Epigenetics inheritance consists in the transmission of epigenetic biomarkers from one generation to the next one. Epigenetic inheritance has been observed in several generations; intergenerational inheritance differs from transgenerational inheritance because needs of a defined stimulus that induce an epigenetic change (i.e. exposure to stress or malnutrition), while the transgenerational one is inherited, generation by generation, without the permanent exposure to a specific risk factor (Fig. 1).



*Fig. 1. Epigenetics biomarkers can be acquired during the fertile period by the male and female or during pregnancy, and inherited by intergenerational or transgenerational inheritance.*

Clinical studies on grandfather show transgenerational effect of high food intake during adolescent period; the excess of food of grandfather at 9-12 y.o., is associated to an increased risk to develop cardiovascular disease and type 2 diabetes in grandchildren (13). On the contrary, when the father or paternal grandmother were exposed to famine during adolescent age, a protection against cardiovascular diseases was observed in the proband; low food intake by grandfather protects proband from diabetes.



Studies on other cohorts show that paternal grandparents excess of food during prepuberal life increases the risk of cancer mortality only in male grandchildren (14). Intergenerational and transgenerational epigenetic inheritance has been observed in preclinical studies due to environmental stimuli; neonatal exposure to permethrin pesticide (i.e., food residue) leads to Parkinson-like disease development later in life and intergenerational inheritance of the neurodegeneration in rats (15).

Early exposure to alcohol in rats is associated to an increase of the sensitivity to stress of new-born animals and in their two generations(16)□High fat diet in drosophila induces intergenerational cardiac lipotoxicity mediated by histone (H3K27) trimethylation (17).

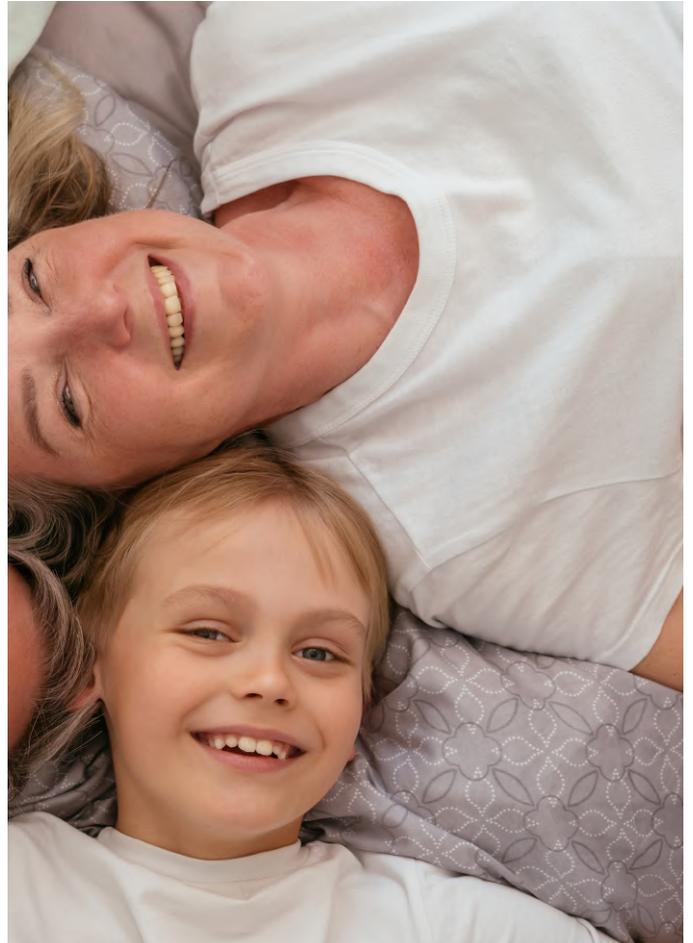
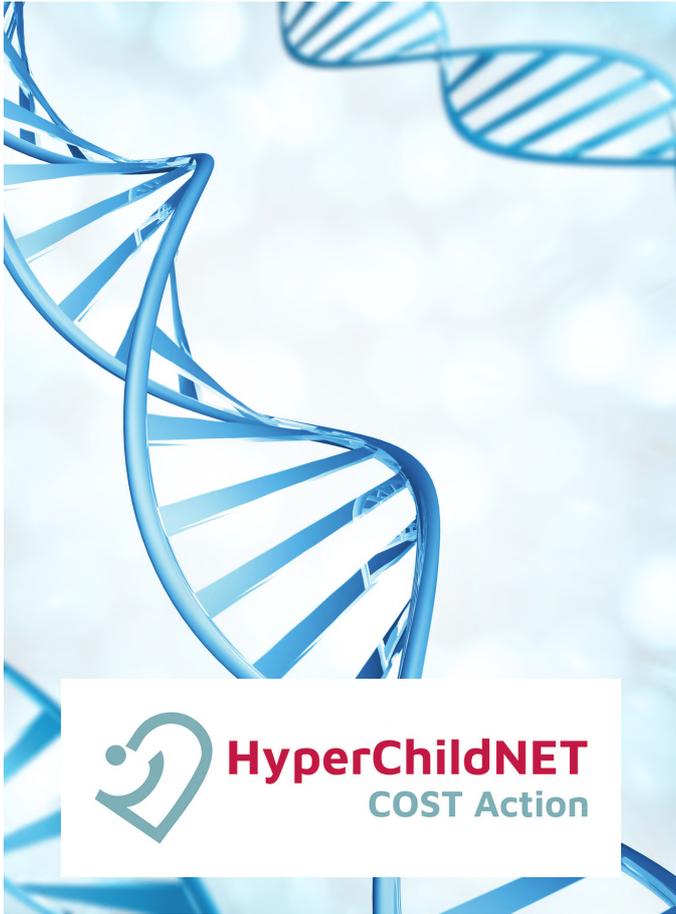
In conclusion, the epigenetic inheritance due to environmental factors (i.e., food intake, chemicals, stress, etc.) can perturb health for several generations; considering that epigenetics can be reversable a strategy to remove the environmental stimulus responsible of the epigenetic inheritance should be considered. Preventive Strategies have been extensively recognized in preclinical study and could represent a new approach to break the intergenerational inheritance.



