Intrauterine growth restriction and risk of diverse forms of kidney disease during the first 50 years of life

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Abstract

Background and objectives: Previous studies have shown that individuals with low birth weight (LBW) or small for gestational age (SGA) have higher risk of kidney failure. The present study investigates birth related exposures and risk of chronic kidney disease and other kidney diagnoses.

Design, setting, participant and measurements: The Medical Birth Registry of Norway has registered extensive medical data on all births in Norway since 1967. The Norwegian Patient Registry has registered diagnostic codes for all admissions and outpatient visits to Norwegian hospitals since 2008. Data from these registries were linked, and risk of chronic kidney disease (CKD) and other groups of kidney disease were analyzed using logistic regression statistics. LBW (<10th percentile), SGA (birth weight <10th percentile for gestational age) and preterm birth (less than 37 weeks) were analyzed as exposures.

Results: A total of 2,663,010 individuals were included. After a mean follow-up of 26 years (max 50 years), 4495 had been diagnosed with CKD and 12,818 with other groups of kidney disease. LBW was associated with an odds ratio (OR) for CKD of 1.72 (1.60-1.90), SGA with an OR of 1.79 (1.65-1.94) and preterm birth with an OR of 1.48 (1.33-1.66). Analyses using diagnosis of chronic kidney disease at stage 3, 4 or 5 as endpoint showed similar results. Results were similar for men and women. We further analyzed adjusted (aOR) for other groups of kidney disease, and found that LBW was associated with an aOR of 1.44 (1.33-1.56) for acute kidney disease, 1.24 (1.14-1.36) for glomerulonephritis, 1.35 (1.17-1.56) for cystic kidney disease and 1.15 (1.06-1.25) for kidney disease due to kidney or urinary tract malformations.

Conclusions: LBW, SGA and preterm birth are associated with higher risk of CKD in the first 50 years of life. Risk of other groups of kidney disease was less pronounced.

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Introduction

In the 1980s, Brenner et al proposed that intrauterine growth restriction cause a low nephron number, which could predispose to hypertension and kidney disease through mechanisms of increased single-nephron glomerular filtration, compensatory nephron hypertrophy and decreased functional reserve [1]. Approximately 60% of the nephrons develop during the third trimester of pregnancy, and kidney development ends between 35 and 36 weeks of gestation[2]. Thus, preterm birth or impaired intrauterine growth may significantly impact the formation of nephrons and reduce nephron number[3].

Previous cohort studies have linked low birth weight and risk of severe kidney failure[4-7] and studies have also linked low birth weight with lower estimated glomerular filtration rate or urinary albumin[2,8-10]. This is believed to be related to lower numbers of nephrons and glomerular hypertrophy that has been shown in low birth weight individuals [3,11,12]. Recent studies have emphasized the interplay between markers of intrauterine growth such as LBW, SGA and prematurity and risk of kidney disease in adult life [2,13-15]. An important paper from the Low Birth Weight and Nephron Number Working Group argued that individuals with low birth weight should undergo screening and follow-up to detect kidney disease or risk factors for kidney disease at an early age[16]. Early detection of individuals at risk of kidney disease, as well as early referral to kidney units may slow disease progression, improve survival in patients with CKD and reduce total treatment cost [17].

There is a need for better data on the association between different markers of intrauterine growth restriction and risk of clinical kidney disease at an earlier stage than severe kidney failure. In this retrospective, register based nationwide cohort study we linked data from Norwegian registries to explore the association between birth related variables such as low birth weight, low birth weight for gestational age, preterm birth and risk of different groups of kidney disease during the first 50 years of life.

Materials and methods

Data sources

Since 1967, the Medical Birth Registry of Norway (MBR) has registered extensive medical data on all births in Norway. The Norwegian Patient registry (NPR) has registered ICD-10 diagnostic codes for all admissions and outpatient visits to Norwegian hospitals since 2008; in Norway most specialist care in the field of nephrology is hospital-based and the data is therefore almost complete for specialist care. ICD-10 codes were registered by the treating physicians. For the present study we obtained data from NPR for the period 2008-2016. Date of death was available from the Norwegian Population Registry. We linked these registries using the national identification number.

All individuals born in Norway between 1967 and 2015 were included. We excluded twins, triplets, quadruples (N= 76,429), individuals who died before age 1 year (N=17,146) and individuals who died before 2008 (N=16,417). Individuals who officially had emigrated from Norway were also excluded (N=80,332).

Birth related variables

LBW was defined as birth weight less than the 10th percentile for gender (2940 g for male, 2850 g for female). From 1967 through 1998, gestational age was based on the last menstrual period and from 1999 onward on routine ultrasonographic examination in gestational week 17 through 20. Based on birth weight, gestational age and gender, a z-score of birth weight for gestational age has been calculated for all single births. We defined SGA as birth weight less than the 10th percentile for gestational age and gender. Preterm birth was defined as birth before 37 weeks of pregnancy. Low birth weight less than 2500 grams was also analyzed as an exposure variable.

Maternal preeclampsia has been diagnosed according to the ACOG criteria [18,19]. For the present study, pre-gestational maternal disease was defined as a diagnosis of maternal diabetes mellitus, kidney disease, rheumatic disease or essential hypertension before pregnancy. Maternal marital status was dichotomized as either single or not single. Congenital malformations in the newborns had been recorded as present if any malformation had been observed before discharge from hospital; in the statistical analyses, a dichotomous variable was used.

