

## Prenatal Growth and CKD in Older Adults: Longitudinal Findings From the Helsinki Birth Cohort Study, 1924-1944

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**Background:** According to the Developmental Origins of Health and Disease (DOHaD) hypothesis, several noncommunicable diseases, including hypertension, type 2 diabetes, and coronary heart disease, have their origins in early life. Chronic kidney disease (CKD) has traditionally been assumed to develop as the result of an interaction between genetic and environmental factors, although more recently, the importance of factors present early in life has been recognized.

**Study Design:** Longitudinal birth cohort study.

**Setting & Participants:** 20,431 people born in 1924 to 1944 in Helsinki, Finland, who were part of the Helsinki Birth Cohort Study were followed up through their life course from birth until death or age 86 years.

**Predictor:** Prenatal growth and socioeconomic factors.

**Outcomes:** Death or hospitalization for CKD.

**Results:** Smaller body size at birth was associated with increased risk for developing CKD. Each standard deviation higher birth weight was associated with an HR for CKD of 0.82 (95% CI, 0.74-0.91;  $P < 0.001$ ). Associations with ponderal index at birth, placental weight, and birth length were also statistically significant ( $P < 0.001$ ,  $P < 0.001$ , and  $P = 0.002$ , respectively), but only among men. Prematurity also predicted increased risk for CKD.

**Limitations:** The study was restricted to people who were born in Helsinki in 1924 to 1944.

**Conclusions:** Smaller body size at birth was associated with increased risk for developing CKD in men. Prematurity was also associated with increased risk for CKD in women. These findings in the Helsinki Birth Cohort Study support the importance of early life factors in the development of CKD.

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Globally, noncommunicable diseases cause more deaths than communicable diseases, and chronic kidney disease (CKD) is one important contributor to the noncommunicable disease burden.<sup>1-3</sup> Traditionally, CKDs have been assumed to develop as the result of an interac-

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tion between genetic and environmental factors, although the importance of factors active early in life has more recently been recognized.<sup>4,5</sup>

According to the Developmental Origins of Health and Disease (DOHaD) hypothesis, several noncommunicable diseases, including hypertension, type 2 diabetes, and coronary heart disease, have their origins in early life.<sup>6-9</sup> This is believed to work through a process called developmental programming, and factors affecting renal development during early life have been recognized as being associated with increased risk for CKD.<sup>4,5,10</sup>

In the 1980s, Brenner et al<sup>11</sup> proposed that intrauterine growth restriction causes a low nephron number in the kidneys. This hypothesis is based on the observation that the number of nephrons is determined by term, with 60% of nephrons formed during the third trimester, and that regardless of possible deficits in nephron number, little if any compensatory growth occurs after term birth. During the life course, a low nephron number results in hyperfiltration and subsequently sodium retention, salt-sensitive hypertension, nephron loss, and CKD caused by secondary focal segmental glomerulosclerosis.<sup>11,12</sup> This has been

shown to be the case and studies have reported an association between low birth weight and CKD. However, most previous studies have been rather small or have not been able to follow up the study cohort until old age.<sup>13</sup>

Within the Helsinki Birth Cohort Study (HBCS), we have followed up through the life course 20,431 people born in 1924 to 1944. The aim of the present study was to focus on prenatal programming of CKD, taking gestational age, socioeconomic factors, and several neonatal characteristics into account.

