Persistent Asymptomatic Isolated Microscopic Hematuria in Israeli Adolescents and Young Adults and Risk for End-Stage Renal Disease

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Context Few data are available on long-term outcomes among adolescents and young adults with persistent asymptomatic isolated microscopic hematuria.

Objective To evaluate the risk of end-stage renal disease (ESRD) in adolescents and young adults with persistent asymptomatic isolated microscopic hematuria.

Design, Setting, and Participants Nationwide, population-based, retrospective cohort study using medical data from 1,203,626 persons aged 16 through 25 years (60% male) examined for fitness for military service between 1975 and 1997 were linked to the Israeli treated ESRD registry. Incident cases of treated ESRD from January 1, 1980, to May 31, 2010, were included. Cox proportional hazards models were used to estimate the hazard ratio (HR) of treated ESRD among those diagnosed as having persistent asymptomatic isolated microscopic hematuria.

Main Outcome Measures Treated ESRD onset, defined as the date of initiation of dialysis treatment or the date of renal transplantation, whichever came first.

Results Persistent asymptomatic isolated microscopic hematuria was diagnosed in 3,690 of 1,203,626 eligible individuals (0.3%). During 21.88 (SD, 6.74) years of follow-up, treated ESRD developed in 26 individuals (0.70%) with and 539 (0.045%) without persistent asymptomatic isolated microscopic hematuria, yielding incidence rates of 34.0 and 2.05 per 100,000 person-years, respectively, and a crude HR of 19.5 (95% confidence interval [CI], 13.1-28.9). A multivariate model adjusted for age, sex, paternal country of origin, year of enrollment, body mass index, and blood pressure at baseline did not substantially alter the risk associated with persistent asymptomatic isolated microscopic hematuria (HR, 18.5 [95% CI, 12.4-27.6]). A substantially increased risk for treated ESRD attributed to primary glomerular disease was found for individuals with persistent asymptomatic isolated microscopic hematuria compared with those without the condition (incidence rates, 19.6 vs 0.55 per 100,000 person-years, respectively; HR, 32.4 [95% CI, 18.9-55.7]). The fraction of treated ESRD attributed to microscopic hematuria was 4.3% (95% CI, 2.9%-6.4%).

Conclusion Presence of persistent asymptomatic isolated microscopic hematuria in persons aged 16 through 25 years was associated with significantly increased risk of treated ESRD for a period of 22 years, although the incidence and absolute risk remain quite low.

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For editorial comment see p 764.
large cohorts, leading to considerable controversy over appropriate evaluation, management, and prognosis. We conducted a nationwide, population-based, retrospective cohort study to evaluate the risk of treated end-stage renal disease (ESRD) in adolescents and young adults with persistent asymptomatic isolated microscopic hematuria.

METHODS

Study Participants

One year prior to their conscription into military service, all eligible Israeli adolescents undergo obligatory medical board examination for health status assessment that includes reviewing the medical file obtained from the primary care physician, taking a medical history and conducting a physical examination (including routine urinalysis), and, if needed, providing referral for further evaluation. All potential recruits undergo baseline measurement of weight and height and a sphygmanometric blood pressure measurement obtained at the right arm in the seated position.

Inclusion criteria for the current study were age 16 through 25 years at the time of medical board examination between 1975 and 1997. Because military service is not mandatory for Israeli non-Jews, the study population included only Jewish recruits, for whom military service is compulsory. Exclusion criteria were the presence of any of the following diagnoses: diabetes mellitus, systemic lupus erythematosus, vasculitis, hypertension, or any known past or current kidney disease at the time of enrollment, including congenital or acquired anomalies of the kidneys or urinary tract, glomerulonephritis, nephrolithiasis, cystic renal disease, urinary tract infection, acute or chronic kidney injury, and proteinuria. Proteinuria was defined by urine dipstick testing. Dipstick levels of 1+ or higher recorded during the initial urinalysis screen were designated as positive and triggered 2 subsequent confirmatory dipstick tests. Participants with at least 1 positive confirmatory result were referred for 24-hour assessment of urine quantitative protein excretion and to a board-certified nephrologist for determination of a specific proteinuria-related diagnosis. Participants with quantitative protein excretion exceeding 200 mg/24 h were excluded from the study cohort.