Outcome variables

The data file from NPR included ICD-10 codes for each episode (admission or outpatient visit) with a kidney disease diagnosis (N01-N09, N17-N19, N25-29 or Q60-64). Of the 17,313 individuals with at least one episode with kidney disease, 6494 had one episode, 2377 had two episodes, 1465 had three episodes, 3934 had 4-9 episodes, 1751 had 10-19 episodes and 1295 had 20 episodes or

more (maximum 1370 episodes). Patients were diagnosed with different combinations and sequences of ICD10 codes. In the present study we analyze whether or not a diagnosis or group of diagnoses had been recorded at least one time.

The main outcome was defined as having been diagnosed with chronic kidney disease (ICD10 code N18) in at least one of the episodes (admissions or outpatient visits). Both main diagnoses and secondary diagnoses were included.

The secondary outcomes were having been diagnosed with different groups of kidney disease: acute kidney disease (N17), glomerular disease (N00-N09), cystic kidney disease (Q61) or kidney or urinary tract malformations (Q60, Q62-Q64). We also analyzed the secondary outcome of having been diagnosed with stage 3, 4 or 5 of kidney disease (these diagnoses were used in the registry for the time period 2010-2016).

Statistical analysis

In the statistical analyses, main and secondary outcomes were analyzed as either present or absent. Main exposure variables were LBW, SGA and preterm birth. Low birth weight < 2.5 kg, combinations of the main exposure variables and different cut-offs for birth weight and birth weight for gestational age were also analyzed. For the included participants, 0.1% had missing data on birth weight and 4.3% for gestational age and z-score. These participants were excluded from the respective analyses. Characteristics of different groups were compared using t-tests for continuous variables and Pearson's chi-square test for categorical variables. In the main analyses, logistic regression statistics was used to investigate the associations between exposure variables and the outcome of interest. In adjusted analyses we adjusted for gender, pre-gestational maternal disease, maternal marital status and congenital malformations recorded shortly after birth. In analyses focusing on the associations in adult age, only individuals born before 1990 were included.

In secondary analyses, we used left truncated Cox regression statistics to complement the logistic regression statistics. Exposure and outcome variables were the same as in the logistic regression analyses. Time until endpoint was age at first occurrence, time until right censoring was age at death or end of 2016. As we did not have data on outcomes until 2008, analyses were left-truncated for the time period until 2008.

A two–tailed probability value of < 0.05 was considered significant. All analyses were performed using STATA version 15.1 (Stata Corp, College Station, Texas).

Results

A total of 2,663,010 individuals were included in the present study, 51.3% were male and mean birth year was 1991 (range 1967-2015). In the period 2008-2016, 17,313 individuals had been diagnosed with a kidney disease, 4495 with chronic kidney disease (CKD), 4659 with acute kidney disease, 4672 with glomerular disease, 1479 with cystic kidney disease and 5085 with congenital malformations of the kidney or urinary tract. Figure 1 shows how the different groups of kidney disease combined for each patient. Patients with CKD most commonly had other groups of kidney disease. Table 1 shows birth related characteristics for the total cohort and for the different groups of kidney disease. Mean age at diagnosis differed between groups, kidney or urinary tract malformations were diagnosed in younger patients and chronic kidney disease in higher age. Participants who were diagnosed with CKD had more often LBW and SGA than participants who were diagnosed with other diseases. The same was observed for combinations of diagnoses, ie. 14.1% of participants with acute kidney disease but not CKD had LBW, 16.1% of participants with CKD but not acute kidney disease had LBW and 16.5% of participants with CKD and acute kidney disease had LBW.

Compared with individuals with birth weight above the 10th percentile, LBW was associated with a higher odds ratio (OR) of 1.72 (1.60-1.90) for development of CKD (Table 2). Corresponding ORs for individuals with SGA was 1.80 (1.75-1.94), for preterm birth 1.50 (1.33-1.66), for birth weight < 2.5 kg 1.85 (1.62-2.10) and for maternal preeclampsia OR was 1.11 (0.94-1.31). There were no clear gender differences, except an impression that women seemed to be less affected by preterm birth and more by maternal preeclampsia (Table 2). The adjusted analyses were repeated in the cohort born before 1990 to focus on the adult population, with very similar results. These analyses described in Table 2 were repeated using cox regression statistics, with virtually identical results. As can be seen from Figure 2, cumulative risk of CKD was higher for both LBW and SGA. We further analyzed odds ratio of being diagnosed with chronic kidney disease stage 3, 4 or 5. In these analyses, LBW was associated with an OR of 1.80 (1.60-2.05) for CKD stage 3, 1.84 (1.56-2.18) for CKD stage 4 and 1.88 (1.58-2.24) for CKD stage 5 (Supplemental Table 1). Corresponding ORs for SGA was 1.89, 2.04 and 1.78, for preterm birth 1.65, 1.59 and 1.44 and for birth weight <2.5 kg 2.09, 1.82 and 1.93.

In Figure 3 we investigated possible dose-response relationships for low birth weight and low birth weight for gestational age. In these analyses we categorized birth weight and birth weight for gestational age according to gender specific percentiles, the following groups were analyzed: below 5th percentile, 5-10th, 10-20th, 20-80th (reference), 80-90th, 90-95th and above 95th percentile cut-offs. Dose-response relationships were observed for both low birth weight and birth weight for gestational age, with higher risks for lower birth weights. Higher risk was seen below the 10th

percentile for both LBW and SGA, but significant slightly higher ORs were seen for the 10-20th percentile groups for men.

