Low birth weight, intrauterine growth restriction and risk of chronic kidney disease in adult age

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Thesis for the degree of Philosophiae Doctor (PhD)
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SCIENTIFIC ENVIRONMENT

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LIST OF ABBREVIATIONS

APOL1	Apolipoprotein L1
BMI	Body mass index
CKD	Chronic kidney disease
CVD	Cardiovascular disease
ICD	International classifications of diseases
eGFR	Estimated glomerular filtration rate
GWASs	Genome-Wide Association Studies
DOHaD	Developmental origins of health and disease
ESRD	End-stage renal disease
aHR	Adjusted hazard ration
HR	Hazard ratio
IUGR	Intrauterine growth restriction
KDIGO	Kidney disease improving global outcomes
LBW	Low birth weight
MBR	Medical Birth Registry of Norway
mRNA	Messenger ribonucleic acid
NCD	Non-communicable disease
NPoR	Norwegian Population Registry
NPR	Norwegian Patient Registry
aOR	Adjusted odds ratio
OR	Odds ratio
PAX2	Paired box gene 2

PMP	Per million people
SD	Standard deviation
SNGFR	Single-nephron glomerular filtration rate
WHO	World Health Organization

LIST OF PUBLICATIONS

I. Gjerde A, Lillas BS, Marti HP, Reisaeter AV, Vikse BE. Intrauterine growth restriction, preterm birth and risk of end-stage renal disease during the first 50 years of life. *Nephrol Dial Transplant.* 2020;35(7):1157-1163.

II. Gjerde A, Reisaeter AV, Skrunes R, Marti HP, Vikse BE. Intrauterine growth restriction and risk of diverse forms of kidney disease during the first 50 years of life. *Clin J Am Soc Nephrol.* 2020;15(10):1413-1423.

III. Gjerde A, Skrunes R, Reisaeter AV, Marti HP, Vikse BE. Familiacontributions to the association between low birth weight and risk of CKD in adult life. *Kidney Int Rep.* 2021;6(8):2151-2158.

ABSTRACT

Background and aims: Studies have shown that adults with low birth weight (LBW) face an increased risk for chronic kidney disease (CKD), high blood pressure and cardiovascular disease (CVD). Previous Norwegian studies have shown that individuals with LBW more often develop kidney failure; however, there is a need for more knowledge regarding risk of more moderate kidney disease, such as chronic kidney disease (CKD).

Methods: This thesis consists of three studies that were conducted as retrospective registry-based cohort studies. Datasets were obtained through linkage of the Medical Birth Registry of Norway (MBR), Norwegian Population Registry (NPoR), Norwegian Renal Registry (NRR) and the Norwegian Patient Registry (NPR) (data available for 2008–2016 for the latter). We included all individuals born in Norway since 1967. For Paper I, we investigated the risk of kidney failure as registered in the NRR, and for Papers II and III, we investigated the risk of diverse forms of kidney disease as registered in the NPR. Relative risk (RR) estimates were obtained by Cox-regression or logistic regression statistics.

Results: In our studies, we were able to include about 2.6 million individuals. In Paper I, 1126 individuals developed kidney failure and individuals with LBW had a RR of 1.61 (95% CI 1.38–1.98) for kidney failure, and individuals with small for gestational age (SGA) had a RR of 1.44 (1.22–1.70). In Papers II and III, 4495 individuals had been diagnosed with CKD and 12,818 with other groups of kidney disease. LBW was associated with a RR of 1.72 (1.60–1.90) for CKD and SGA with a RR of 1.79 (1.65–194). These birth-related factors were more strongly associated with CKD than with other forms of kidney disease. In Paper III, we found that as compared the individuals who did not have LBW and who did not have a sibling with LBW, individuals who did not have LBW but who had a sibling with LBW had a RR of 1.33 (1.19–1.49), individuals with LBW but no siblings with LBW had a RR of 1.74 (1.55–1.95) and individuals with LBW and a sibling with LBW had a RR of 1.77 (1.54–2.04) for CKD.

Conclusion: In our cohort studies with a follow-up of 50 years, low birth weight and intrauterine growth restriction were found to be associated with an increased risk for both kidney failure and CKD. Taken together, our results support the hypothesis that intrauterine growth restriction (IUGR) increases the risk of CKD in adult life.

1. INTRODUCTION

Chronic kidney disease (CKD) affects more than 10% of the population, and its burden is increasing worldwide due to population growth, increasing life expectancy and changing risk factors. Despite the availability of a number of treatment options, the prevalence, morbidity, and mortality rates remain high. Early epidemiologic and experimental studies suggested that developmental programming of chronic adult diseases, including CKD, is linked with the in-utero life of an individual and causes the risk for hypertension and renal disease in later life.

In the 1960s, it was demonstrated that acceleration or retardation of the rate of growth induced by malnutrition during early postnatal life in rats led to distinct and different effects on anatomical, physiological, and chemical development.[1] In the 1980s, Barker introduced his 'fetal origins' hypothesis that mentions that birth weight is inversely associated with the risk of cardiovascular and other metabolic diseases in adult life through a long-term effect of suboptimal intrauterine nutrition on metabolism in later life.[2,3] Around the same time, Brenner hypothesized that inborn nephron deficit owing to intrauterine growth retardation (IUGR) or low birth weight (LBW) predicts long-term risks of hypertension, renal impairment or decreased glomerular function, age-adjusted glomerulosclerosis and later CKD or kidney failure.[4] Furthermore, familial factors (e.g. genetic or environmental) are also reported to cause the risk of kidney disease. An important part of the evidence for increased kidney disease risk comes from the Norwegian registry studies that have shown that LBW was associated with an increased risk for kidney failure in Norway.[5] In our study, we took a step further and investigated the risk of being diagnosed with a kidney disease and extended the follow-up to 50 years. This provided us with more end points and a unique opportunity to investigate subgroups and different combinations of risk factors. Thus, we have demonstrated that LBW was associated with an increased risk for kidney disease during the first 50 years, and familial factors, too, have been shown to contribute to this association. Early detection of individuals at risk as well as early referral to nephrology units may slow down the progress of the disease, improve prognosis in

patients with kidney disease and reduce total treatment cost. Taken together, our findings support the nephron endowment in-utero hypothesis.

2. BACKGROUND

2.1 Historical aspects

Record findings of the last 100 years have shown that adverse living conditions during childhood, such as poor housing and diet, increase the risk of cardiovascular and metabolic diseases.[6] For example, in England and Wales, neonatal mortality rates were associated with LBW. They were high in areas where mothers had poor health and death rates during childbirth were high.[6] These findings suggested that further investigation should also be focused on the intrauterine environment, not only the socioeconomic factors, such as housing, family income, diet and other influences. The medical research council employed a historian to search for old records of birth data. Thus, the birth weight of all babies born 1911 onwards in Hertfordshire County was recorded, and health workers visited their homes periodically throughout their infancy. Follow-up studies of these men and women at 60 years of age and above showed that those who weighed more at the time of birth, if they were breastfed at 1 year, had lower rates of death caused by ischemic heart disease and stroke.[7] Another study from England, including 449 men and women of around 50 years of age, showed that their current blood pressure and risk of hypertension were strongly related to their placental and birth weight.[8] Blood pressure of individuals was highest when their birth weight had been lower than expected from placental weight. Later, a study in Finland followed a cohort of men from Western and Eastern Finland during 1959–1974 and showed an association between socioeconomic conditions in childhood and increased risk for death by coronary heart disease, myocardial infarction and ischemic heart disease.[9] A similar study reported a correlation between coronary heart disease in 1964–1967 and infant mortality rate in different geographical regions of Norway.[10] An important part of the evidence for early-life factors and increased kidney disease risk in the last 15 years has come from the Norwegian registry studies.[5,11,12] Using the

access to unique national registries, these studies showed that subjects born with LBW had a 70% higher risk of developing kidney failure during the first 40 years of life. Around the same time, another study from Finland that followed 20,431 people born during 1924–1944 through their life course[13] confirmed the association between prenatal growth and socioeconomic factors and development of CKD in old adult life. Taken together, these epidemiological and experimental studies suggested that CVDs and CKD are linked with in-utero life, as was proposed by Barker's hypothesis of 'early origins of late disease'.[3] This is also in line with Brenner's hypothesis that intrauterine restriction and malnutrition could cause lower nephron numbers leading to subsequent hypertension, proteinuria and progressive kidney injury.[14]

2.1.1 Non-communicable disease and developmental origins

Most non-communicable diseases (NCDs) are long-term chronic diseases that develop gradually over the course of life. Individual susceptibility to NCDs has traditionally been assumed to be a product of genetic variability and physiological, environmental and behavioural factors. Globally, NCDs cause more deaths than communicable diseases, and CKD contributes significantly to the increasing deaths.[15] Epidemiologic studies across a wide range of countries and over many years have confirmed the observation that early human development affects the risk of NCDs in later life. It has been proposed that risk is graded across the normal range of development and LBW is proposed as the strongest current clinical surrogate marker.[16] Mother's diet as an aspect of developmental environment or her body's composition as an aspect of physiology during pregnancy have been shown as factors that may pose a risk for a later disease, for example the relation between mothers' energy intake in late pregnancy and carotid intima media thickness is found to be an early marker of vascular disease in children.[17] Recent studies have identified mutations in Apolipoprotein L1 (APOL1) that are associated with increased risk of focal segmental glomerulosclerosis among African individuals. However, studies involving genome-wide association have not identified dominant genes or polymorphisms associated with the majority of kidney diseases.[18,19]

The Developmental Origins of Health and Disease (DOHaD) model is a comprehensive pathophysiological model of NCDs that argues that early interventions in life (including *in-utero* development) can reduce the risk of NCDs, rather than solely addressing the risk factors and diseases that manifest in later life[20,21] (Figure 1). Thus, according to the DOHaD model, several NCDs, including hypertension, type 2 diabetes and coronary heart disease, have their origins in early life.[22,23] This is believed to work through the mechanisms of developmental programming or developmental plasticity. Developmental programming refers to the observation that adverse environmental stimuli experienced during a critical period of development in utero can induce long-term structural and functional effects on the developing organism.[24] Developmental plasticity is the ability of an organism to develop in different ways, depending on the particular environment or setting.[25]The reasons for plasticity being restricted to a particular period of life may be the difficulties of reversing developmental processes or the costs in terms of survival or reproductive success of changing the characteristics of the adult organism.[26]

As NCDs are largely preventable, there is an urgent need to raise awareness of the role of developmental programming in renal disease and focus on preventive strategies that can have long-term benefits on health and health cost savings.

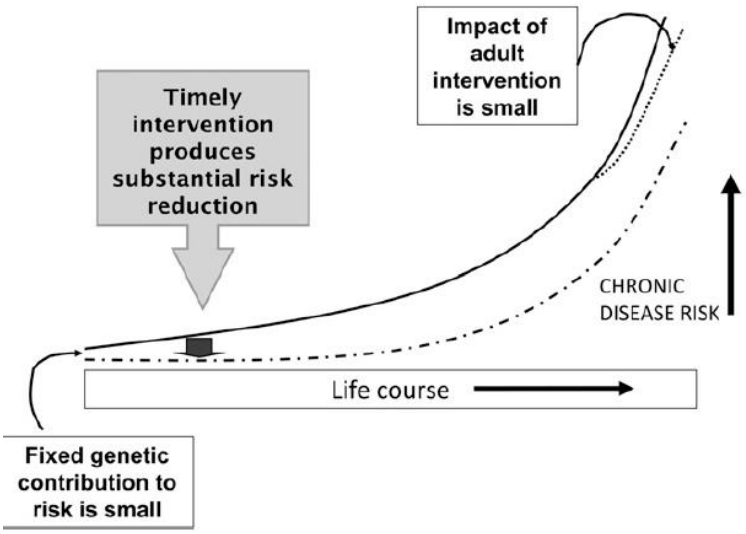

Figure 1: Risk of non-communicable disease increases through the life course. Modified from Hanson et al. (2011) with permission.

2.2 Metabolic imprinting

As described previously, malnutrition in early life seems to affect an individual's susceptibility to suffer from a chronic disease in adulthood. Classic epidemiologic studies of survivors of the Dutch famine of 1944–1945 suggest that perinatal nutrition influences adult body mass index (BMI).[27] More recent evidence that links LBW to increased risk of chronic diseases in old age has contributed to a stronger focus of preventive approaches initiated in the perinatal period.[28-30] Specific nutritional perturbations may occur in utero during critical periods, which may cause long-term changes in development. The work of McCance and Widdowson has shown that early undernutrition has a permanent effect on the subsequent growth of rats, whereas later undernutrition only had a transient effect.[31] Understanding the underlying biology of the effects of perinatal nutritional status on adult diseases is of crucial importance for the possible identification of interventions to improve general human health throughout the life course.

The term *metabolic imprinting* has been used to describe the biological phenomena that may underlie the relationship between intrauterine nutritional influences and subsequent health outcomes.[27] Although many studies have used the term 'metabolic programming' to describe the long-lasting effects of early, in utero nutritional experience, the term 'imprinting' gives a more precise definition. Thus, according to Waterland et al.,[27] the term 'metabolic imprinting' encompasses adaptive responses of the organism to specific nutritional conditions in early life that are characterized by:

1) a susceptibility limited to a critical antogenic window early in development,
2) a persistent effect lasting through adulthood,
3) a specific and measurable outcome, which may differ quantifiably among individuals,
4) a dose–response or threshold relation between a specific exposure and outcome.

The aforementioned characteristics indicate that imprinting may occur only during limited periods of susceptibility, and imprinted responses are memorized by the tissues.

There are several examples of how metabolic imprinting may affect later physiology. A study by Snoeck showed that perinatal undernutrition in rats had permanently reduced pancreatic islet vascularization, suggesting that metabolic effects of early nutrition may result not only from alteration at the cellular level but also from changes in organ structure.[32] A study by Csaba suggested that the concentrations of hormones and hormone analogues present at critical developmental periods permanently affect the hormonal responses to specific stimuli, tissue sensitivity to specific hormones, or both.[33] Further, Dorner et al. introduced the concept that abnormal nutritional environments during the period of brain differentiation could lead to persistent metabolic disturbances through programming of the hypothalamus, affecting the regulation of appetite, growth and behaviour.[34] Later, Lucas et al. proposed a list of four potential mechanisms by which perinatal nutrient environment might persistently affect an organism's structure or function[35]: 1) it may permanently alter gene expression, 2) it may affect clonal selection, 3) it may affect cell number or 4) undernutrition at a critical stage may even fail to fuel a growth process. These proposed mechanisms were used as a starting point of research in this area but were later claimed to be too broad and imprecise; thus, Waterland et al. later proposed a more useful and concise list of specific potential mechanisms[27]:

1) induced variation in organ structure,
2) alterations in cell number,
3) clonal selections,
4) metabolic differentiation, and
5) hepatocyte polyploidization.

These mechanisms will be discussed further in subsequent sections.

2.2.1 Organ structure

Changes in an organ's structure refer to primary, gross morphological alterations during organogenesis and are different from other candidate mechanisms that may result in altered organ structure via changes in cellular or subcellular level.[27] One mechanism leading to changes in an organ's structure may be the ability of individual cells to generate and respond to external signals within the organism. For example,

when patterns of organ vascularization are permanently affected by nutrition during organogenesis, this could affect the cells' responses to blood-borne nutrients or hormonal signals. Organogenesis begins very early in human embryonic development and is nearly completed by the eighth week of gestation.[36] Cellular differentiation continues into postnatal development and transforms foetal organ rudiments into functioning organs. Thus, during the limited period of organogenesis, the fate of cells depends on externally derived, inductive signals from adjacent cells and local concentrations of diverse nutrients and their metabolites. Thus, imbalances in signals and nutrients could result in permanent alterations in the organ structure. Retinoid acid, a derivative of vitamin A, plays an important regulatory role during normal organogenesis. It binds to ligand-activated transcription factors, which in turn regulate the expression of genes involved in morphologic development.[37] The local concentration of this nutrient-derived transducer assists in the establishment of the organ structure. Accordingly, a reduction in nephron number might be mediated through the effects of all-trans retinoic acid on uteric bud branching and vascular growth in kidney development.[38]

Studies investigating the kidney in animal models have shown that the process of nephrogenesis is highly sensitive to a broad range of perturbations in the intrauterine environment. Thus, studies of glucocorticoid exposure, and to a lesser extent maternal retinoic acid, low protein and diabetes, highlight that metabolic insults need only last for a brief moment in time to lead to persistent reduction in kidney mass and nephron number.[39] Another example involved in the process of nephrogenesis is the glial cell line-derived neurotrophic factor (GDNF)–cRet pathway.[39] Expression of the proto-oncogene cRet, a tyrosine kinase receptor, is strongly regulated by maternal vitamin A levels.[40,41] This pathway is likely to be involved in the translations of poor intrauterine environment into a reduced nephron number.

2.2.2 Cell number

During development, organs can increase in size either by the increasing number of cells (hyperplasia) or by the increase in cell size (hypertrophy). Different tissues go through diverse, limited periods of hyperplastic and hypertrophic growth. According to

Waterland et al., the rate of cellular proliferation is directly dependent on nutrient availability and may be indirectly dependent on the organism's general nutritional status via hormonal signals that control cellular proliferation.[27] The researcher claimed that nutrient deficiency or excess during critical periods of hyperplastic growth that affect the rate of cell division may lead to permanent changes in cell number, regardless of nutrient availability at a later time.[27] For example, Winick and Noble showed in their study that severe malnutrition during the period of brain cell hyperplasia resulted in permanent deficits in brain cell number, whereas malnutrition during later periods of brain cell hypertrophy did not have permanent effects.[42] At the same time, if nutrient availability promotes rapid cellular proliferation, the organ may have a permanently increased number of cells. As an organ's metabolic activity is limited by cell number, a permanent effect on cell number could permanently affect metabolism.[42]

Thus, maternal protein or calorie restriction during gestation in experimental animal models is associated with elevated blood pressure, reduced nephron numbers and renal dysfunction in offspring.[43] For example, an iron deficiency can impact kidney development through foetal anaemia and hypoxia.[44] Zink is an antioxidant that exhibits antiapoptotic properties.[45] Accordingly, rats exposed to dietary zinc deficiency during gestation developed reduced nephron numbers, low GFR and high blood pressure.[45] Studies using rat models have also shown that nephron numbers are reduced in offspring in proportion to maternal vitamin A levels.[44]

2.2.3 Clonal selection

Cellular proliferation in all organs involves the initial multiplication of a limited population of founder cells.[27] Founder cells are cells capable of contributing to the establishment of one or more cell populations but are not stem cells.[46] Founder cells in specific organs are not necessarily identical to each other. Although cellular proliferation generally precedes terminal differentiation, successive generations of cells undergo limited differentiation in the early proliferative stage.[27] As cellular proliferation proceeds, it is likely that genetic and epigenetic modifications would occur within individual cells that distinguish them from others in sub-populations of

rapidly dividing cells. Distinguishing characteristics may offer selective advantages to specific clones competing for the available nutrient supply. For example, incorrect base pairing during DNA replication may result in subtle effects on a cell's metabolism. This change would then be passed on to all of its progeny. The basis of clonal selection can be compared with Darwinian evolution, which operates only at the cellular level. Darwinian evolution proposes the survival of the fittest, whereas clonal selection works by disproportionate population growth of the most rapidly proliferating cells.[27] According to this statement, two similar heterogeneous populations of rapidly proliferating cells may develop very distinct metabolic characteristics as a result of diverse microenvironmental conditions. For example, when the nutrient environment has a deficiency of fatty acids, the cells that have excess or more active lipogenic pathways could disproportionately populate the tissue. The latter situation indicates that a possible variation in nutritional status during early development could lead to permanent changes in organ or tissue metabolism.

2.2.4 Metabolic differentiation

It is suggested that metabolic differentiation is the most complex and developmentally relevant potential mechanism of metabolic imprinting. It represents the process by which individual cells develop a stable, quantitative pattern of basal and inducible gene expression. Thus, metabolic differentiation pertains not only to enzymes but also to transcription factors, hormones, hormone receptors, transmembrane transporters and other elements.[27] It is important to distinguish metabolic differentiation from cellular differentiation. Cellular differentiation refers to the developmental process by which multicellular organisms develop a limited number of distinct and stable cell types.[36] Differentiated cells may be characterized as being one type or another based on their structural features and sometimes based on protein markers. However, a fundamental feature of metabolic differentiation is that quantitative as well as qualitative differences in gene expression may distinguish one cell from another.[27] For subtle metabolic differences among cells of similar type, it is important for a cell to have a quantitative pattern of gene expression. Thus, once such a pattern is established during early development, it must be stable. This stability is maintained through epigenetic

mechanisms. Epigenetics is defined as the study of 'mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence'.[47] Epigenetic modifications provide one potential mechanism for how environmental influences in individual`s early life cause long-term changes in susceptibility for chronic diseases.[48] The major components in epigenetic mechanisms and gene expression is regulation are DNA or chromatin protein methylation, acetylation and chromatin remodelling.[48] A recent study demonstrated a link between Paired box gene 2 (Pax2), a transcriptional factor critical for renal morphogenesis, and chromatin methylation.[49] Pax2 gene encodes DNA-binding protein that can specify the intermediate mesoderm, a type of embryonic tissue that subsequently generates the urogenital tract. These data can demonstrate how alterations in an epigenetic regulatory pathway can alter the phenotypes of differentiated kidney cells and lead to CKD.[50] Another example is the activation of p53, a tumour suppressor protein, which results in cell cycle arrest and apoptosis. Of note, tight regulation of p53 activity is an absolute requirement for normal kidney development.[51] Altered p53 gene has been observed in the full-term IUGR rat kidney.[52] It was shown that IUGR increases p53 and Bax (pro-apoptotic gene) and decreases Bcl-2 (anti-apoptotic gene) mRNA levels, leading to enhanced renal apoptosis and reduced glomerular number. Thus, altered methylation of p53 may represent a mechanism that contributes to the foetal origins of adult kidney disease.[48] Another example of an epigenetic mechanism is the observation that treatment of embryonic kidneys with histone deacetylase inhibitor (HDACis) impairs the ureteric bud branching morphogenesis program and provokes renal growth arrest and apoptosis.[49] Epigenetic influences during an individual's early life are not the only cause of long-term changes in chronic disease susceptibility. Emerging evidence suggests that integration of signals from an individual's mother's lifetime nutritional and health experience contributes to inter-generational transfer of environmental information.[48] Thus, offspring of LBW or preterm mothers are likely to have LBW or preterm birth.[53] This supports the hypothesis that epigenetic imprinting plays a role in transmitting epigenetic information from previous generations[54] (Figure 2).