Diagnosis of Persistent Asymptomatic Isolated Microscopic Hematuria

Participants enrolled in the study were initially screened for the presence of microscopic hematuria by the urinary dipstick test, followed by sediment examination by urine microscopy if the dipstick result was positive. The diagnostic criteria for persistent asymptomatic isolated microscopic hematuria were: (1) 5 or more red blood cells per high-power field for urine specimens obtained on 3 separate occasions on different days (female participants were instructed to avoid testing during menstruation); (2) serum creatinine values within the normal range; (3) no abnormalities detected on renal imaging studies (which consisted of intravenous pyelographic contrast imaging performed from 1975 to the late 1980s and renal urinary tract and bladder ultrasound from the late 1980s to the end of enrollment in 1997); (4) being otherwise asymptomatic, with hematuria as the sole finding and not attributed to other known or apparent disease; and (5) further evaluation and confirmation of the diagnosis of asymptomatic isolated microscopic hematuria by a board-certified nephrologist. Participants who fulfilled these criteria for persistent asymptomatic isolated microscopic hematuria were then assigned a specific code number.

The Israeli Treated ESRD Registry

The Israeli treated ESRD database is a national administrative registry maintained by the Ministry of Health. It contains information on patients receiving any form of renal replacement therapy, ie, hemodialysis, peritoneal dialysis, or kidney transplantation. All nephrology dialysis units in Israel report to the Ministry of Health on new patients receiving renal replacement therapy and changes in treatment modality. The database includes demographic data, a primary diagnosis, and initial modality of renal replacement therapy, as well as dates of initiating dialysis, change of dialysis treatment modalities, renal transplantation, and death. Validation of the treated ESRD database includes periodic linkage with the Israeli population registry to update demographic and mortality data. Reports of cadaver-donor transplants in Israel are cross-checked with the National Laboratory for Tissue Matching, and reports on living donor kidney transplants are cross-checked with the National Transplant Center. A single primary diagnosis is recorded for each new patient in the treated ESRD database. The current study cohort was linked to the Israeli treated ESRD registry using the identification number given to all Israeli citizens at the time of birth or immigration.

The institutional review boards of both the Israel Defense Forces and Sheba Medical Center 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 ESRD was defined as the date of initiation of dialysis treatment or the date of renal transplantation, whichever came first, and all treated ESRD cases from January 1, 1980, to May 31, 2010, were included. The causes of treated ESRD were categorized as diabetes, hypertension, glomerulonephritis (including a subcategory for IgA nephropathy), hereditary nephritis, interstitial nephritis, cystic kidney disease, secondary glomerulonephritis, drug-induced, and other causes. The etiology was recorded by the responsible nephrologist at the medical center where the patient was receiving renal replacement therapy; 23% of patients had missing information on etiology of treated ESRD. Follow-up period was measured from the initial medical
board assessment until the initiation of renal replacement therapy (incidence of ESRD), death, or May 31, 2010, whichever came first.

**Statistical Analysis**

Summary statistics for the study group were expressed as mean (SD) or percentage. Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for comparing the incidence of treated ESRD among participants with and without persistent asymptomatic isolated microscopic hematuria. The proportional hazards assumption was tested graphically using log-minus-log graphs. Models were constructed controlling for age, sex, paternal country of origin (Europe/Americas, West Asia, North Africa, and Israel) and period of baseline examination by decade. Additional models controlled for body mass index (BMI) below or above the cutoff for overweight (the sex-specific 85th percentile, ie, 24.2 for male and 24.5 for female participants, calculated as weight in kilograms divided by height in meters squared) and for mean arterial blood pressure, calculated as 2/3 diastolic blood pressure + 1/3 systolic blood pressure and categorized as below or above the sex-specific 90th percentile (98.3 mm Hg for male and 96.7 mm Hg for female participants).

