The Risk of CKD Following Detection of Microscopic Hematuria

Yoo Jin Um, MD[1], Yoosoo Chang, MD, PhD[2,3,4†], Yejin Kim, MHS[2], Min-Jung Kwon,MD, PhD[2,5], Hyun-Suk Jung, MD[1,2], Kyu-Beck Lee, MD, PhD[6], Kwan Joong Joo, MD, PhD[7], In Young Cho, MD, MPH[2,8], Sarah H. Wild, MB BChir, PhD[9]; Christopher D Byrne, MB BCh, PhD[10,11]; Seungho Ryu, MD, PhD[2,3,4]

[1] Total Healthcare Center, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea

[2] Center for Cohort Studies, Total Healthcare Center, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea

[3] Department of Occupational and Environmental Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea

[4] Department of Clinical Research Design & Evaluation, SAIHST, Sungkyunkwan University, Seoul, South Korea

[5] Department of Laboratory Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea

[6] Division of Nephrology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Seoul, Republic of Korea

[7] Department of Urology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

[8] Department of Family Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea

[9] Usher Institute, University of Edinburgh, Edinburgh, U.K.

[10] Nutrition and Metabolism, Faculty of Medicine, University of Southampton, Southampton,

U.K.

[11] National Institute for Health and Care Research Southampton Biomedical Research Centre, University Hospital Southampton, Southampton, U.K.

†Co-Corresponding authors:

Seungho Ryu, Department of Occupational and Environmental Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Samsung Main Building B2, 250 Taepyung-ro 2ga, Jung-gu, Seoul 04514, South Korea

Tel: +82-2-2001-5137; Fax: +82-2-757-0436; Email: sh703.yoo@gmail.com

and

Yoosoo Chang, Department of Occupational and Environmental Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Samsung Main Building B2, 250 Taepyung-ro 2ga, Jung-gu, Seoul 04514, South Korea

Tel: +82-2-2001-5139; Fax: +82-2-757-0436; Email: yoosoo.chang@gmail.com

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 m^2 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 ($P_{interaction} < 0.001$), 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.

Title: Persistent blood in the urine and development of chronic kidney disease

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.[1,2] It has been estimated that global CKD prevalence has increased by 29.3% since 1990 and that CKD was the 12th leading cause of death in the world in 2017.[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.[3,4] Microscopic hematuria is a common incidental finding in urinalysis, and its prevalence has varied between studies, ranging from 0.12–30%.[5,6] More than 50% of patients with microscopic hematuria have no definite identifiable cause,[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.[7-9]

Two studies have reported a relationship between microscopic hematuria with end-stage renal disease risk[10] or increased CKD risk, defined using estimated glomerular filtration rates (eGFRs).[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.[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.

MATERIALS AND 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.[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^2.[15] However, as urinary albumin level was not measured, CKD was defined as

eGFR <60 ml/min/1.73 m^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).[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 (2nd visit) and categorized into four groups: a) no hematuria at baseline and 2nd visit (reference group); b) hematuria at baseline and not at 2nd visit (regressed group); c) no hematuria at baseline and hematuria at 2nd 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 (2nd 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^2 vs. ≥ 25 kg/m^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 (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,[13] 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[17], 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.[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,[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.[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.[20,21] Accordingly, men are prone to renal disease progression, whereas younger women are protected from deterioration.[22] Moreover, a male predominance has been frequently observed in the dialysis population.[23] Several genes that may contribute to differential susceptibilities between sexes have also been reported in animal models.[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.[24,25] Immunoglobulin A nephropathy (IgAN) is one of the most common glomerular diseases, which is known to be the predominant cause of CKD[26,27], constituting the majority of glomerular hematuria cases in South Korea.[28-30] IgAN has been extensively implicated in the association between hematuria and long-term renal dysfunction.[31-33] 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.[24] However, as participants with a history of renal diseases, marked hematuria defined as ≥ 20 RBCs per HPF[13], 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.[6] 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.[7,31] Hb promotes the production of reactive oxygen species and lipid peroxidation[34] and may decrease the availability of nitric oxide, which induces intra-renal vasoconstriction and ischemia leading to renal damage.[35] Hb is also involved in proinflammatory cytokine secretion.[36] 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,[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.[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.[26] According to another multicenter study of renal biopsy registries, the most frequent pathologic diagnosis for primary glomerulonephritis was IgAN.[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.[29] 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 clinical, imaging, and laboratory procedures, and the inclusion of lifestyle factors, and the repeated measurements allowed us to account for possible confounders as time-varying covariates. Lastly, the inclusion of relatively healthy, younger individuals reduced the potential for survivor bias caused by selecting subjects with severe diseases as well as comorbidity-related bias.