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**eBook**

Heart and blood  
vessels disorders  
**4.2 Biology**



# Biology

## Heart and blood vessels disorders

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The growing prevalence of arterial hypertension (AH) in children and adolescents is becoming an ever-greater public health problem. The prevalence of AH in children aged 8-18 years has been estimated to 2%-3.6% and in adolescents aged 18 to 10%[1]. Primary AH currently is one of the most common chronic diseases in adolescents. The epidemic of obesity witnessed in recent years has contributed considerably to the increase in the prevalence of AH, which is as high as 27%-47% in overweight and obese children, respectively[2]. Longitudinal studies have indicated that children and in particular adolescents with AH are likely to suffer from hypertension as adults, including the risk of cardiovascular disease (CVD)[3].

## Target organ lesions in children with arterial hypertension

Although CVDs are very rare in children, elevated arterial pressure can cause damage to target organs, such as increased carotid artery intima-media thickness (cIMT), decreased brachial artery elasticity, increased pulse wave velocity (PWV) through the arterial wall and augmentation index (AIx), pointing to increased arterial stiffness, left ventricular hypertrophy, kidney damage and ocular fundus changes already in childhood and adolescence[4-9]. Target organ lesions due to AH in adolescence imply a considerable risk of cardiovascular events in adulthood.

Wide availability of echocardiography to detect left ventricular hypertrophy (LVH) makes it a target organ damage most frequently searched for in pediatric AH. The prognostic value of LVH in adults with AH as an independent risk factor for CVD has been definitely verified[10]. Recommendations issued in The Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents from 2004 include screening for LVH as a factor to initiate or intensify antihypertensive treatment in the routine work-up for children with AH [11].



## Left ventricular hypertrophy and left ventricular mass assessment

In children, left ventricular mass (LVM) correlates primarily with body mass, but the amount of adipose tissue, gender and arterial pressure also are contributing factors [12]. Repeated LVM measurements in the Bogalusa study suggested that somatic growth was the main determinant of heart growth, but that excessive body mass contributed to increased myocardial mass to greater extent than expected [13]. Determination of LVM in children is complicated due to the cardiac mass association with body mass of a growing child. Numerous studies have demonstrated that LVM index (LVMI), which also includes body height of the child, is the best method of expressing LVM in children.



