Published in final edited form as:
Lancet. 2017 July 22; 390(10092): 424–428. doi:10.1016/S0140-6736(17)30576-7.

A Developmental Approach to the Prevention of Hypertension and Kidney Disease – a report from the Birth Weight and Nephron Number Working Group

Valerie A. Luyckx[#1], **Norberto Perico**[#2], **Marco Somaschini**[3], **Dario Manfellotto**[4], **Herbert Valensise**[5], **Irene Cetin**[6], **Umberto Simeoni**[7], **Karel Allegaert**[8,9], **Bjorn Egil Vikse**[10,11], **Eric A. Steegers**[12], **Dwomoa Adu**[13], **Giovanni Montini**[14], **Giuseppe Remuzzi**[15,16,17], and **Barry M. Brenner**[18,*] **for the writing group of the Low Birth Weight and Nephron Number Working Group**

[1]Institute of Biomedical Ethics, Zürich, Switzerland [2]Clinical Research Center for Rare Diseases Aldo e Cele Daccò, IRCCS - Istituto di Ricerche Farmacologiche Mario Negri, Bergamo, Italy [3]Unit of Neonatology, Sant'Anna Clinic, Lugano, Switzerland [4]Department of Internal Medicine, AFaR Division, Fatebenefratelli Foundation, 'San Giovanni Calibita' Fatebenefratelli Hospital, Isola Tiberina, Rome, Italy [5]Department of Obstetrics and Gynecology, Tor Vergata University, Rome, Italy [6]Unit of Obstetrics and Gynecology, Department of Biomedical and Clinical Sciences, Hospital "L. Sacco", University of Milan, and Centre for Fetal Research Giorgio Pardi, University of Milan, Milan, Italy [7]Service de Pédiatrie, Université de Lausanne, Lausanne, Switzerland [8]Intensive Care and Department of Pediatric Surgery Erasmus Medical Center-Sophia Children's Hospital Rotterdam, The Netherlands [9]Department of Development and Regeneration KU Leuven, Leuven, Belgium [10]Department of Medicine, Haugesund Hospital, Haugesund, Norway [11]Department of Clinical Medicine, University of Bergen, Bergen, Norway [12]Division of Obstetrics and Prenatal Medicine, Department of Obstetrics and Gynaecology, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands [13]School of Medicine and Dentistry, University of Ghana, Accra, Ghana [14]Pediatric Nephrology and Dialysis Unit, Department of Clinical Sciences and Community Health, University of Milan, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milan, Italy [15]Clinical Research Center for Rare Diseases Aldo e Cele Daccò, and Centro Anna Maria Astori, Science and Technology Park Kilometro rosso, IRCCS - Istituto di Ricerche Farmacologiche Mario Negri, Bergamo, Italy [16]Unit of Nephrology, Dialysis and Transplantation, Azienda Socio Sanitaria Territoriale (ASST) Papa Giovanni XXIII, Bergamo, Italy [17]Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy [18]Renal Division, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

[#] These authors contributed equally to this work.

Correspondence to: Giuseppe Remuzzi, MD, FRCP, IRCCS - Istituto di Ricerche Farmacologiche Mario Negri, Centro Anna Maria Astori, Science and Technology Park Kilometro rosso, Via Stezzano, 87, 24126 Bergamo, Italy, Tel: +39 035 421 31 - Fax +39 035 319331, giuseppe.remuzzi@marionegri.it.

[*] see Appendix

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Introduction

In 2008, the World Health Assembly endorsed the Global Noncommunicable Disease (NCD) Action Plan based on the realization that NCDs caused more deaths than communicable diseases worldwide. 1 This plan strongly advocates prevention as the most effective strategy to curb NCDs. The "Life Course Approach", also recently highlighted in the Minsk Declaration, reflects the increasing recognition that early development impacts later-life health and disease. 1,2 Optimization of early development offers the opportunity for true primary prevention of NCDs.

