
The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters.

Citation

Published Version
doi://10.2337/dc07-2348

Accessed
April 27, 2018 2:59:11 AM EDT

Citable Link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:10140033

Terms of Use
This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA

(Article begins on next page)

Caroline S. Fox, MD, MPH1,2
Paul Muntner, PhD3

OBJECTIVE — The prevalence of chronic kidney disease (CKD) increased among U.S. adults from 1988–1994 to 1999–2004. We sought to explore the importance of trends in risk factors for CKD over time.

RESEARCH DESIGN AND METHODS — The prevalence of cigarette smoking, obesity, hypertension, high cholesterol, and diabetes among U.S. adults with stage 3 CKD (estimated glomerular filtration rate <60 ml/min per 1.73 m2) and albuminuria (urinary albumin-to-creatinine ratio ≥30 mg/g), separately, were determined for 1988–1994 and 1999–2004 using data from serial National Health and Nutrition Examination Surveys. The prevalence ratios (PRs) for stage 3 CKD and albuminuria by the presence of these risk factors were compared across survey periods.

RESULTS — The PR for CKD declined between 1988–1994 and 1999–2004 for obesity (PR 1.51 and 1.14 for 1988–1994 and 1999–2004, respectively; P for change = 0.010), hypertension (PR 2.60 and 1.70; P for change = 0.005), and high cholesterol (PR 1.58 and 1.20; P for change = 0.028). However, for diagnosed diabetes, the PR remained unchanged (1.64 and 1.62, P for change = 0.898). Similar results were observed for undiagnosed diabetes (PR of CKD 1.38 and 1.50; P for change = 0.373). The association of cigarette smoking was similar in each time period. Besides obesity, for which the association remained stable over time, similar patterns were observed for the PR of albuminuria.

CONCLUSIONS — In terms of CKD, improvements in hypertension and high cholesterol management have been offset by both diagnosed and undiagnosed diabetes. Further increases in CKD may occur if diabetes continues to increase.

Diabetes Care 31:1337–1342, 2008

From the 1National Heart, Lung, and Blood Institute’s Framingham Heart Study, Framingham, Massachusetts; the 2Division of Endocrinology, Metabolism, and Diabetes, Department of Medicine, Harvard Medical School, Boston, Massachusetts; and the 3Mt. Sinai School of Medicine, New York, New York. Corresponding author: Caroline S. Fox, foxca@nhlbi.nih.gov.
Received 10 December 2007 and accepted 15 April 2008.
© 2008 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See http://creativecommons.org/licenses/by-nc-nd/3.0/ for details.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
measurements and pregnant or menstruating women were excluded, resulting in valid data from 15,216 and 12,778 participants from NHANES III and NHANES 1999–2004, respectively.

### Covariate data

Of relevance to the current analysis, variables collected during the in-home interview were age, race/ethnicity, sex, cigarette smoking, a history of diabetes, and pharmacologic treatment for hypertension, high cholesterol, or diabetes. Participants who reported having smoked ≥100 cigarettes during their lifetime were classified as current or former smokers if they answered affirmatively or negatively, respectively, to the question “Do you now smoke cigarettes?” A fixed stadiometer was used to measure height; a Toledo digital scale was used to measure weight with participants clothed in underwear, a disposable gown, and foam slippers. BMI was calculated as weight in kilograms divided by the square of height in meters; obesity was defined as BMI ≥30 kg/m².

Three blood pressure measurements were obtained using a standard protocol (American Heart Association) during the evaluation. While three additional blood pressure measurements were taken during the NHANES III in-home interview, for comparability, the current analyses were limited to blood pressure measurements from the medical evaluation. Using the mean of all available blood pressure measurements, systolic and/or diastolic blood pressure ≥140 mmHg and/or ≥90 mmHg, respectively, or current use of blood pressure-lowering medication was used to define hypertension.

### Laboratory measurements and exposure definitions

Blood samples were stored at −20°C. For lipid analyses, samples were shipped to the Lipoprotein Analytical Laboratory (Johns Hopkins University, Baltimore, MD). Total cholesterol was measured with the Hitachi 704 Analyzer; high cholesterol was defined as levels ≥240 mg/dl or concurrent pharmacologic lipid-lowering treatment.