LVMI is the ratio of left ventricular mass and child's height raised to the 2.7 power ( $LVMI = LVM \text{ (g)}/\text{height (m)}^{2.7}$ ) [14]. A variety of LVMI borderline values for LVH in children are reported in the literature. The Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents states a borderline LVMI value for LVH of  $51 \text{ (g)}/\text{height (m)}^{2.7}$ , the same as in adults, and this value has been frequently used in pediatric patients as well.<sup>11</sup> However, using percentile curves is recommended in children aged  $\leq 9$  years, whereas 95th percentile of  $40 \text{ (g)}/\text{height (m)}^{2.7}$  and  $45 \text{ (g)}/\text{height (m)}^{2.7}$  should be employed in female and male children aged  $\geq 9$  years, respectively [15].



## Left ventricular hypertrophy and arterial hypertension

Identifying children with AH that are at risk of poor cardiovascular outcome relies primarily on determination of surrogate markers, firstly LVH as a well-known risk factor in adults. Several studies report on positive correlation between arterial pressure level and LVMI [16,18]. Daniels et al. found LVMI above 95th percentile in 8%-41% of children with AH, of which 10%-15.5% had  $LVMI > 51 \text{ g}/\text{m}^{2.7}$ . In the study by Stabouli et al,<sup>9</sup> LVH was recorded in 20% of children with AH. Interestingly, LVH was detected in the same percentage of children with pre-hypertension and those with AH.

This finding indicates that pre-hypertension also poses a risk of cardiovascular sequels and target organ damage as AH. Higher LVMI values were also recorded in the group of children with AH as confirmed by 24-hour continuous noninvasive arterial pressure monitoring (CNAP). Richey et al. found higher LVMI in children with AH as recorded by 24-hour CNAP [19]. McNiece et al. recorded a higher risk of LVH in children with AH grade I and II.<sup>7</sup>

Left ventricular hypertrophy was also detected in children with white-coat hypertension, suggesting that it is by no means a harmless but a clinically relevant condition [20].

According to the study conducted by Lurbe et al., children and adolescents with persistent masked hypertension or those who transitioned from masked to sustained hypertension had a greater LVMI and a higher percentage of LVMI exceeding the 95th percentile compared to normotensive controls [21].

## Left ventricular hypertrophy and vascular phenotype

Arterial hypertension can be the cause but also the sequel of impaired vascular function. Increased arterial stiffness is an independent risk factor for development of CVD in adults. In young individuals, AH and obesity lead to reversible functional changes of vascular tree, which may later become fixed and irreversible. In the initial stage, vascular lesions are reversible, therefore early recognition and treatment of AH is of utmost importance [22].



The most commonly used parameters for the assessment of vascular function in adults are cIMT, PWV and AIx; however, they have not yet been widely adopted in pediatric practice due to unavailable equipment, inadequate method standardization, inappropriately defined diagnostic role, and lack of validation in pediatric patients. There are several studies reporting normal PWV and cIMT values in children and adolescents [23-25]. Other studies point to the association of AH with arterial stiffness and cardiovascular risk in children and adolescents [26,27]. In some studies, increased cIMT, reduced arterial elasticity and arterial stiffness parameters were found to correlate with LVH independently of obesity [16,28].

## Left ventricular hypertrophy and obesity

Obesity and AH have been on a progressive increase in the last few decades. There is a growing body of evidence pointing to the role of these risk factors for CVD in target organ damage such as LVH in children. Although obesity and AH frequently coexist, several studies have demonstrated that obesity has an independent role in LVH development, irrespective of hypertension [29].



Hypertension is present in about 30% of obese children [30]. LVH is frequent in obese children and is associated with systolic hypertension and insulin resistance. In children with AH who are at the same time overweight or obese, LVMI is higher than it would be in the presence of hypertension alone. Obesity in childhood is an independent risk factor for higher LVM in adult age [31]. Numerous hemodynamic and non-hemodynamic factors explain the role of obesity in the development of LVH and cardiac remodeling.



## Left ventricular hypertrophy and obesity

The risk of premature cardiovascular lesion is significantly higher in children with chronic kidney disease (CKD) [32]. LVH is already found in the early stage of CKD in pediatric patients, and at the introduction of dialysis therapy it is present in 69%-82% of these patients [33]. LVH is frequently found in patients following kidney transplantation.