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

References

1.   Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation*. Oct 28 2003;108(17):2154-69. doi:10.1161/01.Cir.0000095676.90936.80

2.   Bikbov B, Purcell CA, Levey AS, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*. 2020;395(10225):709-733. doi:10.1016/s0140-6736(20)30045-3

3.   Kondo M, Yamagata K, Hoshi SL, et al. Cost-effectiveness of chronic kidney disease mass screening test in Japan. *Clinical and experimental nephrology*. Apr 2012;16(2):279-91. doi:10.1007/s10157-011-0567-1

4.   Komenda P, Ferguson TW, Macdonald K, et al. Cost-effectiveness of primary screening for CKD: a systematic review. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. May 2014;63(5):789-97. doi:10.1053/j.ajkd.2013.12.012

5.   Kang M, Lee S, Jeong SJ, et al. Characteristics and significant predictors of detecting underlying diseases in adults with asymptomatic microscopic hematuria: a large case series of a Korean population. *International journal of urology : official journal of the Japanese Urological Association*. Apr 2015;22(4):389-93. doi:10.1111/iju.12697

6.   Ingelfinger JR. Hematuria in Adults. *N Engl J Med*. Jul 8 2021;385(2):153-163. doi:10.1056/NEJMra1604481

7.   Moreno JA, Martín-Cleary C, Gutiérrez E, et al. Haematuria: the forgotten CKD factor? *Nephrology, dialysis, transplantation : official publication of the European Dialysis*

and Transplant Association - European Renal Association. Jan 2012;27(1):28-34. doi:10.1093/ndt/gfr749

8.   Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management: A Review. *JAMA*. Oct 1 2019;322(13):1294-1304. doi:10.1001/jama.2019.14745

9.   Lopez-Vargas PA, Tong A, Sureshkumar P, Johnson DW, Craig JC. Prevention, detection and management of early chronic kidney disease: a systematic review of clinical practice guidelines. *Nephrology (Carlton)*. Sep 2013;18(9):592-604. doi:10.1111/nep.12119

10.   Vivante A, Afek A, Frenkel-Nir Y, et al. Persistent asymptomatic isolated microscopic hematuria in Israeli adolescents and young adults and risk for end-stage renal disease. *Jama*. Aug 17 2011;306(7):729-36. doi:10.1001/jama.2011.1141

11.   Kim H, Lee M, Cha MU, et al. Microscopic hematuria is a risk factor of incident chronic kidney disease in the Korean general population: a community-based prospective cohort study. *QJM*. Jun 1 2018;111(6):389-397. doi:10.1093/qjmed/hcy054

12.   Whiteside JL, Yuen HTH. Asymptomatic microscopic hematuria in women. *Curr Opin Obstet Gynecol*. Dec 2019;31(6):471-476. doi:10.1097/GCO.0000000000000573

13.   Barocas DA, Boorjian SA, Alvarez RD, et al. Microhematuria: AUA/SUFU Guideline. *J Urol*. Oct 2020;204(4):778-786. doi:10.1097/JU.0000000000001297

14.   Chang Y, Ryu S, Choi Y, et al. Metabolically Healthy Obesity and Development of Chronic Kidney Disease: A Cohort Study. *Ann Intern Med*. Mar 1 2016;164(5):305-12. doi:10.7326/m15-1323

15.   Levin A, Stevens PE, Bilous RW, et al. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney international supplements*. 2013;3(1):1-150.