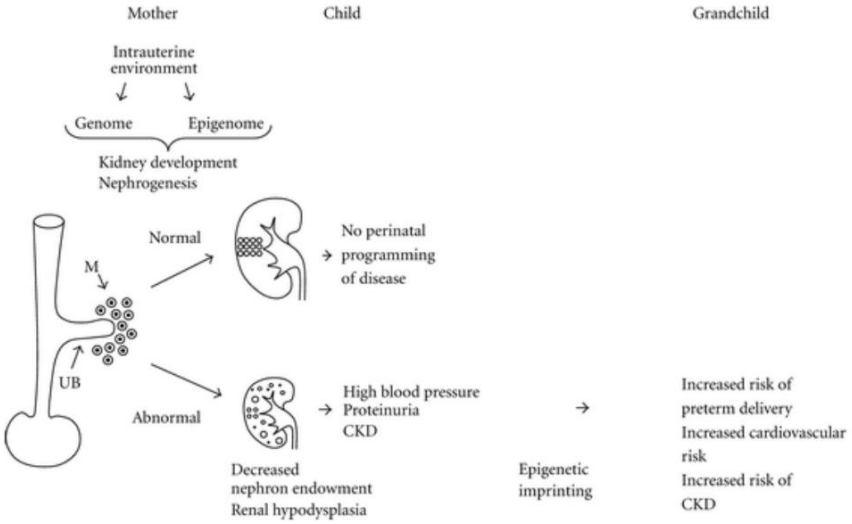

Figure 2: Schematic representation of the proposed impact of an adverse intrauterine environment on the developmental programming of hypertension and chronic kidney disease (CKD). UB: ureteric bud and M: metanephric mesenchyme.
Modified from Chong et al. (2012) with permission.

2.2.5 Hepatocyte polyploidization

Cells that contain more than the normal amount of chromosomes are said to be polyploid.[27] Polyploidy (alias: whole genome amplification) refers to organisms containing more than two basic sets of chromosomes.[55] In mammals, the development of polyploid cells can contribute to tissue differentiation.[55] At the same time, it can be associated with the development of a disease. Polyploidy can occur because of cell fusion or abnormal cell division (endo-replication, mitotic slippage or cytokinesis failure).[55] Polyploidy is a common characteristic of the mammalian liver. Polyploidization mainly occurs during early development, but it also occurs in adults with increasing age or because of cellular stress.[55] In physiological conditions, the conversion from diploidy to polyploidy is a part of developmental and differentiation programs.[56] Polyploidization is seen, for example, in skeletal muscle, heart, placenta, liver, brain and blood cells.[55] In certain tissues, the genesis of polyploid cells is linked to a variety of cellular stressors (mechanical or metabolic stress). This has been shown

for uterine smooth muscle during pregnancy,[57] heart muscle and vascular smooth muscle during aging and hypertension[58,59] and thyroid cells in hyperthyroidism.[60] In adult humans, hepatocytes, cardiomyocytes and megakaryocytes are polyploid.[61] In humans and rats, the period of hepatocyte polyploidization occurs during postnatal development, and it does not continue through adulthood.[62] Hepatocyte polyploizidation is of special interest, because it seems likely to be relevant to metabolic imprinting. During the suckling period, rat hepatocytes are almost exclusively diploid and mononucleated. The initiation of polyploidization appears to coincide with weaning, such as by four to five weeks of age. By the eighth week, a stable ploidy mosaic is established. Hepatocyte polyploidization presumably serves to increase hepatic metabolic activity by enhancing both basal and inducible gene expressions relative to a purely diploid organ.[27] Accordingly, total RNA content, rate of RNA synthesis and activity of specific enzymes correlate with the ploidy of individual rat hepatocytes.[63-65] The signals that determine the timing and extent of hepatocyte polyploidization remain unclear, but because polyploidization is restricted to a limited period of postnatal development, it is possible that nutritional status during this period permanently affects liver ploidy and metabolism in adulthood. Brodsky et al. showed that divergent nutritional status limited to the suckling period in mice had dramatic and persistent effects on cardiomyocyte ploidy.[66] Thus, compared with mice suckled in litters of 16, those suckled in litters of 4 had four times as many diploid tetranucleated cardiomyocytes at 90 days of age.[66] Considering the fact that early postnatal nutrition has a similar influence on hepatocytes, we can expect that hepatic metabolism could be imprinted in this way.

2.3 Mechanisms of developmental plasticity

Developmental plasticity is defined as the ability of an organism to develop in various ways depending on the particular environmental or setting.[25] Developmental plasticity requires stable modulation of gene expression, and it appears to be mediated, at least partly, by epigenetic processes. Thus, the genome interactively influences the mature phenotype and determines sensitivity to later environmental factors and the subsequent risk.[54] There are critical periods in the differentiation and maturation of the tissues and

cells involved in organogenesis through gestation and early postnatal life.[54] Thus, in the kidney, maternal dietary imbalance may lead to developmentally induced deviations from the optimal ratio of body to nephron number.[54] A relative deficiency in the number of nephrons is thought to create an increased risk of inadequate renal function and hypertension later in life.[24] The severity of hypertension in rodent models appears to depend on gender, with males having higher risks.[67] The molecular mechanisms are incompletely understood. In rats, the intrarenal renin–angiotensin system appears to be critical for normal nephrogenesis and may be altered by maternal dietary imbalance, both during the neonatal stage and at later points.[68,69]

Responses to environmental cues during early human development appear to initiate a range of overlapping effects that are induced according to the nature, size and timing of those cues.[25,70] One such example is inadequate maternal nutrition, which can induce a range of phenotypes that have been called 'thrifty', which means that the response usually involves a reduction in somatic growth, which can be specific to an organ or tissues, such as a restricted number of nephrons.[54] Born under such conditions, a foetus gets altered to cope with the consequences of altered body composition. Another form of developmental plasticity is predictive adaptive response (PAR) modifications in which cues received in early life influence the development of a phenotype that is normally adapted to the environmental conditions of later life.[71] When the prediction is accurate, then the organism is matched to it subsequent environment and will cope adequately, ensuring positive selection for the mechanisms mediating such predictive responses.[54] When the predicted and actual environments differ, the mismatch between the individual's phenotype and the conditions in which the individual finds itself can have adverse effects for that individual's later health[71] (Figure 3).

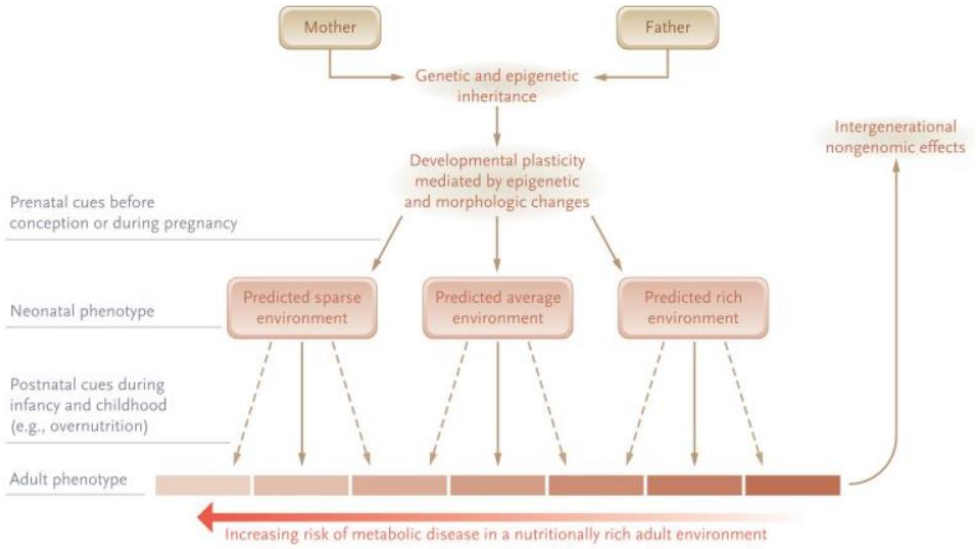

Figure 3: Environmental cues during development, developmental plasticity, and determination of the adult phenotype. Reproduced with permission from Gluckman et al. (2008), Copyright Massachusetts Medical Society.

2.3.1 The thrifty phenotype hypothesis

During the past decade, a number of mechanisms have been proposed to explain the biological basis of the associations observed between birth weight and the risk of adult obesity, diabetes and CVD. In 1968, Neel et al. proposed that 'thrifty' genes were selected during evolution at a time when food resources were scarce and that they resulted in a 'fast insulin trigger,' and thus they enhanced fat storage in later life, which placed the individual at the risk of insulin resistance and type 2 diabetes.[72] Thus, the 'thrifty hypothesis' suggested that when the foetal environment is poor, an adaptive response will optimise the growth of key body organs and alter metabolism in order to enhance postnatal survival under conditions of poor nutrition.[73] The adaptions only become detrimental when nutrition is more abundant in the postnatal environment, than it has been in the pre-natal environment.[74] As an example, people with LBW are more resistant to the effects of the insulin in moving glucose out of the blood stream into tissues. This resistance may be a good adaption for a baby receiving

inadequate amounts of glucose, as it ensures the glucose supply to the brain.[25] However, while persisting into adult life, insulin resistance leads to increased blood glucose and type 2 diabetes, especially in people who have become overweight. Thus, 'thrifty' handling of sugar becomes maladaptive if undernutrition in the womb is followed by overnutrition in later life.[72] Conversely, individuals with more body weight may be particularly at risk of metabolic disorders in harsh environments such as famines.[26] An evidence for this stems from the famine-exposed Ethiopian population, where the incidence of rickets was nine times greater in children who had been reported as having high birth weights than in age-matched control children.[75] No such differences were found in children with normal birth weights.

2.4 Developmental programming of nephron number

As described previously, the term 'programming' has been used to describe the process in which a stimulus or insult at a 'sensitive' or 'critical' period of development has lasting effects on the structure or function of the body.[76] The kidney can be programmed by a variety of intra-uterine and neonatal events, including maternal/neonatal under-nutrition, placental insufficiency, exposure to maternal disease (hypertension, diabetes) or hormones and exposure to pharmaceuticals, alcohol or other toxins.[39] In 1988, Brenner et al. proposed a hypothesis that developmental programming in the kidney might lead to reduced nephron number that could contribute to hypertension through reduction of sodium excretion because of decreased

filtration surface area, and thus, it could further increase the risk of CKD through reduced renal adaptive capacity if further nephrons are lost through injury[14] (Figure 4).

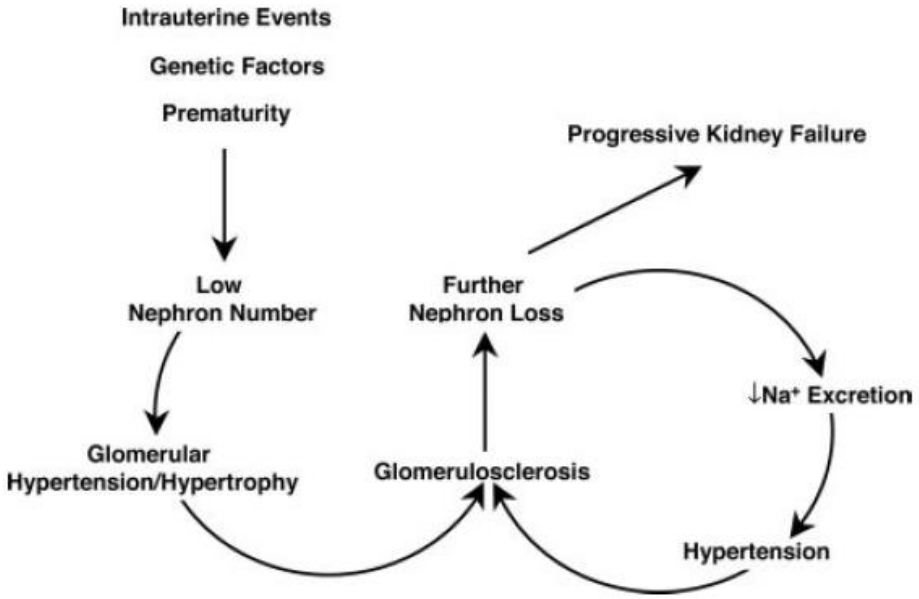

Figure 4: Proposed mechanism of foetal programming for hypertension and renal disease. Modified from Zandi-Nejad et al. (2006), with permission.

This hypothesis was also based on the knowledge that with severe nephron deficits, the remaining glomeruli undergo compensatory hypertrophy (glomerulomegaly) and hyperfiltration (increased single-nephron glomerular filtration rate (GFR)) to sustain adequate renal function. Such kidneys may be conceptualized as 'wearing out' sooner.[77] Animal data shed some light on this evidence as kidneys of mice born with fewer nephrons were less able to withstand subsequent renal 'hits' such as unilateral ureteral obstruction compared with the kidneys of mice with normal nephron numbers.[78] In rat and sheep, congenital or surgical loss of nephrons during foetal life or soon after birth is associated with the spontaneous development of hypertension in adulthood, which is not usually seen in healthy animals undergoing nephrectomy later in life.[79] Thus, loss of nephrons during the critical period when nephrogenesis is

ongoing appears to have a more profound effect on subsequent blood pressure and renal reserve capacity than later loss of nephrons, suggesting that not only the quantity but also the quality of remaining nephrons is important. This is consistent with the findings that renal hypertrophy occurs in congenital single kidneys in humans, and in sheep, it has been found to be associated with an increase in nephron number in the remaining kidney. The timing and cause of a nephron deficit are likely to be key factors in determining the adaptive capacity of the remaining nephrons.[80]

Until recently, nephron numbers have only been measurable post-mortem in humans.[81] Novel approaches have been developed to count and size glomeruli, utilizing computer tomographic (CT) or magnetic resonance imagining (MRI) in conjunction with morphometric analysis of kidney biopsies conducted at a similar time in living humans.[82-84] Using these techniques, both total and non-sclerotic glomerular counts can be determined.[77] Other investigators have estimated functional glomerular numbers through detailed kidney biopsy measurements and determination of renal plasma flow using para-aminohippurate clearance.[85,86] Such techniques may now make it possible to determine nephron numbers in larger populations of patients and to make clinical correlations in the same individuals.[82,83,87] Thus, novel approaches will permit a better understanding of the implications of developmental programming in the kidney in diverse populations.[77]

In humans, approximately 60% of nephrons develop during the third trimester of gestation, and nephrogenesis is complete by 32–34 weeks; therefore, a nephron deficit present at birth persists throughout life. Studies of autopsied kidneys have shown that there is a wide range in the number of nephrons, from approximately 250,000 to over 2 million, with an average of about 1 million nephrons per kidney.[81,88,89] One study calculated that the exact number varies between 400,000 and 1,000,000 nephrons per kidney[90], while another study reported a larger range, between 210,000 and 1,800,000, for the same.[91] The mechanisms leading to such a wide variation in nephron number are currently unknown, but genetic variability, differences in the in-utero environment,

the rate of nephron loss with aging as well as exposure to postnatal renal insults throughout life are the likely key factors.[81,92] A study involving autopsy of 71 infants that died acutely in utero or within 24 hours after birth found that the number of glomerular generations formed within the foetal kidney was directly proportional to gestational age, body weight and kidney weight of the infants.[91,93] Higher nephron number provides a good vascular capacitance reserve to maintain an appropriate kidney function even after postnatal environmental insult.[91] Autopsy studies demonstrate that indigenous Japanese and African Americans have smaller kidneys than Caucasians.[94,95] Another study showed that African Americans had a somewhat greater range of glomerular number than Caucasians, but they also had a greater range of birth weight than Caucasians, indicating that risk was associated more with race and gestational factors than genetic factors.[89]

Nephron number is genetically determined, and several mouse models of single gene deficiency have been proposed, showing an association of gene deficiency with alteration in nephron number.[96] Studies have shown that heterozygous deficient glial cells line–derived neutrophic factor ($GDNF^{+/-}$) mice have been found to possess 30% less nephrons than wild-type $GDNF^{+/+}$mice.[97] GDNF is a key molecular signal in ureteric branching morphogenesis, which plays a primary role in nephron formation.[98]

Conditionally targeted fibroblast growth receptor 2–deficient ($FGFR2^{-/-}$) mice have been reported to have 24% less nephrons that wild-type $FGFR2^{+/+}$ mice.[99] $FGFR2^{+/+}$ is believed to play a crucial role in nephron development, as FGFR2 deficiency results in abnormal uteric branching and renal hypoplasia.[100] Conditional $FGFR2^{-/-}$ mice develop normal appearing nephrons and tubules; however, overall they develop less nephrons.[100]

Tumour growth factor beta ($TGF\beta^{+/-}$) in mice models was shown to have 60% more nephrons at postnatal day 30 compared to wild-type mice.[101,102] As the developing kidney TGFβ normally limits uteric duct branching and elongation, the reduction in TGFβ expression results in greater branching and more total nephrons. As nephron endowment can also be influenced by maternal factors, including maternal nutrition

and body weight,[29] it would be important to determine whether maternal factors or socioeconomic conditions also influence differences in nephron number.

The development of nephron number is critically dependent on two factors: gestational age and a favourable intrauterine environment. It was shown that in the stressed intrauterine environment, development and growth of brain and heart are preserved at the expense of the kidney, other organs and general somatic growth.[103] In both animals and humans, nephron number is strongly correlated with foetal weight and is disproportionately reduced by factors that restrict intrauterine growth.[88,103] Such factors include protein and micronutrient deficiencies, hypoxia, infections, toxins, drugs, metabolic perturbations and probably psychosocial and physical stress.[92] The effects are often reflected in various degrees of IUGR with infants that are of small gestational age and sometimes thin relative to their lengths.[92] It was shown that these infants have smaller kidneys, with the circumferential dimensions often more compromised than their lengths and have fewer nephrons, with glomeruli enlarged in proportion to their reduced numbers.[104,105]

2.5 Birth-related markers of intrauterine conditions

2.5.1 Low birth weight (LBW)

LBW is defined by the World Health Organization (WHO) as a birth weight of less than 2500 g. LBW and IUGR (birth weight below the tenth decile for gestational age) occur more frequently in disadvantaged communities and have been associated with higher incidence of CVD, hypertension, diabetes mellitus and kidney disease.[6,106,107] The worldwide prevalence of LBW is 15.5%, which amounts to about 20 million LBW infants being born each year, 96.5% of them in developing countries.[91] Birth weight and premature birth are the most accessible surrogate markers for intrauterine conditions. Risk factors for LBW and IUGR appear to be relatively consistent among different populations, which are maternal hypertension, maternal smoking, poor maternal weight gain during pregnancy, shorter maternal height, poor antenatal care and lower socioeconomic status.[106,108,109] Researchers have questioned whether a

standardised birth weight cut-off should be used, or whether this value should be modified for different populations.[44] In the United States, the incidence of LBW is twice as high in the African American population compared with the Caucasian population.[106,107] But maternal health, age and socioeconomic status do not entirely explain the disparity in LBW among African American and Caucasian infants.[107] The prevalence of LBW in South Asia is very high, but it is unknown whether these data represent true growth restriction or a normal shift in the curve for population birth weight.[110] Prevalence of LBW has been increasing globally despite different advancements in medical care and reduced rates of complications of foetal growth and pregnancy. The increase in rates of LBW infants may subsequently increase the rates of long-term medical sequelae.[91]

2.5.1.1 Mechanisms

Foetal malnutrition and IUGR may result broadly from maternal undernutrition and/or placental insufficiency.[107] Placental insufficiency results from poor placentation, usually associated with preeclampsia and maternal cardiovascular risk factors.[111]

Both LBW and SGA can identify infants that are relatively smaller at birth, but they do not specify the various growth patterns by which infants may have arrived at their weight at birth. Not all stressors experienced by a developing foetus during gestation manifest as changes in birth. Some small babies have achieved their genetic growth potential and are simply in the lower tail of the birth weight distribution, whereas other babies may have experienced a prenatal nutritional deficit that slowed their growth, but they still have a birth weight within the normal range of the weight distribution.[73]

