

# Risk Factors for Chronic Kidney Disease: A Prospective Study of 23,534 Men and Women in Washington County, Maryland

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**Abstract.** Chronic kidney disease (CKD) is an increasing cause of morbidity and mortality in the United States. Prospective data on risk factors for CKD are limited to men, and few studies examine the importance of smoking. The authors performed a community-based, prospective observational study of 20-yr duration to examine the association between hypertension and smoking on the future risk of CKD in 23,534 men and women in Washington County, Maryland. CKD was identified as end-stage renal disease in the Health Care Financing Administration database or kidney disease listed on the death certificate. All cases were confirmed as CKD by medical chart review. Adjusted relative hazards of CKD were modeled using Cox proportional hazards regression including age as the time variable and baseline BP, cigarette smoking, gender, and diabetes status as risk factors. The adjusted hazard ratio (95% confidence interval) of developing CKD among women was 2.5 (0.05 to 12.0) for normal BP, 3.0 (0.6 to 14.4) for high-

normal BP, 3.8 (0.8 to 17.2) for stage 1 hypertension, 6.3 (1.3 to 29.0) for stage 2 hypertension, and 8.8 (1.8 to 43.0) for stages 3 or 4 hypertension compared with individuals with optimal BP. In men, the relationship was similar but somewhat weaker than in women, with corresponding hazard ratios of 1.4 (0.2 to 12.1), 3.3 (0.4 to 25.6), 3.0 (0.4 to 22.2), 5.7 (0.8 to 43.0), and 9.7 (1.2 to 75.6), respectively. Current cigarette smoking was also significantly associated with risk of CKD in both men and women (hazard ratio in women 2.9 [1.7 to 5.0] and in men 2.4 [1.5 to 4.0]). A large proportion of the attributable risk of CKD in this population was associated with stage 1 hypertension (23%) and cigarette smoking (31%). In conclusion, CKD risk shows strong graded relationships to the sixth report of the Joint National Committee (JNC-VI) on Prevention, Detection Evaluation and Treatment of High BP criteria for BP, to diabetes, and to current cigarette smoking that are at least as strong in women as in men.

End-stage renal disease (ESRD) is an important public health problem in the United States. Forty-five percent of ESRD patients are women, but no prospective data are available on risk factors for ESRD among women. Only 5% of dialysis patients are reported as current cigarette smokers, but many quit smoking only after the onset of severe illness (1). Recall bias regarding smoking and prevalence incidence bias for other risk factors such as hypertension and diabetes support the need for large prospective studies of ESRD to obtain valid and reliable estimates of the risk of CKD associated with these conditions in both men and women.

Data from the United States Renal Data System reveals that over 304,000 people were being treated for ESRD at the end of 1997, and more than 79,000 new cases of ESRD arose during that same year. Furthermore, the prevalence rate of ESRD continues to climb annually, almost doubling during the 1990s (1). It is estimated that there will be over 650,000 cases of ESRD in the year 2010 and that Medicare expenditures will increase to over \$28 billion (2). These staggering statistics highlight the importance of understanding modifiable risk factors as a basis for devising treatment strategies for preventing the development and progression of chronic kidney disease (CKD).

Hypertension has been shown to have a strong, graded association with CKD in prospective studies of men (3–5), but there are no prospective studies looking at this relationship in women. Both the absolute and relative risk of CKD associated with hypertension in women in the general population is unknown. Multiple studies have shown that smoking plays a role in the development and progression of diabetic (6–15) and nondiabetic (16–18) kidney disease. Recent studies suggest that smoking could contribute to both the development and

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progression of CKD in the general population (19–23), but very few studies used a prospective design (24,25). To address these issues, we examined the association of both hypertension and smoking with the later development of CKD in a community-based cohort of volunteers in Washington County, Maryland, both for the group as a whole and stratified by gender.

