Low Birth Weight and Risk of Progressive Kidney Disease

Epidemiological and Morphological Studies

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CONTENTS

SCIENTIFIC ENVIRONMENT

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“noli cedere cognoscere” “never cease to learn”

Anno MMXVI

ABBREVIATIONS

AGA	Appropriate for Gestational Age
BMI	Body Mass Index
CA	Cortical Area
CHD	Coronary Heart Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation
DBP	Diastolic Blood Pressure
DOHaD	Developmental Origins of Health and Disease
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
ESRD	End Stage Renal Disease
GA	Glomerular Area
GD	Glomerular Density
GV	Glomerular Volume
HbA1C	Glycated Hemoglobin
HR	Hazard Ratio
IDMS	Isotope Dilution Mass Spectrometry
IgAN	Immunoglobulin A (IgA) Nephropathy
IGF	Insulin-like Growth Factor
IUGR	Intrauterine Growth Restriction
LBW	Low Birth Weight
MBR	Medical Birth Registry
MEST	**M**esangial hypercellularity, **E**ndocapillary hypercellularity, **S**egmental glomerulosclerosis, **T**ubular atrophy/interstitial fibrosis (Oxford classification)
MUAC	Mid-Upper Arm Circumference
NBW	Normal Birth Weight
NKBR	National Kidney Biopsy Registry
NRR	National Renal Registry
PARs	Predictive Adaptive Responses
PAS	Periodic acid–Schiff (PAS)
PAX2	Paired box gene 2

RAS	Renin Angiotensin System
RET	Rearranged during Transfection gene
SBP	Systolic Blood Pressure
SGA	Small for Gestational Age
SPSS	Statistical Package for the Social Sciences
UNICEF	United Nations Children's Emergency Fund
USRDS	United States Renal Data System
UTI	Urinary Tract Infection
WHO	World Health Organization

LIST OF PUBLICATIONS

I. Paschal Ruggajo, Rannveig Skrunes, Einar Svarstad, Rolv Skjærven, Anna Varberg Reisæther and Bjørn Egil Vikse. Familial Factors, Low Birth Weight, and Development of ESRD: A Nationwide Registry Study. *Am J Kidney Dis. 2016 Apr;67(4):601-8.*

II. Paschal Ruggajo, Einar Svarstad,Sabine Leh, Hans-Peter Marti, Anna Varberg Reisæther ,Bjørn Egil Vikse. Low Birth Weight and Risk of Progression to ESRD in IgA Nephropathy: A Nationwide Registry Study. *PLoS One. 2016 Apr 19;11(4):e0153819.*

III. Paschal Ruggajo, Einar Svarstad,Sabine Leh, Hans-Peter Marti, Anna Varberg Reisæther ,Bjørn Egil Vikse. Low Birth Weight Associates with Glomerular Size in Young IgA Nephropathy.*(Submitted)*.

ABSTRACT

Background: Low Birth Weight (LBW) and Small for Gestation Age (SGA) are surrogate markers for fetal undernutrition and are associated with impaired nephron development in utero as suggested by the Brenner`s hypothesis. We investigated whether familial factors explain the association between LBW and ESRD, whether LBW and/or SGA predict progression to ESRD in IgAN patients and whether LBW and/or SGA is associated with altered glomerular size or density in young IgAN patients with preserved renal function.

Methods: We linked medical birth data from the Medical Birth Registry of Norway (MBR), sibling data from the Norwegian Population Registry, ESRD data from the Norwegian Renal Registry (NRR) and kidney biopsy data from the Norwegian Kidney Biopsy Registry (NKBR). For Paper I and II, data were analysed in a retrospective cohort study design. Exposure variables for Paper I were LBW/ SGA in the participant and/or LBW/SGA in at least 1 sibling. For Paper II, exposure variables were LBW/ SGA among a cohort of IgAN patients. Outcome variable for Paper I and II was development of ESRD and data were analysed with cox regression statistics. For paper III we selected IgAN patients and control patients registered in the NKBR who had registered birth weight in the MBR and preserved renal function (i.e e GFR≥ 60 ml/min/1.73m^2) at time of diagnosis. Differences in glomerular density and volume were investigated between subjects with or without LBW/SGA as well as between IgAN patients and controls.

Results: In Paper I, we found that of 1,852,080 included individuals, 527 developed ESRD. Compared with individuals without LBW and with no siblings with LBW, individuals without LBW but with a sibling with LBW had an hazard ratio (HR) for ESRD of 1.20 (95% CI, 0.91-1.59), individuals with LBW but no siblings with LBW had an HR of 1.59 (95% CI, 1.18 - 2.14), and individuals with LBW and a sibling with LBW had an HR of 1.78 (95% CI, 1.26-2.53). Similar results were observed for individuals who were SGA. In Paper II we found that as compared to patients without LBW, patients with LBW had an increased risk of progression to ESRD with an HR of 2.0 (1.1-3.7) for the total cohort, 2.2 (1.1-4.4) for male and 1.3 (0.30-5.8) for female). Similar results were observed for SGA but further analyses suggested that subjects with both LBW and SGA had the highest risk. In paper III we found that compared to IgAN patients without

LBW or SGA, IgAN patients with LBW and/or SGA had larger glomerular area (16235±3744 vs 14036±3502 μm^3, p-value 0.04), significant in males but not females.

Conclusion; Having been born LBW and/or SGA was associated with higher risk for all-cause ESRD independent of other familial factors shared among siblings. Further, LBW and/or SGA was associated with increased risk for progression to ESRD among young male IgAN patients and were also associated with larger glomeruli (a marker of congenital nephron deficit). Taken together, our results support the Brenner hypothesis.

1. INTRODUCTION

Earlier studies observed that between the 18th and 20th century, death rates from all causes fell appreciably in Europe and proposed that this reduction was probably related to improving living conditions and better nutrition during this period[1]. Subsequently, it was noted that mortality rates from specific causes such as coronary heart disease and stroke in adults correlated to infant mortality rates in the same population 60-70 years earlier and these higher rates were further related to living in less affluent geographical regions[2,3]. David Barker and colleagues proposed that environmental factors (particulary nutrition) during intrauterine and early postnatal life programs the risk for for early onset of non-communicable diseases and premature death during adult life.This theory known by several names,such as “developmental programming”, “fetal origins of adult disease” “developmental onset of adult health and disease”or simply the “Barker`s hypothesis”. The theory has stimulated extensive observational and experimental studies across the world and is now a fully developed field of research.

Brenner et al further hypothesized that adverse intrauterine environment, for example due to placental insufficiency or maternal undernutrition, was associated with impaired fetal nephron development and increased the risk of hypertension and progressive kidney disease in adult life[4]. Low birth weight (LBW) is the most accessible surrogate marker of adverse intrauterine environment. Vikse et al have previously shown that LBW was associated with increased risk for End Stage Renal Disease (ESRD) in Norway[5]. However, both kidney diseases and LBW are more common in certain families than others and thus it is unclear whether other shared familial factors (e.g genetical or environmental) could confound this association.Whereas the association between LBW and all-cause ESRD is now an established paradigm, more insight is still required to explore the Brenner`s hypothesis into specific causes of progressive kidney diseases such as IgA nephropathy (IgAN). Futhermore, investigating whether LBW could correlate with specific markers of congenital nephron deficit (i.e fewer but larger glomeruli) in specific diseases like IgAN, will be yet another step towards understanding the full width of both the Barker`s and Brenner`s hypotheses.

The public health importance of this project is that in countries like Tanzania where the prevalence of LBW is high, cost-effective health interventions like optimal nutrition for women of child bearing age and

pregnant women could significantly reduce the prevelance of LBW and potentially reduce the incidence of future adult renal and cardiovascular disease in the community.

2. BACKGROUND

2.1 Historical perspective and background for the Barker Hypothesis

In 1977, Forsdahl reported a correlation between geographical incidences of coronary heart disease (CHD) mortality during the years 1964-1967 and infant mortality rates during the years 1896-1925 (i.e 70 years earlier); i.e Norwegian counties with higher infant mortality rates showed higher mortality from CHD 70 years later. From his observations, he suggested that poor living conditions in childhood with mal- or undernutrition could increase risk for coronary heart disease in adult life[2].

David Barker and co-workers observed that neonatal mortality rates in different geographical regions of the UK during the years 1921-1925 (that further associated with low birth weight) predicted death rates from strokes and CHD that occurred between the years 1968-78 in the same areas[3]. This ecological observation was followed by a study in the county of Hertfordshire which showed that men and women who had low birth weight and low body weight at one year of age during the period between 1911-1930 had increased mortality rates from stroke and CHD later in life. Interestingly, these effects were found to be linear and graded across the range of birth weights (i.e dose-response relationship)[6]. Motivated by these findings, Barker and co-workers pioneered similar studies involving registered cohorts in other European countries and expanded the work into investigating the concept in other metabolic conditions.

In the Netherlands, extensive research has been conducted on the cohort of offsprings whose mothers were pregnant during the winter of 1944-45 (at the peak of the 2nd world war when the Netherlands was faced with acute shortage and rationing of food, popularly known as the "Dutch hunger winter". This Dutch famine – though a historical disaster – has provided a unique opportunity for investigators to study effects of undernutrition during gestation in humans[7]. From this cohort, Barker and co-workers reported correlations between prenatal exposure to undernutrition and increased risk for reduced glucose tolerance[8], coronary heart disease[9] and obesity[10] in adulthood. Utilising data from the Helsinki Birth Cohort Registry of Finland, Barker and co-workers established the association between reduced growth in utero and infancy with increased incidences of coronary heart disease[11,12], stroke[13] and atherogenic lipid profile[14] during adulthood.

From these studies pioneered and popularized by Barker and co-workers, the "Barker`s hypothesis" was coined, the hypothesis proposes that alterations in fetal nutrition and endocrine environment to the fetus in utero or to the infant during early postnatal life result in developmental adaptations that permanently change the structure, physiology and metabolism of the fetus or infant and consequently predisposes the individual to cardiovascular, metabolic and endocrine diseases in adult life[15,16].

2.1.1 Developmental Origins of Health and Disease (DOHaD) Model

The Developmental Origins of Health and Disease (DOHaD) model is a more comprehensive term furthering the Barker`s hypothesis. The DOHaD model suggests that in addition to the established epidemiological model of disease causation (interaction between host, causative agent and environment), adverse events occurring in an individual during early development *in utero* and early postnatal life increases the individual`s risk for developing non-communicable diseases (such as hypertension, diabetes mellitus, cardiovascular disease and kidney disease etc.)[17,18]. The DOHaD model encompasses other terms in literature referring to the same concept, such synonyms include "developmental programming", "fetal origins of adult disease" or "fetal programming",terms that often are used interchangeably.

2.1.2 Mechanisms of developmental programming and developmental plasticity

During organogenesis in utero, the fetal tissues and organs go through a critical period of development[19]. During this rapid cell division phase, a stimulus or insult can induce anatomical and physiological adaptations which may increase the risk for developing disease during later (adult) life; this process is referred to as *developmental (fetal) programming*[20-23]. In a broader context, this potential or ability of the organism to develop into various phenotypes when subjected to a particular environment/setting during crucial developmental moments in utero is referred to as *developmental plasticity* [24].

Developmental programming may be induced when the fetus (through fetal-placenta interface) or infant (through breastfeeding) receives cues from the mother about her health and nutritional state [25]. The fetal or perinatal responses to these cues may include (but are not limited to) changes in metabolism, tissue sensitivity to hormones and hormone production that differentially and persistently may alter physiological and metabolic set points of the developing organs of the fetus or neonate. Several models have been

proposed to explain the adaptations adopted by the fetus upon receiving cues of actual or perceived nutritional deficiency.

The "thrifty genotype" hypothesis proposes that through evolutionary mechanisms, the human fetus has selected genes that promoted insulin resistance during periods of food shortage,this was an adaptive mechanism that maximized survival advantage among our hunter-gatherer ancestors,inheriting the same genes in the modern human who is born in a significantly richer nutritional environment act maladaptively to predispose an individual to type 2 diabetes mellitus and other metabolic diseases [26,27]. Gluckman et al have proposed that when faced with environmental changes (such as nutritional deficiency) during the window of developmental plasticity in utero,the fetus adapts two types of responses, first the homeostatic responses that offer immediate survival at the expense of future biological trade-offs and second, predictive adaptive responses (PARs) based on anticipation of future adverse conditions[27]. Such responses induce irreversible changes in structure and function (i.e "thrifty phenotype") and may set the stage for disease development especially when the postnatal environment is different from the one predicted by these fetal responses while in utero.