16.   Saleem MO, Hamawy K. Hematuria. *StatPearls*. StatPearls Publishing

Copyright © 2022, StatPearls Publishing LLC.; 2022.

17.   Lenis AT, Lec PM, Chamie K, Mshs MD. Bladder Cancer: A Review. *JAMA*. Nov 17 2020;324(19):1980-1991. doi:10.1001/jama.2020.17598

18.   Okada S, Samejima KI, Matsui M, et al. Microscopic hematuria is a risk factor for end-stage kidney disease in patients with biopsy-proven diabetic nephropathy. *BMJ Open Diabetes Res Care*. Nov 2020;8(2)doi:10.1136/bmjdrc-2020-001863

19.   Wu Y, Zhang J, Wang Y, et al. The association of hematuria on kidney clinicopathologic features and renal outcome in patients with diabetic nephropathy: a biopsy-based study. *Journal of Endocrinological Investigation*. 2020/09/01 2020;43(9):1213-1220. doi:10.1007/s40618-020-01207-7

20.   Sabbatini AR, Kararigas G. Estrogen-related mechanisms in sex differences of hypertension and target organ damage. *Biol Sex Differ*. Jun 1 2020;11(1):31. doi:10.1186/s13293-020-00306-7

21.   Shepard BD. Sex differences in diabetes and kidney disease: mechanisms and consequences. *Am J Physiol Renal Physiol*. Aug 1 2019;317(2):F456-f462. doi:10.1152/ajprenal.00249.2019

22.   Eriksen BO, Ingebretsen OC. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. *Kidney Int*. Jan 2006;69(2):375-82. doi:10.1038/sj.ki.5000058

23.   Bikbov B, Bieber B, Andrusev A, et al. Hemodialysis practice patterns in the Russia Dialysis Outcomes and Practice Patterns Study (DOPPS), with international comparisons. *Hemodial Int*. Jul 2017;21(3):393-408. doi:10.1111/hdi.12503

24.   Niemi MA, Cohen RA. Evaluation of microscopic hematuria: a critical review and

proposed algorithm. *Adv Chronic Kidney Dis*. Jul 2015;22(4):289-96. doi:10.1053/j.ackd.2015.04.006

25.   Lin HY, Niu SW, Kuo IC, et al. Hematuria and Renal Outcomes in Patients With Diabetic Chronic KidneyDisease. *Am J Med Sci*. Sep 2018;356(3):268-276. doi:10.1016/j.amjms.2018.06.005

26.   Kang E, Han M, Kim H, et al. Baseline General Characteristics of the Korean Chronic Kidney Disease: Report from the KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease (KNOW-CKD). *J Korean Med Sci*. Feb 2017;32(2):221-230. doi:10.3346/jkms.2017.32.2.221

27.   Current findings of kidney biopsy including nephropathy associated with hypertension and diabetes mellitus in Korea FAU - Kim, Kipyo FAU - Lee, Sang Ho FAU - Lee, Sung Woo FAU - Lee, Jung Pyo FAU - Chin, Ho Jun FAU. *Korean J Intern Med*. 9 2020;35(5):1173-1187. doi:10.3904/kjim.2020.195

28.   Coppo R, Fervenza FC. Persistent Microscopic Hematuria as a Risk Factor for Progression of IgA Nephropathy: New Floodlight on a Nearly Forgotten Biomarker. *J Am Soc Nephrol*. Oct 2017;28(10):2831-2834. doi:10.1681/ASN.2017060639

29.   Chang JH, Kim DK, Kim HW, et al. Changing prevalence of glomerular diseases in Korean adults: a review of 20 years of experience. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. Aug 2009;24(8):2406-10. doi:10.1093/ndt/gfp091

30.   Shin HS, Cho DH, Kang SK, et al. Patterns of renal disease in South Korea: a 20-year review of a single-center renal biopsy database. *Ren Fail*. Nov 2017;39(1):540-546. doi:10.1080/0886022x.2017.1348955

31.   Moreno JA, Sevillano Á, Gutiérrez E, et al. Glomerular Hematuria: Cause or

Consequence of Renal Inflammation? *Int J Mol Sci*. 2019;20(9):2205. doi:10.3390/ijms20092205

