Risk of CKD Following Detection of Microscopic Hematuria: A Retrospective Cohort Study

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## Risk of CKD Following Detection of Microscopic Hematuria

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<td>Retrospective Cohort Study</td>
<td>Microscopic hematuria: ≥5 red blood cells/HPF</td>
<td>Multivariable-adjusted HR (95% CI) for incident CKD</td>
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| N = 232,220 healthy adults who received regular health exams in South Korea | Measurement at 2 consecutive visits:  
  - No hematuria at both visits  
  - Hematuria followed by no hematuria  
  - No hematuria followed by hematuria  
  - Persistent hematuria | No Hematuria | Regressed | Developed | Persistent |
| 4.8 years of follow-up | CKD: GFR <60 mL/min/1.73 m² or proteinuria | Women | Ref | 1.38 | 2.52 | 3.92 |
| | | | (0.89-2.13) | (1.86-3.41) | (2.88-5.34) |
| | | Men | Ref | 2.80 | 4.44 | 8.34 |
| | | | (1.78-4.40) | (3.18-6.18) | (5.92-11.74) |

**CONCLUSION:** Men and women with microscopic hematuria, especially persistent hematuria, may be at increased risk of CKD.

The association was stronger in men than in women.
Risk of CKD Following Detection of Microscopic Hematuria: A Retrospective Cohort Study

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ABSTRACT

**Rationale & Objective:** Microscopic hematuria is an uncertain risk factor for chronic kidney disease (CKD). We investigated the association between persistent or single episodes of microscopic hematuria and the development of incident CKD overall and separately among men and women.

**Study Design:** Retrospective cohort study.

**Setting and Participants:** A total of 232,220 Korean adults without CKD at baseline who underwent repeated regular health examinations at Kangbuk Samsung Health Study formed the study cohort.

**Exposure:** Microscopic hematuria was defined by ≥5 red blood cells per high-power field. Participants were categorized into one of four groups according to the presence of hematuria at two consecutive examinations: a) no hematuria at both examinations (reference group); b) hematuria followed by no hematuria (regressed hematuria group); c) no hematuria followed by hematuria (developed hematuria group); and d) hematuria at both examinations (persistent hematuria).

**Outcome:** CKD was defined as an estimated glomerular filtration rate <60 ml/min/1.73 m² or proteinuria defined as 1+ or more on dipstick examination.

**Analytical Approach:** Semi-parametric proportional hazards models were used to estimate hazard ratios (95% CIs).

**Results:** During a 4.8-year median follow-up, 2,392 participants developed CKD. Multivariable-adjusted hazard ratios (95% CI) for incident CKD, comparing the “regressed,” “developed,” and
“persistent” hematuria groups to the “no hematuria” group were 1.85 (1.35–2.53), 3.18 (2.54–3.98), and 5.23 (4.15–6.59), respectively. The association between persistent hematuria and incident CKD was stronger in men than women ($P_{\text{interaction}} < 0.001$), although a significant association was observed in both sexes.

**Limitations:** Lack of albuminuria and inability to consider specific glomerular diseases.

**Conclusion:** Men and women with microscopic hematuria, especially persistent hematuria, may be at increased risk of CKD.

**Keywords:** Chronic kidney disease; Microscopic hematuria; Sex differences; eGFR; Proteinuria
PLAIN-LANGUAGE SUMMARY:

Hematuria, which refers to the presence of blood in the urine, is has been reported to associate with increased risk of chronic kidney disease (CKD). However, the relationship between hematuria that persists over time and kidney function is not clear. In this large study consisting of relatively young and healthy Korean adults, we investigated the association between episodes of microscopic hematuria and the development of CKD. We found that microscopic hematuria, especially when persistent, was associated with worse kidney function. These associations were stronger in men compared with women but were readily apparent in both sex groups. Our study suggests that individuals with prolonged hematuria should be monitored, and that they may be candidates for early preventive strategies to decrease the risk of subsequent CKD.
INTRODUCTION

Chronic kidney disease (CKD) contributes to premature mortality both directly and as a risk factor for other non-communicable diseases, including cardiovascular disease.\textsuperscript{1,2} It has been estimated that global CKD prevalence has increased by 29.3\% since 1990 and that CKD was the 12\textsuperscript{th} leading cause of death in the world in 2017.\textsuperscript{2} Early detection of CKD and identification and management of modifiable CKD risk factors and its progression are important to reduce risk of end-stage kidney disease and non-renal complications, including cardiovascular mortality.\textsuperscript{3,4}