The small baby size at birth may be interpreted as a hallmark of collective fetal adaptive responses to adverse intrauterine environment which herald changes in tissue and organ development. These changes may not be evident at birth but the child may be programmed to respond in a maladaptive way in the future adult life when the he/she encounters stimuli or triggers for disease development[27]. The subsequent environmental exposures during infancy, childhood and adulthood seem to model the future risk of developing the disease. For example, it has been observed that British children of South Asian ancestry develop insulin resistance at lower BMI than British children of European ancestry, this phenomenon has been suggested to relate to higher incidence of low birth weight in the former group[28].

Different suggestions have been put forth to explain the possible mechanisms through which fetal programming is effected. At present, nutritional, genetic and epigenetic programming are the most investigated theories related to fetal programming and of these, nutritional programming has been studied more extensively in both human and animal experimental studies.

2.1.2.1 Nutritional Programming

The in utero and early postnatal stages, represents periods of rapid development and maturation for most of the body organs[29]. Maternal nutrition, determined by the quality and quantity of consumed nutrients during this crucial periods, can induce powerful and lasting effects on the development and maturation of the offspring tissues[29]. Rickets diseases, for example, has long been taken as an example of a permanent change in structure due to undernutrition at this critical stage of development during early life[30]. A number of experimental studies have shown association between in-utero undernutrition and persisting changes in insulin resistance, blood pressure, cholesterol metabolism as well as other endocrine, metabolic and immune functions in later life [31-34]. Some of these studies have been replicated in humans[15,20].

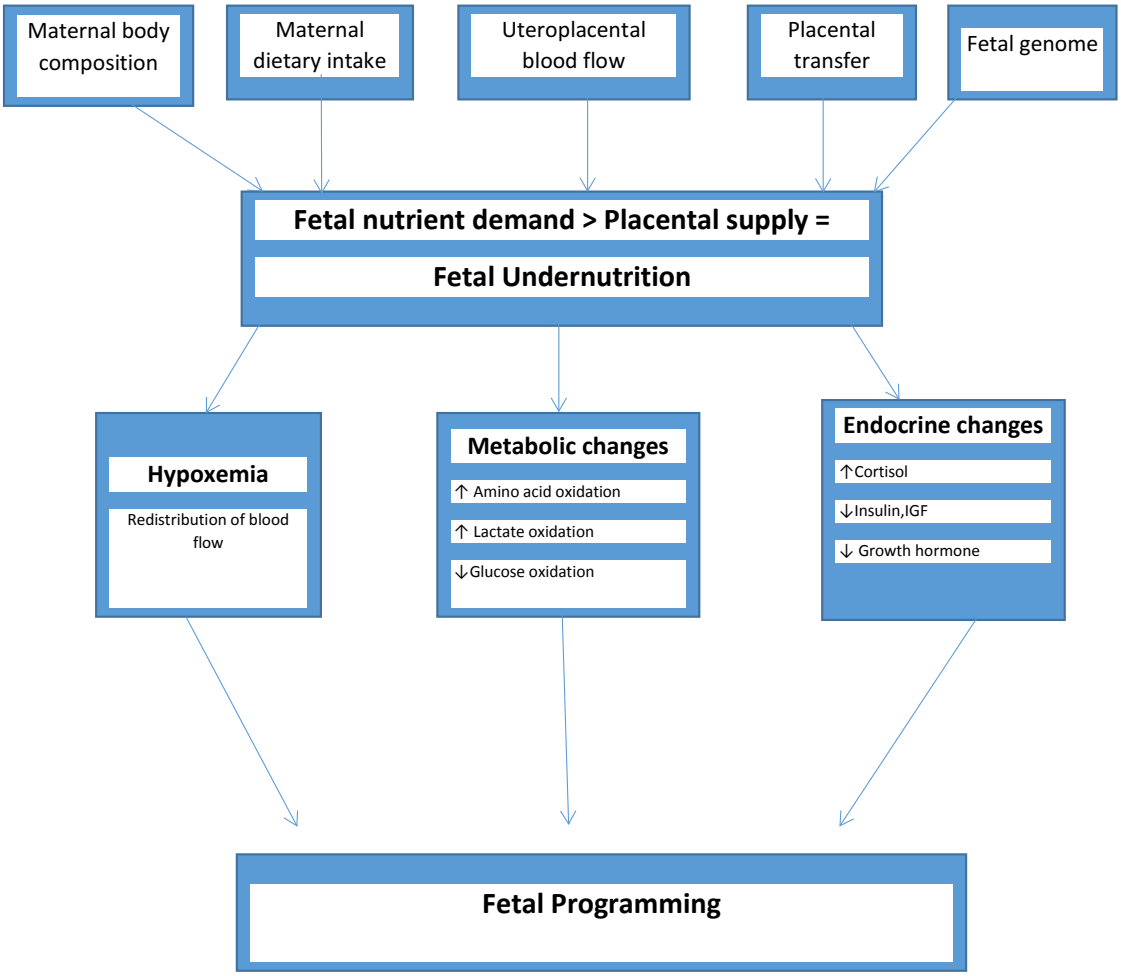

Figure 1: Framework for fetal adaptations to undernutrition.

Adopted from DJP Barker: *In utero* programming of chronic disease. *Clinical Science (1998)* ***95****, 115–128.* Permission to publish in Thesis (non-commercial use) freely permitted by the Publisher.

When faced with undernutrition, the developing fetus summons several adaptations that include changes in metabolism, blood flow re-distribution and production of fetal and placental hormones which regulate fetal growth[35] (Figure 1). As hinted above, insulin resistance is suggested to be a key factor in the pathogenesis of metabolic syndrome and its sequelae (type 2 diabetes, hypertension and cardiovascular disease)[36]. As an adaptation to maintain blood glucose concentration when faced with undernutrition in utero, the fetus develops tissue resistance to insulin, such a response preferentially maintains glucose level to the brain at the expense of glucose transport to the muscles and compromises insulin mediated growth[37]. In chronic states, such an adaptation induces hyperglycemia which has been detected in fetal blood during the late pregnancy period in utero among LBW children[38].

The initial metabolic changes involve increased catabolism by consuming the fetus' own substrate to maintain growth and development, but with prolonged undernutrition, the fetus adaptively slows the metabolic rate and opt to prioritize the distribution of limited nutrients to vital organs (like the brain) at the expense of growth and maturation of other organs[23,39,40]. If this prolonged undernutrition occurs during late gestation when some of the organs (e.g. the kidneys) are at the peak of rapid growth and maturation, these organs end up having less than expected number of functional units at birth and since the kidneys do not have the capacity to catch up with formation of new nephrons after birth, they become less adaptive to future insults and more vulnerable to triggers of chronic kidney diseases [41,42].

Undernutrition also models fetal hormonal production and has impact on hormonal and metabolic interactions between the fetus and the mother through the placenta[43]. Fetal insulin and Insulin-like Growth Factors (IGFs) are presumed to play an important role in regulating fetal growth as serum levels of IGFs in fetal serum changes remarkably in response to changes in fetal nutrition[43]. In situation of maternal undernutrition, the maternal IGF declines followed by a corresponding decline in transfer of glucose and amino acids from mother to fetus compromising the rate of fetal growth[44]. During late gestation and early postnatal life, the role of insulin in driving the linear growth (i.e length of the fetus) is sustained by growth hormone and the IGF-axis[45]. In the context of fetal undernutrition, the respective levels of growth hormone

and IGF are lower whereas levels of counter-regulatory hormones like cortisol are higher [46,47]. These hormonal changes impact cell differentiation and linear growth[35].

Experimental animal studies have provided useful insights on nutritional programming. These studies employ methods that induce fetal undernutrion such as subjecting the pregnant animal model to an environment nutrient imbalance achieved by global reduction in overall maternal food intake[31], protein restriction in the isocaloric diet of the pregnant animal[32] or glucocorticoid exposure without dietary manipulation[48]. Finding from such studies suggest that in the window between conception and weaning, dietary,endocrine and physical challenges to the fetus induces biological mechanics that triggers persistent changes in cardiovascular and metabolic function of offspring that are observed in adult life[25].

Specific nutrient restrictions (e.g. vitamin B12, folate or methionine) from the diet of adult female sheep during the peri-conception period is also associated with altered cell metabolism and higher blood pressure in the offspring later in life[49]. In humans, maternal vitamin B12 and folate deficiency during pregnancy has been associated with childhood insulin resistance in the offspring[50]. Experiments in rats have observed that administration of glucocorticoids to a pregnant rat increases postnatal stress [51] and leads to hypertension and insulin resistance in the offspring in later life as well as increased postnatal stress [52 33]. Further experiments in rats have shown that maternal undernutrition during pregnancy may result in offspring that show central obesity and reduced skeletal-muscle mass, altered insulin sensitivity, altered hepatic metabolism, reduced numbers of nephrons, hypertension, and altered endothelial function, together with altered appetite regulation, level of activity and neuroendocrine control in later life[31,32,34,53].

Literature is still evolving with regard to continuation of nutritional programming during infancy. A study has reported that low birth weight and low body weight at 1 year of age to be associated with glucose intolerance and beta-cell dysfunction among men aged 64 years old[54]. The mode of milk feeding and timing of complementary feeding (weaning) has also been associated with differences in childhood obesity. In a systematic review, Pearce et al found that introducing complementary feeding before the infant was 4 months of age was associated with higher body mass index (BMI) during childhood[55]. Overweight in childhood has been associated with adult obesity[56]. Furthermore, Owen et al has reported that adults who

were breastfed had lower blood pressure and cholesterol as compared to those who were fed with formula milk[57].

2.1.2.2 Genetic Programming

As both low birth weight and adult disease seem to cluster in families it is possible that shared genes could predispose both to low birth weight and to adult disease. It has for example been shown that maternal 825T allele of the G protein subunit β3(GNB3) in healthy pregnant women is associated with lower birth weight of their offspring[37]. Additionally, Siffert has reported that the same 825T mutation in GNB3 subunit associated with obesity, hypertension,diabetes and diabetic nephropathy in adult life [58]. Aditionally, genetic polymorphisms in the maternal sex steroid pathway may interact with type 2 diabetes gene TCF7L2 and predispose to lower offspring birth weight[37,59,60].

2.1.2.3 Epigenetic Programming

Epigenetics is a study of stable and somatically heritable genetic expressions that do not involve changes in the DNA sequence[61,62]. The key epigenetic mechanisms include methylation of cytidine–guanosine (CpG) nucleotides in the promoter regions of specific genes, changes in the chromatin structure through histone acetylation and methylation, and post-transcriptional control by microRNA[63].

Human diploid cells are formed by two alleles, one inherited from each parent. Through DNA methylation (a key mechanism in epigenetics) one of the two parental alleles may be sustained in an active state and the other one remain repressed. This is known as genomic imprinting[61]. Imprinted genes (like IGF2) have been shown to play a role in determining placental transfer capacity and nutrient supply to the growing fetus, this in turn determines the fetal growth and the baby size at birth[61]. During in utero development, the availability of dietary methyl donors and cofactors (such as methionine, choline, folic acid, vitamin B12 etc) is important for one carbon-metabolism which has the potential to alter DNA methylation[64]. In experimental studies, dietary protein restriction alters the offsprings`s phenotype and induces impaired glucose tolerance, dyslipidemia and hypertension which is reversible by folate supplementation [65,66]. Epigenetic modifications of genes coding for renin-angiotensin-system (RAS),

peroxisome proliferator-activated receptors (PPAR) system or the glucocorticoid receptor have been associated with development of cardiovascular diseases[67].

The impact of epigenetic regulation on fetal programming can be traced back during early embryogenesis where uneven splitting of the inner cell mass results in unequal distribution of the genomic materials even among monozygotic twins and can result in persistence of different phenotypes[61,62]. These epigenetic differences accumulate with age and tend to be amplified among monozygotic twins who lived together for the smallest amount of time, underscoring the impact of environmental effects in epigenetic regulation[68-70]. Although the epigenetic modifications are completed during the developmental stage, they may not change the phenotype until adult age when the offspring encounters an environmental trigger for the effects to manifest[25]. The exact window of time during which epigenetic changes may occur in the developing fetus remains unknown but it is speculated that it may extend between peri-conception to postnatal period[49,71].

Through hormonal and nutritional manipulation, experimental studies have demonstrated transmission of epigenetic changes through generations[72,73]. Fetal exposure to excessive glucocorticoids induces low birth weight at birth, hyperinsulinemia and hyperglycemia which persist to the third generation[74]. Furthermore,it has been reported that inducing maternal malnutrition by protein restriction in rats, leads to low birth weight offsprings and may persist for several generations[75]. Epigenetic regulation of imprinted and non-imprinted genes may explain some of these intergenerational inheritances[72,73,76].

