Who Should Be Targeted for CKD Screening? Impact of Diabetes, Hypertension, and Cardiovascular Disease

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To address the highly complex interrelated nature of chronic kidney disease (CKD) and diabetes, hypertension, and cardiovascular disease, we examined CKD prevalence by the predictive effect of demographic factors, comorbid conditions, and CKD risk factors by using National Health and Nutrition Examination Survey (NHANES) 1999-2004 data. NHANES is a nationally representative cross-sectional series of surveys with a complex stratified multistage sampling design. NHANES 1999-2004 participants (n = 15,332; age ≥ 20 years) were interviewed in their homes and asked to participate in standardized medical examinations in mobile centers and provide samples for laboratory tests. Weighted logistic regression modeling was used to assess the importance of individual CKD risk factors. Multiple logistic regressions were performed on patient cohorts, with increasing levels of CKD severity defined by means of estimated glomerular filtration rate. A branching diagram was constructed to address the distribution of CKD grouped by diabetes, hypertension, and cardiovascular disease status. CKD prevalence increases with age (39.2% for age ≥ 60 years). For ages 20 to 59 years, CKD prevalence was greater for participants with diabetes (33.8%) than for those without diabetes (8.2%) and for participants with both diabetes and hypertension (43%) than for diabetic participants without hypertension (25.5%) or nondiabetic participants with hypertension (15.2%). The prevalence was 6.8% for nondiabetic participants without hypertension. Effects of cardiovascular disease are less dramatic when hypertension and diabetes are considered. A CKD screening approach targeting individuals 60 years and older or those with diabetes or hypertension likely would be useful from a public health standpoint.

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INDEX WORDS: Cardiovascular disease; chronic kidney disease; diabetes; health screening; hypertension.

Chronic kidney disease (CKD) is receiving increased public attention, with early prevalence estimates at 11%[1] and more recent estimates showing that 13% of the US population has some evidence of kidney damage.[2] This prevalence appears to eclipse the burden of diabetes in the United States, which is approximately 8% of the population. Based on the newest estimates, approximately 26 million people in the United States have some evidence of decreased glomerular filtration rate (GFR) or increased urinary albumin-creatinine ratio (ACR).[2] Despite the large number of patients with varying stages of CKD, only approximately 100,000 reach end-stage renal disease (ESRD) annually in the United States.[3] Nevertheless, the prevalence of renal replacement therapy (dialysis or kidney transplantation) grew to 471,000 patients by the end of 2005, costing approximately $20 billion of the Medicare budget.[3] Diabetes and hypertension account for 71% of all new ESRD cases in the United States. Go et al[4] showed increasing rates of cardiovascular events and mortality with advancing CKD stages; only 1 in 16 patients reached ESRD. Because CKD has been shown to be an independent risk factor for cardiovascular events and mortality and several clinical trials have shown reductions in the progression of CKD in late stage 4 by using angiotensin-converting enzyme inhibitors and angiotensin receptor blockers,[5,6] early detection and treatment may decrease morbidity and mortality caused by cardiovascular disease, as well as slow the progression to ESRD.

Several investigators have developed predictive models for CKD from the National Health

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Nutrition Examination Survey (NHANES).[2,7,8] Because CKD relates strongly to such major comorbid conditions as diabetes, hypertension, and heart disease, developing predictive modeling by using univariant or multivariant methods is challenging. Scoring systems also have been created, but require addressing multiple comorbid conditions to identify the potential population for screening. To address the highly complex nature of CKD, diabetes, hypertension, and cardiovascular disease, we examined CKD prevalence by means of the predictive effect of demographic factors, comorbid conditions, and CKD risk factors using NHANES data from 1999 to 2004. NHANES data are publicly available and representative of the noninstitutionalized US general population; NHANES uses extensively validated health questionnaires and diagnostic tests.