To further analyze the effects of LBW, SGA and preterm birth, we investigated how combinations of these exposures associated with risk of CKD. As compared to having none of the exposures, individuals with one exposure had a significantly higher risk and the effect seemed similar for the three exposures (Table 3). Individuals with two exposures had a higher risk than individuals with one exposure, especially individuals with LBW and SGA, and individuals with three exposures had an even higher risk (Figure 4). These analyses were also repeated in the cohort born before 1990 to focus on the adult population, showing nearly identical results, except that the OR for individuals with only one exposure was attenuated and only significant for LBW or SGA. Analyses described in Table 3 were repeated using cox regression with virtually identical results. In order to analyze a possible contribution from preeclampsia, we chose to stratify the analyses in Table 3. The results showed that preeclampsia did not significantly affect the contribution of these other exposures (results not shown).

In the above analyses we have used CKD as the main outcome. In Table 4 we presented results for other groups of kidney disease, and showed that birth related risk factors were most strongly associated with the CKD group. Unadjusted and adjusted analyses showed similar results, only the adjusted results are shown in the table. Supplemental Table 2 shows the results for the adult cohort born before 1990.

Discussion

The present study showed that intrauterine growth restriction was associated with a 60-70% higher risk of being diagnosed with chronic kidney disease (CKD) during the first 50 years of life. The associations were similar for CKD stage 3, 4 and 5, similar for men and women and mostly the same in the adult cohort. Different markers of intrauterine growth restriction were tested and LBW and SGA yielded similar results that seemed to be stronger than for preterm birth. There was also significantly higher risks for other groups of kidney disease, but not as strongly as for CKD. Given the high population prevalence of CKD[20-23], and the high comorbidity and mortality in CKD[24] , our results may have public health importance.

The main finding in our study is that it provides evidence that subjects born with LBW and SGA not only have higher risk for development of kidney failure[4,7] but also for the much more prevalent CKD. Global prevalence of CKD has been shown to be about 12%, with stage 3 prevalence 7.6%, stage 4 prevalence 0.4% and stage 5 prevalence 0.1%[20]. In the present study, individuals born with LBW or SGA had an unadjusted OR of about 1.72 for being diagnosed with CKD. In analyses of birth weight percentiles, we observed higher risks for lower birth weights as well as trends towards lower risks for birth weights above normal. In analyses of combinations of birth related exposures, having more exposures were associated with higher risks and LBW and SGA seemed more important than preterm birth. Interestingly, we could not find evidence on gender differences, in difference to other studies [7,9,13,25]

In the present study, cumulative proportion of CKD at 50 years of age was 1.7% in individuals with LBW as compared to 1.0% in those without LBW. The real prevalence of CKD might however be much higher, as there is a well-known under-ascertainment of CKD in administrative databases as these rely on the patient having been referred to specialist care for evaluation[26,27]. A meta-analysis of CKD prevalence did for example show that prevalence of stage 3-5 in population screening is about 12% at 50 years of age[20]. It could be expected that the higher relative risk would be the same irrespective of the higher prevalence with increasing age, the absolute importance of LBW would thus be likely to be higher[20,28]. Review papers have argued for routine follow-up to detect early kidney disease in all individuals with LBW, SGA or preterm birth [2,16] and our study strengthen these arguments. Studies of the effect of screening in adults and older adults seem warranted to assess cost vs benefit.

Our study confirms previous Norwegian studies that LBW, SGA and preterm birth are associated with higher risk for kidney disease in adult age[4,7]. A recent study showed that combination of these exposures are associated with a further higher risk of CKD, and that individuals with only one exposure did not have a higher risk[29]. In contrast, the present study found that also individuals with only one exposure had a higher risk, and the contribution from preterm birth seemed to be weaker.

The importance of SGA has been documented in the present study and several previous studies [4,7,30]. A Swedish study showed an important higher risk associated with preterm birth, an effect that was of the same magnitude as for LBW and SGA in our study[31]. It is however difficult to directly compare these studies as there are considerable overlap between the exposures. The Swedish study did not include data on birth weight and it also showed a much weaker effect for preterm birth after 20 years of age as compared to our study. Our study showed clear associations between LBW and SGA and risk of CKD also in adult age as well as that the findings of the number of exposures also may be important.

Several studies have described the association between LBW and different indicators of kidney disease such as albuminuria, low eGFR, or kidney failure[13]. LBW has also been linked to moderately higher blood pressure [7], impaired glucose homeostasis[32], microalbuminuria, and endothelial dysfunction. In our study we found that LBW also was associated with higher risk of acute kidney disease, glomerular disease, cystic kidney disease and kidney and urinary tract malformations, although these risks were lower than for CKD. As kidney or urinary tract malformations, as well as cystic kidney disease, could cause intrauterine growth restriction, this part of our findings could be expected. In a previous paper we did in fact show that LBW was especially strongly associated with risk of congenital and hereditary kidney disease before age of 15 years [4]. In the present study we did however show a significantly higher risk also in the adult cohort born before 1990 (supplemental Table 2). Unadjusted analyses, adjusted analyses and analyses for the adult cohort showed very similar results and we thus believe that the potential for residual confounding is of smaller significance. The higher risk of glomerulonephritis could also be expected based on previous studies that has suggested that autoimmune disease could be caused by early life perturbations[33], but the higher risk of being diagnosed with glomerulonephritis has to our knowledge previously not been demonstrated in a population based study.

The major strengths of our study are the opportunity to use the national registries to include a large number of participants with prospective registration of birth related variables, the long follow-up period of 50 years and the stability of the Norwegian population with little or no emigration during follow-up. About 2% of the included population had been officially recorded as emigrated and were excluded from the study, but a cross-check by Statistics Norway showed that another 2.% currently were living abroad. Further strengths are that most kidney disease diagnoses are assessed and treated in hospitals, and that we included both main diagnoses and secondary diagnoses in the data. The study population is mostly Caucasian, which is both a strength and a weakness. On the downside, results might be different in other populations. But the upside is that the Norwegian population is quite homogeneous with equal access to specialist health care, this could allow for better internal comparability and reduce potential confounding such as low socio-

economic status, educational level and ethnic origin. We did not have access to these data in our study, but we were able to adjust for single vs non-single mother which is a socio-economic marker.