2.1.3 Parental influences, gender differences and intergenerational aspects of fetal programming

Maternal health and conditions have significant influence on embryo/fetal development through placental cross-talk. This cross-talk is later continued between mother and baby via breastfeeding. Maternal nutritional deficits, hypoxia, subclinical inflammation, infections and illness have potential direct effect to the fetal environment[77,78]. Maternal vitamin D deficiency has been linked to lower muscle mass and higher insulin resistance in offspring[79]. Common maternal metabolic diseases (e.g. diabetes and hypercholesteremia) or behavioural factors (e.g. smoking, use of alcohol and illicit drugs) may also induce

chronic maternal stress and in turn affect the fetus[80]. Similarly, maternal overnutrition, obesity and disrupted maternal lipid metabolism has been linked to premature birth, low birth weight and smaller infants [81,82].

Another maternal factor is the concept of maternal constraint which suggest that fetuses do not grow to their full nutritional and genetic potential because their growth is constrained to limited size of the uterus in the maternal pelvis to allow for possible vaginal delivery and avert obstructed labour[83]. This phenomenon, likely occurring in all pregnancies, is best observed among adolescent mothers, nulliparous pregnancies, pregnant mothers with short stature and pregnancies involving multiple gestation[84].

Intergenerational transmission refers to transmission of recurrent conditions to the first generation of offsprings whereas transgenerational transmission refers transmission from the first generation to the second and further generations. Data from Population Registries has enabled investigation for possible hereditary contributions to recurrent conditions through several generations within the family[85]. The father and the mother contribute somewhat differently to the genomic make-up of the offspring; while the father contributes paternal alleles which form half of the offspring`s genomic alleles, the mother contributes by providing maternal alleles to complement the remaining half, and in addition the mother exclusively provides the fetal mitochondria and the interactive intrauterine environment. These latter mechanisms may allow for intergenerational genetic programming from mother to female offspring for different conditions[85] (Figure 2).

This differential parental contribution leads to different patterns of intergenerational father-offspring or mother-offspring recurrent conditions. This phenomenon is best exemplified by a study based on the Medical Birth Registry of Norway which reported that the relative recurrence risk for pre-eclampsia among mothers who were maternal half-sisters were less as compared to mothers who were paternal half-sisters[86]. Additionally, in case of wrong paternity information, which might be as common as 10%[87], this intricate parental hereditary contributions pattern may be further confounded. Lie et al thus cautioned that contributions from the father, mother and offspring may thus be difficult to interpret and might be both stronger or weaker than estimated. We presume the same phenomenon may disguise the hereditary patterns related to other chronic diseases and birth related variables (LBW, SGA and Preterm birth)[86].

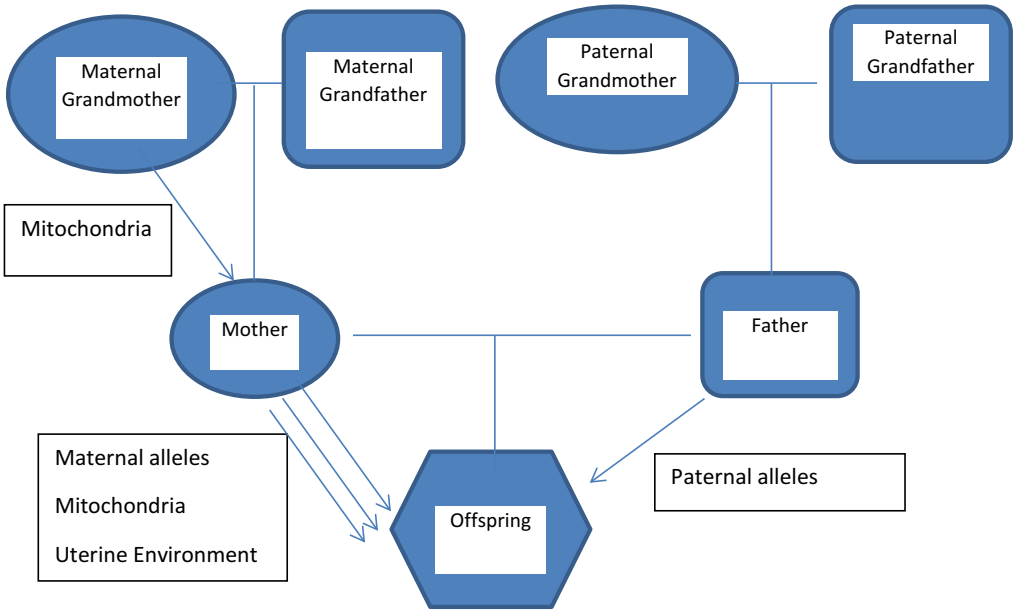

Figure 2: Transgenerational grandparental and parental contribution in fetal programming

Both intergenerational and transgenerational transmission of disease risk are observed in early life programming[29,88]. Increased cardio-metabolic diseases have been observed among obese offspring of families with persistent maternal undernutrition and suboptimal fetal development across more than one generation. For example, female offspring with increased risk of gestational diabetes give birth to children with increased likelihood of becoming diabetic themselves; hence perpetuating the vicious cycle of increased cardio-metabolic risk across subsequent generations[88]. Interest is growing to explore the transgenerational patterns of paternal inheritance, Bygren et al reported that grandchildren of men who were overfed in their pre-pubertal growth period had a significantly shorter life span [89]. Similarly, another previous study has reported that BMI of the studied individuals independent of parental BMI correlated strongly with grandparental BMI [90].

In a large population scale, the transgenerational effects of fetal programming have been shown in studies following-up cohorts of individuals who were exposed to the Dutch hunger winter (1944-45). It was observed for example, that pregnant women exposed to famine influenced the nutrition status of their daughters who also subsequently gave birth to LBW babies themselves (i.e grandchildren of pregnant women exposed to famine)[91]. The transgeneration phenomenon has been replicated in experimental studies in which laboratory rats fed with protein-deficient diet over twelve generations showed progressively and cumulatively greater fetal growth retardation over several generations and it took three generations to return to normal growth rates upon refeeding with normal diet[16,92].

There is growing evidence that there could be differences in the effect/impact of fetal programming between male and female gender. So far, evidence is still restricted to experimental studies. While Langley-Evans et al have reported that both male and female rat offspring of modestly protein-restricted mothers developed hypertension, other investigators report that modest protein restriction to pregnant rats does not lead to hypertension in adult female offsprings[32 93-95] . Other experimental manipulations, including pharmacological suppression of RAS during development[96] and surgical reduction of number of glomeruli at birth[97,98], have resulted in adult hypertension for both female and male offsprings.

2.1.4 Developmental programming and adult disease

2.1.4.1 Cardiovascular Diseases

The pioneering studies on developmental programming followed observations from community surveys by Barker et al who noted that incidence rates of ischaemic heart disease in England and Wales correlated with differences in infant mortality rates that were recorded in the same geographical locations several decades before. Subsequently, using registry data from different countries in Europe, Barker and co-workers were able to demonstrate associations between increased cardiovascular mortality and low birth weight and low body weight at 1 year of age [3,6-12]. While initial studies suggested that low birth weight was the dominant factor in this association, subsequent work has highlighted that other birth related parameters such as preterm birth[99], stunting[100] and low ponderal index[11,100] were also associated variably increased risk for future cardiovascular diseases.

In a study involving men and women from India (n=517), the prevalence of coronary heart disease among those born LBW (birth weight ≤2.5 kg) was higher than that among those born with birth weight of ≥3.1 kg (11% vs 3%)[101]. Furthermore, the Nurses' Health Study of 70,297 nurses in the US reported that the relative risk for non-fatal coronary heart disease and mortality fell two folds across the range of birth weights and was associated with low birth weight in a dose-response manner [102].

Further, studies in adults who suffered fetal growth retardation in utero have revealed changes in electrophysiological changes and cardiac remodelling as compared to controls[103]. Also, significant QT interval prolongation and long QT abnormalities on ECG tracings have been reported among young adults born preterm and had extremely low birth weight compared to normal controls[99]. Additionally, it has been reported that individuals exposed to the Dutch famine in early gestation had more atherogenic lipid profile[104], higher BMI[10] and higher concentrations of fibrinogen and factor VII[105] and therefore had increased risk for CHD than controls.

2.1.4.2.Hypertension

Hypertension is highly prevalent and affects more than 25% of adults globally[106]. The underlying cause is unknown but speculated to involve a complex interplay between polygenic predisposition and environmental factors [107,108]. Studies in monozygotic twins have suggested that environmental triggers

might be more important than genetic factors in predisposition to developing hypertension[109]. Several meta-analyses have shown a consistent association between low birth weight and increment in blood pressure. In one meta-analysis, a 2.28 mmHg increment in systolic blood pressure (SBP) was reported among those born with LBW (<2.5kg) as compared to those born with birth weight > 2.5 kg [110]. Also,another study that pooled more than 34 studies of 66,0000 participants, a 1kg higher birth weight was associated with a 3.5mmHg decrease in systolic blood pressure[111].Generally, an extensive review of studies has shown that the reported magnitude in the difference in SBP per 1kg difference in birth weight was influenced by the study size with a trend towards smaller differences in large study sizes,for example in one such studies it was noted that each 1 kg increase in birth weight was associated with; 1.9 mmHg lower blood pressure in studies with less than 1000 participants, 1.5 mmHg lower blood pressure in studies with 1000-3000 participants and 0.6 mmHg lower blood pressure in studies with more than 3000 participants), underscoring the potential for publication bias in reporting large differences observed in smaller studies[112]. Studies on preterm birth have shown similar effect on raised blood pressure [113-116].

Several maternal, fetal and childhood parameters have been studied in relation toevidence of of fetal programming in development of hypertension in adulthood. The placenta/fetal weight ratio provides a crude measure of adaptive responses by the placenta in maximizing the extraction of nutrients from the mother in favour of the nutritionally-challenged fetus[111]. Studies among children and adults born at term in England[117-119] and Australia[120] revealed that both systolic and diastolic blood pressure were higher among individuals born relatively smaller in relation to their placental sizes. However, other studies have suggested otherwise[121,122]. This observed inconsistency might be related to different time points during gestation when these studies were conducted, evidence from animal studies suggest that fetuses exposed to undernutrition in the utero are affected differently if the experimental undernutrition is induced at different time points during gestation[123,124].

The relationship between maternal blood pressure on one hand and offspring`s birth weight and blood pressure on the other hand is an interesting area of study. One such study reported that ambulatory monitored blood pressure (AMBP) of the mother was inversely associated with the offspring birth weight[125].

It is possible that the low birth weight in offspring of hypertensive mothers is a result of placental dysfunction with uterine vasoconstriction and reduced nutrient supply to the fetus[111].Preeclampsia,which can be looked upon as a more extreme form of gestational hypertension,have also been strongly associated with a higher chance of low birth weight offspring[126] Studies among twins have shown that the twin with lowest birth weight had higher adult blood pressure as compared to the larger twin, this finding suggest the the role of developmental programming in hypertension[109].Interestingly,low birth weight has also been shown to increase risk of gestational hypertension in own later pregnancies[127].

Other possible mechanistic associations between fetal programming and adult hypertension include poor maternal weight gain during pregnancy[128-130], accelerated childhood growth as a result of post-natal catch up growth which amplifies programming adaptations that occurred in utero[131], activated fetal renin-angiotensin system related to intrauterine growth retardation[132], reduced number of nephrons due to retarded fetal growth resulting in increased intra-glomerular filtration pressure, glomerular injury and eventual glomerulosclerosis that set the stage for a vicious cycle of hypertension and progressive glomerular injury[133,134]. Other possible mechanisms involves the hypothalamic-pituitary-adrenal axis that might reset the blood pressure controlling mechanisms[135,136], reduced elastic recoil of the aorta[137-139] and a high resting heart rate due to increased sympathetic nervous system activity[140,141].

2.1.4.3.Type II Diabetes

Significant association between low birth weight and development of type 2 diabetes mellitus have been previously reported[6,54,142-145]. Studies among the Pima Indians have revealed an odds ratio of 3.8 for diabetes among men and women with birth weight less than 2.5 kg as compared to controls [146]. In the Health Professionals Study, [147] it was reported that after adjustment for body mass index, the odds ratio for development of diabetes in individuals born LBW (2.5 kg or less) was 1.9 as compared to a control group who weighed between 3.2-3.9 kg at birth. Other birth-related measures are also important in this aspect, for example, a study in Sweden showed that thinness at birth (measured as ponderal index) was a stronger factor than LBW in the association with developing type 2 diabetes mellitus[144], also low birth height was found to be associated with higher levels of HbA1C in Jamaican children[144].

