Review article

Cardiovascular prevention in childhood: a consensus document of the Italian Society of Cardiology Working Group on Congenital Heart Disease and Cardiovascular Prevention in Paediatric Age

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Cardiovascular diseases (CVD) may be manifested from a very early age. Genetic and environmental (epigenetic) factors interact to affect development and give rise to an abnormal phenotypical expression of genetic information, although not eliciting changes in the nucleotide sequence of DNA. It has been scientifically proven that increased oxidative stress (OS) caused by disease (*overweight, obesity, diabetes*), nutritional imbalances, unhealthy lifestyles (*smoking, alcohol, substance abuse*) in the mother during pregnancy may induce placental dysfunction, intrauterine growth restriction, prematurity, low birth weight, postnatal adiposity rebound, metabolic alterations and consequent onset of traditional cardiovascular risk factors.

OS represents the cornerstone in the onset of atherosclerosis and manifestation of CVD following an extended asymptomatic period. OS activates platelets and monocytes eliciting the release of pro-inflammatory, pro-atherogenic and pro-oxidising substances resulting in endothelial dysfunction, decrease in flow-mediated arterial dilatation and increase in carotid intima-media thickness. The prevention of CVD is defined as primordial (*aimed at preventing risk factors development*), primary (*aimed at early identification and treatment of risk factors*), secondary (*aimed at reducing risk of future events in patients who have already manifested a cardiovascular event*), and tertiary (*aimed at limiting the complex outcome of disease*). Atherosclerosis prevention should be implemented as early as possible. Appropriate screening should be carried out to identify children at high risk who are apparently healthy and implement measures including dietary and lifestyle changes, addition of nutritional supplements and, lastly, pharmacological treatment if risk profiles fail to normalise. Reinstating endothelial function during the reversible stage of atherosclerosis is crucial.

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Introduction

Cardiovascular diseases (CVD) represent the major clinical manifestation of atherosclerosis, an extended chronic-inflammatory-degenerative process which, as demonstrated by numerous keynote research studies, is known to originate during perinatal development and childhood.[1] CVD, particularly myocardial infarction (MI), are one of the leading causes of morbidity and mortality even amongst younger generations. In Italy, >130 000 individuals are affected by MI each year, with 20% relapsing over the following 12 months. Prevalence in the field of CVD has almost doubled from 271 million in 1990 to 523 million in

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2019. Worldwide, the number of deaths from CVD is on a constant upwards trend, increasing from 12 million in 1990 to 18.6 million in 2019. Mortality from MI alone has however decreased in recent decades thanks to the continual advances made in the field of medicine, with the percentage of deaths attributed to MI falling from 73% in 1999 to 56% in 2018. However, this decline has not been consistently observed in younger patients. A recent update issued by the American Heart Association (AHA) indicates the ongoing prevalence of CVD in almost half of the US population over the age of 40 years, and in 25% of young adults between the ages of 20 and 39 years.[2]

Consensus procedure

The RAND/UCLA appropriateness method was used to reach consensus among participants.[3]

The RAND is a modified Delphi methodology which is used in public health.[4] It was developed with the aim of identifying the collective opinion of experts and enabling the quantification of their agreement. Since consensus does not require to reach a full agreement among participants, a prespecified target agreement of 70% was selected.

A panel of experts, enrolled on the basis of their research, academic and practical background, and level of English language proficiency, were chosen among the members of the Italian Society of Cardiology (SIC) and those of the Working Group on Congenital Heart Disease and Cardiovascular Prevention in Paediatric Age of the same society.

A questionnaire was created, inviting the experts to rate the outlined questions. The latter were submitted to each expert member via e-mail. To produce an overall score (1–10) for each question, the experts were required to score them on the basis of a Likert scale ranging from 1 (strongly disagree) to 10 (strongly agree).

The consensus was finalized as follows:

(1) a strong recommendation (in favour) was made when 80% or more of the voting experts supported the position for a particular question;
(2) a moderate recommendation was made when the votes in favour of the question were between 70 and 80%;
(3) a 'no recommendation' option was adopted when the 70% threshold was not reached.

The results of the questionnaire and related level of recommendations are summarised in Table 1. Each topic has been extensively discussed throughout the text.

Atherosclerosis as an ongoing process and Barker hypothesis

The misconception that atherosclerosis and CVD are only clinically relevant throughout adulthood and old age has changed in recent years. In the 1980s, Barker hypothesized that the most frequently acquired dysmetabolic diseases, typically observed in adulthood, might be linked to the phenomenon of '*fetal programming*': maternal malnutrition during gestation, insufficient to meet the demands of the fetus, may critically affect growth, thus permanently compromising the structure and physiology of different organs and raising susceptibility in the neonate of developing disorders such as kidney failure, arterial hypertension, type 2 diabetes mellitus and CVD in adulthood.[5–7] In line with this theory, known as the 'Barker hypothesis', an interaction between environmental and genetic factors promotes the onset of diseases that progress throughout the embryonal, fetal and neonatal stages.[8,9] Based on this hypothesis, the onset of ischaemic cardiopathy in adulthood is linked to a low birth weight and malnutrition during the initial stages of life.[10]

Early oxidative stress and maternal health

Fetal growth is a complex process dependent on both genetic makeup and the intrauterine environment. An appropriate nutritional intake during pregnancy and breastfeeding is crucial in promoting normal development in the fetus/neonate. Dietary imbalances in the mother, excessive alcohol intake and inappropriate drug use can lead to morpho-functional modifications of the gametes with adverse health effects on the conceived offspring such as intrauterine growth restriction (IUGR), lower gestational age, low birth weight, postnatal adiposity rebound, metabolic alterations and consequent onset of CV risk factors. In subsequent years, IUGR may elicit the onset of nonalcoholic hepatic steatosis and metabolic syndrome (MS).