It has also been a topic of arguments as to what extent maternal nutrition is implicated in the foetal origins of adult disease. Earlier studies have provided evidence that maternal nutrition has been adequate in the majority of the populations in which the foetal origins hypothesis has been tested[111] and that long-term surveys of maternal nutrition indicate that variation in food supply produces a relatively minor effect on birth weight.[112] It was shown that foetal growth in late gestation is normally limited by maternal size and her capacity to supply nutrients to her foetus, a phenomenon known

as ‘maternal constraint’.[113] Foetal growth in late gestation is normally regulated by foetal nutrient supply so that large changes in maternal diet may have a relatively small impact on this supply if there is a large margin of ‘safety’ in the capacity of the placenta to ensure adequate transport of maternal nutrients to the foetus.[114] A further important factor is the balance of macro- and micro-nutrients in the maternal diet. It has been shown that in industrial countries, a combination of high carbohydrate intake in early pregnancy and low-protein intake in late pregnancy was associated with a reduced placental weight, birth weight, low ponderal index and reduced placental weight.[115,116]

‘Catch-up’ and ‘catch-down’ growth have been defined on the clinical basis of a change in weight or length that results in significant centile crossing on standard infant growth charts. Studies have shown that 90% of infants who were born SGA show some catch-up growth within the first 6 months of life, and that infants whose growths was restricted at birth and show early postnatal catch-up growth tend to overshoot their genetic target and have a higher BMI, fat mass and truncal fat distribution during childhood.[117]

2.5.1.2 Known risk factors

Internationally, LBW in humans is often associated with a small maternal size, particularly in mothers with low weight for their height, which is a consequence of generations of suboptimal nutrition.[118] At the same time, distinguished malnutrition and specific protein deficiency are also important factors that cause LBW. The global impact of maternal smoking on foetal growth and potential nephron number is reported as significant.[118,119] It was also reported that maternal alcohol ingestion may impair nephrogenesis.[92] Maternal hypertension is a significant risk factor for LBW and is shown to be more prevalent among Black than White women, making the population-attributable risk of LBW highest among babies of hypertensive Black mothers.[106]

2.5.1.3 Known associations with cardiovascular/metabolic outcomes in adult life

LBW has been shown to influence human kidney development and the later health of adults. LBW induced by a maternal low-protein diet with subsequent induction of diabetes in animal models demonstrated that animals with LBW had reduced nephron numbers and that rats with LBW and diabetes had a greater proportional increase in renal size and glomerular hypertrophy compared with normal birth weight controls after 1 week of diabetes.[120] Thus, this study demonstrated that renal response to injury in the setting of a reduced nephron number may be exaggerated and could lead to accelerated loss of renal function. Compensatory adaptions to reduced nephron numbers result in increased SNGFR and hyperfiltration. Hyperfiltration may be clinically detected as microalbuminuria.[77]

IUGR produced in rats by uterine artery ligation, maternal dietary protein restriction, or vitamin A deficiency resulted in a nephron deficit of up to 30% with a 50% reduction in GFR compared to those of normal weight.[88,121] A study by Celsi et al. found that prenatal administration of dexamethasone in rats was associated with LBW and fewer glomeruli compared with controls.[122] In this study, GFR was reduced, albuminuria was increased, urinary sodium excretion was lower and tissue sodium content was higher.[122] Studies examining the effect of LBW on the activity of the renin–angiotensin system have found that renin and angiotensin activity is reduced in LBW animals, possibly consistent with a degree of volume expansion secondary to sodium retention.[68,69] Thus, these findings support the 'low glomerular endowment' hypothesis initially put forward by Brenner et al. that a congenital deficit in nephron number is thought to be susceptible to developing hypertension, because pressure natriuresis curves are shifted and elevation of blood pressure is required to maintain a balance between normal sodium intake and excretion.[14]

Recent studies from different countries have demonstrated an increased prevalence of microalbuminuria and proteinuria among adults who were born with LBW.[123-127] Other

researchers have shown the relationship between birth weight and diabetic nephropathy, with especially increased susceptibility among individuals with LBW.[127,128] Rossing et al. examined women with insulin-dependent diabetes mellitus, and nephropathy was present in 75% of those with a birth weight below the tenth percentile (≤2.7 kg), compared with 35% of those with birth weight above the 90th percentile (≥4kg)[128]; however, this relationship was not presented in men. Some other studies have found a more severe outcome of renal disease and more rapid progression in IgA nephropathy, membranous and minimal change nephropathies and chronic pyelonephritis among individuals with LBW.[12,129-132] Lackland et al. examined birth weight in patients with kidney failure and found that the OR for kidney failure was 1.4 (95% CI =1.1–1.8) for those with birth weight <2.5 kg compared with those with normal weight.[132]

Many animal models have demonstrated the association of LBW with hypertension in later life induced by exposure to a low-protein diet, dexamethasone, gentamicin, vitamin A deficiency or uterine ischemia.[69,122,133,134] Other models proposed mechanisms of susceptibility to hypertension were modulation of activity of the RAS, the sympathetic nervous system and the cardiovascular system.[73] In human studies, it was early reported by Barker and Osmond that blood pressure was higher in those who were born with LBW. In a cohort of 46–64-year-old adults, mean systolic blood pressure was 11 mmHg lower in those with birth weight of at least 7.5 lbs (3.4 kg) as compared to those with birth weight of less than 5 lbs (2.27).[3] Later meta-analyses have supported these findings.[135]

Studies on twins have attempted to separate the relative impact of environmental influences and genetic predisposition on the development of higher blood pressure. A study of twin pairs that were 18–34 years of age, using 24-hour ambulatory blood pressure monitoring, found higher blood pressure in the LBW twin but only among women.[136] A Swedish study of 16,265 twins found a correlation between LBW and later-life hypertension within dizygotic and monozygotic twin pairs.[137] These data

suggest that intrauterine environmental factors appear to exert an impact on later blood pressure, independent of genetic background. Now epidemiologic evidence has also supported an association between LBW and higher blood pressure in populations of varied ethnic and geographic origins.[24,107] The majority of studies have been conducted on White populations, although studies of various Black populations support the inverse relationship between birth weight and blood pressure.[138,139] The kidney is an organ central to the development of hypertension. The relationship between renal sodium transporters, intravascular-fluid-volume homeostasis and hypertension has been proposed in several studies and is well known. In addition, genetic mutations associated with hypertension are mutations in proteins that are expressed in the kidney.[140] These factors have been demonstrated in renal transplantation, where blood pressure in the recipient after transplantation has been shown to be related to the blood pressure or hypertension risk factors of the donor. In other words, hypertension 'follows' kidney.[141] It confirms the mechanism that a congenital alteration in renal sodium transporters, as a result of a congenital reduction in nephron number, might have an impact on blood pressure.[137]

Similar to the studies that explore the association of LBW and hypertension and increased risk of renal disease, there are studies that have found associations between LBW and diabetes mellitus.[142-144] A study by Hales demonstrated a strong association between reduced growth in early life and impaired glucose tolerance and non-insulin-dependent diabetes among men aged 64.[143] Poulsen et al. investigated the effect of intrauterine restriction among monozygotic twins and showed that the twin with diabetes was found to have LBW compared with the genetically identical twin without diabetes.[145] Increased prevalence of diabetes together with the metabolic syndrome in individuals with LWB have been reported in several studies.[146-152] Bavdekar et al. have investigated a cohort of 8-year-old Indian children and have found the association between LBW and increased blood pressure, higher total and LDL cholesterol and increased insulin resistence.[153] Many studies showed that LBW children exhibit most metabolic patterns later in life.[151,154] Accelerated weight gain or an increase in BMI has been associated with amplified risk of adult hypertension, type 2 diabetes and CVD.[155-157] This can support the 'thrifty phenotype hypothesis' that states that undernourished

foetus makes metabolic adaptions, resulting in developmental programming of adult disease often manifesting as obesity, insulin resistance and hypertention.[155,158,159]

2.5.2 Small for gestational age (SGA)

The classification of SGA was defined by the 1995 WHO expert committee as infants below the 10th centile of a birth weight for gestational age, gender-specific reference population.[110] It is stated that SGA occurs in more than 30 million infants every year.[160] Globally, 16% of infants are SGA at birth, ranging from 7% in industrialized countries to 41.5% in South Asia.[161] Various criteria have been used to identify SGA infants. The most common definitions are: 1) children born below the 10th percentile of birth weight or 2) children with a birth weight of <2 SDs below the mean.[161] Children can also be further classified into full-term (37–42 week) and preterm (<37 week) gestational age.[161] Infants can then be sub-classified into SGA for weight, SGA for lengths or SGA for both weight and length.[162]

Children born SGA comprise a heterogeneous group with a broad spectrum of clinical characteristics.[163] SGA can occur as IUGR alone and/or together with premature birth. It can also occur at term without any prenatal complications. The aetiology of SGA is frequently unknown; the current estimates suggest that 40% of SGA births have no identifiable pathology.[164] Of those 60% of SGA infants in whom an aetiology is identified, about 50% involve maternal factors, 5% involve foetal abnormalities and <5% are due to placental pathology.[164]

Risk factors for being born SGA include foetal, placental, maternal and environmental factors.[162,165] Maternal risk factors include inadequate nutrition, hypoxia, diabetes mellitus, short stature, LBW, Indian or Asian ethnicity, nulliparity, mother born SGA, cigarette smoking and maternal substance abuse.[164] Maternal medical history of hypertension, renal disease, antiphospholipid syndrome and infectious diseases may also be associated with SGA.[165] Foetal risk factors include congenital anomalies, chromosomal abnormalities, infections and hormone abnormalities involving insulin, leptin, thyroid hormones and insulin-like growth factors (IGF-1 and IGF-2).[164]

Pregnancy-related risk factors include heavy bleeding, placental insufficiency and abruption, preeclampsia and gestational hypertension.[164,165]

The clinical criteria for SGA require:1) accurate knowledge of gestational age (ideally based on first-trimester ultrasound exam), 2) accurate measurement of weight, length and head circumference at birth, 3) a cut-off against reference data from a relevant population.[166] As mentioned previously, epidemiologic studies most often use the 10th percentile of birth weight for gestational age in a reference population as a cut-off, but in clinical settings, SGA is typically diagnosed when birth weight and/or length is at least 2 SDs below the mean for gestational age, using appropriate reference data.[162,165] Thus, neonates with either LBW or low birth length or both for gestational age should be considered as SGA.[162] The term SGA refers not to foetal growth but to the size of the infant at birth; the term 'intrauterine growth restriction' (IUGR) suggests diminished rate of growth of the foetus, as documented by at least two intrauterine growth assessments.[162] Thus, SGA and IUGR are not synonymous. According to Lee et al., IUGR indicates the occurrence of a pathophysiologic process in utero, inhibiting foetal growth.[162] A child who is born SGA has not necessarily suffered from IUGR, and infants who are born after a short period of IUGR are not necessarily SGA.[162] The definition of SGA does not take into consideration background growth-modifying factors such as maternal size, ethnicity and parity.[166] These modifying factors can be used in statistical analyses to generate a corrected birth weight, which increases the chance of correctly identifying a baby with abnormal foetal growth.[167]

Accurate gestational age dating and measurement of birth weight and length are critical for SGA diagnosis.[166] The accuracy of gestational age depends on the method used. Gestational age based on the last menstrual period (LMP) is widely used to derive the date of delivery based on the assumption that the window between the date of the LMP and ovulation is 14 days.[168] The use of ultrasound for dating has become an important part of the clinical assessment of gestational age, particularly in industrialized countries where most pregnant women have one or more ultrasound examinations during pregnancy.[168] An estimate based on the LMP produces greater

error compared with clinical or obstetrical requires estimates using early ultrasound assessment.[168] Explanations for this involve inaccurate maternal recall, variation in lengths of menstrual cycle and misinterpretations of early pregnancy bleedings as menstruation.

It is a major challenge to define an appropriate global reference for SGA. This is important, as the estimated prevalence of babies born SGA varies substantially depending on the reference population chosen.[110] In certain situations, it may be difficult to distinguish between babies who are SGA and not SGA when gestational age data are incomplete or inaccurate. This is a particular challenge in low-income countries, where access to ultrasound, and even healthcare facilities, is limited, but the burden of SGA babies is high. In Norway, the definition is based on birth weight, gestational age, plurality and gender, which provides the possibility to distinguish between SGA, appropriate for gestational age and large for gestational age.[169]

SGA is associated with increased mortality and morbidity due to infections, neurologic disease and injuries throughout childhood. In addition, SGA is associated with an increased risk of most of the same conditions as described previously for LBW.

2.5.3 Preterm birth

Explanations for iatrogenic preterm birth include maternal factors, such as preeclampsia and foetal distress.[170] The birth of a healthy infant at term depends on the establishment of the maternal–foetal vascular interface early in gestation and ongoing placental development during pregnancy.[171] Spontaneous preterm delivery is associated with histopathological evidence of disordered placentation. Doppler velocimetry provides insight into placental vascular development and is an important tool in the clinical management of pregnancies that affect abnormal placental blood flow.[172] Other vascular complications are preeclampsia, gestational hypertension and IUGR.[173] Evidence of familial aggregation of preterm birth has also been found, which shows that preterm birth could be partly explained by genetic factors.[174] Early-onset preeclampsia, which is a common reason for induced preterm birth, is also a potential

genetic contributor to preterm delivery.[175] Epidemiological studies have shown that environmental risk factors for preterm birth also include poverty, limited maternal education, young maternal age, unmarried status and inadequate prenatal care.[170] Likely, these environmental risk factors may mediate the familial effects and are difficult to discern from genetic factors. Svensson et al. investigated the importance of genes and the environment for preterm birth and suggested an important role of maternal genes on the risk of preterm birth, while foetal genes were found to be important for induced, but not spontaneous, preterm birth.[174]

Preterm birth is defined as birth before week 37 of pregnancy and represents a major source of neonatal and infant morbidity and mortality and has long-term consequences for disease in adulthood. The incidence of preterm births varies from 5% to 14% worldwide and has increased over the last decades; about 13 million infants are born preterm each year.[176] Evidence from clinical and experimental studies suggests that preterm birth is associated with developmental changes that may result in long-term, chronic NCDs.[177]

It is suggested that preterm subjects are exposed to altered regulation of a number of biological organs. Studies by Keijzer-Veen has shown a link between preterm birth and elevated blood pressure.[178,179] These studies included 422 young adults with very preterm birth or LBW and showed higher incidences of high blood pressure and lower kidney function than in the normal population. The studies also showed that SGA amplified these associations. A large meta-analysis study found that adults born with very LBW (<1500 g) had 3.4 mmHg (95% CI = 2.2–4.6) higher systolic and 2.1 mmHg diastolic pressure (95% CI = 3.2–6.3) compared to adults born at term.[180] A slight increase in arterial blood pressure in young adulthood has a significant impact on later health, as studies have shown that a 5–10 mmHg increase in diastolic blood pressure is associated with a 34% increased risk of stroke.[181,182] A large Swedish population-based study demonstrated that birth before 32 weeks was associated with a nearly twofold increased risk for cerebrovascular disease, adjusted HR 1.89, (95% CI =1.01–3.64) compared to term-born individuals, whereas individuals born at 32–36

weeks were not at increased risk.[183] These findings suggest that individuals born preterm have slightly elevated blood pressure in young adulthood and are susceptible to develop hypertension with other associated cardiovascular and renal complications.[177]

Preterm birth interrupts the development and maturation of the kidneys during a critical growth period.[184] The third trimester of pregnancy is the most active period of foetal nephrogenesis, during which more than 60% of nephrons are formed.[185,186] Interruption of nephrogenesis results in a lower nephron number, which may lead to progressive renal impairment later in life by mechanisms of increase in single-nephron glomerular filtration, compensatory nephron hyperthrophy, microalbuminuria, arterial hypertension, glomerulosclerosis, overt proteinuria, progressive fibrosis, CKD and a reduction in nephron number.[187] The associations between birth weight, glomerular number and glomerular size are also shown.[89] Preterm birth is a known risk factor for neonatal acute kidney injury and is associated with an increased risk of CKD later in childhood.[188-192] Because of considerable advances in neonatal and paediatric treatment, more then 95% of preterm-born infants survive into adulthood.[193] Understanding the long-term risk of CKD and applying preventive strategies during the most susceptible period of early development is of vital importance.

In our Norwegian studies, we have used national reference values from the study of Skjærven et al. to define LBW, SGA and preterm birth.[169]

This is illustrated in Figure 5.

Preterm birth is a complex multifactorial disorder. Further studies on the role of perinatal and neonatal conditions and the underlying pathophysiological mechanisms are required for providing preventive guidance to health-care providers as well as families and preterm-born individuals.

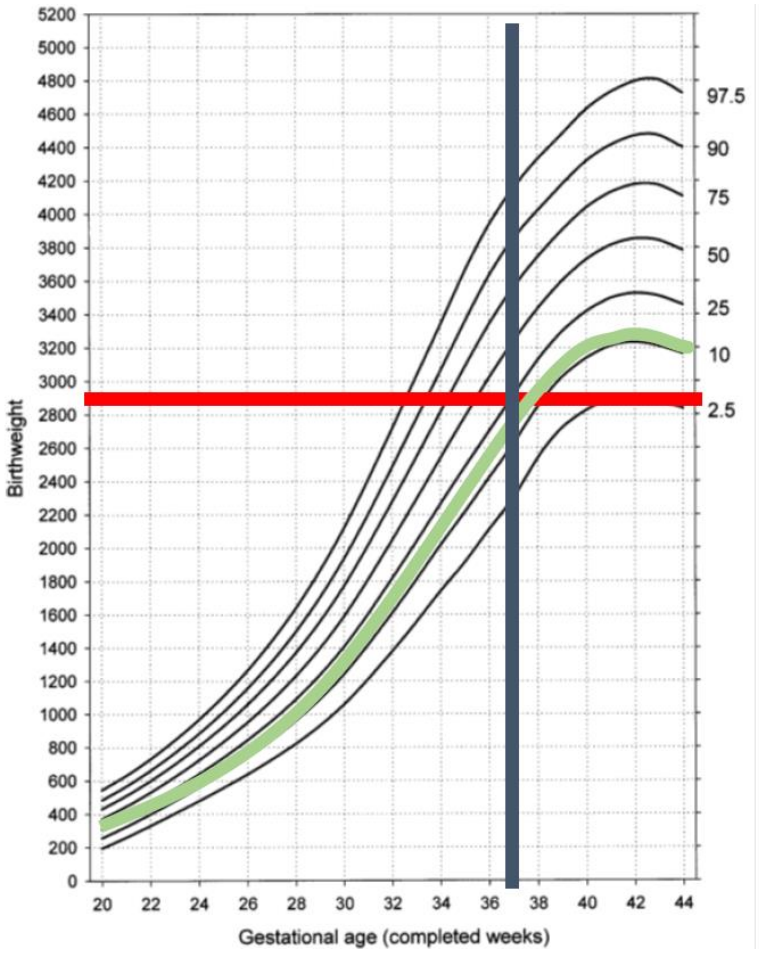

Figure 5: Summarized figure depicting thresholds for LBW (red), SGA (green) and preterm birth (grey). NB: LBW cut-off and SGA distribution applicable for Norwegian population. Modified from Skjærven et al. (2000), with permission.

2.6 Chronic kidney disease (CKD)

2.6.1 General

CKD is an important contributor to mortality from NCDs, and it is estimated that CKD affects over 13% of adults and is increasing in its prevalence.[194,195] The global increase in the incidence and prevalence of CKD is being driven by the global increase in the prevalence of diabetes mellitus, hypertension, obesity and aging.[196] Other causes of CKD are chronic glomerulonephritis, chronic pyelonephritis, chronic use of anti-inflammatory medication, autoimmune diseases, polycystic kidney disease, congenital

malformations and prolonged acute renal disease. CKD was the primary cause of deaths in 1.2 million cases in 2017, and the number has been projected to rise to 2.2 million by 2040 in a best-case scenario and up to 4.0 million in a worst-case scenario.[197] The number of people receiving renal replacement therapy now exceeds 2.5 million and is projected to double to 5.5 million by 2030.[198] The number of patients with kidney failure treated with dialysis has increased dramatically in the United States from 209,000 in 1991 to 472,000 in 2004 and 782,818 in 2019.[199] Currently, over 1.4 million patients are receiving renal replacement therapy worldwide. In Norway, about 550 people annually develop kidney failure, and the number of people received renal replacement therapy has increased from 1433 in 1990 to 5406 by the end of the 2020.[200] The burden of CKD studies predominantly stems from high-income countries, while the absence of kidney registrars in most low-income and middle-income countries has made it difficult to ascertain the true burden of CKD in these countries.[196] It has been estimated that 2.3–7.1 million people worldwide have died prematurely from lack of access to renal replacement therapy in 2010.[198]

2.6.2 Classification

In 2002, the US Kidney Disease Outcomes Quality Initiative (KDOQI) proposed a definition of CKD with five stages, which has been adopted internationally: 'kidney damage' or 'decreased kidney function' (GFR < 60 mL/min/1.73 m^2) for ≥ 3 months.[201] CKD were classified into five stages by KDOQI guidelines using thresholds of estimated glomerular filtration rate (eGFR) within the CKD range and/or evidence of structural renal changes.

The classification was later revised in 2012, and the new KDIGO guidelines included the levels of albuminuria[202] (Figure 6).