METHODS

NHANES is conducted by the National Centers for Health Statistics of the Centers for Disease Control and Prevention (CDC). NHANES 1999-2004 consisted of nationally representative cross-sectional health examination surveys using a complex stratified multistage probability cluster sampling design.[9] Participants were interviewed in their homes and asked to participate in standardized medical examinations in mobile centers and provide samples for laboratory tests. Details of NHANES methods and scope are available on the CDC website.[10] NHANES 1999-2004 included 15,332 participants 20 years and older. Biochemical data included serum creatinine level; urine albumin level; urine creatinine level; age; race; ethnicity; sex; personal history of diabetes, hypertension, or cardiovascular disease; smoking status, body mass index from height and weight; and family history of diabetes, hypertension, or cardiovascular disease. CKD was defined using estimated GFR (eGFR) and urinary ACR. GFR was estimated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation[11] with creatinine level standardized through recalibration to the Cleveland Clinic laboratory and subsequently to the National Institutes of Standards by using the Roche enzymatic assay.[12-14] $\text{eGFR} = 175 \times (\text{standardized serum creatinine})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ for women}) \times (1.21 \text{ for African Americans})$. ACR of 30 mg/g or greater was considered abnormal. CKD stages were defined as stage 1, eGFR greater than 90 mL/min/1.73 m^2, ACR of 30 mg/g or greater; stage 2, eGFR of 60 to 89 mL/min/1.73 m^2, ACR of 30 mg/g or greater; stage 3, eGFR of 30 to 59 mL/min/1.73 m^2; stage 4, eGFR of 15 to 29 mL/min/1.73 m^2; and stage 5, eGFR less than 15 mL/min/1.73 m^2.

Analysis

Estimated CKD prevalence was calculated for each potential risk-factor group, including age, race, ethnicity, sex, and personal history of diabetes, hypertension, or cardiovascular disease. To obtain national estimates and corresponding SEs from the complex NHANES sample, sampling weights and survey design were implemented using SUDAAN software (Research Triangle Institute, Research Triangle Park, NC).[15] Weighted logistic regression modeling was used to assess the importance of individual risk factors for CKD. Multiple logistic regressions were performed on patient cohorts with increasing levels of CKD severity based on the definition of positive microalbuminuria (ACR $\geq$ 30 mg/g) or eGFR less than 60, 50, 40, and 30 mL/min/1.73 m^2. Age, sex, race/ethnicity, and self-reported diabetes, hypertension, and cardiovascular disease were used as predictors in logistic regressions. A branching diagram of CKD distribution was constructed to address the distribution of CKD grouped by diabetes, hypertension, and cardiovascular disease status.

RESULTS

CKD prevalence increases with age, such that for patients 60 years and older, 39.2% had evidence of CKD stages 1 through 5 and 27.6% had an eGFR less than 60 mL/min/1.73 m^2 (Table 1). Based on sex, percentages ranged between 6.5% and 13.6% of men with evidence of kidney disease and between 9.7% and 17.5% of women. Similar rates of disease were evident according to racial and ethnic groups. For example, CKD stages 1 through 5 were present in 16.0% of non-Hispanic whites; 9.5% had an eGFR less than 60 mL/min/1.73 m^2. Based on these broad definitions, percentages with CKD were slightly lower in non-Hispanic black participants. Participants with self-reported diabetes, hypertension, or cardiovascular disease had high rates of CKD prevalence. Participants with a family history of diabetes or hypertension showed only small differences in CKD prevalence. A family history of heart attack or angina before age 50 years made little difference in CKD prevalence.

Adjusted odds ratios for the major predictors of eGFR less than 60 mL/min/1.73 m^2 or ACR of 30 mg/g or greater are listed in Table 2. Sensitivity of the analysis was tested by addressing different eGFR levels and evidence of increased ACR based on the standard CKD definition of eGFR less than 60 mL/min/1.73 m^2 or ACR of 30 mg/g or greater and eGFR less than 50, 40, and 30 mL/min/1.73 m^2 or ACR of 30 mg/g or greater. For the overall CKD population based on a definition of eGFR less than 60 mL/min/1.73 m^2 or increased ACR, the likelihood of CKD increases with age, is greater in women, is 17% greater in non-Hispanic blacks versus whites,

Table 1. CKD Prevalence by Risk Group: National Health and Nutrition Examination Survey 1999-2004