Developmental programming in the kidney has been recognized for over 2 decades but its contribution to the global burden of kidney diseases remains underappreciated by policy makers. 3 Given the many factors known to impact fetal kidney development, including maternal health and nutrition, exposure to stress, poverty, pollutants, drugs and infections during gestation, 3 a holistic strategy to prevent such programming effects is consistent with the "Life-Course" approach and aligns with the United Nations Sustainable Development Goals (SDG) to foster health. 2,4

Chronic kidney disease (CKD) is an important contributor to the NCD burden that has been relatively neglected in the Global NCD Action Plan, despite CKD being a major cause of hypertension, and a major risk multiplier of cardiovascular disease 1,5 While the prevalence of CKD in many lower-income countries remains unknown, CKD is more prevalent among disadvantaged populations within industrialized nations, e.g. African Americans and Aboriginal Australians. 6 People receiving dialysis or transplantation are projected to double from 2.6 million in 2010 to 5.4 million in 2030. 7 Between 2.3 and 7.1 million adult people died from lack of access to dialysis and transplantation in lower-income countries in 2010. 7 Given the clinical consequences 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 workgroup, including international expert obstetricians, neonatologists and nephrologists (see Appendix), was convened. We argue that the Global NCD Action Plan does not adequately address the impact of developmental origins of NCDs which is globally but is particularly important in low- and middle-income countries (LMICs) where developmental risk is highest and the burden of NCDs is growing fastest. 8 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 heath cost savings worldwide, integrating obstetrical, neonatal and nephrology perspectives.

Gestational age, birth weight, nephron number and kidney disease risk

Barker and colleagues were the first to show that adults who had been of low birth weight (LBW, <2.5 kg) were at higher risk of cardiovascular disease. 9 Subsequently, Brenner and colleagues proposed that developmental programming in the kidney may reduce nephron number, which could contribute to hypertension through limitation of sodium excretion

Europe PMC Funders Author Manuscripts

because of a reduced filtration surface area, and could increase the risk of CKD by reducing renal adaptive capacity if further nephrons are lost through injury. 10 This hypothesis plausibly linked the observations that LBW, hypertension and CKD occur more frequently in disadvantaged populations. 10 Most nephrons form during the third trimester in utero, therefore preterm birth (PTB) or insults experienced during this phase may impact nephrogenesis and reduce nephron number. 3 Indeed, intrauterine growth restriction (IUGR, which differentially impacts the growth of splanchnic organs), PTB, and LBW are all associated with a low nephron number as well as with higher blood pressure in later life. 3,11 A lower nephron number is associated with adult hypertension. 3A meta-analysis found that LBW confers a 70% increased risk of CKD, defined as albuminuria, reduced glomerular filtration rate (GFR) or end-stage kidney disease (ESKD) compared to normal birth weight. 12 Similarly, PTB has also been associated with lower GFRs and higher albuminuria in young adulthood. 13 These findings support the developmental programming hypothesis.

Given the challenges of measuring nephron number in vivo, IUGR, PTB and LBW remain the best clinical surrogates given the likely lower nephron numbers in these individuals. 3 The global risks of PTB and LBW are around 10 and 15% respectively, therefore millions of children are born at risk of CKD. 3 The associated risk was estimated among US adolescents where for every 13 LBW individuals, 1 had a reduced GFR and 1 an increased systolic blood pressure. 14 This risk increases with age. 14 A low nephron number alone, however, may not cause CKD, but a kidney with fewer nephrons may be less able to withstand additional renal injury. 3

The mother and fetus

Maternal characteristics not only affect fetal growth, but also gametogenesis and embryonic development which impact a child's health at birth and in later life. 15 Optimizing maternal health before pregnancy can therefore improve fetal health. 16 Pre-conception care including dietary modification, normalization of glycemic control and blood pressure control is especially important for women with chronic diseases. 16 Pre-conception health is also related to maternal lifestyle, education, nutrition, work conditions, stress and socio-economic status. 16 Teenage pregnancy is often unplanned and teenage mothers have higher rates of LBW, PTB and preeclampsia. 3 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 pre-conception care, including health and lifestyle education, is the immediate post-partum period. Achievement of pre-gestational weight has proven benefits for future pregnancy and offspring. 17 In addition, mothers at high risk of future complications can be identified and followed as required.

Maternal nutrition impacts risks of infertility, abortion, fetal malformations and pregnancy-related diseases such as IUGR, preeclampsia and gestational diabetes (GDM). 16,18 Preeclampsia or GDM increase the infant's risk of subsequent hypertension and CKD. 19 Maternal obesity increases the risk of high birth weight (HBW) and LBW, and maternal diabetes is a risk factor for HBW, all outcomes associated with programmed renal risk in the offspring. 3 Healthy diet and micronutrient intake during the pre-conception period and throughout pregnancy are associated with improved birth outcomes and can impact kidney

development. 3,16 Tobacco, alcohol and caffeine consumption also impact fetal growth, PTB and kidney development and should be avoided. 18