32.   Sevillano AM, Gutierrez E, Yuste C, et al. Remission of Hematuria Improves Renal Survival in IgA Nephropathy. *J Am Soc Nephrol*. Oct 2017;28(10):3089-3099. doi:10.1681/ASN.2017010108

33.   Yu GZ, Guo L, Dong JF, et al. Persistent Hematuria and Kidney Disease Progression in IgA Nephropathy: A Cohort Study. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. Jul 2020;76(1):90-99. doi:10.1053/j.ajkd.2019.11.008

34.   Patel RP, Svistunenko DA, Darley-Usmar VM, Symons MC, Wilson MT. Redox cycling of human methaemoglobin by H2O2 yields persistent ferryl iron and protein based radicals. *Free Radic Res*. Aug 1996;25(2):117-23. doi:10.3109/10715769609149916

35.   Heyman SN, Brezis M. Acute renal failure in glomerular bleeding: a puzzling phenomenon. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. 1995;10(5):591-3.

36.   Vaziri ND. Causal link between oxidative stress, inflammation, and hypertension. *Iran J Kidney Dis*. Jan 2008;2(1):1-10.

37.   Tracz MJ, Alam J, Nath KA. Physiology and pathophysiology of heme: implications for kidney disease. *J Am Soc Nephrol*. Feb 2007;18(2):414-20. doi:10.1681/ASN.2006080894

38.   Clark WF, Macnab JJ, Sontrop JM, et al. Dipstick proteinuria as a screening strategy to identify rapid renal decline. *J Am Soc Nephrol*. Sep 2011;22(9):1729-36. doi:10.1681/ASN.2010111217

Table 1. Baseline characteristics according to hematuria category (n = 232 220)

Characteristics	Overall	Hematuria change category			
		None (G1)	Regressed (G2)	Developed (G3)	Persistent (G4)
Number of participants	232,220	225,757	2,282	2,753	1,428
Age (years)	38.2 (7.6)	38.2 (7.6)	39.5 (8.6)	39.5 (8.2)	41.3 (8.6)
Men (%)	58.9	59.8	29.9	30.0	26.3
Seoul center (%)	58.2	57.8	69.6	66.0	77.1
Alcohol intake (%)[a]	23.9	24.1	14.4	15.7	13.2
Current smoker (%)	23.4	23.6	13.8	14.6	14.8
HEPA (%)	15.8	15.9	13.6	15.6	14.0
Education level (%)[b]	84.9	85.1	81.9	80.8	80.5
History of diabetes (%)	1.9	1.9	1.0	1.4	1.0
History of hypertension (%)	7.1	7.1	5.9	5.7	7.5
History of CVD (%)	0.8	0.8	0.8	0.8	0.7
Anti-lipid medication use (%)	1.9	1.9	1.6	1.8	2.5
Obesity (%)[c]	28.4	28.7	19.2	19.8	18.3
Body mass index (kg/m^2)[d]	23.3 (3.3)	23.4 (3.3)	22.5 (3.3)	22.5 (3.4)	22.3 (3.0)
SBP (mmHg)[d]	109.6 (12.9)	109.7 (12.9)	105.8 (13.2)	105.6 (12.7)	105.5 (13.1)
eGFR (mg/dl)[d]	102 (13.6)	102 (13.6)	103.5 (13.6)	104.2 (13.5)	102.4 (13.7)
DBP (mmHg)[d]	70.2 (9.8)	70.3 (9.8)	67.9 (9.9)	67.3 (9.5)	67.4 (9.7)
Glucose (mg/dl)[d]	94.9 (13.7)	95 (13.7)	92.5 (10.5)	93.0 (12.7)	92.9 (9.8)
Total cholesterol (mg/dl)[d]	193.8 (33.9)	193.9 (33.9)	189.7 (33)	189.6 (33)	190.6 (32.6)
LDL-C (mg/dL)[d]	120.7 (31.9)	120.8 (31.9)	115.1 (31.1)	115.3 (30.8)	115.8 (30.5)
HDL-C (mg/dL)[d]	58.5 (15.1)	58.4 (15.1)	62.0 (15.2)	61.8 (15.7)	62.0 (15.3)
Triglycerides (mg/dL)[e]	91 (65-136)	92 (65-137)	76 (57-111)	79 (59-114)	78 (58-114)
GGT (U/L)[e]	21 (13-36)	21 (13-36)	16 (11-26)	16 (11-25)	15 (11-24)
ALT (U/L)[e]	18 (13-28)	18 (13-28)	15 (11-22)	15 (11-21)	14 (11-21)
HOMA-IR[e]	1.2 (0.79-1.79)	1.2 (0.79-1.79)	1.06 (0.73-1.61)	1.1 (0.73-1.66)	1.09 (0.73-1.65)
hsCRP[e]	0.4 (0.2-0.9)	0.4 (0.2-0.9)	0.4 (0.2-1)	0.4 (0.2-0.8)	0.4 (0.2-0.9)