The common denominator underlying the pathogenesis of type 2 diabetes mellitus and indeed other components of metabolic syndrome like obesity, hypertension and hyperlipidaemia seem to be both the deficiency of insulin production and insulin resistance[148]. Barker et al found that the metabolic syndrome (defined by impaired glucose tolerance, hypertension and raised serum lipids) was more common in men and women with low birth weight[149]. In a study among different ethnic groups (Mexican-Americans and non-Hispanic whites in Texas, USA), a higher prevalence of insulin resistance was found among those born with lower birth weight in both ethnicities[150]. Furthermore, studies conducted among participants of different age groups in different populations have revealed higher plasma insulin concentrations among those born low birth weight [151-153]. Further evidence for the association between low birth weight and insulin resistance has been reported in a previous study in which both men and women who suffered undernutrition in utero during the Dutch famine were found to have higher mean 2h-plasma glucose concentration than those born before or conceived after that famine period [8].

The mechanistic explanation linking low birth weight to development of insulin resistance are uncertain but probably involves developmental programming and risk of obesity discussed above[148]. It is also possible that when faced with undernutrition in utero, the fetus adaptively reduces the metabolic dependence to glucose and rely on oxidation of alternative substrates (amino acids, lactate etc.) for energy and growth, this glucose-sparing metabolism might lead to the insulin resistance that has been reported in childhood and that seems to persist to adulthood[111]. In one study, it was also reported that babies born SGA have fewer pancreatic β-cell mass than controls born appropriate for gestational age [154-160].

2.2 Human markers of intrauterine programming

To investigate the impact of developmental programming on later health in humans, it is not possible to actively underfeed or overfeed fetuses. Human studies on developmental programming must thus investigate LBW, SGA and preterm birth as accessible surrogate markers of adverse intra-uterine environment and investigate the effects of these on disease in later life [4]. One of the few exceptions is the Dutch famine that allowed for a deeper investigation of intrauterine programming due to maternal undernutrition. Most other studies must however use surrogate markers of intrauterine growth restriction and these will be presented below. It must however be mentioned that not all intrauterine adverse events will manifest as low birth weight or preterm birth and these parameters alone cannot fully capture all offspring at risk of developing diseases as a result of developmental programming[4].

2.2.1 Low birth weight (LBW)

LBW is universally defined as birth weight < 2500g, normal birth weight as birth weight between 2500-4000g and high birth weight and/or macrosomia to be birth weight >4000 or 4500g[116]. If we use 2500g as a cut-off value for LBW, the global incidence of LBW is 15% and varies widely between developed and developing countries, suggesting a high proportion of children worldwide that are potentially subjected to future effects of fetal programming and thus increased probability of developing non-communicable disease[18,116].

In general terms, birth weight is determined by two major processes; duration of gestation and intrauterine growth rate and therefore can be caused by multiple factors that reduce gestation period or retard intrauterine growth[161]. These may be genetic or constitutional factors (e,g infant gender and ethnicity, parental height and weight etc), demographic factors (e.g maternal age, socioeconomic status, marital status etc), obstetric factors (parity, prior abortion, inter-pregnancy interval, preterm birth, hypertensive disorders of pregnancy etc.), nutritional factors (maternal gestational weight gain, protein intake, vitamin and elemental supplementation etc.), factors related to maternal morbidity during pregnancy (malaria, recurrent UTIs, genital tract infections etc.), maternal exposure to toxic substances (cigarette smoking, alcohol consumption, narcotic addiction etc.) and factors associated with antenatal care (number of antenatal visits, quality of antenatal care etc.)[4,161]. The most important causes of LBW differ in different region of the world.

In the lower and middle income countries, LBW is largely due to maternal undernutrition, preterm delivery, multiple gestation and having LBW mothers [116]. In developed countries LBW is largely due to placental insufficiency related to intrauterine growth retardation, maternal gestational hypertension, pre-eclampsia/eclampsia, maternal/partner smoking and intrauterine infections (due to congenital rubella, cytomegalovirus etc.)[162].

Using the cut-off value of 2500g as a threshold for defining LBW, there is a wide disparity on prevalence of LBW in different populations across the world which may reflect inherent genetic and environmental differences within and between these populations. For example, using this cut-off, the prevalence of LBW in south Asia is very high, casting doubt as to whether this is related to true growth restriction in utero or a shift in the normal population birth weight distribution curve [4].Adult body weight and height are also lower in Asian populations than in European populations[163,164].

LBW can also be defined as birth weight below the 10th percentile population-and-gender specific birth weight distribution curves, this definition may be epidemiologically more correct as it takes into account the fact that the effects of developmental programming have been observed to occur in a dose-response manner across a range of birth weight rather than being confined to either side of the cut-off value[165]. For example in the Norwegian population, the gender-specific birth weight below 10th percentile corresponds to weight below 2.87 kg for male and below 2.80 kg for female, but if the 2500g threshold is used in the same population the incidence of LBW drops to only 3.3% which may not include all neonates at risk of the effects of LBW in that population[166].

2.2.2 Small for gestational age (SGA)

SGA refers to fetuses or neonates whose bodyweight and/or crown-heel length is less than expected for their gestational age and gender[167,168]. Unlike birth weight, gestational age and body length at birth are not routinely recorded in many national birth registry databases. This has made it difficult to measure prevalence of SGA on a global basis and numbers range from 2.3 to 10% of all infants born worldwide[168-170]. In its broader definition, the term SGA may be subclassified further to encompass SGA with low birth weight, SGA with low birth length and SGA with both low birth weight and length[171].

Some of the potential causes for SGA include maternal disease (e.g. preeclampsia, gestational hypertension, severe chronic infections,etc), maternal social conditions (e.g. malnutrition, low pregnancy BMI and low weight gain, smoking, alcohol, low social economic status etc.), fetal problems (multiple births, intrauterine infections, malformations etc.), environmental problems (high altitude, toxic substances etc.) and placental abnormalities (infarcts, hematomas, partial abruption etc.)[172]. Intrauterine growth retardation (IUGR) and SGA have been used interchangeably. However, IUGR refers to a specific underlying mechanism that deter the fetus from growing to its expected dimensions which may not necessarily lead to SGA, and conversely, not all SGA neonates have suffered IUGR in utero[171].

SGA is associated with increased mortality and morbidity in the perinatal period due to respiratory complications, hypotension, hypoglycaemia and neonatal death[173,174]. During childhood, SGA is associated with delayed cognitive development, neurological impairment and learning disabilities[175,176]. During adolescence, studies have shown associations between being born SGA and risk of type 2 diabetes mellitus, renal insufficiency and impaired reproductive function [177-179]. In relation to the fetal programming, SGA has been associated with increased risk for developing ischemic heart disease[180], insulin resistance[155,181,182], type 2 diabetes[183] and development of metabolic syndrome[184] in adulthood.

As noted above, birth weight, birth length and accurate gestation age records are required parameters to create population-specific distribution curves for SGA. Due to incomplete or inaccurate data on birth length and gestational age (estimated by fetal ultrasound assessment or date of the last menstrual period in the mother), only a few countries in the world have established reliable standard SGA growth curves for the whole population[185,186]. In Norway, these are based on birth weight, gestational age, plurality and gender and thus offers a possibility for classifying offsprings into SGA, appropriate for gestational age, and large for gestational age[186]. New Zealand has improved the growth curves further by factoring in other variables known to affect birth weight such as ethnicity, parity, maternal height and weight in early pregnancy and gender of the baby to create customized growth curves and birth weight percentiles that correlate with individual`s Apgar scores, neonatal morphometry indices and adverse gestation events than the basic standard population-based charts[187-193].

2.2.3 Preterm Birth

Preterm birth (also termed as premature birth) is defined as birth before 37th weeks of gestation[116]. In the Unites States alone, over 500,000 preterm babies were born in the year 2008 (equivalent to 12.3% of all live births) and is regarded as a leading cause of infant mortality and morbidity[194]. Traditional risk factors for preterm birth include pre-eclampsia, multiple pregnancy, gestational diabetes mellitus, premature rupture of membranes, placental dysfunction, uterine/cervical dysfunction, fetal malformation or injury etc[195]. Up to half of all deliveries before 30 weeks of gestation may be explained by maternal inflammation or infection states[196].

Dalzier reported increase in hypertension, systolic blood pressure and insulin resistance among those born preterm[197]. Also, studies conducted among infants born before 32nd week of gestation report increased risk of cardiac complications, independent of birth weight, as compared to infants born at term. In relation to adult disease, Bassareo has reported a significant prolongation of QT intervals in the ECG tracings of ex-preterm infants born 20 to 30 years earlier[99].

However, as compared to LBW and SGA, the role of premature birth in fetal programming has been controversial and inconclusive[197]. This could at least in part, be related to selection bias due to the historical poor survival rates for infants born before 30 weeks of gestation that existed 20 years ago [194]. During this period, advances in medical interventions have dramatically improved fetal and neonatal survival for infants born at 28 weeks or earlier, rendering the cut-off of 37 weeks used in most of the previous studies barely mildly preterm by today`s standards[194]. Nowadays, a substantial proportion of infants born between gestational weeks 23 and 28 (extremely preterm) survives and thus increasingly constitute the new preterm birth study population in most of the recent epidemiological studies[198]. This improvement in survival of preterm population might explain the different strengths in the association between preterm birth and developmental programming that is observed among studies conducted over the last 20 years or so. It is however clear that many preterm birth infants also will have low birth weight and epidemiological studies will always have problems dissecting the relative importance of these two closely related variables.

2.2.4 Other markers of fetal programming.

In addition to the traditional markers of fetal programming (LBW,SGA and preterm birth) discussed above and summarized in Figure 3 below, other parameters of infant body proportion such as thinness, shortness, small trunk at birth and others may represent differing fetal adaptations to undernutrition, hypoxia and other influences and have been shown to associate with long-term consequences to health and disease in adulthood[16]. As these have not been investigated in the present thesis, we refer to previous studies for a more thorough discussion on these markers in relation to fetal programming, e.g. ponderal index (birth weight/length^3)[100], crown-heel length[100], head circumference[100], placental weight/ birth weight[11] and mid upper arm circumference (MUAC)[199] are some of the commonly used parameters in literature.

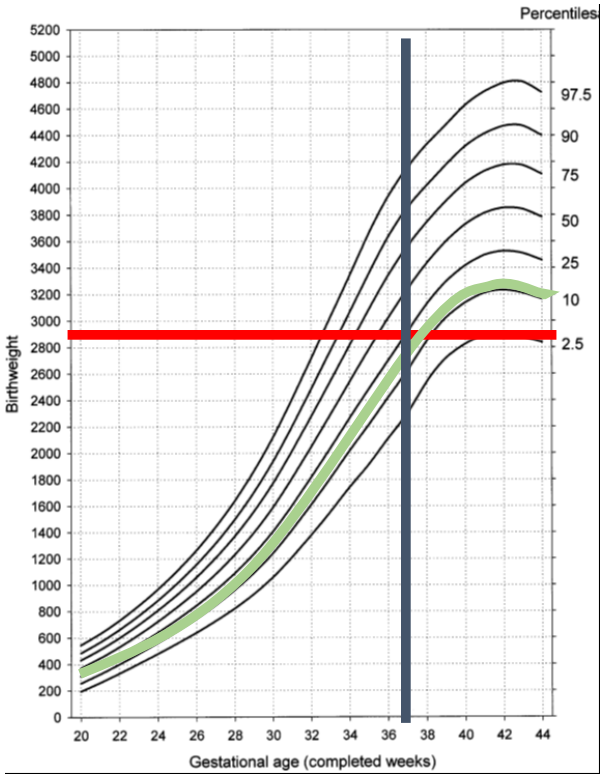

Fig 3; Summarized figure depicting thresholds for LBW (red), SGA (green) and Preterm birth (grey).

NB: LBW cut-off and SGA distribution applicable for Norwegian Population.

2.3 Developmental programming in kidney disease

2.3.1 Brenner`s hypothesis

In the late 1980s, after noting the association between LBW and hypertension, Brenner and co-workers suggested that a developmentally programmed deficit in nephron number could explain why some individuals had increased susceptibility to development of hypertension and renal disease[200]. They postulated that LBW individuals had less nephron endowment and hence reduced effective glomerular surface area for excretion of the sodium load. According to the acknowledged Guyton theories, sodium retention is considered an important cause of higher blood pressure[201]. Consequently,this could lead to a vicious cycle of elevated blood pressure, accelerated glomerular injury, progressive sclerosis and eventual nephron loss (Figure 4). The Brenner hypothesis has since been supported by numerous observational, experimental and glomerular histomorphometric studies around the globe and has stimulated tremendous interest in investigating further the association between birth weight, nephron number, hypertension and progressive kidney disease[202-207].