Microscopic hematuria is a common incidental finding in urinalysis, and its prevalence has varied between studies, ranging from 0.12–30\%.\textsuperscript{5,6} More than 50\% of patients with microscopic hematuria have no definite identifiable cause,\textsuperscript{6} and low-level hematuria is considered a benign condition. In contrast, hematuria has been proposed as an early marker of CKD; however, its role in CKD risk is not well established in the general population.\textsuperscript{7-9}

Two studies have reported a relationship between microscopic hematuria with end-stage renal disease risk\textsuperscript{10} or increased CKD risk, defined using estimated glomerular filtration rates (eGFRs).\textsuperscript{11} However, no studies have evaluated the association between microscopic hematuria changes and CKD, based on two measurements separated in time. Additionally, in contrast to hematuria in men, microscopic hematuria in young women is commonly considered a benign finding.\textsuperscript{12,13} However, whether there are sex-specific differences in the association between microscopic hematuria and CKD is uncertain.

We aimed to evaluate the relationship between persistent hematuria, single episodes of hematuria and no evidence of hematuria, and CKD risk; and tested whether the association between hematuria and CKD risk differed by sex.

METHODS
The Kangbuk Samsung Health Study is a cohort study of South Korean men and women aged ≥18 years who receive annual or biennial comprehensive health examinations at the Kangbuk Samsung Hospital Health Screening Center clinics in Seoul and Suwon, South Korea, as previously described.\textsuperscript{14}

The present analysis included all study participants who received comprehensive health examinations at least twice between January 1, 2011 and December 31, 2018 and at least one additional follow-up visit before December 31, 2020 (n = 276,655). Since our purpose was to evaluate the association of hematuria status at two visits on subsequent CKD development after adjusting for potential confounding factors, we excluded 44,435 participants with one or more of exclusion criteria (Figure 1). The final sample included 232,220 CKD-free participants at baseline. This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital (no. 2021-12-033), which waived the informed consent requirement because de-identified data routinely collected during health screening examinations were used for analysis.

**Measurements**

Data on demographic factors, family history, health habits, and medical history were collected using a standardized, self-administered questionnaire; and anthropometry and blood sampling were performed by trained staff during examinations (further details in the Online-only Material).

Serum creatinine was measured using the Jaffe method. The eGFR was calculated using the CKD Epidemiology Collaboration equation. Low GFR was defined as eGFR <60 ml/min/1.73 m\textsuperscript{2}.\textsuperscript{15} However, as urinary albumin level was not measured, CKD was defined as eGFR <60 ml/min/1.73 m\textsuperscript{2} or the presence of proteinuria in lieu of albuminuria as a kidney damage marker.

Fresh and midstream spot urine samples were collected without preservatives; all tests were
completed within 1 h of urine collection. Urinalysis of protein and red blood cells was performed using a URiSCAN strip (YD Diagnostics, Yong-In, Korea) on the URiSCAN Pro II urine chemistry analyzer (YD Diagnostics) until 2014 and the URiSCAN Super Plus (YD Diagnostics) thereafter (further details in the Supplement). Urine protein was reported in six grades: absent, trace, 1+, 2+, 3+, and 4+ (corresponding to the following protein levels: undetectable, 10, 30, 100, 300, and 1000 mg/dL, respectively). Proteinuria was defined as a grade ≥1+. Microscopic examination was performed on the urine specimens by centrifugation at 1800 rpm for 3 min and reported in eight grades: 0–1, 1–3, 3–5, 5–10, 10–20, 20–30, many (≥30 and countable) and numerous cells (countless) per high-power field (HPF). Microscopic hematuria was defined as the presence of ≥5 red blood cells per HPF under 400 × magnification (DMLS2; Leica, Lockbourne, OH, USA).\textsuperscript{16} A urinalysis based on single time urine collection was performed at each visit.

Hematuria changes were determined according to the presence of hematuria at baseline and the subsequent visit (2\textsuperscript{nd} visit) and categorized into four groups: a) no hematuria at baseline and 2\textsuperscript{nd} visit (reference group); b) hematuria at baseline and not at 2\textsuperscript{nd} visit (regressed group); c) no hematuria at baseline and hematuria at 2\textsuperscript{nd} visit (developed group); and d) hematuria at both baseline and the subsequent visit (persistent group).

