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REVIEW ARTICLE

Preterm Birth: Long Term Cardiovascular and Renal Consequences

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Abstract: ***Background*:** Cardiovascular and chronic kidney diseases are a part of non-communicable chronic diseases, the leading causes of premature death worldwide. They are recognized as having early origins through altered developmental programming, due to adverse environmental conditions during development. Preterm birth is such an adverse factor. Rates of preterm birth increased in the last decades, however, with the improvement in perinatal and neonatal care, a growing number of preterm born subjects has now entered adulthood. Clinical and experimental evidence suggests that preterm birth is associated with impaired or arrested structural or functional development of key organs/systems making preterm infants vulnerable to cardiovascular and chronic renal diseases at adulthood. This review analyzes the evidence of such cardiovascular and renal changes, the role of perinatal and neonatal factors such as antenatal steroids and potential pathogenic mechanisms, including developmental programming and epigenetic alterations.

***Conclusion*:** Preterm born subjects are exposed to a significantly increased risk for altered cardiovascular and renal functions at young adulthood. Adequate, specific follow-up measures remain to be determined. While antenatal steroids have considerably improved preterm birth outcomes, repeated therapy should be considered with caution, as antenatal steroids induce long-term cardiovascular and metabolic alterations in animals' models and their involvement in the accelerated cellular senescence observed in human studies cannot be excluded.

Keywords: Preterm infant, small for gestational age, preeclampsia, antenatal glucocorticoids, nephron number, hypertension, cardiovascular disease, chronic kidney disease, DOHaD, programming, noncommunicable diseases, adult.

1. INTRODUCTION

The incidence rates of Preterm Birth (PTB) vary from 5 % to 14 % worldwide and have increased over the last decades; about 13 million infants are born preterm each year [1, 2]. Preterm birth is the leading cause of neonatal mortality especially in low and middle-income countries [1, 2]. However, with improved perinatal and neonatal care over the last three decades, a growing cohort of early preterm-born infants has survived the neonatal period and has entered adulthood.

Although a number of preterm born infants, including extremely premature birth newborns, survive with no or mild neuro-developmental impairment and enjoy a satisfying quality of life, evidence from clinical and experimental studies suggests that PTB is associated with developmental changes that may expose them to long-term chronic, Non-Communicable Diseases (NCDs). The incidence of NCDs is increasing especially in low and middle-income countries and is the leading cause of death worldwide [3, 4]. Cardiovascular Diseases (CVDs) are known to be the first cause of premature mortality in high-income countries; however, the health impact of Chronic Renal Disease (CRD) is underestimated. CRD is a silent and insidious disease that affects about 10% of the population. Cardiovascular and renal systems overlap; CRD, in turn, increases the occurrence of cardiovascular events and death [5].

While preterm subjects are exposed, on the long-term, to altered regulation of a number of biologic organ/systems, this review focuses on the link between preterm birth and the risk of long-term cardiovascular and renal diseases, on the role of perinatal and neonatal conditions and on the underlying pathophysiological mechanisms. Possible preventive guidance from infancy to adulthood addressed to health care providers, families and preterm individuals will be considered as well.

2. PRETERM BIRTH AND LONG-TERM CARDIOVASCULAR AND RENAL ISSUES: CLINICAL EVIDENCE

2.1. Cardiovascular Consequences

The link between PTB and elevated Blood Pressure (BP) is clearly established [6-8]. The POP Study included 422

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young adults (mean age 19-year-old) born preterm with Gestational Age (GA) less than 32 weeks (or birth weight < 1500 g) in the Netherlands. The proportions of participants in the pre-hypertensive stage or with hypertension (HTN) were 45% and 10 % respectively [9, 10]. A recent, large meta-analysis study found that systolic (SBP) and diastolic (DBP) blood pressure levels were on average 3.4 mmHg (95% confidence interval, 2.2-4.6) and 2.1 mmHg (1.3-3.0) higher, respectively, in preterm young adults than those of their peers born at term [8]. These differences were higher in preterm born women and remained significant after adjustments for age, gender, maternal smoking or family history of arterial HTN. Morover, these differences were found across variuos situations that led to preterm birth, with a significantly higher impact of maternal preeclampsia. Such differences may translate into a higher risk of gestational hypertension or preeclampsia, as shown in the Canadian cohort study [11]. A slight increase in arterial blood pressure at young adulthood has an important impact on health later on. [12, 13]. For instance, a 5 - 10 mmHg increase in DBP is associated with a 34 % increased risk of stroke [14, 15]. Such a modest difference in BP might also contribute to a 2 fold increased risk of cerebrovascular disease, as reported in adult blood preterm individuals in a large Swedish population based study [16]. These findings suggest that infants who are born preterm have modestly elevated BP at young adulthood, but are susceptible to develop HTN with associated other cardiovascular and renal complications.

