Fetal programming of atherosclerosis: may the barker hypothesis explain the susceptibility of a subset of patients to develop stroke or cardiac infarct?

C. GEROSA[1], G. FAA[1,2], D. FANNI[1], G. CERRONE[1], J.S. SURI[3], D. BARCELLONA[4], P. CONI[1], T. CONGIU[1], M.L. LAI[1], M. PIRAS[1], F. CAU[1], F. COGHE[5], A. BALESTRIERI[6], R. CAU[6], G. ORRU'[7], A. SCANO[7], P. VAN EYKEN[8], G. LA NASA[9], M. CAMPAGNA[10], M. CASTAGNOLA[11], Y. GIBO[12], F. MARONGIU[4], L. SABA[6]

[1]Division of Pathology, Department of Medical Sciences and Public Health, AOU of Cagliari, University of Cagliari, Cagliari, Italy
[2]Department of Biology, College of Science and Technology, Temple University, Philadelphia, PA, USA
[3]Stroke Monitoring and Diagnostic Division, AtheroPointTM, Roseville, CA, USA
[4]Internal Medicine, Department of Medical Sciences and Public Health, AOU of Cagliari, University of Cagliari, Cagliari, Italy
[5]Division of Chemical Chemistry and Microbiology, Azienda Ospedaliero Universitaria (AOU) di Cagliari – University Hospital San Giovanni di Dio, Cagliari, Italy
[6]Division of Radiology, Department of Medical Sciences and Public Health, AOU of Cagliari, University of Cagliari, Cagliari, Italy
[7]Section of Microbiology, Department of Medical Sciences and Public Health, AOU of Cagliari, University of Cagliari, Cagliari, Italy
[8]Department of Pathology, Oost Limburg Regional Hospital, Genk, Belgium
[9]Division of Hematology, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy
[10]Occupational Health Section, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy
[11]Laboratorio di Biologia Molecolare e Biochimica, IRCCS Santa Lucia, Rome, Italy
[12]Hepatology Clinic of Matsumoto, Matsumoto, Japan

Abstract. – The risk stratification of young adults between subjects who will develop a mild form of atherosclerosis and subjects who will undergo a severe disease remains inaccurate. In the eighties of the previous century, David JP Barker has demonstrated the relationship between fetal conditions and occurrence of pathologies in adulthood. In this paper, the multiple evidence that might explain the increased susceptibility to severe forms of atherosclerosis, including stroke and cardiac infarct, in subjects who underwent intrauterine growth restriction (IUGR) will be analyzed. Specifically, we will review those inter-connected data indicating an association between a low weight at birth and an adult phenotype which might favor a severe outcome of atherosclerosis. Young and adult subjects born too small (IUGR) or too early (pre-terms) might represent a subgroup of "at risk subjects", more susceptible toward severe forms of atherosclerosis. Given that low birth weight (LBW) may be considered a surrogate of IUGR, this phenotypic feature could be considered among those indispensable clinical data collected in every patient presenting with atherosclerosis, irrespectively of age. According to the hypothesis that structural arterial changes might represent the link between LBW and susceptibility to atherosclerosis later in life, we suggest that the prevention of atherosclerosis should begin at birth. Regenerative and physiological substances such as thymosin Beta-4 could be challenged for a new "arterial regenerative medicine" in the perinatal period. The goal of this new approach should be the reinforcement of the structure of the arterial wall, allowing LBW newborns to avoid the most severe complications of atherosclerosis later in life: a dream that our research could contribute to bringing to life.

Key Words:
Atherosclerosis, Fetal programming, Barker hypothesis, Stroke.

Corresponding Author: Daniela Fanni, MD; e-mail: daniela.fanni@unica.it

Introduction

Atherosclerotic cardiovascular disease, including myocardial infarction, ischemic cardiomyopathy, stroke and peripheral arterial disease, accounts for most of the mortality worldwide[1]. An epidemiologic transition has been observed in recent years, regarding the incidence of atherosclerotic disease in different geographical areas. Previously considered a major health problem restricted to the industrialized world, today atherosclerosis is spreading around the globe, with high picks of incidence in the more populous developing areas[2,3]. Multiple factors are involved in the changing landscape of atherosclerosis. Undernutrition and micronutrient deficiency continue to affect mothers and children of developing countries. Moreover, low birth weight (LBW) and retarded fetal growth are at least twice as common in developing countries. As a consequence, the association between LBW and atherosclerosis should be considered in these geographical zones[4] (Figure 1).