A correlation was recorded between glomerular filtration decrease and LVM increase [33]. In children with CKD, there are multiple factors favoring LVH development, including AH, increased arterial stiffness and diastolic dysfunction of the heart. As LVH is occasionally found in adults with a history of kidney disease in childhood, echocardiographic monitoring at 6- to 12-month intervals is recommended in CKD patients and those on dialysis, along with reducing other CVD risk factors [34].



## Conclusion

Left ventricular hypertrophy is a measure of heart damage as a target organ in children with AH. Echocardiographic determination of LVM is part of the algorithm recommended for the work-up of children with AH and is used when deciding on the introduction of drug therapy, as well as in therapeutic response evaluation. Therefore, it is recommended that every child with hypertension undergoes initial and then follow up echocardiography. Although European guidelines recommend measurement of cIMT and PWVao , these parameters are still not listed as a mandatory examination and they have not yet been widely adopted in pediatric practice.



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# ARTERIAL HYPERTENSION IN CHILDREN AND ADOLESCENTS

**eBook**

Adipose tissue & arterial  
hypertension  
**4.3 Biology**



# Biology

## Novel insights into adipose tissue & arterial hypertension

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There is no doubt, that the relationship between excess of fat tissue and arterial hypertension (AH) exists. However, we may not realize how strong this relationship is. If you analyze epidemiological studies, it becomes clear that arterial hypertension occurs in about 5% of children and adolescents in the general population, while in children with excess body weight it can reach up to one third (1,2). The pathophysiological effects of overweight and increased fat mass are diverse and affect multiple organ systems. Many studies conducted in recent years have allowed to elucidate many details regarding the role of adipocytes in the development of hypertension. Nevertheless, some issues still remain incompletely explained. The important factors seem to be adipocyte-derived hormones, but the mechanism linking them to hypertension is not fully understood.

## Role of leptin

Leptin is one of the most potent adipocyte-derived hormones. It suppresses appetite and increases energy expenditure through its receptors in the hypothalamus. Consistent with its effects on energy expenditure, leptin increases sympathetic nervous system (SNS) activity, which increases the thermogenic brown adipose tissue (3–5). The activation of SNS may be associated with the increase of arterial stiffness and subsequent increase of blood pressure. What's even more interesting, leptin receptors were found directly in the aorta as well as numerous in vasculatures, and its level was related to the amount of adipose tissue (6,7) Leptin is also considered one of the factors contributing to the inflammation process in the arterial wall and subsequent endothelial dysfunction (8).