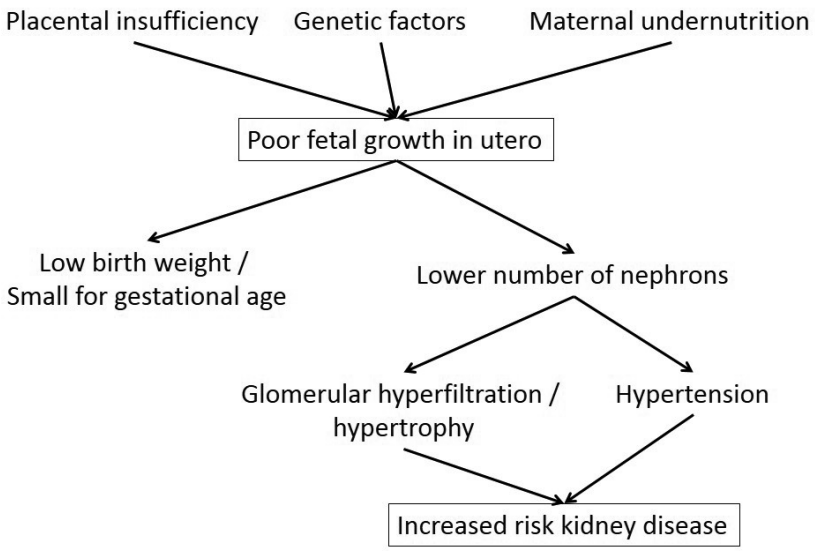

Figure 4. Overview of Brenner hypothesis

Nephron numbers has been estimated to range between 900,000 and 1,000,000 per kidney but recent studies using modern counting techniques suggest a more than tenfold variation in total number of nephrons among adult individuals[208,209]. In the largest autopsy study carried out so far, Bertram et al found that among African Americans the number of nephrons per kidney ranged from 210,332 to 2,702,079 (almost 13 fold variation) as compared to a range from 227,327 to 1,660,232 (more than 7 fold variation) among Caucasians[209]. Similarly, among white infants who died before 3 months of age in Australia, the number of nephrons ranged from 241,181 to 1,106,062 (more than 4.5 fold variation) which implies that the variation in nephron number observed in adults may have been established well before birth[210].

2.3.2 Exploration of Brenner`s hypothesis

The number of nephrons in both children and adults correlates linearly with birth weight and a stereological study has estimated that for every 1kg increase in birth weight ,there are 257,426 more nephrons per kidney[211]. It has been shown that nephrogenesis is completed in utero at around 36th week of gestation for infants born at term and that no more nephrons are formed after this point[212]. The total number of nephrons per kidney in an adult individual therefore reflects the number of nephrons at birth minus nephrons lost as a result of cumulative lifetime insults to the nephrons[18]. One clinical implication for the observed wide range of nephrons endowment in a given population is that for any two individuals with comparable clinical attributes but belonging to extreme ends of the nephron number scale, a loss of similar number of functioning nephrons could mean the individual with fewer nephrons would loose a higher proportion of the remaining nephrons than the one with more nephrons and consequently progress faster towards kidney failure [213,214].

Birth weight (including SGA) and prematurity are crude surrogate markers for adverse intra-uterine conditions[4]. In a population registry study in Norway, Vikse et al found that the relative risk for development of ESRD was 1.7 for those born LBW and 1.5 for those born SGA as compared to NBW and AGA individuals respectively[5]. In the south-eastern United States, a region with high rates of ESRD among ethnic African Americans, both black and white individuals born LBW had increased risk for development of ESRD (odds ratio of 1.4), a finding that was true for both genders and for all causes of ESRD[215,216]. In the

same region however, stereological studies have suggested that low nephron number and possibly LBW might play a role in the development of hypertension among white subjects but not among African Americans, this may be related to the proposition that while having low nephron number could contribute to development of essential hypertension, other factors (such as plasma renin levels) may be play a dominant role in maintaining of the normal and elevated blood pressure[211]. In the Northern Territory of Australia, a region inhabited by indigenous Australians (predominantly Aborigines) where both the rates of LBW and ESRD are high, a previous study has shown that among 317 adults (35% with LBW), odds ratio for overt albuminuria was 2.82 among LBW individuals as compared to controls with higher birth weight[217].

Small for gestation age (SGA) is more indicative of underlying intra-uterine growth retardation than LBW as the latter also may result from preterm birth. A previous study investigated the independent effect of SGA on kidney volume (a surrogate marker for nephron number) and it was found that mean kidney volume for individuals born SGA was significantly less than controls born appropriate for gestational age (AGA) [207,218,219]. In Denmark a study reported that SGA was associated with small kidneys at birth and impaired kidney growth in early childhood[220].

Among infants born preterm, abnormal nephrogenesis has been reported to continue up to 40th day post-delivery [221]. This phenomenon is especially observed among preterm infants who had growth restriction in utero but thereafter had improved postnatal nutrition or received appropriate postnatal pharmacological intervention[222]. Unlike LBW and SGA, isolated preterm birth has shown inconsistent association with renal insuffiency, however this association gets stronger when the analysis involves babies born very preterm birth (i.e birth before 32nd week of gestation) who are often very low birth weight as well[223].

2.3.3 Surrogate markers of nephron mass

Manual counting of exact number of glomeruli in the kidney can only be achieved ex-vivo (i.e using autopsied kidneys) by employing labour intensive and time-consuming stereological techniques[203]. In addition to the birth weight related parameters (LBW, SGA and preterm birth) that have been reviewed above [42,221,224], ultrasonographic parameters (low kidney mass, low kidney volume)[207,210,220,225], histomorphometric parameters (glomerular density and glomerular volume)[224] have all been correlated with the number of glomeruli (Nglom) and are thus variably used as surrogate markers of nephron number in different studies.

2.3.3.1 Renal Mass and Renal Volume

Kidney weight has a direct correlation with Nglom but both parameters can only be measured ex-vivo. However, kidney volume can be measured by ultrasonography in utero and varies directly proportional to kidney weight. Kidney volume can thus be used as a proxy for renal mass in estimating Nglom in vivo[218]. A previous study among aboriginal babies showed that kidney sizes among children born LBW or SGA were consistently less compared to kidney sizes among controls born NBW or AGA[207]. However,the major limitation for this association is that ultrasound measurements cannot make a distinction between pathological hypertrophy and normal growth of the kidney with age and this can potentially confound the interpretation[203].

2.3.3.2 Glomerular Density and Glomerular Volume

Glomerular density(GD) is a measure of number of glomeruli per unit area of renal cortex and glomerular volume (GV) is a calculated measure of glomerular size that is derived from the glomerular tuft area (GA) after incorporating several mathematical assumptions[226]. Keller reported a significant reduction in number of nephrons and increase in glomerular volume among white patients with primary hypertension[227]. In support of developmental programming, a glomerular histomorphometric study among dead neonates in Cuba showed that compared to normal birth weight controls, LBW neonates had a significant 12.2% lower glomerular density and a 2.3 fold larger glomerular volume[224].

2.3.3.3 Genetic polymorphisms

The search for genetic factors that influence the number of nephrons during kidney development in utero is an emerging field of interest in renal programming. Genetic studies have described a 10% decline in kidney volume among normal newborn with gene mutations for PAX2 haplotype and RET (genes that are involved in branching of the ureteric bud during nephrogenesis in utero) consistent with subtle renal hypoplasia [210,228]. It is however,still uncertain how these genetic polymorphisms associate with adult renal disease.

2.4 IgA Nephropathy

2.4.1 Epidemiology of IgA nephropathy

IgA nephropathy was first described in 1968 by Berger and Hinglais [229]. It is regarded as the most common primary glomerulonephritis in the world[230,231]. Primary IgAN can occur at any age but peak incidence is mostly reported to be in the second or third decade of life[232-234]. The male to female ratio varies considerably ranging from 2:1 in Asia to 6:1 in northen Europe and the US[235]. By race,primary IgAN is more common among whites and Asians and less common in people of African origin[236,237]. Among indigineous populations, prevalence of primary IgAN is reported to be high among Native Americans from New Mexico[238] and Australian Aborigines[239] but less prevalent among Polynesians from New Zealand[240].

Prevalence rates for primary IgAN (expressed as a proportion of cases with primary glomerulonephritis) are highest in Asia and much lower in the western world probably reflecting varying thresholds and indications for local nephrologists in performing kidney biopsies.In Japan for example,screening for urinary abnormalities is done routinely for all school-aged children, and therefore nephrologists are more likely to require a kidney biopsy and diagnose symptom-free IgAN patients than in Europe an the US where a biopsy would often be reserved for worsening proteinuria,hematuria or renal function [241]. Varying genetic differences could also explain the observed inter and intra-regional differences in prevalence of IgAN. Several previous studies have reported familial clustering of IgAN.[235,242].

2.4.2 Pathophysiological mechanisms of development and progression of IgA nephropathy

IgAN is uniquely defined by immunohistochemical findings (light microscopy is not diagnostic) and is characterized by predominance of diffuse IgA deposits in the glomerular mesangium which may be accompanied by co-deposits of C3,IgG or less commonly IgM[231]. Frequently detected accompanying complement abnormalities include; Complement C3,properdin, C4 or C4d, C5b-C9 terminal complement complex and mannose-binding lectin whereas C1q is usually absent[231]. Light microscopic features vary greatly and may include increased mesangial hypercellularity, focal necrosis and segmental scarring and variably,crescents in the Bowman`s space[231,235]. Electron ultrastructure shows electron-dense deposits corresponding to immune deposits seen in immunofluorescence and focal thinning of the glomerular basement membrane [231,235].

The pathogenesis of IgAN has been shown to be a result of multiple factors(multihit) and is systemic in nature[243]. The mechanism of injury in IgAN is orchestrated by abnormal glycosylation pattern of circulatory IgA1 that has a galactose deficiency in some carbohydrate side chain (o-glycans) that are attached to a hinge region segment of the heavy chain. These poorly galactosylated IgA1 results from an imbalance of relevant enzymes in IgA1 secreting cells in the mucosal tissue, altered homing of these cells between the mucosal and systemic compartments may allow mucosal cells to secrete poorly galactosylated (mucosal type- IgA1) into the circulation[244,245]. Due to galactose deficiency,the IgA1 hinge region neoepitope is exposed to the circulating naturally-occurring IgG or IgA1 antibodies and thus forming immune complexes in the circulation or in situ after glomerular deposition of galactose-deficient IgA1[246].This formation of immune complexes is essential for nephritogenicity of galactose-deficient IgA1.

Following this immune complex deposition,activated mesangial cells secrete components of the extracellular matrix that enhance release of various mediators of renal injury like angiotensin II and aldosterone[247], cytokines[247] and growth factors[248] which upon acting for some time induces formation of mesangial hypercellularity,complement activation,podocyte injury,increased glomerular permeability and glomerular and interstitial scarring[249,250]. Clinically,these lesions will eventually manifest as hypertension,proteinuria,hematuria and progressive renal dysfunction[249] . Henoch-Schonlein Purpura (HSP) nephritis and IgAN share many laboratory and pathological features on kidney biopsy prompting the suggestion that the two diseases represent systemic (HSP) vs renal (IgAN) manifestations of a single disease process[246]. Reported genetic risk factors of IgAN are mutations in the genes of the major histocompatibility complex (MHC) that might be distinct in different regions of the world, hence further explaining the varying IgAN prevalences observed among different ethnicities of the world[251,252].

2.4.3 Prognostic markers in IgA nephropathy

The search for clinical and pathological markers that can predict prognosis of IgAN is ongoing. IgAN patients have elevated serum levels of galactose-deficient IgA1 but due to low sensitivity and specificity of this marker in clinical practice, kidney biopsy remains necessary for definitive diagnosis of IgAN[246,253]. Serum levels of glycan-specific IgG correlates with proteinuria and risk of progression to ESRD[254,255].

Among IgAN patients,increased urinary excretion of several factors such as podocytes[256],epidermal growth factors and complement C3[257,258] and decreased serum levels of CD89-IgA complexes[259] correlate with severe histologic changes, however these changes are not limited to IgAN alone and therefore are non-pathognomonic. Using capillary electrophoresis and mass spectrometry ,proteomic analysis of urinary peptides have shown potential to distinguish IgAN from healthy controls[260,261]. However,neither of these are used in routine clinical practice as yet .

The clinical outcome of IgAN is variable and range from stable asymptomatic disease to progressive nephropathy and eventual ESRD[262]. A previous study in Norway has reported that age-and-sex adjusted mortality rate in IgAN patients was two times as high as compared to general Norwegian population[263]. Berthoux et al has published the prognostic absolute renal risk (ARR) score based on presence or absence of hypertension, proteinuria of > 1g/24 hrs and severe histopathological lesions[264]. Validating this ARR model in the Norwegian population, Knoop et al have shown that adding initial GFR and age to the model significantly improved the accuracy of the model in predicting risk of ESRD or death[265].