This global spread has been paralleled by an evolution of concepts regarding pathogenesis, prevention, and therapy of atherosclerosis, changing the landscape of this complex multifactorial disease[5] (Figure 2). The clinical spectrum of patients with atherosclerosis is broad, ranging from asymptomatic subjects to mild-moderate disease, to patients with severe and critical illness, including stroke and cardiac infarct[6]. The changing face of atherosclerosis regards even the classic candidates for heart attack and stroke. Previously, at-risk groups for severe complications of atherosclerosis were identified in middle-aged smoking men, with hypertension
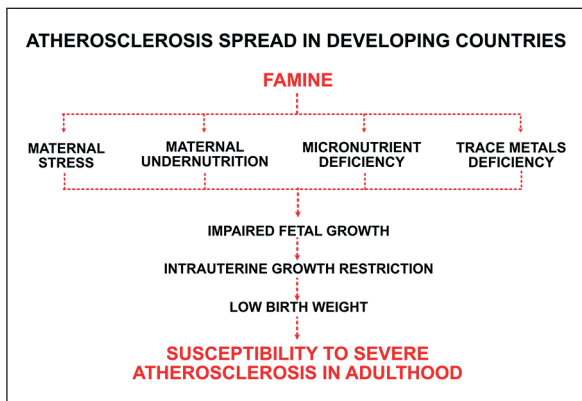

Figure 1. Schematic representation of the multiple factors involved the spread atherosclerosis in developing countries.
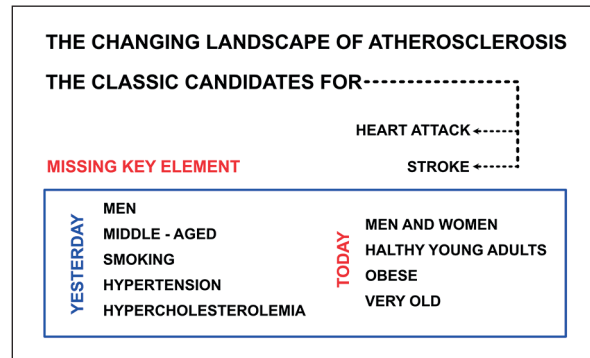

Figure 2. Schematic representation of the differences between the previous classic candidate and today classic candidate in the changing landscape of atherosclerosis.

and hypercholesterolemia. Today we have to focus our attention on younger people, obese and women, as well as to very old people[7]. However, even if some important parameters of risk have been identified in the past years, the models of risk related to the occurrence of stroke and myocardial infarction are largely imperfect. This suggests that there are missing key elements that need to be identified. Risk factors should be identified, in particular, for apparently healthy young adults at higher risk for undergoing severe complications related to the atherosclerotic process[8]. Their early identification might allow planning of effective targeted therapies in the early course of the disease. Among the multiple new concepts relating to atherosclerosis, environmental conditions occurring during pregnancy have been indicated as a risk factor for the development of atherosclerosis later in life[9,10]. In particular, maternal dyslipidemia might induce preterm birth and change the phenotype of the newborn, favoring the insurgence of a metabolic syndrome and atherosclerosis in adulthood[11]. LBW in neonates undergoing intrauterine growth restriction (IUGR) has been indicated as a potential risk factor for endothelial cell dysfunction, which later on might predispose to early insurgence of atherosclerosis[12]. According with this hypothesis, vascular susceptibility to undergo plaque formation in the arterial wall might be programmed before birth.

In this review, we will discuss the evidence emerging from the literature on the possible association between a derangement in fetal development of the cardiovascular system and the early insurgence and progression of atherosclerotic plaques later in life.

The Barker Hypothesis

In the eighties of the previous century, David J.P. Barker published a pivotal study[13] in which maternal malnutrition during gestation was correlated with the susceptibility of the newborn to develop atherosclerosis and ischemic heart disease in adulthood. The Barker's hypothesis was based on epidemiological data on the occurrence of coronary heart disease in subjects whose body weight at birth was recorded. A statistically significant correlation was found between the death rates from coronary heart disease and birth weight. Higher rates of cardiac attack were evidenced in subjects with LBW as compared to subjects with a birth weight in the normal range[14,15]. Over the years, the Barker's hypothesis has been confirmed by evidence collected in multiple human diseases. IUGR has been associated with a susceptibility to undergo end-stage kidney disease in adulthood. The following sequence of events has been proposed: (1) malnutrition during gestation; (2) negative influence on kidney development; (3) low nephron number at birth; (4) vascular lesions in middle and small kidney arterial vessels; (5) glomerulosclerosis; (6) kidney failure[16]. Interestingly, in recent years multiple studies allowed a better understanding of the underlying pathways that link LBW to an increased cardiovascular risk[4].

