

# A developmental approach to the prevention of hypertension and kidney disease: a report from the Low Birth Weight and Nephron Number Working Group



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## Introduction

In 2008, the World Health Assembly endorsed WHO's Global Action Plan for the Prevention and Control of Non-Communicable Diseases (NCDs) 2013–2020,<sup>1</sup> based on the realisation that NCDs cause more deaths worldwide than do communicable diseases. This plan strongly advocates prevention as the most effective strategy to curb NCDs. Furthermore, the life-course approach, which was highlighted in the Minsk Declaration,<sup>2</sup> reflects increasing recognition that early development affects later-life health and disease.<sup>1</sup> Optimisation of early development offers the opportunity for true primary prevention of NCDs.

Developmental programming in the kidney has been recognised for more than two decades, but its contribution to the global burden of kidney diseases remains underappreciated by policy makers.<sup>3</sup> In view of the many factors known to affect fetal kidney development, including maternal health and nutrition, exposure to stress, poverty, pollutants, drugs, and infections during gestation,<sup>3</sup> a holistic strategy to prevent such programming effects is consistent with the life-course approach and aligns with the United Nations (UN) Sustainable Development Goals to foster health.<sup>2</sup>

Chronic kidney disease is an important contributor to the NCD burden that has been relatively neglected in WHO's Global Action Plan for the Prevention and Control of NCDs, despite chronic kidney disease being a major cause of hypertension and a major risk multiplier of cardiovascular disease.<sup>14</sup> Although the prevalence of chronic kidney disease in many low-income countries remains unknown, the disease is most prevalent among disadvantaged populations within industrialised nations—eg, African-Americans and Aboriginal Australians.<sup>5</sup> The number of people receiving dialysis or transplantation is projected to double, from 2·6 million in 2010 to 5·4 million in 2030.<sup>6</sup> In 2010, 2·3–7·1 million adults died from lack of access to dialysis and transplantation in low-income countries.<sup>6</sup> In view of the clinical outcomes and often prohibitively high costs of treatment, prevention and early detection are the only sustainable solutions to address this growing global burden.

To address the neglected issue of developmental programming of kidney disease and hypertension, a multidisciplinary working group was convened, including international expert obstetricians, neonatologists, and

nephrologists (appendix). We argue that WHO's Global Action Plan for the Prevention and Control of NCDs does not adequately address the effect of developmental origins of NCDs, particularly in low-income and middle-income countries, where developmental risk is highest and the burden of NCDs is growing fastest.<sup>7</sup> The working group identified the need to raise awareness of the role of developmental programming in renal disease and suggests locally adapted preventive strategies that could have long-term benefits on health and health cost-savings worldwide, integrating obstetric, neonatal, and nephrology perspectives.

## Gestational age, birthweight, nephron number, and kidney disease risk

Barker and colleagues<sup>8</sup> were the first to show that adults born at low birthweight (<2·5 kg) were at increased risk of cardiovascular disease. Subsequently, Brenner and colleagues<sup>9</sup> proposed that developmental programming in the kidney might reduce nephron number, which could contribute to hypertension through limitation of sodium excretion because of a decreased filtration surface area, and could increase the risk of chronic kidney disease by reducing renal adaptive capacity if further nephrons are lost through injury. This hypothesis plausibly linked the observations that low birthweight, hypertension, and chronic kidney disease occur more frequently in disadvantaged populations.<sup>9</sup> Most nephrons form during the third trimester in utero; therefore, preterm birth or insults experienced during this phase might affect nephrogenesis and reduce nephron number.<sup>3</sup> Indeed, intrauterine growth restriction (which affects the growth of splanchnic organs), preterm birth, and low birthweight are all associated with a low nephron number as well as higher blood pressure in later life.<sup>3,10</sup> A lower nephron number is associated with adult hypertension.<sup>3</sup> Findings of a meta-analysis<sup>11</sup> indicate that low birthweight confers a 70% increased risk of chronic kidney disease—defined as albuminuria, reduced glomerular filtration rate, or end-stage kidney disease—compared with normal birthweight. Similarly, preterm birth has also been associated with a lower glomerular filtration rate and higher albuminuria in young adulthood.<sup>12</sup> These findings support the developmental programming hypothesis.

