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HEALTH SCIENCES

Precocious evaluation of cardiovascular risk and its correlation with perinatal condition

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Abstract: The cardiovascular disease is the main cause of worldwide death. This profile is potentialized by the increased severity of infections in people with obesity, type 2 diabetes and hypertension. Children and adolescents are target groups for the prevention of non-communicable diseases. The Developmental Origins of Health and Disease concept points that perinatal conditions are an important risk factor to development of non-communicable disease in adulthood. In this context, the present review identifies perinatal factor that induces precocious cardiovascular risk factors, related with cardiometabolic syndrome. The low or high birth weight and caesarean delivery are risk factors that induce increased occurrence of cardiovascular risk biomarkers in children and adolescents, while the breast feeding or feeding with breast milk from the birth until two years-old is a protector strategy. Evaluation of perinatal conditions associated with precocious identification of cardiovascular risk factors in children and adolescents is an efficient strategy to prevent and control cardiovascular mortality; through interventions, as lifestyle changes during vulnerable windows of development, able to set up the risk to cardiometabolic disease.

Key words: infancy, adolescence, cardiovascular risk, perinatal life.

INTRODUCTION

The cardiovascular diseases are the main cause of worldwide death (WHO 2018b). More than 85% of premature death (people between 30 and 69 years-old) due to non-communicable diseases happen in underdeveloped and developing countries (WHO 2018d). This profile may be potentialized by the increased severity of infections in people with cardiometabolic diseases, as observed in the actual pandemic of COVID-19 and other infection disease common in Latin America, as Dengue or Chagas diseases (Lucchetti et al. 2019, Lee et al. 2020, Richardson 2020). Central obesity, raised triglycerides, reduced high density lipoprotein cholesterol (HDL), raised blood pressure (BP) and raised fasting plasma glucose are a cluster of interconnect physiological, biochemical, clinical and metabolic factors that define the cardiometabolic syndrome, which directly increases the risk of cardiovascular death (Federation 2015, von Bibra et al. 2016). The lifestyle characterized by excess of discretionary food and sedentarism induces a chronic inflammatory state, which has been considered a relevant physio-pathological mechanism of cardiometabolic diseases (Kaur 2014).

The World Health Organization (WHO) indicates that the increased cardiovascular death in the low-income countries is due to the lower access to precocious prevention and treatment programs (WHO 2018b). Children and adolescent have been considered a key social group for a sustainable future and are target for

preventive intervention of non-communicable disease (Kleinert & Horton 2016). Adolescents, between 10 and 19 years-old, are approximately 1/6 of the worldwide population (WHO 2017), and the prevalence of overweight and obesity has been increasing in this group along last years. This transition in the health condition is a concern due to its closed correlation with physical and psychological alterations in this population (Steinbeck 2009, Patton et al. 2016). The overweight and obesity are the first cardiovascular risk markers, more and more, observed in childhood and adolescence, predicting obesity in adulthood and its associated mortality (Patton et al. 2016, WHO 2018a). The early exposure to unhealthy lifestyle and environmental insults, as pollutants and endocrine disruptors, may be contributing to this situation (Graf & Ferrari 2016, Golestanzadeh et al. 2019). Furthermore, the socio-economic transition experienced in Latin America would promote a discrepancy between the nutritional environment during early life and the adult environment causing a mismatch between the fetal programming of the subject and its adult circumstances created by the imposition of new lifestyle, which would induce a programming to the cardiometabolic syndrome in adulthood (Lopez-Jaramillo et al. 2011).

In the last decades, epidemiological, clinical and experimental studies have been used to design the "Developmental Origins of Health and Disease" (DOHaD) concept, which points to the importance of perinatal insults as risk factors to develop non-communicable disease in adulthood, including obesity, hypertension, type 2 diabetes and dyslipidemia (Uauy et al. 2011, Murphy et al. 2016). These studies have shown that the pregnancy, lactation and adolescence are critical phases of life susceptible to programming health conditions in adulthood (McMillen & Robinson 2005). The physiopathology mechanisms underlying these health disfunction implicates epigenetic related organs' formation and function (Wadhwa et al. 2009).

Studies contextualized by DOHaD concept made possible to identify the perinatal factors (stimuli or insults) that modulate the programed susceptibility to cardiometabolic disease later in life. Some of these "insults" are: gestational diabetes, obesity or excessive weight gain during pregnancy, preterm birth, macro and microsomia, cesarean delivery, nutritional condition during pregnancy and/or lactation, fast body weight gain in the first year of life, psycho-emotional stress, among others (Luo et al. 2010, Owen et al. 2011, Mathias et al. 2014, Alexander et al. 2015, Murphy et al. 2016).