LBW and Severe Outcome of Atherosclerosis

According with the Barker's hypothesis, the knowledge of LBW might help to identify a subgroup of young/adult subjects, apparently in good health, but at higher risk for develop the severe forms of atherosclerosis. However, an open question remains: which is the linkage between LBW and a severe course of atherosclerosis? The first answer regards the biological implications of LBW. In those newborns at term, LBW (<2,500 g) has been indicated as a robust surrogate of IUGR, and a strong predictor of long-term morbidity[17]. LBW may be also related to preterm labor, prematurity being associated with the incomplete development of multiple fetal organs, including lungs[18] kidneys[19] and brain[20-23]. According to the developmental origin of diseases in adulthood (DODA), LBW might represent the "first hit". LBW might reflect epigenetic factors occurring during gestation and should represent a predisposition to develop cardiovascular disease later in life. Exposure to other environmental factors in the postnatal life, including a fat diet, might represent the "second hit". The latter is necessary for the clinical presentation of the disease, determining an additive model where predisposition and external causes interact to produce a critical condition. The study by Goodfellow et al[24] may clarify the link between IUGR and a predisposition of the arteries of LBW newborn to undergo atherosclerosis later in life. Starting from the knowledge that hypertension and ischemic heart disease are associated with LBW, a condition defined 'the Small Baby Syndrome', the authors tested the hypothesis that endothelial dysfunction might precede the development of atherosclerotic plaques in LBW subjects. To verify this hypothesis, Goodfellow and coworkers measured by ultrasonic 'wall-tracking' of flow-related brachial artery dilatation both in low (<2.5 kg) and normal (3.0-3.8 kg) birth weight subjects. Flow-related dilatation was impaired in LBW children, as compared to normal birth weight subjects. These findings indicate that endothelial dysfunction represents the major consequence of fetal malnutrition, contributing to the insurgence of the 'Small Baby Syndrome' later in life. A further study aimed at verifying the impact of LBW on the cardiovascular risk in adulthood, confirmed the association of LBW with reduced flow-mediated dilatation and with endothelial dysfunction in young adults. According with the authors, LBW should be considered a relevant factor in the pathogenesis of atherosclerosis later in life[25].

The Relationship Between Fetal Programming and the Molecular Pathways Triggered by Atherosclerosis: the Pro-Thrombotic Pro-Inflammatory Phenotype

Trying to explain the correlation between LBW and a severe outcome of atherosclerosis implies to consider the multiple molecular pathways triggered inside the atherosclerotic plaque[5]. The first one is related to the hemostasis and thrombosis system, which has been indicated as a key factor in the evolution of the atherosclerotic plaque. Changes in the hemostasis and thrombosis system are involved in the insurgence of intra-plaque hemorrhage, intravascular coagulation, thrombosis and embolism in a subset of patients.

IUGR may have relevant consequences on the hemostasis and thrombosis system. Both fibrinogen and Factor VII serum levels in adults are influenced by maternal malnutrition during gestation and by LBW[26-28]. A study aimed at verifying the association between IUGR and susceptibility

to develop thrombotic events later in life revealed an association between LBW and polymorphisms for factor V Leiden and prothrombin, ending with a thrombophilic phenotype in adulthood[29]. According with these studies, LBW might be considered a robust surrogate for dysregulation of the homeostasis and thrombosis system. Moreover, LBW should be interpreted as a predictor of insurgence of intra-plaque hemorrhage or thrombotic events in the atherosclerotic plaque later in life. Failure in adequate controlling of the homeostasis of some coagulative factors seems therefore an outcome of LBW.

Nevertheless, a massive inflammatory and coagulative response may be very dangerous in the evolution of the atherosclerotic plaque, because it can lead to a diffuse thrombotic angiopathy. As reported above, endothelial susceptibility due to LBW may represent a critical background for the insurgence and progression of atherosclerosis[24,25].

A pro-thrombotic phenotype associated with LBW is essentially due to the involvement of the endothelial cells, which change their anti-thrombotic properties into a pro-thrombotic behavior. The endothelial cells of people who have in their background a LBW could be more prone to react to the cytokine storm elicited by multiple factors[30].

Again, it could be a realistic option to consider that endothelial cells of people born with a LBW could loss the fine balance between anti- and pro-coagulant forces, a typical feature of endothelial cells in physiology[31]. In healthy subjects, the hemostatic system can avoid an excess of fibrin formation and deposition within the blood vessels on the one hand but can stop bleeding on the other. A fine regulation is therefore required to assure an optimal balance. All actions of the hemostatic system are therefore controlled to maintain people distant from both Scylla (bleeding) and Charybdis (thrombosis)[32].

Fibrinolysis is another important defensive system, whose action is to remove fibrin from the endothelial cell surface. Fibrinolysis is in turn well balanced by a fine control of its inducers and inhibitors[33]. Finally, endothelial cells can provide also substances, such as nitric oxide, prostacyclin and an ADP deactivation molecule, in order to maintain platelets distant from their layer, thus avoiding their aggregation and involvement in the thrombotic process[34].

If, on one hand, endothelial cells in healthy subjects protect the host from thrombus formation, on the other hand, they become strongly prothrombotic when a direct injury occurs. In other words,