### Methods

#### Participants

The HBCS includes 2 birth cohorts. The older cohort of 7,086 people born in 1924 to 1933 at Helsinki University Central Hospital, and who also went to school in the city, has been described in greater detail previously.<sup>14</sup> A younger cohort is made up of 13,345 people born in 1934 to 1944 at Helsinki University Central Hospital or the Helsinki City Maternity Hospital in Helsinki, Finland. These were the only public hospitals operating in the city at the time.<sup>15</sup>

#### Measurements

Birth records from both cohorts include data for birth weight, length at birth, head circumference, placental weight, last menstrual period, and maternal age, height, and weight before delivery. Ponderal index, defined as weight divided by the cube of height, was calculated. Gestational age at delivery was calculated from last

menstrual period dates. The birth records include information for socioeconomic factors and paternal occupation. These cohorts have been followed up longitudinally by linkage to national Finnish registers, which provide information for both morbidity and mortality.<sup>15</sup>

### Outcomes

We used data from the 20,431 individuals from both cohorts of the HBCS. They all lived in Finland in 1971, when a unique identification number was allocated to each member of the Finnish population. Using this unique identification number, we followed up individuals from January 1, 1971, through December 31, 2010, by linking their birth data to the Finnish National Death Register and the national Care Register for Health Care (previously the Hospital Discharge Register).

All hospital admissions in Finland are recorded in the national Care Register for Health Care.<sup>16</sup> All deaths are recorded in the national Causes of Death Register.<sup>17</sup> The Death Register includes the date and cause of death, coded according to *International Classification of Diseases, Eighth Revision (ICD-8)* until the end of 1986, thereafter *ICD, Ninth Revision (ICD-9)* until the end of 1996, and *ICD, Tenth Revision (ICD-10)* from 1997 onward. Deaths from CKD were identified via linkage to the Finnish National Death Registry. All deaths are based on physician-written death certificate data. Definition of CKD was according to the diagnoses in [Table S1](#) (provided as online supplementary material).

The Care Register for Health Care is a continuation of the Hospital Discharge Register, which has data for patients discharged from hospitals in 1969 to 1993. The Hospital Discharge Register was replaced with the Care Register for Health Care as of 1994. The purpose of the register is to collect data for the activities of health centers, hospitals, and other institutions providing inpatient care and the clients treated in them, as well as home nursing clients, for the purposes of statistics, research, and planning. The outcome variables used when assessing hospitalization for CKD are itemized in [Table S1](#) and are based on the diagnoses provided (ICD codes) by the treating physician as the reasons for hospitalization.

In the present study, we used the combination of hospitalization and death from CKD as an outcome in order to optimize and maximize the number of individuals with CKD. However, using this approach does not allow us to capture the actual timing of onset of CKD.

We used the father's occupation as an indicator of childhood socioeconomic position, as described previously.<sup>18</sup> Through Statistics Finland, we obtained data for occupation from census data from 1970 to 2000.<sup>19</sup> We used the maximum attained occupational status, grouped into manual worker, self-employed, and lower or higher official.

### Analytical Approach

We used a Cox proportional hazards model to analyze the data. We always stratified the analysis using

combinations of sex and year of birth and always included early-life and adult socioeconomic variables in categories. We followed up each individual to the first of the 5 following events: migration away from Finland, death attributable to kidney disease, death from another cause, hospitalization for kidney disease, and reaching January 1, 2011, still alive. Either death or hospitalization from kidney disease was taken as the outcome of study. We tested the proportional hazards assumption by comparing hazard ratios (HRs) in distinct age intervals and explored differences in associations of neonatal measures with kidney disease between men and women by including interaction terms and among the 4 sub-causes by setting up a 3-df  $\chi^2$  test. To compare HRs across subcauses, we used the standard test for heterogeneity in fixed-effects meta-analysis. We included neonatal measurements in standardized form so that their associations with risk for kidney disease could be compared directly, but also illustrated the results with categorical analyses.

Of the 20,431 individuals included in HBCS, 1,336 (6.5%) migrated away from Finland before any CKD, 6,116 (29.9%) died of other causes before any CKD, 375 (1.8%) had CKD hospitalization or death (for 14, the CKD death had no prior CKD hospitalization), and 12,604 were still alive at the end of follow-up in 2011, without having migrated or had CKD.