Glucose was measured on previously frozen plasma at the University of Missouri at Columbia. Self-report of a prior diagnosis of diabetes with current use of an oral hypoglycemic agent or insulin was used to define diagnosed diabetes. For participants without diagnosed diabetes who attended a morning NHANES study visit after fasting 8 h or longer (n = 7,329 and 5,572 for NHANES III and NHANES 1999–2004, respectively), undiagnosed diabetes was defined as plasma glucose ≥126 mg/dl.

### Outcome definitions

Serum creatinine was measured using the modified kinetic method of Jaffe (Hitachi 917 analyzer). Serum creatinine concentrations were calibrated to the assays used for the development of the modification of diet in renal disease (MDRD) equation (19). GFR was estimated with the simplified MDRD equation. Individuals with an estimated GFR (eGFR) of 30–59 ml/min per 1.73 m² were considered to have stage 3 CKD.

Urine albumin and creatinine concentrations were measured in the same laboratory during both surveys. Urinary albumin was measured using a solid-phase fluorescence immunoassay; urinary creatinine was measured using modified kinetic method of Jaffe (Astra Analyzer; Beckman Coulter Synchron). Albuminuria was defined as urinary albumin-to-urinary creatinine ratio ≥30

---

**Table 1—CVD factors among NHANES III and NHANES 1999–2004 participants 20 years of age and older with and without stage 3 CKD**

<table>
<thead>
<tr>
<th></th>
<th>Stage 3 CKD</th>
<th>Age-adjusted P for time-period difference</th>
<th>No stage 3 CKD</th>
<th>Age-adjusted P for time-period difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NHANES III</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>71.5 (0.8)</td>
<td>70.7 (0.6)</td>
<td>13.499</td>
<td>11.459</td>
</tr>
<tr>
<td>Mean DBP (mmHg)</td>
<td>140.8 (1.1)</td>
<td>138.9 (0.9)</td>
<td>120.2 (0.4)</td>
<td>122.8 (0.4)</td>
</tr>
<tr>
<td>Mean total cholesterol (mg/dl)</td>
<td>232.1 (3.0)</td>
<td>206.8 (1.8)</td>
<td>203.1 (0.8)</td>
<td>202.2 (0.7)</td>
</tr>
<tr>
<td>Glycated hemoglobin (%)</td>
<td>6.03 (0.07)</td>
<td>5.83 (0.04)</td>
<td>5.35 (0.02)</td>
<td>5.46 (0.02)</td>
</tr>
<tr>
<td><strong>NHANES 1999–2004</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>70.7 (0.6)</td>
<td>70.7 (0.6)</td>
<td>10.4 (0.6)</td>
<td>10.6 (1.0)</td>
</tr>
<tr>
<td>Mean DBP (mmHg)</td>
<td>138.9 (0.9)</td>
<td>138.9 (0.9)</td>
<td>73.2 (0.3)</td>
<td>72.7 (0.2)</td>
</tr>
<tr>
<td>Mean total cholesterol (mg/dl)</td>
<td>206.8 (1.8)</td>
<td>206.8 (1.8)</td>
<td>202.2 (0.7)</td>
<td>202.2 (0.7)</td>
</tr>
<tr>
<td>Glycated hemoglobin (%)</td>
<td>5.83 (0.04)</td>
<td>5.83 (0.04)</td>
<td>5.46 (0.02)</td>
<td>5.46 (0.02)</td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise indicated. *Among participants with a diagnosis of hypertension; †among participants with a diagnosis of high cholesterol. All P values (except age) for comparing mean levels and prevalence between NHANES III and NHANES 1999–2004 are age adjusted. DBP, diastolic blood pressure; HT, hypertensive; SBP, systolic blood pressure.
mg/g. The protocols for NHANES III and NHANES 1999–2004 were approved by the National Center for Health Statistics of the Centers for Disease Control and Prevention Institutional Review Board.