it is reasonable to advance the hypothesis that endothelial cells of people with LBW are more prone to elicit a prothrombotic response towards cytokines released from innate immunity cells, including monocytes. According with this hypothesis, LBW subjects' endothelial cells might undergo an excessive response to any injury, which would be repaired in normal subjects. A lower threshold towards a chronic endothelial dysfunction is perhaps the mechanism that in a long time could make the endothelial cells' behavior less "friendly" and protective. The exposition of tissue factor, the trigger of the coagulative cascade[35], along with the involvement of activated platelets at the sites of the injury, could be the result of a chronic endothelial irritative response. To better understand this mechanism, one should realize that our hemostatic system is always working, even in normal subjects, as a car engine idles. A small amount of fibrin deposition, in physiology, is removed by fibrinolysis. This fine control of the hemostatic system protects vessels from thrombotic occlusions. However, if this mechanism is not properly able to maintain this delicate balance, a progressive endothelial dysfunction may develop. As it happens in chronic diseases, endothelial degradation may occur in the atherosclerotic plaques. Atherosclerosis might thus develop more rapidly in those subjects with LBW than in patients with normal birth weight. The outcome of this LBW-related endothelial dysfunction may be the susceptibility to undergo severe cardiovascular or cerebral events, including myocardial infarction and stroke. Even within the atherosclerotic plaque, a dysregulation in the monocytes capturing oxidized lipoproteins (LDL) may easily lead to the rupture of the fibrous cap of the plaque. In physiological homeostatic conditions, macrophages undergo apoptosis, being efficiently cleared by a process called efferocytosis. However, in advanced atherosclerosis, defective efferocytosis may result in necrosis of these uncleared macrophages, ending with the formation of the necrotic core that can facilitate the rupture of the atherosclerotic plaque[36]. A loss of this control may further contribute to the progression of the inflammatory burden of the atherosclerotic plaque (Figure 3).

Fetal Programming of Cardiovascular Diseases

The first studies of Barker et al[13] were mainly focused on the role played by an adverse intrauterine environment on the susceptibility to develop cardiovascular diseases later in life. Ma-
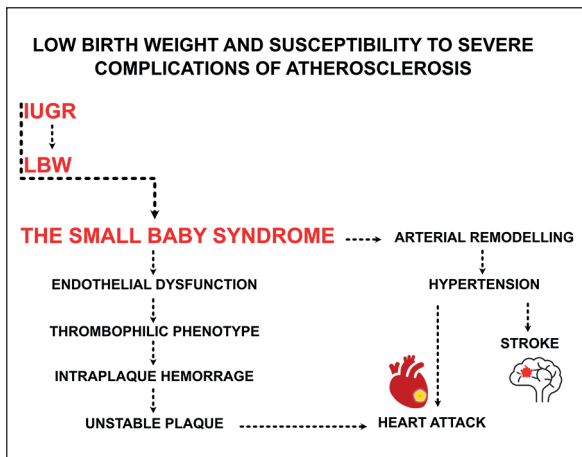
Figure 3. Schematic representation of the mechanisms leading to the increased susceptibility of the severe complications of atherosclerosis in IUGR and LBW.

ternal and fetal malnutrition during gestation was shown to be associated with the susceptibility to undergo ischemic heart disease in adulthood, originating the theory of the fetal origins of coronary heart disease[37,38]. More recently, multiple studies[39] have shown that IUGR results in heart remodeling, ending with a less efficient heart later in life. These findings confirmed the existence of long-term cardiovascular consequences caused by fetal growth restriction and LBW[40].

Among the multiple open questions regarding the relationship between LBW and the susceptibility to develop severe adult diseases, one concerns the identification of the cells involved in fetal maldevelopment due to an adverse intrauterine environment. Endothelium has been indicated as the main target of maternal malnutrition, and fetal endothelial dysfunction during gestation has been implicated in the insurgence of multiple organ failure in the newborn[41]. Endothelial damage has been proposed as the principal responsible for vascular remodeling, which might persistently modify the elastic properties of the arterial wall[42]. The sequence of events hypothesized is the following: (1) endothelial dysfunction (starting in the intrauterine life); (2) changes in thickness of the intima and media of aorta, carotid arteries and coronary vessels; (3) changes in arterial stiffness; (4) susceptibility to undergo hypertension[43].

Fetal Programming of the Immune Response

The immune system has been included among the multiple physiological systems in which intrauterine fetal programming may have relevant consequences persisting in adulthood[44]. Physical, social, and psychological maternal stress during pregnancy may cause significant changes in cytokine production persisting after birth[45]. Evidence[46] indicate that negative prenatal exposure represents a risk factor for the development of immune diseases later in life. Intrauterine growth restriction may also be associated with dysfunction of the innate immune system in preterm infants. LBW newborns are characterized by the inability to determine an appropriate immune response[47]. Collectively, these data suggest that immune diseases in children and in adults may have developmental origins and should be included in the Barker's hypothesis[48]. It could be interesting to know, in each patient affected by atherosclerosis, whether the immune response is controlled and balanced against foreign challenges. In other words, is an excess of the immune response a key factor associated to severe forms of atherosclerosis[49]? The recent report of plasma cells clusters in a subset of patients with carotid atherosclerotic plaques reinforced the hypothesis that an exaggerated immune response might represent a pathogenetic factor responsible for endothelial damage in a subset of patients with atherosclerosis[50]. Collectively, these data could explain why the burden of atherosclerosis is so different among the patients, ranging from an asymptomatic condition to a fatal outcome. Ideally, a test investigating both the individual immune harmonization and the response to a foreign attack would be very useful in patients affected by atherosclerosis, to assess the individual immune capacity in front of a "friendly fire".