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min per 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Figure 6: Prognosis of CKD GFR and albuminuria categories (G1–G5) and albuminuria (A1–A3). Green: low risk, yellow: moderate risk, orange: high risk, red: very high risk for CKD progression. Modified from Levin et al. (2014) with permission.[203]

The revised classification has been suggested to have a higher specificity for detecting patients with grade 3/4 CKD, who are likeliest to progress, and a greater ability of avoiding those who are less likely to progress.[204] At the same time, patients without impaired eGFR but with elevated albuminuria may also be at a higher risk of adverse kidney and cardiovascular outcomes.[205] Thus, it was suggested that albuminuria would have substantial benefits for the early identification of such patients, proactive management of the disease and health-care resource planning.[202] Through the combined assessment of GFR and albuminuria, a patient can be more accurately evaluated as one having low, moderately increased, high or very high risk of worsening function and other complications.[202]

KDIGO has led the global kidney community in the past by developing guidelines to declare definitions for terms of kidney disease as well as staging the system to classify

the severity of CKD. Thus, the term ‘end stage’ was claimed to be patient insensitive and suggested a stigma. The term ‘kidney failure’, which is defined as GFR<15 mL/min/1.73 m^2, or treatment by dialysis was proposed as a decent replacement for end-stage renal disease (ESRD). In this work, we follow the recommendations and use the term ‘kidney failure’.

2.6.3 Epidemiological risk factors for CKD

The key risk factors for CKD are the increasing age of the population, diabetes mellitus and hypertension.[206] Polycystic kidney disease is an example of a hereditary cause of CKD.[207] Diabetes is the largest single cause of ESRD in the United Kingdom, accounting 30–40% of all causes.[206] In many developing countries, chronic glomerulonephritis is often caused by infections and is the leading cause of CKD.[208] In many Arab countries, obstructive uropathy constitutes a major cause of ESRD (40%).[206] The most common underlying causes of obstructive uropathy are renal calculi and schistosomiasis. An epidemic of CKD of unknown cause, also known as Mesoamerican nephropathy, has emerged in Central America over the past two decades and primarily affects young men in agricultural communities.[209] There is also growing evidence for other modifiable risk factors associated with lifestyle such tobacco use, alcohol, dyslipidemia, obesity and analgesic abuse, which can be linked to kidney disease. The prevalence of ESRD differs greatly worldwide. The main causes of ESRD are diabetes, hypertension, glomerulonephritis (including vasculitis-related glomerulopathies) and polycystic renal diseases. Other causes are chronic pyelonephritis, tubulointerstitial nephritis, systemic autoimmune diseases, amyloidosis and kidney tumours. According the United States Renal Data System, the highest prevalence of treated ESRD in 2018 was in Taiwan (3587 pmp), Japan (2653 pmp) and the United States (2354 pmp).[199] Diabetes is a major cause of ESRD worldwide.[199] In Norway, during 2020, 537 patients started renal replacement therapy, and hypertension was the main cause of renal failure with 39% of patients. Diabetes was the primary diagnosis in 16% of the patients.[210]

2.6.4 Natural course and prognosis of CKD

CKD is often progressive and irreversible, and it is associated with a higher cardiovascular risk. Patients with pathology remain asymptomatic most of the time, presenting the complications typical of renal dysfunction only in more advanced stages.[211] Diagnosis is commonly made after chance findings from screening tests (urinary dipstick or blood test) or when symptoms become severe. The best available indicator of overall kidney function is GFR, which is either measured via exogenous markers (DTPA, iohexol) or estimated using equations.[212] Presence of proteinuria is associated with an increased risk of CKD progression. Other indicators of renal injury are changes in renal imaging, haematuria/leukocyturia, persistent hydroelectrolytic disorders and histological changes in kidney biopsy.[211] Kidney biopsy samples can show definitive evidence of CKD through common kidney changes, such as glomerular sclerosis, tubular atrophy and interstitial fibrosis.[212] Complications include anaemia due to reduced production of erythropoietin by the kidney; reduced red-blood-cell survival and iron deficiency and mineral bone disease caused by disturbed vitamin D, calcium and phosphate metabolism.[212] Treatment of CKD can be conservative (patients without indication for dialysis) or replacement therapy (haemodialysis, peritoneal dialysis and kidney transplantation). The objectives of conservative treatment for CKD are to slow down the progression of kidney dysfunction and treat complications such as anaemia and CVDs as well as preparation for kidney replacement therapy. A nephrology consultation should be obtained early in the course of the diagnostic evaluation in patients with persistent proteinuria, nephritic syndrome (haematuria, proteinuria and hypertension), sustained haematuria, no clear cause of CKD or type 2 diabetes with proteinuria but no coexistent retinopathy or neuropathy.[213] Patients in whom kidney function declines relatively rapidly (>5mL/min/1.73 m^2 per year) may also benefit from nephrology consultation. Besides medications, non-drug therapies, such as lifestyle and dietary modifications, should be recommended. Recommendations should also include limitations of alcohol intake as well as quitting smoking.

2.6.5 Birth-related risk factors and risk of CKD

LBW has been shown to influence kidney development and later health.[88] Experimental studies on animals showed that IUGR produced by uterine artery ligation, maternal dietary protein restriction or vitamin A deficiency resulted in a nephron deficit of approximately 30% with a reduction in GFR of 50%.[121,134] Compensatory adaptations to reduced nephron number results in an increased single-nephron GFR and hyperfiltration. The latter is associated with microalbuminuria. Previous studies have shown an increased prevalence of microalbuminuria and proteinuria among adults who had been born LBW.[123-125,214] Hoy et al. found a higher incidence of kidney failure and albuminuria among Australian Aboriginals who were born with LBW.[123] In addition, the degree of albuminuria was strongly correlated with both renal and non-renal deaths in these studies.[124,126] Other studies have shown that subjects who have been born LBW had a greater severity and more rapid progression of Immunoglobulin A (IgA) nephropathy, membranous nephropathy, minimal change disease and chronic pyelonephritis.[129-131] It has also been reported that spontaneous secondary focal and segmental glomerulosclerosis were more common in adolescents and adults who were very LBW.[215-217] Hsu et al. and Hirano et al. reported a strong association between LBW and childhood CKD, defined as obstructive uropathy and kidney dysplasia among children attending paediatric renal clinics compared with the general paediatric population.[218,219] Hsu et al. have also found association between maternal gestational diabetes and overweight with childhood CKD.[218] According to Hirano et al., 20% of childhood CKD was associated with LBW.[219] Earlier, a meta-analysis including over 2 million individuals reported a 70% increased risk of CKD in individuals with LBW.[220] Norwegian population-based study reported a higher risk for kidney failure with LBW among individuals of 18 years of age or below as compared with those of 18–45 years of age, indicating an increased impact of congenital renal abnormalities, causing kidney failure at a younger age.[11]

2.6.6 Genetic factors and the risk of CKD

Although it was earlier established that risk factors for CKD, such as hypertension and diabetes, explain 50–70% of cases, however, familial clustering of CKD suggested that genetic factors or shared environmental factors are also important in developing of disease.[221-225] During the last 20 years, genome-wide association studies (GWASs) have become a popular tool to explore genomic regions associated with renal function metrics and the risk of CKD.[226] These studies also shed more light on the genetic architecture of kidney diseases, including the role of APOL1 gene in progression of various nephropathies in individuals of African ancestry.[227] GWASs also yielded breakthroughs in our knowledge on the strong signals (HLA-DQA1 and PLA2R1) associated with the risk of membranous nephropathy and the pathogenesis of IgA nephropathy.[228,229] In addition, at the same time, new technologies for genetic testing allowed us to identify the genetic bases for a large number of rare kidney diseases.[230] For example, GWASs identified nearly 100 genetic loci associated with low estimated GFR.[231] A recent GWAS meta-analysis on GFR and albuminuria have supported an indirect genetic component for CKD.[231,232] These studies reported the association between a large number of genetic loci and CKD markers such as eGFR and albuminuria. In a study by Wuttke et al., a genetic risk score for lower eGFR was found to be significantly associated with clinically diagnosed CKD in a large population of 452,264 individuals.[233] Teumer et al. identified and characterized 68 loci associated with albuminuria and also highlighted its potential causal genes, driver variants, targets tissues and pathways.[232]. Advanced statistical fine-mapping approaches and newly emerging multi-tissue gene expression data provide new opportunities to identify putative causal variants, effector genes and target tissue from the results of GWAS meta-analyses.[233]

Although familial clustering has long been recognized, there are still several gaps in the knowledge concerning how genetics contributes to CKD predisposition in the general population. Most familial aggregation studies on CKD have focused on its later stages, such as kidney failure.[221,222,225,234] Some kidney diseases have a genetic origin (e.g. adult polycystic kidney disease, alport syndrome etc.). At the same time, in many familial aggregation studies, it might be difficult to discern shared

environmental factors from genetic factors. Environmental susceptibility factors that might be shared in families and increase risk of CKD involve diet, lifestyle, passive smoking or infectious disease. A recent study by Zhang et al. quantified familial aggregation of CKD and estimated the heritability of kidney disease and its related traits in the general population (155,911 participants, predominantly European ancestry) and observed moderate-to-high heritability of kidney traits and related biomarkers.[235] Zhang et al. reported 1.19% prevalence of CKD in the studied cohort as a whole, and 5.8% prevalence of CKD in families where at least one member was affected by CKD.[235] The major finding in this study is that subjects with a first-degree family member affected by CKD have a threefold higher risk of CKD, even in its early stage. Importantly, the study also demonstrated that the spouses of subjects with CKD also had a higher CKD recurrence risk ratio compared to the risk in the general population. Thus, the study by Zhang et al. provided additional knowledge supporting both environmental and genetic contribution to CKD.

2.6.7 Gender effects in the risk of CKD

Earlier epidemiological studies have shown higher blood pressure levels in men than women, and these differences emerged during adolescence and persisted throughout adulthood until menopause.[236-238] It was described earlier that female subjects have 15% fewer glomeruli on average than male subjects with no apparent difference in blood pressure.[239] Sex differences in arterial pressure observed in humans are also seen in animal models, with higher arterial pressure in normotensive males compared with female dogs, rats and rabbits.[39] The mechanisms underlying sex differences in blood pressure are not well understood, but sex hormones and sex chromosome are likely to contribute.[39] Gender-specific differences in the foetal programming of hypertension and renal disease have also been reported, demonstrating that males are more adversely affected than females.[68,240-242] One hypothesis to explain gender-specific differences in the association of birth weight and CKD might be that oestrogen could counterbalance the impact of birth weight on the progression of CKD by decreasing the proliferative and pro-sclerotic properties of mesangial cells and decreasing

collagen synthesis.[243] It was hypothesized that hypertension typically occurs earlier in men and with an early exposure to insulin resistance, or angiotensin-mediated pro-fibrotic effects of testosterone makes men more susceptible to the effects of a reduced nephron number.[244-247] Another hypothesis is that female foetuses may be less vulnerable to adverse in-utero environments, and therefore, they may be less likely to develop disease in adulthood. It has been documented that a common pathway in many models of foetal programming of hypertension is a reduction in placental 11β-HSD2 levels and thus an increased exposure of the foetus to maternal glucocortikoids.[248] It has also been documented that the placenta of female foetuses have higher 11β-HSD2 levels than those of males, indicating that males may be exposed to higher levels of glucocorticoids than females, and therefore, they may be more adversely affected.[249] In the discussion of a gender-specific difference in the magnitude of the association between LBW and kidney disease and/or function, some studies have demonstrated stronger effects in men.[243,250] Although there might be differences in measuring outcomes such as early stages of CKD versus kidney failure, it is also possible that gender-specific differences are caused by biases in creatinine-based formulae for the estimation of GFR.[251]

2.7 Markers of foetal programming

In our studies, foetal growth is often identified retrospectively through standards of birth weight by gestational age.[169] SGA is arbitrarily defined as infants with birth weight below the 10th percentile at the attained gestational age. The MBR now holds more than 50 years of data. The gestational age is based on the reported date of the LMP. Standards for birth weight by gestational age differ between populations, and it changes over time due to both improved living conditions and changes in obstetrical routines. Birth weight in the Norwegian population is high, and standards from other populations may not be representative, especially for term weeks.[169]

3. AIMS OF THE THESIS

I. Investigate the association between LBW, SGA and preterm birth and increased risk of kidney failure during the first 50 years of life

II. Investigate the association between birth-related variables and risk of CKD, different groups of kidney diseases and different stages of CKD

III. Investigate possible modification by family factors on the association between adverse birth-related risk markers and risk of CKD during the first 50 years of life

4. MATERIALS AND METHODS

4.1 Included registries

4.1.1 The Norwegian Population Registry (NPoR)

The NPoR contains demographical information on all individuals alive in Norway since 1960. This information is organized by an eleven-digit personal identification number. Registration in the population registry is mandatory and is not subject to individual consent. Maternal and paternal information is virtually complete for all individuals born in Norway after 1952. By using data from this registry, it was possible to identify siblings defined as individuals with the same mother and father for Paper III.

4.1.2 The Medical Birth Registry of Norway (MBRN)

Since 1967, the Medical Birth Registry of Norway (MBRN) has registered extensive medical data on all births in Norway (total population of 5.1 million).[252] The notification form includes extensive data on the details of maternal health and newborn's birth and is completed by the attending midwife or doctor immediately after birth. For studies in this thesis, data from the MBRN were available from 1967 through December 2015 for Papers I, II and III.

4.1.3 The Norwegian Renal Registry (NRR)

The Norwegian Renal Registry (NRR) has registered information since 1980 on patients developing kidney failure, who are in need of renal replacement therapy. The treating nephrologists report all patients to the registry, and the registry is considered virtually complete. This database contains information on the cause of kidney failure, treatment modality and further follow-up. Data from this registry were available from 1980 through 2016 and were used primarily for Paper I.

4.1.4 The Norwegian Patient Registry (NPR)

The NPR has registered the International Classification of Diseases, Tenth Revision (ICD-10) diagnostic codes for all admissions and outpatient visits to Norwegian hospitals since 2008. In Norway, most specialist care in the field of nephrology is hospital-based, therefore, the data are almost complete for specialist care. ICD-10 codes are registered by treating physicians. In our studies, data from NPR were available for the period of 2008–2016.

4.1.5 Data linking

Data from these four registries were linked based on the 11-digit national personal identification number, which is unique for each individual in Norway.

4.2 Summary of methods

4.2.1 Ethics

All three studies were approved by the regional ethics committee with approval number 2017/627. The studies were described in detail according to the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) checklist for observational studies.

4.2.2 Summary of methods – Paper I

All individuals born alive in Norway between 1967 and 2016 were included. Twins, individuals who died before 1 year of age and individuals who died before 1980 were excluded. Data from the MBRN were used as exposure variables, and these data were linked with the NRR, which had registered outcome variables.

LBW was defined as birth weight less than the gender-specific 10th percentile (2.94 kg for males and 2.85 kg for females). Preterm birth was defined as gestational age <37

weeks. SGA was defined as a birth weight less than the 10th percentile for gestational age, using previously published gender-specific references in Norway.[169,253]

The main outcome was the development of kidney failure, and its onset was defined as the date of starting chronic dialysis treatment or undergoing renal transplantation. Individuals who did not develop kidney failure were followed up until December 31, 2016, or the date of death. Causes of kidney failure were divided into five categories: glomerular diseases, intestinal diseases, congenital or hereditary disease, diabetic nephropathy and other causes.

4.2.3 Summary of methods – Paper II

For Papers I and II, we included all individuals born alive in Norway between 1967 and 2016. Data from NPR were used for outcome variables, and data on diagnosed kidney diseases were available for the period 2008–2016. Twins, triplets and quadruplets as well as individuals who died before attaining the age of 1 year and before 2008 were excluded. Individuals who had officially emigrated from Norway were also excluded.

Exposure variables in Paper II were identified almost identically to those in Paper I.

Outcome variables in Paper II were defined by NPR as having been registered with a kidney disease diagnosis (ICD-10 codes N01–N09, N17–N19, N25–N29, or Q60–Q64) during the period 2008–2016. The main outcome was defined as having been diagnosed with CKD (ICD-10 code N18) in at least one episode (admissions or outpatient visits). Both the main and secondary diagnoses were included. The secondary outcomes were having been diagnosed with different groups of kidney diseases: acute kidney disease (N17), glomerular disease (N00–N09), cystic kidney disease (Q61), or kidney or urinary tract malformations (Q60, Q62–Q64). We also analysed the secondary outcome of having been diagnosed with stage 3–5 kidney disease. (These diagnoses were used in the registry for the time period 2010–2016.)

4.2.4 Summary of methods – Paper III

All individuals registered in the MBRN between 1967 and 2015 who had at least one sibling registered in the MBRN during the same period were included. Siblings were defined as individuals with the same mother and father. Individuals with no siblings and those with more than seven siblings were excluded to enable practical data handling and to avoid effect modification by a very large number of siblings. As was done for Paper II, we used data from the NPR for outcome variables in Paper III.

Exposure variables in Paper III were LBW, SGA and preterm birth in the individual him/herself and/or at least one of his/her siblings. The same outcome variables as those used in Paper II were used.

4.2.5 Statistical methods

In Paper I, data were analysed in a cohort design with birth-related variables for the individuals as exposure variables and kidney failure as the outcome variable. Hazard ratio (HR) estimates were obtained using Cox regression statistics. The beginning of the follow-up was set at the date of birth. Risks after 18 years of age were analysed separately. Because no cases of kidney failure were registered between 1967 and 1979, individuals born in this period were left-truncated in the survival analyses before January 1980. We used the counting process formulation of proportional hazards.

In the main analyses of Paper II, logistic regression statistics were used to investigate the associations between the exposure variables and the outcome variables of interest. The main and secondary outcomes were analysed as either present or absent. In analyses focusing on the associations in adult age, only individuals born before 1990 were included. In the secondary analyses, we used left-truncated Cox regression statistics to complement the logistic regression statistics. Time until end point was age at first occurrence and time until right censoring was age at death or end of 2016. As we did not have data on outcomes until 2008, the analyses were left-truncated for the time period until 2008.

In the main analyses of Paper III, logistic regression statistics were used to investigate the associations between exposure variables and the outcome variables of interest. The main exposure variables were birth-related variables for the included individual and/or his/her sibling. The same outcome variables as in Paper II were analysed. As for Paper II, Cox regression statistics were used to complement the logistic regression statistics.

For all papers, statistical analyses were performed using STATA (Stata Corp., College Station, TX).

5 RESULTS

Overall, the three papers have shown that having been born with LBW and SGA is associated with a 70–80% increased risk of kidney disease. This finding was shown for being diagnosed with kidney failure, CKD and kidney disease in general. In general, the risk increased with higher numbers of adverse birth-related risk markers (LBW, SGA and preterm birth). In Paper I, we showed that the risk was not increased if the participants had only one birth-related risk factor, while in Paper II we found the risk was increased also for those who only had one risk factor. Overall, our results have allowed for much deeper analyses of different cut-offs and sub-groups than those of previous studies. The results of each study will be further presented in the subsequent text.

5.1 Summary of results – Paper I

Paper I included 2,679,967 individuals, of whom 1881 developed kidney failure during follow-up at a mean age of 27.9 ± 11.5 years. Individuals who later developed kidney failure more often had LBW (16% versus 10%), SGA (16% versus 10%) or preterm birth (7.3% versus 4.8%) as compared with individuals who did not develop kidney failure. Compared with individuals with birth weight above the 10th percentile, LBW was associated with an increased HR of 1.68 (1.44–1.97) for the development of kidney failure. The corresponding HR for individuals with SGA was 1.49 (1.27–1.75) and for preterm birth was 1.65 (1.31–2.07). Analyses adjusted for birth year, gender, maternal disease, maternal preeclampsia, maternal marital status and malformations in the newborn showed identical results. The results were largely the same for males and females.

We further investigated possible dose–response relationships for LBW and SGA (below 5th percentile, 5th–10th 10th–20th 20th–80th (reference group), 80th–90th, 90th–95th, and above the 95th percentile cut-offs). Dose–response relationships were observed both for LBW and SGA with higher risks for LBWs and non-significant

trends for lower risk in the 90th–95th percentile groups. These analyses were stratified for gender and showed that the risk increased below the 10th percentile and that this was a reasonable cut-off.

The analyses of combinations of LBW, SGA and preterm birth showed that as compared to individuals with zero risk markers, individuals with one risk marker did not have increased risk of kidney failure with aHR of 1.05 (0.84–1.31), individuals with two risk markers had an increased risk with aHR of 1.67 (1.40–1–98) and individuals with three risk markers had an increased risk with aHR of 2.96 (1.84–4.76).

In separate analyses of risks of different causes of kidney failure, LBW, SGA and preterm birth seemed to be similarly associated with the different causes of kidney failure.

5.2 Summary of results – Paper II

A total of 2,663,010 individuals were included in the study, and in the period 2008–2016, 17,313 individuals had been diagnosed with kidney disease (4495 had been diagnosed with CKD, 4659 had been diagnosed with acute kidney disease, 4672 had been diagnosed with glomerular disease, 1479 had been diagnosed with cystic kidney disease, and 5085 had been diagnosed with congenital malformations of the kidney or urinary tract).

Compared with individuals with birth weights above the 10th percentile, LBW was associated with a higher OR of 1.72 (95% CI =1.60–1.90) for the development of CKD. The corresponding ORs were 1.80 (1.75–1.94) for SGA, 1.50 (1.33–1.66) for preterm birth, 1.85 (1.62–2.10) for birth weight <2.5 kg and 1.11 (0.94–1.31) for maternal preeclampsia. There were no clear gender-specific differences. The adjusted analyses were repeated in the cohort born before 1990 to focus on the adult population, showing similar results. We analysed the OR of being diagnosed with CKD stages 3–

5. In these analyses, LBW was associated with an OR of 1.80 (1.60–2.05) for CKD stage 3, 1.84 (1.56–2.18) for CKD stage 4 and 1.88 (1.58–2.24) for CKD stage 5. Corresponding analyses were performed for SGA, preterm birth and birth weight <2.5 kg, showing almost similar results.