Characteristic	CKD Stages 1-5*		eGFR < 60 mL/min/1.73 m^2	
	Sample Size in Subgroup	Prevalence ± SE (%)	Sample Size in Subgroup	Prevalence ± SE (%)
All participants	13,120	15.6 ± 0.44	13,274	8.2 ± 0.34
Age (y)				
20-39	4,668	6.1 ± 0.50	4,720	0.8 ± 0.14
40-59	3,900	11.7 ± 0.67	3,929	4.4 ± 0.58
≥60	4,552	39.2 ± 0.79	4,625	27.6 ± 0.81
Sex				
Men	6,251	13.6 ± 0.5	6,328	6.5 ± 0.33
Women	6,869	17.5 ± 0.49	6,946	9.7 ± 0.45
Race/ethnicity				
Non-Hispanic white	6,700	16.0 ± 0.48	6,775	9.5 ± 0.4
Non-Hispanic black	2,449	15.6 ± 0.82	2,494	5.8 ± 0.41
Mexican American	3,000	11.3 ± 0.82	3,021	2.3 ± 0.38
Other	971	15.7 ± 1.19	984	5.2 ± 0.85
Self-reported diabetes				
Yes	1,277	44.4 ± 1.42	1,294	22.0 ± 1.66
No	11,838	13.5 ± 48	11,974	7.2 ± 0.35
Self-reported hypertension				
Yes	4,104	29.7 ± 0.91	4,153	18.4 ± 0.87
No	8,882	10.4 ± 0.39	8,983	4.4 ± 0.27
Self-reported CVD†				
Yes	1,483	42.7 ± 1.48	1,512	31.2 ± 1.29
No	11,570	12.9 ± 0.40	11,694	6.0 ± 0.3
Diabetes, hypertension, or CVD†				
Yes	4,836	30.0 ± 0.76	4,895	18.2 ± 0.79
No	5,437	9.3 ± 0.54	5,492	3.8 ± 0.41
Self-reported kidney disease				
Yes	364	58.3 ± 3.44	372	43.0 ± 3.78
No	12,726	14.6 ± 0.41	12,870	7.4 ± 0.31
Current smoker				
Yes	2,861	12.8 ± 0.61	2,894	4.3 ± 0.44
No	10,241	16.5 ± 0.54	10,359	9.5 ± 0.4
Body mass index ≥ 30 kg/m^2				
Yes	4,160	18.2 ± 0.74	4,190	8.5 ± 0.5
No	8,634	13.9 ± 0.58	8,705	7.7 ± 0.41
Family history of diabetes				
Yes	6,388	16.0 ± 0.63	6,442	7.9 ± 0.45
No	6,461	15.1 ± 0.67	6,555	8.5 ± 0.49
Family history of hypertension at age < 50 y				
Yes	3,757	13.6 ± 0.84	3,790	6.1 ± 0.47
No	8,752	16.4 ± 0.55	8,856	9 ± 0.43
Family history of heart attack or angina at age < 50 y				
Yes	1,627	14.1 ± 1.16	1,647	7.8 ± 0.80
No	11,059	15.8 ± 0.6	11,183	8.2 ± 0.43

Note: Non–age-adjusted analysis. Conversion factor for units: eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667.

Abbreviations: ACR, albumin-creatinine ratio; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.

*CKD stages were defined as stage 1, eGFR > 90 mL/min/1.73 m^2 and ACR ≥ 30 mg/g; stage 2, 60 ≤ eGFR ≤ 89 mL/min/1.73 m^2 and ACR ≥ 30 mg/g; stage 3, 30 ≤ eGFR ≤ 59 mL/min/1.73 m^2; stage 4, 15 ≤ eGFR ≤ 29 mL/min/1.73 m^2; stage 5, eGFR < 15 mL/min/1.73 m^2.

†Self-reported CVD includes a personal history of 1 or more of the following conditions: congestive heart failure, coronary heart disease, angina/angina pectoris, myocardial infarction, or stroke.