## Methods

### Population

Washington County, MD, is a semi-rural community that is predominantly white. The county population was 103,000 in 1970 and 113,000 in 1980. The CLUE (the name comes from the slogan “give us a clue to cancer”) Study was initiated in 1974 in Washington County as a cancer research project. As part of this study, approximately 26,000 adult volunteers completed a health interview and donated 15 ml of blood; BP measurement was offered as a service to participants (26). Data were collected on age, race, cigarette smoking, and medication use. Participants residing in Washington County, MD, were the base population for the present study. Both the original CLUE study and the follow-up procedures were approved by the Institutional Review Board of the Johns Hopkins School of Public Health.

### Kidney Disease Follow-Up

The outcome of interest was the development of CKD detectable by the requirement for dialysis or transplantation or by the notation of kidney disease on the death certificate and confirmed by medical record review. ESRD was detected by record linkage of CLUE records to the Health Care Financing Administration (HCFA) database in February, 1994; the HCFA database contains information on all patients who have received dialysis care funded through HCFA, covering approximately 93% of all dialysis patients (27). Death with CKD was identified by a comprehensive medical record review of all deaths by February 1994 for which renal disease (ICD-9 codes 250.4, 274.1, 275.4, 403, 404, 580 to 589, 593.9) was listed on the death certificate. CKD was defined as the presence of any of the following: (1) CKD in a discharge summary and/or renal consultation note, or (2) at least two serum creatinine values  $> 2.0$  mg/dl over the period of follow-up. Individuals with acute renal failure who did not meet the CKD criteria, even those receiving renal replacement therapy for acute renal failure ( $n = 4$ ), were excluded. This design provides a highly specific detection of CKD, which should result in valid estimates of relative risk despite not detecting many cases of milder CKD, which developed during this long follow-up period. Nonresidents of Washington County ( $n = 2421$ ) and subjects who had incomplete records with regard to age and BP were excluded ( $n = 327$ ).

### Baseline Risk Factor Assessment

The risk factors of interest were systolic and diastolic BP, diabetes status, smoking status, and years of education. BP was measured in 1974 by a nurse, who took three measurements with a standard sphygmomanometer while the individual was seated and recorded the lowest value. A variable for BP category was created on the basis of the sixth report of the Joint National Committee (JNC-VI) on Prevention, Detection Evaluation and Treatment of High BP, and individuals were placed in one of the following categories by the higher of systolic or diastolic BP: optimal  $< 120$  mmHg systolic or  $< 80$  mmHg diastolic; normal = 120 to 129 mmHg systolic or 80 to 84 mmHg diastolic; high-normal = 130 to 139 mmHg systolic or 85 to 89 mmHg diastolic; stage 1 hypertension = 140 to 159 mmHg

systolic or 90 to 99 mmHg diastolic; stage 2 hypertension = 160 to 179 mmHg systolic or 100 to 109 mmHg diastolic; stage 3 or 4 hypertension  $\geq 180$  mmHg systolic or  $\geq 110$  diastolic. Treated diabetes status was determined by the presence on the medication list of a medication for hyperglycemia. Two smoking variables were assessed by questionnaire: ever (yes/no) *versus* never, and current (yes/no) *versus* former or never.

### Assessment for Prevalent CKD in the Cohort

To ensure that CKD was not prevalent in the cohort, laboratory values were obtained on a subset of cases ( $n = 85$ ) and non-cases ( $n = 175$ ) matched for age, race, gender, hypertension, and diabetes. We were unable to check laboratory values on the entire cohort because the CLUE study is a cancer research study, and serum must be saved for the original intent of the researchers. GFR was estimated using the abbreviated equation from the Modification of Diet in Renal Disease (MDRD) Study [Estimated GFR =  $\exp(5.228 - 1.154 \times \ln(\text{sCr}) - 0.203 \times \ln(\text{age}) - 0.299$  if female + 0.192 if African-American)] (28). Median values for creatinine and for estimated GFR were calculated in cases and non-cases.