As for Paper I, we investigated possible dose–response relationships for LBW and SGA and demonstrated similar results. We also analysed the combined effects of LBW, SGA and preterm birth and showed that compared to having none of these risk markers, individuals with one risk marker had a significantly higher risk with an aOR of 1.52 (1.37–1.69), individuals with two risk markers had an aOR of 1.76 (1.61–1.93) and individuals with all three risk markers had an aOR of 2.67 (2.09–3.41).

We also performed analyses for other forms of kidney disease and showed that birth-related risk factors were more strongly associated with CKD than with other forms of kidney disease.

5.3 Summary of results – Paper III

Of 1,847,565 included individuals, 1,006,856 individuals had one sibling, 633,746 had two siblings and 208,806 had three or more siblings. Of the included individuals, 3336 had been diagnosed with CKD.

Compared with individuals without LBW and with no siblings with LBW, individuals without LBW but sibling with LBW had an OR of 1.31 (95% CI, 1.18–1.46) for CKD, individuals with LBW but no siblings with LBW had an OR of 1.80 (1.60–2.02) and individuals with LBW and a sibling with LBW had an OR of 1.80 (1.56–2.08). After adjustments for gender, maternal disease and number of recorded siblings, the results were almost identical. The analyses were repeated for the cases of SGA, preterm birth and having at least 1 of 3 risk markers. SGA analyses revealed almost identical results, whereas preterm birth seemed to have a less pronounced association. Being born with LBW, SGA or preterm birth was associated with higher risks of CKD than having a

sibling with one of these risk markers. Unexpectedly, no considerable increase in risk was observed when both the individual and his sibling had the risk factor.

We further analysed whether the OR of CKD increased with higher numbers of birth-related risk markers in the included individuals (LBW, SGA or preterm birth). Analyses were stratified based on whether at least one sibling had at least one of the risk markers. Individuals with a higher number of risk markers have higher risks. This was evident in individuals who did not have siblings with risk markers and in those who had siblings with risk markers.

As was done in Papers I and II, we analysed the risk of various forms of kidney disease based on whether the individual or at least one of his/her siblings had LBW, SGA or preterm birth. Analyses revealed stronger associations for CKD than for the other forms of kidney disease; otherwise, no important differences from the main analyses were seen.

6 DISCUSSION

6.1 Discussion of methods

6.1.1 Study design

All three studies are retrospective, registry-based cohort studies based on linking data from established national registries: MBR, NPoR, NRR and NPR. Data from these registries were linked based on the eleven-digit national personal identification number, which is unique for each individual in Norway. The unique eleven-digit national number is the same in all registries and used by all administrative and health services—offering a complete and exact linkage. For all studies, we included all individuals born alive in Norway from 1967 and collected the follow-up data until the end of 2016, which allowed for a maximum of 50 year follow-up. The duration was longer then used in previous studies. Compared with a previous Norwegian study from 2016, we were able to analyse a much larger number of endpoints in our studies.[11]

One of the major strengths of our study is the opportunity to use national registries to include a large number of participants with prospective registration of birth-related variables and near-complete follow-up. Another strength is the stability of the Norwegian population, with little or no emigration during follow-up. About 2% of the included population had been officially recorded as emigrated and was excluded from the study, but a crosscheck by Statistics Norway showed that another 2% were currently living abroad. Most kidney diseases diagnosed in Norway are assessed and treated in hospitals, and we included both the main diagnoses and secondary diagnoses in the data.

All individuals born in Norway between 1967 and 2015 were included. We excluded individuals who had at least one sibling (including themselves) with multiple births, individuals who died before attaining 1 year of age, individuals who died before 2008 and individuals who had officially emigrated from Norway. In order to do this, we had to trace back to raw data, and during that process we found that we had also excluded subjects who had officially emigrated from Norway.

In Paper III, we also excluded individuals with no siblings and those with more than seven siblings. In Paper III data, we selected all individuals who had at least one sibling registered in the MBRN during the same period (1967 and 2015). To avoid including a family with two siblings twice, we chose to use the individual as a unit but not the family, so the same family would not be calculated several times. We also believe that using individual data rather than family data allows for more reliable adjustment for confounders.

A limitation of our study is that we could not record the end points until 2008. Our data reflects the prevalence of CKD during the years 2008–2015. Given the wide range of 0–50 years, we believe that our data could also reflect the incidence of CKD.

6.1.2 Definitions and cut-off value for birth-weight risk markers

LBW was defined as birth weight less than the gender-specific 10th percentile. For Papers II and I, LBW was calculated as 2.94 kg for males and 2.85 kg for females. In Paper III, LBW was defined as 2.97 kg for men and 2.89 kg for women. Researchers have questioned whether a standardised birth weight cut-off should be used. Another question is whether this value should be modified for different populations.[44] The prevalence of LBW in South Asia is high, but it is unknown whether these data represent true growth restriction or a normal shift in the curve for population birth weight.[44] LBW can also reflect both genetic and environmental differences between populations. It was previously proposed that alternative growth reference curves should be adapted for local populations. This may increase the accuracy of predicting perinatal outcomes for infants of small gestational age.[254] In Papers I and II, we analysed different cut-offs for birth weight and SGA and showed that the risk increased below the 10th percentiles for both genders but did not increase much with lower values. The group that of 10th–20th percentiles was an intermediate group that was moderately associated with endpoints in some analyses. It is uncertain whether these results would be similar in other populations where the 10th percentile would be at significantly lower birth weights.

6.1.3 Effect modification

It has previously been demonstrated that breastfeeding was associated with a lower possibility of developing blood pressure at a later time in children born prematurely.[255] In our study, we did not have access to data on breastfeeding. However, a later systematic review compared how breastfeeding in infancy and bottle-feeding formula milk affect the development of blood pressure found a modest effect on blood pressure in later life.[256]

In our studies, we adjusted for maternal pre-gestational disease (diabetes mellitus, hypertension, rheumatic disease renal disease). Maternal preeclampsia in all our studies was defined as an increased blood pressure that is >140/90 mmHg and proteinuria after 20 weeks of gestation.[253] We did not have access to the severity or onset of preeclampsia. In Paper I, we have adjusted for maternal preeclampsia in the main analyses to avoid the potential confounder between LBW and kidney failure. In Paper II, we decided to remove maternal preeclampsia as a potential confounder in the analyses and perform stratified analyses for preeclampsia. We also added preeclampsia as a fourth risk factor. Our results did not show that preeclampsia modified the effects of the other risk markers.

We did not have data on maternal birth weight. The latter is associated with own birth weight[257] and it would be interesting to investigate how it is associated with risk of kidney disease, but these data were not available in our studies. However, we could not adjust for maternal cigarette smoking in our study. A meta-analysis from 2017 reported a significant association between active maternal smoking during pregnancy and LBW, with an OR of 2.00 (1.77–2.26).[258]

An important confounder in all our studies is that we have no information on whether the individuals we follow develop other risk factors of kidney disease, such as diabetes, hypertension, dyslipidemia and other risk factors of kidney disease. Being able to adjust for this information could yield important information on the underlying mechanisms, but it would not be appropriate to adjust for such intermediate factors in the main analyses between birth-related markers and kidney disease.

Previous studies have reported that age, gender and number of siblings may modify the association between LBW and kidney failure.[5,259] To avoid the effect modification, we have adjusted for these factors.

Other potential confounders on which we did not have data were socioeconomic status, educational level and ethnic origin. We did not have access to these data in our study, but we were able to adjust for single versus non-single mothers, which is a socioeconomic marker.

6.1.4 Statistical considerations

In Paper I, HR estimates were obtained by Cox regression statistics with the start of follow-up at the date of birth of an individual. The outcome was the development of kidney failure, and the onset was defined as the date on which long-term dialysis treatment or renal transplantation started. The Cox regression method is robust and allows for simultaneous investigation of the effect of several risk factors.

HR is the ratio of hazards and equals the hazard rate in the group under investigation divided by the hazard rate in the control group. The hazard rate represents the probability that an individual would experience an event at a particular point in time after the intervention, while we used the HR to measure the effect of intervention on an outcome of interest over time compared to the control group. HR is reported most commonly in time-to-event analysis or survival analysis when we are interested in knowing how long it takes for a particular event/outcome to occur. The outcome event in Paper I is kidney failure. Because no cases of kidney failure were registered between 1967 and 1979, individuals born in this period were left-truncated in the survival analyses before January 1980. Consequently, the counting process formulation of proportional hazards (Cox regression) was applied. This customization is robust, as long as the strength of the different risk factors has not changed during the period where we did not have follow-up data. It is unlikely that this could have occurred during the period 1967–1979 for Paper I, but since it was likelier for the period 1967–2007, these Cox regression statistics were not used as the main analysis in Papers II and III.

However, there are some potential residual confounding factors in our retrospective cohort study. First, we had no data on comorbid conditions such as CVDs, diabetes and obesity, and we were not able to adjust for these risk factors. This might be a potential confounder in our analyses. Second, congenital malformations can manifest later in life. In our previous studies, we have shown that the association between LBW and kidney failure was stronger during the first 14 years of life than after 15 years.[5] In Paper I, the age at which kidney failure occurs differs for different causes of kidney failure. For hereditary or congenital kidney disease, the age at kidney failure was lower for those with LBW than for individuals without LBW. Our analyses showed a higher HR value for the development of kidney failure due to hereditary or congenital diseases compared to other kidney diseases.

In Papers II and III, we used logistic regression statistics to investigate the association between exposure variables and the outcome of interest. We adjusted for gender, pre-gestational maternal disease, maternal marital status and congenital malformations recorded after birth. As discussed previously, logistic regression statistics were chosen because we lacked follow-up information for the period 1967–2007 in this study. In the secondary analyses, we used left-truncated Cox regression statistics to complement the logistic regression. As the duration of endpoint detection was shorter than the duration of total follow-up, Papers II and III should be considered more as prevalence studies than as incidence studies. Thus, our data reflect the prevalence of CKD during the period 2008–2015. However, given the wide age range of 0–50 years, we do believe that our data also reflect the incidence of CKD and that the different ages of the included population during the follow-up period of 2008–2016 allow for approximate incidence analysis.

Although it is more appropriate for a cohort study to use relative risk, we used OR. OR and relative risk are usually comparable in magnitude when the studied disease is rare. In our study, the prevalence of CKD was only 1% even in the high-risk groups; thus, we also found virtually identical results for OR using logistical statistics and risk ratio using Generalized linear model (GLM) statistics. We believe that in practice, OR is a

good approximation to the relative risk, and this is also a strong argument to use logistic regression.

6.1.5 External validity

The Norwegian population is mainly Caucasian; therefore, the results might be different in other populations. As discussed previously, the thresholds for LBW and SGA may differ in other populations. Another factor is that the Norwegian population is quite homogeneous with equal access to specialist health care, which allows for better internal comparability and lowers the impact of some potential confounding factors, such as low socioeconomic status, educational level and ethnic origin. A possible limitation concerning generalisability in our studies is underreporting of CKD in administrative databases. We did not have information from general practice, and many patients who fulfil criteria for CKD (e.g. by having an eGFR less than 60 mL/min/1.73 m^2) will not be diagnosed with CKD at an admission or outpatient clinic. The criterion for allowing diagnostic coding is that a diagnosis must have been treated or been part of an important decision. Because we included diagnoses from a series of admissions and consultations between 2008 and 2016, we increased the chance of being registered with a diagnosis at least once. It is uncertain whether our results would be different if we were able to include all individuals who fulfilled CKD criteria as having an outcome.

As already mentioned, the strength of our study is the sample size, which is large enough to stratify analyses for sub-groups and also strengthens the reliability of our results. The prevalence of kidney failure in Norway is lower than in many other populations, and progression of CKD to kidney failure is also rarer compared to other populations.[260] This could be explained by environmental factors, genetic factors or the generally good health-care facilities in Norway, where the entire population has good access to the same public health care. Such differences could also confound the association between birth-related factors and kidney disease in other populations.

6.2 Discussion of main results

6.2.1 Risk of CKD vs. kidney failure

Paper I supports previous studies that there is a significant association between markers of intrauterine restrictions such as LBW, SGA and prematurity and the development of kidney failure in later life.[13,44,220,261] We can conclude that LBW was associated with increased risk for kidney failure during the first 50 years. A limitation of our study is that kidney failure is a rare outcome, and despite 2,679,967 included individuals, only 1181 developed kidney failure.

In Paper II, we showed that LBW and SGA were associated with a 60%–70% higher risk of being diagnosed with CKD during the first 50 years of life. Thus, we provided evidence that individuals born with LBW and SGA not only have higher risk for development of kidney failure but also for the much more prevalent CKD.[5,11] Global prevalence of CKD has been shown to be about 12%, with stage 3 prevalence of about 8%, stage 4 prevalence at 0.4% and stage 5 prevalence at 0.1%.[262] We showed that individuals born with LBW or SGA had an OR of about 1.72 for being diagnosed with CKD. The risk was the same for CKD stages 3, 4 and 5. In Paper II, the cumulative proportion of CKD at 50 years of age was 2%, and individuals with LBW were compared with 1% with those without LBW. However, we suspect that the real prevalence of CKD might be much higher because of the underreporting of CKD in administrative databases.[263,264] A meta-analysis of CKD prevalence showed that the prevalence of stage 3–5 in population screening is about 12% at 50 years of age.[262] We would argue that the higher relative risk that we observed in our study would be the same in the total population with CKD and with increasing age. Thus, the absolute importance of LBW is higher, and our findings strengthen this evidence.

6.2.2 Effects of different adverse birth-related risk markers

The studies in this thesis support our previous studies that LBW, SGA and preterm birth are associated with development of kidney failure later in life. The most novel finding in Paper I was that none of the risk markers LBW, SGA or preterm births was associated with increased risk if present alone; at least two of the risk markers needed to be present for an increased risk. This importantly narrowed the cohort with increased risk that might need further follow-up (15.6% of the population in Paper I had at least one risk marker, whereas only 8.6% had two or more risk markers). However, this result could not be reproduced in Paper II, where we analysed the risk of CKD, and as this study had an even higher number of endpoints, we would trust these results more.

Compared to our previous studies from 2008 by Vikse et al. and from 2016 by Ruggagio et al., Paper I included a higher number of individuals (2.7 million vs. 1.8 million) and a longer follow-up time (49 vs. 42 years). In addition, the study from 2016 included only those subjects who had at least one sibling, while Paper I included the whole population. These changes led to a significant increase in the number of cases with kidney failure, which doubled from 527 to 1181, and thus allowed for much stronger analyses of sub-groups, percentile groups and gender differences. In the study by Vikse et al., it was suggested that LBW was more predictive for developing kidney failure then SGA.[5] However, in the study by Ruggajo et al., SGA and LBW were similarly associated with kidney failure in the main analyses, but SGA was a stronger risk factor than LBW for 18–42 years of age and in the analyses of non-congenital and non-hereditary kidney disease.[11] In Paper I, LBW tended to be a stronger risk marker for kidney failure than SGA and preterm birth. Eriksson et al. reported that LBW and premature birth were associated with CKD in older people, and recently Crump et al. showed that premature birth was an important risk marker for CKD before 20 years of age, but that there did not seem to be an increased risk after 20 years of age.[13,184]

It has been argued that SGA should be taken into consideration when analysing the effects of birth weight because LBW at short gestational age might be physiologically

normal, whereas LBW at term probably reflects severe placental insufficiency.[5] While LBW could be explained mostly by short gestational age in many cases, SGA is more often explained by compromised intrauterine nutrition. Ruggagio's results showed that the effect of SGA was significantly stronger in those with preterm birth versus those with term birth at adult age, whereas the effect of LBW was similar in those with preterm or term birth.[11] In our previous paper, we found that LBW was especially strongly associated with the risk of congenital and hereditary kidney disease before 15 years of age.[5] However, in Paper II, we also showed a significantly increased risk in the adult cohort born before 1990. We believe that congenital formations could be responsible for LBW and/or preterm birth in certain cases. However, this was thoroughly analysed in Paper II, and we believe it is unlikely to be an important explanation of our findings.

LBW is the most accessible and used marker of adverse intrauterine environment, and it results from either IUGR or preterm birth.[265] IUGR is measured in our study by a proxy as birth weight for gestational age, but as described in the introduction, it should be measured directly during pregnancy by ultrasonography. Taken together, Papers I–III confirm the findings of previous studies that LBW, SGA and preterm birth are associated with increased risk for kidney disease in adult age, and all risk markers seemed to be important.[5,11] The papers further show that LBW and SGA seem to be equally important and associated with a 70% increased risk of CKD or kidney failure, but that preterm birth is associated with a slightly lower increased risk of about 50%.

Studies have indicated that preterm birth might be an important risk marker for adult kidney disease.[184,220] Pregnancy forms a vulnerable period, as nephrons are formed only until week 32–34 of pregnancy, and preterm birth affects nephron formation.[266] In our studies, preterm birth was a weaker risk marker than LBW and SGA.

6.2.3 Thresholds for defining LBW and SGA

The WHO defines LBW as birth weight <2500 g, and several studies have confirmed that this is associated with CKD and kidney failure.[5,220,243,265] In the main analyses of our studies, LBW has been defined as a birth weight less than the 10th percentile of the included population (about 2.8–2.9 kg). We defined SGA using gender-specific standard curves previously worked out for the Norwegian population, but SGA cut-offs are also likely to be slightly different for various populations around the world. It is important to note that birth weight less than 2500 g is quite rare in the Norwegian population, and only about 3.5% of the population have been born with birth weight less than 2500 g. In Papers II and I, we investigated different cut-offs for LBW and showed that the risks increased at lower than the 10th percentile and that the risks only increased slightly at less than the 5th percentile or less than 2.5 kg. Therefore, we argue that the 10th percentile is the best way to identify individuals at increased risk in the Norwegian population. A similar approach was used for SGA showing much the same results, and also for SGA, we would argue that using the 10th percentile seemed to be the best to identify individuals at increased risk.

As discussed in Section 6.1.5, our studies cannot answer whether our cut-offs for birth weight, the WHO cut-off of 2.5 kg, or the national 10th percentile should be used to identify newborns at risk in other populations. A major challenge is the selection of an appropriate global reference. There are important international variations in the average birth weight. More studies are needed to investigate this association in other populations and conduct a potential cost-benefit analysis of such follow-up. In most developing countries, the LBW is defined <2.5 kg, and there is often imprecise data for gestational age and SGA. Thus, it seems logical to focus on birth weight percentiles in such studies.

6.2.4 Adverse birth-related risk markers and different kidney diseases

Several studies have described the association between LBW and different indicators of kidney disease, such as albuminuria, low eGFR, or kidney failure.[220] In our Papers I–III, we found that LBW was also associated with a higher risk of acute kidney

disease, glomerular disease, cystic kidney disease and kidney and urinary tract malformations. In Paper I, we observed stronger risk estimates for kidney failure due to hereditary or developmental diseases, but the risks were otherwise similarly associated with the different causes of kidney failure. We propose that congenital urinary tract malformations and hereditary renal disease might be a cause of LBW. As kidney or urinary tract malformations can cause IUGR, our findings could be expected. In our previous study, we showed that LBW was especially strongly associated with the risk of congenital and hereditary kidney disease before 15 years of age.[5] In Paper I, we decided to repeat the main analyses using kidney failure due to causes other than hereditary or congenital disease as the outcome variable. We observed almost identical risks as we did in the analyses of the adult age group. In Paper II, we also showed a significantly higher risk in the adult cohort born before 1990. Previous studies showed that young IgA individuals born with LBW or/and SGA, had larger glomerular area at the time of diagnosis than IgA individuals born with normal weight.[267] It was proposed that a larger glomerular area could be a marker of a lower number of total glomeruli and larger glomeruli might explain the higher risk of progressive renal disease in young IgA patients with LBW or/and SGA.[12] However, we did not find a higher risk of being diagnosed with glomerulonephritis in our study, although this could be expected as autoimmune disease have been proposed to have association with early-life perturbations.[12]

In Papers II and III, we showed that patients diagnosed with kidney or urinary tract malformations were diagnosed at a younger age and CKD was diagnosed in older patients. Our analyses revealed stronger associations for CKD than for other forms of kidney disease, but there were statistically significantly increased risks for other forms of kidney disease as well, such as acute kidney disease, glomerulonephritis and hereditary kidney disease.

In Papers I–III, the overall finding was that the increased risk was similar for all sorts of kidney disease and causes of kidney failure. This supports Brenner's hypothesis that impaired nephron endowment with a lower glomerular number and compensatory large glomeruli lead to increased risk of progression in any kidney disease.[12,14,268]

6.2.5 Nephron endowment, genetic factors or shared environmental factors

As discussed previously, our findings are in general support of Brenner's hypothesis of impaired nephron endowment in individuals with LBW and/or SGA and that it increases the risk of CKD and kidney failure in adult life. However, it is possible to argue that a plausible explanation for the association between LBW/SGA and adult disease could be explained by familial aggregations and familial factors. A study from the MBR suggested that both maternal and foetal genetic factors may influence the duration of pregnancy.[269] At the same time, gestational age and birth weight may also be explained by environmental factors that are often shared among relatives, such as smoking, diet and socioeconomic status. As several studies have clearly shown that genetic factors contribute to the risk of kidney disease, it has been suggested that the same genetic factors could explain both LBW and risk of kidney disease. Paper III aimed to investigate this further and add to the knowledge of our previous analysis by Ruggajo et al.[11] Paper III showed that individuals with LBW have a significantly higher risk of kidney disease than those who have a sibling with LBW, thus strengthening the argument that intrauterine programing itself is an important risk marker for adult kidney disease.[259] However, in Paper III, we also observed a 30% higher risk for individuals who did not have LBW or SGA but who had a sibling with one of these risk markers. Such an effect was not observed in the previous study by Ruggajo et al.[11] But it indicates that there are relevant contributions from genetic or shared environmental factors also that, to a small degree, may confound the association between LBW and SGA and later risk of kidney disease.