**Statistical analyses**

Descriptive statistics were used to summarize the participants’ characteristics according to the hematuria categories.

The primary endpoint was incident CKD. Decreased eGFR and proteinuria were analyzed separately as secondary endpoints. Visit 2 was defined as the start of follow-up for our study participants since the hematuria status category was based on both baseline and subsequent visit
(2\textsuperscript{nd} visit) values. Each participant was followed from the second visit until the development of CKD or their last health exam before December 31, 2020, whichever came first. The incidence rate was calculated as the number of incident cases divided by person-years during the follow-up period. Hazard ratios (HRs) with 95% CIs for incident CKD were estimated using Cox proportional hazards models. The proportional hazards assumption was assessed using graphs of the estimated log (−log [SURVIVAL]); no violation of the assumption was observed.

Hazard ratios were initially adjusted for age and sex, and then further adjusted for center; screening examination year; alcohol consumption; smoking status; physical activity level; BMI; education level; lipid lowering medication use; and history of diabetes, hypertension, and cardiovascular disease (Model 1). Model 2 was further adjusted for total cholesterol, high-density lipoprotein cholesterol, triglyceride, and glucose levels; systolic BP; and eGFR. To incorporate changes in hematuria status and changes in covariates during the follow-up period, we conducted time-dependent analyses, wherein hematuria change category, smoking, alcohol consumption, physical activity, BMI, anti-lipid medication use, history of diabetes, history of hypertension, history of cardiovascular disease, total cholesterol, HDL-C, triglyceride, glucose, and SBP were treated as time-varying covariates, and baseline sex, center, year of screening, education level, and eGFR were treated as time-fixed variables In the time-dependent models, hematuria changes were determined for each patient as the hematuria status change between visit 2 and baseline (visit 1), visit 3 and visit 2, visit 4 and visit 3, and in the same way thereafter.

Subgroup analyses were performed by age (<40 vs. ≥40 years), sex (women vs. men), menopausal status (pre vs. post-menopausal), current smoking (no vs. yes), alcohol intake (< 20 vs. ≥ 20 g/day), health-enhancing physical activity (no vs. yes), BMI (<25 kg/m\textsuperscript{2} vs. ≥ 25 kg/m\textsuperscript{2}), HOMA-IR (<2.5 vs. ≥2.5), hsCRP level (<1.0 mg/L vs. ≥ 1.0 mg/L), hypertension (no vs. yes),
and diabetes (no vs. yes). The interactions according to subgroup characteristics were tested using likelihood ratios to compare models with and without multiplicative interaction terms.

To examine the robustness of our findings, we performed several sensitivity analyses (see Online-only Material).

Statistical analyses were performed using STATA version 16.0 software (StataCorp LP, College Station, TX, USA). All reported P-values were two-tailed; statistical significance was set at $P < 0.05$.

RESULTS

The study participants’ baseline characteristics are presented according to hematuria status categories at baseline and the second visit (Table 1 [all participants]; eTables 1 and 2 [men and women]). The interval between first and second visits for assessment of hematuria was 1.7 years (interquartile range, 1.0–2.0 years). At baseline, the mean (standard deviation) participant age was $38.2 \pm 7.6$ years, and 59% were men. The persistent hematuria group were more likely to be older, with higher proportions of women and prevalence of hypertension than other groups.

Within over one million person-years of follow-up (median, 4.8 years; interquartile range, 2.5–6.4 years), 2,392 participants developed CKD (incidence rate, 2.3 per 1,000 person-years overall; 2.2 for women; and 2.3 for men), including 1689 cases of incident proteinuria and 758 cases of incident eGFR <60 ml/min/1.73 m$^2$ (Table 2). After adjustment for potential confounders, the multivariable-adjusted HRs (95% CI) for the “regressed,” “developed,” and “persistent” groups versus the “no hematuria” group for CKD development were 1.85 (1.35–2.53), 3.18 (2.54–3.98), and 5.23 (4.15–6.59), respectively (Model 2). Significant associations persisted after treating hematuria status and other confounders as time-varying factors in the regression models. These associations were observed in men and women, although were more
pronounced in men (P for interaction <0.001). When the risk of low eGFR and proteinuria were assessed as separate endpoints, the patterns were similar (Tables S3 and S4).