The main weakness is that we could not record endpoints until 2008. Our data thus reflects prevalence of CKD during the years 2008-2015. Given the wide age range of 0-50 years we believe that our data also could reflect incidence of CKD. Based on these reflections we decided to perform the main statistics as logistic regression statistics, but also performed left-truncated survival statistics to investigate the age-associated risk of CKD. These two approaches showed mainly identical results. As discussed above, there is probably an under-reporting of CKD in this administrative databases[26,27,34]. An important weakness is also that chronic kidney disease documented in patient journals by albuminuria or lower estimated glomerular filtration rate will not be coded in the diagnostic databases if not relevant for the patient care that was given. The treating physicians decide which ICD-10 diagnostic codes to use, and although we believe that these mostly are correct, diagnostic codes of kidney disease have to our knowledge not been validated in Norway. Other limitations include lack of data on other important risk factors such as diabetes, hypertension, smoking, dyslipidemia and other exposures of kidney disease.

Conclusions

We have shown that intrauterine growth restriction is associated with a 60-70% higher risk of being diagnosed with CKD during the first 50 years of age. Findings were similar for men and women, and were similar for LBW and SGA. Future studies will need to address whether screening of subjects with intrauterine growth restriction could have a beneficial cost-benefit ratio and also how intrauterine growth restriction modifies the effect of other known kidney disease exposures. Starting now, we suggest that clinicians should ask their kidney patients for information on birth history.

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

Disclosures: None

Data Sharing Statement: Anonymized data for main analyses will be shared on request.

Supplemental Material:

Supplemental table 1. Associations of low birth weight, small for gestational age or preterm birth with chronic kidney disease stage 3, 4 or 5.

Supplemental Table 2. Associations of low birth weight, small for gestational age or preterm birth with diverse forms of kidney disease. Analyses for cohort born before 1990.

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Table 1. Characteristics of participants in the Norwegian Patient Registry

Characteristic	Total	Diagnostic groups					Any kidney disease
		Chronic kidney disease	Acute kidney disease	Glomerular disease	Cystic kidney disease	Congenital malformations	
N	2,663,010	4495	4659	4672	1479	5085	17,313
% male	51%	61%[c]	62.1%[c]	52.5%	49.2%	57.3%[c]	57.3%[c]
Birth year	1991±14	1979±11[c]	1980±11[c]	1987±14[c]	1991±16	2003±11[c]	1989±15[c]
Duration follow-up*(years)	26±14	33.1±11.0	32.6±11.5	24.9±13.5	20.7±15.9	8.5±10.9	23.1±15.6
% maternal marital status single	10%	11.6%[c]	13.1%[c]	10.5%[a]	9.7%	7.8%[c]	10.7%[c]
% LBW (<10th percentile)	10%	16.1%[c]	14.6%[c]	12.5%[c]	14.8%[c]	13.4%[c]	13.7%[c]
% SGA (<10th percentile)	10%	16.5%[c]	15.3%[c]	12.2%[c]	13.5%[c]	10.6%	13.1%[c]
% preterm birth (<37 weeks)	4.6%	6.6%[c]	5.9%[c]	5.3%[a]	7.9%[c]	7.0%[c]	6.1%[c]
% birth weight <2.5 kg	3.2%	5.7%[c]	4.9%[c]	4.5%[c]	5.2%[c]	4.9%[c]	4.9%[c]
% 1 risk factor**	6.9%	9.5%[c]	8.8%[c]	7.5%[a]	9.3%[c]	6.9%	7.9%[c]
% 2 risk factor**	8.0%	12.7%[c]	12.2%[c]	9.8%[c]	11.1%[c]	11.1%[c]	10.8%[c]
% 3 risk factor**	0.64%	1.5%[c]	0.94%[c]	1.0%[c]	1.5%[c]	1.3%[c]	1.1%[c]
% congenital malformations	3.0%	6.6%[c]	4.6%[c]	3.9%[c]	25%[c]	29.4%[c]	12.6%[c]
% Apgar 5 minutes < 7	0.96%	2.5%[c]	3.0%[c]	0.96%	2.6%[c]	1.9[c]	2.0%[c]
% Maternal disease before pregnancy***	2.4%	3.3%[c]	2.8%	3.1%[b]	7.8%[c]	4.2%[c]	3.6%[c]
% Maternal preeclampsia	2.9%	3.2%[c]	2.6%	2.9%	4.5%[c]	3.0%	3.1%[c]

[a]p<0.05, [b]p<0.01, [c]p<0.001 as compared to total

*Duration of follow-up until diagnosis or end of 2016.

**LBW (low birth weight), SGA (small for gestational age) or preterm birth.

***Maternal diagnosis of diabetes mellitus, chronic kidney disease, rheumatic disease or essential hypertension before pregnancy.