In the present study, as in our previous studies, we did not observe significant gender-specific differences in the association between LBW and SGA and later kidney disease. Although other studies have earlier shown a stronger effect of LBW in males than females, especially studies with CKD as the main outcome.[13,220,243,250] The later study by Crump et al. investigated the effect of premature birth on the development of CKD and association between CKD and preterm birth was found both for males and females.[184] However, it was interesting to find that having a sibling with LBW was only statistically significantly associated with CKD for men and not for women. The same trend could also be seen for SGA and preterm birth, with weaker effects in

women than men. These findings may imply that male foetuses may be more sensitive to environmental factors as well as biological factors given their growth rate. Thus, we can propose that this association could also indicate that the genetic contribution might be stronger in men than in women.

7 CONCLUSIONS AND PERSPECTIVES

Our overall findings have shown that LBW and SGA are associated with a 70% higher risk of developing kidney failure and CKD during the first 50 years of life. Our findings strengthen the hypothesis that the intrauterine environment is important for proper kidney development and for the risk of kidney disease in adult life. The WHO defines LBW as a birth weight less than 2.5 kg, but in our studies, we find an increased risk for birth weight and birth weight for gestational age of less than the 10th percentile and propose that this threshold is the best to identify individuals at risk of kidney disease. However, it is still uncertain which cut-offs are best in other populations. We suggest that future studies should investigate further which thresholds for LBW may be the most appropriate for identifying individuals at increased risk of kidney disease in adult age.

The LBW and Nephron Number Working Group suggested that growth restricted, preterm or LBW infants should undergo annual blood pressure measurement at least from 3 years of age, with the addition of annual urinalysis.[270] Early detection of individuals at risk of kidney disease as well as an early referral to kidney units may slow down the disease progression, improve rate of survival in patients with CKD and reduce total treatment cost. It may call for screening for hypertension, diabetes mellitus and proteinuria. An alternative could be to screen all adults at 30, 40 or 50 years of age who had LBW, SGA or preterm birth. Such an approach could be more effective at identifying individuals in need of further medical follow-up, but an important limitation is that many adults do not know their birth weight or gestational age. More studies are needed on the benefit, cost and possibility of screening with LBW for kidney disease.

Finally, we suggest that clinicians at check-ups for cardiovascular or kidney disease should ask patients about birth weight and premature birth and these data should be registered in a medical record that is available for clinicians at any time.

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Familial Contributions to the Association Between Low Birth Weight and Risk of CKD in Adult Life

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Introduction: Previous studies have revealed that individuals with low birth weight (LBW) have higher risk of chronic kidney disease (CKD) and that LBW and CKD cluster in families. This study investigates how familial factors affect the association between birth-related risk markers and risk of CKD.

Methods: The Medical Birth Registry (MBR) of Norway has registered all births in Norway since 1967. Sibling data were available through the Norwegian Population Registry. The Norwegian Patient Registry has registered diagnostic codes for all admissions and outpatient visits to Norwegian hospitals since 2008. Data from these registries were linked. Risk of CKD according to whether the individual himself or at least one of his siblings had LBW was analyzed using logistic regression statistics.

Results: Of 1,847,565 individuals, 3336 had been diagnosed with CKD. Compared with individuals without LBW and no siblings with LBW, individuals without LBW but who had a sibling with LBW had adjusted odds ratio (aOR) of 1.33 (1.19–1.49), those with LBW but no siblings with LBW had aOR of 1.74 (1.55–1.95), and those with LBW and a sibling with LBW had aOR of 1.77 (1.54–2.04) for CKD. Similar results were found for LBW for gestational age, but preterm birth revealed weaker associations.

Conclusion: Individuals who have a sibling with LBW have an increased risk of CKD later in life, and individuals who themselves have LBW have an even higher risk. Our findings suggest that there are familial contributions to the nephron endowment *in utero* hypothesis.

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Several hypotheses have been proposed during the past decades suggesting that birth weight is inversely associated with risk of cardiovascular and other metabolic diseases in adult life through mechanisms of malnutrition *in utero*,[1] unmeasured socioeconomic confounding,[2] and genetic or other intergenerational factors influencing both birth weight and adult disease risk.[3] Several studies have also revealed that both maternal and paternal genetic factors are associated with offspring birth weight.[4–6] At the same time, there is a strong association between family history of end-stage kidney disease and increased risk of end-stage kidney disease.[7–11] Despite a large number of studies during the past decades, the environmental versus familial contribution to the increased familial risk of kidney disease is still unclear.

The nephron endowment *in utero* hypothesis stated that as kidneys are developed *in utero*, risk of kidney disease in later life could be partially determined at birth.[12] Several studies have supported this, and individuals with LBW seem to have a 70% to 80% increased risk of kidney disease in adult life.[13,14] To investigate whether this association was confounded by familial factors, our research group previously published a study that investigated whether having a sibling with LBW was associated with an increased risk of end-stage kidney disease; the study revealed that only individuals who themselves had LBW had an increased risk and not individuals who had a sibling with LBW.[15] No studies have however investigated the possible confounding role of familial factors in the association between birth-related risk markers and later CKD in general.

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The MBR of Norway has registered data on all births in Norway since 1967, and sibling data have been registered in the Norwegian Population Registry. All patients who had been diagnosed with kidney disease during admissions or outpatient visits to Norwegian hospitals during the period 2008 to 2016 had been registered in the NPR. We linked these registries and studied how risk of CKD was affected by whether the individual himself or at least one of his/her siblings had LBW or small for gestational age (SGA). We hypothesized that family factors might modify effects of adverse birth-related markers and risk of CKD.

METHODS

The MBR of Norway has registered extensive medical data on all births in Norway since 1967. Maternal and paternal national identification numbers have been registered in the Norwegian Population Registry. The NPR has registered International Classification of Diseases Tenth Revision (ICD-10) diagnostic codes for all admissions and outpatient visits to Norwegian hospitals since 2008; in Norway, most nephrologists are hospital based, and the data are therefore almost complete for specialist care. ICD-10 codes were registered by the treating physicians. In this study, we obtained data from the NPR for the period 2008 to 2016. The Norwegian Populaton Registry had date of death for all participants who died, until the end of 2016. We linked these registries using the national identification number.

All individuals registered in the MBR between 1967 and 2015 who had at least 1 sibling registered in the MBR during the same period were selected (N = 2,016,267). Siblings were defined as individuals with the same mother and father. Individuals with no siblings and those with more than 7 siblings (N = 3789) were excluded to enable practical data handling and to avoid effect modification by very large number of siblings (with higher risks of at least 1 with LBW by chance). We also excluded individuals who had at least 1 sibling (including themselves) with multiple births (N = 69,751), those who died before age 1 year (N = 12,606), those who died before 2008 (N = 14,428), and those who had officially emigrated from Norway (N = 66,282). That left 1,849,411 individuals to be included in the analyses.

Birth-Related Variables

LBW was defined as birth weight less than the 10th percentile for gender (2970 g for men, 2880 g for women). From 1967 to 1998, gestational age was based on the last menstrual period and from 1999 onward on routine ultrasonographic examination in gestational weeks 17 to 20. For use in this study, gestational age was available for 95.6% of the participants and birth weight was available for 99.93% of the participants. On the basis of birth weight, gestational age, and gender, a z-score of birth weight for gestational age was calculated. We defined SGA as birth weight less than the 10th percentile for gestational age and gender (the 10% with the lowest z-score for each gender) (cutoff −1.30 for men and −1.28 for women). Preterm birth was defined as birth before 37 weeks of gestation. LBW, less than 2500 g, was also analyzed as an exposure variable.

In this study, pregestational maternal disease was defined as a diagnosis of maternal diabetes mellitus, kidney disease, rheumatic disease, or essential hypertension before pregnancy. Maternal marital status was dichotomized as either single (divorced or not living with partner) or not single (married or living with partner). Congenital malformations in the newborns were recorded as present if any malformation were observed before discharge from the hospital after birth; in the statistical analyses, a dichotomous variable was used.

Outcome Variables

The main outcome was defined as having been diagnosed with CKD (ICD-10 code N18) in at least one of the hospital contacts (admissions or outpatient visits). Both main and secondary diagnoses were included. The secondary outcomes were having been diagnosed with the following different groups of kidney disease: acute kidney disease (N17), glomerular disease (N00–N09), hereditary cystic renal disease (Q61), or kidney or urinary tract malformations (Q60, Q62–Q64).

The data file from NPR included ICD-10 codes for each hospital contact (admission or outpatient visit) with a kidney disease diagnosis (N01–N09, N17–N19, N25–N29, or Q60–Q64). Of the 1,849,411 individuals, 11,553 were registered with at least 1 episode of kidney disease (maximum 1370 episodes); 4464 had 1 episode, 1603 had 2 episodes, 925 had 3 episodes, 2475 had 4 to 9 episodes, 1146 had 10 to 19 episodes, and 940 had greater than or equal to 20 episodes. Patients were diagnosed with different combinations and sequences of ICD-10 codes, and for this study, we focused on whether or not a diagnosis or group of diagnoses had been recorded at least once.

Statistical Analysis

Data were analyzed in a cohort design with birth-related variables for the included individual and his/her sibling(s) as exposure variables and CKD and other kidney diagnoses as outcomes. Characteristics of different groups were compared using t tests for continuous variables and Pearson's chi-square test for categorical variables. Risks were analyzed using

Table 1. Characteristics of included subjects and maternal health according to whether the subject or at least 1 sibling had LBW. Norway, 1967 to 2016

Characteristic	Neither individual nor sibling with LBW	Individual without LBW, sibling with LBW	Individual LBW, sibling not LBW	Individual and sibling with LBW
N total	1,483,071	181,507	111,387	71,600
Mean number of siblings	1.6 ± 0.8	1.9 ± 1.0[a]	1.5 ± 0.7[a]	1.7 ± 0.9[a]
Mean number of years of follow-up	28.4 ± 12.4	29.0 ± 12.2[a]	29.2 ± 12.6[a]	29.2 ± 12.4[a]
Proportion with preterm birth	1.5%	2.6%[a]	28.0%[a]	28.1%[a]
Proportion with SGA	3.5%	9.4%[a]	60%[a]	65%[a]
Proportion with maternal preeclampsia	2.1%	2.7%[a]	8.5%[a]	8.1%[a]
Proportion with 5-min Apgar score <7	0.7%	0.6%	2.6%[a]	2.4%[a]
Proportion with maternal disease[b]	2.2%	2.5%[a]	2.7%[a]	3.4%[a]
Form of kidney disease				
N with chronic kidney disease	2413	388[a]	326[a]	209[a]
N with acute kidney disease	2499	368[a]	275[a]	185[a]
N with glomerulonephritis	2666	375[c]	245[c]	177[a]
N with hereditary cystic kidney disease	706	109[c]	70[c]	49[c]
N with kidney or urinary tract malformations	2065	23	193[b]	152[a]

LBW, low birth weight; SGA, small for gestational age.
[a]$P < 0.001$.
[b]Maternal disease was defined as maternal diabetes mellitus, kidney disease, rheumatic disease, or essential hypertension diagnosed before pregnancy.
[c]$P < 0.01$ as compared with the group with neither individual nor sibling with LBW.

logistic regression statistics. In adjusted analyses, gender, pregestational maternal disease, maternal marital status, and congenital malformations in the newborn were included in the logistic regression statistics and aORs were obtained. In separate analyses focusing on the associations in adulthood, only individuals born before 1990 were included.

In secondary analyses, we used Cox regression statistics to complement the logistic regression statistics. Exposure and outcome variables were the same as in the logistic regression analyses. Time until end point was calculated as number of months from birth to first occurrence of an exposure, and time until right censoring was calculated as number of months from birth to death or from birth until end of 2016. As we did not have data on outcomes until 2008, analyses were left truncated for the time period until 2008. Graphs of cumulative risk (hazard) were prepared using the Nelson–Aalen estimate of risk groups.

A two-tailed probability value of less than 0.05 was considered significant. Mean plus or minus SD is given for continuous variables, and estimate (95% confidence interval) is given for risk estimates. All analyses were performed using STATA version 15.1 (Stata Corp., College Station, TX).

RESULTS

This study included a total of 1,849,411 individuals, of whom 1,006,859 individuals had 1 sibling, 633,746 had 2 siblings, and 208,806 had 3 or more. Mean number of siblings was 1.6 plus or minus 0.8, and mean number of years of follow-up was 28.4 plus or minus 12.7 years. Of the included individuals, 2413 were diagnosed with CKD, 2499 with acute kidney disease, 2666 with glomerulonephritis, 706 with hereditary cystic kidney disease, and 2065 individuals with kidney or urinary tract malformations.

Characteristics of included individuals for 4 subgroups based on whether the individuals or at least one of his or her siblings had LBW are found in Table 1. As compared with individuals who neither had LBW themselves or a sibling with LBW, adverse birth-related risk markers were as expected more common for individuals who themselves had LBW, but were also more common for individuals who had a sibling with LBW.

Risk of CKD

Compared with individuals who did not have siblings with LBW, having at least 1 sibling with LBW was associated with an OR of 1.38 (1.25–1.50) for development of CKD. Similar associations were observed for SGA and preterm birth with ORs of 1.36 (1.24–50) and 1.35 (1.25–1.46) respectively. As stated previously, adverse birth-related risk markers were more common in individuals who had a sibling with LBW, and this could confound the analyses. In further analyses, we therefore analyzed the combined effects.

Compared with individuals without LBW and with no siblings with LBW, individuals without LBW but a sibling with LBW had an OR of 1.31 (1.18–1.46), individuals with LBW but no siblings with LBW had an OR of 1.80 (1.60–2.02), and individuals with LBW and a sibling with LBW had an OR of 1.80 (1.56–2.08) (Table 2 and Figure 1). After adjustments for sex, maternal disease, and number of recorded siblings, results were almost identical. The analyses were repeated for SGA, preterm birth, and having at least 1

Table 2. Risk of CKD according to whether the individual or at least 1 of his/her siblings had LBW, SGA, or preterm birth. Norway, 1967 to 2016

				Unadjusted model		Adjusted model[a]	
Subject	**Sibling**	**N (total)**	***n* (CKD)**	**OR**	***P* value**	**OR**	***P* value**
Not LBW	Not LBW	1,480,658	2413	1.0 (ref)		1.0 (ref)	
	LBW	181,119	388	1.31 (1.18–1.46)	<0.001	1.33 (1.19–1.49)	<0.001
LBW	Not LBW	111,061	326	1.80 (1.60–2.02)	<0.001	1.74 (1.55–1.95)	<0.001
	LBW	71,391	209	1.80 (1.56–2.08)	<0.001	1.77 (1.54–2.04)	<0.001
Not SGA	Not SGA	1,425,817	2337	1.0 (ref)		1.0 (ref)	
	SGA	160,734	323	1.23 (1.10–1.39)	<0.001	1.25 (1.11–1.41)	<0.001
SGA	Not SGA	109,379	320	1.79 (1.59–2.00)	<0.001	1.74 (1.55–1.95)	<0.001
	SGA	62,188	207	2.03 (1.76–2.34)	<0.001	2.03 (1.76–2.34)	<0.001
Not preterm birth	Not preterm birth	1,665,238	2926	1.0 (ref)		1.0 (ref)	
	Preterm birth	102,736	219	1.21 (1.06–1.39)	0.006	1.23 (1.07–1.41)	0.003
Preterm birth	Not preterm birth	60,597	161	1.51 (1.29–1.77)	<0.001	1.44 (1.27–1.69)	<0.001
	Preterm birth	17,494	40	1.30 (0.95–1.78)	0.098	1.24 (0.91–1.70)	0.2
Not LBW 2.5 kg	Not LBW 2.5 kg	1,684,907	2938	1.0 (ref)		1.0 (ref)	
	LBW 2.5 kg	108,507	232	1.23 (1.07–1.40)	0.003	1.24 (1.08–1.42)	0.002
LBW 2.5 kg	Not LBW 2.5 kg	40,928	149	2.09 (1.77–2.46)	<0.001	2.08 (1.80–2.45)	<0.001
	LBW 2.5 kg	11,723	27	1.32 (0.90–1.93)	0.151	1.30 (0.90–1.91)	0.166
Not LBW, SGA, or preterm birth	Not LBW, SGA, or preterm birth	1,319,347	2088	1.0 (ref)		1.0 (ref)	
	LBW, SGA, or preterm birth	252,227	492	1.23 (1.17–1.36)	<0.001	1.20 (1.08–1.33)	0.001
LBW, SGA, or preterm birth	Not LBW, SGA, or preterm birth	154,815	407	1.66 (1.50–1.85)	<0.001	1.50 (1.50–1.88)	<0.001
	LBW, SGA, or preterm birth	119,676	359	1.90 (1.70–2.12)	<0.001	1.70 (1.50–1.90)	<0.001

CKD, chronic kidney disease; LBW, low birth weight; OR, odds ratio; ref, reference; SGA, small for gestational age.
[a]Adjusted for gender, maternal disease (defined as maternal diabetes mellitus, kidney disease, rheumatic disease, or essential hypertension diagnosed before pregnancy), and number of recorded siblings categorized as 1, 2, or greater than or equal to 3.

of the 3 risk markers. SGA analyses revealed almost identical results, whereas preterm birth seemed to have a less pronounced association (Table 2 and Figure 2). Being born with LBW, SGA, or before 37 weeks of gestation was associated with higher risks than having a sibling with one of these risk markers, but the latter was consistently associated with ORs of 1.2 to 1.3. Unexpectedly, no considerable risk increase was observed when both the individual himself and his sibling had the risk factor. In a separate analysis in which a cutoff for birth weight of 2.5 kg was used to define LBW, we found that as compared with individuals without LBW and with no siblings with LBW, individuals without LBW but a sibling with LBW had an OR of 1.23 (1.07–1.40), those with LBW but no siblings with LBW had an OR of 2.08 (1.77–2.46), and those with LBW and a sibling with LBW had an OR of 1.32 (0.90–1.93) (notably, only 27 individuals developed CKD in this latter group). After adjustments, almost identical results were found (Table 2). These analyses were repeated separately for men and women. The results revealed that having a sibling with LBW or

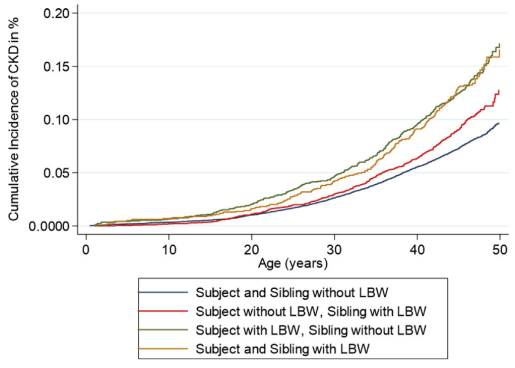

Figure 1. Cumulative risk of CKD according to whether the individual or at least one of his or her siblings had LBW. Risk of CKD was increased both for individuals who had LBW themselves and for those who themselves did not have LBW but who had a sibling with LBW. The graphs separate most strongly in adult age. CKD, chronic kidney disease; LBW, low birth weight.

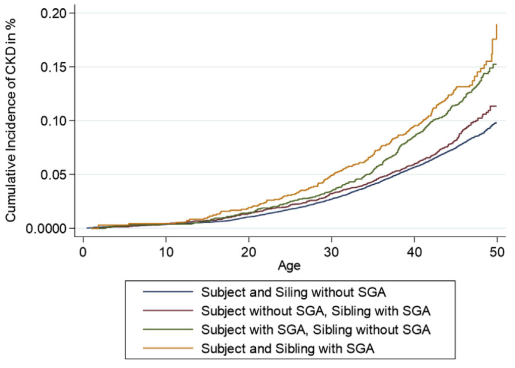

Figure 2. Cumulative risk of CKD according to whether the individual or at least one of his or her siblings was born SGA. Risk of CKD was increased both for individuals who had SGA themselves and for individuals who themselves did not have SGA but who had a sibling with LBW. The graphs separate most strongly in adult age. CKD, chronic kidney disease; LBW, low birth weight; SGA, small for gestational age.

Table 3. Risk of CKD according to number of risk markers in the individuals (LBW, SGA, or preterm birth) and siblings

			Unadjusted model		Adjusted model[a]		Cohort born before 1990 Adjusted model[a]		
Siblings	No. of risk markers	Total, N	OR (95% CI)	*P* value	aOR (95% CI)	*P* value	Total, N	aOR (95% CI)	*P* value
No sibling with LBW, SGA, or preterm birth	0	1,257,320	1.0 (ref)		1.0 (ref)		628,773	1.0 (ref)	
	1	74,756	1.35 (1.15–1.60)	<0.001	1.31 (1.14–1.54)	<0.001	42,229	1.21 (1.02–1.45)	0.029
	2	71,081	1.90 (1.63–2.20)	<0.001	1.81 (1.56–2.10)	<0.001	38,154	1.70 (1.45–2.00)	<0.001
	3	4176	2.59 (1.60–4.20)	<0.001	2.41(1.50–4.00)	0.001	1765	3.00 (1.72–4.94)	<0.001
At least 1 sibling with LBW, SGA, or preterm birth	0	237,385	1.24 (1.17–1.38)	<0.001	1.26 (1.14–1.40)	<0.001	129,396	1.18 (1.05–1.32)	<0.003
	1	41,761	1.83 (1.52–2.20)	<0.001	1.81 (1.50–2.16)	<0.001	24,427	1.60 (1.31–1.96)	<0.001
	2	67,277	1.92 (1.66–2.23)	<0.001	1.90 (1.64–2.20)	<0.001	38,228	1.82 (1.56–2.12)	<0.001
	3	5703	2.80 (1.90–4.14)	<0.001	2.62 (1.76–3.90)	<0.001	2600	2.91 (1.87–4.52)	<0.001

aOR, adjusted odds ratio; CI, confidence interval; CKD, chronic kidney disease; LBW, low birth weight; No., number; OR, odds ratio; ref, reference; SGA, small for gestational age.
[a]Adjusted for gender, maternal disease (defined as maternal diabetes mellitus, kidney disease, rheumatic disease, or essential hypertension diagnosed before pregnancy), and number of recorded siblings categorized as 1, 2, or greater than or equal to 3.