Discussion

According to the evidence we summarized above, it is reasonable to hypothesize that atherosclerosis should be introduced in the spectrum of human diseases whose severity might be influenced by fetal programming. In particular, a growing body of data[51] suggest a possible relevant role for fetal programming in shaping the susceptibility of adult subjects, apparently in good health, to undergo a severe clinical course of atherosclerosis. Thus, according with the Barker's hypothesis[48], considering the relevant consequences of IUGR persisting in the adult life, LBW could be added to the other risk factors utilized in clinical practice for assessing disease severity and mortality, in the evaluation of patients with atherosclerosis.

This is supported by multiple relevant findings, which indicate LBW as an important index of fetal growth restriction. LBW is associated with suboptimal development of multiple critical organs, including lungs, heart, vessels, kidneys, and brain (Figure 4). Regarding the cardiovascular system, IUGR is associated with an adaptive fetal response, which includes the following pathological changes:

– Changes in fibrinogen and Factor VII serum levels and dysregulation of the hemostasis and thrombosis system[27];
– Acquisition of a pro-thrombotic phenotype, with higher susceptibility to develop thrombotic events[29];
– Heart remodeling, ending with a less efficient cardiac function[39];
– Endothelial dysfunction, which represents a risk factor for the insurgence and progression of atherosclerosis[24,25];
– Remodeling of arteries, including changes in the elastic properties of the arterial wall, a structural change predisposing to the insurgence and progression of atherosclerosis[43];
– Dysfunction of the innate immune system[47], which represents a risk factor for immune diseases in childhood and adulthood[44].

Conclusions

Based on data reported in this paper, our working hypothesis, aligned with a long-standing research line in the field of fetal programming
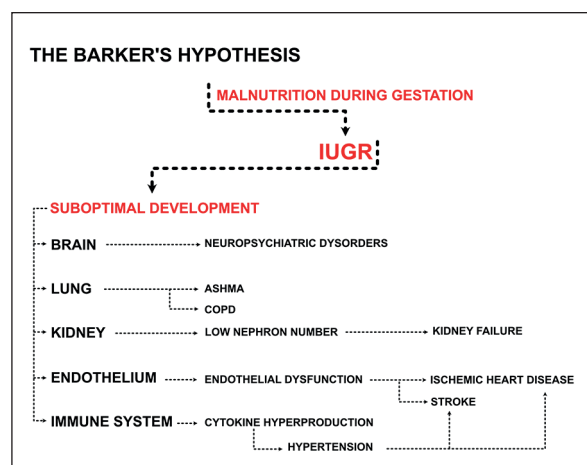

Figure 4. Schematic representation of the Barker's hypothesis applied to the developmental origin of atherosclerosis based on malnutrition during gestation.

of adult human diseases[19-23,52-58], indicates that young and adult subjects born too small (IUGR) or too early (pre-terms) should be considered as a distinct subgroup of "at risk subjects" for the development of severe, if not fatal, forms of atherosclerosis. The adaptive fetal response to reduction of nutrient supply during gestation is responsible for a specific phenotype, characterized by persisting metabolic, functional, and structural changes in critical organs, including the arterial wall. These structural and cell changes might favor the insurgence of the cytokine storm and the development of diffuse thrombotic events. These are the most relevant critical events for the development of the unstable plaque, the atherosclerotic lesion typically associated with the most severe forms of atherosclerosis.

Given that self-reported LBW has been demonstrated to be a good surrogate of IUGR[59], we suggest that its acquisition should be included among the indispensable data from every subject affected by atherosclerosis. The identification of a new "at risk" group, among young/adults undergoing atherosclerosis, might allow in clinical practice the identification of the severe form of the disease in the early phases. The identification of this "at risk" group in the pre-symptomatic phase might give significant advantages in the therapeutic approach. Knowing individual birth weight could be used for identifying subjects at a higher cardiovascular risk in the general population, starting from childhood. In these subjects, more precise prevention of cardiovascular disease could be afforded by a periodical follow up in their life, overall checking for minimizing other adjunctive risk factors (the second hit) such as obesity, smoking and wrong diet.

Finally, once accepted that the development of atherosclerotic plaques in adulthood may be related to something that went wrong during gestation, a new challenge is presenting to scientists involved in atherosclerosis: which way to put things back to track? Starting from the assumption that self-repair is the best medicine for any broken tissue, researchers should first consider the physiological regenerative approach previously proposed for the prevention of chronic renal disease due to disarrangement in kidney development[52]. Following this approach, prevention of atherosclerosis should start at birth[54]. Regenerative and physiological substances, such as thymosin Beta-4[60], could be challenged against this dangerous phenomenon first in the basic research, and then, by planning clinical trials in newborns

with LBW, providing a very long follow-up. Arterial regenerative medicine in the perinatal period might thus reinforce the structure of the arterial wall, allowing LBW newborns to escape atherosclerosis later in life: a dream that our research could bring to life.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Shay CM, Spartano NL, Stokes A, Tirschwell DL, VanWagner LB, Tsao CW, American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2020 Update: A Report from the American Heart Association. Circulation 2020; 141: e139-e596.