Data were complete for all variables except for BMI, mean arterial pressure, and paternal country of origin, which were available for 96.7%, 91.9%, and 88% of the study population, respectively, with missing values receiving a separate category in the models.

Stratified analyses were conducted by strata of sex, age at enrollment, decade of enrollment, and years of follow-up. Sensitivity analyses were restricted to participants who had at least 5 years of follow-up, treated ESRD diagnosed from 1989, and best-worst scenario analysis for ESRD due to primary glomerular disease. This latter analysis considered the following diagnoses as ESRD due to primary glomerular disease: hereditary nephritis, IgA nephropathy, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, membranous nephropathy, glomerulonephritis not otherwise specified, and rapidly pro-

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**Figure 1. Participant Assessment, Designation, and Outcomes**

- **Primary medical evaluation**
  1. Review of all available medical files
  2. Review of health summary filled out by participant's family physician
  3. Detailed medical interview and physical examination by physician
  4. Measurement of weight, height, and blood pressure
  5. Urine dipstick test

- **Secondary medical evaluation**
  1. Three additional urine microscopy tests
  2. Renal and bladder imaging studies
  3. Measurement of serum creatinine level

- **Evaluation by nephrologist**
  1. Five or more RBCs per high-power field on each urine test
  2. Serum creatinine values within normal range
  3. Normal renal imaging study results
  4. Hematuria as sole finding not attributable to other disease

1237869 Participants in target population

- Participants without hematuria and without medical conditions conferring increased risk for ESRD
  - 199036 Without confirmed persistent asymptomatic isolated microscopic hematuria included in primary analysis (control group)
  - 539 Developed ESRD at end of follow-up

- Participants with hematuria and without medical conditions conferring increased risk for ESRD
  - 3690 With confirmed persistent asymptomatic isolated microscopic hematuria included in primary analysis
  - 26 Developed ESRD at end of follow-up

- Participants with medical conditions conferring increased risk for ESRD
  - 34243 At risk for ESRD excluded from primary analysis
  - 350 Developed ESRD at end of follow-up

ESRD indicates end-stage renal disease; RBC, red blood cell.

*Evaluated by a specialist and additional tests performed as needed.
Persistent Asymptomatic Isolated Microscopic Hematuria and Treated ESRD

During 26,278,598 person-years of follow-up, 565 participants developed treated ESRD, for an overall incidence rate of 2.15 per 100,000 person-years. The characteristics of those who developed treated ESRD, by study group, are reported in Table 2. Baseline data for participants with persistent asymptomatic isolated microscopic hematuria who developed ESRD (n = 539 [0.04%]) were similar to those of participants without the condition who developed ESRD (n = 539 [0.04%]) in all aspects except for BMI: the former had lower BMI levels compared with the latter (mean, 20.6 [SD, 2.87] and 22.9 [SD, 4.33], respectively; P =.001). Participants with persistent asymptomatic isolated microscopic hematuria were younger at ESRD diagnosis compared with their counterparts (mean age at diagnosis, 34.7 [SD, 6.6] and 38.6 [SD, 8.5] years, respectively; P =.02) and had a shorter follow-up (Table 2). The mean age at the end of follow-up was 38.4 (SD, 8.4) years (range, 18-60 years).