### Statistical Analyses

The significance of baseline differences between cases and non-cases was estimated using two sample *t* tests. Baseline information was also compared between those cases with ESRD per the HCFA database and those who died with CKD, also using two sample *t* tests. Hazard ratios for CKD were obtained by gender using Cox proportional hazards analysis with age as the time variable and the following baseline risk factors: JNC-VI BP category, smoking status (current *versus* not), and treated diabetes. Participants were entered into the analysis at the age of participation in CLUE and were withdrawn from follow-up at the time of onset of CKD or February 18, 1994 (the date when follow-up for CKD was completed). Addition of years of education did not significantly change the results, so this variable was not included in the final model. Kaplan-Meier curves were generated to study age at the diagnosis of CKD. Population attributable risks were calculated using the fitted Cox model to predict the impact on CKD risk of eliminating risk factors one at a time from the entire study population (29). For example, the predicted risk was calculated for all individuals after changing the smoking status of all smokers to nonsmoking, and the new total risk of CKD in the study population was compared with the original risk of CKD. Statistical analyses were performed with Stata Statistical Software (Stata Corp, College Station, TX) (30).

## Results

### Descriptive Data

A total of 23,534 participants had complete records in 1974 with regard to BP and age and resided in Washington County, MD. During the subsequent 20 yr (425,653 person-years of observation), 143 cases of CKD were identified. Record linkage to HCFA in 1994 for patients with treated ESRD yielded 51 cases (median year, 1989). A detailed medical record review of 168 participants based on kidney disease on death certificates identified another 92 cases of CKD (median year, 1988) and 76 who did not have CKD. Of the 76 subjects who did not have CKD, four were receiving hemodialysis for acute renal failure.

Cases of CKD were significantly more likely to be older in age, hypertensive, report ever smoking cigarettes, and less

educated than non-cases (Table 1). There were more cases than non-cases who reported current cigarette smoking, though this difference did not achieve statistical significance ( $P = 0.06$ ). Ninety-nine percent of cases and non-cases were white. Those individuals who were identified by death certificate report were significantly older than those by record linkage with HCFA. Comparison of cases of CKD by method of identification reveals that the two groups are similar in terms of race, gender, BP, treated diabetes, cigarette smoking, and years of education. Examination of serum creatinine in cases showed that 78 (92%) of 85 of cases had a value less than 1.5 mg/dl. The median serum creatinine was 0.8 mg/dl, and the median estimated GFR in this group was 103 ml/min per 1.73 m<sup>2</sup>. Similarly, the median serum creatinine value in a subset of 175 non-cases matched to cases by age, gender, race, diabetes medication, and BP who underwent serologic testing was 0.7 mg/dl, with 171 (98%) of 175 less than 1.5 mg/dl, and the median estimated GFR was 111 ml/min. The difference in serum creatinine was statistically significant ( $P < 0.01$ ), but the difference in estimated GFR was not higher ( $P = 0.19$ ). Sensitivity analyses that excluded all cases with a baseline estimated GFR less than 60 ml/min per 1.73 m<sup>2</sup> showed similar results to those presented in the paper. A greater percentage of men than women developed CKD, and the unadjusted incidence of CKD showed a graded increase by BP category (Table 2). This pattern was seen in men and women as well as in the population as a whole.

### Survival Analysis of CKD

Kaplan-Meier curves of the risk of CKD by age at baseline and JNC-VI BP category are shown in Figure 1. When compared with optimal BP, stages 2 to 4 hypertension were all significantly associated with the subsequent development of CKD when adjusted for age, treated diabetes, and cigarette smoking (Table 3). The associations of high-normal BP and