Table 2. Associations of low birth weight, small for gestational age, preterm birth, or maternal preeclampsia with subsequent diagnosis of chronic kidney disease

Exposure		Unadjusted			Adjusted					Adjusted	
		Total cohort			Men			Women		Cohort born before 1990	
		N CKD	OR (95% CI)	p	N CKD	OR (95% CI)*	p	N CKD	OR (95% CI)*	p	OR (95% CI)*	p
Birth weight <10th percentile - LBW	No	3759	1.0 (ref)		2304	1.0 (ref)		1455	1.0 (ref)		1.0 (ref)	
	Yes	724	1.72(1.60-1.90	<0.001	427	1.56 (1.411.73)	<0.001	297	1.72(1.51-2.00)	<0.001	1.58 (1.45-1.73)	<0.001
Z-score <10th percentile - SGA	No	3564	1.0 (ref)		2174	1.0 (ref)		1390	1.0 (ref)		1.0 (ref)	
	Yes	708	1.79 (1.65-1.94)	<0.001	430	1.52 (1.37-1.70)	<0.001	278	1.51 (1.33-1.72)	<0.001	1.51 (1.40-1.63)	<0.001
Preterm birth	No	4196	1.0 (ref)		2541	1.0 (ref)		1655	1.0 (ref)		1.0 (ref)	
	Yes	299	1.48 (1.33-1.66)	<0.001	198	1.55 (1.34-1.80)	<0.001	101	1.40 (1.14-1.71)	0.001	1.35 (1.17-1.55)	<0.001
Birth weight < 2.5 kg	No	4235	1.0 (ref)		2587	1.0 (ref)		1648	1.0 (ref)		1.0 (ref)	
	Yes	260	1.85 (1.62-2.10)	<0.001	152	1.87 (1.58-2.20)	<0.001	108	1.80 (1.49-2.2)	<0.001	1.79 (1.55-2.07)	<0.001
Maternal preeclampsia	No	4352	1.0 (ref)			1.0 (ref)			1.0 (ref)		1.0 (ref)	
	Yes	143	1.11 (0.94-1.31)	0.2		1.18 (0.94-1.50)	0.15		1.44 (1.12-1.9)	0.005	1.26 (1.04-1.33)	0.018

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

Table 3. **Associations for subsequent diagnosis of chronic kidney disease according to whether the individuals had low birth weight, were small for gestational age, or were born preterm . Separate analyses for total cohort and the cohort born before 1990.**

Exposure	Total cohort (born 1967-2015)					Cohort born before 1990			
	Total N	N CKD	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	p-value	Total N	N CKD	Adjusted OR * (95% CI)	p-value
Term, Not LBW or SGA	2,147,243	3248	1.0 (ref)	1.0 (ref)		955,093	2681	1.0 (ref)	
Term, not LBW, SGA	99,862	240	1.59 (1.39-1.81)	1.57 (1.38-1.79)	<0.001	56,462	210	1.32 (1.14-1.52)	<0.001
Term, LBW, not SGA	33,877	74	1.44 (1.15-1.82)	1.41 (1.12-1.78)	0.002	13,199	53	1.41 (1.07-1.85)	0.01
Preterm, not LBW or SGA	40,540	89	1.45 (1.17 -1.79)	1.40 (1.13-1.72)	0.002	19,327	62	1.11 (0.86-1.43)	0.4
Preterm, not LBW, SGA	No data	No data				No data			
Term, LBW and SGA	137,891	402	1.92 (1.74-2.14)	1.88 (1.70-2.10)	<0.001	72,175	345	1.70 (1.52-1.90)	<0.001
Preterm, LBW, not SGA	65,013	141	1.43 (1.21-1.70)	1.36 (1.15-1.61)	<0.001	25,427	103	1.40 (1.15-1.71)	0.001
Preterm, LBW and SGA	16,299	66	2.67 (2.10 -3.42)	2.50 (2.00-3.18)	<0.001	6,174	47	2.63 (1.96-3.53)	<0.001
Number of risk factors**									
0	2,147,243	3248	1.0 (ref)	1.0 (ref)		995,093	2681	1.0 (ref)	
1	174,279	403	1. 52(1.37-1.69)	1.50(1.35-1.66)	<0.001	88,988	325	1.28 (1.14-1.44)	<0.001
2	202,904	543	1.76 (1.61-1.93)	1.72(1.57-1.89)	<0.001	97,602	448	1.62 (1.47-1.79)	<0.001
3	16,299	66	2.67 (2.09-3.41)	2.49(1.95-3.19)	<0.001	6,174	47	2.63 (1.96-3.53)	<0.001

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

** Number of the risk factors LBW (defined by <10th percentile), SGA (defined by <10th percentile) and preterm birth (<37 weeks).

Table 4. **Associations of low birth weight, small for gestational age or preterm birth with diverse forms of kidney disease**

Exposure		Chronic kidney disease		Acute kidney injury		Glomerulonephritis		Hereditary kidney disease		Malformations of the kidney or urinary tract	
		N	aOR (95% CI)*	N	aOR (95% CI)*	N	aOR (95% CI)*	N	aOR (95% CI)*	N	aOR (95% CI)*
Birth weight <10th percentile – LBW	No	3759	1.0 (ref)	3971	1.0 (ref)	4086	1.0 (ref)	1258	1.0 (ref)	4394	
	Yes	724	1.62 (1.50-1.76)	678	1.44 (1.33-1.56)	581	1.24 (1.14-1.36)	219	1.35 (1.17-1.56)	679	1.15 (1.06-1.25)
Z-score <10th percentile - SGA	No	3564	1.0 (ref)	3730	1.0 (ref)	3900	1.0 (ref)	1240	1.0 (ref)	4465	
	Yes	708	1.52 (1.40-1.65)	675	1.60 (1.49-1.73)	543	1.18 (1.070-1.30)	194	1.31 (1.12-1.52)	531	1.13 (1.03-1.23)
Preterm birth	No	4196	1.0 (ref)	4385	1.0 (ref)	4423	1.0 (ref)	1362	1.0 (ref)	4727	
	Yes	299	1.49 (1.33-1.68)	274	1.30 (1.15-1.47)	249	1.17 (1.03-1.33)	117	1.43 (1.18-1.74)	358	1.08 (0.97-1.21)
Birth weight < 2.5 kg	No	4235	1.0 (ref)	4429	1.0 (ref)	4464	1.0 (ref)	1402	1.0 (ref)	4835	
	Yes	260	1.84 (1.62-2.08)	230	1.56 (1.36-1.79)	208	1.40 (1.21-1.60)	77	1.30 (1.03-1.63)	250	1.07 (0.94-1.22)