Figure 2 shows the association between persistent asymptomatic isolated microscopic hematuria and treated ESRD during the follow-up period. The incidence rates of treated ESRD were 34.0 (95% CI, 22.2-49.9) per 100,000 person-years among participants with persistent asymptomatic isolated microscopic hematuria and 2.05 (95% CI, 1.88-2.23) per 100,000 person-years among those without the condition, yielding an unadjusted HR of 19.5 (95% CI, 13.1-28.9). Controlling for age, sex, paternal country of origin, period of enrollment, BMI, and blood pressure at baseline had minimal effect on these estimated HRs for treated ESRD (HR, 18.5 [95% CI, 12.4-27.6]) (Table 3). Restricting the study population to those who had at least 5 years of follow-up also did not materially change the HR estimate (19.2 [95% CI, 12.9-28.6]).

To exclude the possibility of misclassification bias attributable to less accurate imaging techniques during the initial years of the study and to
eliminate concern that dates of treated ESRD incidence before 1989 were inaccurate, we analyzed treated ESRD in a subgroup of participants enrolled after 1989, all of whom underwent renal ultrasonography. Persistent asymptomatic isolated microscopic hematuria among the 587,211 participants diagnosed after 1989 was still strongly and independently associated with treated ESRD (HR, 18.9 [95% CI, 6.81-52.2]). We further studied the association for the whole population with logistic regression and with imputation of different incidence dates between 1980-1988, and those analyses yielded identical estimates. The fraction of treated ESRD attributed to microhematuria was 4.3% (95% CI, 2.9%-6.4%).

### Risk Factors for Specific Causes of Treated ESRD

Reported etiologies for ESRD by study group are reported in Table 2. We further analyzed persistent asymptomatic isolated microscopic hematuria as a risk factor for specific treated ESRD etiologies. Incidence rates of primary glomerular disease–associated ESRD were 19.6% (95% CI, 11.0-32.4) vs 0.55% (95% CI, 0.47-0.65) per 100,000 person-years among participants with and without the condition, respectively. The HR for treated ESRD attributed to primary glomerular disease, adjusted for age, sex, country of paternal origin, study period, BMI, and mean arterial pressure, was 32.4 (95% CI, 18.9-55.7). In a best-worst sensitivity analysis, assuming all missing etiologies of ESRD in the control group were attributable to primary glomerular disease yielded an HR of 18.8 (95% CI, 11.1-31.8). The assumption that all missing etiologies in the group with hematuria were attributable to primary glomerular disease yielded an HR of 43.1 (95% CI, 26.7-69.4).

### COMMENT

In this long-term, nationwide, population-based, retrospective cohort study, persistent asymptomatic microscopic hematuria was strongly associated with the incidence of treated ESRD. These results were independent of potential ESRD risk confounders, such as age, sex, country of origin, BMI, and blood pressure. Our results suggest that persistent asymptomatic isolated microscopic hematuria among adolescents and young adults may be a strong predictive risk marker of future ESRD, attributable mostly to glomerular disease as the primary etiology.

Several limitations of this study warrant consideration. First, the annual prevalence of asymptomatic isolated microscopic hematuria was relatively low in the period 1975-1979 (0.1%-0.2%) compared with subsequent years (0.2%-0.5%). Second, data on persistent asymptomatic isolated microscopic hematuria were collected from 1975 forward, whereas data on treated ESRD were collected from 1980 forward. We addressed these issues by stratifying our analyses by year of cohort enrollment and follow-up period, which yielded similar results.

Third, clinical information, such as normal baseline creatinine levels and normal findings from renal imaging