Precocious signals of cardiometabolic programming may be observed during infancy and adolescence, even without visible or significant changes in health condition at this life period. Studies have shown that evaluation of vascular and metabolic health in children and adolescents may be altered, pointing to their important role as precocious cardiovascular risk markers. Among the vascular and metabolic studied markers we may find: systolic and diastolic blood pressure levels; intima-media thickness of carotid and aorta arteries; distensibility and elasticity of arteries; pulse wave velocity; flow mediated vasodilatation; caliber of the retinal arteries and vein; adiposity; body weight gain; HDL and total cholesterol; blood levels of apolipoprotein B; hypertriglyceridemia; IR-HOMA; insulinemia; fasting glycemia; leptinemia and adiponectinemia (Sun et al. 2013, Perng et al. 2014a, b). Using these cardiovascular markers in adolescence correlated with perinatal conditions may be a useful strategy to identify individuals that need precocious intervention to control cardiometabolic syndrome development.

Little studies in the literature correlates the precocious presence of cardiovascular risk factors in people exposed to perinatal insults. This review discourse about the correlation between the classic cardiovascular risk factors identified during childhood and adolescence and some perinatal conditions that program to cardiometabolic disease later in life. We evidence that precocious identification of this correlation may improve control and prevention of cardiometabolic disease and its long-term cardiovascular risk.

Developmental Origins of Health and Disease (DOHaD)

The occurrence of non-communicable disease in adulthood may be associated with disfunctions programmed during susceptible phases of development (de Oliveira et al. 2013). This process was indicated in the Barker hypothesis, proposed in the late 1980s, which points that the exposition to insults during critical phases of development of the organism, induces permanent changes in the body structure, function and metabolism, increasing the risk to disease in adulthood (Barker 1990). This hypothesis allowed to mint the DOHaD concept, which considers that phases with big plasticity of organs and systems are critical periods to predispose conditions of health or disease in adulthood, as the cardiometabolic, psycho-emotional, allergies and cancers (Blakemore & Choudhury 2006, Wadhwa et al. 2009, de Oliveira et al. 2013).

The DOHaD concept has an embracing impact with a multidisciplinary implication, mainly due to the diversity of precocious insults capable to program health condition in adulthood, for example, nutrition, stress, physical activity, pollutants exposure and chemical agents, among others (Suzuki 2017). The most studied life phases in the DOHaD context are gestation and lactation (Fall 2009); however, recent investigations have pointed to the gametes and adolescence as susceptible phases to programming (McPherson et al. 2014, Ibanez et al. 2017, de Oliveira et al. 2018).

Baker and collaborators used epidemiological evidences to indicate that there are a inversed correlation between the birth weight and cardiovascular or type 2 diabetes in adulthood (Barker & Osmond 1986, Barker 1999). They showed that individuals submitted to intrauterine malnutrition may suffer long-term predisposition to a series of non-communicable diseases, been programed to the nutritional deficiency throughout life. It is well described that when there is a mismatch between the nutritional condition in uterus and the nutritional condition extra-uterus, as the low availability of nutriments during gestation life and hypercaloric exposure after birth, it is observed an increased risk to develop metabolic syndrome in adulthood (Lakshmy 2013).

The "programming" term was first proposed by Lucas (1991), while discourse about the underling mechanisms of DOHaD (Lucas 1991). The programming happen when an environmental stimuli or insult occur during critical windows of development (periods of plasticity that allow the organism to change its morpho-physiology according to environmental conditions) (Lucas 1991). Epigenetic changes (DNA methylation, histone modifications and non-codding RNAs) compose the response mechanisms to the early life environmental conditions. The epigenetics changes mediate the effect of early life insults on obesity and comorbidities developed later in life (Bianco-Miotto et al. 2017) and may be associated with cardiometabolic markers that may predict the future health condition.

The effects of nutritional insults in a population were studies in people that lived the "Dutch Hunger" between 1944 and 1945, during the

Second World War. Among this people, pregnant woman were affected by deep undernutrition; their children were included in studies evaluating the association between the perinatal condition and long-term health (Roseboom et al. 2006). It was shown that exposure to extreme hunger during any stage of pregnancy was associated with glucose intolerance, in adulthood; while exposure to undernutrition in the beginning of pregnancy increased the risk to cardiac disease, atherosclerosis, dyslipidemia, coagulation disfunction, exacerbated response to stress, breast cancer and obesity (Roseboom et al. 2006).