In further stratified analyses of pre- and postmenopausal women (Table S5), persistent hematuria and increased CKD risk were consistently observed in both pre- and postmenopausal women without significant interaction by menopausal status. Specifically, the multivariable-adjusted HR (95% CI) for incident CKD comparing the persistent and reference (no hematuria) groups was 4.24 (3.04–5.91) and 3.82 (1.64–8.91) for pre- and postmenopausal women, respectively (P for interaction = 0.8).

The associations between hematuria status and incident CKD were similar across further subgroups (Table S6); however, these associations were stronger in young adults aged <40 years (vs. ≥40 years) and current smokers (vs. noncurrent smokers).

In analyses with persistent CKD observed in at least one subsequent follow-up visit (Table S7) or analyses using the different definition for microscopic hematuria as presence of ≥ 3 red blood cells per HPF, the results were almost the same (Table S8).

Finally, after excluding 328 participants who developed incident genitourinary cancer during follow-up (Table S9), or after excluding participants with microscopic hematuria with RBC count ≥20/HPF (Table S10) which may indicate undiagnosed genitourinary disease, the associations between hematuria changes and CKD risk also persisted in both men and women.

DISCUSSION

In this large-scale prospective cohort study, microscopic hematuria status was significantly associated with subsequent CKD incidence. After adjusting for potential confounders, the risk of both decreased eGFR and proteinuria was significantly increased in participants with persistent hematuria compared to people without hematuria. Although this association was stronger in men,
higher risk of incident CKD among people with hematuria was observed in both sexes, with a similar strength of association observed in both pre- and postmenopausal women. In sensitivity analyses using persistent CKD (the observation of CKD at both the first time point and the subsequent follow-up visit), or in analyses after excluding individuals who developed incident genitourinary cancer or high-level hematuria at baseline, the associations between persistent hematuria and CKD were consistent.

Several studies have reported a relationship between microscopic hematuria and adverse renal outcomes. In a cohort study of 1,230,626 Israeli young adults aged 16—25 years, the presence of persistent asymptomatic hematuria, defined as ≥5 RBC per HPF on 3 separate occasions on different days, was associated with increased risk of treated end-stage renal disease during 21.9 years of follow-up.10 Several studies also reported that microscopic hematuria is a risk factor of end-stage kidney disease in patients with diabetic nephropathy.18,19 However, these studies were conducted in populations with existing renal conditions and did not directly assess the role of hematuria as early signs of asymptomatic chronic kidney disease. Another community-based cohort study of 8,719 Korean participants showed that microscopic hematuria was associated with increased risk of incident CKD in the general population setting.11 However, structural renal diseases or menstrual status in women were not considered; thus, it is unclear whether the increased CKD risk can be attributed to isolated asymptomatic hematuria. In particular, hematuria cases may be transient, although data investigating the association between transient or persistent hematuria and CKD development are scarce. Furthermore, male sex is considered an important risk factor for urological malignancy and CKD, when hematuria is detected; whereas microscopic hematuria, particularly in premenopausal women, is commonly considered a benign finding.12,13 There were few studies reporting that microscopic hematuria was a risk
factor for end-stage kidney disease in diabetic nephropathy, and was associated with worse renal outcomes more strongly in men.\textsuperscript{18,19} However, no previous studies have evaluated sex-related differences in the association between microscopic hematuria and CKD.

In our study, although significant associations between CKD risk and persistent hematuria were found in both sexes regardless of menopausal status, the association between hematuria and CKD was stronger in men. The reason for the sex differences in our findings is unclear and may involve complex interplay among multiple factors. Women are more likely to have blood in the urine than men, owing to menstruation, pregnancy, or atrophy,\textsuperscript{12} none of which reflect pathological conditions or associations with CKD. Thus, incidental findings of microscopic hematuria are commonly considered contamination, particularly in women of reproductive age.\textsuperscript{12} In our program, however, women are advised against health examinations during menstrual periods to reduce the potential for false positives; thus the possibility of contamination due to menstruation is supposedly low. Nonetheless, the prevalence of hematuria at any level was considerably higher among women than men in our population, suggesting that microscopic hematuria for reasons other than menstruation may also be more prevalent in women. There is also a biological basis for sex dimorphism in these associations, which involves the effect of sex hormones, especially estradiol. Estradiol exerted protective effects against renal injury, especially glomerulosclerosis, in several experimental studies.\textsuperscript{20,21} Accordingly, men are prone to renal disease progression, whereas younger women are protected from deterioration.\textsuperscript{22} Moreover, a male predominance has been frequently observed in the dialysis population.\textsuperscript{23} Several genes that may contribute to differential susceptibilities between sexes have also been reported in animal models.\textsuperscript{21} Additional studies are required to better understand the differential association between hematuria and CKD risk according to sex. However, we observed a consistent association
between persistent hematuria and increased CKD risk, and this finding suggests that the assumption that hematuria in non-menstruating pre-menopausal women is benign may not always be accurate.