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**Table 2. Characteristics of Participants With Treated End-Stage Renal Disease According to Persistent Asymptomatic Isolated Microscopic Hematuria Category**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With Hematuria (n = 26)</th>
<th>Without Hematuria (n = 539)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment baseline characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex, %</td>
<td>21 [80.7] (62.4-92.6)</td>
<td>419 [77.7] (74.1-81.1)</td>
<td>.72</td>
</tr>
<tr>
<td>Country of origin, %±</td>
<td></td>
<td></td>
<td>.28</td>
</tr>
<tr>
<td>Europe/Americas</td>
<td>3 [11.5] (3.0-28.3)</td>
<td>156 [28.9] (25.2-32.9)</td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>9 [34.6] (18.4-54.1)</td>
<td>143 [26.5] (22.9-30.4)</td>
<td></td>
</tr>
<tr>
<td>North Africa</td>
<td>11 [42.3] (24.6-61.6)</td>
<td>160 [29.6] (25.9-33.7)</td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td>1 [3.8] (1.9-17.5)</td>
<td>15 [2.8] (1.63-4.45)</td>
<td></td>
</tr>
<tr>
<td>Blood pressure, mean, mm Hg±</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>23 [118] (113-122)</td>
<td>378 [121] (120-122)</td>
<td>.22</td>
</tr>
<tr>
<td>Diastolic</td>
<td>23 [72.9] (68.9-76.9)</td>
<td>378 [74.4] (73.7-75.1)</td>
<td>.48</td>
</tr>
<tr>
<td>Mean</td>
<td>23 [87.9] (84.1-91.7)</td>
<td>378 [90.1] (89.4-90.8)</td>
<td>.21</td>
</tr>
<tr>
<td>BMI, mean±</td>
<td>25 [20.6] (19.4-21.8)</td>
<td>474 [22.9] (22.5-23.3)</td>
<td>.001</td>
</tr>
<tr>
<td>Characteristics at ESRD diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis, mean, y</td>
<td>26 [34.7] (32.1-37.3)</td>
<td>539 [38.6] (37.9-39.3)</td>
<td>.02</td>
</tr>
<tr>
<td>Follow-up time, mean, y</td>
<td>26 [15.7] (13.1-18.3)</td>
<td>539 [20.6] (19.9-21.3)</td>
<td>.004</td>
</tr>
<tr>
<td>Treated ESRD etiologies, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 [3.8]</td>
<td>111 [20.6]</td>
<td></td>
</tr>
<tr>
<td>Hereditary nephritis</td>
<td>4 [15.4]</td>
<td>7 [1.3]</td>
<td></td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>4 [15.4]</td>
<td>30 [5.5]</td>
<td></td>
</tr>
<tr>
<td>Glomerular disease (excluding IgA nephropathy)</td>
<td>7 [26.9]</td>
<td>108 [20]</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 [3.8]</td>
<td>27 [5]</td>
<td></td>
</tr>
<tr>
<td>Cystic kidney disease</td>
<td>1 [3.8]</td>
<td>39 [7.2]</td>
<td></td>
</tr>
<tr>
<td>Chronic interstitial nephritis</td>
<td>0 [0]</td>
<td>14 [2.6]</td>
<td></td>
</tr>
<tr>
<td>Secondary glomerulonephritis or vasculitis</td>
<td>0 [0]</td>
<td>42 [7.8]</td>
<td></td>
</tr>
<tr>
<td>Drug induced</td>
<td>0 [0]</td>
<td>9 [1.6]</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous conditions</td>
<td>3 [11.5]</td>
<td>20 [3.7]</td>
<td></td>
</tr>
<tr>
<td>Uncertain or unrecorded cause</td>
<td>5 [19.2]</td>
<td>132 [24.5]</td>
<td></td>
</tr>
<tr>
<td>Primary glomerular disease, %</td>
<td>15 [57.7] (38.4-75.4)</td>
<td>145 [26.9] (23.3-30.8)</td>
<td>.001</td>
</tr>
<tr>
<td>Renal transplantation, %</td>
<td>21 [80.7] (62.4-92.6)</td>
<td>298 [55.2] (51.1-59.5)</td>
<td>.01</td>
</tr>
<tr>
<td>Died, %</td>
<td>3 [11.5] (3.0-28.3)</td>
<td>80 [14.8] (12.0-18.0)</td>
<td>.78±</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; ESRD, end-stage renal disease.
± Calculated as weight in kilograms divided by height in meters squared. Data available from 96.7% of the study population.
*Defined as any of the following: IgA nephropathy, glomerular disease, hereditary nephritis.