Table 2. Odds Ratios of eGFR Less Than 60 mL/min/1.73 m^2 or ACR of 30 mg/g or Greater: National Health and Nutrition Examination Survey 1999-2004

Characteristic	Odds Ratio (95% confidence interval)			
	eGFR < 60 mL/min/1.3 m^2 or ACR ≥ 30 mg/g	eGFR < 50 mL/min/1.3 m^2 or ACR ≥ 30 mg/g	eGFR < 40 mL/min/1.3 m^2 or ACR ≥ 30 mg/g	eGFR < 30 mL/min/1.3 m^2 or ACR ≥ 30 mg/g
Age (y)				
20-49	1	1	1	1
50-59	1.73 (1.27-2.35)	1.38 (1.03-1.85)	1.22 (0.87-1.70)	1.21 (0.87-1.70)
60-69	2.72 (2.03-3.64)	1.84 (1.35-2.50)	1.7 (1.24-2.34)	1.68 (1.23-2.3)
≥70	8.12 (6.48-10.17)	5.51 (4.22-7.21)	4.29 (3.25-5.65)	3.59 (2.68-4.81)
Sex				
Men	1	1	1	1
Women	1.30 (1.17-1.46)	1.25 (1.08-1.44)	1.16 (0.99-1.36)	1.09 (0.94-1.27)
Race/ethnicity				
Non-Hispanic white	1	1	1	1
Non-Hispanic black	1.17 (1.01-1.37)	1.51 (1.28-1.79)	1.64 (1.38-1.95)	1.71 (1.45-2.03)
Mexican American	1.01 (0.84-1.22)	1.31 (1.09-1.58)	1.41 (1.16-1.72)	1.45 (1.19-1.76)
Other	1.21 (0.92-1.59)	1.48 (1.15-1.92)	1.59 (1.21-2.09)	1.6 (1.21-2.12)
Self-reported diabetes				
Yes	2.83 (2.30-3.48)	3.41 (2.73-4.25)	3.68 (2.99-4.55)	3.67 (2.9-4.63)
No	1	1	1	1
Self-reported hypertension				
Yes	1.79 (1.52-2.10)	1.74 (1.47-2.07)	1.68 (1.43-1.99)	1.65 (1.39-1.96)
No	1	1	1	1
Self-reported cardiovascular disease				
Yes	1.62 (1.30-2.02)	1.73 (1.30-2.29)	1.51 (1.09-2.09)	1.33 (0.98-1.82)
No	1	1	1	1

Note: Conversion factor for units: GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667.
Abbreviations: ACR, albumin-creatinine ratio; eGFR, estimated glomerular filtration rate.

and is greater in participants with diabetes, hypertension, or cardiovascular disease. Results are similar using a definition of eGFR less than 50 mL/min/1.73 m^2 or increased ACR, with increased odds of CKD for non-Hispanic blacks of 1.51 compared with 1.17 by using the definition eGFR less than 60 mL/min/1.73 m^2. Absolute values for diabetes also increase from 2.83 to 3.41. For eGFR less than 40 mL/min/1.73 m^2 or increased ACR, odds ratios for non-Hispanic blacks increased to 1.64, and for eGFR less than 30 mL/min/1.73 m^2 or increased ACR, to 1.71. Estimated odds of CKD decreased in the group with self-reported cardiovascular disease with eGFR less than 30 mL/min/1.73 m^2 or ACR of 30 mg/g or greater.

Based on the sensitivity analysis of decreasing kidney function (Table 2), a branching diagram was developed, showing CKD distribution by the major diseases (Fig 1). Because eGFR less than 60 mL/min/1.73 m^2 and ACR of 30 mg/g or greater was common at 60 years and older (39%), the diagram was developed for ages 20 to 59 years. For each branch, the diagram shows the weighted number of individuals estimated from the sample, actual sample size, percentage with evidence of CKD stages 1 through 5, and the SE for the group. Separating NHANES participants based on the presence or absence of diabetes not unexpectedly shows a substantially greater prevalence of CKD stages 1 through 5 for those with diabetes (33.8%) than for those without diabetes (8.2%).

Further separating diabetic and nondiabetic participants by history of hypertension shows increased CKD prevalence for those with both diabetes and hypertension at 43%. The prevalence for diabetic participants without hypertension is 25.5%. For nondiabetic participants, the presence of hypertension increases the percentage with CKD; 15.2% show evidence of CKD stages 1 through 5 compared with 6.8% of nondiabetic participants without hypertension.

