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ORIGINAL ARTICLE

Acute pyelonephritis in children and the risk of end-stage kidney disease

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Abstract

Background Pyelonephritis is the most common serious bacterial infection during childhood. The long-term importance of kidney scarring is unclear.

Objective To assess the risk of end-stage kidney disease (ESKD) in adolescents and young adults with history of pyelonephritis.

Study Design A nationwide, population-based, historical cohort study, including 1,509,902 persons (62% male) examined for military service between 1967 and 1997. Participants with a history of pyelonephritis were sub-grouped according to presence of kidney scarring and baseline kidney function. Data were linked to the Israeli ESKD registry to identify incident ESKD cases. Cox proportional hazards models were used to estimate the hazard ratio (HR) of treated ESKD (dialysis or kidney transplant).

Results Pyelonephritis was diagnosed in 6979 participants (0.46%). 6479 had normal kidney function and no evidence of kidney scarring, 400 had normal kidney function with evidence of scarring, and 100 demonstrated reduced baseline kidney function. Treated ESKD developed in 2352 individuals (0.2%) without history of pyelonephritis, 58 individuals (0.9%) with normal kidney function, history of pyelonephritis and no kidney scarring, 14 individuals (3.5%) with normal kidney function, history of pyelonephritis and kidney scarring, and 23 individuals (23.0%) with history of pyelonephritis and reduced baseline kidney function, yielding HR of 3.3, 34.8 and 43.2, respectively, controlling for age, gender, paternal origin, enrollment year, body mass index, and blood pressure, and accounting for death as a competing risk.

Conclusion History of pyelonephritis was associated with significantly increased risk of treated ESKD, particularly when associated with kidney scarring or reduced baseline kidney function.

Keywords Chronic kidney disease · Clinical epidemiology · Dialysis · End-stage kidney disease · Kidney transplantation · Pyelonephritis

Introduction

Acute pyelonephritis, sometimes referred to as febrile urinary tract infection (UTI), is the most common serious bacterial infection during childhood [1]. In addition to the risks during the acute infection, it has been proposed that acute pyelonephritis can result in long-term deterioration of kidney function [2, 3], due to subsequent kidney scarring, the incidence of which is controversial. For instance, while a recent study found scars in 10% of children [4, 5], previous studies have reported rates reaching 61% [5, 6]. Therefore, in the past, following acute pyelonephritis, children underwent a thorough work-up and were closely followed [2]. However, it was recently suggested that the risk

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of chronic kidney disease (CKD) due to acute pyelonephritis might actually be low [7, 8]. First, many scars previously attributed to pyelonephritis are now known to occur in utero, representing developmental abnormalities [9, 10]. Second, most available studies relied on short follow-up periods and highly heterogeneous cohorts [2, 11–18]. Moreover, most studies were not population-based and were biased in retrospectively selecting children on basis of the presence of scars or vesicoureteral reflux (VUR). Furthermore, previously published data have shown that kidney function was well preserved two decades following the first episode of UTI, except for children with bilateral kidney scarring [16]. Accordingly, most current guidelines suggest a less aggressive approach in the management of children following acute pyelonephritis [19].

In a recent nationwide population-based study, we demonstrated that pyelonephritis during childhood was associated with significantly increased risk of end-stage kidney disease (ESKD) [20]. Herein, 1,509,902 individuals, assessed at a mean age of 17.7 years, were followed for 30 years so as to determine to what extent the presence of kidney scarring or reduced kidney function at baseline affect the risk of ESKD.

