

# History of Childhood Kidney Disease and Risk of Adult End-Stage Renal Disease

**TO THE EDITOR:** In their article, Calderon-Margalit et al. (Feb. 1 issue)<sup>1</sup> do not indicate whether the study participants had a history of prematurity or low birth weight. Were the persons who had a history of prematurity and presumed low nephron endowment at higher risk for the development of later end-stage renal disease (ESRD) than those who did not have such a history?

Also, was the prevalence of congenital anomalies of the kidney and urinary tract higher among persons classified as having “pyelonephritis” than among those who did not have that diagnosis? The overdiagnosis of “pyelonephritis” is suggested by the high prevalence (65.7%) during the 1967–1979 enrollment period (Table 1 of the article, available at NEJM.org), when there was less precision concerning the diagnosis of pyelonephritis than during later periods of enrollment. It is curious that more male participants than female participants were classified as having had “pyelonephritis” (55% vs. 45%) (Table 1 of the article). One would not have expected this finding in a country where circumcision is practically universal.

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No potential conflict of interest relevant to this letter was reported.

1. Calderon-Margalit R, Golan E, Twig G, et al. History of childhood kidney disease and risk of adult end-stage renal disease. *N Engl J Med* 2018;378:428–38.

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**TO THE EDITOR:** In the large retrospective cohort study by Calderon-Margalit et al., the risk of ESRD during adulthood was approximately four times as high among persons with a history of childhood kidney disease as the risk among persons who had no such history, even if renal function was apparently normal during adolescence. The authors interpret this finding as the result of loss of nephrons leading to hyperfiltration of residual nephrons and progressive decline in renal function.<sup>1</sup>

We contend that another, non–mutually exclusive interpretation is possible. Various kinds

of acute and chronic injuries are associated with a maladaptive tissue repair regulated by epigenetic changes with accelerated cellular aging and loss of function.<sup>2</sup> For example, patients with type 1 diabetes who have hyperglycemia during the early phase of the disease have an increased incidence of a diabetic nephropathy, even after a long period of normal metabolic control.<sup>3</sup> Similarly, kidney injury during childhood might initiate epigenetic changes that, together with hyperfiltration of the residual nephrons, promote renal fibrosis and progression to ESRD.<sup>4</sup> Since epigenetic modifications are reversible, these changes are an attractive therapeutic target to counteract the long-term deleterious effects of seemingly self-limited renal injuries.

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No potential conflict of interest relevant to this letter was reported.

1. Brenner BM, Humes HD. Mechanics of glomerular ultrafiltration. *N Engl J Med* 1977;297:148–54.

2. Ghosh AK, Rai R, Flevaris P, Vaughan DE. Epigenetics in reactive and reparative cardiac fibrogenesis: the promise of epigenetic therapy. *J Cell Physiol* 2017;232:1941–56.

3. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 2003;290:2159–67.

4. Tang C, Dong Z. Epigenetic regulation in acute kidney injury: new light in a dark area. *Kidney Int* 2015;88:665–8.

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**TO THE EDITOR:** Calderon-Margalit et al. present important data from the Israeli ESRD registry that suggest that childhood kidney disease requires lifetime follow-up because, although kidney function returns to normal by adolescence, the childhood history still confers a lifetime risk of ESRD. Kidney diseases in childhood include congenital anomalies of the kidney and urinary tract, pyelonephritis, and glomerular disease.

These data may have an implication for the future suitability of a person to be a living kid-