

Cardiovascular prevention beyond traditional risk factors: the perinatal programming

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Abstract

It has been long time since “traditional” risk factors for cardiovascular diseases (familial history, smoking habit, diabetes, dyslipidemia, arterial hypertension, ageing, and gender) have been recognized. They are used to provide risk charts to predict the onset of a fatal or non-fatal cardiovascular event (myocardial infarction or stroke) in the next ten years. However, this approach does not explain why a minority of subjects who are not affected by the above mentioned risk factors suffer from heart attack or stroke. Hence, in order to explain these exceptions, researchers have made their efforts to identify other new and previously unmentioned predisposing causes. Prematurity at birth and intrauterine growth restriction, expressed as low birth weight, have been recognized as belonging to these. The aims of this review are to explain the reasons of this recently reported association as well as cite the most recent scientific evidences supporting this theory.

Keywords

Cardiovascular diseases, risk factors, prematurity, birth weight, intrauterine growth factor, perinatal programming.

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Introduction

It has been long time since “traditional” risk factors for cardiovascular diseases have been recognized. They include familial history, smoking habit, diabetes, dyslipidemia, arterial hypertension, ageing, and gender and are used to provide risk charts to predict the onset of a fatal or non-fatal cardiovascular event (myocardial infarction or stroke) in the next ten years.

However, this approach does not explain why a minority of subjects who are not affected by the above mentioned risk factors suffer from heart attack or stroke. Hence, in order to explain these exceptions, researchers have made huge efforts to identify other new and previously unmentioned predisposing causes. Prematurity at birth and intrauterine growth restriction, expressed as low birth weight, have been recognized as belonging to these.

In this regard, the first report dates back about 15 years, when the breakthrough about the association between low birth weight and coronary artery disease was published. Specifically, Eriksson et al., analyzing a cohort of 4,630 males born in Helsinki between 1934 and 1944, demonstrated an inverse correlation between these two parameters [1].

Likewise, Dalziel tried to clarify how gestational age and reduced fetal growth contribute toward the increase of cardiovascular risk. Consequently, 458 young adults (147 born at term and 311 preterm) aged about 30 years were enrolled. Their weight, height, BMI, blood pressure, lipid profile, and morning cortisol were measured. Preterm birth was found to be associated with high systolic blood pressure and insulin resistance onset in the third decade. This study showed also a significant correlation with reduced gestational age, but not birth weight corrected for gestational age. As a whole, these findings highlighted that is preterm birth, rather than intrauterine growth restriction, the main cause of the raised cardiovascular risk in these subjects [2].

The association between preterm birth and/or low birth weight and cardiovascular diseases seems to be mediated by the subsequent occurrence of overweight/obesity and in turn glucose intolerance, diabetes, dyslipidemia, and arterial hypertension in this kind of patients.

Overall, it is the metabolic syndrome which seems to be responsible for this link. This was confirmed by means of metabolomics, a new laboratory technique which enables to study the metabolic processes

involved in a number of diseases simply analyzing bodily fluids such as blood and urine. In a recent study, enrolling young adults who had been born preterm and with an extremely low birth weight (< 1 kg), metabolomics revealed hyperexpression of myoinositol, a molecule strongly involved in metabolic syndrome development [3].

Risk of overweight and obesity

Preterm and low birth weight babies, when surviving, are usually overfed by their mothers, because of an unconscious feeling that this would compensate for their initial hard situation. This behaviour, mainly due to their mothers' anxiety, overlaps with the dysfunctional metabolism in these young subjects, so that they are affected by an increased uptake of nutrients. It is what neonatologists and pediatricians define as “thrifty phenotype”, namely a phenotype decidedly thin at birth and dangerously overweight later [4].

Risk of hypercholesterolemia

Another important relationship which has been identified is that between low birth weight and hypercholesterolemia in adulthood.