Methods

Study participants

We conducted a historical cohort study of Israeli adolescents, which included potential army recruits. One year prior to their conscription into military service, all eligible Israeli adolescents undergo mandatory medical board examination by a committee of two trained military physicians that includes reviewing the medical file obtained from the primary care physician, taking a medical history and conducting a physical examination (including routine urinalysis). In case a nephrological problem is suspected (e.g. history of acute pyelonephritis), the conscript is referred to a board-certified nephrologist for confirmation or exclusion of the diagnosis [21]. Inclusion criteria for this study were age 16 through 25 years at the time of medical board examination, which took place between 1967 and 1997. Because military service is not mandatory for Israeli non-Jews, the study included only Jewish recruits. Exclusion criteria were the presence of any of the following diagnoses, which confer an increased risk of ESKD: diabetes mellitus, any rheumatic disease, cancer, hypertension, or any past or current kidney disease at the time of enrollment, including congenital or acquired anomalies of the kidneys or urinary tract, glomerulonephritis, nephrolithiasis, or cystic kidney disease. We also excluded participants with acute or chronic kidney injury or proteinuria, which were not associated with concomitant acute pyelonephritis. Nonetheless, participants with history of acute pyelonephritis and reduced kidney function at baseline were included as an additional comparison group.

Clinical assessment and diagnosis

All future conscripts provide copies of all available medical records, including health summary from their primary physicians, and undergo a physical examination that includes measurement of height, weight, and heart rate, sphygmomanometric blood pressure measurement obtained in the right arm in the seated position, and a dipstick urinalysis test. If a kidney-related diagnosis cannot be ruled out, the future conscript is sent for additional tests and referred to a board-certified nephrologist. The accuracy and completeness of the medical information and diagnoses are additionally verified by a committee of two trained military physicians. Each diagnosis is assigned a numerical code and recorded in a central database.

Diagnosis of pyelonephritis, kidney scarring, and concomitant CKD

Participants who had at least one prior episode of acute pyelonephritis according to a form submitted by their family physician underwent blood tests to assess creatinine levels and kidney imaging studies (kidney ultrasound, and/or intravenous pyelography (IVP)/DMSA scan) to detect CAKUT and kidney scarring. Notably, whereas the event of pyelonephritis took place prior to enrollment and was identified in the medical evaluation during recruitment, the measurement of kidney function and structure (e.g. scarring) took place at enrollment into the study once a diagnosis of history of acute pyelonephritis was found. All participants with recurrent pyelonephritis, kidney scarring or with abnormal kidney function at enrollment were referred to a board-certified nephrologist for final diagnosis confirmation. Participants with history of pyelonephritis were subsequently divided into three groups: (1) normal kidney function and no evidence of kidney scarring at the initial, pre-recruitment evaluation; (2) normal kidney function and kidney scarring; and (3) abnormal kidney function.

The Israeli treated ESKD Registry

The Israeli treated ESKD database is a national administrative registry maintained by the Ministry of Health [22]. It contains information on patients receiving any form of kidney replacement therapy (KRT), i.e. hemodialysis, peritoneal dialysis, or kidney transplantation. All dialysis units in Israel, public and private, report to the Ministry of Health on new patients receiving KRT and changes in treatment modality. The database includes demographic data, a primary diagnosis, and initial KRT modality, as well as dates of initiating dialysis,

change of dialysis treatment modalities, kidney transplantation, and death. Validation of the database includes periodic linkage with the Israeli population registry to update demographic and mortality data. Reports of cadaver donor transplants in Israel are crosschecked with the National Laboratory for Tissue Matching, and reports on living donor kidney transplants are crosschecked with the National Transplant Center. The current study cohort was linked to the Israeli treated ESKD registry using the identification number given to all Israeli citizens at the time of birth or immigration. The institutional review board of the Israel Defense Forces approved the study and waived the requirement for informed consent on the basis of preserving participants' anonymity.

Outcome variables and follow-up

Onset of treated ESKD was defined as the date of initiation of dialysis or kidney transplantation, whichever came first, and all treated ESKD cases from January 1, 1980, to December 31, 2014, were included. Follow-up period was measured from the initial medical board assessment until KRT initiation (incidence of ESKD), death, or December 31, 2014, whichever came first.