stage 1 hypertension neared statistical significance ( $P = 0.075$  and 0.055, respectively). The results were similar when stratified by gender, though statistical significance was only achieved in stages 2 and 3 or 4 in women and in stage 3 or 4 in men. Treated diabetes and cigarette smoking were also significantly associated with the later development of CKD. Analyses combining optimal and normal BP as the reference group should similar results to those presented. The above associations were similar when excluding cases with an elevated serum creatinine at baseline (7 values greater than 1.4 mg/dl and 11 values greater than 1.2 mg/dl). The attributable risks, which combine the relative risks and prevalence of the risk factors in this population, are shown in Figure 2. The BP category with the greatest attributable risk is stage 1 hypertension, though even high-normal BP is important in its association with the outcome of CKD. The attributable risk for cigarette smoking is staggering, at nearly half that seen for all BP categories combined. The low attributable risk for treated diabetes is likely secondary to the fact that we could only detect diabetes on the basis of the presence of medications for hyperglycemia on the medication list from 1974.

Analyses of BP as a continuous variable yielded similar results. Higher systolic and higher diastolic BP were associated with an relative hazards of CKD of 1.02 (95% CI 1.01-1.03) and 1.04 (95% CI 1.03-1.06), respectively after adjustment for age, gender, smoking, and diabetes treatment ( $P < 0.001$ ). In a model containing both systolic and diastolic BP, the latter were no longer statistically significant.

### Discussion

This study demonstrates a strong graded increased risk of developing CKD with JNC-VI criteria for hypertension in a community-based cohort of predominantly white persons. Stages 2, 3, and 4 of hypertension were significantly associated with the outcome of CKD when adjusted for age, gender,

Table 1. Baseline characteristics of 23,534 individuals in the CLUE study in 1974 by case status, and by method of identification for the 143 cases of chronic kidney disease (CKD)<sup>a</sup>

Baseline characteristic	Developed CKD		Method of Identification as a Case of CKD	
	No $n = 23,391$	Yes $n = 143$	HCFA Linkage $n = 51$	Death Certificate $n = 92$
Mean age, yr (SD)	41 (17)	56 (15) <sup>d</sup>	49 (16)	60 (13) <sup>c</sup>
Race, % white	99	99	96	100
Treatment for hypertension, %	11	36 <sup>d</sup>	37	35
Mean SBP, mmHg (SD)	134 (19)	152 (25) <sup>d</sup>	149 (19)	154 (28)
Mean DBP, mmHg (SD)	82 (11)	89 (12) <sup>d</sup>	91 (13)	88 (11)
Treated diabetes, %	1.6	17.5 <sup>d</sup>	24	14
Cigarette smoking				
% ever	53	62 <sup>b</sup>	61	63
% current	31	38	31	41
Mean education, yr (SD)	11 (3)	10 (3) <sup>d</sup>	11 (3)	10 (3)

<sup>a</sup> CKD defined as treated ESRD or death with kidney disease noted on the death certificate and confirmed as chronic kidney disease on medical chart review.

<sup>b</sup>  $P < 0.05$ , <sup>c</sup>  $P < 0.01$ , <sup>d</sup>  $P < 0.001$  comparing cases to noncases.

<sup>e</sup>  $P < 0.001$  comparing cases by method of identification.

Table 2. Cumulative incidence of CKD<sup>a</sup> by JNC-VI BP category in 23,534 participants in the CLUE Study, followed from 1974 to 1994

JNC-VI BP Category	Cumulative Incidence, % (n <sup>b</sup> )		
	Men	Women	Total Population
Optimal	0.13% (782)	0.07% (2904)	0.08% (3686)
Normal	0.22% (1831)	0.20% (3502)	0.21% (5333)
High-normal	0.59% (2042)	0.36% (2471)	0.47% (4513)
Stage 1 hypertension	0.71% (3523)	0.66% (3459)	0.69% (6982)
Stage 2 hypertension	2.00% (1050)	1.51% (1123)	1.75% (2173)
Stage 3 or 4 hypertension	3.18% (377)	2.13% (470)	2.60% (847)
Overall	0.78% (9605)	0.49% (13,929)	0.61% (23,534)

<sup>a</sup> CKD defined as treated ESRD or death with kidney disease noted on the death certificate and confirmed as chronic kidney disease on medical chart review.