Even before conception, the various techniques used for assisted reproduction (ART) (in-vitro manipulations of gametes or embryos in a synthetic culture environment) can trigger oxidative stress (OS) and in turn negative cardiovascular effects in the offspring.[11,12]

It is now widely accepted that the peri-conceptional environment, nutrition and lifestyle of the parents may produce long-term effects on their children's health[13,14] (see Fig. 1). The child's cardiovascular health depends on the health of the pregnant mother.[15,16]

It is widely acknowledged that increased OS caused by pathological conditions in the mother during pregnancy (overweight, obesity and diabetes), nutritional imbalances and unhealthy pre and/or peri-conceptional lifestyles

Table 1 Questionnaire

Question	Level of agreement
1. Atherosclerosis is an ongoing process which starts in childhood in the form of fatty streak	High
2. Fetal programming or Barker hypothesis refers to the interaction between environmental and genetic factors in promoting the onset of many pathologies, cardiovascular diseases included	Moderate
3. Maternal lifestyle (such as dietary imbalances, excessive alcohol intake, drug abuse, smoking habit) can influence offspring's cardiovascular health in the future	Moderate
4. Oxidative stress can start since fetal life	High
5. Increased oxidative stress is characterised by reduced release of nitric oxide and increased production of r*eactive oxygen species* (*ROS*)	High
6. Oxidative stress triggers increased intima-media thickness and arterial rigidity in the medium and long term	High
7. Cardiovascular diseases are caused by the harmful combination of genetic and environmental (epigenetic) factors	High
8. The presence of risk factors in infancy (such as sedentary life, diabetes, smoking habit, overweight/obesity) is associated with an accelerated progression of atherosclerosis	High
9. Oxidative stress is responsible for affecting the expression of numerous microRNA levels	Moderate
10. Breastfeeding has less salt content than infant formula milk. As such, it can help in preventing hypertension	Moderate
11. Early identification of the children who are at increased risk of developing cardiovascular diseases is crucial (primary prevention)	High
12. Cardiovascular risk in children is often underestimated or ignored	High
13. The diagnosis of familial hypercholesterolemia is based on LDL cholesterol levels the most	High
14. Hypertension can start during childhood in the form of elevated blood pressure values in comparison with body size and gender	Moderate
15. The Mediterranean diet is well balanced and exerts a protective action against the occurrence of cardiovascular diseases	Moderate
16. Generally speaking, the first approach against cardiovascular risk factors in children is based on lifestyle modifications. Medical treatment is started when the former is not enough	High

(smoking, alcohol and substance abuse) may result in placental dysfunction and IUGR. Maternal stress during pregnancy induces fetal stress characterised by overproduction of reactive oxygen species (ROS) and consequent oxidative damage to mitochondrial DNA. Mitochondria provide the energy needed for cell function; accordingly, a reduction in numbers or functional alteration of mitochondria may damage cells, particularly those with a high energy demand, such as beta-pancreatic cells, endothelial cells, renal cells and cardiomyocytes, thus contributing to the onset of cardiometabolic diseases. Environmental and epigenetic factors may interact with genetic factors to affect uterine reprogramming of cells, resulting in remodelling at subcellular, tissue and organ levels with possible phenotypical fetal cardiac remodelling.[17,18]

Small for gestational age infants display high and early onset rates of hypertension (immature nephrogenesis results in the development of kidneys with a reduced number of filtrating units known as nephrons), stroke and diabetes in adulthood.[19–22]