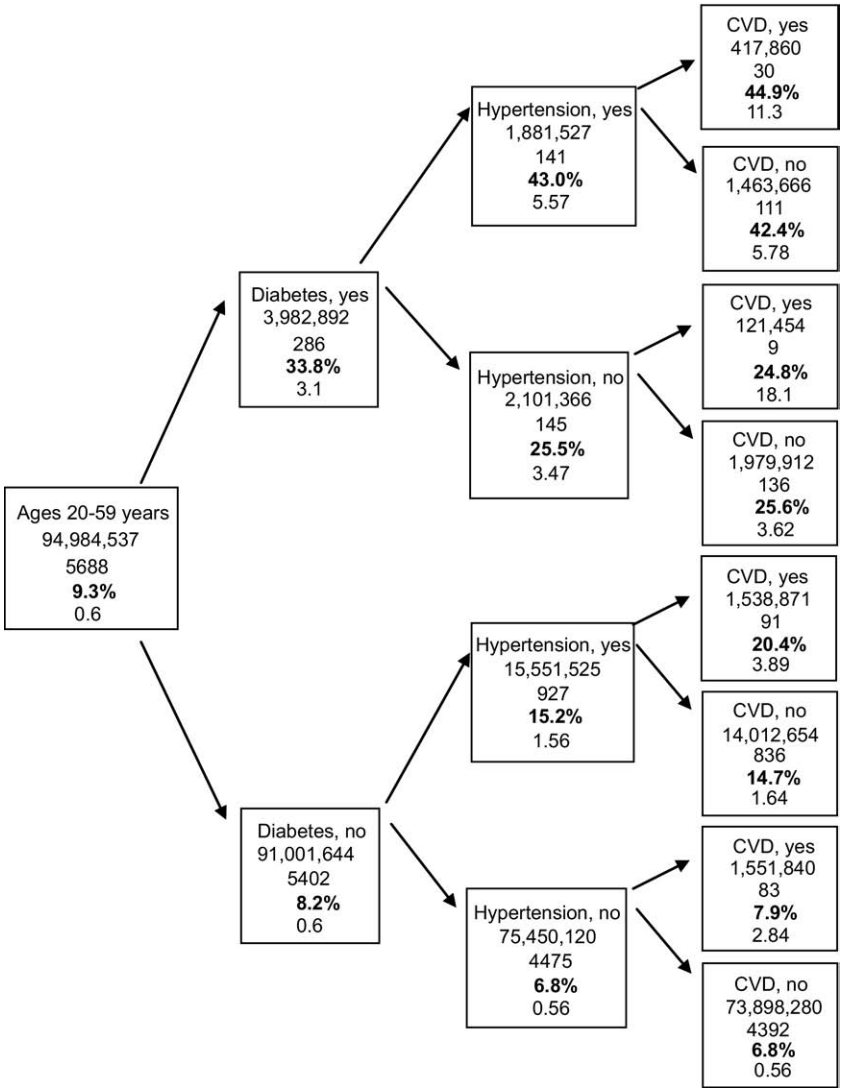

Figure 1. Branching diagram shows the distribution of chronic kidney disease (CKD) grouped by diabetes, hypertension, and cardiovascular disease (CVD) status. Values top to bottom: weighted number of individuals estimated from the sample, actual sample size, percentage with CKD, and SE. CKD stages 1 to 5 defined by estimated glomerular filtration rate (GFR) and albumin-creatinine ratio in milligrams per gram. Conversion factor for units: GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, $\times$0.01667. Data from the National Health and Nutrition Evaluation Survey 1999-2004.

The different effects of cardiovascular disease are much less dramatic when hypertension and diabetes status are considered. For example, CKD prevalence is 44.9% for participants with diabetes, hypertension, and cardiovascular disease and 42.4% for those with diabetes and hypertension, but not cardiovascular disease. Results are similar for participants with diabetes and cardiovascular disease, but not hypertension (24.8%), and for those with diabetes, but not hypertension or cardiovascular disease (25.6%). The presence of cardiovascular disease in the nondiabetic population affected participants with hypertension more than those with no history of hypertension. Thus, a target group selected by age, diabetes, and hypertension status appears to offer high yield for a potential screening program for evidence of CKD.