Statistical analysis

Summary statistics for the study group were expressed as mean (SD) or percentage. Cox proportional hazards models [23] were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for comparing the incidence of treated ESKD among participant sub-groups. The proportional hazards assumption was tested graphically using log–minus-log graphs. Cox's proportional hazards models were constructed controlling for age, sex, paternal origin (Europe/Americas, West Asia, North Africa, and Israel), period of baseline examination by decade, body mass index (BMI) according to the accepted cutoffs for overweight and obesity (BMI of 25 and 30 kg/m^2, respectively), systolic blood pressure (categorized as below or above the sex-specific 95th percentile), and presence of hematuria. Multiple imputations for missing data and the analysis of death as a competing risk were made with the use of SAS Enterprise Miner software, version 14.1 (SAS Institute). Two-sided P value < 0.05 was considered to indicate statistical significance. All other statistical analyses were conducted using SPSS version 24 (IBM).

Results

Study population

Figure 1 shows the study design, with stratification according to history of acute pyelonephritis, with or without kidney scarring and kidney function at baseline. The cohort comprised 1,509,902 adolescents and young adults (61.7% male). These were assessed prior to enrollment by a committee of two trained army doctors. The assessment included a review of all available medical records, including a structured letter provided by the treating physician, a detailed medical interview and physical examination, measurement of weight, height and blood pressure, and a urinary dipstick test. In case a history of pyelonephritis was found or suspected, further assessment by a nephrologist was carried out, which included blood test and kidney imaging. Of the 1,509,902 participants who met entry criteria, 1,502,923 had no history of acute pyelonephritis and 6979 (0.46%) had a history of at least one episode of acute pyelonephritis. Among the latter, 6479 had normal kidney function at the initial evaluation and no evidence of kidney scarring, 400 had normal kidney function at the initial evaluation but evidence of kidney scarring, and 100 demonstrated reduced kidney function at baseline (Fig. 1).

The participants' mean age at recruitment was 17.7 ± 1.0, with a relatively higher proportion of females among participants with a history of pyelonephritis compared to those without a history of pyelonephritis (44.0% vs. 38.2%, respectively). Interestingly, among those with a history of pyelonephritis, the subgroup with scarring also had a higher percentage of females compared to the subgroup without scarring (51.6% vs. 43.4%, respectively) (Table 1).

Acute pyelonephritis and ESKD

Our study encompassed 45,843,259 person-years of follow-up, with a mean follow-up of 30.4 years. Table 2 and Fig. 2 show the association between the different types of history of acute pyelonephritis and ESKD during the follow-up period, as assessed by the Cox Proportional Hazards Model, after accounting for death as a competing risk.

Among participants without a history of acute pyelonephritis, during a follow-up period of 30.3 ± 9.1 years, ESKD developed in 2352 individuals (0.2%), yielding an incidence of 5.2 cases per 100,000 person years. Among participants with a history of acute pyelonephritis with normal kidney function at baseline and no kidney scarring, 58 individuals (0.9%) developed ESKD, during a mean follow-up period of 36.5 ± 10.0 years. After controlling for age, sex, paternal origin, enrollment period, BMI, presence of microhematuria, and blood pressure, this group demonstrated an adjusted HR of 3.3 (95% CI 2.5-4.3) compared to participants without a history of acute pyelonephritis.

Participants with a history of acute pyelonephritis with normal kidney function at the initial evaluation and scarring exhibited an even greater risk of ESKD, with 14 individuals (3.5%) developing ESKD over a follow-up period of 27.6 ± 7.7 years, for an adjusted HR of 34.8 (95% CI