In this respect, between 1994 and 1996 more than 100,000 employees from the British telephone company were studied, measuring their weight at birth and total cholesterol. Complete data were obtained only in 18,286 men and 7,557 women (age range 17-64 years). The study showed that male gender and weight at birth cooperate in predicting the future blood cholesterol levels in adult age. As a general rule, the lower the birth weight, the higher the cholesterol level in men, but not in women (specifically, a 1 kg drop in birth weight leads to an increase of 0.07 mmol/L in cholesterol, being this relationship not modified after the adjustment for confounding factors). To sum up, the association between weight at birth and blood cholesterol concentration is strongly influenced by gender and the lack of this association in women is not explained by menopause [5].

However, it should be highlighted that, when comparing the relationship between weight at birth and total cholesterol with that between the latter and BMI, the first association is by far weaker than the second and has lower influence on public health compared with juvenile obesity. Such a conclusion derive from a metanalysis involving 32 studies and 1,532 subjects from the Great Britain. In details,

an inverse correlation between birth weight and cholesterol level was demonstrated, as the reduction of 1 kg in birth weight leads to an increase of 0.061 mmol/L in cholesterol [6]. Not only is this true, but the difference in blood cholesterol concentration due to a reduction of one quartile of birth weight (0.03 mmol/L) resulted to be about one quarter of that due to an equivalent increase in BMI (0.11 mmol/L), irrespective of the age of the examined individuals [6].

The gender influence in the above stated inverse correlation was confirmed also by another meta-analysis conducted on 30 studies and involving more than 50,000 patients. This research demonstrated again that the inverse correlation between the two variables was stronger in males. This gender difference could be explained by the fact that, during foetal growth, different biological processes take place in males and females, leading to different birth weights. Further studies are nevertheless required to confirm these conclusions [7].

Another meta-analysis about this issue selected 79 studies with around 70,000 subjects. Sixty-five studies showed an inverse correlation between blood cholesterol concentration and birth weight. However, the above stated correlation was stronger in those studies with a small sample size or carried out during childhood. These findings led the authors to conclude that, despite the existence of an inverse correlation between weight at birth and total cholesterol, such a relationship probably has a weak influence in inducing a significant increase in cardiovascular risk during adulthood [8].

Risk of diabetes

Preterm birth and low birth weight seem to trigger the future development of type 2 diabetes.

However, the strength of this correlation remained uncertain until 2008, when a systematic review of all published data about this theme was conducted [9]. Among the 327 studies originally selected, only 31 were considered relevant. They included 150,000 subjects. The correlation between the two variables was expressed as odds ratio per kg of increased weight. Statistical models were then built in order to exclude the effect of confounding factors such as macrosomia, BMI, gestational diabetes, and socioeconomic status. An inverse correlation between low birth weight and type 2 diabetes was found in 23 out of 31 studies, with a statistical significance in 11. However, the popula-

tions in the studies were quite heterogeneous, as testified by the fact that in north American natives the prevalence of maternal diabetes was higher compared to that in those from other countries [9]. The odds ratio for type 2 diabetes, adjusted for age and gender, was 0.75 per kg. The correlation between birth weight and future onset of type 2 diabetes was stronger for a weight below 3 kg. The correction for adult BMI modifies slightly this correlation (odds ratio 0.76 and 0.70 before and after correction, respectively). Summing up, in the majority of the studied populations an inverse proportion was detected between birth weight and risk of type 2 diabetes [9].

A more recent study was conducted in a Danish population to evaluate the association between prematurity/low birth weight and onset of type 2 diabetes. In this study the effect of insulin resistance and pancreatic beta-cells function was taken into account as well [10]. About 5,000 middle-aged and former preterm Danish subjects were examined. Results demonstrated that a 1 kg reduction in birth weight was associated with a 51% increased risk of diabetes onset. Furthermore, while there was an inverse proportionality between low birth weight and insulin resistance, prematurity *per se* is associated only with a reduced insulin sensitivity. It was hypothesized that the association between low birth weight and type 2 diabetes depends on both pancreatic beta-cells function and reduced insulin sensitivity, while prematurity is related with an increased risk of type 2 diabetes onset only through reduced insulin sensitivity and regardless of the fetal growth [10].