The Oxford classification for IgAN has suggested the standardized histopathological classification based on scores of glomeruli showing **M**esangial hypercellularity, **E**ndocapillary hypercellularity, **S**egmental sclerosis and percentage **T**ubular atrophy/interstitial fibrosis (abbreviated as MEST-score), with additional features including presence of cellular/fibrocellular crescents and arteriosclerosis score[266]. Of these, mesangial hypercellularity, segmental sclerosis and tubular atrophy/interstitial fibrosis have been shown to independently predict renal outcome whereas endocapillary hypercellularity predicts benefit from glucocorticoid/immunosuppressive therapy[246,267]. An updated review of 13 studies evaluating the Oxford classification showed has shown the independent prognostic value of tubular atrophy in 10 studies and for segmental sclerosis and mesangial hypercellularity in 4 studies each[266].

2.4.4 Studies of the Brenner hypothesis in IgA nephropathy

While the Brenners hypothesis linking congenital nephron deficit (due to intrauterine growth restriction) to future hypertension and progressive nephropathy is now an established paradigm as discussed above[200,268], little is still known about the applicability of this hypothesis in predicting the clinical course and

prognosis of ESRD due to specific glomerular diseases like IgAN. In a small study of children, intrauterine growth retardation (IUGR) was associated with higher rates of progressive IgAN by showing that children born IUGR had significantly higher percentage of sclerotic glomeruli and higher incidence of arterial hypertension than non-IUGR controls[269]. These findings may support the hypothesis that IUGR might be one of the non-immune mechanisms affecting the clinical course and prognosis of renal diseases.

Futher insight on Brenner hypothesis on IgAN may be gained by considering studies that have reported on morphological glomerular dimensions that have been reported to be surrogate markers of congenital nephron deficit. For example,Tsuboi et al showed that reduced glomerular density and enlarged glomeruli associated with progressive IgAN and suggested that reduced glomerular density in particular, could serve as an early marker for long term prognosis of in IgAN[270,271].

3.AIMS OF THE THESIS

I. To investigate whether familial factors explain the association between LBW and ESRD.

II. To investigate whether being born LBW and/or SGA predict progression to ESRD in IgA nephropathy.

III. To investigate whether LBW and/or SGA in young adult IgAN patients with preserved renal function associate with altered glomerular histomorphometry.

4. MATERIALS AND METHODS

4.1 Registries

4.1.1. The Medical Birth Registry of Norway (MBR)

Since 1967, the Medical Birth Registry (MBR) of Norway has registered extensive medical data on all births in Norway (total population of 5.1 million)[272]. The notification form includes extensive data on maternal health and newborn birth details and is completed by the attending midwife or doctor immediately after birth. For studies in this thesis, data from the MBR were available through December 2009 for Paper I and through December 2013 for Papers II and III.

4.1.2. The Norwegian Population Registry (NPR)

The Norwegian Population Register records administrative tax data for all registered residents in Norway and contains maternal and paternal national identification numbers for almost all individuals born in Norway since 1953. By use of data from this registry, it was possible to identify siblings defined as individuals with the same mother and father for Paper I[166].

4.1.3. The Norwegian Renal Registry (NRR)

All patients in Norway developing ESRD (defined as starting maintenance haemodialysis or undergoing renal transplantation) have been registered in the Norwegian Renal Registry since 1980. The treating nephrologists report all patients to the registry and is considered to be virtually complete. For Paper I, data were available through December 2009 and for Papers II and III, through December 2013.

4.1.4.The Norwegian Kidney Biopsy Registry (NKBR)

The Norwegian Kidney Biopsy Registry has registered clinical and morphologic data for all patients who have had a kidney biopsy performed in Norway since 1988. For use in Paper II and III, data was available through December 2013.

4.1.5. The National Cause of Death Registry

The National Cause of Death Registry comprises data on all deaths. Data were available through December 2009 for Paper I and December 2013 for Paper II and III.

4.1.6.Data Linking

Data from the registries were linked using an 11-digit national personal identification number which is unique for each individual in Norway .

4.2 Summary of Methods

4.2.1 Summary of Methods paper I

In Paper I, all individuals registered in the MBR from 1967 to 2009 who had at least one sibling registered in the MBR during the same period were included. We excluded individuals with no siblings, with seven or more siblings, those who either themselves or at least one of their siblings were a result of a multiple gestation and those who died before the year 1980. We defined siblings as individuals born from the the same mother and father.

Exposure variables were; (1) LBW defined as birth weight less than 10^{th} percentile specific for gender (corresponding to cut-off value of 2.87kg for male and 2.80kg for female); (2) SGA defined as birth weight birth weight less than 10^{th} percentile for gestational age specific for gender using a previously published gender-specific weight for gestational age reference values in Norway[186] and (3) Preterm birth defined as birth before 37^{th} week of gestation.

Outcome variable was development of end-stage renal disease (ESRD), and onset was defined as the date of starting dialysis treatment or undergoing renal transplantation. Subjects who did not develop ESRD were followed until December 2009 or up to date of death.

Data were analyzed in a cohort design. Hazard ratio (HR) estimates were obtained by Cox regression statistics, start of follow-up was set at the date of birth. LBW of the included subject and/or at least one of its siblings was the main explanatory variable, but risk estimates associated with SGA and Preterm Birth of the subject and/or at least one of its siblings were also analysed. Because no cases with ESRD had been registered between 1967 and 1979,we used the counting process formulation of proportional hazards (Cox regression).

4.2.2 Summary of Methods paper II

For Paper II study participants were individuals born in Norway and registered in the MBR who had a diagnosis of IgA Nephropathy (IgAN) as registered in the National Kidney Biopsy Registry (NKBR).

Exposure variable were; (1) LBW defined as birth weight less than the 10^{th} percentile specific for gender (i.e 2.93 kg for male and 2.80 kg for female), different birthweight cut-offs were also tested for different gender; (2) SGA defined based on national data on birth weight, gestational week, gender and plurality, a z-score denoting standard deviation from mean of birth weight for each week of gestational age as in Study I but different cut-offs were used in order to define 10% of the study population with SGA.

Outcome variable was development of end-stage renal disease (ESRD), and onset was defined as the date of starting dialysis treatment or undergoing renal transplantation. Subjects who did not develop ESRD were followed until December 2013 (censoring data for death were not available for Paper II).

Data were analysed in a cohort design and HR estimates were obtained by Cox regression analyses. Analyses were performed for the total cohort, but also separately for male and female. Associations between birth weight variables ,clinical and histopathological variables at time of biopsy were investigated. Due to low number of endpoints, we chose to only perform adjusted analyses for eGFR.

4.2.3 Summary of Methods paper III

We selected cases and controls from patients registered in the described registries. Eligible patients had registered birth weight, eGFR >60 ml/min/1.73m^2 at time of biopsy and did not develop ESRD during follow-up. From these eligible patients, we selected 5 groups of patients:(1) 20 patients randomly selected out of the 230 eligible patients registered in the Kidney Biopsy Registry with a diagnosis of IgAN and who were neither LBW nor SGA, (2) all 13 patients with LBW but not SGA, (3) all 15 patients with SGA but not LBW and (4) all 14 patients with both LBW and SGA. As some of the selected patients did not have available kidney biopsy tissue, we were able to include 18, 11, 10 and 12 case patients in these respective groups. In addition, (5) we selected 20 patients who were neither LBW nor SGA, had normal findings on kidney biopsy (biopsy was indicated for proteinuria or haematuria) and had eGFR >60 ml/min/1.73m^2 as

normal controls; this control group was age-and-sex matched with the group of IgAN cases without LBW or SGA.

Exposure variables were LBW, SGA and preterm births as defined for Paper II and outcome variables were glomerular histopathological (using MEST score as per Oxford classification on IgAN) and histomorphometric parameters (mainly glomerular density,diameter,area, and volume). Glomerular Density (GD) was determined as a ratio of number of glomeruli per cortical area in that profile. Glomerular tuft area (GA) was determined as the area enclosed within the perimeter of the capillary tuft. Glomerular volume (GV) was mathematically derived from the measured GA by applying the formula $GV= (GA)^{3/2}x\ \beta /d$, where $\beta =1.38$ and $d=1.01$[273,274, 275].

Data were analysed in a case-control design. In the main analysis, outcome variables were compared between the four IgAN sub-groups described above but due to few differences, in further analyses all groups with LBW and/or SGA were combined. Futhermore, IgAN patients without LBW or SGA were compared to controls with normal kidney biopsies. Continuous variables were compared using student t-tests while categorical variables were compared using Chi-square tests. Linear regression statistics were used to determine the association between glomerular volume and birth weight-related variables, clinical and histopathological variables.

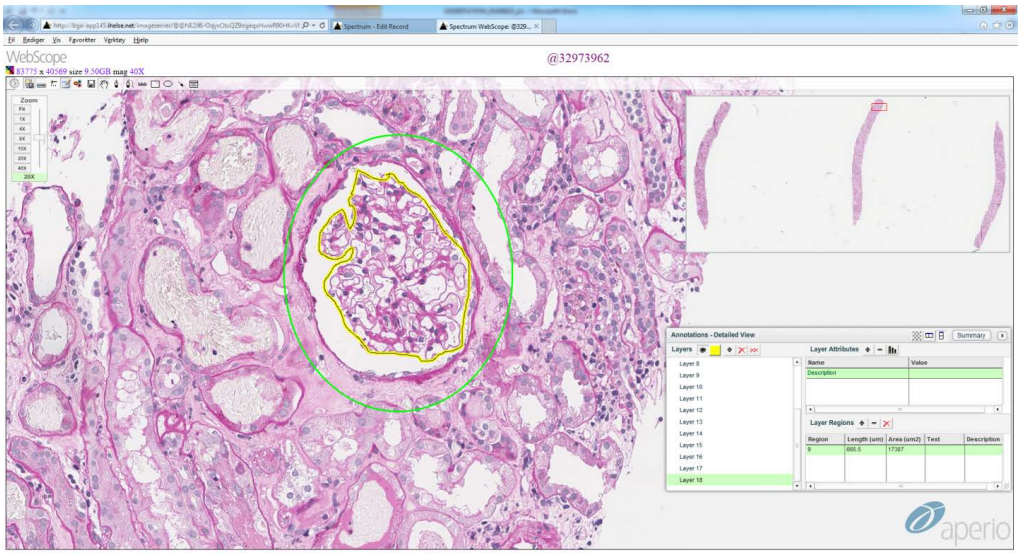

Figure 5; Webscope digital scan showing glomerular tuft area (GA) (yellow annotation). Glomerular volume was calcutated from this GA as described in the Methods Section (Courtesy: Sabine Leh)

5 SUMMARY OF MAIN RESULTS

5.1 Summary of results – Paper I

For our study described in Paper I, a total of 1,852,080 individuals were included out of whom 527 developed ESRD during follow-up. By definition, 10% of the included individuals had LBW, and 13.5% of the included individuals had at least 1 sibling with LBW; respective numbers for SGA were 9.8% and 13.1%. Mean number of siblings was 1.7 ± 1.0, and mean duration of follow-up was 20.9 ± 12.0 (maximum, 42.1) years. Compared to individuals without LBW and with no siblings with LBW, individuals without LBW but with a sibling with LBW had an HR for ESRD of 1.20 (95% CI, 0.91-1.59), individuals with LBW but no siblings with LBW had an HR of 1.59 (95% CI, 1.18-2.14), and individuals with LBW and a sibling with LBW had an HR of 1.78 (95% CI, 1.26-2.53). Similar results were observed for individuals who were small for gestational age (SGA). When analyses for LBW and SGA were repeated in term births, being LBW was associated with an HR of 1.56 (95% CI, 1.18-2.07) and SGA was associated with an HR of 1.64 (95% CI, 1.30-2.07). A separate analyses for non-congenital causes of ESRD and for ESRD in the different age groups (less than or more than 18 years of age) showed that SGA was a stronger factor than LBW in development of ESRD due to non-congenital causes and among those aged 18 years or more (adults).

LBW was associated with a similar HR for developing ESRD in both males and females. Analyses adjusted for birth year, sex, maternal disease, maternal preeclampsia, and number of recorded siblings showed virtually identical results. In a separate analysis using 2.5 kg as a cut-off for defining LBW, LBW was associated with a HR of 2.25 (95% CI, 1.59-3.19) and a dose response pattern was observed when we separately analyzed by decremental birth weight in the individual and/or sibling(s). Compared to individuals born at term who were not SGA, individuals born preterm and not SGA had an HR for ESRD of 1.09 (95% CI, 0.69-1.73), individuals born at term with SGA had an HR of 1.54 (95% CI, 1.20-1.96), and individuals born with SGA and preterm had the highest risk for developing ESRD with an HR of 4.03 (95% CI, 2.08-7.80).