In view of the challenges of measuring nephron number in vivo, intrauterine growth restriction, preterm

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birth, and low birthweight remain the best clinical surrogates because of the likely lower nephron numbers in these individuals.<sup>3</sup> The global risks of preterm birth and low birthweight are around 10% and 15%, respectively; therefore, millions of children are born at risk of chronic kidney disease.<sup>3</sup> The associated risk was estimated among US adolescents:<sup>13</sup> for every 13 individuals born at low birthweight, one had reduced glomerular filtration rate and one had raised systolic blood pressure, and this risk increases with age. A low nephron number alone, however, might not cause chronic kidney disease, but a kidney with fewer nephrons could be less able to withstand additional renal injury.<sup>3</sup>

### The mother and fetus

Maternal characteristics play a part in fetal growth, gametogenesis, and embryonic development, which affect a child's health at birth and in later life.<sup>14</sup> Optimising maternal health before pregnancy can, therefore, improve fetal health.<sup>15</sup> Preconception care—including dietary modification, normalisation of glycaemic control, and blood pressure control—is especially important for women with chronic diseases.<sup>15</sup> Preconception health is also related to maternal lifestyle, education, nutrition, work conditions, stress, and socioeconomic status.<sup>15</sup> Teenage pregnancy is typically unplanned, and teenage mothers have high rates of low-birthweight babies, preterm births, and pre-eclampsia.<sup>3</sup> A comprehensive approach spanning social and structural factors, in addition to access to health care, is important to interrupt the programming cycle. A practical time to initiate such preconception care—including health and lifestyle education—is the immediate post-partum period. Achievement of pregestational weight has proven benefits for future pregnancy and offspring.<sup>16</sup> Moreover, mothers at high risk of future complications can be identified and followed up as required.

Maternal nutrition affects the risk of infertility, abortion, fetal malformations, and pregnancy-related diseases such as intrauterine growth restriction, pre-eclampsia, and gestational diabetes.<sup>15,17</sup> Pre-eclampsia or gestational diabetes increase the infant's risk of subsequent hypertension and chronic kidney disease.<sup>18</sup> Maternal obesity amplifies the risk of high birthweight and low birthweight, and maternal diabetes is a risk factor for high birthweight, all outcomes associated with programmed renal risk in the offspring.<sup>3</sup> Healthy diet and micronutrient intake during the preconception period and throughout pregnancy are associated with improved birth outcomes and can affect kidney development.<sup>3,15</sup> Tobacco, alcohol, and caffeine consumption also influence fetal growth, preterm birth, and kidney development and should be avoided.<sup>17</sup>

Discussion has taken place about whether fetal growth standards should be customised for ethnic origin, maternal characteristics, and parity.<sup>19</sup> Measurement of fundal height should be part of the routine assessment of all pregnant women to monitor fetal

growth, and women with uterine size below expected—as well as those at higher risk—should undergo ultrasound evaluation for fetal growth.<sup>20</sup> Doppler velocimetry of uterine, umbilical, and cerebral arteries, and the ductus venosus, is useful to monitor fetal growth and plan timing of delivery if indicated.<sup>21</sup> Such measurements are important to detect intrauterine growth restriction that might not meet diagnostic criteria for small-for-gestational-age or low birthweight but still reflects programming risk.<sup>21</sup> Maternal rest and treatment of hypertension and anaemia might improve intrauterine growth restriction; however, delivery should be delayed if possible to improve fetal maturity. Strategies to reduce the risk of subsequent preterm birth in women who have a history of premature delivery—eg, progesterone administration, cervical cerclage, smoking cessation, and decreasing the number of embryo transfers during assisted reproduction—have been successful.<sup>22</sup>

A mother's own developmental experience affects her risk of pregnancy complications. Maternal prematurity or low birthweight are risk factors for having a preterm or low-birthweight infant. The odds of gestational diabetes or pre-eclampsia are also raised in women who were preterm.<sup>23</sup> However, having a low-birthweight infant, pre-eclampsia, or gestational diabetes does not merely affect risk in the offspring. Women having a low-birthweight infant, pre-eclampsia, or both have a higher life-time risk of end-stage kidney disease and cardiovascular disease compared with women without these events, and those with gestational diabetes have an increased risk of developing diabetes.<sup>23,24</sup> Women with such high-risk pregnancies must, therefore, be identified and followed up in the long term.