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studies for the participants with hematuria, were reported rather than measured. Therefore, we do not have participants’ glomerular filtration rate values. Fourth, we cannot rule out the possibility that trace dipstick proteinuria may have remained undetected or unreported during the initial screening; it is possible that some participants who subsequently developed treated ESRD had microalbuminuria, a suggested risk factor for ESRD among patients with microscopic hematuria. Nevertheless, even if this were the case, microscopic hematuria would still represent an important clinical marker for an increased risk of renal disease in these participants, in the absence of abnormal measures for these other clinical indices of renal injury at the time of screening assessment. Last, our study was limited to Jewish recruits, so its generalizability may be limited.

The strengths of our study are that it included very large cohorts with detailed clinical assessment parameters together with a long follow-up period and comprehensive documentation of ESRD, thereby enabling the determination of the risks for this disease with relatively low incidence. Moreover, persistent asymptomatic isolated microscopic hematuria was diagnosed only after a nephrologic assessment had excluded other renal pathologies. The availability of such a large mass-screening setup enabled us to establish that the prevalence of per-

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**Figure 2.** Cumulative Incidence of Treated ESRD among Participants With and Without Persistent Asymptomatic Isolated Microscopic Hematuria

**Table 3.** Association Between Persistent Asymptomatic Isolated Microscopic Hematuria and Treated End-Stage Renal Disease According to the Cox Proportional Hazards Models by Sex, Age at Study Enrollment, Decade of Enrollment, and Follow-up Period

<table>
<thead>
<tr>
<th>Variable</th>
<th>With Hematuria</th>
<th>Without Hematuria</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All ESRD</td>
<td>No./100 000 Person-Years</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>All participants</td>
<td>3690</td>
<td>26</td>
<td>199 936</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2755</td>
<td>21</td>
<td>720 289</td>
</tr>
<tr>
<td>Female</td>
<td>935</td>
<td>5</td>
<td>479 647</td>
</tr>
<tr>
<td>Age at enrollment, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤17</td>
<td>2276</td>
<td>13</td>
<td>1 022 599</td>
</tr>
<tr>
<td>&gt;17</td>
<td>1414</td>
<td>13</td>
<td>177 337</td>
</tr>
<tr>
<td>Year of enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1975-1979</td>
<td>206</td>
<td>6</td>
<td>189 541</td>
</tr>
<tr>
<td>1980-1989</td>
<td>1732</td>
<td>16</td>
<td>477 761</td>
</tr>
<tr>
<td>1990-1997</td>
<td>1752</td>
<td>4</td>
<td>532 634</td>
</tr>
<tr>
<td>Follow-up, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4</td>
<td>3686</td>
<td>0</td>
<td>1 199 770</td>
</tr>
<tr>
<td>5-9</td>
<td>3677</td>
<td>4</td>
<td>1 196 066</td>
</tr>
<tr>
<td>10-19</td>
<td>3665</td>
<td>15</td>
<td>1 198 878</td>
</tr>
<tr>
<td>Excluding first 5 y of follow-up</td>
<td>3677</td>
<td>26</td>
<td>1 196 066</td>
</tr>
</tbody>
</table>

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

aNegative persistent asymptomatic isolated microscopic hematuria is the reference category in all models (P<.001 for all).
bAdjusted for sex, age, country of origin, and period of baseline examination by decade of enrollment.
cAdjusted for covariates in model 1 plus body mass index and mean blood pressure.
Persistent asymptomatic isolated microscopic hematuria was 0.3% among adolescents and young adults. This value is within the lower range of previously reported prevalence.1,7,9,15 Most likely because we required persistence of hematuria and microscopic confirmation rather than relying solely on isolated dipstick tests, which reportedly yield high rates of false-positive results.10 In addition, the workup of positive hematuria cases (ie, renal function tests and kidney imaging studies in addition to a nephrologist's evaluation) excluded other known causes of persistent microscopic hematuria, such as congenital renal malformations and urolithiasis.20