The used experimental nutritional insults include: exposure to high-fat and/or high-caloric diets, low protein diet, overnutrition exposure, caloric and/or nutritional restriction exposure, hyper-sodic diets, among others (Schwingshackl et al. 2017). In addition to the nutritional insults other factors are able to programming, as pollutants, sedentarism, tabaco, drugs and pesticides (Kelishadi & Poursafa 2014). The exposure to these insults may program the individual to develop a series of diseases in adulthood, as hypertension, type 2 diabetes, pulmonary and kidney diseases, osteoporosis, schizophrenia, depression, breast cancer, polycystic ovarium syndrome, among others (Ozanne et al. 2004).

Evaluation of cardiovascular risk

The cardiovascular risk is used to identify people with greater probability to die from heart attack or stroke. The main traditional risk factors to cardiovascular disease are the age, sex, hypertension, tabaco, dyslipidemia, and type 2 diabetes. It is well known that these risk factors are grouped and interact with each other, increasing the risk in a synergic way (Almeida 2010). A range of other markers have been described as: the cardiovascular inflammation (plasmatic C protein, interleukin 6, leucocyte number, periodontal disease, among others); other cardiovascular changes (intima-media thickness, pulse waive velocity, endothelial disfunction, among others); metabolic changes (dysbiosis, obesity, fasting glycemia, insulin resistance, among others); and other nontraditional markers (D vitamin, markers of bone turnover, infections with some microorganisms and psycho-emotional factors, among others) (Almeida 2010, Al-Rubaye et al. 2018, Traghella et al. 2018).

It is well known that the "global cardiovascular risk" is a calculation of the absolute risk of having a fatal cardiovascular disease over a specified period (Piepoli et al. 2016). However, this term may be inappropriate, as no cardiovascular risk assessment system accommodates all known risk factors (Cooney et al. 2009). Several of the under cited cardiovascular risk factors consider the condition short time before the disease is diagnosed, however the cardiometabolic diseases have a silent and slow progression. Furthermore, the DOHaD concept points that there is an important impact of early life on the cardiovascular risk. In this context not only the cardiovascular risk factors need to be review but also the evaluated life period.

Several algorithms and cardiovascular risk scores were developed based on populational studies and are used to evaluate the cardiovascular health or cardiometabolic age in order to assist in cardiovascular disease prevention strategies (Almeida 2010, Malachias et al. 2016). However, these scores do not consider the perinatal life condition and its known environmental insults, which are relevant to cardiometabolic disease development and increased cardiovascular risk in adulthood.

The identification of cardiovascular risk is useful to perform interventions and reduce the incidence events due to coronary disease,

peripheral vascular disease, and cerebrovascular disease. To this end, the WHO proposes a categorization of the prevention strategies as primaries (which consider people with risk factors without clinical manifestation of cardiovascular disease) and secondaries (which consider people with diagnosed or established cardiovascular diseases) (WHO 2007).

The cardiovascular risk and the DOHaD concept

A risk factor is defined as: an environmental exposure; innate or acquired characteristic; or a behavior or lifestyle associated with increased probability to develop a disease. The environmental condition during critical windows of development may also affect the cardiovascular risk. Epidemiologic and experimental studies have been pointing to the correlation between a range of perinatal insults and the cardiovascular risk in adult life (Gillman et al. 2007, Kelishadi & Poursafa 2014, Murphy et al. 2016).

Among the perinatal conditions correlated with an increase cardiovascular risk in adulthood we may find the insults on the fetus or babies (as examples: nutritional problems, exposure to toxic products, nursing, fast catch-up growth, preterm birth or cesarean) and insults on the mother during gestation and lactation (as example: nutritional condition, body weight gain during pregnancy, heath condition as gestational diabetes or eclampsia) (Kelishadi & Poursafa 2014).

The Figure 1 shows some cardiometabolic disfunction observed in adulthood and its correlated precocious risk factors. It describes the critical windows of development and the risk factors identified in each life phase, which may be related with cardiometabolic syndrome in adulthood. Some perinatal risk factors and its correlation with cardiometabolic outcomes will be described below.