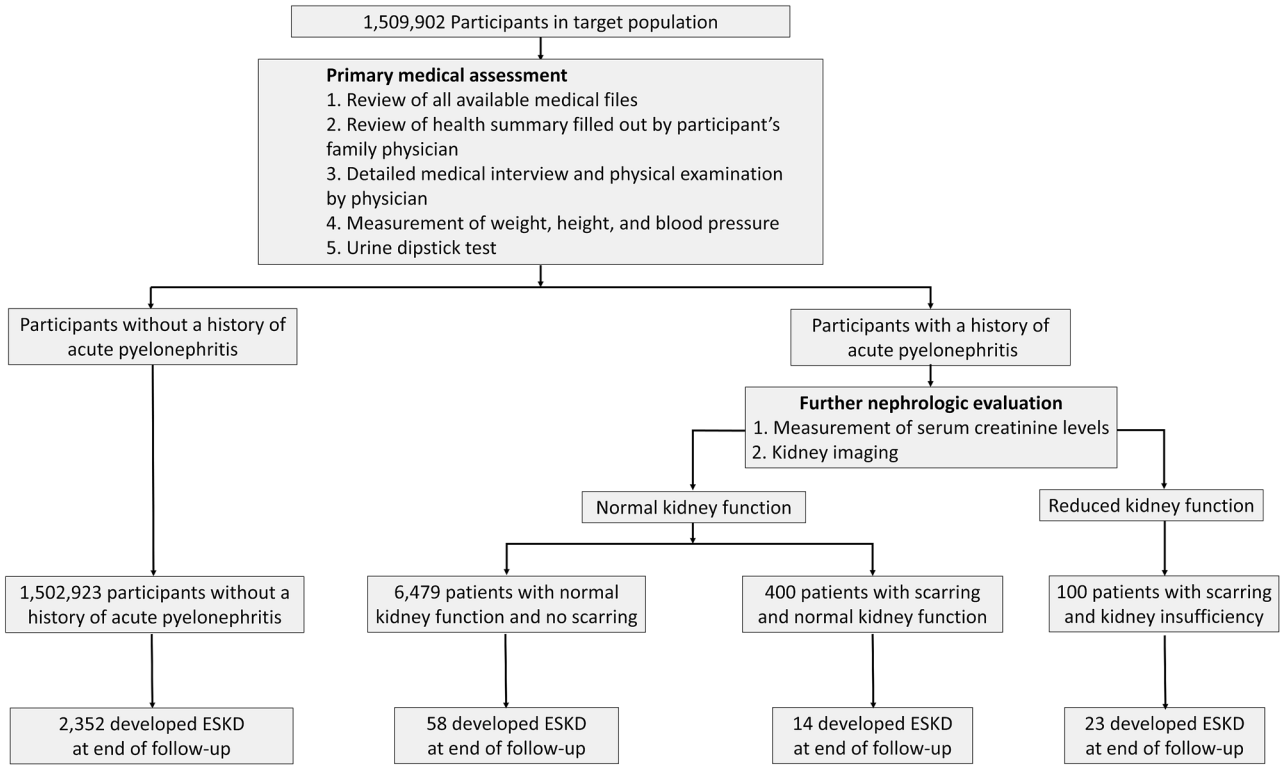

Fig. 1 Participant assessment, designation, and outcome

22.2–54.7) compared to patients with no history of acute pyelonephritis (Table 2 and Fig. 2).

Lastly, as expected, participants with a history of acute pyelonephritis, scarring and kidney insufficiency at baseline demonstrated the highest risk for ESKD, with 23 individuals (23.0%) developing ESKD during a mean follow-up of 32.2 ± 15.1 years, resulting in a HR of 43.2 (95% CI 29.0–64.4).

In order to determine whether the use of older imaging modalities might have affected the results, we stratified the cohort according to enrollment period (Table S1). We found that participants with normal kidney function and history of acute pyelonephritis with kidney scarring enrolled during the 1980s (HR: 20.6 [95% CI 6.6–64.3) and 1990s (HR: 23.7 [95% CI 3.3–171.4) still had a significantly higher risk of ESKD compared to participants with no history of acute pyelonephritis. Similar results were found in the group with history of acute pyelonephritis and reduced kidney function at baseline (HR: 136.3 [95% CI 19.0–981.0] and HR: 367.0 [95% CI 110.6–1217.3] during the 1980s and 1990s, respectively). Similarly, the group with normal kidney function at the initial evaluation and history of acute pyelonephritis without scarring enrolled during the 1980s also has a higher risk of ESKD (HR: 4.3 [95% CI 1.1–17.3]). The only exception was the subgroup with normal kidney function at baseline and a history of acute pyelonephritis without scarring, enrolled during the 1990s, which did not include any participants who developed ESKD until the end of follow-up. This might represent the short follow-up period for this group, which has the lowest level of kidney injury.