Statistical methods
Characteristics of the populations with and without stage 3 CKD and with and without albuminuria were calculated for each time period. Characteristics included age, race/ethnicity, sex, mean levels of systolic and diastolic blood pressure, BMI, total cholesterol, glycated hemoglobin, use of blood pressure– and cholesterol-lowering medications, and prevalence of cigarette smoking, obesity, hypertension, high cholesterol, and diagnosed and undiagnosed diabetes. The statistical significance of differences in the means and prevalence estimates across the two surveys was determined using the Wald $\chi^2$ test. Test statistics were calculated as the difference in prevalence estimates divided by the standard error of the difference, calculated as the square root of the sum of each estimate’s variance. The prevalence ratios (PRs) of stage 3 CKD and albuminuria associated with cigarette smoking, obesity, hypertension, high cholesterol, and diagnosed and undiagnosed diabetes were estimated for each time period, separately, using log-binomial regression models including adjustment for age, race, sex, hypertension, and self-reported diabetes. The statistical significance of changes in the PRs over time was calculated using two sample $t$ tests (i.e., the difference in the $\beta$-coefficients from the regression models divided by the square root of the sum of their variance).

Sample weights that account for the complex survey design of NHANES, including unequal probabilities of selection, over-sampling, and nonresponse, were applied for all analyses using SUDAAN (Version 9.1; Research Triangle Institute, Research Triangle Park, NC). Standard errors were estimated using the Taylor series linearization method.

RESULTS
Demographic and risk factors among individuals with and without stage 3 CKD
Demographic characteristics, risk factor levels, and the prevalence of risk factors among individuals with and without stage 3 CKD in the two time periods are shown in Table 1. Among individuals with stage 3 CKD, the prevalence of cigarette smoking declined and obesity, hypertension, and high cholesterol remained stable. However, the prevalence of diagnosed diabetes increased (13.0 and 16.8% for NHANES III and NHANES 1999–2004, respectively), although this did not reach statistical significance ($P = 0.093$). Among individuals without CKD, the prevalence of obesity, hypertension, high cholesterol, and diagnosed diabetes increased, whereas the prevalence of undiagnosed diabetes was stable.

The PR for CKD associated with cigarette smoking was similar in both time periods, while the PR for CKD associated with obesity, hypertension, and high cholesterol was significantly lower in 1999–2004 compared with 1988–1994 (Fig. 1). For example, the PR for CKD associated with hypertension was 2.60 (95% CI 2.00–3.38) in NHANES III and decreased to 1.70 (1.43–2.02) in NHANES 1999–2004 ($P$ for change $= 0.005$). However, for CKD associated with diagnosed diabetes, the PR remained unchanged (1.64 in NHANES III and 1.62 in NHANES 1999–2004; $P$ for change $= 0.898$). Similar results were observed for undiagnosed diabetes: the PR for CKD was 1.38 and 1.50 in NHANES III and NHANES 1999–2004, respectively; $P$ for change $= 0.373$).

Risk factors among individuals with and without albuminuria
Among individuals with albuminuria, the prevalence of cigarette smoking decreased between 1988–1994 and 1999–2004. The prevalence of hypertension, high cholesterol, and undiagnosed diabetes remained stable, whereas the prevalence of obesity and diagnosed diabetes increased (Table 2). The PRs for albuminuria associated with cigarette smoking and obesity was similar for 1988–1994 and 1999–2004 (Fig. 2). However, the PRs for albuminuria associated with hypertension and high cholesterol decreased over the time period under study ($P = 0.024$ and 0.020, respectively). The PR for albuminuria associated with diag-
Trends in CKD risk factors

Table 2—CVD risk factors among NHANES III and NHANES 1999–2004 participants 20 years of age and older with and without albuminuria