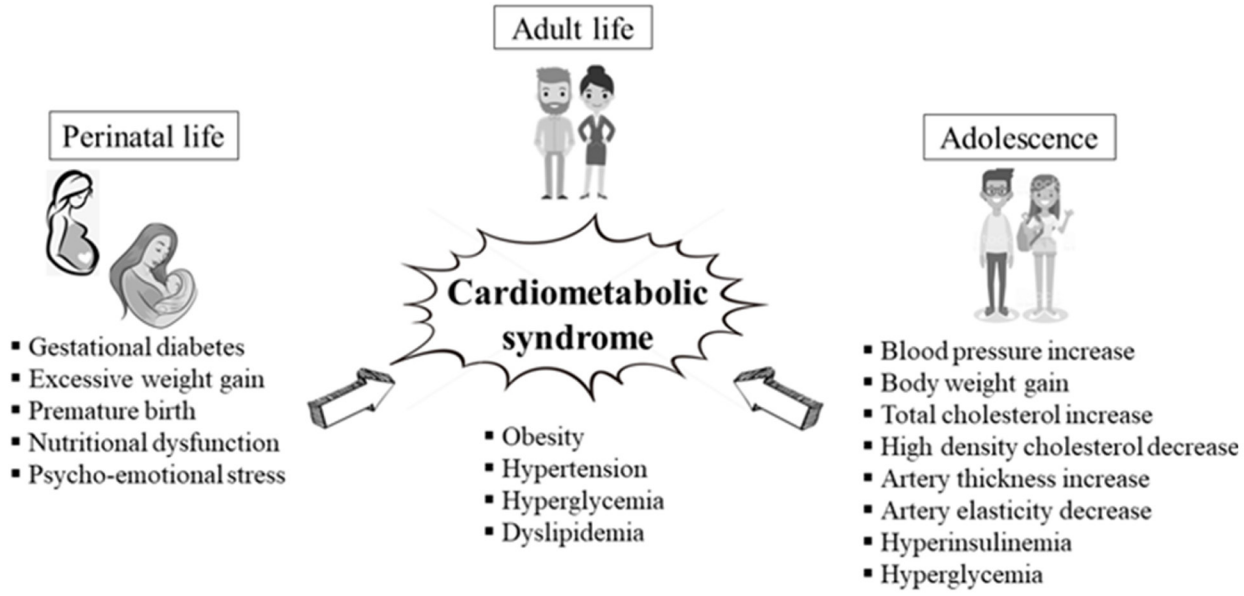

Figure 1. Cardiometabolic disfunction in adulthood and early cardiovascular risk factors. The life period with increased cardiometabolic outcomes correlated with early risk factors is shown in the center of the figure; in the laterals it is shown the life period susceptible to intervention.

Type of delivery

Is has been shown that the type of delivery affects the long term condition of the organism (Hyde et al. 2012), however little studies evaluated the correlation between the type of delivery and the cardiovascular risk in the offspring. It is suggested an increased risk in young people born by cesarean section (Horta et al. 2013).

It was shown that increased blood pressure is observed in young adults (23 years-old) born by cesarean section, compared with vaginal delivery (Horta et al. 2013). However, when it was evaluated in adolescents the effect of cesarian section to increased blood pressure disappears (Pluymen et al. 2016).

The body mass index, used to estimate overweight and obesity, is not different in one-year-old babies born by cesarian section or vaginal delivery (Haji et al. 2014). However the overweight signals were observed from infancy until young adults born by cesarian section (Horta et al. 2013, Pluymen et al. 2016).

Perinatal body weight and mortality

The studies, precursors to the DOHaD concept, carried out by Barker and collaborators and published in the late 1980s, correlates the perinatal condition with development of cardiovascular diseases. These studies showed a strong geographic correlation between perinatal mortality (between 1921 and 1925) and heart attack mortality in adulthood (between 1968 and 1978) (Barker & Osmond 1986). They also showed a strong geographic correlation between stroke, in the period of 1968 and 1978, and the neonatal mortality in the period between 1911 and 1925 (Barker et al. 1989). These studies suggest that these correlations may depend on perinatal factors that may drive the blood pressure level and other functions of the organism. Barker and collaborators also pointed that there is a strong relationship between the reduced growth in fetal life and early childhood with the appearance of cardiovascular risk factors and mortality in adulthood. It was observed an increased blood pressure in adult people (between 59 and 70 years-old) associated with low birth weight; while the glucose intolerance and ischemic heart disease in adulthood were associated with low body weight at one year of live (Barker & Martyn 1992).