There is discussion whether fetal growth should be customized for ethnicity, maternal characteristics, and parity. 20 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. 21 Doppler velocimetry of uterine, umbilical, cerebral arteries, and ductus venosus is useful to monitor fetal growth and plan timing of delivery if indicated. 22 Such measurements are important to detect IUGR that may not meet diagnostic criteria for small for gestational age (SGA) or LBW but still reflects programming risk. 22 Maternal rest, and treatment of hypertension and anemia may improve IUGR, however delivery should be delayed if possible to improve fetal maturity. Strategies to reduce the risk of subsequent PTB in women who experienced prior PTB such as progesterone administration, cervical cerclage, smoking cessation and decreasing the number of embryo transfers during assisted reproduction have been successful. 23

A mother's own developmental experience impacts her risk of pregnancy complications. Maternal prematurity or LBW are risk factors for having a preterm or LBW infant. The odds of GDM or preeclampsia are also increased in women who were preterm. 24 Having a LBW infant, preeclampsia or GDM do not only impact risk in the offspring, however. Women having a LBW infant and/or preeclampsia have an increased life-time risk of ESKD and cardiovascular disease compared to women without these events, and those with GDM have an increased risk of developing diabetes. 24,25 Women with such high risk pregnancies must therefore be identified and followed long-term.

Neonatal acute kidney injury

Prematurity and very low birth weights (VLBW, < 1500 g) are major risk factors for neonatal acute kidney injury (AKI), which occurs in 16 – 40 % of such infants. 26 Pediatric ICU survivors have an increased risk of CKD 1-3 years after AKI. 27 This risk is probably higher in preterm infants, given the reduced nephron number. 28,29 Preterm and critically ill newborns are highly susceptible to toxic renal injury because of renal functional immaturity and incomplete nephrogenesis, and peripartum asphyxia, drug exposure and nutrition can irreversibly impact nephron development 26. Awareness of neonatal AKI risk is crucial and simple measures could attenuate this risk (Box 1). Any AKI episode must be communicated upon discharge from neonatal hospitalization. 30 Given the lack of standard definitions and poor utility of creatinine in neonates, new biomarkers may permit better prediction and early detection of AKI and drug-related nephrotoxicity prompting early intervention to improve patient outcomes. 26

Regular monitoring of preterm and LBW individuals throughout life

As recommended by WHO and UNICEF, all babies should be weighed at birth. LBW, PTB, IUGR or birth after preeclampsia or GDM should be documented as risk factors for later-life hypertension and CKD. Exclusive breastfeeding should be promoted in the first 6 months

Europe PMC Funders Author Manuscripts

and other food sources should be introduced prudently to allow regular and balanced growth. 16

Although no evidence-based recommendations exist, we suggest that growth-restricted, preterm or LBW infants as well as those exposed to preeclampsia or GDM undergo annual blood pressure measurement at least from age 3, with the addition of an annual urinalysis. If an infant was very premature (< 32 weeks), VLBW or experienced AKI, we suggest screening initiation before 1 year of age. 29 If other risk factors are present (high blood pressure, previous AKI, proteinuria, cardiovascular diseases, renal anomalies, obesity or diabetes) renal function evaluation, including proteinuria, should be performed at least every 2 years. 26,29 Where possible a baseline renal ultrasound should be performed to detect small kidneys, asymmetry or structural abnormalities. Screening of growth-restricted, preterm and LBW individuals during childhood should be performed at well child checks, medical visits or at 2 year intervals throughout school years. In low resource settings simplified screening could coincide with public health interventions such as vaccination campaigns, or conducted 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 pediatrician or pediatric nephrologist where possible. From 18 years onwards, blood pressure, BMI, and urinalysis should be monitored at least biannually until age forty and yearly thereafter. Fasting blood sugar should be monitored in those with elevated BMI after age 30. Any preterm or LBW women becoming pregnant should be closely monitored for gestational weight gain, fetal growth and preeclampsia. Education about lifestyle and avoidance of nephrotoxins is important for families of preterm or LBW children. Rapid catch-up growth should be avoided to prevent obesity-associated exacerbation of renal risk. 3 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 may be at increased risk of accelerated loss of renal function in the single remaining kidney. 31 Recent studies have suggested that some living donors may be at increased risk of ESKD. 32 Developmental renal programming may 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 lower birth weights, especially if donors were over age 50. 31 Questioning about birth circumstances should be routine in all potential donors. We suggest that any potential donor who was preterm or LBW should not be accepted for donation if there is any proteinuria, elevation of blood pressure, diabetes or a BMI >25 kg/m^2, and accepted donors should be closely followed, ideally by a nephrologist life-long.