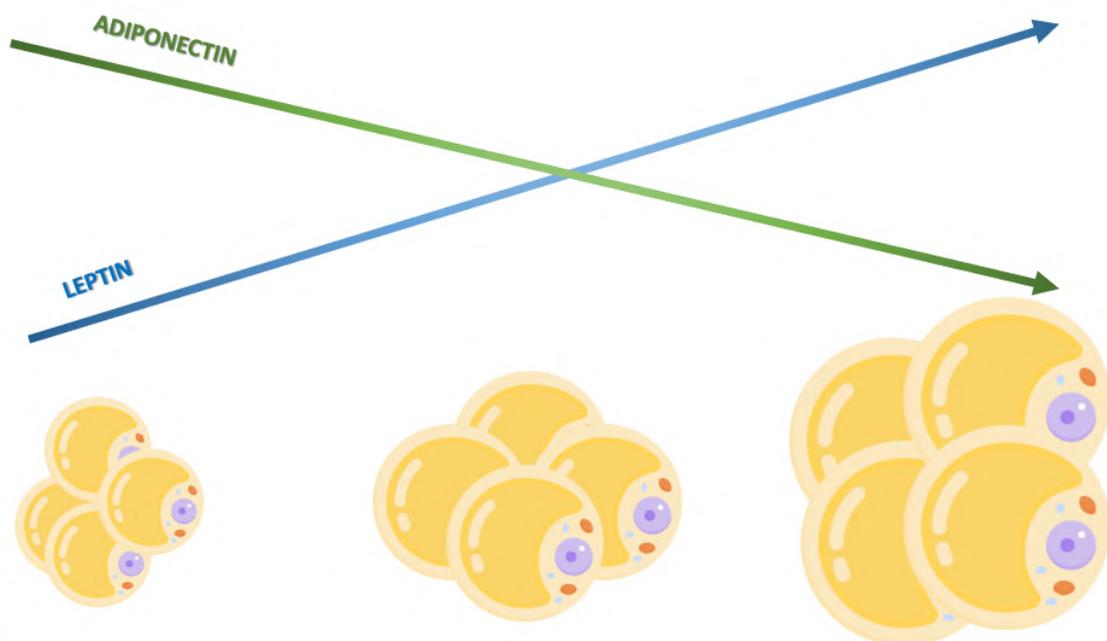


Leptin may also affect the renin–angiotensin–aldosterone system causing sodium retention and subsequent volume expansion (9,10)□That renal sympatho-activation and salt retention due to leptin stimulation seem to play a pivotal role in the increase in arterial pressure induced by this hormone. Interestingly, it has been shown, that adrenergic blockade reversed the increase in arterial pressure induced by leptin demonstrating the importance of the sympathetic nervous system in the arterial pressure response to leptin (11).

## Role of adiponectin

Adiponectin is an adipokine abundantly produced and secreted by adipose tissues. It has a beneficial effects on multiple tissues, including the heart, liver,<sup>93</sup> pancreatic  $\beta$ -cells, the brain, bone, kidneys, blood vessels, and immune cells. In contrast to other adipokines, the circulating levels of adiponectin are inversely proportional to total fat mass. Moreover, despite comparable levels of adipose tissue, metabolically healthy obesity (healthy) individuals display higher levels of circulating adiponectin, when compared with metabolically abnormal obesity (unhealthy) individuals (12,13).

Therefore, in people with excess body fat, the beneficial effects of adiponectin, such as antidiabetic, anti-inflammatory, antiatherogenic, and cardioprotective actions (14,15). Apart of mentioned above, it has a significant role in the inhibition of renin secretion. Thus, its reduced concentration level observed in patients with obesity, leads to an increase in the activity of the renin-angiotensin-aldosterone axis (16). Whether high adiponectin levels can account for all of the beneficial metabolic characteristics of metabolically healthy obesity individuals is currently not clear (12).



*Fig. 1. Changes in the concentration of adiponectin and leptin depending on the content of adipose tissue in the body.*

## Role of fat tissue in the activation of Angiotensin–Renin–Aldosterone system

The role of renin-angiotensin-aldosterone system is known to increase blood pressure. Physiologically renin is released from the kidneys as a reaction to a decrease in blood volume or sodium concentration level. Increased renin levels generate angiotensin I synthesis, which subsequently stimulates vasoconstriction - as a consequence, blood pressure increases. Angiotensin II stimulates the adrenal cortex to secrete aldosterone, which additionally maintains the correct volume through sodium retention (17). Contrary to lean hypertensive subjects, patients with obesity show a positive paradoxical correlation between sodium intake and aldosterone levels.



In non-obese patients, excessive sodium intake is expected to decrease aldosterone secretion by inhibiting the renin–angiotensin system(18). This effect is greatly diminished in patients with obesity. This lack of salt inhibitory effect on the activity of the renin-angiotensin-aldosterone axis in obese subjects appears to be caused by several of adipose tissue-derived factors. It has been suggested, that some adipokines, as yet unidentified, may directly stimulate aldosterone release from adrenals in the way independent from angiotensin II (19). Moreover, it has been proven that angiotensinogen and angiotensin I, and angiotensin II may be produced directly in adipocytes, and may stimulate adipose tissue cells to induce local production of aldosterone by autocrine/paracrine stimulation independently from the inhibitory effect of excessive salt consumption (20)

Conclusion: The adipose tissue is a metabolically active source of adipocytokines, hormones with a significant impact on the regulation of blood pressure.