The Ethics Committee at the National Public Health Institute in Helsinki approved the study. Data were linked by permission from the Ministry of Health and Social Affairs, National Institute for Health and Welfare, and Statistics Finland. This is a register-based study and therefore informed consent is not needed.

### Results

[Table 1](#) shows descriptive data for neonatal measurements and socioeconomic characteristics in the study cohorts. It also summarizes the number of individuals identified with CKD in 4 subgroups of kidney disease and their age at onset. There were 226 (2.1%) men and 149 (1.5%) women who had CKD diagnosed, with median ages of first diagnosis at 64.3 and 64.9 years, respectively. We defined CKD and its subtypes using the ICD codes shown in [Table S1](#). Of 375 people with CKD diagnosed, the subgroups are hypertensive kidney disease (n = 54; 14%), diabetic kidney disease (n = 60; 16%), chronic kidney failure (n = 126; 34%), and other, including nephritis (n = 135; 36%).

Father's occupational status was not associated with CKD. Relative to offspring of manual worker fathers, HRs for the other categories are 0.96 (95% confidence interval [CI], 0.63-1.45) for those with fathers having upper-middle-class occupations, 0.77 (95% CI, 0.56-1.07) for those with fathers having lower-middle-class occupations, and 1.08 (95% CI, 0.73-1.58) for unspecified. However, individuals who themselves attained lower occupational

**Table 1.** Descriptive Data for Study Population by Sex

Characteristic	Men (n = 10,614)		Women (n = 9,817)	
	No. Missing	Value	No. Missing	Value
Neonatal measurement				
Weight, g	0	3,459 ± 497	0	3,332 ± 472
Length, cm	73	50.4 ± 1.9	72	49.8 ± 1.9
Head circumference, cm	83	35.2 ± 1.5	77	34.5 ± 1.4
Ponderal index, kg/m <sup>3</sup>	73	26.8 ± 2.4	72	26.8 ± 2.3
Gestational age, wk	613	39.6 ± 1.8	512	39.8 ± 1.8
Placental weight, g	27	645 ± 123	18	635 ± 121
Father's occupation type				
Upper middle class		949 (8.9%)		795 (8.1%)
Lower middle class		1,809 (17.0%)		1,714 (17.5%)
Manual worker		7,148 (67.3%)		6,616 (67.4%)
Unspecified		708 (6.7%)		692 (7.0%)
Adult occupation type				
Upper middle class		1,992 (18.8%)		1,343 (13.7%)
Lower middle class		2,380 (22.4%)		4,882 (49.7%)
Self-employed		950 (9.0%)		666 (6.8%)
Manual worker		4,496 (42.4%)		2,128 (21.7%)
Unspecified		796 (7.5%)		798 (8.1%)
Cases of kidney disease				
Any kidney disease		226 (2.1%)		149 (1.5%)
Hypertensive		34 (15.0%) <sup>a</sup>		20 (13.4%) <sup>a</sup>
Diabetic		45 (19.9%) <sup>a</sup>		15 (10.1%) <sup>a</sup>
Chronic kidney failure		75 (33.2%) <sup>a</sup>		51 (34.2%) <sup>a</sup>
Other, including nephritis		72 (31.9%) <sup>a</sup>		63 (42.3%) <sup>a</sup>
Median age at kidney disease, y		64.3 [54.2-71.9]		64.9 [50.8-73.6]

Note: Unless otherwise indicated, values are given as mean ± standard deviation, median [interquartile range], or number (percentage).

Abbreviations: Q1, lower quartile; Q3, upper quartile.

<sup>a</sup>Unless otherwise indicated, the denominator for calculating the percentage of each kidney disease subtype is the total number of individuals who had kidney disease.

status had higher rates of CKD. Again, relative to manual workers, HRs for the other categories of the individual's own adult occupation are 0.71 (95% CI, 0.53-0.96) for upper-middle-class occupation, 0.74 (95% CI, 0.57-0.96) for lower-middle-class occupation, 0.51 (95% CI, 0.31-0.83) for the self-employed, and 1.39 (95% CI, 0.83-2.35) for unspecified.