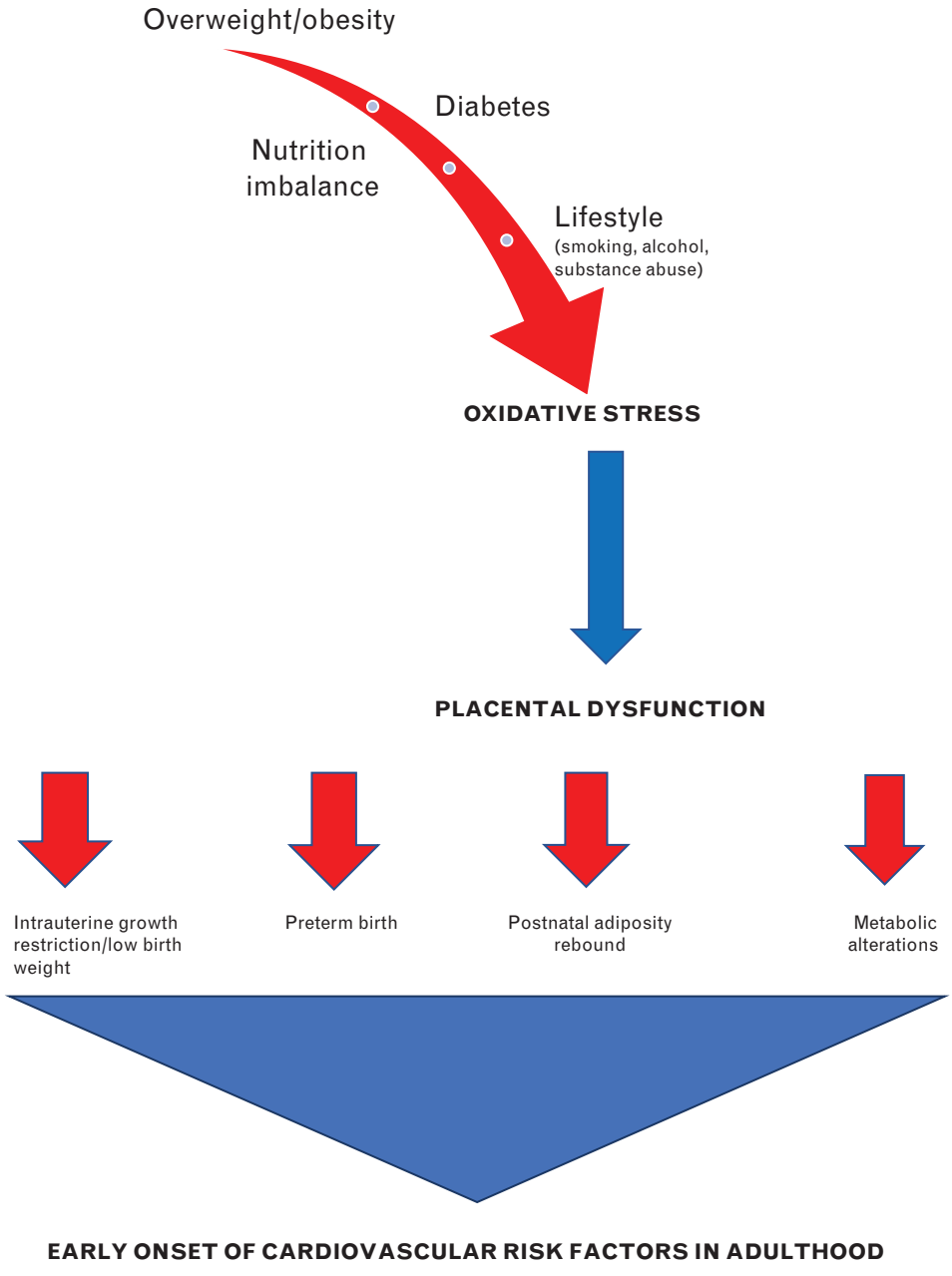
Also the prevalence of coronary artery disease is higher in these people than in their peers born with normal weight in the medium and long term.[23]

An inverse and independent of body mass index (BMI) relationship between low birth weight and stroke among adult men has recently been described. As such low birth weight should be considered in stroke risk assessment.[24]

Fetal exposure to high cholesterol levels, diabetes and obesity in the mother is associated with an increased risk for and progression of atherosclerosis. Infants born to mothers affected by hypercholesterolaemia during pregnancy display atherosclerotic lesions of the abdominal aorta, which are not present in infants born to mothers with normal cholesterol levels.[25] Indeed, maternal hypercholesterolaemia in pregnancy may give rise to hypercholesterolaemia and lipid peroxidation in fetal plasma with consequent endothelial dysfunction and formation of early onset atherosclerotic lesions due to OS.[26–28]

Moreover, smoking and maternal exposure to a series of environmental pollutants both in pregnancy and during breastfeeding may elicit epigenetic alterations of genic expression implicated in the onset and progression of CVD. Specifically, if the mother smokes this may induce epigenetic modifications in her offspring, with renal alterations (reduced number of nephrons), endocrine (obesity, diabetes) and metabolic changes [reduction in high-density lipoprotein cholesterol (HDL-C), with consequent decrease in protective properties against atherosclerosis].[29,30] At the age of 5 years, babies born to mothers who smoke display increased carotid intima-media thickness (IMT) and reduction of flow-mediated dilation (FMD), both indices of subclinical atherosclerosis which may also be manifested following exposure to passive smoking.[26,31,32] Exposure to passive smoking in the offspring of smoker parents is associated with a higher risk of developing carotid artery plaques in adulthood versus children of nonsmoker parents.[33] Moreover, children affected by allergic rhinitis who are exposed to passive smoking manifest a decrease of nitric oxide (vasodilator) and FMD, increased IMT, increased levels of isoprostanes and nicotinamide-adenine dinucleotide phosphate oxidase (NADPH oxidase), indicating an increased OS.[34] Nox2-generated OS reduces NO bioavailability thus impairing FMD in children exposed to second-hand smoke.[35] Likewise, exposure to environmental pollutants (heavy metals such as nickel, cadmium and arsenic and ionizing radiation or ultraviolet rays) may result in endothelial dysfunction with alteration of endothelial

Fig. 1



Perinatal programming of cardiovascular risk factors.

permeability, subendothelial leukocyte adhesion and migration and subsequent production of foam cells, promoting the formation of atherosclerotic plaques.[36]

It has been demonstrated how CV risk factors in childhood [raised low-density lipoprotein cholesterol (LDL-C), reduced high-density lipoprotein cholesterol (HDL-C), arterial hypertension, obesity, diabetes, smoking, lack of physical activity and low intake of vegetables] may lead after a 6-year period of exposure to an increased IMT in young adulthood.[37]

A large prospective cohort study enrolling children and adolescents (aged 3–19 years) evaluated the relationship between five risk factors during childhood [e.g. body mass index (BMI), systolic blood pressure, total cholesterol level, triglyceride level, and juvenile smoking] and adverse cardiovascular events occurring during adulthood after a mean follow-up of 35 years. A harmful association was proved between the risk factors alone or in combination and the onset of adverse cardiovascular events as early as 40 years of age as well as death before the age of 60.[38]

Also, the familial environment has a significant impact on children's outcome in terms of health.[39]