Subsequently, to gain better understanding of the temporal decline in kidney function among the different subgroups, we stratified participants according to follow-up duration and analyzed ESKD incidence for each 10-year interval in females and males (Tables S2–S3). Interestingly, among females (Table S2) with history of acute pyelonephritis the risk of ESKD was already significantly higher during the first decade of follow-up compared to participants without history of acute pyelonephritis. This was true for both those with (HR = 8.4 [95% CI 1.1–62.5]) and without (HR = 90.8 [95% CI 12.2–675.3]) kidney scarring. In contrast, males with a history of acute pyelonephritis exhibited an increased risk for ESKD only from the second decade onwards (Table S3).

In addition, we assessed the primary diagnosis at commencement of ESKD treatment for each subgroup, defined as either Diabetes Mellitus (DM, i.e. the most common cause of CKD [24]), other or unknown (Table S4). As expected, among participants with normal kidney function without history of acute pyelonephritis, DM was

Table 1 Baseline characteristics of 1,510,343 participants examined between 1975 and 1997 according to history of acute pyelonephritis (AP), kidney function (as determined at the initial, pre-recruitment evaluation) and the presence of kidney scarring

Characteristic	No history of AP (N = 1,502,923)	History of AP with normal kidney function and no scarring (N = 6479)	History of AP with scarring and normal kidney function (N = 400)	History of AP with scarring and kidney insufficiency (N = 100)
Age at assessment, mean (SD), years	17.7 (1.1)	17.8 (1.0)	18.1 (1.1)	18.6 (1.5)
Female sex, No. (%)	574,736 (38.2)	2813 (43.4)	224 (56.0)	34 (34.0)
Father's place of birth, No. (%)				
Europe/Americas	643,634 (42.8)	2840 (43.8)	188 (47.0)	66 (66.0)
West Asia	377,182 (25.1)	1678 (25.9)	91 (22.8)	8 (8.0)
North Africa	364,155 (24.2)	1548 (23.9)	93 (23.2)	8 (8.0)
Israel	68,313 (4.5)	253 (3.9)	14 (3.5)	0 (0.0)
Unknown	49,639 (3.3)	160 (2.5)	14 (3.5)	18 (18.0)
SBP, No. (%)				
< 95th percentile	1,024,576 (68.2)	2249 (34.7)	307 (76.7)	7 (7.0)
≥ 95th percentile	68,934 (4.6)	97 (1.5)	22 (5.6)	1 (1.0)
Unknown	409,413 (27.2)	4133 (63.8)	71 (17.7)	92 (92.0)
BMI, No. (%)				
< 25	1,279,412 (85.1)	5805 (89.6)	333 (83.3)	11 (11.0)
25–29	134,860 (9.0)	348 (5.4)	33 (8.3)	3 (3.0)
≥ 30	24,660 (1.6)	85 (1.3)	9 (2.2)	1 (1.0)
Unknown	63,991 (4.3)	241 (3.7)	25 (6.2)	85 (85.0)
Period of enrollment, No. (%)				
1967–1979	503,311 (33.5)	4562 (70.4)	89 (22.3)	75 (75.0)
1980–1989	480,386 (32.0)	702 (10.8)	165 (41.3)	9 (9.0)
1990–1997	519,226 (34.5)	1215 (18.8)	146 (36.5)	16(16.0)

AP acute pyelonephritis, SBP systolic blood pressure, *BMI* body mass index

Table 2 Association between history of acute pyelonephritis with and without kidney scarring and reduced kidney function, and treated end-stage kidney disease according to the Cox Proportional Hazards Model