Table 2 shows HRs for neonatal measurements and CKD. Every additional standard deviation of birth weight is associated with an HR for CKD of 0.82 (95% CI, 0.74-0.91; P < 0.001). Associations with ponderal index,

placental weight, and birth length are also statistically significant, although not those with head circumference or gestational age. These associations are confined to men. Interaction tests (the product of sex and the neonatal variable) suggest statistically significant differences in the effect size in men and women for birth weight, ponderal index, and placental weight (P for interaction values of 0.006, 0.03, and 0.03, respectively).

Tables 3 and S2 show further exploration of the association between CKD and birth weight. The association in men and women is nominally stronger at age younger than

**Table 2.** Association of Neonatal Measurements and Chronic Kidney Disease

Neonatal Measurement <sup>a</sup>	Men and Women		Men		Women		P for Interaction
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	
Birth weight	0.82 (0.74-0.91)	<0.001	0.73 (0.64-0.83)	<0.001	0.99 (0.84-1.16)	0.9	0.004
Birth length	0.88 (0.79-0.97)	0.01	0.81 (0.71-0.93)	0.002	0.99 (0.84-1.17)	0.9	0.07
Head circumference	0.93 (0.84-1.03)	0.2	0.91 (0.80-1.05)	0.2	0.95 (0.81-1.12)	0.6	0.7
Ponderal index	0.86 (0.77-0.95)	0.003	0.78 (0.68-0.89)	<0.001	0.99 (0.84-1.17)	0.9	0.02
Gestational age	0.99 (0.89-1.10)	0.8	0.95 (0.83-1.09)	0.4	1.05 (0.89-1.24)	0.6	0.4
Placental weight	0.86 (0.78-0.95)	0.004	0.78 (0.69-0.90)	<0.001	1.00 (0.85-1.17)	0.9	0.03

Note: The Cox model is stratified on combinations of sex and year of birth and also includes early life and adult socioeconomic status.

Abbreviations: CI, confidence interval; HR, hazard ratio.

<sup>a</sup>Standardized units.

**Table 3.** Further Exploration of Association Between Birth Weight and Chronic Kidney Disease

	Men and Women		Men		Women	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
All kidney disease	0.82 (0.74-0.91)	<0.001	0.73 (0.64-0.83)	<0.001	0.99 (0.84-1.16)	0.9
Age at kidney disease						
≤60 y	0.76 (0.64-0.89)	<0.001	0.67 (0.54-0.83)	<0.001	0.91 (0.70-1.18)	0.5
>60 y	0.87 (0.76-0.99)	0.03	0.77 (0.65-0.91)	0.002	1.05 (0.85-1.29)	0.7
Cause of kidney disease						
Hypertensive	0.63 (0.48-0.82)	<0.001	0.57 (0.40-0.80)	0.001	0.75 (0.48-1.16)	0.2
Diabetic	0.77 (0.60-0.99)	0.04	0.69 (0.51-0.93)	0.01	1.08 (0.65-1.81)	0.8
Chronic kidney failure	0.83 (0.69-0.99)	0.03	0.71 (0.57-0.90)	0.004	1.03 (0.78-1.36)	0.8
Other, including nephritis	0.95 (0.80-1.12)	0.5	0.87 (0.69-1.10)	0.3	1.04 (0.81-1.33)	0.8

Note: Birth weight is measured in standardized units. The Cox model is stratified on combinations of sex and year of birth and also includes early life and adult socioeconomic status. *P* values for the difference in effect size between those up to age 60 years and those older than 60 years were 0.20 (men and women), 0.31 (men), and 0.41 (women). Similarly, *P* values for difference in effect size according to subcause were 0.08 (men and women), 0.21 (men), and 0.60 (women). Abbreviations: CI, confidence interval; HR, hazard ratio.