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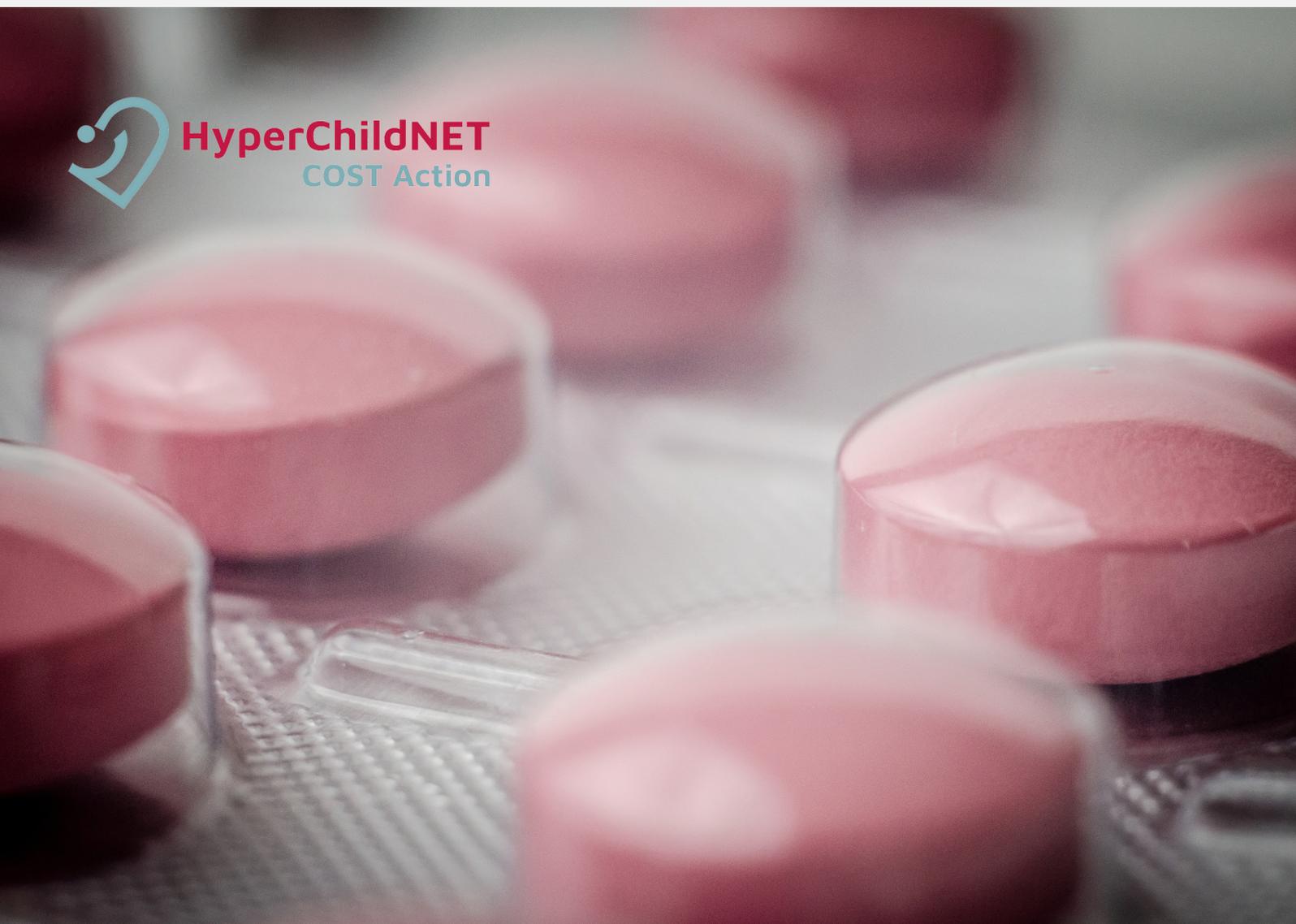
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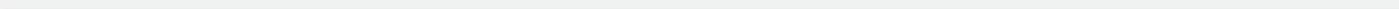




# ARTERIAL HYPERTENSION IN CHILDREN AND ADOLESCENTS

**eBook**

Treatment strategies  
**5.1 Pharmacotherapy**



# Pharmacotherapy:

## Treatment strategies

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The main goal of hypertension treatment is to reduce the risk of morbidity and mortality caused by hypertension complications. Lifestyle modification plays an important role in decreasing the blood pressure, but in many patients pharmacological treatment is necessary.

According to current recommendations, pharmacological treatment should be implemented in patients with secondary and symptomatic hypertension and in the presence of hypertension mediated organ damage (HMOD).

In grade 1 hypertension, lifestyle modification should be recommended and if there is no success in normalizing blood pressure (BP) after 12 months, pharmacotherapy should be started. Treatment is started with low doses of a single drug under blood pressure control. In the absence of the expected decrease in BP after 4 to 8 weeks of treatment, the dose of the drug should be gradually increased or switched to a preparation from another group of drugs if side effects occur.