	History of acute pyelonephritis			
	Normal kidney function and no scarring (N = 6479)	Scarring and kidney insufficiency (N = 400)	Scarring and normal kidney function (N = 100)	No history of acute pyelonephritis (N = 1,502,923)
Incidence rate of ESKD—No. of cases per 100,000 person-years	24.5	126.9	714.5	5.2
Mean follow-up—year (SD)	36.5 (10.0)	27.6 (7.7)	32.2 (15.1)	30.3 (9.1)
Age at end of follow-up—year (SD)	54.3 (9.9)	45.7 (7.9)	50.8 (15.2)	48.0 (9.3)
Died-No. (%)	306 (4.7)	14 (3.5)	11 (11.0)	40,250 (2.7)
Hazard ratio (95% CI) for ESKD from any cause in adulthood				
Unadjusted	3.1 (2.4–4.0)	35.1 (22.3–55.1)	92.0 (62.5–135.5)	Reference
Adjusted[a]	3.3 (2.5–4.3)	34.8 (22.2–54.7)	43.2 (29.0–64.4)	Reference

Kidney function refers to the initial, pre-recruitment evaluation

[a]Adjusted for age, gender, paternal origin, enrollment year, body mass index, and blood pressure

the primary diagnosis in over 35% of cases, consistent with previous reports [25]. In contrast, DM was significantly less common as a primary diagnosis in the other subgroups, while 'unknown' primary diagnosis was significantly more common (27.6–64.3%) compared to participants with no history of pyelonephritis (18.9%), especially in the group with history of acute pyelonephritis and scarring. This suggests that a history of acute

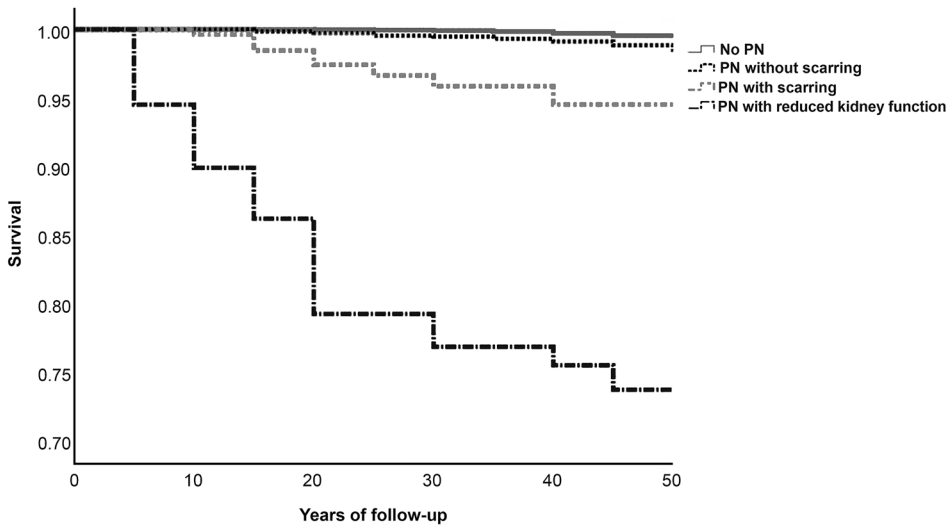

Fig. 2 Survival curve demonstrating the incidence of Treated ESKD among Study Participants. *PN* history of acute pyelonephritis

pyelonephritis with scarring might contribute to the development of ESKD among this group of patients.

Discussion

In this study, we found that history of acute pyelonephritis among adolescents and young adults, especially when accompanied by kidney scarring, may be a strong predictive risk marker of future ESKD.

Our findings indicate that history of acute pyelonephritis results in significantly worse outcomes than previously suggested [7, 8]. This can be explained by the higher number of participants and longer follow-up in our study. As for the subgroup with history of acute pyelonephritis and no scarring, which exhibited significantly higher rates of ESKD, further research is needed to determine whether this is dependent upon additional factors (e.g. VUR grade and number of pyelonephritis events). It should also be noted that the absolute risk of ESKD among these participants is still very low (< 1%). Several explanations might account for the higher risk for ESKD in this subgroup. First, acute kidney injury represents an independent risk factor for future CKD and ESKD, even in patients with normal kidney function [26, 27]. Hence, it is possible that acute pyelonephritis results in loss of nephrons and reduced kidney function, even if at subclinical levels initially. Similarly, pneumonia during childhood was recently shown to result in increased risk for chronic lung disease [28], indicating that severe parenchymal infections may have significant clinical impact. It is also possible that contemporary imaging modalities fail to detect very small scars.