SGA tended to be associated with higher risks for men than women (Supplementary Table S1).

We compared the unadjusted results in Table 2 during the first 40 years of life with those from the previous study by Ruggajo *et al.*[15] of risk of ESKD. These analyses revealed much similar results, but there was a trend toward higher risk estimates in this study of CKD (Supplementary Table S2). The analyses from Table 2 were also repeated using Cox regression statistics, revealing nearly identical results (results not found). As hereditary or congenital kidney disease could cause LBW or SGA, we performed a separate analysis excluding all individuals who on at least 1 occasion had been diagnosed with hereditary cystic disease or congenital kidney disease, revealing nearly identical results.

In the analyses in Table 3, we analyzed whether OR of CKD increased with higher number of birth-related risk markers in the included individuals (LBW, SGA, or preterm birth). Analyses were stratified based on whether at least one of the siblings had at least one of the risk markers. As can be found, individuals who had a higher number of risk markers had higher risks. This was evident in both individuals who had siblings without risk markers and those who had siblings with risk markers. Individuals who had a sibling with LBW, SGA, or preterm birth, and who themselves had 3 risk factors, had the highest risk with an aOR of 2.6 (1.8–3.9). Individuals with 0 risk markers but who had a sibling with LBW, SGA, or preterm birth had a statistically significantly increased risk with aOR of 1.3 (1.1–1.4). Similar findings were found for individuals born before 1990 and thus revealed to be the same in the adult population. Similar results were found using Cox regression statistics (results not found).

Risk of Various Forms of Kidney Disease

In further analyses, we analyzed risk of various forms of kidney disease based on whether the individual or at least one of his/her siblings had LBW, SGA, or preterm birth. These analyses were performed on much the same data set as in our previous study, and age differences at first diagnosis and combinations of diagnoses were the same[14]; patients diagnosed with kidney or urinary tract malformations were diagnosed at a younger age and CKD was diagnosed in older patients. Importantly, patients could be included in several disease groups. Analyses revealed stronger associations for CKD than for the other forms of kidney disease (acute kidney disease, glomerulonephritis, hereditary cystic kidney disease, and kidney or urinary tract malformations) (Table 4).

DISCUSSION

This study confirms previous studies revealing LBW and SGA to be associated with a 70% to 80% higher risk of CKD in adult age. This study is to the best of our knowledge the first to show that siblings of individuals with LBW, SGA, or preterm birth also have a statistically significant 20% to 30% higher risk of CKD. Interestingly, if the individual him/herself had LBW, SGA, or preterm birth, the risk did not increase further if a sibling also had one of these risk markers. Of note, the higher risk in siblings was statistically significant also for other forms of kidney disease, such as acute kidney disease, glomerulonephritis, and hereditary kidney disease. Most previous studies have investigated risk of end-stage kidney disease, which is a rare end point; our study reveals an increased risk for most stages of CKD.

In the 1980s, Barker *et al.*[1] revealed that birth weight was inversely associated with risk of cardiovascular and other metabolic diseases in adult life. The associations between size at birth and disease in adulthood have been explained by alterations in fetal nutrition and endocrine status caused by intrauterine malnutrition, resulting in a permanent change in the structure, physiology, and metabolism of affected individuals, predisposing them to disease in adulthood.[16] Nevertheless, LBW may also be explained by the genes of the fetus and maternal genes affecting the quality of

Table 4. Risk of various forms of kidney disease according to whether the individual or at least 1 of its siblings had adverse birth-related risk markers. Norway, 1967–2016

Risk marker		Chronic kidney disease		Acute kidney disease		Glomerulonephritis		Hereditary cystic kidney disease		Kidney or urinary tract malformations	
Subject	Sibling	n	aOR (95% CI)[a]	n	aOR (95% CI)[a]	n	aOR (95% CI)[a]	n	aOR (95% CI)[a]	n	aOR (95% CI)[a]
Not LBW	Not LBW	2413	1.0 (ref)	2499	1.0 (ref)	2666	1.0 (ref)	706	1.0 (ref)	2065	1.0 (ref)
	LBW	388	1.33 (1.19–1.48)	368	1.23 (1.10–1.36)	375	1.16 (1.04–1.30)	109	1.31 (1.06–1.60)	236	0.96 (0.83–1.10)
LBW	Not LBW	326	1.75 (1.56–2.00)	275	1.45 (1.28–1.64)	245	1.21 (1.06–1.38)	70	1.20 (0.99–1.60)	193	1.10 (0.94–1.28)
	LBW	209	1.78 (1.54–2.05)	185	1.54 (1.33–1.80)	177	1.37 (1.18–1.60)	49	1.40 (1.04–1.81)	152	1.43 (1.21–1.70)
Not SGA	Not SGA	2337	1.0 (ref)	2390	1.0 (ref)	2568	1.0 (ref)	715	1.0 (ref)	2107	1.0 (ref)
	SGA	323	1.25 (1.11–1.40)	302	1.13 (1.00–1.29)	337	1.16 (1.04–1.31)	79	1.02 (0.82–1.30)	221	0.96 (0.77–1.10)
SGA	Not SGA	320	1.74 (1.55–1.96)	316	1.71 (1.52–1.92)	236	1.20 (1.04–1.36)	66	1.13 (0.88–1.46)	156	0.91 (0.78–1.08)
	SGA	207	2.03 (1.76–2.34)	164	1.60 (1.37–1.88)	160	1.42 (1.21–1.67)	47	1.52 (1.13–2.04)	111	1.21 (1.00–1.47)
Not preterm	Not preterm	2926	1.0 (ref)	2956	1.0 (ref)	3082	1.0 (ref)	823	1.0 (ref)	2352	1.0 (ref)
	Preterm	219	1.23 (1.07–1.41)	210	1.18 (1.02–1.35)	218	1.15 (1.0–1.32)	47	0.92 (0.70–1.24)	154	1.07 (0.90–1.26)
Preterm	Not preterm	161	1.44 (1.23–1.70)	124	1.12 (0.67–1.05)	126	1.11 (0.93–1.33)	43	1.22 (0.90–1.70)	119	1.20 (1.0–1.44)
	Preterm	40	1.24 (0.91–1.70)	46	1.47 (1.10–1.97)	40	1.22 (0.90–1.70)	21	1.91 (1.22–3.0)	30	1.01 (0.70–1.45)

aOR, adjusted odds ratio; CI, confidence interval; LBW, low birth weight; ref, reference; SGA, small for gestational age.
[a]Adjusted for gender, maternal disease (defined as maternal diabetes mellitus, kidney disease, rheumatic disease, or essential hypertension diagnosed before pregnancy), and number of recorded siblings categorized as 1, 2, or greater than or equal to 3.

the intrauterine environment.[4] A study from the MBR of Norway suggested that both maternal and fetal genetic factors may influence the duration of pregnancy.[5] At the same time, gestational age and birth weight may also be explained by environmental factors that often are shared among relatives, such as smoking, diet, and socioeconomic status. A study by Lunde *et al.*[4] investigated the genetic contributions to birth weight and found that approximately 50% of the variation in birth weight could be explained by genetic factors and that 9% to 15% of the variation could be explained by shared environmental factors. As kidney disease also has clear genetic contributions,[7–11,17] it has therefore been suggested that the same genetic factors could explain both LBW and risk of kidney disease. This study has revealed that individuals with LBW have a significantly higher risk than those who have a sibling with LBW, thus strengthening the argument that intrauterine programming itself is an important risk marker for adult kidney disease.

As discussed previously, an alternate explanation could be that much of the increased risk in individuals with LBW is because of genetic factors and shared environmental factors, and not because of intrauterine nephron endowment. Twin studies can provide an opportunity to test some of these hypotheses as twins share their maternal and early family environment factors and some or all of their genes.[18,19] These have however revealed different results, and whereas a meta-analysis from 2004 concluded that there was an important contribution from shared genetic and environmental factors,[18] others have revealed that the actual birth weight itself and fetoplacental factors seem to be more important.[19,20] In our study, we revealed a contribution from familial factors but cannot discern whether this is because of genetic or shared environmental factors. It is however important to note that the 20% to 30% higher risk for individuals who had a sibling with LBW or SGA is much smaller than the 70% to 80% increased risk that was found if the individual himself had LBW or SGA. In line with previous studies of heredity in kidney disease,[9–11] the risk seems to be increased for most types of kidney disease and not specific to particular diseases, although some diseases have clear mendelian inheritance. A study by Hoy *et al.*[21] revealed that APOL1 risk allele status was strongly associated with age-related nephron loss in African Americans. Other genetic factors may have similar effects in other populations.

It has been discussed earlier whether LBW, SGA, or preterm birth is the most important risk marker. This study confirms previous findings from our group that LBW and SGA seem to be equally important and that preterm birth seems to be a weaker risk marker.[14,22] This contrasts other studies which have revealed that preterm birth is also an important risk marker.[23,24]

In this study, similar to our previous studies, we did not observe significant sex differences in the association between LBW and SGA and later kidney disease. It was however interesting to find that having a sibling with LBW was only statistically significantly associated with CKD for men and not for women. The same trend could be found also for SGA and preterm birth with weaker effects in women than men.

The major strengths of our study are the opportunity to use the national registries to include a large number of participants with sibling data and prospective registration of birth-related variables of high quality. The long follow-up period of 50 years and the fact that most kidney disease diagnoses are assessed

and treated in hospitals and thus included in this study are also important. The study population is mostly Caucasian, which is both a strength as the population is quite homogenous and a weakness as our findings may not have similar strength for other ethnic groups. Another strength of our study is that the Norwegian health care system is founded on the principles of universal access and individuals with a low socioeconomic status have the same access and right as the rest of the population.

The main weakness is that we could not record end points until 2008. Our data thus reflect prevalence of CKD during the years 2008 to 2015. Given the wide age range of 0 to 50 years, we believe that our data also could reflect incidence of CKD. Based on these reflections, we decided to perform the main statistics as logistic regression statistics, but also performed left-truncated survival statistics to investigate the age-associated risk of CKD. These 2 approaches revealed mainly identical results. It is also possible that there was under-reporting of CKD in our study, as only diagnosed kidney disease that is relevant for the patient care is recorded, not all patients who fulfill the criteria for CKD according to reduced estimated glomerular filtration rate or albuminuria. The treating physicians decide which ICD-10 diagnostic codes to use, and although we believe that these mostly are correct, diagnostic codes of kidney disease have to the best of our knowledge not been validated in Norway. Other limitations include lack of data on other important risk factors, such as diabetes, hypertension, smoking, dyslipidemia, and other exposures of kidney disease. It would also be interesting to have data on birth weight of individual's mothers and fathers, but these data were not available.

In conclusion, our findings strengthen the hypothesis that intrauterine environment is important for risk of kidney disease in adult life. There is however a significant contribution from familial factors that could be related to either genetic or environmental factor. Future studies should attempt to identify which genes or environmental factors could explain the association between intrauterine growth restriction, nephron number, and risk of kidney disease in adult life.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Sex-stratified analysis of risk of CKD according to whether the individual or at least one of his/her siblings had LBW, SGA, or preterm birth. Norway, 1967–2016.

Table S2. Risk for ESKD in Ruggajo *et al.*[15] and risk of CKD during the first 40 years of age in this study according to whether included individual or at least 1 sibling had LBW, SGA, or preterm birth. Unadjusted analyses.

STROBE Statement (PDF).

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ORIGINAL ARTICLE

Intrauterine growth restriction, preterm birth and risk of end-stage renal disease during the first 50 years of life

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ABSTRACT

Background. Low birth weight (LBW) is associated with a higher risk of end-stage renal disease (ESRD). The relative impacts of absolute birth weight, birth weight in relation to gestational age and preterm birth are, however, uncertain.

Methods. The Medical Birth Registry of Norway has since 1967 recorded data on all births. All patients with ESRD since 1980 have been registered in the Norwegian Renal Registry. Data from these registries were linked. All individuals registered in the Medical Birth Registry were included and the development of ESRD was used as endpoint in Cox regression statistics. LBW and LBW for gestational age [small for gestational age (SGA)] according to the 10th percentiles were used as the main predictor variables.

Results. Of the 2 679 967 included subjects, 1181 developed ESRD. Compared with subjects without LBW, subjects with LBW had an adjusted hazard ratio (aHR) for ESRD of 1.61 (1.38–1.98). SGA had an aHR of 1.44 (1.22– 1.70). Further analyses showed that as compared with subjects who had none of the risk factors LBW, SGA and preterm birth, subjects with one risk factor had an aHR of 1.05 (0.84–1.31), subjects with two risk factors had an aHR of 1.67 (1.40–1.98) and subjects with three risk factors had an aHR of 2.96 (1.84–4.76).

Conclusions. We conclude that LBW was associated with increased risk for ESRD during the first 50 years. Our analyses add to previous knowledge showing that only subjects with at least two of the risk factors LBW, SGA or preterm birth have increased risk.

Keywords: CKD, ESRD, low birth weight, prematurity, small for gestational age

INTRODUCTION

In 1988, Brenner *et al.* hypothesized that low birth weight (LBW) might predispose for chronic kidney disease (CKD) in adult age through a mechanism of impaired nephron endowment *in utero* [1]. This hypothesis was later supported by several studies, and measures of LBW have been associated with increased risk of albuminuria, end-stage renal disease (ESRD) and CKD [2]. Recent papers thus argue for screening for kidney disease in subjects with LBW [2–4].

The World Health Organization (WHO) defines LBW as birth weight <2500 g and several studies have confirmed that this is associated with CKD and ESRD [2, 5–7]. Other measures of LBW or preterm birth have also been associated with increased risk, such as birth weight less than the 10th percentile, gestational age <37 weeks and LBW for gestational age [small for gestational age (SGA)] [5, 7–9]. A previous Norwegian study showed that SGA might be more important than LBW in adult patients and that preterm birth might further increase the risk [7]. LBW could on the other hand be more strongly associated with ESRD before 18 years of age due to hereditary or developmental disorders [7, 8]. Based on the existing literature there thus seems to be an important need for further studies of the relative contributions of different markers of LBW as well as a possible gender difference.

The Norwegian studies described above had investigated the association between markers of LBW and risk of ESRD for the first 38–42 years of life [7, 8]. In this study, we have linked the Norwegian registries once more and the new data allowed for follow-up until 50 years of age and a deeper analysis of the relative contributions of LBW, SGA and preterm birth. We also analysed different cut-offs for LBW and SGA as well as possible gender differences. We hypothesized that LBW and SGA would be associated with increased risk of ESRD and that preterm birth and gender modify this risk.

MATERIALS AND METHODS

Since 1967, extensive data on all births in Norway as well as maternal disease and conditions of the newborn have been registered in the Medical Birth Registry of Norway for all births of

16 weeks gestation or more; data were available until the end of 2016. Since 1980, data (including date of onset and cause of ESRD) on all patients developing ESRD (defined as starting chronic dialysis treatment or undergoing renal transplantation) have been registered in the Norwegian Renal Registry; data were available until December 2016. The Norwegian Population Registry has the registered date of death for all inhabitants for the relevant period of time until 31 December 2016.

We included all individuals born alive in Norway between 1967 and 2016. We excluded twins, individuals who died before age 1 year and individuals who died before 1980. Data were recorded in the Medical Birth Registry of Norway and linked with the Norwegian Renal Registry and the Norwegian Population registry using the national identification number (unique for each citizen and used by all administrative and health services—offering a complete and exact linkage).

The study protocol was approved by the regional ethics committee with approval number 2017/627.

Explanatory variables

Birth weight was measured immediately after birth. LBW was defined as birth weight less than the gender-specific 10th percentile (2.94 kg for male and 2.85 kg for female). Preterm birth was defined as gestational age <37 weeks. Based on gender, gestational age and birth weight, *z*-score of birth weight for gestational age has been calculated for all single births. SGA was defined as birth weight less than the 10th percentile for gestational age using previously published gender-specific reference values in Norway [10].

Maternal preeclampsia was defined as increased blood pressure to >140/90 mmHg and proteinuria after 20 weeks of gestation [11]. We did not have an access to information about the severity or onset of preeclampsia. We defined pregestational maternal disease as maternal diabetes mellitus, kidney disease, rheumatic disease or essential hypertension diagnosed before pregnancy. Malformations in the newborns had been recorded as present if any malformation had been observed before dismissal from the hospital; in the statistical analyses, a dichotomous variable was used.

Outcome variables

The outcome was development of ESRD and onset defined as the date of starting dialysis treatment or undergoing renal transplantation. Subjects with kidney failure who did not receive chronic dialysis treatment or kidney transplantation were not recorded as having an outcome. Subjects who did not develop ESRD were followed until 31 December 2016 or date of death. Causes of ESRD were divided into five categories: glomerular diseases, interstitial diseases, congenital or hereditary disease (congenital kidney or urinary tract malformations, cystic kidney disease and other heritable causes of renal disease), diabetic nephropathy and other causes (hypertensive nephropathy, renal vascular disease, tumours, rare causes and unknown cause).

Statistical analyses

Data were analysed in a cohort design with birth-related variables for the subject as exposure variables and ESRD as the outcome variable. Hazard ratio (HR) estimates were obtained by Cox regression statistics, start of follow-up was set at the date of birth. Participants with missing data were not included in the statistical analyses. Birth weight was missing for 0.09% of included participants and gestational age was missing for 4.3%. Adjusted analyses were performed for the main analyses by including birth year, gender (male versus female), maternal disease (yes versus no), maternal preeclampsia (yes versus no), maternal marital status (single versus non-single) and malformations in the newborn (yes versus no) in the statistical analyses. Risks after 18 years of age were analysed separately. Analyses using different gender-specific cut-offs for birth weight and *z*-score and gender stratified analyses were performed.

Because no cases with ESRD had been registered between 1967 and 1979, subjects born in this period were left truncated in the survival analyses before January 1980. Consequently, the counting process formulation of proportional hazards (Cox regression) was applied. This method does not include index subjects in the analysis until an event could be registered, i.e. a subject born in 1973 would be included in the analyses at 7 years of age and right censored at age 43 years if he/she did not develop ESRD or died.

If not otherwise stated, values are reported as means (SD), or HR estimates with 95% confidence intervals (CIs) are given; $P < 0.05$ was considered statistically significant and all tests were two-tailed. The analyses were performed using the STATA SE Edition 15.1 statistical package (StataCorp).

RESULTS

Study participants

A total of 2 679 967 individuals were included in this study and 1181 of these developed ESRD during follow-up at a mean age of 27.9 ± 11.5 years. The mean age at ESRD was 26.5 ± 13.0 years for LBW and 27.5 ± 11.9 years for SGA. Characteristics of included individuals are shown in Table 1. In Supplementary data, Table S1, we have shown characteristics according to birth weight percentile. Individuals who later developed ESRD more often had LBW (16.1% versus 10%), SGA (15.5% versus 10%) or preterm birth (7.3% versus 4.8%) as compared with individuals who did not develop ESRD (Supplementary data, Table S2).

Risk associated with birth-related variables

At ages 10, 20, 30, 40 and 50 years, 0.0037, 0.014, 0.040, 0.083 and 0.14%, respectively, of included individuals had developed ESRD. Compared with individuals with birth weight above the 10th percentile, LBW was associated with an increased HR of 1.68 (1.44–1.97) for development of ESRD (Table 2). Corresponding HRs for individuals with SGA was 1.49 (1.27–1.75), for preterm birth 1.65 (1.31–2.07), for birth weight < 2.5 kg 2.0 (1.59–2.56) and for maternal preeclampsia HR was 1.53 (1.12–2.08). Results were largely the same in males and females, except for preterm birth, which was not significantly associated with ESRD in females.

Table 1. Characteristics of participants

Characteristic	LBW (<10th percentile)		SGA (<10th percentile)	
	No	Yes	No	Yes
Total number	2 408 569	270 217	2 306 286	257 156
Number with ESRD	990	191	932	183
Number with ESRD per 1 000 000 participants follow-up year	17.0	29.89	16.27	25.96
Mean ± SD duration follow-up, years	25.26 ± 14.35	25.61 ± 14.50*	24.84 ± 14.48	27.41 ± 14.5*
Mean ± SD age at ESRD, years	28.29 ± 11.17	26.53 ± 13.0	28.08 ± 11.39	27.57 ± 11.92
Mean ± SD parity	0.95 ± 1.07	0.78 ± 1.07*	0.96 ± 1.07	0.72 ± 1.01*
Mean ± SD birth weight, g	3656 ± 435	2517 ± 421*	3626 ± 490	2729 ± 379*
Mean ± SD *z*-score	0.136 ± 1.21	−1.38 ± 1.16*	0.18 ± 0.2	−1.8 ± 0.46*
Mean ± SD gestational age, weeks	39.94 ± 1.57	37.29 ± 3.13*	39.69 ± 1.93	39.53 ± 2.1*
Preterm birth (%)	1.78	3.1*	4.63	6.42*
Apgar score 5 min <7 (%)	0.75	2.89*	0.9	1.65*
Maternal preeclampsia (%)	2.21	8.87*	2.47	6.52*
Maternal disease[a] (%)	2.32	3.31*	2.37	2.74*
Congenital malformations (%)	2.86	4.67*	2.99	3.78
Congenital malformations of kidney or urinary tract (%)	0.10	0.15*	0.10	0.12

[a]Maternal disease defines as pregestational diabetes mellitus, kidney or urinary tract disease, rheumatic disease or essential hypertension.
*$P < 0.001$.