A growing evidence shows that PTB is associated with changes in heart structure and function [17-20]. Left Ventricular Mass (LVM) has been shown to be 2 fold higher during the first months of life in preterm infants compared to those born at term (+ 56% *vs.* + 34 %, respectively) [16, 17]. Lewandowsky *et al*. also found a similar pattern of increased LVM (mean difference of + 10 g/m^2) with an abnormal geometric shape and reduced systolic and diastolic ventricular functions in young adults born preterm [19]. The LVM was inversely related to GA and independent on BP. Data on heart structure and function in preterm born subjects are still scarce and conflicting [20]. However, structural changes are of concern since ventricular hypertrophy is a known risk factor for heart failure and mortality for coronary diseases [21, 22]. A Swedish population-based study has shown such a possible association [23]. Compared with individuals born at term, the risk of heart failure was 17 and 4 fold higher after extremely (<28 weeks) and very (28 to 31 weeks) PTB respectively.

2.2. Renal Consequences

Several studies have demonstrated a link between low birth weight and Chronic Kidney Disease (CKD) [24-26]. In a recent meta-analysis which included 18 studies (n = 46,249), low birth weight was associated with CKD with overall Odds Ratio (OR) of 1.73 (95% confidence interval [CI], 1.44 to 2.08), proteinuria (OR, 1.81; 95% CI, 1.19 to 2.77) and end-stage renal disease (OR, 1.58; 95% CI, 1.33 to 1.88) [24]. Unfortunately, GA was not accurately investigated in almost all studies, although PTB may be considered to account for approximately 80 % of low birth weight. In young adults born preterm, Glomerular Filtration Rate (GFR) seems preserved within normal ranges although it has been found positively correlated to body weight, not to GA, as reported in the POP Study [10, 27]. In this study, GFR increased by 1.2 to 3.0 ml/min per 1.73 m2 per 1 BW-SDS increase [10]. Only one study has shown a reduced kidney size and volume in young adults born preterm with an appropriate birth weight for GA (AGA) [28]. Available data regarding long-term consequences of preterm birth on renal functions and structure are rare and support the preserved GFR and reduced kidney size (which is a surrogate marker of nephron mass) in young adulthood. But it is not excluded that renal functions could rapidly decline over time in this vulnerable population. The association between low birth weight and CKD has been demonstrated in several studies [29, 30-32]. In a case-control study, Lackland *et al*. [29] found in African Americans and Caucasians participants from the southeastern United States, a U-shaped association between birth weight and CKD, with the highest odds ratio of renal failure in the lowest birth weight group. Nelson *et al*. [30] found in 308 Pima Indians aged 20 to 61 years, a strong association between low birth weight (< 2500g) and abnormal urinary albumin excretion measured by albumin/creatinine ratio (ACR ≥ 30 mg/g). Moreover, data from a cohort of 526 subjects in Norway showed that an increased risk of End-Stage Renal Disease (ESRD) is associated to low birth weight (< 10^{th} percentile) compared with birth weight between 10^{th} and 90^{th} percentiles [31]. The National Kidney Foundation's Kidney Early Evaluation Program (KEEP) [32], revealed in 12364 participants (2902 men and 9444 women), a gender-dependent association between birth weight and CKD. In this study, the adjusted odds ratio of CKD was 1.65 for men with a birth weight < 2500g as compared to men with a birth weight between 3000g and 3999g. However, there was no association among women. On the other hand, Lackland *et al*. [29] found in their cohort of 2676 men and 1014 women, that low birth weight is significantly associated with higher risk of ESRD compared with normal birth weight for women, but not for men. The gender differences in the association between low birth weight and CKD can be explained by the measuring outcomes. In the KEEP study, outcome measures include early stages of CKD and the study of Lackland *et al*. measured end-stage renal disease.

