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

Johan G. Eriksson, Minna K. Salonen, Eero Kajantie, and Clive Osmond

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.

Complete author and article information provided before references.

Correspondence to J.G. Eriksson (johan.eriksson@helsinki.fi)

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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.[1-3] Traditionally, CKDs have been assumed to develop as the result of an interaction between genetic and environmental factors, although the importance of factors active early in life has more recently been recognized.[4,5]

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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.[6-9] 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.[4,5,10]

In the 1980s, Brenner et al[11] 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.[11,12] 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.[13]

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.[14] 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.[15]

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.[15]

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.[16] All deaths are recorded in the national Causes of Death Register.[17] 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.[18] Through Statistics Finland, we obtained data for occupation from census data from 1970 to 2000.[19] 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 subcauses by setting up a 3-*df* χ^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