DISCUSSION

The increasing prominence of CKD as a major public health problem has led to better understanding of the complex interrelationship among CKD, diabetes, hypertension, and cardiovascular events.[2,4,7] Strategies to identify at-risk populations may have a public health benefit. Because cardiovascular event rates are accelerating and death rates are increased in the CKD population, intervention programs targeted at the high-risk

CKD population with diabetes and hypertension may yield more active risk-factor identification and treatment.

Our findings, like other findings, indicate CKD risk factors to be age, sex, race, ethnicity, cardiovascular disease, diabetes, and hypertension. However, our analysis shows that CKD crosses major areas of public health concern as it relates to diabetes and hypertension. This is not unexpected because 2 major complications of diabetes and hypertension are CKD and ESRD. In addition, ESRD incidence data indicate that 45% of new ESRD cases are secondary to diabetes and another 26% are related to hypertension.[3]

Other factors that have been used to screen populations at risk of CKD include family history of hypertension, diabetes, or CKD. NHANES data include no information about family history of CKD, but include information about family history of diabetes or hypertension. These factors were analyzed in the NHANES sample and showed no consistent findings regarding their predictive value. In logistic regression models, family history of diabetes or hypertension was no longer predictive based on individual histories of hypertension or diabetes. These findings on a general population level may be limited because of limitations in the details of questions as asked or poor general knowledge of kidney disease in the population. For example, in the National Kidney Foundation Kidney Early Evaluation Program (KEEP), which targets participants with diabetes or hypertension or a family history of diabetes, hypertension, or kidney disease, only 2% of participants with evidence of kidney disease knew they had evidence of kidney disease.[16] Therefore, fully assessing the utility of family history of kidney disease, diabetes, or hypertension as a risk factor may be difficult in a general population setting.

In designing a public health program to increase awareness of CKD in the general population and provide insight to physicians into high-risk populations, targeted populations with high rates of abnormalities and high rates of CKD appear to be of benefit. The public health message should be simple enough to easily communicate the common terms and diseases that place people in risk groups and encourage testing for evidence of CKD. From this standpoint, the simple message is that individuals 60 years or older and those with diabetes or hypertension should be checked for evidence of kidney disease. This message could be transmitted easily through public health programs.

The targeted screening approach for evidence of kidney damage or kidney disease is consistent with work published by Boulware et al[17] showing that general population screening should be targeted toward individuals older than 60 years and those with hypertension. Previous clinical practice guidelines have recommended proteinuria and serum creatinine testing in the diabetes population, thereby supporting the findings from this general NHANES analysis.[18] Additionally, the American Heart Association has recommended screening for CKD in individuals with diabetes or hypertension, also supporting findings from the NHANES analysis.[18]

The CKD analysis presented here, along with analyses by other investigators using NHANES national representative samples, provide important insight into the relationships among diabetes, hypertension, and CKD. However, the NHANES population may be limited because of potential biases related to the ability to participate not only in the questionnaire portion, but also in the physical examination portion of the survey. Also, NHANES includes little information about history of kidney disease, particularly family histories of individuals on dialysis therapy or undergoing kidney transplants. Secondary limitations relate to family history of hypertension, which is referenced for only participants 50 years and older. This issue may be particularly important in the African American population, where hypertension is common in younger people. In addition, evidence of obesity in minority populations is increasing, especially in African Americans and African American women in the United States.[19-22] Another possible limitation of the NHANES sample may relate to specific rare diseases, such as polycystic kidney disease, interstitial kidney disease, and glomerular diseases. These diagnoses account for 29% of patients who reach ESRD, but are relatively rare conditions in the general population. Therefore, we cannot comment about specific risk groups for familial and genetic diseases, such as polycystic kidney disease, from the size of the national sample.

In summary, we used NHANES 1999-2004 data from the nationally representative population of the United States to determine target populations for potential CKD detection programs. Our findings are similar to other findings and highlight the observation that CKD, diabetes, and hypertension relate substantially to each other in the general population. Targeting specifically for cardiovascular disease appears to have a lower yield than the approach of identifying individuals 60 years or older or with self-reported diabetes or hypertension. The usefulness of family history of diabetes or hypertension cannot be determined at this time based on the limited data from the NHANES questionnaire and the likely small sample size in the NHANES population.

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