3. INFLUENCE OF PERINATAL AND NEONATAL CONDITIONS

Perinatal and neonatal conditions may shape the link between PTB and long-term chronic diseases. Preterm birth is associated with various perinatal conditions, such as preeclampsia or maternal hypertensive disorders, gestational diabetes, chorioamnionitis, preterm premature rupture of membranes, and Intra-Uterine Growth Restriction (IUGR). After birth, infants have to face up, untimely and with immature organ functions, an extra-uterine, stressing environment that involves a different physiology for nearly all known biologic systems, and includes oxidative stress and exposure to drugs, sub-optimal nutrition, life support and intensive care techniques.

Preeclampsia is independently associated with vascular alterations and elevated BP levels [8, 33, 34]. Growing evidence from experimental studies has linked antenatal glucocorticoids and long-term metabolic, cardiovascular and renal

diseases [35]. Antenatal glucocorticoids are widely used in perinatal care as part of a short course of glucocorticoids prescribed for women at risk of preterm birth which reduce the risk of neonatal morbidity and mortality [36]. Benefits may be further increased after repeated doses, but with adverse consequences on fetal growth. A growing trend towards reduced GFR and increased markers of insulin resistance has been reported in young adults born preterm and exposed prenatally to a short course of glucocorticoids [37, 38]. Although reassuring, long-term follow-up is required since experimental findings highlight long-term occurrence of cardiovascular and renal diseases after a short course of antenatal glucocorticoids [36, 39].

Preterm infants born very/extremely preterm or Small for Gestational Age (SGA) are at particular risk of cardiovascular and renal diseases [10, 13, 40]. In a Swedish population-based study of more than 300 000 twenty-year-old men, Johansson S *et al*. have shown that the risk of hypertension was inversely correlated to GA and was 2 fold higher in extremely preterm individuals (GA < 28 weeks) [41]. Superimposed SGA seems to increase the risk of cardiovascular and renal diseases. In a Young Finns Study, the cardiovascular risks were elevated showing mean SBP levels that are 7 mmHg higher in SGA preterm group than in the AGA preterm group [13]. The prevalence of proteinuria was about 2-fold higher in SGA (3.8 %) than in AGA (1.6 %) individuals in the POP Study [10].

Nutrition and growth during infancy and childhood are key determinants of adult health. Accelerated catch-up growth, especially following early postnatal growth restriction may bear deleterious long-term consequences on cardiovascular, metabolic and renal functions and structure [42-46]. We and other groups have previously reported that although adults who were born preterm in the 80's - 90's have represented an accelerated growth pattern, a large proportion of them suffers from Extra-Uterine Growth Restriction (EUGR) [45, 47, 48]. The "sensitive period of development" during which growth and nutrition have critical effects on long-term cardiovascular and renal health is still unknown. Growth as early as during the neonatal period can influence cardio-metabolic parameters [45, 49, 50]. In young adult-born preterm, Kerkhof *et al*. have shown that neonatal asymmetric overgrowth (weight gain + 0.5 SD) and rapid weight gain up to 3 months after hospital discharge were associated with metabolic disturbances, with high fat deposition and abnormal insulin sensitivity [48, 49]. Nutritional practice in neonatal intensive care units has evolved during the last decade with a shift toward increased protein and energy intake from birth onwards to prevent EUGR. High protein content post-discharge formulas are often used to achieve catch-up growth. The long-term renal and cardiovascular consequences of such nutritional approach are unknown. Recent experimental findings highlight short and long-term adverse renal effects of neonatal high protein diet especially in low birth weight offspring [51, 52]. In a randomized clinical trial, the team of Lucas A has shown lower blood pressure and better insulin sensitivity in breastfed preterm born adolescent [53, 54]. Lewandowsky *et al*. also found improved myocardial function and heart structure in breastfed young preterm adults [55]. Protein intake during the neonatal period can impact adult health later on. In the Finns preterm cohort, Matinolli HM *et al*. have shown that young preterm adult neonatally exposed to protein deficiency, at a time when protein and calories intake were usually limited in NICUs, have reduced muscle mass [56]. This phenotype may decrease sensitivity to insulin. It can be speculated that EUGR and caloric-protein deficiency affect the development of various system and expose preterm born infants to early catch-up growth with adverse long-term cardiovascular and metabolic functions. However, further investigations are needed to determine the long-term consequences of neonatal and infant nutrition and to accurately define the growth profile at risk of cardiovascular and renal diseases. While fetal growth restriction has been shown to exert long-term effects on cardio-vascular and metabolic health, postnatal nutrition is more likely to act a second hit after the effects of antenatal conditions and the stress of being born preterm.