In fact, children from low-income areas are more likely to be overweight and obese and engage in fewer sport activities in comparison with those belonging to high-income families.[40,41]

It has also been observed that children living with both parents have greater awareness of cardiovascular risk factors and more correct eating habits than their counterparts whose parents are separated.[42,43]

Over recent years, the number of grandparents who take care of their grandchildren has been on an upward trend. Coexistence with grandparents is beneficial for children and adolescents' health, most of all when they are primary caregivers. Their role in controlling grandchildren is crucial in terms of limiting junk food intake and promoting physical activity thus reducing the risk of obesity.[44]

Not only that, but as grandparents are involved in childcare, mothers have more job opportunities, thus increasing income and improving children's health in a virtuous circle.[45]

These findings all support the notion whereby the presence of risk factors in infancy is associated with an increased progression of atherosclerosis in adulthood.[46,47] Furthermore, overweight or obese children also display an increased IMT in adulthood compared with their nonobese peers.[48,49]

Oxidative stress and atherosclerosis

Helmut Sies, an eminent German scientist, gained recognition as a pioneer in the field of OS following publication of numerous papers from 1985 onwards.[50]

OS is characterised by the overproduction of ROS and a decrease in antioxidant enzymes. Under physiological conditions, ROS and antioxidants achieve an equilibrium, whilst under conditions of stress an increased production of ROS is observed, resulting in inflammation, cell proliferation, cardiomyocyte apoptosis, leucocyte migration and fibrosis: processes which all contribute towards compromising vascular function and eliciting onset of early atherosclerosis.[51] OS underlies the development of CVD, manifested following an extended period in which patients are asymptomatic.[52]

Over a lifetime, numerous situations may be capable of laying the basis for development of OS. As an example, ART may elicit onset of OS and negatively affect the cardiovascular system of offspring thus conceived.[11] Indeed, ART is associated with in-vitro manipulation of gametes or embryos in a synthetic culture medium devoid of natural antioxidants. Numerous factors may contribute to the onset of OS in the context of ART, including cryopreservation, gamete and embryo manipulation, visible light, pH fluctuations, temperature fluctuations, partial pressure of oxygen (PaO2), centrifuging, and culture medium. Accordingly, the lack of natural antioxidants and overproduction of ROS hamper the presence of a sustained pro-oxidant/antioxidant equilibrium *in vitro*, with resulting OS producing a potentially negative effect on the embryo. Parents involved in the donation of gametes for ART may likewise be the cause of increased OS if they have an unhealthy lifestyle, resulting in permanent negative effects on the offspring in terms of early onset of cardiovascular disease.[11,53–55]

Generally speaking, all traditional cardiovascular risk factors (hypercholesterolaemia, smoking, diabetes, arterial hypertension, overweight/obesity) are associated with increased OS, promoting the progression of atherosclerosis and CVD.[56]

Increased OS acts by decreasing nitric oxide production (NO) in endothelial cells, consequently resulting in endothelial dysfunction.[57] In these conditions, vasal endothelium loses its antioxidant and anti-inflammatory capacities and, conversely, produces pro-oxidant and pro-inflammatory substances. An increased vascular permeability to lipoproteins, higher expression of inflammatory cytokines and adhesion molecules, and migration of monocytes in the subendothelial space occurs, thus creating the conditions for production of foam cells, which are key drivers in the atherosclerotic process, and subsequently resulting in the onset of CVD. A study of hypercholesterolemic children demonstrated how increased OS promotes platelet activation and consequent release into the blood of high amounts of sCD40L – a pro-atherogenic and pro-inflammatory protein significantly correlated with LDL-C.[58]

Experimental studies performed using animal models suggest that NADPH oxidase plays a crucial role in modulating arterial tone, contributing to the pathogenesis of anatomical and functional alterations of the arterial wall in children affected by early onset atherosclerosis.[59,60] Patients affected by chronic granulomatosis X linked with a congenital gp91phox deficiency (one of the five catalytic subunits of NADPH oxidase) present with an increased FMD and significant decrease of OS. This finding supports the hypothesis indicating the involvement of NADPH oxidase in the modulation of vasal tone by enhancing vasoconstriction.[61] Platelet studies therefore may represent a valid, noninvasive means of measuring NADPH oxidase regulation in patients at risk of or manifesting overt atherosclerosis.[62]

OS is associated with arterial dysfunction and increased IMT in children with high cholesterol levels. Platelet expression of gp91phox, the catalytic unit of NADPH oxidase, may be implicated in the pathogenesis of anatomical and functional alterations of the arterial wall in children with hypercholesterolaemia.[63]

Furthermore, in children with concomitant cardiovascular risk factors including hypercholesterolaemia and obesity, NOX2, the catalytic core of NADPH oxidase, underlies the onset of initial manifestations of atherosclerotic disease.[64] Subsequently, using advanced echocardiographic techniques (2D and 3D speckle tracking echocardiography) early onset alterations in myocardial contractility were detected for the first time in these children. In particular, compared with healthy controls, a reduced strain was detected in the left ventricle in children with dyslipidaemia. In patients who were both obese and affected by hypercholesterolaemia strain reduction affected both ventricles.[65]

Additionally, hypercholesterolemic children displayed significant monocyte activation with consequent increase in myeloperoxidase compared with healthy controls. The latter is a glycoprotein released by polymorphonucleate neutrophils and involved in oxidative processes through the production of hypochlorous acid, a potent oxidant. Hypercholesterolemic children are subjected to prolonged OS, with myeloperoxidase playing a key role in promoting overproduction of ROS implicated in LDL oxidation, and subsequent production of foam cells, the first step of the atherosclerotic process.[66]

Beyond genetics: epigenetics and cardiovascular risk

Over the last two decades numerous epidemiological and experimental studies have been undertaken in an attempt to clarify the pathogenesis of atherosclerosis.