Reduced insulin sensitivity, or insulin resistance, therefore plays a pivotal role in the pathogenesis of diabetes in preterm and/or low birth weight subjects. In order to evaluate the influence of foetal growth on insulin resistance during childhood, 31 subjects born preterm and appropriate for gestational age (AGA) together with 28 born preterm and small for gestational age (SGA) were compared to 30 born at term with normal weight individuals (control group). Preterm patients showed a reduced insulin sensitivity and higher blood pressure values in comparison with controls [11].

Risk of high blood pressure

Preterm newborns with intrauterine growth restriction are also at increased risk of future onset of arterial hypertension. For example, when evaluating at ambulatory blood pressure monitoring

50 former preterm newborns in their twenties (21 SGA, 29 AGA), they showed a daytime systolic blood pressure significantly higher than in controls. Conversely, no significant difference was detected in diastolic and nocturnal pressures [12, 13].

Generally speaking, the greater the intrauterine growth restriction, the higher the blood pressure values (systo-diastolic hypertension and “non dipper” pattern). On the contrary, as you go toward at term birth, these alterations tend to reduce [14].

This predisposition to develop high blood pressure was attributed to an interruption in renal parenchyma development, since nephrogenesis usually is completed at 31st-32nd week of gestation. Many preterm patients are born before their kidneys are totally formed. The earlier the birth, the more incomplete the nephrogenesis [15]. The latter means that the kidneys have a low nephron number [16]. An inverse relationship between this number and gestational age, as well as a direct correlation with birth weight, were shown either in animal and human models [17, 18]. The consequences of an impairment in kidneys development are their reduced filtrating surface, hyperfiltration of each residual nephron, glomerulosclerosis, and increased renal cells apoptosis [19].

It is well known that renal injury plays a crucial role in predicting the future onset of arterial hypertension and cardiovascular diseases in adult age. It is the so called “foetal origin hypothesis” or “Guyton hypothesis” [20]. In this respect, a decidedly strong inverse correlation between birth weight and arterial hypertension was already described [21].

Three hypotheses were described to explain the foetal origin of high blood pressure:

1. The renal hypothesis was previously mentioned and relies on the low nephron number. A variant of this hypothesis links arterial hypertension with alterations in postglomerular hemodynamics, which lead to a rise in sodium absorption and renin-angiotensin system activation. Indeed, the drop in nephron number may be balanced by a compensatory hypertrophy of those remaining, so that the total filtrating surface keeps unchanged [22].
2. The vascular hypothesis is based on the inverse relationship between birth weight and the content of elastin at arterial walls [14, 23]. Increased arterial stiffness is responsible of vasoconstriction and surge in blood pressure [24, 25].

3. Lastly, the neuroendocrine hypothesis claims that maternal exposition to glucocorticoids is responsible for intrauterine growth restriction as well as renin-angiotensin system activation, with subsequent increase in sympathetic activity, tubular sodium reabsorption, aldosterone secretion, arteriolar vasoconstriction, and decreased secretion of antidiuretic hormone by the pituitary gland. In this respect, in a few animal models it was shown that low birth weight is associated with renal activation of the renin-angiotensin system [26].

The association between preterm birth/low birth weight and hypertension may also be influenced by racial factors, as suggested by one study in which the anti-hypertensive efficacy of the administered drugs vary according to the race and gender of the enrolled former preterm. Specifically, in African-American ex-preterm women the most effective compounds were Calcium-antagonists, while in Caucasian ex-preterm men were ACE-inhibitors [27].

It is needed to point out that many authors reported that the association between low weight at birth and the onset of high blood pressure affects mainly the systolic values rather than the diastolic [28].

Furthermore, several animal and clinical models support the hypothesis that there are gender-related differences in the long-term control of arterial blood pressure.

In fact, female subjects show a lower extent of hypertension and vascular impairment compared with males. Even though the underlying specific mechanisms are still under debate, it seems that the influence exerted by sex hormones and renin-angiotensin-aldosterone system play a pivotal role [29, 30].