### Neonatal acute kidney injury

Prematurity and very low birthweight (<1500 g) are major risk factors for neonatal acute kidney injury, which occurs in 16–40% of infants with such features.<sup>25</sup> Paediatric intensive-care unit survivors have an increased risk of chronic kidney disease 1–3 years after acute kidney injury.<sup>26</sup> This risk is probably high in preterm infants because of the reduced nephron number.<sup>27,28</sup> Preterm and critically ill newborn babies are highly susceptible to toxic renal injury because of renal functional immaturity and incomplete nephrogenesis, and peripartum asphyxia, drug exposure, and nutrition can affect nephron development irreversibly.<sup>25</sup> Awareness of neonatal acute kidney injury risk is crucial; simple measures could attenuate this risk (panel 1).<sup>29</sup> Any episode of acute kidney injury should be communicated on discharge from neonatal admission.<sup>31</sup> In view of the absence of standard definitions and poor use of creatinine in neonates, new biomarkers could permit better prediction and early detection of acute kidney injury and drug-related nephrotoxicity, prompting early intervention to improve patients' outcomes.<sup>25</sup>

**Panel 1: Recommendations for actions<sup>29</sup>**

- Gestational age and birthweight should be recorded for all infants to identify those who are growth-restricted, preterm, and low-birthweight
- A gestational age less than 37 weeks or a birthweight less than 2.5 kg (low birthweight), growth restriction, or being born from a pregnancy complicated by pre-eclampsia or gestational diabetes should be documented prominently in an infant's medical record
- Growth-restricted, preterm, and low-birthweight infants should be monitored regularly for hypertension, excessive weight gain, albuminuria, and hyperglycaemia
- Awareness of the risk of acute kidney injury in preterm and growth-restricted infants must be raised and preventive strategies implemented:
  - Consistent definitions for acute kidney injury should be used (neonatal acute kidney injury KDIGO [Kidney Disease Improving Global Outcomes] classification)<sup>25</sup>
  - Use of potentially nephrotoxic drugs (antibiotics such as aminoglycosides and vancomycin, antifungals such as amphotericin B, and non-steroidal anti-inflammatory drugs) and radiocontrast agents should be minimised in low-birthweight, preterm, and growth-restricted neonates
  - When used, nephrotoxic drugs should be administered at the lowest effective dose, drug levels should be monitored, and attention should be paid to fluid balance and renal function
  - Fluid management should be tailored to optimise circulating volume and blood pressure
  - Implementation of early-warning systems in electronic health records should be considered to identify at an early stage neonates with or at risk of acute kidney injury<sup>30</sup>
- Neonatal acute kidney injury episodes should be recorded and communicated in the medical record to facilitate complete handoff of care
- Nutrition and growth in neonates and early childhood should be optimised through promotion of breastfeeding and putting emphasis on healthy balanced diets and regular physical activity
- Mothers of growth-restricted, preterm, or low-birthweight babies or who have pre-eclamptic pregnancies should be monitored in the long term
- Mothers with gestational diabetes should be followed up in the long term
- The first and all subsequent peripartum periods should be used to educate women about nutrition, weight control, and preconception counselling
- More resources should be allocated to enhance maternal health, fetal growth, and full-term pregnancies
- Resources should be allocated globally to enhance maternal health, fetal growth, and full-term pregnancies by leveraging UN Sustainable Development Goal 3, to ensure healthy lives and promote wellbeing for all at all ages:
  - By 2030, reduce the global maternal mortality ratio to less than 70 per 100 000 lives
  - By 2030, end preventable deaths of newborns and children younger than 5 years, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 livebirths and under-5 mortality to at least as low as 25 per 1000 livebirths
  - By 2030, ensure universal access to sexual and reproductive health-care services—including for family planning, information, and education—and the integration of reproductive health into national strategies and programmes
  - Achieve universal health coverage, including financial risk protection, access to quality essential health-care services, and access to safe, effective, quality, and affordable essential medicines and vaccines for all
  - Strengthen the implementation of WHO's Framework Convention on Tobacco Control in all countries, as appropriate
  - Substantially increase health financing and recruitment, development, training, and retention of health workforce in developing countries
- Potential living kidney donors with a history of preterm birth, growth restriction, or low birthweight, or women who had pre-eclampsia should be warned of potential greater long-term risk
- Consistent with WHO's emphasis on a life-course approach, an annual global Birth Day could be launched to raise awareness about birth circumstances (birthweight, gestational age, exposure to gestational diabetes, or pre-eclampsia) and their possible outcomes in later life, and to emphasise a healthy lifestyle to combat these risks