<sup>b</sup> Number of individuals in the BP category.

treated diabetes, and cigarette smoking. When stratifying by gender, statistical significance was also reached for stages 2, 3, and 4 hypertension in women and for stage 3 and 4 in men. There was also a strong association between CKD and both treated diabetes and cigarette smoking. Among BP categories, stage 1 hypertension was the most common and thus had the greatest attributable risk of CKD at 2650 per million population (23% of CKD risk). The attributable risk of cigarette smoking in this population was staggering at 3640 per million population (31% of CKD risk).

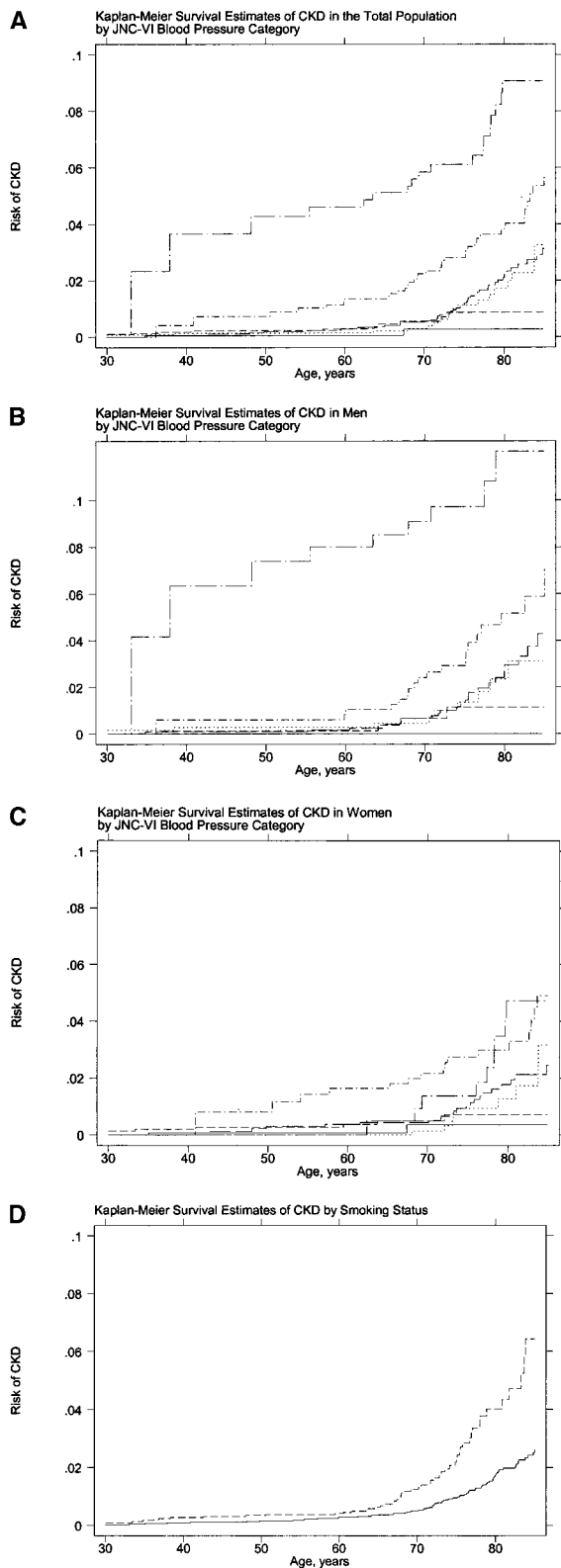
The strong relationship between hypertension and CKD has been shown prospectively in men. The MRFIT study looked at over 330,000 men and found that higher BP is associated with a higher incidence of end-stage renal disease (4,5). Perry *et al.* (3) looked at nearly 12,000 hypertensive male veterans and found that the risk ratio of end-stage renal disease for pretreatment systolic BP of 165 to 180 mmHg was 2.8 and for levels greater than 180 mmHg was 7.6 when compared with a systolic BP of  $\leq 140$  mmHg. A prospective study of over 100,000 men and women in Japan showed that diastolic BP was the strongest predictor of the later development of end-stage renal disease, though the results were not stratified by gender (31). None of these studies reported the risk in women, a group that constituted 47% of new cases of treated end-stage renal disease in 1999 (32).