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

Supplemental table 1. **Associations of low birth weight, small for gestational age or preterm birth with chronic kidney disease stage 3, 4 or 5**

Exposure		CKD stage 3		CKD Stage 4		CKD stage 5	
		N	OR (95% CI)	N	OR(95% CI)	N	OR (95% CI)
Birth weight <10th percentile	No	1501	1.0 (ref)	809	1.0 (ref)	722	1.0 (ref)
	Yes	304	1.80 (1.60-2.05)	167	1.84 (1.56-2.18)	152	1.88 (1.58-2.24)
Z-score <10th percentile	No	1415	1.0 (ref)	763	1.0 (ref)	694	1.0 (ref)
	Yes	297	1.89 (1.67-2.14)	173	2.04 (1.73-2.41)	137	1.78 (1.48-2.13)
Preterm birth	No	1676	1.0 (ref)	913	1.0 (ref)	823	1.0 (ref)
	Yes	133	1.65 (1.38-1.97)	70	1.59 (1.25-2.03)	57	1.44 (1.10-1.88)
Birth weight < 2.5 kg	No	1692	1.0 (ref)	927	1.0 (ref)	827	1.0 (ref)
	Yes	117	2.09 (1.73-2.52)	56	1.82 (1.39-2.38)	53	1.93 (1.46-2.55)

Supplemental Table 2. **Associations of low birth weight, small for gestational age or preterm birth with diverse forms of kidney disease. Analyses for cohort born before 1990.**

Exposure		Chronic kidney disease		Acute kidney injury		Glomerulonephritis		Hereditary kidney disease		Malformations of the kidney or urinary tract	
		N	aOR (95% CI)*	N	aOR (95% CI)*	N	aOR (95% CI)*	N	aOR (95% CI)*	N	aOR (95% CI)*
Birth weight <10th percentile – LBW	No	3095	1.0 (ref)	3085	1.0(ref)	2362	1.0(ref)	631	1.0(ref)	560	1.0(ref)
	Yes	582	1.58 (1.45-1.73)	524	1.43(1.30-1.57)	341	1.23(1.10-1.38)	93	1.23 (0.99-1.54)	78	1.17(0.92-1.50)
Z-score <10th percentile - SGA	No	2907	1.0 (ref)	2879	1.0(ref)	2204	1.0(ref)	594	1.0(ref)	524	1.0(ref)
	Yes	602	1.51 (1.40-1.65)	556	1.41(1.30-1.55)	361	1.22(1.10-1.36)	108	1.33 (1.10-1.64)	83	1.16(0.92-1.50)
Preterm birth	No	3471	1.0(ref)	3418	1.0(ref)	2580	1.0(ref)	693	1.0(ref)	614	1.0(ref)
	Yes	241	1.38(1.17-1.55)	197	1.25(1.10-1.45)	125	1.10(0.90-1.30)	38	1.22(0.88-1.70)	26	0.96(0.66-1.42)
Birth weight < 2.5 kg	No	3483	1.0(ref)	3446	1.0(ref)	2594	1.0(ref)	705	1.0(ref)	613	1.0(ref)
	Yes	202	1.80(1.55-2.07)	169	1.51(1.30-1.78)	111	1.32(1.09-1.60)	26	1.15(0.75-1.65)	27	1.28(0.87-2.00)

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

Figures and legends

Figure 1. Number of individuals diagnosed with combinations of different groups of kidney disease. Patients with CKD most commonly had other groups of kidney disease. In patients with CKD, 14% also had acute kidney disease, 25% had glomerular disease, 6% had cystic kidney disease, 3% had kidney or urinary tract malformations, 9% had several groups of kidney disease and 44% were coded with CKD alone.