Recommended doses of hypotensive drugs in children and adolescents are included in Table 19 in 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. (Lurbe E et al, 2016). Some, the most often used see in Table 1.

**Table 1. Selected antihypertensive medications for use in children and young adults on the basis of 2016 European Society of Hypertension guidelines (Lurbe E et al, 2016)**

Class of drugs	Drug	Recommended starting dose (per day)	Maximal dose (per day)	Dosing interval
ACE inhibitors	Ramipril	1.5-6 mg/kg		Daily
	Enalapril	0.08-0.6 mg/kg		Daily
ARBs	Candesartan	0.16-0.5 mg/kg		Daily
	Valsartan	0.4 mg/kg	40-80 mg	Daily
Calcium channel blockers	Amlodipine	0.06-0.3 mg/kg	5-10 mg	Daily
Diuretics	Hydrochlorothiazide	0.5-1 mg/kg	3 mg/kg/day	Daily
	Spironolactone	1 mg/kg	3.3 mg/kg up to 100 mg	Daily-twice daily
Beta blockers	Metoprolol	0.5-1 mg/kg	2 mg/kg	Daily-twice daily
Peripheral alpha-blockers	Doxazosin	1 mg	4 mg	Daily

In patients with secondary or grade 2 hypertension, combination therapy is recommended. In children and adolescents, drugs from 5 main drug groups are used:

1. angiotensin converting enzyme inhibitors (ACEIs)
2. angiotensin AT1 receptor blockers (ARBs - angiotensin receptor blockers)
3. calcium channel blockers (CCBs - calcium channel blockers)
4. beta-blockers (BB - beta blockers)
5. diuretics (diuretics)

In children and adolescents with primary hypertension, ACEIs, CCBs and ARBs are most commonly used. In girls of childbearing age, CCBs or BBs are recommended, and oral contraception is recommended for treatment with ACEIs and ARBs.

In patients with secondary HTN, the pathomechanism of hypertension and potential side effects of the drug should be considered in drug selection. In patients with chronic kidney disease (CKD), drugs that block the renin-angiotensin axis are recommended, while drugs that affect carbohydrate and lipid metabolism - BBs and thiazide diuretics - are contraindicated in children with diabetes.

Combination treatment should use drugs with different mechanisms of action - for example, drugs that block the renin-angiotensin axis with calcium channel blockers that cause vasodilation and diuretics that reduce water and sodium retention. The combination of 2 drugs affecting the RAAS (e.g., ACEI with ARB) is not recommended due to the increased risk of side effects.

The use of long-acting drugs - dosed once a day - improves patient cooperation and treatment effectiveness.



During pharmacological treatment, an important aspect is to achieve good BP control without side effects of the applied treatment. In assessing the effectiveness of treatment, we rely on home measurements, office measurements and periodically recommend 24-hour blood pressure measurements, especially when there are large differences in BP values between home and office measurements and in patients with increased cardiovascular risk.

Studies in recent years have shown that the risk of damage to various organs already increases at BP values above 90 pc and even above 75th percentile. In children with primary hypertension, we aim to achieve BP below 95 pc for age, sex and height for children < 16 years or below 140/90 mmHg in adolescents 16 years or older. Based on expert opinion, achieving blood pressure levels below the 90th percentile is a reasonable recommendation.



In children with type 1 or type 2 diabetes, blood pressure should be lowered below the 90th percentile, and in those aged 16 years below 120/80 mmHg. In children with chronic kidney disease (CKD) BP should be lowered below the 75th percentile. Based on ESCAPE Study results in children with CKD and proteinuria the goal should be to go below the 50th percentile. Achieving good blood pressure control reduces the risk of organ damage in children and cardiovascular complications in adults.



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# Pharmacotherapy

Pharmacotherapy is therapy using pharmaceuticals. It includes surgical therapy, radiation therapy, physical therapy, and other medical treatments. Among physicians, sometimes the term medical pharmacotherapy is distinguished from surgery. Experts in pharmacology are thus distinguished from surgeons. The medical use of pharmaceutical drugs requires specialized knowledge, training, and scientific background. Pharmacology is a branch of the biological sciences. The



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HyperChildNET is a COST Action (CA 19115) aimed at establishing a European sustainable and multidisciplinary network focused on acquiring a holistic understanding of the factors affecting high blood pressure in children in order to propose and implement corrective and preventive actions both globally and locally.

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