Current recommendations from the JNC-VI are to aim for a BP below 130/85 mmHg only if certain conditions are present, such as diabetes, heart failure, and renal insufficiency (33). Our data from a community-based cohort show that the bulk of CKD comes from those individuals in the stage 1 category for hypertension, and even high-normal BP is important in its association with CKD. While the relative risk of CKD is higher in more severe hypertension, there are many more people who fall into the high-normal category so the attributable risk of CKD in these lower BP categories has a marked public health impact. This is supported by cross-sectional data from the Third National Health and Nutrition Examination Survey, which shows that elevated serum creatinine is common, underdiagnosed, and strongly related to inadequate treatment of

high BP (34). Given that over 50% of CKD in our study arose from individuals with high-normal BP or with stage 1 hypertension, the strategies used to treat hypertension in these individuals will have a strong impact on the future trajectory of the epidemic increase in CKD in the United States.

Clinical trial data show that antihypertensive therapy can retard the progression of kidney disease, with greatest protection found with the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists, particularly among patients with proteinuria (35–42). The African-American Study of Kidney Disease (AASK) trial showed that ACE inhibitors were more effective than  $\beta$ -blockers and dihydropyridine calcium channel blockers in slowing the decline in GFR in people with hypertension (43), though surprisingly this study did not find that aggressive hypertensive control slowed the progression of renal disease compared with good BP control (MAP 102 to 107 to a MAP  $< 92$ ). Our observational results show a gradient of risk even between optimal ( $< 120/80$  mmHg) and high-normal BP (130–139/85–89 mmHg). The risk in this limited BP range was not statistically significant in our study, although it was in the MRFIT study. Hypertension in observational studies reflects a long period, often decades before the baseline and decades of follow-up time, in marked contrast to the limited follow-up in clinical trials. Thus, observational studies and clinical trials are in agreement supporting BP lowering to below the hypertensive range; the benefits of further lowering are more difficult to determine. Results from recent clinical trials have shown that low BP goals can be successfully achieved, even in patients with CKD. For example, the African-American Study of Hypertension reported mean treated systolic and diastolic BP of 134 and 84 mmHg (37). In the Hypertension Optimal Treatment (HOT) trial, the subset of participants who had serum creatinine values of 1.5 mg/dl or higher ( $n = 470$ ) were able to achieve their target BP as often as those who did not, though they required more antihypertensive medications to do so (44). Thus, to quell the morbidity and mortality associated with the current epidemic of CKD, it is important to pursue more aggressive BP control among both men and women than prac-





**Figure 1.** Kaplan-Meier curves of the risk of chronic kidney disease (CKD) in 23,534 people in Washington County, MD, by age and the following risk factors: (A) JNC-VI BP category in the total population; (B) JNC-VI BP category in men; (C) JNC-VI BP category in women; (D) smoking status at entry into CLUE Study. (A through C), stage 3 or 4, - - - -; stage 2, · · · ·; stage 1, —; high-normal, ····; normal, - - - -; optimal, —. (D) current smoker, - - - -; former/never smoker, —.

ticed currently (34), particularly among patients with stage 1 hypertension.