4. DEVELOPMENTAL DISTURBANCES

Preterm birth occurs during key phases of fetal growth and development. Rapid fetal growth is supported in part by arterial growth and the capillary network development. The myocardium develops in low blood pressure system and the kidney in a "stress-free environment", as depuration functions are ensured by the placenta. The intra-uterine environment provides various vascular trophic/growth factors, hormones, progenitors and stem cells essential for the optimal growth and development of the fetus. A premature exposure to the extra-uterine environment may accelerate the maturation process at the expense of proliferative mechanisms, alter developmental programming of long-term biologic functions and injure key organs, with lifelong consequences including an increased vulnerability to cardiovascular and renal diseases at adulthood.

4.1. Preterm Birth and the Cardiovascular System

Changes in micro and macro-vascular structure and functions have been observed in children and young adult born preterm [27, 57-63]. These changes which predominaly affect preterm infants born SGA or after maternal preeclampsia, include reduction in aortic size, peripheral capillary rarefaction (decreased retinal and cutaneous capillary density), altered intima-media thickness, increased arterial stiffness, and impaired arterial endothelium-dependent vasodilation [27, 34, 57-64]. Altered vascular structure or function seems established early in the neonatal period, even before any possible influence of postnatal nutrition. We have reported impaired arterial stiffness in preterm infants at term corrected age, which seems sustained at adulthood [47, 64, 65]. The underlying mechanism is incompletely understood but may involve inadequate elastin synthesis and altered endothelial function [57, 66]. Appropriate angiogenesis is necessary for the development of all organs and systems, and if altered, may pave the way to increased vascular resistance and systemic HTN later on. We recently reported impaired angiogenic activities of circulating Endothelial Colony-Forming Cells (ECFCs) from cord blood of preterm infants [67]. These Progenitor Endothelial Cells (PECs) affect angiogenesis, fetal growth/development, and vascular repair mechanisms [68]. As compared with term infants, these EPCs from preterm infants were decreased in number, showed impaired

proliferation and migration activities and were unable to form robust capillary networks *in vitro* and *in vivo* [67]. Theses dysfunctions were related to both premature senescence process (through decreased expression of SIRT1) and an anti-angiogenic environment involving the VEGF/ sVEGF/PF4 pathway [69, 70]. The influence of particular perinatal conditions is little known. An additional factor consisted of the biogenesis of pro-senescent microparticles by endothelial colony forming cells, driven by SIRT1-dependent epigenetic regulation of MKK6 [71]. However, such changes are reversible as PECs of preterm infants exposed *in vitro* to resveratrol, show restored angiogenic properties [69]. In addition, many of the infants enrolled in these studies received antenatal steroids which may contribute to accelerated maturation and development arrest.

Preterm birth is associated with changes in myocardial functions and structure. In humans, 80% of cardiomyocytes number is reached at term. After birth, the proliferation processes gradually cease and move on to postnatal maturation with cardiomyocyte enlargement [72]. When PTB occurs, the heart development occurs in an unanticipated environment and needs to face up transitional hemodynamic changes from low to high resistance hemodynamic system. In moderately preterm lambs, Bensley *et al*. have demonstrated that the heart exhibited hypertrophic and abnormal cardiomyocyte maturation with increased rate of triploid cells, a marker of cardiomyocyte dysfunction and interstitial fibrosis [73]. Cardiomyocytes number was unchanged in these animals born moderately preterm. Other perinatal conditions surrounding frequently PTB can alter the heart development [74]. In particular, fetal growth restriction and neonatal exposure to hyperoxia in immature animals have been reported to induce cardiomyocyte deficit, ventricular hypertrophy and long-term susceptibility to heart failure [75, 76].