<table>
<thead>
<tr>
<th></th>
<th>Albuminuria</th>
<th></th>
<th></th>
<th>No albuminuria</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>for time-period</td>
<td></td>
<td></td>
<td>for time-period</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>difference</td>
<td></td>
<td></td>
<td>difference</td>
</tr>
<tr>
<td>n</td>
<td>1,810</td>
<td>1,711</td>
<td>—</td>
<td>13,406</td>
<td>11,067</td>
<td>—</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>57.3 (0.9)</td>
<td>56.3 (0.7)</td>
<td>0.380</td>
<td>44.2 (0.5)</td>
<td>45.6 (0.3)</td>
<td>0.016</td>
</tr>
<tr>
<td>Male sex</td>
<td>43.6 (2.3)</td>
<td>47.9 (1.3)</td>
<td>0.053</td>
<td>51.2 (0.4)</td>
<td>50.3 (0.4)</td>
<td>0.778</td>
</tr>
<tr>
<td>Black race</td>
<td>15.8 (1.2)</td>
<td>14.3 (1.6)</td>
<td>0.4</td>
<td>10.4 (0.6)</td>
<td>10.4 (1.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Mean SBP (mmHg)</td>
<td>137.9 (1.1)</td>
<td>138.2 (0.8)</td>
<td>0.346</td>
<td>120.0 (0.4)</td>
<td>122.6 (0.4)</td>
<td>0.021</td>
</tr>
<tr>
<td>Mean DBP (mmHg)</td>
<td>77.0 (0.5)</td>
<td>74.2 (0.6)</td>
<td>&lt;0.001</td>
<td>73.1 (0.3)</td>
<td>72.4 (0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>On anti-HT medicines</td>
<td>60.0 (2.2)</td>
<td>66.8 (2.0)</td>
<td>0.005</td>
<td>51.5 (1.3)</td>
<td>61.4 (1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>28.0 (0.3)</td>
<td>29.3 (0.4)</td>
<td>&lt;0.001</td>
<td>26.5 (0.1)</td>
<td>27.9 (0.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean total cholesterol (mg/dl)</td>
<td>220.3 (1.7)</td>
<td>206.3 (2.1)</td>
<td>&lt;0.001</td>
<td>203.4 (0.9)</td>
<td>202.4 (0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>On cholesterol lowering medications</td>
<td>18.0 (2.8)</td>
<td>51.8 (2.8)</td>
<td>&lt;0.001</td>
<td>11.9 (1.0)</td>
<td>39.6 (1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glycated hemoglobin (%)</td>
<td>6.24 (0.08)</td>
<td>6.16 (0.05)</td>
<td>0.267</td>
<td>5.31 (0.02)</td>
<td>5.41 (0.01)</td>
<td>1.00</td>
</tr>
<tr>
<td>Cigarette smokers</td>
<td>27.0 (1.8)</td>
<td>20.5 (1.4)</td>
<td>0.002</td>
<td>28.8 (0.9)</td>
<td>20.7 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obese</td>
<td>32.2 (1.7)</td>
<td>39.3 (2.2)</td>
<td>0.001</td>
<td>22.0 (0.6)</td>
<td>29.0 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>57.6 (2.3)</td>
<td>57.4 (1.8)</td>
<td>0.496</td>
<td>21.2 (0.8)</td>
<td>27.4 (0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>37.3 (1.9)</td>
<td>33.6 (1.7)</td>
<td>0.658</td>
<td>23.5 (0.7)</td>
<td>25.1 (0.6)</td>
<td>0.044</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosed</td>
<td>18.0 (1.3)</td>
<td>21.6 (1.1)</td>
<td>0.01</td>
<td>2.4 (0.2)</td>
<td>4.3 (0.2)</td>
<td>0.014</td>
</tr>
<tr>
<td>Undiagnosed</td>
<td>11.6 (1.9)</td>
<td>14.1 (2.3)</td>
<td>0.822</td>
<td>3.0 (0.3)</td>
<td>2.9 (0.3)</td>
<td>0.861</td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise indicated. All P values (except age) for comparing mean levels and prevalence between NHANES III and NHANES 1999–2004 are age adjusted. DBP, diastolic blood pressure; HT, hypertensive; SBP, systolic blood pressure.

Nosed diabetes decreased from 3.28 to 2.69 (P = 0.079), whereas the PR for albuminuria associated with undiagnosed diabetes increased nonsignificantly P = 0.594).