Although high serum levels of oxidised LDL-C represent the leading cause in the onset of the disease, a wide range of aetiological and pathogenetic factors of genetic and environmental origin (epigenetics) act in unison to promote the onset and progression, on a local and systemic level, of atherosclerosis. In mammals, epigenetic factors induce biochemical modifications comprising DNA methylation and histone modification resulting in changes to the chromatin structure and small noncoding RNA pathway as a biological response to environmental stress factors that may then be transmitted to the offspring, thus affecting atherosclerotic risk. Recent studies have focussed on the investigation of microRNAs, which are short noncoding RNA sequences playing a fundamental role in vascular physiology and pathophysiology from the initial stages of embryonal development. Numerous studies have demonstrated their role in modulating genes involved in both physiological development of the cardiovascular system and in pathophysiological mechanisms underlying CVD from the initial stages of embryonal development (*cardiac modelling and heart failure, arrhythmias, fibrosis, atherosclerosis, myocardial and cerebral ischaemia*).[67]

MicroRNAs are implicated in the pathogenesis of atherosclerosis, and therefore of CVD.[68] In view of the stability of microRNA in serum, a modified expression (reduced or increased) may reflect the presence of pathological conditions. Moreover, microRNAs are indicated for use as noninvasive biomarkers in the early detection of asymptomatic coronary artery disease in obese children with MS.[69]

OS is capable of affecting expression levels of numerous microRNAs. Evidence has been provided demonstrating an up-regulation of microRNAs 33a and 33b, implicated in the modulation of cholesterol homeostasis, and microRNA 200c, associated with endothelial dysfunction, in hypercholesterolemic children.[70,71]

OS-induced up-regulation of microRNA 200c has also been observed in patients with psoriasis and correlates with both the severity of the disease and determinants of cardiovascular risk. The up-regulation of microRNA 200c may play a major role in inflammation and OS augmentation underpinning the psoriatic process, inducing anatomical and functional modifications (cardiac hypertrophy, diastolic dysfunction, increased arterial stiffness) and raising the risk of adverse cardiovascular events in these patients.[72]

Breastfeeding. The breastfeeding of neonates versus bottle feeding should be strongly encouraged based on enhanced nutritional and psycho-affective properties, and should be extended for as long as possible. Key health organisations all advocate breastfeeding as an optimal source of nutrition in infants. Breastfed infants display a reduced risk of atopic dermatitis and gastroenteritis, as well as a frequently higher intelligence quotient (IQ) later in life. Benefits for the mother include a reduced risk of breast cancer, ovarian cancer, cardiometabolic diseases (type 2 diabetes mellitus, arterial hypertension and CVD) and postpartum depression.[73–77] Infant formula moreover has a higher sodium content than breast milk and may predispose to onset of hypertension, although this effect has recently been subjected to debate.[78,79]

Weaning

The World Health Organization recommends that weaning should commence between the 5th and 6th months of age. The early introduction (before the 4th month) of

complementary foods, particularly of high protein and energy content, may be associated with overweight and obesity in later years.[70,80]

Adiposity rebound

Adiposity rebound represents the second rise in BMI, which usually occurs between the ages of 5 and 7 years. After the first year, BMI levels decrease physiologically. Young age at adiposity rebound represents a known trigger for later obesity and increased cardiovascular risk in both genders. Adiposity rebound may also be caused by the dietary introduction of excess protein during the first year.[81,82] BMI trajectories from infancy to adulthood vary from person to person, with a high BMI trajectory over the first few years of life being predictive of an increased cardiovascular risk.[83] The CARDIA-study demonstrated how the maintaining of BMI levels within the physiological range and an appropriate lifestyle correlate with a low cardiovascular risk profile.[84]

Early identification of children at increased cardiovascular risk: an underestimated problem

The identification from an early age of apparently healthy children at increased risk of early onset atherosclerosis and CVD for the purpose of enrolling them in a follow-up and treatment programme is crucial. The main aim is to normalise endothelial function whilst atherosclerosis is still at a reversible stage. A healthy lifestyle and nutrition adhered to by the whole family represent the first and most important steps.[85]

Currently, primary prevention remains firmly focussed on traditional cardiovascular risk factors (*familiarity, smoking, diabetes, hypercholesterolaemia, arterial hypertension, overweight/obesity*) although, as illustrated previously, numerous other epigenetic factors associated with embryonal and fetal development are of comparable importance.[86]

Appropriate screening should be carried out to identify children and adolescents at high cardiovascular risk with the aim of commencing treatment as early as possible, preferably *in utero*, implementing lifestyle measures and, where necessary, pharmacological treatment.[86–89]

During pregnancy preventive strategies should be developed before the onset of cardiovascular diseases. Women with cardiovascular risk factors should undergo prepregnancy counselling with a multidisciplinary team. Counselling should take place at least 6 months prior to planned conception. Cardiovascular risk factors should be periodically re-evaluated throughout pregnancy.[90]

Regarding the specific risk factors, the European Society of Cardiology (ESC) recommend treating high blood pressure when systolic values are $\geq$140 mmHg and/or diastolic values $\geq$90 mmHg.[91]

Beta blockers and calcium-channel blockers are the suggested medications.[92]

The American Diabetic Association (ADA) recommend strict glycaemic control with a haemoglobin A1c target of $<$6.5% before conception.[93] During pregnancy the following glycaemic targets are recommended:

(1) Fasting: glucose $<$95 mg/dl (5.3 mmol/l) and
   (a) 1 h postprandial glucose $<$140 mg/dl (7.8 mmol/l) or
   (b) 2 h postprandial glucose $<$120 mg/dl (6.7 mmol/l).