While diabetes and hypertension are well-described risk factors for CKD, cigarette smoking is not widely appreciated to be a risk factor for CKD. Regalado *et al.* (45) showed in a prospective study of 53 patients with hypertensive nephropathy that the decline in kidney function that occurred after a mean of 35 mo was best predicted by cigarette smoking, confirming prior discoveries that cigarettes increase the risk for progression of kidney disease (12,18). These authors proposed that the likely mechanism by which smoking contributes to the progression of kidney disease is via damage to arterioles and progressive vascular injury. Two cohort studies suggest that cigarette smoking plays a role in the development of kidney disease in the general population. Whelton *et al.* (24) showed a graded increase in the incidence of ESRD by number of cigarettes smoked in men screened for the MRFIT study, and Mulder *et al.* (25) showed an increase in urinary albumin excretion in smokers. Our data show that current smoking is associated with a 2.5 times greater risk of later developing CKD in the population as a whole and when stratified by gender. Possible mechanisms for smoking-related renal injury include the following: an increase in BP and heart rate; alteration of diurnal BP rhythm; an increase in sympathetic nerve activity; an increase in renal vascular resistance leading to a decrease in GFR; arteriosclerosis of renal and intrarenal arteries and arterioles; tubulotoxicity; a direct toxic effect on endothelial cells; increased clotting of platelets (46).

There are several limitations to our study. First of all, as in other very large cohorts, follow-up was passive. We did not have data on losses due to migration. Because we could only detect CKD when people either started on renal replacement therapy or when evidence of CKD was noted in the medical record of participants who died, we had low sensitivity to detect milder CKD. Fortunately, a low sensitivity of detecting a rare disease will result in a loss of power but little bias in estimates of relative hazard. However, it is important to note that detected CKD in this study is only a small subset of all CKD, and absolute risk estimates from this study cannot be used to infer the risk of all stages of CKD as defined by the National Kidney Foundation (47). Furthermore, we did not have serial serum creatinine values, so we could not comment on progression of disease. It is possible that there was some prevalent CKD in the cohort on entry into the study that was unrecognized because we did not have baseline serum creatinine values on all participants, though analysis of a subgroup of cases and matched controls who did have serum creatinine values showed only a small fraction had reduced kidney function at baseline. Furthermore, the outcome of CKD was heterogeneous, as we included those people requiring renal replacement therapy as well as those who died with chronic renal insufficiency. Those who died with renal insufficiency made up the majority of the cases and were significantly older than the group with end-stage renal disease, though the rest of their demographics were similar. Similarly, CKD encompasses a broad range of etiologies that could have different risk factors in terms of development and progression, and it is possible that

**Table 3.** Adjusted relative hazard of CKD<sup>a</sup> in total population and stratified by gender in 23,534 participants in the CLUE Study, followed from 1974 to 1994<sup>b</sup>