5.2 Summary of results – Paper II

For our study described in Paper II, a total of 471 IgAN patients (70.8% males) were included of whom 74 (15.7%) developed ESRD. Mean age at biopsy was 23.8±7.7 years and mean duration of follow-up after biopsy was 10.3±6.7 years.

At the time of kidney biopsy, there was no difference observed between IgAN patients born LBW or SGA and those without LBW in terms of clinicopathological characteristics for the total cohort. Male IgAN patients born LBW or SGA did however have higher systolic blood pressure (132 mmHg vs 123 mmHg, p-value < 0.001) and higher diastolic blood pressure (80 mmHg vs 76 mmHg, p-value 0.01) than male patients born without LBW or SGA; this was not significant for females.

Compared to patients with birth weight above the 10th percentile, LBW was significantly associated with higher risk of developing ESRD, HR 2.0 (95% CI 1.1–3.7; p = 0.03). Similarly, SGA was also significantly associated with development of ESRD; HR 2.2 (1.2–4.2); p = 0.02. When the analyses were done separately for male and female patients, both SGA and LBW remained statistically significant predictors of ESRD in males, but not females. After adjustments for eGFR, neither LBW nor SGA were significantly associated with increased risk for ESRD.

To explore these associations further, we analyzed for risk of developing ESRD by decremental birth weights and decremental percentiles of birth weight for gestational age using 25th, 20th, 15th, 10th and 7.5th percentile cut-off thresholds. In these analyses, a dose-response relationship was observed. Analysis using a cut-off of 2.5 kg was not significantly associated with increased risk for ESRD, however this analysis was limited by the low number of patients as only 20 patients had birth weight less than 2.5 kg, of whom only 3 developed ESRD. Interestingly, IgAN patients who were both LBW and SGA had an especially increased risk of ESRD than those born with only SGA or LBW,thus patients with only one marker did not have a statistically significant increased risk for developing ESRD.

5.3 Summary of results – Paper III

A total of 51 patients with IgAN were included in the study, of these 24 (47.1%) were males. We included the following sub-groups of IgAN patients; 18 IgAN patients without LBW or SGA (IgAN controls),11 IgAN patients with LBW but not SGA, 10 IgAN patients with SGA but not LBW and 12 IgAN patients with both LBW and SGA. Mean age at biopsy was 23.6 years and mean eGFR was 95.3 ml/min/1.73m^2. At the time of kidney biopsy, patients without LBW or SGA had comparable clinical characteristics to patients with LBW and/or SGA.

Glomerular size measurements as well as histopathological MEST-score for IgAN were similar between groups with either LBW and/or SGA and we therefore combined these groups in the main analyses. In histomorphometric analysis; as compared to IgAN patients without LBW or SGA, IgAN patients with LBW and/or SGA had larger glomerular area (16235±3744 vs 14036±3502 μm^2, p-value 0.04). Further analyses stratified by gender showed that glomerular area and glomerular volume were different only in males (17636±3285 vs 13346±2835 μm^2, p-value 0.04 and 3.24±0.88 μm^3 vs 2.14±0.68 vs, p-value 0.003) but not in females. Glomerular density was not different between groups. In a sensitivity analysis, we tested whether including only patients with 9 glomeruli or more [208] would change the results for glomerular volume but the findings were almost the same and still statistically significant.

To investigate whether development of IgAN altered glomerular morphometric measurements, we chose to compare results for IgAN patients without LBW and/or SGA (N=18) to a group of age-and-sex matched normal controls were also without LBW or SGA (N=19). There was no significant differences in birth weight-related parameters and glomerular histomorphometric characteristics observed between the two groups.

In linear regression analysis we showed inverse associations between glomerular volume and birth weight on one side and with z-score of birth weight for gestational age on the other side. After adjustments for gender, age and body weight at time of biopsy; birth weight, gestational age and history of maternal pre-eclampsia associated with glomerular volume.

6.DISCUSSION

6.1 Methodological discussion

6.1.1 Study design: Cohort study and Case-Control study

We conducted a retrospective-cohort study design for our Papers I and II based on linking data from established nationwide registries; Medical Birth Registry of Norway (MBR), Norwegian Population Registry, Norwegian Cause of Death Registry, Norwegian Renal Registry (NRR) and Norwegian Kidney Biopsy Registry (NKBR) as described above. Tracking individual information from all these registries is possible in Norway as every individual has an 11-digit personal number which uniquely identifies him/her and it is part of the mandatory information required in all formal documents and registries. By using statistical softwares it is therefore possible to link individual`s information from the MBR to the other appropriate registries as it will be recorded using the same personal number in all registries.

We therefore included individuals registered in the MBR since 1967 who had at least 1 sibling registered in the the same registry (siblings defined as individuals born from the same mother and father) in Paper I. We then followed up these individuals for development of ESRD. For Paper II, we included all patients diagnosed with IgAN in the NKBR since 1988 and who were born in Norway after 1967 and had their birth data registered in the MBR. Our first two studies with a retrospective cohort design (Paper I and II) involved a complete registration of clearly defined exposures (LBW, SGA and Preterm Birth), had a concrete outcome (ESRD) with long follow-up time (beyond 40 years from birth) had in our opinion a robust study design.

For Paper III, we conducted a case-control design. We first selected from patients with registered IgAN who had registered birth weight in the MBR, preserved renal function (i.e eGFR >60 ml/min/1.73m^2) and had not developed ESRD at the time of biopsy. We chose these criteria so as to minimize the potential confounding effect of advanced glomerulosclerosis and/or fibrosis at the time of biopsy to allow for investigation of a cohort who had not yet developed severe kidney damage (i.e low risk IgAN group). From these IgAN patients, we selected 4 subgroups of patients according to their LBW/SGA status combination. The selection of these four subgroups were chosen to investigate possible differential effects of LBW and

SGA that was observed in study II. We also selected a control group with normal finding on biopsy and without LBW and/or SGA (which was age-and-sex matched to the subgroup of IgAN patients without LBW or SGA).

6.1.2 Definitions and cut-off value for birth-weight related parameters

LBW was defined as birth weight less than the population and gender-specific 10th percentile. Using population and gender-specific birth weight distribution curves to define LBW as birth weight below the 10th percentile gender-specific birth weight may be epidemiologically more correct than using the global cut-off set at 2.5 kg as per WHO guidelines. The 10th percentile definition takes into account the fact that the effects of developmental programming occur across the range of birth weights in a dose-response manner and are not confined to either side of a fixed cut-off value[4]. There is a wide disparity on prevalence of LBW across different populations when the 2.5kg threshold is used to define LBW which may reflect both genetic and environmental differences between populations. For example in Paper I,using 10th percentile we defined LBW to be below 2.87 kg for male and below 2.80 kg for female in Norway which in both gender is higher than the global 2.5kg cut-off [166]. Had we used the 2.5kg cut-off in study 1,the prevalence of LBW in Norway would be 3.3% which is much less compared to the as global incidence for LBW reported to be about 15% [116]. For papers II and III, LBW was defined as birth weight less than the 10th percentile specific for gender in participants of study II (corresponding to 2.93 kg for males and 2.69 kg for females).

There is ongoing debate among researchers whether a globally standardized birth weight cut-offs should be adopted for different geographical populations or whether it is more appropriate to tailor the cut-offs for specific populations being studied as we did in our studies[4]. A practical issue is that if we apply strict definitions of LBW to our studies of the Norwegian population (were prevalence of LBW is relatively very low), the studies will be very difficult to interpret due to low number of subjects in subgroups. We defined SGA using gender specific standard curves worked out previously for the Norwegian population[186] but also here we used the 10th percentile for the z-score in the populations we investigated. Previous studies recommend that growth reference charts tailored to local populations predict accurate outcomes of SGA[276]. For preterm birth, we used a universal definition of birth at gestational age less than 37 weeks.

6.1.3 Renal histopathologic and histomorphometric data

For paper III, glomerular histomorphometric parameters (glomerular area,volume and density) were the primary outcomes, we also investigated on the association between histopathological changes and LBW/SGA. To standardize our reporting on histopathological changes, we adopted the MEST scoring system recommended by Oxford classification for IgA nephropathy which has identified four histological lesions as independent prognostic factors;**M**esangial hypercellularity , **E**ndocapillary hypercellularity , **S**egmental glomerulosclerosis and **T**ubular atrophy/interstitial fibrosis [266].

For histomorphometric evaluation, we used high resolution digital images on a computer screen using annotating pen-tool software (Spectrum^{TM}, Aperio Technologies.Inc) to demarcate each glomerulus, glomerular tuft areas and cortical areas.. Glomerular area (GA) was defined as an area bound by outer capillary loops of the glomerular tuft. Glomerular density (GD) was defined as the number of glomeruli per cortical area, and this was deduced for total number of glomeruli, for sclerosed glomeruli and non-sclerosed glomeruli.. For estimation of glomerular volume (GV) we used the Weibel-Gomez formula expressed as $GV=(GA)^{3/2}x\ \beta/d$; where GV=glomerular volume, GA= mean glomerular tuft area,β=1.38 (assuming glomerulus is spherical in shape) and d is a size distribution coefficient that is used to adjust for the variation in glomerular size, we used d=1.01 as adopted from other studies[271,274,275].

6.1.4 Effect modifications by other variables

We assessed the impact of reported effect modifiers on the association between LBW and ESRD in Paper I. Previous studies have reported birth year (age), gender[5] and number of siblings[277] as potential individual factors that may modify this association,but our main results were not affected after adjusting for these factors. However,we could not adjust for the type of infant milk feeding (whether breastfed or bottlefed), a previous study has associated bottle-milk infant feeding with increased risk of future hypertension[57,278]. We also adjusted for maternal pregestational disease conditions (diabetes mellitus, kidney disease, rheumatic disease or essential hypertension)[279], maternal preeclampsia[280] but could not adjust for maternal cigarette smoking which has been previously reported to be associated LBW offsprings[281], progressive kidney disease and paradoxically, reduced risk for maternal pre-eclampsia[282]. Further, In Paper II we adjusted the main outcome analysis for estimated GFR at the time of kidney biopsy. For Paper III we

adjusted the main analysis for gender,age and body weight at the time of kidney biopsy all of which could modify the association between LBW and progressive nephropathy. In general, unadjusted and adjusted analyses showed the similar findings.

6.1.5 Potential Study limitations

6.1.5.1 Study designs

As mentioned earlier, our first two studies were based on a robust retrospective-cohort study design with a relatively long follow-up time and based on firmly established registries with complete registration of exposure variables (birth weight related variables) and a concrete outcome endpoint (ESRD). However, ESRD is inherently a rare outcome and takes a long time to develop. For example in Paper I, only 0.03% of the included individuals developed ESRD despite a follow time of up to 42 years from birth, and in Paper II only 15.7% of the total IgAN cohort developed ESRD after up to an age of 46 years form birth. This low absolute risk of ESRD yielded numbers of patients adequate for investigation of risk factors for the main outcome, but was too few for reliable analyses of risk factors for specific causes of ESRD and yielded low number of patients with endpoints in some subgroups. Furthermore, the effect size among females in Study II may have been attenuated due to smaller sample size (type 2 statistical error).

6.1.5.2 Missing information

Due to non-availability of data on death in Paper II, we could not censor for death. Also, for the same paper, we did not have information regarding the treatment of IgAN patients which could potentially modify progression towards developing ESRD. However, this limitation may have been offset by the fact that most of IgAN patients in Norway are treated by nephrologists and therefore likely to have received standardized treatment according to international recommendations on management of IgAN, which included ACE-inhibition or angiotensin receptor blockade for those with either high blood pressure or proteinuria during the 1990`s and since the early 2000's steroid treatment have been increasingly used for those with proteinuria ≥1 gr/24h and preserved kidney function after a trial period with angiotensin.

6.1.5.3 Technical limitations

In our Paper III, we reported on glomerular volumes from kidney tissue specimens obtained from patients using percutaneous kidney biopsy needle as part of the routine clinical care. This method yields

only a limited sample of glomeruli as compared to stereological methods using the physical dissector/fractionator method which is considered as the gold standard. Such stereological methods e.g. Cavalieri, Weibel-Gomez, Maximal Planar Area or Dissector Principle are laborious, time consuming, costly and require the whole kidney tissue and are therefore of limited accessibility for routine studies. A previous study has illustrated that reliable mean estimates of GV can be obtained by measuring 9 or more glomeruli; in white patients, measuring fewer than 6 glomeruli reduced the precision [283]. For selection of patients in Paper III, even though some patients had fewer than 6 glomeruli, the GV estimates were statistically significant between groups. Further, results for glomerular volume were the same in a sensitivity analysis where only patients with 9 glomeruli or more were included. We would thus argue that in studies with limited number of available patients and tissue, accurate estimates of GV could also be obtained by measuring fewer glomeruli.