[a]≥20 g/day; [b]≥ college graduate; [c]BMI ≥25 kg/m^2.

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

Hematuria change category	Hematuria status at 1st and 2nd visits		Person-years	Incident cases	Incidence density (/ 10³ PY)	Age adjusted HR (95% CI)	Multivariable-adjusted HR[a] (95% CI)		HR (95% CI)[b] in a model with time-dependent variables
	1st test	2nd test					Model 1	Model 2	
Total (n = 232 220)									
None (G1)	none	none	1,028,474	2,195	2.1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Regressed (G2)	hematuria	none	9,893	40	4.0	1.79 (1.31-2.45)	1.82 (1.33-2.50)	1.85 (1.35-2.53)	1.83 (1.34-2.51)
Developed (G3)	none	hematuria	12,573	80	6.4	2.80 (2.24-3.50)	3.00 (2.39-3.75)	3.18 (2.54-3.98)	3.15 (2.51-3.94)
Persistent (G4)	hematuria	hematuria	6,381	77	12.1	4.80 (3.82-6.03)	5.27 (4.18-6.64)	5.23 (4.15-6.59)	5.02 (3.99-6.33)
Women (n = 95 363)									
None (G1)	none	none	407,493	816	2.0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Regressed (G2)	hematuria	none	6,930	21	3.0	1.39 (0.90-2.14)	1.37 (0.89-2.11)	1.38 (0.89-2.13)	1.38 (0.89-2.13)
Developed (G3)	none	hematuria	8,751	44	5.0	2.29 (1.69-3.10)	2.39 (1.76-3.23)	2.52 (1.86-3.41)	2.54 (1.87-3.44)
Persistent (G4)	hematuria	hematuria	4,766	43	9.0	3.66 (2.69-4.98)	3.85 (2.83-5.23)	3.92 (2.88-5.34)	3.73 (2.74-5.08)
Men (n = 136 857)									
None (G1)	none	none	620,981	1,379	2.2	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Regressed (G2)	hematuria	none	2,963	19	6.4	2.77 (1.76-4.36)	2.71 (1.73-4.27)	2.80 (1.78-4.40)	2.72 (1.73-4.28)
Developed (G3)	none	hematuria	3,822	36	9.4	4.02 (2.89-5.60)	4.12 (2.95-5.73)	4.44 (3.18-6.18)	4.23 (3.04-5.89)
Persistent (G4)	hematuria	hematuria	1,615	34	21.0	8.48 (6.03-11.92)	9.02 (6.41-12.68)	8.34 (5.92-11.74)	8.22 (5.84-11.57)

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 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); HR, hazard ratio; PY, person-years; SPB, systolic blood pressure.

Figure legend

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 = 6031)
- History of kidney disease (n = 8719)
- Ultrasonography-diagnosed kidney disease or postsurgical status including renal stone, hydronephrosis, renal tumor, chronic kidney disease, polycystic kidney disease, and partial or total nephrectomy (n = 10 747)
- eGFR <60 ml/min/1.73 m^2 at baseline (n = 526)
- Proteinuria at baseline (n = 1078)
- Development of chronic kidney disease at the second visit (n = 2776)

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