**Regular monitoring of preterm and low-birthweight individuals throughout life**

As recommended by WHO and UNICEF, all babies should be weighed at birth. Low birthweight, preterm birth, intrauterine growth restriction, or birth after pre-eclampsia or gestational diabetes should be recorded as risk factors for later-life hypertension and chronic kidney disease. Exclusive breastfeeding should be promoted in the first 6 months, and other food sources should be introduced prudently to allow regular and balanced growth.<sup>15</sup>

Although no evidence-based recommendations exist, we suggest that growth-restricted, preterm, or low-birthweight infants—as well as those exposed to pre-eclampsia or gestational diabetes—undergo annual blood pressure measurement at least from age 3 years, with addition of annual urinalysis. If an infant was very premature (<32 weeks), had very low birthweight, or had acute kidney injury, we suggest screening initiation before age 1 year.<sup>28</sup> If other risk factors are present (eg, high blood pressure, previous acute kidney injury, proteinuria,

**Panel 2: Suggestions for further research studies**

- To develop and validate in-vivo approaches to measure nephron number or functional renal mass
- To characterise nephron numbers in different populations (eg, India, Asia, sub-Saharan Africa, Latin America, Indigenous Americans and Canadians)
- To highlight geographical distribution of gestational age and birthweight to identify risk factors and focus implementation strategies
- To better understand the effect of diabetic pregnancy on renal programming
- To better understand gender differences in programming risks
- To investigate the relative effect of growth restriction and prematurity and whether either can be decreased through simple interventions
- To study the relative perfusion and growth of various organs in growth-restricted fetuses to better understand timing and pathophysiology of programming risks
- To follow up birth cohorts that have received gestational or early childhood nutritional supplements into early adulthood, to detect the long-term effect of micronutrient supplementation
- To validate diagnostic criteria for neonatal acute kidney injury
- To develop guidelines for monitoring renal function in low-birthweight and preterm children (eg, serum creatinine vs cystatin C, timing of follow-up)
- To better assess safety of drugs commonly used in pregnancy for their potential effects on renal programming
- To do implementation research to ascertain the effectiveness of potential interventions to reduce growth restriction and premature birth, particularly in low-resource settings
- To consider randomised controlled trials of angiotensin-converting-enzyme inhibitors starting at age 6 years for very-low-birthweight infants with high blood pressure or renal disease
- To identify new early biomarkers (metabolomics, genetic, epigenetic) to detect individuals with low birthweight who are at major risk for disease in adulthood and with sufficient precision to permit personalised follow-up
- To identify interactions between diet, microbiota, and the individual enterotype in the production of metabolites toxic to the kidney
- To do pharmacovigilance studies on potential nephrotoxic drugs
- To investigate mechanisms of developmental renal toxicity (in vitro and in animal models)
- To improve understanding of the relation between low birthweight, low nephron number, and subsequent risk of pre-eclampsia
- To examine the risk of chronic kidney disease across the continuity of birthweight
- To improve understanding of the relations between low birthweight, low nephron number, and development of chronic kidney disease with ageing