The management of diabetes involves both pharmacologic and nonpharmacologic measures, including a carbohydrate-controlled diet and regular physical exercise.[94]

Women with familial hypercholesterolemia (FH) and hypertriglyceridemia are particularly at risk during pregnancy as there are very few options for their treatment. Statins, niacin, fibrates, and ezetimibe are all strongly contraindicated because of the risk of fetal malformation. The guidelines recommend women stopping statin therapy at least 4 weeks before quitting taking contraceptives and during pregnancy and lactation.[94]

Omega-3 fatty acids and bile acid sequestrants are the only safe drugs which can be administered during pregnancy. Diet and aerobic exercise are essential as well.[94]

To prevent obesity-related complications and improve maternal and fetal outcomes, guidelines suggest regular weight control before conception and during pregnancy. Controlled diet and regular exercise help a lot in preventing gestational diabetes, need for caesarean section, and infantile macrosomia from occurring.[95]

Weight control should be extended up to 3 months following delivery.[96]

When starting preventive strategies

In the released official documents there is no consensus as to whether children at high risk of developing atherosclerosis should be identified through early screening strategies. This may at least in part be explained by the fact that cardiovascular risk factors in children are often underestimated.[97]

However, in 2011, the National Heart, Lung, and Blood Institute (NHLBI) recommended lipid panel screening in all children and adolescents aged 9–11 and 17–19, respectively.[98]

In 2016, however, the US Preventive Services Task Force (USPSTF) did not recommend the screening of children and adolescents, since the evidence regarding its effectiveness was considered poor.[99]

Risk factors in children and accelerated atherosclerosis

Diagnosis of familial hypercholesterolemia in paediatric age

A family history of premature coronary artery disease in addition to the detection of elevated LDL-C levels represent the two key elements to highly suspect family hypercholesterolemia (FH).

In particular:

(1) An LDL-C level $\geq$5 mmol/l (190 mg/dl) detected through two consecutive checks, separated by 3 months of low lipid diet, is highly indicative of FH.
(2) A history of premature coronary artery disease in a first- or second-degree relative and/or elevated LDL-C in one parent, in combination with an LDL-C level $\geq$4 mmol/l (160 mg/dl) is highly indicative of FH.
(3) If one the parent has a genetic diagnosis of FH, an LDL-C level $\geq$3.5 mmol/l (130 mg/dl) suggests the presence of FH.
(4) All possible causes of secondary hypercholesterolemia must be excluded before making a diagnosis of FH.
(5) If a pathological mutation on the LDL receptor is identified in a first-degree family member, testing of the child is recommended.
(6) If a parent dies from early coronary artery disease and the child has moderate hypercholesterolemia, he/she should get genetic testing for FH and plasma levels of lipoprotein a [Lp(a)] should be evaluated.[100,101]

Screening for familial hypercholesterolemia in affected children and adolescents

Family screening using both phenotypic strategies and genetic testing is recommended. If DNA test is not available, a phenotypic strategy based on age, gender, and LDL-C levels should be used.

Children with suspected heterozygous FH should be screened starting from the age of 5. Screening for homozygous FH should be done at the first clinical suspicion (e.g. when both parents are affected or in the presence of xanthomas and/or xhantelasmas).

The age of screening in childhood should be the same for both genders.[102,103]

Clinical management of familial hypercholesterolemia in children and adolescents

Family screening for serum lipids and detection of mutated genes should be performed in familial forms of hypercholesterolaemia.[104–106] Early identification of children with FH before puberty is very important with the aim of starting lifestyle modifications and ensuring long-term adherence to them.

Children with an established diagnosis of FH should be treated with a hypolipidemic diet at the time of diagnosis and therapy with statins initiated between ages 8 and 10 years. In the homozygous form of the disease, drug treatment should be started at the time of diagnosis. In all children and adolescents diagnosed with FH, the concentration of Lp(a) should be quantified for a more accurate cardiovascular risk stratification. There is no reason to start treatment at a different age based on gender. For children and adolescents between the ages of 8 and 10 years, the level of LDL-C should be reduced by 50%. For those aged $\geq$10 years, particularly if there are other risk factors, including elevated Lp(a) levels, the target level LDL-C should be $<$3.5 mmol/l (130 mg/dl). The benefit of reducing LDL-C levels should be balanced with the side effects of drug treatment in the long term.