2) Dai H, Much AA, Maor E, Asher E, Younis A, Xu Y, Lu Y, Liu X, Shu J, Bragazzi NL. Global, regional, and national burden of ischemic heart disease and its attributable risk factors, 1990-2017: results from the global Burden of Disease Study 2017. Eur Heart J Qual Care Clin Outcomes 2020; qcaa076.

3) Petry N, Rohner F, Phall MC, Jallow B, Ceesay AA, Sawo Y, Darboe MK, Barrow S, Sarr A, Ceesay PO, Fofana MN, Prentice AM, Wegmüller R, Wirth JP. Prevalence and co-existence of cardiometabolic risk factors and associations with nutrition-related and socioeconomic indicators in a national sample of Gambian women. Sci Rep 2021; 11: 12057.

4) Delisle H. Programming of chronic disease by impaired fetal nutrition. Evid Implic For 2002; WHO. Available at: https://apps.who.int/iris/bitstream/handle/10665/67126/WHO_NHD_02.3.pdf.

5) Libby P. The changing landscape of atherosclerosis. Nature 2021; 592: 524-533.

6) Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, Tokgözoğlu L, Lewis EF. Atherosclerosis. Nat Rev Dis Primer 2019; 5: 56.

7) Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, Bonny A, Brauer M, Brodmann M, Cahill TJ, Carapetis J, Catapano AL, Chugh SS, Cooper LT, Coresh J, Criqui M, DeCleene N, Eagle KA, Emmons-Bell S, Feigin VL, Fernández-Solà J, Fowkes G, Gakidou E, Grundy SM, He FJ, Howard G, Hu F, Inker L, Karthikeyan G, Kassebaum N, Koroshetz W, Lavie C, Lloyd-Jones D, Lu HS, Mirijello A, Temesgen AM, Mokdad A, Moran AE, Muntner P, Narula J, Neal B, Ntsekhe M, Moraes de Oliveira G, Otto C, Owolabi M, Pratt M, Rajagopalan S, Reitsma M, Ribeiro ALP, Rigotti N, Rodgers A, Sable C, Shakil S, Sliwa-Hahnle K, Stark B, Sundström J, Timpel P, Tleyjeh IM, Valgimigli M, Vos T, Whelton PK, Yacoub M, Zuhlke L, Murray C, Fuster V, GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update from the GBD 2019 Study. J Am Coll Cardiol 2020; 76: 2982-3021.

8) Arora S, Stouffer GA, Kucharska-Newton AM, Qamar A, Vaduganathan M, Pandey A, Porterfield D, Blankstein R, Rosamond WD, Bhatt DL, Caughey MC. Twenty Year Trends and Sex Differences in Young Adults Hospitalized with Acute Myocardial Infarction. Circulation 2019; 139: 1047-1056.

9) Palinski W, Napoli C. The fetal origins of atherosclerosis: maternal hypercholesterolemia, and cholesterol-lowering or antioxidant treatment during pregnancy influence in utero programming and postnatal susceptibility to atherogenesis. FASEB J 2002; 16: 1348-1360.

10 Block T, El-Osta A. Epigenetic programming, early life nutrition and the risk of metabolic disease. Atherosclerosis 2017; 266: 31-40.

11 Nasioudis D, Doulaveris G, Kanninen TT. Dyslipidemia in pregnancy and maternal-fetal outcome. Minerva Ginecol 2019; 71.

12) Leduc L, Levy E, Bouity-Voubou M, Delvin E. Fetal programming of atherosclerosis: Possible role of the mitochondria. Eur J Obstet Gynecol Reprod Biol 2010; 149: 127-130.

13) Barker DJ, Osmond C. Diet and coronary heart disease in England and Wales during and after the second world war. J Epidemiol Community Health 1986; 40: 37-44.

14) Osmond C, Barker DJ, Winter PD, Fall CH, Simmonds SJ. Early growth and death from cardiovascular disease in women. BMJ 1993; 307: 1519-1524.

15) Barker DJ, Osmond C, Simmonds SJ, Wield GA. The relation of small head circumference and thinness at birth to death from cardiovascular disease in adult life. BMJ 1993; 306: 422-426.

16) Zoccali C. [Nephropathy associated with arterial hypertension: genes and Barker's hypothesis]. G Ital Nefrol Organo Uff Della Soc Ital Nefrol 2002; 19: 517-522.

17) Hughes MM, Black RE, Katz J. 2500-g Low Birth Weight Cutoff: History and Implications for Future Research and Policy. Matern Child Health J 2017; 21: 283-289.

18) Kotecha SJ, Edwards MO, Watkins WJ, Henderson AJ, Paranjothy S, Dunstan FD, Kotecha S. Effect of preterm birth on later FEV1: a systematic review and meta-analysis. Thorax 2013; 68: 760-766.

19) Faa G, Gerosa C, Fanni D, Nemolato S, Locci A, Cabras T, Marinelli V, Puddu M, Zaffanello M, Monga G, Fanos V. Marked interindividual variability in renal maturation of preterm infants: Lessons from autopsy. J Matern Fetal Neonatal Med 2010; 23: 129-133.