cardiovascular diseases, renal anomalies, obesity, or diabetes), renal function evaluation—including proteinuria—should be undertaken at least every 2 years.<sup>25,28</sup> When possible, a baseline renal ultrasound should be done to detect small kidneys, asymmetry, or structural abnormalities. Screening of growth-restricted, preterm, and low-birthweight individuals during childhood should be done at well-child checks, medical visits, or at 2-year intervals from age 5 years to age 19 years. In low-resource settings, simplified screening could coincide with public health interventions—eg, vaccination campaigns—or be undertaken by community health workers. Screening should be integrated with other health activities, if possible, to avoid labelling children as sick.

Abnormalities in kidney function or ultrasound should be followed up by a paediatrician or paediatric nephrologist when possible. From age 18 years onwards, blood pressure, body-mass index (BMI), and urinalysis should be monitored at least every 2 years until age 40 years, and annually thereafter. Fasting blood sugar should be monitored in individuals with elevated BMI after age 30 years. Any preterm or low-birthweight women becoming pregnant should be monitored closely for gestational weight gain, fetal growth, and pre-eclampsia. Education about lifestyle and avoidance of nephrotoxins is important for families of preterm or low-birthweight children. Rapid catch-up growth should be avoided to prevent obesity-associated exacerbation of renal risk.<sup>3</sup> From childhood onwards, a prudent dietary pattern (reduced sodium, carbohydrates, and saturated fat) should be combined with enhanced physical activity and avoidance of smoking.

**Caution in potential living kidney donors**

Kidney donors who have a reduced nephron number could be at increased risk of accelerated loss of renal function in the one remaining kidney.<sup>32</sup> Study findings have suggested that some living donors might be at increased risk of end-stage kidney disease.<sup>33</sup> Developmental renal programming could be a potential modifier of this risk, with a handful of studies suggesting more frequent hypertension or renal dysfunction developing over time among donor populations known to have a lower birthweight, particularly if donors were older than 50 years.<sup>32</sup> Questions about birth circumstances should be routine in all potential donors. We suggest that any potential donor who was preterm or low birthweight should not be accepted for donation if there is any proteinuria, elevation of blood pressure, or diabetes, or they have a BMI greater than 25 kg/m<sup>2</sup>, and accepted donors should be followed up closely, ideally by a nephrologist for the duration of their life.

**Conclusion**

Our recommendations highlight the opportunity to prevent chronic kidney disease in later life by reducing growth restriction, prematurity, and other conditions leading to low birthweight and low nephron number at birth, through coordinated interventions of obstetricians, neonatologists, nephrologists, midwives, and family doctors (panel 1). Such strategies are especially relevant for resource-poor countries that have the simultaneous burdens of maternal, fetal, and childhood undernutrition and poor health, the rising epidemics of NCDs, and scant access to screening and primary care. The working group has identified many remaining gaps that require further action (panel 2). A health system-wide approach is needed to develop effective implementation strategies to positively affect the programmed risk of kidney disease. Our recommendations are in line with the UN Sustainable Development Goals, whereby ending poverty

and hunger, achieving food security, reducing teenage pregnancy, educating and empowering women and girls, improving maternal health, improving access to care, reducing inequalities and reducing conflicts, and managing chronic diseases can all reduce the risk of prematurity and low birthweight and improve renal health of subsequent generations.

#### Contributors

GR and BMB had the idea for the Viewpoint. VAL, GR, NP, BMB, MS, DM, HV, IC, US, KA, BEV, EAS, DA, and GM prepared the first draft of the report, as members of the writing group for the Low Birth Weight and Nephron Number Working Group. All other members of the Working Group (appendix) contributed to the report by providing overall guidance and suggestions in their specific area of expertise.

#### Declaration of interests

We declare no competing interests.

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