Microscopic hematuria can be classified into glomerular or non-glomerular origin. Immunoglobulin A nephropathy (IgAN) is one of the most common glomerular diseases, which is known to be the predominant cause of CKD, constituting the majority of glomerular hematuria cases in South Korea. IgAN has been extensively implicated in the association between hematuria and long-term renal dysfunction. Non-glomerular causes of hematuria that may also be linked to CKD include genitourinary cancer, renal structural disorders such as nephrolithiasis, or polycystic kidney disease. However, as participants with a history of renal diseases, marked hematuria defined as ≥ 20 RBCs per HPF, or any structural effect on abdominal sonography were excluded, there is a low likelihood of the aforementioned pathologies being associated with microscopic hematuria in our study. Indeed, more than 50% of patients with microscopic hematuria have no identifiable cause. Previous experimental evidence suggests putative mechanisms by which persistent hematuria may have direct adverse effects on kidney function. For example, hemoglobin (Hb), heme, iron, or other molecules released by the lysis of RBCs are involved in tubular injury pathogenesis. Hb promotes the production of reactive oxygen species and lipid peroxidation and may decrease the availability of nitric oxide, which induces intra-renal vasoconstriction and ischemia leading to renal damage. Hb is also involved in proinflammatory cytokine secretion. Furthermore, when Hb is oxidized and destabilized within the cell, heme, a potent oxidant, is released into the intracellular environment where it induces proinflammatory and profibrotic pathways, contributing to a chronic inflammatory response in the kidneys and increasing cellular susceptibility to oxidative
damage,\textsuperscript{31,36,37} all of which play a key role in the pathogenesis of CKD. As renal biopsies were not feasible to establish the pathogenesis of CKD with persisting hematuria within our study, further studies are warranted to establish definite mechanistic explanations for the association we have observed between hematuria and CKD.

Our study had several limitations. First, we examined the presence of proteinuria using a dipstick test. Although the evaluation of albuminuria may be more accurate, dipstick proteinuria is inexpensive and commonly used in primary care. Moreover, the diagnostic utility of the dipstick proteinuria test has been demonstrated in screening settings.\textsuperscript{38} Second, the assessment of glomerular disease via renal biopsy was not performed, since renal biopsies were not feasible (nor ethical) in this cohort. According to data published in Korea, the most common cause of CKD was glomerulonephritis, followed by diabetic nephropathy, hypertension, polycystic kidney disease, and other unclassified disease.\textsuperscript{26} According to another multicenter study of renal biopsy registries, the most frequent pathologic diagnosis for primary glomerulonephritis was IgAN.\textsuperscript{27} However, although we excluded all the patients with known renal diseases at baseline, we were not able to determine the specific causes of CKD pertaining to our study cohort due to the lack of renal biopsy data. Third, diagnostic work-up is warranted to evaluate the underlying clinical diagnoses of incident kidney disease detected at screening examination. However, we were not able to identify the details of diagnostic work-up and the results, since we used anonymized de-identified data routinely collected during health screening visits. Fourth, although significant associations were observed between persistent hematuria and CKD, the number of incident cases of CKD in our study was small. Therefore, despite the significance of our findings, the clinical utility of hematuria as a marker contributing to CKD development may be limited and remains to be determined in additional studies. Finally, causes of microscopic hematuria may vary between
populations with different demographic factors such as age or race/ethnicity. For instance, IgA nephropathy is the most predominant cause of hematuria in Korea and is known to be more common in East Asian countries than in Western countries. Moreover, hematuria of unknown cause may be more prevalent in our population comprising relatively healthy young and middle-aged adults compared to populations with existing comorbidities or of older age, although the exact underlying pathology could not be determined in our study; thus, our findings may not be generalizable to populations with different demographic characteristics or risk/comorbidity distribution.