We found male predominance among participants with persistent asymptomatic isolated microscopic hematuria. This is in line with the male predominance reported in IgA nephropathy21 and hereditary nephritis22 and unlike the reported finding of possible mild female predominance in thin basement membrane disease.23 Those 3 etiologies are considered by most authors to be predominant for persistent asymptomatic isolated microscopic hematuria in this age group.24,29,29 The association with progression to chronic kidney disease is best established for IgA nephropathy21 and Alport syndrome.22 In contrast, thin basement membrane disease, a common etiology for microscopic hematuria, had been considered benign by most authors, although recent studies have suggested otherwise.23,30 Because renal biopsies are not typically part of the evaluation of microscopic hematuria, it is difficult to estimate the prevalence of cases clearly attributable to each disease category and to efficiently predict the risk for future chronic kidney disease among patients with persistent asymptomatic isolated microscopic hematuria. Among the treated ESRD etiologies of those patients in the current study, we found IgA nephropathy and hereditary nephritis to contribute equally to its occurrence. Moreover, hereditary nephritis may be much more widespread than commonly believed, and some cases may have been misdiagnosed as benign thin basement membrane disease.23,30

Among participants with hematuria, early detection of ESRD with more assiduous follow-up might bias the results. Nevertheless, early detection of chronic kidney disease likely would have triggered therapeutic interventions with the potential of slowing progression to ESRD, decreasing rather than increasing the hazard ratio. Treated ESRD is an advanced clinical outcome, and its detection and universal registration in the Israeli health care system should not be influenced by diligence of health care follow-up, in contrast to early presymptomatic stages of chronic kidney disease. Another potential bias is that intravenous pyelographic contrast imaging performed for evaluation prior to 1989 could have caused increased kidney failure; however, restricting our study population to the post-1989 subgroup did not materially change the results.

In our study, participants with ESRD and with persistent asymptomatic isolated microscopic hematuria were considerably younger at ESRD onset compared with those with ESRD and no similar history (mean age at diagnosis, 34 vs 38 years, respectively). This may be related to the difference in underlying renal diseases between the study groups (Table 2). The condition was associated with an increased relative risk for the development of ESRD attributable to primary glomerular disease (multivariate-adjusted HR, 32.4 [95% CI, 18.9-55.7]). Consequently, our findings suggest that persistent asymptomatic isolated microscopic hematuria detected during adolescence and young adulthood is an early marker for primary glomerular injury and may be the first sign of an occult renal disease. As such, there may be a window during which the diagnosis of asymptomatic isolated microscopic hematuria following urine screening can provide an alert to the future development of symptoms or renal failure.

Follow-up ended before the study population reached the age at which ESRD peaks. ESRD is rare in young adults, as reflected by the low incidence rates observed in our study. However, because ESRD is the tip of the iceberg, estimated to represent only 2% of all patients with chronic kidney disease, interpretation of our findings should consider the much wider spectrum and far larger numbers of individuals with chronic kidney disease.31,32 Therefore, demonstrating that persistent isolated microscopic hematuria is a risk marker for ESRD highlights the importance of early detection of predialysis chronic kidney disease for the application of current and future strategies to slow the deterioration to ESRD. It also shows the importance of considering complications and comorbid conditions across the range of chronic kidney disease.33

Our study was not designed to examine the effectiveness of mass screening for microscopic hematuria in children and young adults. However, the additional cases attributed to persistent microhematuria, even if few, because they represent individuals who are younger at ESRD onset, probably represent loss of many quality-adjusted life years owing to productivity loss and to ESRD-related comorbid conditions. In light of our findings, future studies are warranted to evaluate the utility of population screening in improving clinical outcomes.

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