All subtle cardiovascular changes observed in healthy young adult constitute risk factors of CVDs. Capillary microvascular rarefaction is a major determinant of HTN through increased vascular resistance [77]. Increased arterial stiffness, intima-media thickness and impaired endothelium-dependent vasodilation relate to arteriosclerosis and other cardiovascular events [78, 79]. These vascular changes and the further development of HTN worsen ventricular hypertrophy which in turn increases the risk of cardiovascular death [22].

4.2. Preterm Birth and Kidney Development

Low birth weight is associated with nephron deficit in humans and animals but the impact of PTB on nephron endowment is still debated [44]. In humans, nephrogenesis ends achieves prenatally at around 34–36 weeks and 60 % of the nephrons are formed during the third trimester of pregnancy, mostly between 28 and 34 weeks of gestation. In the case of an extremely preterm infant, nephrogenesis ends approximately 40 days after birth [80]. Thus, the final endowment of nephrons is both dependent on gestational age at birth and intrauterine environment [81]. The average nephron number per kidney is ±750,000, with a wide interindividual range (250,000–1,900,000) [82]. Birth weight is the principal marker of nephron endowment, but various factors including IUGR, maternal diet restriction, micronutrient deficiency, iron deficiency, maternal gestational diabetes, chorioamnionitis, maternal gestational administration of glucocorticoids or exposure to other drugs/toxics, can induce nephron deficit [44]. According to Brenner's hypothesis, nephron deficit increases Single Nephron Glomerular Filtration Rate (SNGFR) to meet excretory demands [16]. Blood pressure is also elevated to ensure sufficient natriuresis, named "pressure natriuresis". These adaptive hemodynamic changes are responsible for glomerular hypertension, glomerular and tubular enlargement, renal hypertrophy and renal injury. Low Birth Weight (LBW) results in a reduced number of nephrons with secondary glomerular hypertension and development of non-nephrotic Focal Segmental Glomerulosclerosis (FSGS) [81]. However, a recent study conducted by Conti *et al.* found in a cohort of 89 children with idiopathic nephrotic syndrome, that LBW constitutes a risk factor of FSGS and cortico-dependence, and children with nephrotic syndrome and LBW needed heavier immunosuppressive treatment compared to children with normal birth weight [83]. Conti *et al.* suggest a conditioning role for hemodynamic and podocyte changes due to reduced nephron endowment in children with LBW [83]. Moreover, various postnatal factors including nutrition and protein intake can subsequently amplify this adaptive mechanism. In low birth weight rat offspring, we and others have found out that neonatal overfeeding or high protein intake induced hypertension, proteinuria, accelerated renal insufficiency and glomerular sclerosis [51, 52, 84, 85]. Nephron deficit appears as a vulnerable condition when other postnatal "hits" accelerate the development of CRD and HTN. A rationale exists for avoiding EUGR, and subsequently the need for catch-up growth [47], targeting as much as possible linear growth over the fetal and postnatal periods based on individualized growth charts and precision or individualized fine-tuning of nutrition, although such approach needs to be confirmed by randomized controlled trials.

While intrauterine growth restriction is associated with nephron deficit by an average of 30-35%, the effects of PTB on nephron endowment are still debated. Nephron formation may continue after birth but with premature cessation of nephrogenesis [86]. Studies of autopsies indicate an accelerated maturation and enlarged glomeruli [86, 87]. These structural changes have been observed in preterm animals as well [88, 89]. It must be kept in mind that the babies included in these studies were likely to be the sickest among the patients and to have suffered from prolonged postnatal stress (IUGR, dys-nutrition, inflammation/infection, oxidative stress) which might have compromised the progress of nephrogenesis. In particular, Bacchetta *et al*. have shown reduced kidney volume (surrogate marker of nephron mass) and GFR in 7-year-old children born preterm and AGA and subsequently exposed to early EUGR [90]. Acute renal insufficiency is associated with reduced renal volume (approximate marker of nephron mass) in preterm children [91]. Experimental studies in immature animals also found detrimental effects of neonatal undernutrition and oxidative stress on nephron endowment [84, 92, 93]. In contrast, neonatal overfeeding enhances nephron endowment suggesting that environmental factor can promote postnatal nephrogenesis [85]. The renal effects of antenatal glucocorticoids are unknown in humans while experimental studies have dem-

onstrated significant nephron deficit in offsprings [39]. The severity of immaturity may also play a critical role. When comparing the experimental findings one can speculate that the earlier the PTB occurs during nephrogenesis, the greater is the nephron deficit [88, 89]. An autopsy study of 122 adults showed a significant association between birth weight and nephron number [94]. Altogether, these data suggest that nephron formation is compromised at least in the most immature infants, in SGA preterm infants and in sickest infants who have severe neonatal complications and EUGR. More studies are clearly needed to assess factors influencing the postnatal renal development in preterm infants.