Table 2. HR for ESRD according to birth-related variables

Risk marker		Unadjusted			Adjusted[a]								
		All			All		Men			Women			
		n	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	*n*	HR (95% CI)	*P*-value	*n*	HR (95% CI)	*P*-value
Birth weight <10th percentile	No	981	1.0 (ref)		1.0 (ref)		628	1.0 (ref)		353	1.0 (ref)	
	Yes	191	1.68 (1.44–1.97)	<0.001	1.61 (1.38–1.88)	<0.001	118	1.55 (1.27–1.89)	<0.001	73	1.71 (1.33–2.27)	<0.001
Z-score <10th percentile	No	932	1.0 (ref)		1.0 (ref)		592	1.0 (ref)		330	1.0 (ref)	
	Yes	183	1.49 (1.27–1.75)	<0.001	1.44 (1.23–1.69)	<0.001	116	1.46 (1.19–1.79)	<0.001	67	1.40 (1.07–1.82)	0.013
Preterm birth	No	1100	1.0 (ref)		1.0 (ref)		698	1.0 (ref)		405	1.0 (ref)	
	Yes	81	1.65 (1.31–2.07)	<0.001	1.54 (1.22–1.92)	<0.001	58	1.64 (1.25–2.15)	<0.001	23	1.32 (0.86–2.01)	0.2
Birth weight <2.5 kg	No	1109	1.0 (ref)		1.0 (ref)		710	1.0 (ref)		399	1.0 (ref)	
	Yes	72	2.0 (1.59–2.56)	<0.001	1.91 (1.50–2.43)	<0.001	43	1.86 (1.36–2.54)	<0.001	29	1.98 (1.35–2.90)	<0.001
Maternal preeclampsia	No	1139	1.0 (ref)		1.0 (ref)		725	1.0 (ref)		414	1.0 (ref)	
	Yes	42	1.53 (1.12–2.08)	0.006	1.48 (1.09–2.02)	0.012	28	1.52 (1.04–2.22)	0.029	14	1.41 (0.82–2.41)	0.203

[a]Adjusted for birth year, gender, maternal disease (defines as maternal diabetes mellitus, kidney disease, rheumatic disease or essential hypertension diagnosed before pregnancy), maternal preeclampsia, maternal marital status and malformations in the newborn.

In Table 2, we observed higher HR for LBW if defined by birth weight <2.5 kg as compared with LBW defined by <10th percentile (2.94 kg for males and 2.85 kg for females). We therefore decided to investigate possible dose–response relationships for LBW and LBW for gestation age. In these analyses, we categorized birth weight and birth weight for gestational age according to gender-specific percentiles and the following groups were analysed: below 5th percentile, 5–10th, 10–20th, 20–80th (reference), 80–90th, 90–95th and above the 95th percentile cut-offs. Dose–response relationships were observed both for LBW and birth weight for gestational age with higher risks for lower birth weights and non-significant trends for lower risk in the 90–95th percentile groups (Table 3). There was, however, a difference as the 5–10th percentile groups were only significant for LBW (P = 0.001) and not for birth weight for gestational age (P = 0.1). When these analyses were stratified for gender, we observed that the risk of ESRD was increased at the 5–10th percentile both for men and for women in LBW (P = 0.001 and 0.045, respectively). When these analyses were stratified by maternal preeclampsia, we observed that maternal preeclampsia did not impact this risk.

Risks associated with combinations of LBW, SGA and preterm birth

To further analyse the different effects of LBW, SGA and preterm birth, we investigated how combinations of these variables associated with risk of ESRD. Compared with individuals who had been born at term without LBW and SGA, having been born at term with SGA and LBW [adjusted HR (aHR) = 1.71 (1.41–2.09)], having been born preterm with LBW but without SGA [aHR = 1.54 = (1.11–2.13)] and having been born preterm with LBW and SGA [aHR = 2.96 (1.84–4.76)] were associated with increased risk of ESRD (Table 4). Based on these results, we chose to perform an analysis in which we counted the risk markers (LBW, SGA and preterm birth). Compared with individuals with zero risk markers, individuals

Table 3. Risk of ESRD for different percentile cut-offs for birth weight and birth weight for gestational age, separate analyses stratified for gender

Risk marker	All				Men		Women	
	Total, *n*	ESRD, *n*	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Birth weight								
<5th percentile	135 599	105	1.89 (1.53–2.32)	<0.001	1.84 (1.38–2.36)	<0.001	2.04 (1.47–2.83)	<0.001
5–10th percentile	134 809	86	1.48 (1.18–1.85)	0.001	1.48 (1.12–1.96)	0.006	1.46 (1.00–2.13)	0.045
10–20th percentile	270 389	130	1.10 (0.91–1.33)	0.3	1.24 (0.98–1.55)	0.047	0.86 (0.61–1.22)	0.4
20–80th percentile	1 615 278	667	1.0 (ref)		1.0 (ref)		1.0 (ref)	
80–90th percentile	258 169	97	0.97 (0.78–1.20)	0.8	0.98 (0.75–1.28)	0.9	0.94 (0.66–1.35)	0.8
90–95th percentile	129 163	39	0.80 (0.58–1.10)	0.2	0.89 (0.61–1.31)	0.6	0.62 (0.34–1.13)	0.1
>95th percentile	132 049	48	0.98 (0.73–1.32)	0.9	0.79 (0.52–1.20)	0.3	1.29 (0.84–1.98)	0.2
Birth weight for gestational age (*z*-score)								
<5th percentile	129 628	111	1.74 (1.42–2.12)	<0.001	1.68 (1.30–2.18)	<0.001	1.84 (1.33–2.54)	<0.001
5–10th percentile	127 528	72	1.20 (0.94–1.54)	0.1	1.33 (1.00–1.82)	0.06	1.00 (0.65–1.55)	0.9
10–20th percentile	261 890	121	1.03 (0.85–1.26)	0.7	1.06 (0.83–1.36)	0.6	1.02 (0.74–1.40)	0.9
20–80th percentile	1 534 279	624	1.0 (ref)		1.0 (ref)		1.0 (ref)	
80–90th percentile	256 637	95	0.96 (0.77–1.19)	0.7	1.03 (0.80–1.34)	0.9	0.83 (0.57–1.23)	0.4
90–95th percentile	12 140	36	0.75 (0.54–1.06)	0.1	0.80 (0.53–1.20)	0.3	0.68 (0.38–1.22)	0.2
>95th percentile	126 340	56	1.16 (0.88–1.53)	0.3	1.05(0.73–1.50)	0.8	1.34 (0.87–2.06)	0.2

Table 4. HR for ESRD according to whether the individuals had LBW, SGA or were born preterm

Risk marker	Total follow-up period				Age 18–50 years			
	Total, *n*	ESRD, *n*	aHR[a] (95% CI)	*P*-value	Total, *n*	ESRD, *n*	aHR[a] (95% CI)	*P*-value
Term, not SGA or LBW	2 162 166	851	1.0 (ref)		1 348 384	689	1.0 (ref)	
Term, SGA, not LBW	100 971	52	1.01 (0.76–1.34)	0.9	74 138	44	1.03 (0.76–1.40)	0.8
Term, not SGA, LBW	34 160	11	0.89 (0.50–1.61)	0.7	18 793	6	0.60 (0.27–1.34)	0.3
Term, SGA and LBW	139 520	113	1.71 (1.41–2.09)	<0.001	96 560	87	1.56 (1.24–1.96)	<0.001
Preterm, not SGA or LBW	40 909	23	1.26 (0.83–1.91)	0.3	28 252	18	1.20 (0.76–1.93)	0.3
Preterm, SGA, not LBW	No data	No data			No data			
Preterm, not SGA, LBW	65 631	38	1.54 (1.11–2.13)	0.009	37 335	28	1.41 (0.97–2.06)	0.07
Preterm, SGA and LBW	16 482	18	2.96 (1.84–4.76)	<0.001	9624	12	2.44 (1.36–4.35)	0.003
Number of risk factors[b]								
0	2 162 166	851	1.0 (ref)		1 348 384	689	1.0 (ref)	
1	176 040	86	1.05 (0.84–1.31)	0.7	121 183	68	1.00 (0.78–1.29)	0.9
2	205 151	151	1.67 (1.40–1.98)	<0.001	133 895	115	1.52 (1.25–1.85)	<0.001
3	16 482	18	2.96 (1.84–.76)	<0.001	9624	12	2.44 (1.37–4.34)	0.003

[a]Adjusted for birth year, gender, maternal disease (defines as maternal diabetes mellitus, kidney disease, rheumatic disease or essential hypertension diagnosed before pregnancy), maternal preeclampsia, maternal marital status and malformations in the newborn. [b]Number of the risk factors LBW (defined by <10th percentile), SGA (defined by <10th percentile) and preterm birth (<37 weeks).

with one risk marker did not have increased risk of ESRD [aHR = 1.05 (0.84–1.31)], individuals with two risk markers had an increased risk with aHR = 1.67 (1.40–1.98) and individuals with three risk markers had an increased risk with aHR = 2.96 (1.84–4.76). Figure 1 illustrates the same finding but also illustrates that the groups separate in adult age.

Risk factors for ESRD due to different causes

Among the 1181 individuals who developed ESRD, 486 developed ESRD as a result of glomerular disease, 113 as a result of interstitial disease, 303 as a result of congenital or inherited disease, 187 as a result of diabetic nephropathy and 144 due to other causes. Corresponding numbers for individuals who developed ESRD after 18 years of age were 406, 96, 172, 157 and 129. Table 5 shows risk for specific causes of ESRD according to the three different main risk markers: LBW, SGA and preterm birth.

For individuals with ESRD due to hereditary or developmental disease, age at ESRD was lower for subjects with LBW as compared with subjects with normal birth weight (19.2 versus 24.0 years; P = 0.01). For other causes of ESRD, age at ESRD was similar, i.e. 26.7 versus 27.6 years (P = 0.5) for glomerular disease, 29.8 versus 28.6 years (P = 0.7) for interstitial disease, 36.0 versus 36.8 years (P = 0.6) for diabetic nephropathy and 34.1 versus 31.8 years (P = 0.3) for other kidney disease.

We observed the strongest risk estimates for ESRD due to hereditary or developmental diseases, but risks were otherwise similarly associated with the different causes of ESRD. There is a possibility that congenital urinary tract malformations and hereditary renal disease might be a cause of low weight. We therefore decided to repeat the main analyses in Table 4 using ESRD due to other causes than hereditary or congenital disease as the outcome variable. In these analyses, we observed almost identical HRs as we did in the analyses of the adult age group

18–50 years (right part of Table 4), i.e. slightly lower risk estimates than for all-cause ESRD.

DISCUSSION

This study showed that LBW was associated with a 70% increased risk and SGA was associated with a 50% increased risk for development of ESRD during the first 50 years of life. Some previous studies have observed that males are more affected by LBW than females [2, 6, 9, 12], but we observed no gender difference in our study. The most novel finding was, however, that none of the risk markers LBW, SGA or preterm birth was associated with risk of ESRD if present alone; at least two of the risk markers needed to be present in order to see an increased risk. This importantly narrows the cohort with increased risk that might need further follow-up. As the number of individuals with ESRD has doubled since the last Norwegian studies [7, 8], this study offers more certain analyses of gender differences, combination of risk markers and different cut-offs for LBW and SGA.

Our study supports previous studies [2, 4, 9, 13, 14] that there is a significant association between markers of intrauterine growth such as LBW, SGA and prematurity and later development of ESRD in adult age. The risk was increased for all causes of ESRD and this supports the Brenner hypothesis that impaired nephron endowment with lower glomerular number and compensatory larger glomeruli lead to increased risk of progression in any kidney disease [1, 25, 26, 28]. The plausible mechanisms of impaired nephron endowment, and thus which risk marker is more important, has been discussed in several studies [7, 9, 15, 16, 27]. Eriksson *et al.* reported that LBW and prematurity were associated with CKD in older people [9] and recently Crump *et al.* showed that prematurity was an important risk marker for CKD before the age of 20 years, but that there did not seem to be an increased risk after the age of 20 years [27]. The relative importance of the different risk markers thus seems to change with age. LBW is the most accessible and used marker of adverse intrauterine environment and it results from either intrauterine growth restriction or preterm birth [5]. Intrauterine growth restriction is measured in our study as birth weight for gestational age, but could also be measured during pregnancy by clinical examination or ultrasonography. Our study confirms the findings of previous studies that LBW, SGA and preterm birth are associated with increased risk for kidney disease in adult age [7, 8], and all risk markers seemed to be important. Previous studies have shown that combination of these risk markers increases risk further [17]. We found the same in this study, but we also showed that participants who only had one of the risk markers LBW, SGA or preterm birth did not have an increased risk. This has never been shown before and should be investigated further. Studies have argued that all subjects with either LBW, SGA or preterm birth should have some sort of follow-up to detect early kidney disease [3, 18], which according to our study would constitute 15.6% of the population (Table 4). Importantly, this could be reduced to 8.6% by including only subjects with at least two of the risk markers. More studies are needed to investigate this association in other populations and to address the potential cost versus benefit of such follow-up. As most developing countries define low birth weight <2.5 kg and often have imprecise data for gestational age and SGA, our results should be used with caution in such settings. It should also be mentioned that our data only discuss risk of severe kidney disease and that screening for cardiovascular risk factors such as hypertension and diabetes mellitus might be beneficial also in individuals with only one risk marker.

There seems to be a dose–response relationship between the severity of preterm birth, LBW or SGA and risk of kidney disease in adult age. In our main analyses, we have defined LBW and SGA as less than the 10th percentile in order to have sufficient numbers of outcomes in subgroups. In both this and previous studies, we have however shown that using the WHO

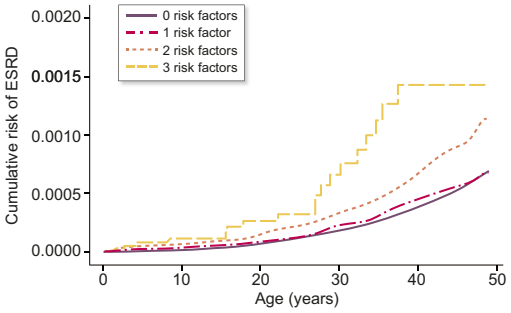

FIGURE 1: Risk of ESRD according to number of birth-related risk factors (birth weight <10th percentile, birth weight for gestational age <10th percentile and preterm birth).

Table 5. HR for different causes of ESRD according to birth characteristics

Risk marker		Glomerular disease		Interstitial disease		Hereditary/ developmental disease		Diabetic nephropathy		Other renal diseases	
		n	HR (95% CI)	*n*	HR (95% CI)	*n*	HR (95% CI)	*n*	HR (95% CI)	*n*	HR (95% CI)
Birth weight <10th percentile	No	421	1.0 (ref)	95	1.0 (ref)	239	1.0 (ref)	159	1.0 (ref)	113	1.0 (ref)
	Yes	65	1.33 (1.03–1.74)	15	1.36 (0.80–2.35)	61	2.26 (1.70–3.00)	28	1.50 (1.00–2.25)	28	2.12 (1.40–3.21)
Z-score <10th percentile	No	385	1.0 (ref)	90	1.0 (ref)	234	1.0 (ref)	148	1.0 (ref)	116	1.0 (ref)
	Yes	79	1.56 (1.23–1.99)	15	1.26 (0.73–2.18)	51	1.70 (1.25–2.31)	27	1.32 (0.88–1.99)	22	1.41 (0.89–2.31)
Preterm birth	No	466	1.0 (ref)	107	1.0 (ref)	274	1.0 (ref)	173	1.0 (ref)	132	1.0 (ref)
	Yes	20	0.96 (0.61–1.50)	6	1.25 (0.55–2.83)	29	2.32 (1.60–3.41)	14	1.82 (1.06–3.14)	12	2.04 (1.13–3.70)

cut-off of 2.5 kg yielded higher risk estimates [19]. In this study, we explored the association between different cut-offs for LBW and SGA and risk of developing ESRD; further more, we also investigated possible gender differences that have been suggested by other studies [6, 12]. For both LBW and SGA, HRs increased with lower cut-offs and was statistically significant at lower than the 10th percentile for LBW but only for less than the 5th percentile for SGA. Overall, these analyses supported the use of the 10th percentile cut-off for LBW but one could argue that the 5th percentile should be used for SGA. As all previous studies investigating SGA have used the 10th percentile [7, 20–22], we have decided to do the same. Use of the 10th percentile for LBW in Norway defined all newborns with a birth weight of <2.8–2.9 kg as LBW. Our study cannot answer whether this cut-off, the WHO cut-off of 2.5 kg or the national 10th percentile should be used to identify newborns at risk in other populations. A major challenge is selection of an appropriate global reference [20]. LBW could be a marker of intrauterine growth restriction, but in an international context it could also include newborns who are small due to genetic factors, maternal smoking or maternal undernutrition. Prevalence of offspring with birth weight <2.5 kg is for example very high in South Asia, but it is unknown whether these data represent true growth restriction or normal development of smaller offspring [14]. At the same time, using the 10th percentile cut-off might be problematic in populations affected by undernutrition, in which the cut-off should preferably be defined in subpopulations without undernutrition.

The major strength of our study is the opportunity to use the national registries to include a large number of participants with prospective registration of birth-related variables and near-complete follow-up. Compared with a previous Norwegian study from 2016 [8], we have in this study a much larger number of included subjects. This was mostly due to follow-up until 2016 (versus 2009) and inclusion of the whole population (versus only those with at least one sibling). One limitation is that ESRD was not registered between 1967 and 1980, and the counting processes of Cox regression were therefore used for statistical analyses and likely compensated this limitation. The study population is mostly Caucasian so results might be different in other populations groups. Another limitation is that ESRD is a rare endpoint, and even though we included 2.7 million participants, only 1181 developed ESRD. This is, however, twice the number as compared with our previous studies [7, 8]. Potential confounders could be low socio-economic status, smoking, educational level and ethnic origin. We did not have access to these data in our study but we were able to adjust for single versus non-single mother, which is a socio-economic marker. A weakness is also that we had no information on diseases diagnosed after the prenatal period and could therefore not adjust for diseases developed in adulthood.

In conclusion, we have shown that markers of LBW are associated with development of ESRD during the first 50 years of life. Our study also showed that the risk markers LBW, SGA and preterm birth may not be associated with development of ESRD if present alone. Furthermore, our study investigated cut-offs for LBW and SGA and suggested that using the 10th percentile could be the best, but it is still uncertain which cut-offs are the best in other populations. We suggest that our results should be investigated further in other populations and preferably also using lower CKD stages as outcomes. Early detection of individuals with high risk of kidney disease would allow for early intervention to delay disease progression and the most clinically relevant might be screening for hypertension, diabetes mellitus and proteinuria [3, 23, 24]. Our study indicates that this might be beneficial in persons with at least two of the risk factors LBW, SGA or preterm birth.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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CONFLICT OF INTEREST STATEMENT

None of the authors have any conflicts of interest regarding this study. Results presented in this article have not been published previously in whole or part, except in abstract format.

(See related article by Terstappen and Lely. Long-term renal disease after prematurity or fetal growth restriction: who is at risk? *Nephrol Dial Transplant* 2020; 35: 1087–1090)

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Renal handling of zinc in chronic kidney disease patients and the role of circulating zinc levels in renal function decline

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ABSTRACT

Background. Zinc deficiency is commonly encountered in chronic kidney disease (CKD). The aims of this study were to assess whether zinc deficiency was related to increased renal excretion of zinc and to the progression of CKD.

Methods. Plasma and 24-h urinary zinc levels, urinary electrolytes and uromodulin were measured in 108 CKD patients and 81 individuals without CKD. Serum creatinine values were collected for 3 years to calculate the yearly change in estimated glomerular filtration rate (eGFR). Multivariable regression analysis was performed to assess the association between baseline zinc levels and yearly change in eGFR.

Results. CKD patients had lower circulating zinc levels and higher 24-h urinary zinc excretion than non-CKD participants (612.4 ± 425.9 versus 479.2 ± 293.0 μg/day; $P = 0.02$). Fractional excretion (FE) of zinc was higher and it significantly increased at more advanced CKD stages. Zinc FE was correlated negatively with 24-h urinary uromodulin excretion ($r = -0.29$; $P < 0.01$). Lower baseline plasma zinc levels were associated with a faster yearly decline of renal function in age, gender, diabetes and hypertension adjusted models, but this relationship

Errata for
Low birth weight, intrauterine growth restriction and risk og chronic kidney disease in adult age

Anna Gjerde

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Errata

Side 14 Feil årstall : "1967-1967" – rettes til "1964-1967"

Side 41 Stavefeil: «more the» rettes til «more then»

Side 67 Stavefeil: «LBW of SGA» rettes til «LBW or SGA»

Side 70 Feil symbol: « LBW as birth weight > 2500g» rettes til « LBW as birth weight < 2500g»

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