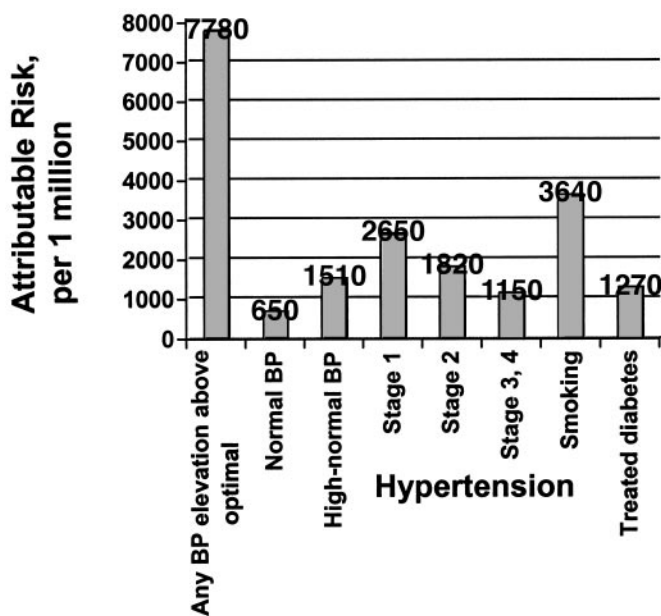
Baseline Risk Factor	Men Relative Hazard (95% CI)	Women Relative Hazard (95% CI)	Total Population Relative Hazard (95% CI)	Adjusted Relative Risk from Men in MRFIT <sup>c</sup> (95% CI)
<b>JNC-VI BP category<sup>d</sup></b>				
Optimal	1.0	1.0	1.0	1.0
Normal	1.4 (0.2–12.1)	2.5 (0.5–12.0)	1.8 (0.5–6.5)	1.2 (0.8–1.7)
High-normal	3.3 (0.4–25.6)	3.0 (0.6–14.4)	3.0 (0.9–10.3)	1.9 (1.4–2.7)
Stage 1 hypertension	3.0 (0.4–22.2)	3.8 (0.8–17.2)	3.2 (1.0–10.4)	3.1 (2.3–4.3)
Stage 2 hypertension	5.7 (0.8–43.0)	6.3 (1.3–29.0)	5.7 (1.7–18.9)	6.0 (4.3–8.4)
Stage 3 or 4 hypertension	9.7 (1.2–75.6)	8.8 (1.8–43.0)	8.8 (2.6–30.3)	Stage 3: 11.2 (7.7–16.2) Stage 4: 22.1 (14.2–34.3)
Treated Diabetes, yes <i>versus</i> no	5.0 (3–10)	10.7 (6–19)	7.5 (4.8–11.7)	
Current cigarette smoker, yes <i>versus</i> no	2.4 (1.5–4)	2.9 (1.7–5)	2.6 (1.8–3.7)	
Gender, female <i>versus</i> male			0.6 (0.4–0.8)	

<sup>a</sup> CKD defined as treated ESRD or death with kidney disease noted on the death certificate and confirmed as chronic kidney disease on medical chart review.

<sup>b</sup> Adjusted for age, cigarette smoking, treated diabetes, and gender (where applicable).

<sup>c</sup> Based on JNC-V BP category.

<sup>d</sup> *P* < 0.001 in test for trend by BP category in all groups.



**Figure 2.** Adjusted attributable risk of CKD per 1 million population for each JNC-VI BP category and for smoking and diabetes in 23,534 participants of the CLUE Study, 1974–1994. Adjusted in a model including JNC-VI BP category, treated diabetes, smoking, and gender with age as the time variable. CKD is defined as treated ESRD or death with kidney disease noted on the death certificate and confirmed as CKD on medical chart review.

the presence of CKD may indicate large vessel renal artery disease in this largely white population. While we adjust for age, gender, treated diabetes, and hypertension, we acknowledge that residual confounding by other conditions associated

with hypertension remains in our adjusted estimates. Finally, our population was predominantly white, so our results cannot necessarily be generalized to nonwhites.

The most important strength of our study is the powerful study design—a large prospective study of 20-yr duration. The benefit of such a long follow-up time outweighs the potential downside one faces when conducting such a study; namely, that risk factors and treatments have changed over time. Furthermore, it was conducted in a community setting where approximately 25 percent of the residents of the county enrolled. The relative homogeneity of the population enhances internal validity.

There is great debate as to whether hypertension causes kidney disease or *vice versa*. However, the data certainly show an increased risk of CKD subsequent to both hypertension and smoking in women as well as men. This suggests that hypertensive women, too, must be aggressively targeted in an effort to stop the current epidemic of CKD. Furthermore, the fact that the attributable risk of CKD among BP categories was the highest for stage 1 hypertension shows that it is these individuals who will go on to make up the bulk of CKD. While we traditionally think of targeting people with malignant hypertension for aggressive intervention, our findings would suggest that optimal treatment of stage 1 hypertension would have a greater public health impact on reducing CKD than would targeting only patients with stages 3 and 4 hypertension. Lastly, physicians already know to advise patients not to smoke; this study suggests that cigarette smoking contributes to the development and/or progression of CKD and thus adds another important reason to quit and patients should be advised of this.

## Acknowledgments

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