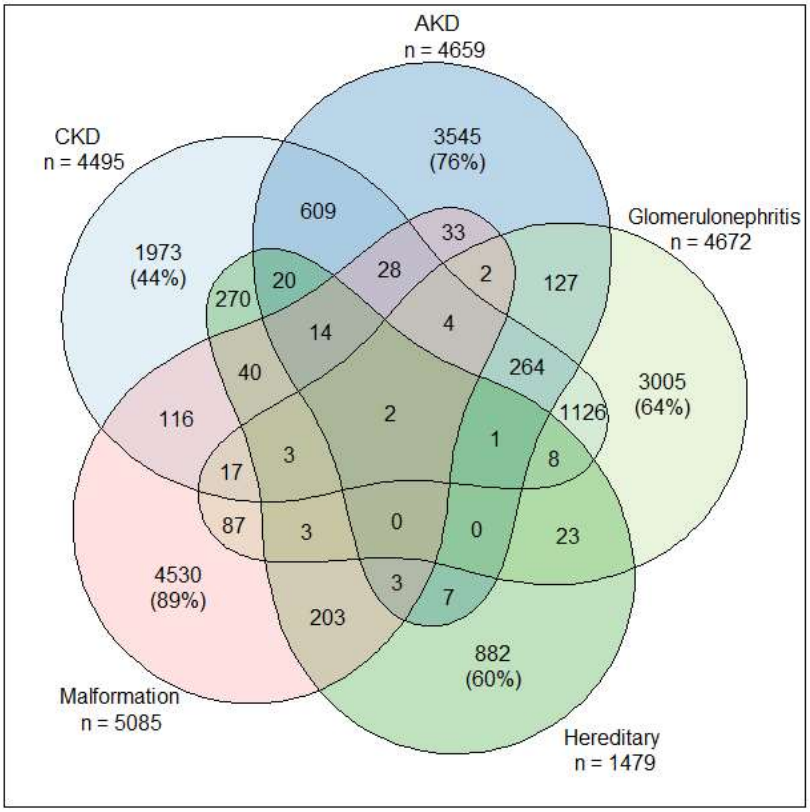
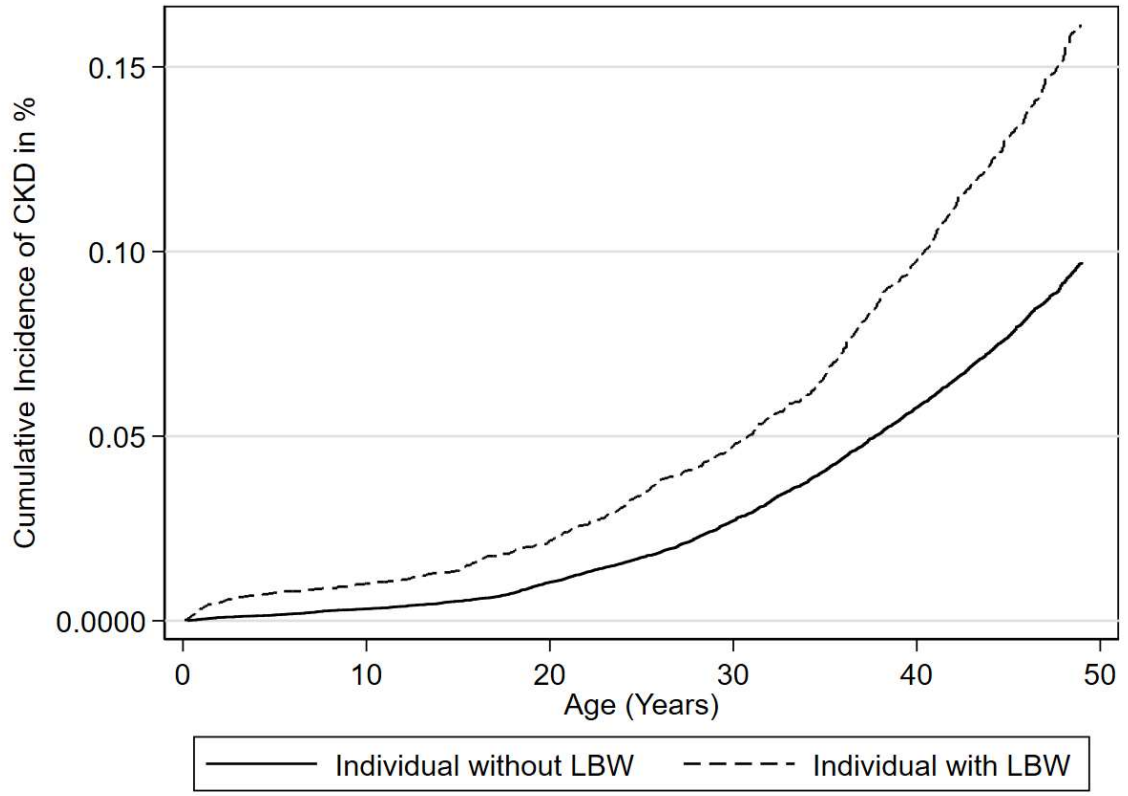


Figure 2. Cumulative incidence (%) of CKD according to LBW and SGA. Cumulative risk of CKD was higher for both LBW and SGA, and the graphs separate most strongly in adult age. Cumulative proportion with CKD at 50 years of age was 1.0% in individuals without LBW and 1.7% in individuals with LBW (top). Similar association was found in individuals with and without SGA (bottom).