Conclusion

Our recommendations highlight the opportunity to prevent CKD in later life by reducing growth restriction, prematurity and other conditions leading to LBW and low nephron number at birth, through coordinated interventions of obstetricians, neonatologists,

nephrologists, midwives, and family physicians (Box 1). Such strategies are particularly relevant for resource-poor countries that experience the simultaneous burdens of maternal, fetal and childhood undernutrition and poor health, the rising epidemics of NCDs and the lack of access to screening and primary care. The working group has identified many remaining gaps that require further action as outlined in Box 2. A health system wide approach is required to develop effective implementation strategies to positively impact the programmed risk of kidney disease. Our recommendations are in line with the SDGs proposed by the United Nations 4, where 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, as well as managing chronic diseases, can all reduce the risk of prematurity and LBW and improve renal health of subsequent generations.

Acknowledgements

The workshop was held on April 2, 2016 at the Clinical Research Centre for Rare Diseases *Aldo e Cele Daccò*, IRCCS - Mario Negri Institute for Pharmacological Research, Bergamo, Italy. We are extremely grateful for the support and generosity of the Menarini International Foundation and also want to thank Dr. Alessandro Casini's for his enthusiasm (Rozzano, Milan, Italy). Furthermore we would like to acknowledge the additional contribution of the Chiesi Foundation (Parma, Italy). This meeting was organized under the auspice of the Italian Society of Nephrology (SIN).

Appendix

Low Birth Weight and Nephron Number Working Group

Dwomoa Adu (Ghana), Karel Allegaert (Belgium), Chiara Benedetto (Italy), Barry M. Brenner (USA), Irene Cetin (Italy), Jennifer Charlton (USA), Robert Chevalier (USA), Monica Cortinovis (Italy), Rosario D'Anna (Italy), Johannes Duvekot (The Netherlands), Joaquin Escribano (Sapin), Vassilios Fanos (Italy), Enrico Ferrazzi (Italy), Tiziana Frusca (Italy), Richard Glassock (USA), Wilfried Gyselaers (Belgium), Valerie Luyckx (Switzerland), Dario Manfellotto (Italy), Federico Mecacci (Italy), Giovanni Montini (Italy), Clive Osmond (United Kingdom), Norberto Perico (Italy), Luca Ramenghi (Italy), Giuseppe Remuzzi (Italy), Paola Romagnani (Italy), Antonio Santoro (Italy), Umberto Simeoni (Switzerland), Marco Somaschini (Switzerland), Eric A. Steegers (The Netherlands), Herbert Valensise (Italy), Bjorn Egil Vikse (Norway).

References

1. WHO. Action plan for the global strategy for the prevention and control of noncommunicable diseases, 2013-2020. At http://www.who.int/nmh/events/ncd_action_plan/en/
2. Ketting E, Khomasuridze T. Towards a new WHO European Action Plan for human rights-based sexual and reproductive health (SRH). 2016; 84:8–11. at http://www.euro.who.int/_data/assests/pdf_file/0009/289962/The-Minsk-Decalaration-EN-rev1.pdf.
3. Luyckx VA, Brenner BM. Birth weight, malnutrition and kidney-associated outcomes--a global concern. Nat Rev Nephrol. 2015; 11:135–149. [PubMed: 25599618]
4. UN Sustainable Development Goals. Available at http://sustainabledevelopment.un.org
5. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016; 388:1545–1602. [PubMed: 27733282]