Following the studies from Dr. Barker, several research groups explored the relationship between body weight and cardiovascular disease in adulthood. Studies in adolescents and young adults showed a U shape curve for the cardiovascular risk, with increased risk in people with low or high birth weight (Suzuki et al. 2000, Skilton et al. 2014, Stansfield et al. 2016).

Breast-feeding

The WHO and the United Nations Children's Fund (UNICEF) propose exclusive breast-feeding in the first six months of life, when other safe foods should be introduced with breastfeeding for at least two years of life (WHO 2018c). Epidemiological studies assessing the impact of breastfeeding on cardiovascular risk are controversial, however there are many confounding factors, such as time or exclusive breastfeeding, in addition to socio-economic and paternal factors. (Owen et al. 2011, Horta et al. 2015).

The benefice of breast-feeding on cardiovascular mortality is not conclusive (Owen et al. 2011); however, meta-analysis studies have shown that breast-feeding reduces total blood cholesterol and triglycerides, as well as, blood pressure, obesity and type 2 diabetes. Four meta-analysis, supported by the WHO, performed in sequence, considering publications from 1966 and 2018, will be examined bellow (Horta et al.

2007, 2015, Horta & Victora 2013, Horta & De Lima 2019).

These meta-analysis studies point to an small benefice of breast-feeding to blood pressure levels (Horta et al. 2007, 2015, Horta & Victora 2013); been more evident on children and adolescent (Horta et al. 2015). The meta-analysis published in 2015 indicates that only systolic blood pressure was improved, which may depend on the heterogeneity of the included studies (Horta et al. 2015). The study published in 2013 points the socioeconomic conditions as the main confounding factor, while in the publication from 2007, it was not possible to identify the main confounding factor, however they suggest that the heterogeneity would contribute to the super estimation of the depressor effect of breast-feeding (Horta et al. 2007, Horta & Victora 2013). The mechanism leading to the benefice of breast-feeding on blood pressure would be related with the sodium amount in the formulas for babies nutrition and fatty acids in the breast milk, which are important to the development of vascular endothelium, among other factors (Horta & Victora 2013).

The two first studies published in 2007 and 2011, show that total cholesterol is increased in breast feed children; however the adults show a reduction in this parameter (Owen et al. 2011, Horta & Victora 2013). The authors point that this pattern may depend on the down-regulation of the Hydroxymethylglutaryl coenzime A (HMG-CoA), the key enzyme to the cholesterol synthesis, due to increased levels of cholesterol early in life (Horta & Victora 2013). The study published in 2015 did not identify an association between breast-feeding and total cholesterol, however this difference may due to the age of evaluation (Horta et al. 2015).

The overweight has been considered an important cardiovascular risk marker, which is reduced by the breast-feeding (Horta et al. 2007, 2015, Horta & Victora 2013). The benefice of breast-feeding in reduce overweight/ obesity do not appear to be affected by age of evaluation, neither other confounding factors as parents socioeconomic or anthropometric conditions at birth (Horta et al. 2015). However, studies with lower participant number appear to super estimate the benefice of breast-feeding (Horta et al. 2007).

The four meta-analysis point to the protective effect of breast-feeding against type 2 diabetes (Horta et al. 2007, 2015, Horta & Victora 2013, Horta & De Lima 2019). In the studies published in 2013, 2015 and 2019 the benefice of breast-feeding on type 2 diabetes is greater in adolescents (Horta & Victora 2013, Horta et al. 2015, Horta & De Lima 2019). This protector effect of breast-feeding may depend on long-chain fatty acids present in the breast milk, which may improve skeletal muscle, protect against insulin resistance and beta-cells failure (Horta & Victora 2013). The pattern of insulin secretion dependent on early life feeding may interfere, as the formula for baby's nutrition induces increased insulin secretion, which may induce precocious beta-cells failure and type 2 diabetes (Horta & Victora 2013).

Mechanism correlating perinatal insults and cardiovascular risk

Experimental studies have done some light on the mechanisms enrolled in the relation between the perinatal condition and the cardiometabolic disease development later in life. However, the complete panorama on the physio-pathological mechanisms is still unclear. It is necessary to better understand how organs under development in perinatal life are programed and how the brain regulates the organism to face this condition. This scenery may depend on epigenetic mechanisms and consequent alterations in organs development

and brain cardiometabolic regulation, which would overcharge the body function, resulting in precocious ageing.