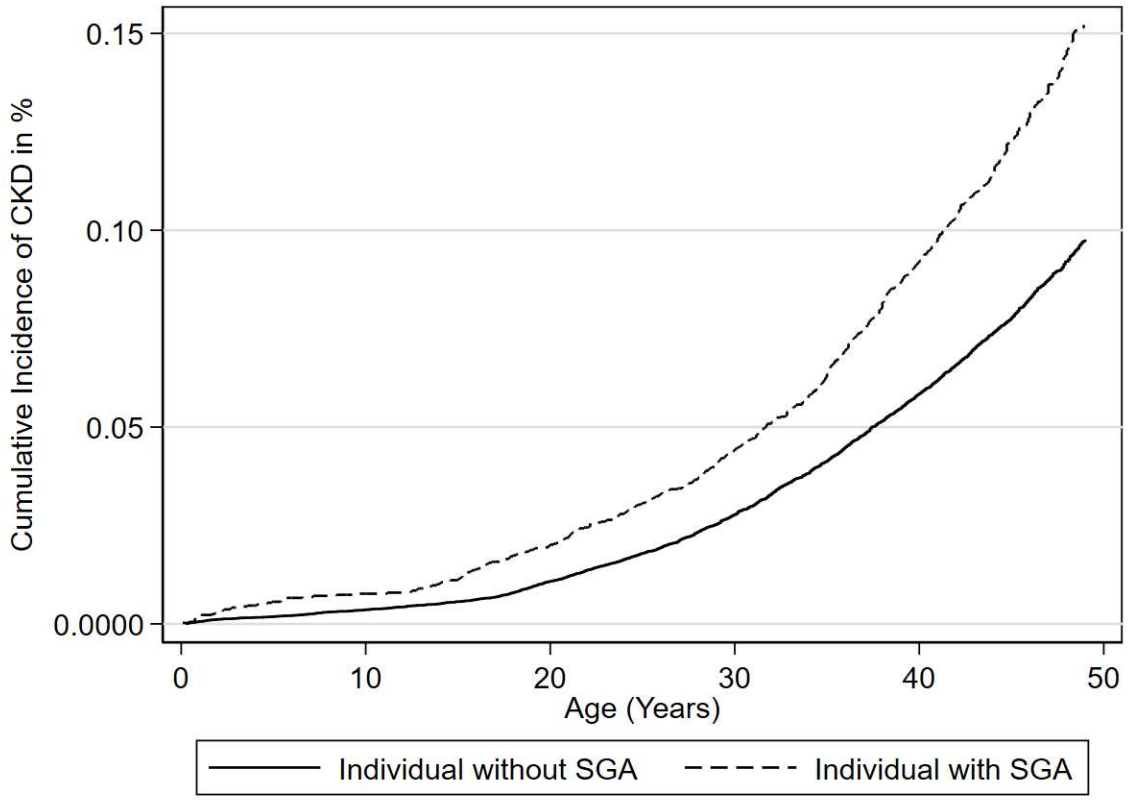


Figure 3. Odds ratio for CKD according to different percentiles for birth weight (top) and birth weight for gestational age (bottom). Dose-response relationships were observed for both low birth weight and birth weight for gestational age, with higher risks for lower birth weights. Higher risk was seen below the 10th percentile for both LBW and SGA, but significant slightly higher ORs were seen for the 10-20th percentile groups for men.

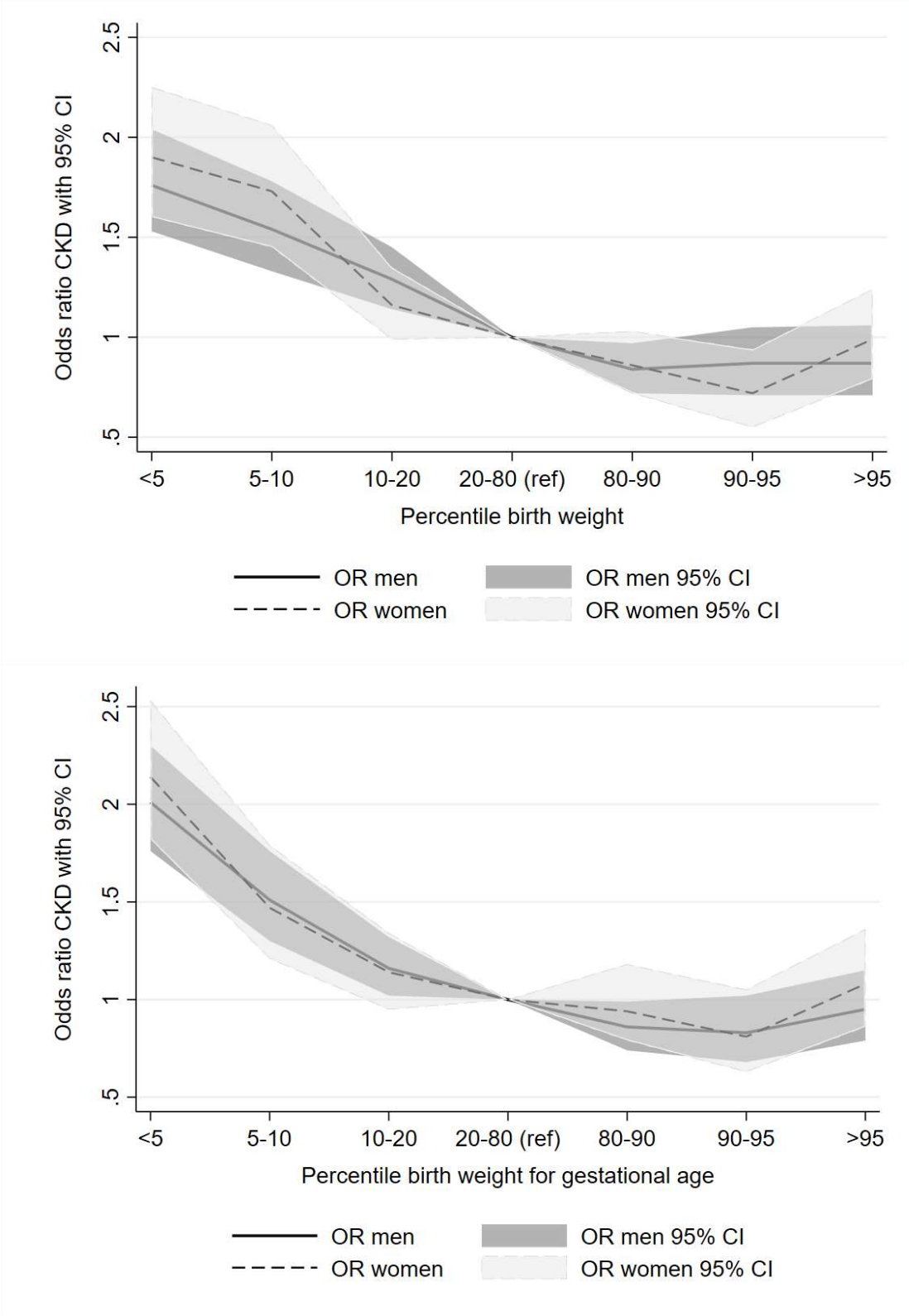


Figure 4. Cumulative Incidence (%) of CKD according to number of birth related risk factors (birth weight <10th percentile, birth weight for gestational age <10th percentile and preterm birth). Compared to having none of the exposures, individuals with one exposure had a significantly higher risk. Individuals with two exposures had a higher risk than individuals with one exposure and individuals with three exposures had an even higher risk.

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