All the previously reported evidences highlight how arterial hypertension may have origin in the early life. The precise mechanism responsible for this was yet not fully elucidated, but probably is caused by more than one factor interacting.

Risk of early atherosclerosis

As previously mentioned, low birth weight is associated with an increased risk of early coronary artery disease in adulthood. Whether this risk may be identified since childhood or adolescence is still under debate. Endothelial dysfunction is the reduced endothelial ability to dilate in response to stimuli such as ischemia or sublingual nitrates

administration. It is considered a preclinic lesion and the first step of atherosclerotic process [31].

Based on these premises, 315 young adults (165 women and 150 men, aged 20-28 years) were enrolled to evaluate the ability of their brachial artery to dilate, taking into account both the endothelial-dependent (flow-mediated dilation) and the endothelial-independent (nitrates-mediated dilation) components. The vasoactive response was tested in relation to typical cardiovascular risk factors (namely smoking habit, dyslipidemia, blood pressure, insulinemia, physical exercise tolerance, BMI, combined risk score) and also birth weight [32]. Low birth weight was found to be associated with a decreased flow-mediated dilation, but not endothelial-independent dilation. Specifically, the difference in dilation at brachial artery between the lowest and the highest quintile of birth weight was the same to that existing between smokers and non-smokers. The presence of the above stated risk factors strength the statistical significance of this correlation [32].

The presence of a marked endothelial dysfunction was recently confirmed also in a small group of young adults (mean age 23 years) who had been born preterm and with an extremely low birth weight. It is conceivable that such an early dysfunction could play a central role so as to facilitate the subsequent atherogenic process [31].

Risk of arrhythmias

Low birth weight is also associated with the risk of early onset of atrial fibrillation in subjects of both genders without classical risk factors (i.e. hypertension, mitral valve diseases), which means that early life factors, although pretty far back, can be involved in the pathogenesis of this kind arrhythmia [33, 34].

This relationship was not modified even after adjustment for traditional risk factors and racial group at multivariate analysis [35]. The association between birth weight and atrial fibrillation seems to be U-shaped, being the lowest and the highest weight (macrosoma, i.e. birth weight > 4 kg) mostly correlated with the onset of this arrhythmia [36].

Regarding a pathophysiological explanation of this association, it may be hypothesized that in these patients an anatomic and electrical remodelling occurs [37]. As pioneer in this field, our research group demonstrated that in young adults who had been born with an extremely low birth weight, the

prevalence of interatrial septal aneurysms is about 30%, while it is 0.2-3.2% in the general population [38].

It is in line with the traditional Hanley's hypothesis, according to which extremely mobile interatrial aneurysms are responsible for the onset of atrial fibrillation in adult age [39]. The high prevalence of septal hypermobility in these subjects may be explained by the presence of a marked gradient of pressure between the two atria at preterm birth (atrial stretching), as in case of prolonged patency of ductus arteriosus or pulmonary hypertension [40].

A pathological remodelling involving also the left ventricle was recently described in those born preterm and/or with intrauterine growth restriction [41]. This may explain some abnormalities of repolarization (i.e. prolonged QTc and QT dispersion) often detected at basal electrocardiogram in these subjects [42-44]. From a practical point of view, it implies an extreme caution in administering to them certain drugs, sometimes available without prescription, which are capable of further prolonging QT tract (for example diuretics, proton pump inhibitors, some antibiotics, psychotropic compounds) [42].

Risk of heart failure

It was recently reported that a number of young adults born preterm develop heart failure, notwithstanding they have a structurally normal heart [45]. This may be explained by the altered myocytes growth (hypertrophy and interstitial fibrosis) caused by the prematurity-induced abrupt interruption in physiological myocardial development, with consequent increased in left ventricular mass and systo-diastolic dysfunction [45].