Despite limitations, our study has several notable strengths, including the longitudinal, prospective design that enabled us to observe the temporal associations between the changes in hematuria status with the risk of incident CKD. In addition, the large sample size, the use of carefully standardized procedures for clinical and laboratory measures and imaging, the capture of lifestyle factors, and the repeated measurements permitted us to factor in potential confounders as time-varying covariates. Moreover, because the study included relatively healthy, younger participants, there was less potential for comorbidity-related bias and for survivor bias due to selecting participants with severe diseases.

Our results showed that persistent or single episodes of microscopic hematuria were associated with CKD risk in men and women. Further studies are necessary to test whether hematuria, especially persistent hematuria, can help identify both men and women at high risk of CKD and whether appropriate management of hematuria can help decrease subsequent CKD risk and progression to renal failure.

**Article Information**
Authors’ Contributions: Study conception and design: YJU, YC, SR; data acquisition: YJU, YC, M-JK, H-SJ, SR; data analysis: SR; data interpretation: YJU, YC, YK, M-JK, H-SJ, K-BL, KJJ, IYC, SHW, CDB, SR. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual’s own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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doi:10.1681 ASN.2017010108


doi:10.1681 ASN.2010111217
Table 1. Baseline characteristics according to hematuria category (n = 232 220)

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<tr>
<th>Characteristics</th>
<th>Overall</th>
<th>None (G1)</th>
<th>Regressed (G2)</th>
<th>Developed (G3)</th>
<th>Persistent (G4)</th>
</tr>
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<tbody>
<tr>
<td>Number of participants</td>
<td>232 220</td>
<td>225 757</td>
<td>2 282</td>
<td>2 753</td>
<td>1 428</td>
</tr>
<tr>
<td>Age (years)</td>
<td>38.2 (7.6)</td>
<td>38.2 (7.6)</td>
<td>39.5 (8.6)</td>
<td>39.5 (8.2)</td>
<td>41.3 (8.6)</td>
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<tr>
<td>Men (%)</td>
<td>58.9</td>
<td>59.8</td>
<td>29.9</td>
<td>30.0</td>
<td>26.3</td>
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<tr>
<td>Seoul center (%)</td>
<td>58.2</td>
<td>57.8</td>
<td>69.6</td>
<td>66.0</td>
<td>77.1</td>
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<td>Alcohol intake (%)</td>
<td>23.9</td>
<td>24.1</td>
<td>14.4</td>
<td>15.7</td>
<td>13.2</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>23.4</td>
<td>23.6</td>
<td>13.8</td>
<td>14.6</td>
<td>14.8</td>
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<tr>
<td>HEPA (%)</td>
<td>15.8</td>
<td>15.9</td>
<td>13.6</td>
<td>15.6</td>
<td>14.0</td>
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<tr>
<td>Education level (%)</td>
<td>84.9</td>
<td>85.1</td>
<td>81.9</td>
<td>80.8</td>
<td>80.5</td>
</tr>
<tr>
<td>History of diabetes (%)</td>
<td>1.9</td>
<td>1.9</td>
<td>1.0</td>
<td>1.4</td>
<td>1.0</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>7.1</td>
<td>7.1</td>
<td>5.9</td>
<td>5.7</td>
<td>7.5</td>
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<tr>
<td>History of CVD (%)</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Anti-lipid medication use (%)</td>
<td>1.9</td>
<td>1.9</td>
<td>1.6</td>
<td>1.8</td>
<td>2.5</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>28.4</td>
<td>28.7</td>
<td>19.2</td>
<td>19.8</td>
<td>18.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.3 (3.3)</td>
<td>23.4 (3.3)</td>
<td>22.5 (3.3)</td>
<td>22.5 (3.4)</td>
<td>22.3 (3.0)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>109.6 (12.9)</td>
<td>109.7 (12.9)</td>
<td>105.8 (13.2)</td>
<td>105.6 (12.7)</td>
<td>105.5 (13.1)</td>
</tr>
<tr>
<td>eGFR (mg/dl)</td>
<td>102 (13.6)</td>
<td>102 (13.6)</td>
<td>103.5 (13.6)</td>
<td>104.2 (13.5)</td>
<td>102.4 (13.7)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>70.2 (9.8)</td>
<td>70.3 (9.8)</td>
<td>67.9 (9.9)</td>
<td>67.3 (9.5)</td>
<td>67.4 (9.7)</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>94.9 (13.7)</td>
<td>95 (13.7)</td>
<td>92.5 (10.5)</td>
<td>93.0 (12.7)</td>
<td>92.9 (9.8)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>193.8 (33.9)</td>
<td>193.9 (33.9)</td>
<td>189.7 (33)</td>
<td>189.6 (33)</td>
<td>190.6 (32.6)</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>120.7 (31.9)</td>
<td>120.8 (31.9)</td>
<td>115.1 (31.1)</td>
<td>115.3 (30.8)</td>
<td>115.8 (30.5)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>58.5 (15.1)</td>
<td>58.4 (15.1)</td>
<td>62.0 (15.2)</td>
<td>61.8 (15.7)</td>
<td>62.0 (15.3)</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>91 (65-136)</td>
<td>92 (65-137)</td>
<td>76 (57-111)</td>
<td>79 (59-114)</td>
<td>78 (58-114)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>21 (13-36)</td>
<td>21 (13-36)</td>
<td>16 (11-26)</td>
<td>16 (11-25)</td>
<td>15 (11-24)</td>
</tr>
<tr>
<td>HOMA-IR e</td>
<td>1.2 (0.79-1.79)</td>
<td>1.2 (0.79-1.79)</td>
<td>1.06 (0.73-1.61)</td>
<td>1.1 (0.73-1.66)</td>
<td>1.09 (0.73-1.65)</td>
</tr>
<tr>
<td>hsCRP e c</td>
<td>0.4 (0.2-0.9)</td>
<td>0.4 (0.2-0.9)</td>
<td>0.4 (0.2-1)</td>
<td>0.4 (0.2-0.8)</td>
<td>0.4 (0.2-0.9)</td>
</tr>
</tbody>
</table>