6. Couser WG, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. Kidney Int. 2011; 80:1258–1270. [PubMed: 21993585]
7. Liyanage T, Ninomiya T, Jha V, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. Lancet. 2015; 385:1975–1982. [PubMed: 25777665]
8. Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet. 2013; 382:427–451. [PubMed: 23746772]
9. Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet. 1986; 1:1077–1081. [PubMed: 2871345]
10. Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure. Less of one, more the other? Am J Hypertens. 1988; 1:335–347. [PubMed: 3063284]
11. de Jong F, Monuteaux MC, van Elburg RM, Gillman MW, Belfort MB. Systematic review and meta-analysis of preterm birth and later systolic blood pressure. Hypertension. 2012; 59:226–234. [PubMed: 22158643]
12. White SL, Perkovic V, Cass A, et al. Is low birth weight an antecedent of CKD in later life? A systematic review of observational studies. Am J Kidney Dis. 2009; 54:248–261. [PubMed: 19339091]
13. Keijzer-Veen MG, Schrevel M, Finken MJ, et al. Microalbuminuria and lower glomerular filtration rate at young adult age in subjects born very premature and after intrauterine growth retardation. J Am Soc Nephrol. 2005; 16:2762–2768. [PubMed: 15987756]
14. Khalsa DD, Beydoun HA, Carmody JB. Prevalence of chronic kidney disease risk factors among low birth weight adolescents. Pediatr Nephrol. 2016; 31:1509–1516. [PubMed: 27117307]
15. Steegers-Theunissen RP, Steegers EA. Embryonic health: new insights, mHealth and personalised patient care. Reprod Fertil Dev. 2015; 27:712–715. [PubMed: 25771352]
16. Good Maternal Nutrition - The best start in life. at http://www.euro.who.int/__data/assets/pdf_file/0008/313667/Good-maternal-nutrition-The-best-start-in-life.pdf?ua=1
17. Bogaerts A, Van den Bergh BR, Ameye L, et al. Interpregnancy weight change and risk for adverse perinatal outcome. Obstet Gynecol. 2013; 122:999–1009. [PubMed: 24104777]
18. Cetin I, Mando C, Calabrese S. Maternal predictors of intrauterine growth restriction. Curr Opin Clin Nutr Metab Care. 2013; 16:310–319. [PubMed: 23385473]
19. Geelhoed JJ, Fraser A, Tilling K, et al. Preeclampsia and gestational hypertension are associated with childhood blood pressure independently of family adiposity measures: the Avon Longitudinal Study of Parents and Children. Circulation. 2010; 122:1192–1199. [PubMed: 20823385]
20. McCarthy EA, Walker SP. International fetal growth standards: one size fits all. Lancet. 2014; 384:835–836. [PubMed: 25209473]
21. Sovio U, White IR, Dacey A, Pasupathy D, Smith GC. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. Lancet. 2015; 386:2089–2097. [PubMed: 26360240]
22. DeVore GR. The importance of the cerebroplacental ratio in the evaluation of fetal well-being in SGA and AGA fetuses. Am J Obstet Gynecol. 2015; 213:5–15. [PubMed: 26113227]
23. Chang HH, Larson J, Blencowe H, et al. Preventing preterm births: analysis of trends and potential reductions with interventions in 39 countries with very high human development index. Lancet. 2013; 381:223–234. [PubMed: 23158883]
24. Boivin A, Luo ZC, Audibert F, et al. Pregnancy complications among women born preterm. CMAJ. 2012; 184:1777–1784. [PubMed: 23008489]
25. Vikse BE. Pre-eclampsia and the risk of kidney disease. Lancet. 2013; 382:104–106. [PubMed: 23727168]
26. Selewski DT, Charlton JR, Jetton JG, et al. Neonatal Acute Kidney Injury. Pediatrics. 2015; 136:e463–473. [PubMed: 26169430]
27. Mammen C, Al Abbas A, Skippen P, et al. Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: a prospective cohort study. Am J Kidney Dis. 2012; 59:523–530. [PubMed: 22206744]

28. Bruel A, Roze JC, Quere MP, et al. Renal outcome in children born preterm with neonatal acute renal failure: IRENEO-a prospective controlled study. Pediatr Nephrol. 2016; 31:2365–2373. [PubMed: 27335060]
29. Chaturvedi S, Ng KH, Mammen C. The path to chronic kidney disease following acute kidney injury: a neonatal perspective. Pediatr Nephrol. 2016; doi: 10.1007/s00467-015-3298-9
30. Carmody JB, Swanson JR, Rhone ET, Charlton JR. Recognition and reporting of AKI in very low birth weight infants. Clin J Am Soc Nephrol. 2014; 9:2036–2043. [PubMed: 25280497]
31. Mueller TF, Luyckx VA. The natural history of residual renal function in transplant donors. J Am Soc Nephrol. 2012; 23:1462–1466. [PubMed: 22797183]
32. Mjoen G, Hallan S, Hartmann A, et al. Long-term risks for kidney donors. Kidney Int. 2014; 86:162–167. [PubMed: 24284516]
33. Hanna MH, Askenazi DJ, Selewski DT. Drug-induced acute kidney injury in neonates. Curr Opin Pediatr. 2016; 28:180–187. [PubMed: 26735892]