Another factor potentially involved in this harmful association is massive corticosteroids administration, which was common in the early 90's for prevention and treatment of bronchopulmonary dysplasia in high grade preterm babies (gestational age < 28 weeks) [46, 47]. Corticosteroids significantly improved their respiratory performance, dropped the need of oxygen and mechanical ventilation and decreased mortality [48]. In the short-term, they induced a transient hypertrophic cardiomyopathy that usually disappears after their discontinuation [48]. However, corticosteroids administration in neonatal age may have long-term consequences on

heart as well. In fact, they inhibit the mitosis of cardiomyocytes, which in turn leads to a reduced number of cells in adult heart, compensatory dilated cardiomyopathy and systolic dysfunction. This may also give reason for the reduced expectancy of life in rats treated with corticosteroids during the neonatal period [48].

Other scientific evidences

The theory of a link between preterm birth/low birth weight and increased cardiovascular risk is supported by many other evidences. For example, epicardial fat, an emerging cardiovascular risk factor, is significantly thicker in those born preterm and associated with an augmented cardiac mass. Since the latter was widely recognized to be able to predict the incidence of future cardiovascular diseases, epicardial fat seems to be an easy tool to predict future adverse events in these subjects [49].

What is the most striking in these patients is that also asymmetric dimethylarginine (ADMA), a direct inhibitor of endothelial nitric oxide which is considered to be predictive of future cardiovascular death, is significantly increased compared to controls [50]. ADMA is inversely related with gestational age, since the lower the gestational age, the higher the ADMA blood concentration, which accumulates because of an impaired renal clearance [51]. Furthermore, in this scenario ADMA values linearly correlate with early markers of renal dysfunction, thus predicting the possible future development of a cardio-renal syndrome [52, 53].

Therapeutical future perspectives

Since metabolomics, a new laboratory technique, has been proving to be able to reveal the metabolic processes responsible for a great number of diseases, including the cardiovascular, it could be argued whether it would be possible a “regenerative” medicine, that is a medicine capable of repairing the previously mentioned unfavourable consequences developed during perinatal life [54-56].

In this respect, a great hope relies on the presence of pluripotent staminal cells even in the heart of human newborns, whose stimulation may contribute toward repairing the damage [57]. It is well known that salamander limb regenerates completely after its amputation and zebrafish

heart returns to normal even after an extensive damage. It is the presence of stem cells that makes it possible. In these animals they are still quite efficient, while in the human beings they have lost this capacity. However worldwide researchers are steady working to control cells reprogramming and make regenerative medicine being possible [58].

In conclusion, prematurity at birth and low birth weight are new and decidedly important cardiovascular risk factors, thus confirming the so called “Barker hypothesis”, according to which events occurred during the perinatal period, notwithstanding the long time spent, may influence patients’ future life. This influence is defined also as “perinatal programming” (Tab. 1) [59, 60]. As the percentage of preterm newborns surviving until adulthood is dramatically increasing because of the progress in medical sciences, over the recent years a new population at increased cardiovascular risk is emerging [61, 62].

Table 1. The consequences for cardiovascular apparatus of being born preterm and/or with a low birth weight.

	Preterm birth-induced damage	Supposed etiology
1	Overweight/obesity	Maternal overfeeding (owing to psychological factors) Increased food absorption due to metabolic alterations
2	Hypercholesterolemia (male gender)	Hormones?
3	Type 2 diabetes	Reduced pancreatic beta cells function + insulin-resistance (low birth weight related) Insulin-resistance (preterm birth related)
4	High blood pressure	Impairment in nephrogenesis (low nephron number) Increased arterial stiffness (reduced elastin synthesis) Renin-angiotensin system activation
5	Atherosclerosis	Endothelial dysfunction (reduced flow-mediated dilation)
6	Arrhythmias	Anatomic, electrical, and neuroendocrine atrial remodelling (atrial fibrillation) Ventricular remodelling (increased QT tract length and QTc dispersion)
7	Heart failure	Reduced number of myocytes/ Interstitial fibrosis

Declaration of interest

The Authors declare that there is no conflict of interest.

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