60 years than at older ages, but not statistically significantly ( $P = 0.2$ ). It is also nominally stronger for hypertensive kidney disease than for the other causes group, but again not statistically significantly ( $P = 0.08$ ). Table S1 provides equivalent results for the other 5 neonatal measurements. Table 4 also includes data for gestational age in groups. Although there is no linear trend across the groups, individuals who were born preterm (at gestational week < 34) have higher rates of CKD. This was only statistically significant among women. Table S3 shows incidence rates of CKD in the study population.

Table 4 illustrates the results, presenting birth weight in categories, and shows the continuous reduction in risk for men associated with greater weight at birth. The pattern is less clear for women, although it is the lightest 2 groups that have the greatest HRs.

Using an equivalent approach, 3,265 (16%) of the 20,431 individuals were found to have been hospitalized

or have died of coronary heart disease during follow-up; 139 (37%) of the 375 individuals with CKD overlapped with this group. Among those with no coronary heart disease, the HR for CKD disease was 0.87 (95% CI, 0.77-0.99) per additional standardized unit of birth weight ( $P = 0.04$ ), and among those with coronary heart disease, it was similar at 0.79 (95% CI, 0.66-0.93) per additional standardized unit of birth weight ( $P = 0.005$ ).

## Discussion

We observed that small body size at birth is associated with increased risk for developing CKD. This finding was not confined to low birth weight only, but was also observed for other markers of intrauterine growth restriction. Our findings in relation to the association between small body size at birth and CKD were confined to men. Prematurity also seemed to predict increased risk for CKD. These

**Table 4.** Association of Birth Weight and Gestational Age With Chronic Kidney Disease

	Men and Women			Men			Women		
	Cases/Person-y <sup>a</sup>	Rate <sup>b</sup>	HR (95% CI)	Cases/Person-y <sup>a</sup>	Rate <sup>b</sup>	HR (95% CI)	Cases/Person-y <sup>a</sup>	Rate <sup>b</sup>	HR (95% CI)
Birth weight, kg									
≤2.50	21/26	82	1.3 (0.8-2.1)	10/12	87	1.0 (0.5-1.9)	11/14	78	1.9 (1.0 to 3.7)
2.51-3.00	76/112	68	1.2 (0.9-1.6)	46/47	99	1.3 (0.9-1.8)	30/65	46	1.3 (0.8 to 2.1)
3.01-3.50	149/273	55	1.0 (reference)	101/129	78	1.0 (reference)	48/144	33	1.0 (reference)
3.51-4.00	105/209	50	0.9 (0.7-1.2)	56/116	48	0.6 (0.5-0.9)	49/93	53	1.6 (1.1 to 2.4)
>4.00	24/65	37	0.6 (0.4-1.0)	13/42	31	0.4 (0.2-0.7)	11/23	48	1.4 (0.8 to 2.8)
Gestational age at delivery									
<34 completed wk	12/6	188	2.6 (1.4-4.6)	6/3	179	2.1 (0.9-4.9)	6/3	199	3.2 (1.4 to 7.4)
34-36 completed wk	26/38	68	1.0 (0.7-1.6)	19/20	95	1.3 (0.8-2.2)	7/18	38	0.7 (0.3 to 1.4)
37-38 completed wk	55/128	43	0.7 (0.5-1.0)	39/67	58	0.9 (0.6-1.3)	16/61	26	0.5 (0.3 to 0.9)
39-40 completed wk	173/322	54	1.0 (reference)	99/161	62	1.0 (reference)	74/161	46	1.0 (reference)
≥41 completed wk	79/152	52	1.0 (0.8-1.3)	43/74	58	1.0 (0.7-1.4)	36/78	46	1.1 (0.7 to 1.6)
Unknown	30/37	82	1.4 (0.9-2.0)	20/19	103	1.6 (1.0-2.7)	10/17	58	1.1 (0.6 to 2.1)

Note: The Cox model is stratified on combinations of sex and year of birth and also includes early life and adult socioeconomic status. Abbreviations: CI, confidence interval; HR, hazard ratio.