6.1.5.3 External validity /generalizability

Our studies are based on comprehensive and up-to-date national registries with complete national inclusion and registration of end points which makes the results highly generalizable and reproducible.The outcome (ESRD) in the first two studies is a concrete end point and an important clinical disease of public health importance which makes the study valid in many places in the world. However, the definition of LBW used in our studies for both genders is higher than the international threshold of 2.5 kg adopted by the WHO which is not specific for gender. We have argued above that this might be advisable. In our opinion, if our studies were to be replicated elsewhere, local population and gender specific birth weight and local birthweight for gestational age distribution curves to define SGA should preferrably be used. However,we reported that when we separately repeated our main analysis using the 2.5 kg cut off and different gender specific percentile cut offs (i.e 5^{th},15^{th} ,20^{th}) we obtained stronger effect estimates with a dose-response pattern in both instances, underscoring the validity of our findings and synchronicity with the international definition of LBW. Overall, we therefore believe that our findings can be applied to other populations but that the strengths of the associations might differ based on which cut-off is used.

The male/female ratio in IgAN is very variable across the world ranging from a balanced male to female ratio in the far east region to a stronger predilection towards male gender in northern Europe (about three-quarters of our IgAN cohort in Paper II were males). Therefore the lack of strength on the effect measures among females in Paper II may at least in part be attributed to the lack of statistical power (type 2 error) due to their smaller sample size compared to males,however,the persistence of male predominancy despite a fairly balanced gender ratio in our Paper III underscores the importance of investigating further the observed gender impact. A different trend might therefore be observed in places where the gender ratio is different.

6.2 Discussion of the Main Results

We found that after more than forty years of follow up, having been born LBW or SGA was associated with increased risk of developing ESRD, consistent with findings from similar previous studies. This increased risk was not modified if siblings had or did not have LBW and argues against familial contribution to the association. Of note,SGA was a more important risk marker than LBW for development of non-congential ESRD in adult age, underscoring the need for investigating SGA further in future studies. Among young IgAN patients, having LBW or SGA predicted progression towards ESRD and patients with both LBW and SGA had the highest risk. These associations were only significant in males and not in females. Furthermore, we found that at the time of diagnosis, IgAN patients born LBW and/or SGA had larger glomeruli, significant for total cohort and males, but not females. Additionally, GV was negatively correlated to GD. Summing up, all our findings are in support of the hypothesis that *in utero* programming of nephron deficit predisposes to progressive kidney disease in adult life as postulated by Brenner et al.

In our studies, we found that LBW and/or SGA were significantly associated with ESRD in the general population and in a specific cohort of young IgAN patients (significant in males). Birth weight related variables such LBW, SGA and preterm birth are well-studied surrogate markers of adverse in utero environment, in particular intrauterine undernutrition resulting from various maternal and fetal conditions[4]. Barker`s theory of developmental programming associates fetal growth restriction with increased risk of developing several chronic diseases conditions during adulthood[284]. Brenner further hypothesized that congenital nephron deficit programs future development of hypertension and progressive kidney disease [134]. Using birth weight as the most accessible surrogate marker of in-utero condition, stereological studies have established that birth weight is positively correlated with glomerular number/density and negatively correlated with glomerular size, the latter being suggested as a marker of compensation against progressive nephron loss[224]. These findings have been replicated for all-cause ESRD[211] and for specific causes such as hypertensive nephrosclerosis[216] and IgAN-associated ESRD[270].

We have shown that the association between LBW and ESRD in an individual is not modified by LBW in his/her siblings. Individuals who themselves were not LBW but who had a sibling with LBW had a non significantly increased HR of 1.20 (95% CI, 0.91-1.59), and identical analyses for SGA showed an HR of 1.00 (95% CI, 0.73-1.36). This finding which is backed up by a large sample size in our study (N=1,852,080, N with ESRD=527), shows that LBW and/or SGA in siblings does not affect risk of ESRD and thus genetic or environmental contributions to the association seem to be insignificant. We consider this finding from our first study to be very novel and important contribution to literature because to our knowledge, previous studies have not shown that LBW is associated with ESRD independent of confounding familial factors (shared genetic or environment factors) among siblings. Previous studies had shown that LBW, cardiovascular risk factors and chronic kidney diseases show clear aggregation in some families than others and this was thus an important hypothesis to test.

In our studies we report that SGA either alone or in combination with LBW is an important and independent risk factor for ESRD. Most of the previous studies have reported stronger association between LBW and ESRD[5,215,216]. For example in our Paper I, we showed that SGA and LBW were similarly associated with ESRD in the main analyses, but SGA was a stronger risk factor than LBW for developing ESRD in adult individuals (i.e those with 18 years or older) as well as for ESRD due to non-congenital and non-hereditary causes. Additionally, the effect of SGA was significantly stronger in those born preterm unlike the effect of LBW which was similar in both preterm or term birth subgroups. The effects of prenatal programming are expected to increase with age and therefore non-congenital ESRD in adult age should be regarded as a more clinically interesting outcome than all-cause ESRD.

Whereas LBW could be explained merely by short gestational age in many cases, SGA to a larger extent indicate presence of IUGR resulting from placental insufficiency or sub-optimal intrauterine nutrition. Therefore,our findings suggest that placental insufficiency, as indicated by SGA, might be an important explanatory factor for impaired nephron development, and that the effect might be especially important if born preterm. In addition, we reported in Paper II that patients born both LBW and SGA had much higher risk for developing IgAN-associated ESRD than those born only SGA or LBW, and that

patients with only one of the markers did not have a statistically significant increased risk for ESRD. While these findings can partly be explained by the synergistic effect of combined LBW and SGA on congenital nephron deficit and the low N's in subgroups, it is an interesting finding to investigate further in future studies. It it therefore important that future research work should strive to tease out the independent effect of LBW and SGA. Of immediate relevance it is possible that IgAN patients born with both LBW and SGA may need a closer clinical follow-up.

In our Paper II and and III, the effect measures were significant in males than females. Whereas the observed difference in gender in Paper II could be explained by the difference in sample sizes between gender (males comprised 70.8% of the total cohort) and hence prone to type II error, stronger effect among males persisted in Paper III in which males comprised less than half (47.1%) of the total cohort, therefore the gender difference deserves discussion and would be an interesting research area for future studies. The male:female ratio for prevalence of IgAN nephropathy varies widely across the world, being lowest (2:1) in the far east region and highest in northern Europe[285-287] (up to 6:1) where our study was conducted. The disparity in both the overall prevalence of IgAN is reported to be at least in part, influenced by the local nephrologist`s threshold for performing a kidney biopsy as well as the local laboratory capacity to perform immunohistochemistry or immunofluorescence which is required for accurate diagnosis of IgAN[288]. Previous studies however, have suggested that females may be protected against the detrimental effects of LBW on progressive renal disease[289-291] and against the impact of impaired intrauterine nephron endownment compared to males[94,292]. A few animal studies have reported that modest protein restriction to pregnant rats leads to hypertension in adult male but not female offsprings[94,95,293] , but other experimental manipulations like pharmacological suppression of RAS during development or surgical reduction of number of glomeruli at birth have reported no gender difference in programming of future hypertension[32,97,98].

In our papers II and and III, we reported that LBW and/or SGA were associated with progressive IgAN.. While literature is awash with studies reporting on the association between LBW and all-cause ESRD or ESRD due to hypertensive/diabetic nephropathy, only a few studies have reported on the

association between LBW and a specific-glomerular disease underlying the aetiology for ESRD. IgAN is the most frequently occurring primary idiopathic glomerulonephritis worldwide with large cohort of undiagnosed "latent" IgAN in the general population[231,285,294]. IgAN is a good model for a classic chronic glomerulonephritis that leads to chronic renal failure due to the following arguments; the clinical phenotype of IgAN ranges from stable and asymptomatic to chronic nephropathy with a high rate of progressive renal failure[246,295,296]and IgAN has peak incidence in the 2nd and 3rd decade of life (when patients have relatively fewer confounding comorbidities). Zidar et al[269] for example, reported higher mean percentage of sclerotic glomeruli among patients who suffered IUGR in utero. On the other hand, only a few studies have reported on the association between glomerular changes in specific glomerular diseases like IgAN consistent with congenital nephron deficit in support of the Brenner`s hypothesis[270,271]. Intrauterine nutritional deficiencies have been reported to also be associated with later chronic allergic and autoimmune diseases[297] and it is possible that LBW and/or SGA may be associated with a stronger immune response. In our opinion, evidence of increased immune response are however relatively weak and we have therefore chosen to interpret our findings of increased risk of progressive disease as an effect of lower number of functioning nephrons with decreased reserve capacity.

Using histomorphometry, we showed that at the time of biopsy, young IgAN patients born LBW and/or SGA have larger glomeruli compared to age and sex matched controls born without LBW or SGA who had normal kidney biopsy findings, the association being significant in males. Importantly, we found a positive dose-response correlation between birth weight and glomerular volume mirroring previous studies on the association between LBW and glomerular size and density[211,224]. However, we did not establish a significant association between LBW and reduced glomerular density as reported in those studies. Furthermore, previous studies by Tsuboi et al reported that large glomeruli represents compensatory mechanisms against renal function deterioration in progressive IgAN and reported a strong predictive relationship between low glomerular density and progressive IgAN [270,271]. Our study has thus served as a link between these studies by showing that larger glomeruli is a common denominator for both LBW/SGA as well as progressive IgAN. The fact that we were able to show a significant association between LBW and

glomerular volume in a cohort of young IgAN patients with preserved renal function (low risk group of IgAN patients) underscores the strength of our finding and calls for future studies to research more on this entity as well as the observed gender difference discussed earlier.

Brenner postulated that a nephron deficit would lead to large glomeruli with hyperfiltration that would increase risk of glomerular damage[298]. A previous study has reported higher mean percentage of sclerotic glomeruli among IgAN patients who had suffered intra-uterine growth retardation [269]. Further, Ikezumi et al reported association between LBW and development of focal segmental glomerulosclerosis in children and proposed that this was probably related to glomerular prematurity and podocytopenia [299]. In our paper, there were non-significant trends towards more glomerular sclerosis in those with low birth weight but the degree of glomerular sclerosis was mild in our study as we selected patients with preserved kidney function. In our opinion, our study supports the Brenner hypothesis that large glomeruli with hyperfiltration is a link between low birth weight (as a marker of congenital nephron deficit) and progressive kidney disease.

In summary, our studies have shown that LBW and/or SGA are associated with higher risk for all cause-ESRD independent of familial factors. We thus suggest that birth weight related variables (especially LBW and/or SGA) should be part of the medical history sought by clinicians when they evaluate, prognosticate and follow up patients with chronic kidney disease.

7. CONCLUSIONS AND PERSPECTIVES

Our overall findings are supporting the association between LBW and increased risk of progressive nephropathy as hypothesized by Brenner. Other studies have shown that the Barker hypothesis also holds. From a public health point of view, this suggests that efforts directed towards reducing LBW have the potential to reduce risk of adult renal and cardiovascular disease. These findings from the Norwegian population where the prevalences of LBW is relatively low (about 3.3% using the 2.5kg threshold to define LBW) might be even more important in other regions of the world where the LBW is more commonespecially in the the sub-saharan region where the prevalence of LBW is estimated to as high as 13-15% in the population . On the same note, LBW in countries like Tanzania is more likely to be due to maternal undernutrition as contrasted to Norway where intrauterine growth retardation due to placental insufficiency or maternal smoking for example, are the more likely causes. This could mean that cost-effective health interventions like optimal nutrition (in terms of quantity, quality and appropriate supplementation of nutrients) targeting women of child bearing age and pregnant women in countries like Tanzania would significantly reduce the prevelance of LBW and potentially reduce the incidence of future adult renal and cardiovascular disease in the community. We propose then that at a public health scale, it may be cost effective for governments in low and middle-income countries like Tanzania to give priority towards improving maternal and fetal nutrition as this might improve health of the pregnant mother, the infant as well as the growing child and adult. Such preventive measures could have larger effects and in the long run be cheaper than treatment of advanced cardiovascular and renal disease.

Additionally, small for gestational age (SGA) is an important birth weight parameter in its own right. We have shown that SGA was a better risk marker than LBW among adults as well as for non-congenital and non-hereditary causes of ESRD and that the risk of developing all cause-ESRD and IgAN-related ESRD was higher when LBW coexisted with SGA. Future studies should strive to tease out the independent impact of SGA as a risk factor for future ESRD.

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