Adherence to treatment should be verified if children with heterozygous FH do not reach the 'target' levels of LDL-C. Patients who do not adhere to treatment should be addressed to specialized centres, the same as for those affected by the heterozygous form of the disease.[101]

Blood pressure screening in paediatric age

Arterial hypertension in children and adolescents is a frequently overlooked health issue. Indeed, arterial hypertension is mistakenly considered a disease confined to adults. On the contrary, children should be screened for high arterial blood pressure on a yearly basis from the third year, or at each appointment in the presence of risk factors such as obesity and/or dyslipidaemia.[107]

There is no agreement regarding the utility of screening children for high blood pressure. In fact, the American Academy of Paediatrics (AAP) recommend that blood pressure should be annually measured in all children and adolescents aged $\geq$3 years, whereas the USPSTF have outlined that there is insufficient evidence to support such a screening.[108]

Hypertension seems to involve about 10% of the paediatric population, with some regional fluctuations. However, as blood pressure is labile in paediatric age, caution is needed before making a diagnosis of hypertension in children.[109]

Early vascular ageing syndrome

Early vascular ageing (EVA) is a definition which was first introduced in 2008. It refers to early deterioration in arterial structure and function, leading to increased arterial rigidity, mimicking the effects of ageing. It develops as a consequence of exposure to adverse environmental and genetic factors since fetal life.[110] Arterial rigidity is a strong predictor of adverse cardiovascular events and all-cause mortality in middle-aged and elderly people. It is also a marker of early atherosclerosis in young individuals.[111] It is interesting to note that, in a philosophical way, some authors think that the relationship between cardiovascular diseases and age is an unavoidable effect of living longer and, as such, proof of robustness rather than something we should cope with.[112] A typical example of EVA is seen in children with high blood pressure. They show an accelerated biological development, their biological age being 4–5 years older than their real age. Arterial wall has a decreased elastin content and an increased quantity of collagen for age and gender.[113] Not only their arterial rigidity, but also their anthropometric and neuro-immuno-metabolic features are the same as those described in adults with primary hypertension.[114] With the epidemic in childhood obesity and the increased rate of hypertension detected in paediatric age there is an urgent need for stratifying cardiovascular risk for youth, the earlier the better with a view of shedding light on cardiovascular risk late in life and delaying EVA. As such, uniformity in stating what is normal concerning arterial elasticity is crucial.[115]

Screening for obesity in children and adolescents

The AAP recommend that weight should be measured in all patients from the age of 2, whilst the USPSTF suggest that the screening should involve children 6 years of age and older. In case of overweight or obesity, behavioural treatment for weight reduction is suggested.[116] Overweight in paediatric age is usually defined as a BMI between the 85th and 94th percentiles, and obesity as a BMI $\geq$95th percentile.[117]

Childhood obesity has been found to be strongly linked with both preclinical and clinical manifestations of atherosclerosis in adulthood.[118]

Furthermore, preventing and treating childhood overweight/obesity could reduce not only the risk of atherosclerosis but also a number of other adverse health outcomes when they are adults, namely: morbid obesity, MS, type 2 diabetes, hypertension with left ventricular hypertrophy and diastolic dysfunction.[119–123]

Diabetes screening

Diabetes refers to a series of metabolic disorders characterized by hyperglycaemia. Type 2 diabetes is characterized by insulin resistance and progressive loss of insulin secretion by pancreatic β cells.[124]

Conversely, type 1 diabetes is the result of autoimmune destruction of β cells, which usually leads to absolute insulin deficiency. Prediabetes is the term used for individuals whose blood glucose levels [*measured by plasma glucose level or haemoglobin A1c* (*HbA1c*) *level*] are higher than normal but do not meet the criteria for diabetes. The definitions of prediabetes and diabetes in children and adolescents are the same as in adults. A fasting plasma glucose level between 100 and 125 mg/dl (5.6–6.9 mmol/l), an HbA1c level from 5.7% to 6.4%, or a 2-h afterload glucose level between 140 and 199 mg/dl (7.8–11.0 mmol/l) is consistent with prediabetes.[125]

A fasting plasma glucose level of 126 mg/dl (7.0 mmol/l) or higher, an HbA1c level of 6.5% or higher, or a 2-h afterload glucose level of 200 mg/dl (11.1 mmol/l) or higher is consistent with the diagnosis of type 2 diabetes. The diagnosis of prediabetes or type 2 diabetes should be confirmed with repeating tests before starting interventions.[126]

Although there is insufficient scientific evidence to recommend for or against screening in patients with no signs or symptoms, prediabetes and type 2 diabetes may be detected by measuring fasting glucose or HbA1c levels, or with an oral glucose tolerance test.[127]

The American Diabetes Association recommend risk-based screening for type 2 diabetes after onset of puberty or at age 10 in children who are overweight (BMI $\geq$85th percentile) or obese (BMI $\geq$95th percentile) and with one or more additional risk factors for diabetes.[128]

Children considered at high risk of diabetes should be screened every 3 years if the first test is normal or more frequently if their BMI increases.

Physical activity and healthy eating habits continue to be the cornerstones of diabetes prevention. Although no drugs are approved by the Food and Drug Administration (FDA) for diabetes prevention, strong evidence supports the use of metformin in adults with prediabetes. Metformin and insulin remain the traditional medications, while liraglutide has recently been indicated for children over the age of 10 in both the United States and Europe.[129]

Rates of progression from prediabetes to type 2 diabetes range from 5.8% to 18.3% per year, depending on the population studied. The rate of type 2 diabetes is on an upward trajectory in young people, most commonly at the onset of puberty. The most important risk factor for type 2 diabetes is obesity. Young people with type 2 diabetes have a higher risk of hypertension, elevated cholesterol levels, and nonalcoholic fatty liver disease.[130]

Particularly if left untreated, diabetes can lead to negative health outcomes as time goes by, including heart attack, stroke, renal failure, and blindness.[131]

A screening programme conducted in a sample of schoolchildren of the Mountain Community of Serre Calabre, Italy (approx. 1650 patients) using diagnostic criteria of the International Diabetes Federation corrected for the paediatric age range resulted in the identification of a 2.3% prevalence of MS.[132] Further analysis of the subgroups in this population allowed the percentile distribution of the different components of MS to be defined.[133] By adopting more stringent diagnostic criteria than those of the International Diabetes Federation ($\geq 90^{\circ}$ percentile for waist circumference, triglycerides, glycaemia, systolic and diastolic blood pressure and $\leq 10^{\circ}$ for HDL-C), the definition of MS based on the presence of at least three abnormal components (three out of five) yielded a higher prevalence of MS (4.2%) than that detected previously (2.3%).[134]