Herein, we found that the lifetime prevalence of history of acute pyelonephritis was 0.46% among adolescents and young adults. Interestingly, few studies have examined the cumulative risk of acute pyelonephritis during childhood. A study from Sweden [29] found a cumulative risk of approximately 2% for UTI until the age of 11 years, with the proportion of febrile UTI among these ranging from 27 to 50% in older children and neonates to 89–100% in children below 1 year (excluding neonates), altogether arriving at similar numbers to ours. Another Swedish study reported a rate of 1.9% of pyelonephritis according to questionnaires filled in at the age of 7 years. A study in a general practice in Manchester identified a diagnosis of febrile UTI in 0.49% of children aged 14 years or under, during a four-year follow-up period [30]. Two explanations for the higher risk in our cohort are the higher number of participants and older age of initial assessment.

Interestingly, we detected higher rates of scarring among females. It has been previously suggested that a distinction should be made between primary kidney damage preceding infection and UTI-associated scars [1], with the former reported to be more frequent in males, whereas the latter is more frequent in females [9]. Previous studies did not show consistent results with respect to the relationship between gender and risk of detecting scars following acute pyelonephritis [5, 31–33]. In light of the higher prevalence of dysplastic kidney lesions in males, we presume that the higher rate of scarring in females in our cohort likely reflects post-infection scarring rather than congenital dysplastic lesions.

Several limitations should be considered when interpreting this study. First, data on history of acute pyelonephritis were collected from 1967 onwards, whereas data on treated ESKD were collected from 1980 onwards. We addressed these issues by stratifying our analyses by follow-up period, which yielded similar results. In addition, the study spans a very long period, from the 1960s to the 1990s. Hence, it is possible that the diagnostic tools used in the early period (e.g. ultrasound devices) had a lower

resolution compared to more modern systems, and thus the comparison between the different periods should be interpreted with caution. Second, we did not have precise information on the event of pyelonephritis during childhood (e.g. age, presentation etc.). Third, clinical information, such as creatinine levels and kidney imaging study results were reported rather than measured. Moreover, no data about clinical events during the follow-up period were available. Nonetheless, this is true for both the study and control populations. As for the clinical data, it is based on the evaluation of at least three physicians (primary care physician, a committee of two military doctors, and in cases of history of acute pyelonephritis, also a board-certified nephrologist), making the data highly reliable. Fourth, our study was limited to Jewish recruits, so its generalizability may be limited. Moreover, our cohort included a nationally representative group of Jewish men but not Jewish women, since orthodox women are exempt from military service. Hence, there is overrepresentation of males in the study. Lastly, we cannot exclude selection bias for the more severe cases of acute pyelonephritis. Nonetheless, we estimate this bias to be minimal, considering the prominent symptoms of acute pyelonephritis which almost invariably require medical intervention.

The main strengths of this study are reliance on a very large cohort having a population-based screening for history of kidney disease with detailed clinical assessment parameters alongside a long follow-up period and comprehensive documentation of ESKD.

Notably, ESKD represents only ~ 2% of all cases of CKD, which affects approximately 30 million people in the USA alone [34]. Hence, the results of this study should be taken in a broader context and could have implications on a much larger number of patients. Our results favor a more aggressive approach towards acute pyelonephritis in children, including early treatment, which has been shown to reduce kidney scarring among children with VUR [35]. In addition, closer evaluation (e.g. kidney imaging to detect scarring) and follow up of patients with history of acute pyelonephritis should be considered in order to detect the subgroup of patients that could progress toward CKD, and exercise relevant interventions that can halt the deterioration to ESKD, an approach which has also been suggested to deliver more quality of life at lower costs in the long run [36].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving Human Participants and/or Animals This study was performed in line with the principles of the Declaration of Helsinki. The institutional review board of the Israel Defense Forces approved the study and waived the requirement for informed consent on the basis of preserving participants' anonymity.

Informed consent The institutional review board of the Israel Defense Forces approved the study and waived the requirement for informed consent on the basis of preserving participants' anonymity.

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