20) Piras M, Fanos V, Ravarino A, Marcialis MA, Vinci L, Pintus MC, Faa G. Fetal programming of Parkinson's and Alzheimer's diseases: the role of epigenetic factors. J Pediatr Neonatal Individ Med 2014; 3: e030270.

21) Faa G, Marcialis MA, Ravarino A, Piras M, Pintus MC, Fanos V. Fetal programming of the human brain: is there a link with insurgence of neurodegenerative disorders in adulthood? Curr Med Chem 2014; 21: 3854-3876.

22) Faa G, Manchia M, Pintus R, Gerosa C, Marcialis MA, Fanos V. Fetal programming of neuropsychiatric disorders. Birth Defects Res Part C - Embryo Today Rev 2016; 108: 207-223.

23) Fanni D, Gerosa C, Rais M, Ravarino A, Van Eyken P, Fanos V, Faa G. The role of neuropathological markers in the interpretation of neuropsychiatric disorders: Focus on fetal and perinatal programming. Neurosci Lett 2018; 669: 75-82.

24) Goodfellow J, Bellamy MF, Gorman ST, Brownlee M, Ramsey MW, Lewis MJ, Davies DP, Henderson AH. Endothelial function is impaired in fit young adults of low birth weight. Cardiovasc Res 1998; 40: 600-606.

25) Leeson CP, Kattenhorn M, Morley R, Lucas A, Deanfield JE. Impact of low birth weight and cardiovascular risk factors on endothelial function in early adult life. Circulation 2001; 103: 1264-1268.

26) Barker DJ, Meade TW, Fall CH, Lee A, Osmond C, Phipps K, Stirling Y. Relation of fetal and infant growth to plasma fibrinogen and factor VII concentrations in adult life. BMJ 1992; 304: 148-152.

27) Martyn CN, Meade TW, Stirling Y, Barker DJ. Plasma concentrations of fibrinogen and factor VII in adult life and their relation to intra-uterine growth. Br J Haematol 1995; 89: 142-146.

28) Roseboom TJ, van der Meulen JH, Ravelli AC, Osmond C, Barker DJ, Bleker OP. Plasma fibrinogen and factor VII concentrations in adults after prenatal exposure to famine. Br J Haematol 2000; 111: 112-117.

29) Verspyck E, Borg JY, Le Cam-Duchez V, Goffinet F, Degré S, Fournet P, Marpeau L. Thrombophilia and fetal growth restriction. Eur J Obstet Gynecol Reprod Biol 2004; 113: 36-40.

30) Saba L, Gerosa C, Wintermark M, Hedin U, Fanni D, Suri JS, Balestrieri A, Faa G. Can COVID19 trigger the plaque vulnerability—a Kounis syndrome warning for "asymptomatic subjects". Cardiovasc Diagn Ther 2020; 10: 1352-1355.

31) Neubauer K, Zieger B. Endothelial cells and coagulation. Cell Tissue Res (e-pub ahead of print 20 May 2021.

32 Barcellona D, Marongiu F. The hemostatic system. 1st Part. J Pediatr Neonatal Individ Med JPNIM 2020; 9: e090106-e090106.

33 Kwaan H, Lisman T, Medcalf RL. Fibrinolysis: Biochemistry, Clinical Aspects, and Therapeutic Potential. Semin Thromb Hemost 2017; 43: 113-114.

34 van der Meijden PEJ, Heemskerk JWM. Platelet biology and functions: new concepts and clinical perspectives. Nat Rev Cardiol 2019; 16: 166-179.

35 McVey JH. The role of the tissue factor pathway in haemostasis and beyond. Curr Opin Hematol 2016; 23: 453-461.

36 Kavurma MM, Rayner KJ, Karunakaran D. The walking dead: macrophage inflammation and death in atherosclerosis. Curr Opin Lipidol 2017; 28: 91-98.

37) Barker DJ. Fetal origins of coronary heart disease. Br Heart J 1993; 69: 195-196.

38) Barker DJ. Fetal origins of coronary heart disease. BMJ 1995; 311: 171-174.

39) Crispi F, Bijnens B, Figueras F, Bartrons J, Eixarch E, Le Noble F, Ahmed A, Gratacós E. Fetal growth restriction results in remodeled and less efficient hearts in children. Circulation 2010; 121: 2427-2436.

40) Crispi F, Miranda J, Gratacós E. Long-term cardiovascular consequences of fetal growth restriction: biology, clinical implications, and opportunities for prevention of adult disease. Am J Obstet Gynecol 2018; 218: S869-S879.

41) Faa G, Fanni D, Gerosa C, Nemolato S, Faa A, Obinu E, Puxeddu E, Fraschini M, Iacovidou N, Zaffanello M, Fanos V. Multiple organ failure syndrome in the newborn: Morphological and immunohistochemical data. J Matern Fetal Neonatal Med 2012; 25: 68-71.