*a ≥ 20 g/day; b ≥ college graduate; c BMI ≥ 25 kg/m².

Data are d the mean (standard deviation), e median (interquartile range), or percentage.

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; G1, no hematuria at baseline and no hematuria at 2nd visit (reference group); G2, hematuria at baseline and no hematuria at 2nd visit (hematuria regressed group); G3, no hematuria at baseline and hematuria at 2nd visit (hematuria developed group); G4, hematuria at baseline and hematuria at 2nd visit (persistent hematuria group); GGT, gamma-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; HEPA, health-
enhancing physical activity; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.
Table 2. CKD (decreased eGFR or proteinuria) incidence and hazard ratio by hematuria category, overall and by sex

<table>
<thead>
<tr>
<th>Hematuria change category</th>
<th>Hematuria status at 1st and 2nd visits</th>
<th>Person-years</th>
<th>Incident cases</th>
<th>Incidence density (/ 10^3 PY)</th>
<th>Age adjusted HR (95% CI)</th>
<th>Multivariable-adjusted HR(^a) (95% CI)</th>
<th>HR (95% CI)(^b) in a model with time-dependent variables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1(^{st}) test</td>
<td>2(^{nd}) test</td>
<td></td>
<td></td>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>Total (n = 232 220)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (G1)</td>
<td>none</td>
<td>none</td>
<td>1,028,474</td>
<td>2,195</td>
<td>2.1</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Regressed (G2)</td>
<td>none</td>
<td>hematuria</td>
<td>9,893</td>
<td>40</td>
<td>4.0</td>
<td>1.79 (1.31-2.45)</td>
<td>1.82 (1.33-2.50)</td>
</tr>
<tr>
<td>Developed (G3)</td>
<td>hematuria</td>
<td>none</td>
<td>12,573</td>
<td>80</td>
<td>6.4</td>
<td>2.80 (2.24-3.50)</td>
<td>3.00 (2.39-3.75)</td>
</tr>
<tr>
<td>Persistent (G4)</td>
<td>hematuria</td>
<td>hematuria</td>
<td>6,381</td>
<td>77</td>
<td>12.1</td>
<td>4.80 (3.82-6.03)</td>
<td>5.27 (4.18-6.64)</td>
</tr>
<tr>
<td>Women (n = 95 363)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (G1)</td>
<td>none</td>
<td>none</td>
<td>407,493</td>
<td>816</td>
<td>2.0</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Regressed (G2)</td>
<td>none</td>
<td>hematuria</td>
<td>6,930</td>
<td>21</td>
<td>3.0</td>
<td>1.39 (0.90-2.14)</td>
<td>1.37 (0.89-2.11)</td>
</tr>
<tr>
<td>Developed (G3)</td>
<td>hematuria</td>
<td>none</td>
<td>8,751</td>
<td>44</td>
<td>5.0</td>
<td>2.29 (1.69-3.10)</td>
<td>2.39 (1.76-3.23)</td>
</tr>
<tr>
<td>Persistent (G4)</td>
<td>hematuria</td>
<td>hematuria</td>
<td>4,766</td>
<td>43</td>
<td>9.0</td>
<td>3.66 (2.69-4.98)</td>
<td>3.85 (2.83-5.23)</td>
</tr>
<tr>
<td>Men (n = 136 857)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (G1)</td>
<td>none</td>
<td>none</td>
<td>620,981</td>
<td>1,379</td>
<td>2.2</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Regressed (G2)</td>
<td>none</td>
<td>hematuria</td>
<td>2,963</td>