Self-reported diabetes

In a secondary analysis, diagnosed diabetes was redefined to include participants who self-reported diabetes regardless of whether they were on medication. Using this definition, the prevalence of diabetes increased between 1988–1994 and 1999–2004 from 16.0 to 19.1% among those with CKD and from 4.9 to 6.2% among adults without CKD. Also, the prevalence of diabetes increased from 21.4 to 24.1% and from 3.9 to 5.3% among adults with and without albuminuria, respectively. Similar to the main results, the PRs of CKD and albuminuria associated with self-reported diabetes did not change significantly over time (each P > 0.30; data not shown).

CONCLUSIONS

Principal findings

The current study suggests that the association of obesity, hypertension, and high cholesterol with CKD has declined over time. Conversely, we observed no change in the association between diabetes and CKD. With the exception of obesity, for which the association with albuminuria did not change over time, similar trend results were observed for albuminuria.

In the context of the current literature

Diabetes is a critical risk factor for CKD and albuminuria (6,21,22) and accounts for nearly half of all incident cases of end-stage renal disease in the U.S. (8). Numerous studies have shown that the prevalence and incidence of diabetes continue to increase (13–16). The increase in number of U.S. adults with diabetes has lead to an increase in the attributable risk for diabetes as a CVD risk factor relative to other traditional risk factors (23). Rates of treatment and control of CVD risk factors among people with diabetes remains poor (18). Although U.S. vital statistics document a marked decline in cardiovascular mortality over the past several decades, recent data suggest that individuals with diabetes have not experienced the same mortality reductions (24). We extend these findings to relations between diabetes and CKD and show that the PR for CKD did not decline over the past decade.

In contrast, results for hypertension and high cholesterol are more encouraging. While hypertension has increased among U.S. adults over the past decade (11), rates of hypertension treatment and control have also increased. The improvement in overall management of hypertension, despite its increasing prevalence, is reflected in the reduced PR for hypertension as a CKD risk factor. Rates of high cholesterol have decreased over time (12). Dietary...
improvements are likely partially responsible for these trends as well. Similar to the results for hypertension, our results indicate that an added benefit of these interventions may be the reduced risk of CKD and albuminuria associated with high cholesterol.

Strengths and limitations

Strengths of the current study include the well-characterized NHANES datasets, large sample size, and nationally representative data. We were able to examine CKD as defined by reduced eGFR as well as albuminuria, a well-established risk factor for CKD (25,26). Further, albuminuria identifies different subsets of individuals at risk for CVD and all-cause mortality as compared with CKD alone (27). Limitations include the use of the MDRD equation to estimate GFR instead of a direct measurement (28), which would not be feasible in a large population-based study. Further, the MDRD equation underestimates eGFR in healthy individuals (29); how this impacts the dichotomous classification of CKD is uncertain. We used a study design that incorporated serial cross-sectional studies and therefore cannot infer causality between risk factors and CKD. However, we believe that this study design is the most powerful for determining overall trends in disease burden. Our sample was limited to individuals with stage 3 CKD due to small numbers of individuals with more severe CKD. Measures of albuminuria were based on a spot-urine collection. However, the correlation between 24-h collections and spot urine is acceptable (30). We relied on fasting plasma glucose and not an oral glucose tolerance test to define diabetes. Therefore, we may have underestimated the prevalence of undiagnosed diabetes in our sample. However, it is unlikely that this occurred differentially between NHANES III and NHANES 1999–2004. Therefore, this is unlikely to account for the observed findings.

Implications

Increases in obesity have lead to rises in the prevalence of diabetes. As diabetes continues to increase, the prevalence and incidence of CKD may continue to increase as well. Currenty, individuals with diabetes are suboptimally managed with respect to CVD risk factors and overall glucose management (18). Less than half of individuals with CKD in the Framingham Heart Study had optimal A1C levels (31). Further, among individuals with CKD, diabetes, hypertension, and dyslipidemia, less than 10% of participants had optimal management of all of their risk factors. Improvement in CVD risk factor management, particularly diabetes, will be necessary to prevent further increases in CKD prevalence. Whether interventions focusing on weight loss and cholesterol reduction will reduce the risk of CKD require further study.

In conclusion, improvements in hypertension and high cholesterol management have been offset by both diagnosed and undiagnosed diabetes. Further increases in CKD may occur if diabetes continues to increase.

Acknowledgments—C.S.F. and P.M. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

Trends in CKD risk factors