One of the key mechanisms underlying the early life programming of cardiometabolic diseases is the epigenetics, as its mainspring is the memory of early developmental decision even after the determination/differentiation stimulus has disappeared (Safi-Stibler & Gabory 2020). Studies have pointed that perinatal insults induce epigenetic modulation, as DNA methylation, histone modifications and non-coding RNAs, which result in altered gene regulation without modification of the DNA sequence. This epigenetic programming alters gene expression due to modifications on genome architecture and accessibility inducing changes in cellular or tissue function that can thereby be relatively stably transmitted earlier in life until adulthood (Zhu et al. 2019).

Experimental animal models are, now, the best option to study the implication of epigenetic in the DOHaD context, as it is possible to evaluate the epigenetic modifications in multiple time points along lifetime. Most of the studies focus on DNA methylation and primarily adopt a candidate approach, as the transcription factors because its ability to regulate expression of a network of genes (Bianco-Miotto et al. 2017). Some specific genes showing disrupted DNA methylation in offspring exposed to altered maternal nutrition in utero include Pparα (peroxisome proliferator–activated receptor-α), a major regulator of lipid metabolism; NR3C1 (the glucocorticoid receptor), a key regulator of metabolism; and PEPCK (phosphoenolpyruvate carboxykinase) and HMGCR (HMG-CoA reductase), which catalyse rate-controlling steps in gluconeogenesis and cholesterol production, respectively (Sun et al. 2013). Furthermore, the histones modifications appear to be an important epigenetic target of programmed dysregulation, as they may be present before changes in DNA methylation (Bianco-Miotto et al. 2017).

Some common pathological process involved in cardiometabolic disease are associated with epigenetic modifications. Some example are: the inflammation associated with global hypermethylation (Sun et al. 2013); the obesity associated with epigenetic changes in adiponectin gene promoters, differentiation and maturity of adipocyte, and epigenetic dysregulation of pro-opiomelanocortin (POMC) and glucocorticoid receptor (GR) in the hypothalamus resulting in hyperphagia and altered energy balance regulation (Zhu et al. 2019); increased expression of angiotensin-I-converting enzyme (ACE) associated with hypomethylation (activation) of the promoter region of the ACE (Goyal et al. 2019); among several others epigenetic-related mechanism of cardiometabolic diseases.

Several perinatal condition may promote epigenetic programming of cardiometabolic disease. Goyal et al. (2019) discriminate some of these insults where some maternal factors are smoking, maternal diseases, alcohol exposure and drug addictions; while some fetal factors are congenital disorders, multiple fetuses and abnormal placement; and some environmental factors are high altitude leading to hypoxia, pollution exposure and low nutrient availability (Goyal et al. 2019). The factors mentioned above may affect the type of delivery, the perinatal body weight and mortality and/or the breast-feeding quality, which are pointed here as perinatal cardiovascular risk factors.

CONCLUSIONS

The present review points to some perinatal risk factors (low birth weight, absence of breast feeding and delivery by cesarian section)

that are associated with occurrence of classic cardiovascular risk biomarker (increased blood pressure, dyslipidemia, hyperglycemia, overweight and obesity). Additionally, these risk factors may appear early in life, from infancy and adolescence, before the cardiometabolic syndrome and its comorbidities are installed in adulthood. The mechanism underlying the correlation between the perinatal condition and precious cardiovascular risk biomarker may depend on epigenetic programming.

Using perinatal biomarkers associated with precocious evaluation of classic cardiovascular risk, during infancy and adolescence, may allow to identify people with increased risk to develop the cardiometabolic syndrome in adulthood. This tracking may contribute to primary prevention strategies to reduce cardiovascular mortality. Considering the precocity of intervention during infancy and adolescence, non-therapeutic strategies as life-style changes (diet control and physical activity) may allow more efficient and long-term outcomes, in the context of DOHaD concept.

Additionally, the promotion of good diet, physical activity, good access to micronutrients and reduced exposure to environmental pollutants, during pregnancy period would improve the fetus development and reduce pre-term birth. Furthermore, these interventions during lactation period, would control the mismatch between pre- and post-birth life as well as the fast catch-up growth, guarantying the benefice of breast feeding.

The public health authorities should consider some changes in the actual social and laboral structure as well as the awareness of the population on DOHaD knowledge to allow a better caring of pregnancy and lactation, and interventions in adolescents with increased cardiovascular risk. Interventions in the schools, labor relationship for women and health system may be a challenge with short-term negative economic impact; however, it might save several lives and promote an important long-term reduction in the economic cost with cardiometabolic diseases treatments.

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