Nonpharmacological approach: nutrition and lifestyle: the role of Mediterranean diet

A Mediterranean diet, appointed intangible World Heritage in 2010 due to its key nutritional and cultural traits, may produce a positive impact on dietary-induced epigenetic modifications.[135] The findings obtained in a meta-analysis suggest that a Mediterranean diet is associated with a lower prevalence and progression of CVD, exerting positive effects on individual components. A Mediterranean diet may be readily adopted by populations of diverse cultural origins.[136]

A large epidemiological study revealed how both cardiovascular risk factors and serum total cholesterol levels in children are frequently overlooked. However, children following a Mediterranean diet present with a lower BMI and lower serum total cholesterol levels compared with those adhering to other types of diet. Moreover, children who spend more time playing sports or in the open air display better adherence to the Mediterranean diet versus children who stay inside for hours watching television or using their computers. Adherence to a Mediterranean diet represents a decisive factor in the prevention of CVD.[137] However, the IDEFICS (*identification and prevention of dietary- and lifestyle-induced health effects in children and infants*) study revealed how, in Italy, only one out of every two schoolchildren follows a Mediterranean diet, with the percentage reducing further as they age.[138] Furthermore, it has recently been proved that a dietary intervention with the Mediterranean diet in children with familial or polygenic hyperlipidaemia improves their lipid profile in terms of reaching the target levels of LDL-C but not of HDL-C.[139]

The dietary addition of nutritional supplements such as high viscosity glucomannan significantly improves metabolic imbalances, reducing blood pressure and body weight.[140,141] Likewise, red rice yeast extract and policosanols have been used for the first time in hypercholesterolemic children to obtain a significant reduction in both total and LDL cholesterol and apoprotein B.[142] The importance of practising aerobic activities as a game rather than being obliged to frequent a gym should also be underlined. Increased physical activity and a reduction of sedentary behaviours contribute towards improving metabolic health in children and adolescents.[143–145] Regular physical activity also regulates endothelial function in children.[146] Conversely, a sedentary lifestyle implies an increased risk of developing early onset atherosclerosis and CVD.[147–150]

Should lifestyle changes over a period of 6–12 months not produce the desired results, specific pharmacological treatment should be initiated in children over the age of 8–10 years.[100]

The use of metformin in the prevention of diabetes mellitus has not been formally trialled in the paediatric population and long-term data are limited. Metformin has however been used in clinical trials of nondiabetic children yielding beneficial effects with regard to weight loss.[100,151,152] The first step to be taken, prior to pharmacological treatment, in diabetic children is represented by the establishing of lifestyle changes. Administration of metformin associated with a low-fat diet and physical activity represents the first-line therapeutic option in diabetic children over the age of 10 years.[153]

Hypertension in children is initially treated by attempting to normalise blood pressure by means of lifestyle changes (weight loss if overweight or obese), a healthy diet (including fresh fruit and vegetables, fibre and low-fat dairy products, and reduced salt intake) and regular aerobic exercise. Use of tobacco and alcohol should be avoided in all adolescents, particularly those with hypertension, as it raises the risk of CVD. Children affected by arterial hypertension that fails to normalise despite the implementation of lifestyle changes should be prescribed antihypertensive medication.[154–157]

Conclusions

The prevention of cardiometabolic diseases may be implemented at different stages of life. Prevention may be primordial (*aimed at preventing risk factors*), primary (*aimed at the early identification and treatment of risk factors*), secondary (*aimed at reducing the risk of future events in patients who have previously manifested a cardiovascular event*) and tertiary (*aimed at limiting and controlling the complex outcome of disease*).[158,159]

Genetic and environmental factors (also known as epigenetic factors) are capable of interacting as early as the

gestational stage to induce genetic reprogramming *in utero*, thus giving rise to the early onset of atherosclerosis in children and adolescents and to CVD in young adults. Epigenetic processes influence gene expression, producing important changes in cell differentiation and function and thus impinging on the health and adaptability of the organism. In this respect, not only do childhood cardiovascular risk factors predict subclinical adult cardiovascular disease, but they are also linked to clinical events, including the fatal, in mid-life.[160]

Epigenetic risk factors represent a new and exciting challenge due to their potential for recognising cardiovascular risk from a very early age and the possibility of developing innovative therapeutic options frequently constituted by lifestyle changes. As an example, an appropriate intake of calories and micro and macro-nutrients should be ensured prior to conception and during pregnancy and a healthy lifestyle followed with the aim of producing a positive impact on epigenetic factors.[66,161–163] Prevention means also limiting drug administration to the most severe form of early onset of CV risk factors, thus reducing the medical care economic burden as well.[164]

Likewise, the prevention of MI in young adults constitutes a further substantial public health challenge. The majority of young people affected by MI present with preexisting CV risk factors (obesity, diabetes, hypertension and dyslipidaemia), as well as higher usage of tobacco and rates of substance abuse, even post-MI.[165] However, these patients are less likely to be treated with preventive therapies, frequently being categorized as low risk. No efforts should be spared in promoting primary and secondary prevention in this field.[164]

These challenges should represent a priority task in the future of modern medicine.[165]

Conflicts of interest

There are no conflicts of interest.

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