4.3. Epigenetic Mechanisms

The mechanisms by which PTB or perinatal and neonatal conditions affect the development of various organ making preterm infants vulnerable cardiovascular and renal diseases are unknown, but may involve altered developmental programming and epigenetic mechanisms.

There is increasing evidence that early epigenetic imprinting, which memorizes early interactions between genes and the environment, and translates them into durable changes in gene expression, is strongly influenced by PTB [95]. This is not as surprising as the fact that epigenetics are key mechanisms in normal cell differentiation, therefore in organ and function development, by silencing part of the genome which is not involved in the differentiated cell functions, and enhancing the expression of the genes specifically involved in such functions. Arrested development and altered developmental programming are likely factors, within the general frame of the Developmental Origins of Health and Disease concept (DOHaD). Accordingly, during the sensitive and vulnerable period of early development, stimuli related particularly to stress, nutrition and toxicants do not only have short term effects, but may also influence lifelong health and may rely on epigenetic changes of genes regulation as a molecular support. Emerging findings show that all three principal mechanisms of epigenetic alterations, DNA methylation, histones modifications and non coding RNAs have been associated with changes in the expression of specific genes involved during development, and in PTB.

Pham *et al.* have found a reduced methylation rate of the P53 gene, involved in apoptosis in IUGR rats kidneys with nephron number deficit [96]. Studies from our group have identified several epigenetic modifications underlying the altered angiogenic capacity of preterm infants endothelial progenitor cells, which shows that the multiple epigenetic mechanisms are at work. The deficit in SIRT1 expression associated with accelerated senescence in these cells is related to a modification in the methylation of the Lys in position 9 in histone 3 [69], while the pro-senescence characteristics of endothelial microparticles released by senescent ECFCs from preterm infants are associated with a change in histone 3 Lys 9 deacetylation [71]. Conversely, we recently observed that the methylation of the AMOT gene, which codes for amotilin, a pro-angiogenic factor, is inversely correlated with GA in 5 CpG islands of the promoter. The observation that the lower the GA, the higher the methylation rate of the pro-angiogenic gene AMOT contrasts with the otherwise established trend toward increasing genes methylation with GA in preterm infants, and suggests an additional explanation to the decreased angiogenic capacity of preterm infants ECFCs [97].

However, the role of antenatal exposure to exogenous steroids, given to accelerate fetal maturation, needs further investigations to be ruled out as a confounding factor. Animal models experiments suggest indeed that antenatal exposure to synthetic steroids before birth leads to an increased BP and altered genes methylation [39, 98].

CONCLUSION AND PERSPECTIVES

Evidences that young adults born preterm display infraclinical structural and functional changes in key organs, making them at high risk of developing cardiovascular and renal diseases later on. These changes are observable early after preterm birth across the population of preterm born subjects. A variety of stressing events occurring during the perinatal and infancy periods are likely to shape the risk for chronic diseases in such population. Sub-optimal nutrition, typically EUGR associated with excess catch-up growth may act as a second hit. More research, focused on the underlying mechanisms, on identifying early biomarkers of risk and potential therapeutic targets, including epigenetic ones, is needed to better define individual risk profiles and facilitate early prevention [98, 99].

Available data are now sufficient to recommend a specific and extended follow-up in preterm born subjects.

Preventive strategies during the most susceptible period of development (up to term corrected age and during the first two years of life) may mitigate the long-term adverse consequences of PTB. Such strategies may be set at individual and societal levels. Their main components involve efforts to improve global maternal gestational health and nutrition, prevent preterm birth and SGA, avoid repeated courses of antenatal steroids, promote maternal milk as first-line nutrition, avoid EUGR and promote linear growth without overgrowth after hospital discharge, avoid exposure to passive smoking, limit exposure to nephrotoxic drugs from neonatal to adulthood, and to promote a healthy lifestyle including regular physical activity.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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