<sup>a</sup>Person-years of exposure in 1,000s.

<sup>b</sup>Rate is per 100,000 person-years.

findings support the importance of early-life factors in the development of CKD.

According to the DOHaD hypothesis, several non-communicable diseases, including coronary heart disease and hypertension, have their origins in early life.<sup>4-9</sup> The programming impact of early-life and childhood factors on organ development and long-term function has been shown in several other diseases, including CKD. Brenner et al<sup>11</sup> have proposed that the process of developmental programming in the kidneys may result in a reduced nephron number. This reduction in nephrons in the kidneys could contribute to the development of elevated blood pressure and consequently increased risk for CKD.<sup>11</sup> This hypothesis offers a plausible link between low birth weight, hypertension, and CKD. Low birth weight and being born small for gestational age are associated with a low nephron number.<sup>20-23</sup> Our present findings support the hypothesis because there is a continuous reduction in risk for CKD with greater birth weight among men. Not only birth weight but also other markers of nonoptimal prenatal growth, including birth length, ponderal index, and placental weight, showed similar associations with CKD in adult life. We did not observe similar associations in women. These findings are similar to those reported from a large Norwegian register-based cohort study.<sup>24</sup>

There have been several studies describing the association between small body size at birth and different indicators of kidney disease. These outcomes have included measures of urinary albumin excretion rate, estimated glomerular filtration rate, and end-stage renal disease (ESRD).<sup>24-27</sup> A systematic review that included more than 2 million individuals from 32 studies reported that low birth weight confers a 70% increased risk for developing CKD (defined as albuminuria, reduced glomerular filtration rate, or end-stage kidney failure [ESRD]) in later life compared to normal birth weight.<sup>13</sup> However, most studies included in the systematic review were small and follow-up of the individuals ended in early midlife. The largest study included in the systematic review was based on a register study from Norway, comprising all patients born after 1967, when the Medical Birth Registry was initiated, and who had developed ESRD in Norway since 1980. The authors concluded that low birth weight was more strongly associated with ESRD development during the first 14 years of life.<sup>24</sup> However, the maximum follow-up was 38 years. In our study, we followed up people in the HBCS with a maximum follow-up of 86 years, which to our knowledge is the longest follow-up reported in the literature pertaining to early programming of CKD.

Low socioeconomic status (SES) is associated with increased risk for cardiovascular morbidity and mortality.<sup>28,29</sup> Similar associations have been reported between SES and CKD, although the specific role of socioeconomic factors at different stages of the life course remains obscure.<sup>30</sup> In high-income countries, CKD is most prevalent in people from lower socioeconomic groups. However, these associations have not been replicated in all

populations.<sup>31</sup> A similar association has also been reported in relation to low birth weight, hypertension, and CKD.<sup>32</sup> In the present study, we assessed SES throughout the life course. Childhood SES was not associated with CKD. However, adult SES showed an inverse association with CKD; higher SES was associated with significantly lower risk for developing CKD. Factors explaining this association may be environmental and infectious causes and inequities in health care.<sup>33</sup>

Globally, ~10% of infants are born preterm. We found that individuals born preterm before 34 weeks of gestation had an increased risk for CKD. Contrary to the risk associated with low birth weight, this risk was not confined to men; it appeared stronger among women. Although preterm birth is a major risk factor for neonatal acute kidney injury, the risk for manifest CKD surprisingly has been little studied.<sup>23</sup> Circumstantial evidence is provided by studies of lower glomerular filtration rate in prepubertal children born before 30 weeks or <1,000 g, smaller kidney volume in young adults born before 32 weeks or <1,500 g, and a case series of 6 adults with focal segmental glomerulosclerosis who were born before 30 weeks gestation and now aged 15 to 53 years.<sup>34-36</sup> To our knowledge, our study is the first to demonstrate that these findings translate to actual increased risk for CKD in adults born preterm.