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Box 1

Recommendations for Actions

- Gestational age and birth weight should be recorded in all infants to identify growth restricted, preterm and low birth weight infants.
- A gestational age < 37 weeks, or a birth weight < 2.5 kg (low birth weight), growth restriction, or being born from pregnancy complicated by preeclampsia or gestational diabetes should be prominently documented in a person's medical record
- Growth restricted, preterm and low birth weight persons should be monitored regularly for hypertension, excessive weight gain, albuminuria and hyperglycemia
- 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 AKI KDIGO Classification) 26
  - Minimise use of potentially nephrotoxic medications (antibiotics such as aminoglycosides and vancomycin, antifungals such as amphotericin B, and non-steroidal anti-inflammatory drugs) and radiocontrast agents in low birth weight, preterm and growth restricted neonates
  - When used, nephrotoxic drugs should be administered at the lowest effective dose, drug levels should be monitored and attention paid to fluid balance and renal function
  - Fluid management should be tailored to optimize circulating volume and blood pressure
  - Consider implementation of early warning systems in electronic health records to identify neonates with or at risk of acute kidney injury early 33
- Document and communicate neonatal acute kidney injury episodes in medical record to facilitate complete handoff of care
- Optimise nutrition and growth in neonates and early childhood through promotion of breastfeeding and emphasizing healthy balanced diets and regular physical activity
- Mothers of growth restricted, preterm or low birth weight babies or who experiences preeclamptic pregnancies should be monitored long-term
- Mothers with gestational diabetes mellitus should be followed-up long-term
- Use the 1st and all subsequent peripartum periods to educate women about nutrition, weight control, preconception counselling

Europe PMC Funders Author Manuscripts

- More resources should be allocated to enhance maternal health, fetal growth, and full term pregnancies
- Allocate resources globally to enhance maternal health, fetal growth, and full term pregnancies by leveraging Sustainable Developmental Goal 3 '*Ensure healthy lives and promoting the well-being for all at all ages*': 4
  - 3.1) By 2030, reduce the global maternal mortality ratio to less than 70 per 100,000 lives
  - 3.2) By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 25 per 1,00 live births
  - 3.7) 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
  - 3.8) 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
  - 3.a) Strengthen the implementation of the World Health Organization Framework Convention on Tobacco Control in all countries, as appropriate
  - 3.c) 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 birth weight, or women who experienced preeclampsia should be warned of potential greater long-term risk
- Consistent with the WHO's emphasis on a "Life Course Approach", an annual global 'Birth Day' could be launched to raise awareness about birth circumstances (birth weight, gestational age, exposure to GDM or preeclampsia), their possible consequences in later life and to emphasise a healthy life style to combat these risks

Europe PMC Funders Author Manuscripts

Box 2

Suggestions for further research studies needed in the field.

- Develop in vivo approaches to measure nephron number/functional renal mass
- Characterize nephron numbers in different populations (e.g. India, Asia, Sub-Saharan Africa, Latin America, Aboriginal US and Canadians)
- Highlight geographical distribution of gestational age and birth weight to identify risk factors and focus implementation strategies
- Better understand the impact of diabetic pregnancy on renal programming
- Better understand of gender differences in programming risks
- Investigate the relative impact of growth restriction and prematurity and whether either can be impacted through simple interventions
- Study the relative perfusion and growth of various organs in growth restricted fetuses to better understand timing and pathophysiology of programming risks
- Follow-up of birth cohorts that have received gestational/early childhood nutritional supplements into early adulthood to detect the long-term impact of micronutrient supplementation
- Validate diagnostic criteria for neonatal AKI
- Develop guidelines for monitoring renal function in LBW and pre-term children (e.g. serum creatinine vs. Cystatin C, timing of follow up etc.)
- Better assess safety of medications commonly used in pregnancy for their potential renal programming impact
- Conduct implementation research to determine effectiveness of potential interventions to reduce growth restriction and premature birth, especially in low resource settings
- Consider randomized controlled trials of angiotensin converting enzyme inhibitors (ACEi) starting at age 6 for very low birth weight infants with high blood pressure or renal disease
- Identify new, early biomarkers (metabolomics, epigenetic) to detect subjects who are at major risk for disease at adulthood and with sufficient precision to permit personalized follow-up
- Identify interactions between diet, microbiota and the individual enterotype in the production of metabolites toxic to the kidney
- Pharmacovigilance studies on potential nephrotoxic drugs
- Explore mechanisms of developmental renal toxicity (in vitro and animal models)

- Improve understanding of the relationship between low birth weight, low nephron number and subsequent risk of preeclampsia
- Examine the risk of chronic kidney disease across the continuity of birth weight
- Improve the understanding of the relationships between low birth weight, low nephron number and the development of chronic kidney disease with aging

Europe PMC Funders Author Manuscripts