42) Krüger-Genge A, Blocki A, Franke R-P, Jung F. Vascular Endothelial Cell Biology: An Update. Int J Mol Sci 2019; 20: E4411.

43) Visentin S, Grumolato F, Nardelli GB, Di Camillo B, Grisan E, Cosmi E. Early origins of adult disease: low birth weight and vascular remodeling. Atherosclerosis 2014; 237: 391-399.

44) Fowden AL, Giussani DA, Forhead AJ. Intrauterine programming of physiological systems: causes and consequences. Physiol Bethesda Md 2006; 21: 29-37.

45) Coussons-Read ME, Okun ML, Nettles CD. Psychosocial stress increases inflammatory markers and alters cytokine production across pregnancy. Brain Behav Immun 2007; 21: 343-350.

46) Ege MJ, Bieli C, Frei R, van Strien RT, Riedler J, Üblagger E, Schram-Bijkerk D, Brunekreef B, van Hage M, Scheynius A, Pershagen G, Benz MR, Lauener R, von Mutius E, Braun-Fahrländer C, Parsifal Study team. Prenatal farm exposure is related to the expression of receptors of the innate

immunity and to atopic sensitization in school-age children. J Allergy Clin Immunol 2006; 117: 817-823.

47) Tröger B, Müller T, Faust K, Bendiks M, Bohlmann MK, Thonnissen S, Herting E, Göpel W, Härtel C. Intrauterine growth restriction and the innate immune system in preterm infants of ≤32 weeks gestation. Neonatology 2013; 103: 199-204.

48) Chen T, Liu HX, Yan HY, Wu DM, Ping J. Developmental origins of inflammatory and immune diseases. Mol Hum Reprod 2016; 22: 858-865.

49) Foteinos G, Xu Q. Immune-mediated mechanisms of endothelial damage in atherosclerosis. Autoimmunity 2009; 42: 627-633.

50) Cerrone G, Fanni D, Lai ML, Gerosa C, Cau R, Balestrieri A, Orrù G, Senes G, Faa G, Saba L. Plasma cells in the carotid plaque: occurrence and significance. Eur Rev Med Pharmacol Sci 2021; 25: 4064-4068.

51) Crispi F, Crovetto F, Larroya M, Camacho M, Tortajada M, Sibila O, Badia JR, López M, Vellvé K, Garcia F, Trilla A, Faner R, Blanco I, Borràs R, Agustí A, Gratacós E. Low birth weight as a potential risk factor for severe COVID-19 in adults. Sci Rep 2021; 11: 2909.

52) Fanni D, Gerosa C, Nemolato S, Mocci C, Pichiri G, Coni P, Congiu T, Piludu M, Piras M, Fraschini M, Zaffanello M, Iacovidou N, Van Eyken P, Monga G, Faa G, Fanos V. 'Physiological' renal regenerating medicine in VLBW preterm infants: could a dream come true? J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet 2012; 25 Suppl 3: 41-48.

53) Fanni D, Gerosa C, Nurchi VM, Manchia M, Saba L, Coghe F, Crisponi G, Gibo Y, Van Eyken P, Fanos V, Faa G. The Role of Magnesium in Pregnancy and in Fetal Programming of Adult Diseases. Biol Trace Elem Res (e-pub ahead of print).

54) Faa G, Sanna A, Gerosa C, Fanni D, Puddu M, Ottonello G, Van Eyken P, Fanos V. Renal physiological regenerative medicine to prevent chronic renal failure: should we start at birth? Clin Chim Acta Int J Clin Chem 2015; 444: 156-162.

55) Faa G, Fanos V. Renal endogenous stem cells: a new source for regenerative medicine in preterms? J Pediatr Neonatal Individ Med JPNIM 2015; 4: e040224-e040224.

56) Fanos V, Castagnola M, Faa G. Prolonging nephrogenesis in preterm infants: a new approach for prevention of kidney disease in adulthood? Iran J Kidney Dis 2015; 9: 180-185.

57) Fanos V, Gerosa C, Loddo C, Faa G. State of the Art on Kidney Development: How Nephron Endowment at Birth Can Shape Our Susceptibility to Renal Dysfunction Later in Life. Am J Perinatol 2019; 36: S33–S36.

58) Gerosa C, Fanni D, Faa A, Van Eyken P, Ravarino A, Fanos V, Faa G. Low vascularization of the nephrogenic zone of the fetal kidney suggests a major role for hypoxia in human nephrogenesis. Int Urol Nephrol 2017; 49: 1621-1625.

59) Nilsen TS, Kutschke J, Brandt I, Harris JR. Validity of Self-Reported Birth Weight: Results from a Norwegian Twin Sample. Twin Res Hum Genet Off J Int Soc Twin Stud 2017; 20: 406-413.

60) Faa G, Piras M, Mancuso L, Coni P, Pichiri G, Orrù G, Fanni D, Gerosa C, Cao G, Taibi R, Pavone P, Castagnola M. Thymosin beta-4 prenatal administration improves fetal development and halts side effects due to preterm delivery. Eur Rev Med Pharmacol Sci 2021; 25: 431-437.