Although not all individuals with a low nephron number develop CKD, low nephron number is an important predisposing factor to CKD. A kidney with fewer nephrons may be more vulnerable and therefore less able to withstand additional “hits” later in life imposed by nonoptimal growth, as well as conditions such as diabetes, cardiovascular disease, and obesity.<sup>5,23,37</sup>

The term CKD is used to indicate a chronic irreversible loss of kidney function, a process usually taking place gradually over many years. Main risk factors for CKD include hypertension and diabetes, and cardiovascular comorbid conditions are common among people with CKD.<sup>38</sup> In the present study, ~37% of the people with CKD in our cohort had been hospitalized or died of coronary heart disease. However, a similar association between birth weight and CKD persisted after excluding those with simultaneous coronary heart disease.

Our findings were mostly restricted to men. However, it is well known that pregnancies are more likely to have nonoptimal outcomes with male offspring.<sup>39</sup> This is believed to be because boys grow faster than girls. This more rapid growth takes place from an early stage of gestation and consequently makes boys more vulnerable if nutrition is compromised. We have previously shown that boys are not only more vulnerable to undernutrition during prenatal life than girls, but they also have a different path of intrauterine growth, which could make them respond differently in terms of maternal nutrition. We have shown that different markers of maternal nutrition program hypertension differently in the 2 sexes.<sup>40</sup>

Our study has some limitations. The data in the HBCS are restricted to people who were both born in Helsinki in

1924 to 1944 in 1 of the 2 major maternity hospitals and alive in 1971 (the year all Finnish residents were assigned a unique identification number). Thus, our study participants may not be representative of all people in Helsinki. For example, we lack information about people who were born at home and at private clinics or who died or emigrated before 1971. Thus, our study potentially has a different distribution of socioeconomic groups than the entire population of Helsinki at the time. However, as we have previously reported, this cohort had a similar social class distribution during childhood compared with that of the city as a whole. People hospitalized before 1971 or those who died before 1971 are not included in the analyses. However, this is a small part of the study population because CKD rapidly increases with increasing age. Furthermore, the HR with birth weight is very similar in all age groups. Therefore, we do not believe this will influence our findings.

Furthermore, body size at birth is a crude measure of the intrauterine environment, but it has been widely used in the literature as a marker of prenatal development. Among men, the relationship between birth size and CKD was independent of length of gestation, which suggests that it can be attributed to slow fetal growth instead of preterm birth. Finally, we cannot determine the extent to which the associations between thinness at birth and CKD are mediated through other CKD risk factors because we do not have these data available. Another limitation of the study is lack of dietary information for the cohort.

Strengths of our study include a well-characterized sample with information for birth anthropometrics collected from birth records and a long follow-up spanning to old age. Further strengths include reliable hospital birth record–based information for maternal characteristics and register-based information for CKD. The validity of national hospital discharge and mortality registers has been established.<sup>41</sup> Register data for hospital admission and discharge data were available for almost all cohort members who had not migrated or died without hospital in-patient care, thus minimizing loss to follow-up. Moreover, the study cohort has been followed up for a long period; follow-up time extends up to 86 years. The study population is ethnically homogeneous, which is both a strength and a weakness. Few studies have been able simultaneously to assess the association of body size at birth and later risk for CKD.

We conclude that small body size at birth is associated with increased risk for developing CKD in men. Among women, prematurity also increases the risk for CKD. These findings support the importance of early-life factors in the development of CKD.

## Supplementary Material

**Table S1:** Definition of kidney disease used in analyses according to ICD revision in force.

**Table S2:** Further exploration of association between neonatal measurements and CKD.

**Table S3:** Incidence rates of CKD according to age, in men and women combined and separately.

## Article Information

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