<td>19</td>
<td>6.4</td>
<td>2.77 (1.76-4.36)</td>
<td>2.71 (1.73-4.27)</td>
</tr>
<tr>
<td>Developed (G3)</td>
<td>hematuria</td>
<td>none</td>
<td>3,822</td>
<td>36</td>
<td>9.4</td>
<td>4.02 (2.89-5.60)</td>
<td>4.12 (2.95-5.73)</td>
</tr>
<tr>
<td>Persistent (G4)</td>
<td>hematuria</td>
<td>hematuria</td>
<td>1,615</td>
<td>34</td>
<td>21.0</td>
<td>8.48 (6.03-11.92)</td>
<td>9.02 (6.41-12.68)</td>
</tr>
</tbody>
</table>

The p-value for the interaction of sex and hematuria change category in the risk of all CKD (either ckd60 or proteinuria) was < 0.001 (Model 2).

\(^a\)Estimated from Cox proportional hazards models. Multivariable Model 1 was adjusted for age; sex (only for total subjects); center; year of screening; alcohol intake; smoking status; physical activity level; BMI; education level; anti-lipid medication use; and history of diabetes, hypertension, and cardiovascular disease. Model 2: Model 1 plus adjustment for eGFR; total cholesterol, HDL-C, triglyceride, and glucose levels; and SBP.

\(^b\)Estimated from Cox proportional hazard models with hematuria change category, smoking, alcohol consumption, physical activity, BMI, anti-lipid medication use, history of diabetes, history of hypertension, history of cardiovascular disease, total cholesterol, HDL-C, triglyceride, glucose, and SBP as time-dependent categorical variables, and baseline sex, center, year of screening, education level, and eGFR as time-fixed variables.

Abbreviations: BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; G1, no hematuria at baseline and no hematuria at 2\(^{nd}\) visit (reference group); G2, hematuria at baseline and no hematuria at 2\(^{nd}\) visit (hematuria regressed group); G3, no hematuria at baseline but hematuria at 2\(^{nd}\) visit; G4, hematuria at both baseline and 2\(^{nd}\) visit.
baseline and hematuria at 2\textsuperscript{nd} visit (hematuria developed group); G4, hematuria at baseline and hematuria at 2\textsuperscript{nd} visit (persistent hematuria group); HR, hazard ratio; PY, person-years; SPB, systolic blood pressure.
**Figure 1** Flow chart for selection of study participants
Participants who underwent a comprehensive health examination at least twice between 2011 and 2018 at Kangbuk Samsung Hospital and had at least one additional follow-up visits until December 31, 2020 (n = 276,655)

Participants excluded at baseline (n = 44,435; some met multiple exclusion criteria)
- Missing information on urinalysis, body mass index, or serum creatinine (n = 19,060)
- History of malignancy (n = 6,031)
- History of kidney disease (n = 8,719)
- Ultrasonography-diagnosed kidney disease or postsurgical status including renal stone, hydronephrosis, renal tumor, CKD, PKD, and partial or total nephrectomy (n = 10,747)
- eGFR <60 mL/min/1.73 m² at baseline (n = 526)
- Proteinuria at baseline (n = 1,078)
- Development of CKD at the second visit (n = 2,776)

Participants included in the final analysis (n = 232,220)