Apolipoprotein E and Progression of Chronic Kidney Disease

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Context  Apolipoprotein E (APOE) genetic variation has been implicated in diabetic nephropathy with the ε2 allele increasing and the ε4 allele decreasing risk. APOE allelic associations with chronic kidney disease beyond diabetic nephropathy are unknown, with no studies reported in high-risk African American populations.

Objective  To quantify the risk of chronic kidney disease progression associated with APOE in a population-based study including white, African American, diabetic, and nondiabetic individuals.

Design, Setting, and Participants  Prospective follow-up (through January 1, 2003) of Atherosclerosis Risk in Communities (ARIC) study participants, including 3859 African American and 10 661 white adults aged 45 to 64 years without severe renal dysfunction at baseline in 1987-1989, sampled from 4 US communities.

Main Outcome Measures  Incident chronic kidney disease progression, defined as hospitalization or death with kidney disease or increase in serum creatinine level of 0.4 mg/dL (35 μmol/L) or more above baseline, examined by APOE genotypes and alleles.

Results  During median follow-up of 14 years, chronic kidney disease progression developed in 1060 individuals (incidence per 1000 person-years; 5.5 overall; 8.8 in African Americans and 4.4 in whites). Adjusting for major chronic kidney disease risk factors, ε2 moderately increased and ε4 decreased risk of disease progression (likelihood ratio test, P = .03). Further adjustment for low- and high-density lipoprotein cholesterol and triglycerides did not attenuate relative risks (RRs) (ε2: 1.08 [95% CI, 0.93-1.25] and ε4: 0.85 [95% CI, 0.75-0.95] compared with ε3; likelihood ratio test, P = .008). ε4 decreased risk of end-stage renal disease (RR, 0.60 [95% CI, 0.43-0.84]). ε2 was associated with a decline in renal function (RR, 1.25 [95% CI, 1.02-1.53]), though not with events, such as hospitalizations or end-stage renal disease. Risks were similar stratified by race, sex, diabetes, and hypertension (all P values for interaction >.05). Excess risk of chronic kidney disease in African Americans was not explained by APOE alleles.

Conclusions  APOE variation predicts chronic kidney disease progression, independent of diabetes, race, lipid, and nonlipid risk factors. Our study suggests that nonlipid-mediated pathways, such as cellular mechanisms of kidney remodeling, may be involved in the association of APOE alleles and progression of chronic kidney disease.

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individuals. Studies have been inconclusive due to small sample size, with few prospective studies conducted. Additionally, magnitude of risk associated with APOE alleles is uncertain and cannot be averaged across studies due to the wide range of outcome definitions. Among statistically significant findings, the directions of the associations were consistent in all but 1 study.2 10 Carriers of ε2 were more likely to have diabetic nephropathy (both types 1 and 2)23-25 and worse renal function25 in several small case-control studies. On the other hand, among individuals with type 14 and type 217,21 diabetes, ε4 carriers had better renal function and lower risk of diabetic nephropathy. When late stages of kidney disease were examined, associations with ESRD demonstrated a decreased risk among carriers of ε4,21-23 and 1 study suggested increased risk with ε2.22 Thus, allelic effects are in the same direction as APOE risk associations with age-related maculopathy,24 but opposite in direction to those with CHD and Alzheimer disease.5,7

To date, there has been no investigation of APOE alleles and CKD in a large population-based study of African Americans and whites; furthermore, few studies have included persons without diabetes or examined the mediating effects of lipids. With these considerations, we conducted a prospective study of a community-based middle-aged cohort of 14 520 whites and African Americans with the following objectives: to determine risk of CKD progression associated with APOE alleles, to investigate if risk is independent of lipid levels, and to determine if APOE alleles partially explain excess risk of CKD among African Americans. Because the postulated role of APOE in kidney remodeling and in modulating lipid clearance is in common pathways of CKD progression, we hypothesized that the ε2 and ε4 alleles would respectively increase and decrease risk of CKD progression, compared with the ε3 allele, irrespective of kidney disease etiology. Because African Americans have a higher frequency of the ε2 and ε4 alleles, it was unclear if APOE variation would partially explain the increased risk of CKD in African Americans.

METHODS

Study Subjects

The Atherosclerosis Risk in Communities (ARIC) study recruited 15 792 adults aged 45 to 64 years at baseline in 1987 through 1989 from 4 US communities: Forsyth County, North Carolina; Jackson, Miss; suburbs of Minneapolis, Minn; and Washington County, Maryland. Participants underwent 4 standardized examinations approximately every 3 years, with the last visit ending in 1999.25 In addition to yearly telephone interviews, hospitalizations and deaths were ascertained and recorded as described previously, with most recent follow-up to January 1, 2003.25 Institutional review boards of participating institutions approved study protocols. Written informed consent was obtained from participants at each examination. Of 4266 African Americans and 11 478 whites at baseline (N = 15 744), 1224 were excluded from this analysis: 587 without measurements of serum creatinine or lipids at baseline, 40 with severe hypercreatinemia (creatinine ≥2.0 mg/dL [177 µmol/L] for men, ≥1.8 mg/dL [159 µmol/L] for women),26 42 with missing covariates, and 555 who refused use of DNA for research or whose APOE genotype was missing or unknown. There were no significant differences in frequency of APOE genotypes between our study cohort (N = 14 520) and those excluded.

Assessment of Baseline Characteristics

At each visit, demographic, anthropometric, and cardiovascular risk factor data were collected.25 Racial affiliation as African American or white was by self-report. Collection of fasting blood samples and processing for creatinine, total cholesterol, triglycerides, HDL, and low-density lipoprotein (LDL) are described in detail elsewhere, following standard ARIC protocols.25 Triglyceride levels were log transformed because of a skewed distribution. Hypertension was defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or use of antihypertensive medications. Diabetes mellitus was defined as fasting glucose of 126 mg/dL (7 mmol/L) or higher, nonfasting glucose of 200 mg/dL (11.1 mmol/L) or higher, or history/treatment of diabetes. Prevalent CHD was defined as history of CHD revascularization procedures or electrocardiogram evidence of myocardial infarction. Glomerular filtration rate (GFR) was estimated from calibrated serum creatinine with the simplified equation developed using Modification of Diet in Renal Disease Study27 data as follows:

\[
\text{GFR} \text{mL/min/1.73 m}^2 = 186.3 \times (\text{Serum Creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if Female}) \times (1.21 \text{ if African American}).
\]

APOE Genotyping

Genotyping of APOE polymorphisms coding for ε2 and ε4 were detected separately using the TaqMan assay (Applied Biosystems, Foster City, Calif) as previously described28 and completed in 2004 for the entire cohort. The χ statistic for 3666 replicates was 0.97.

Ascertainment of CKD Progression

Progression of CKD was defined as either an increase in creatinine of at least 0.4 mg/dL (35 µmol/L) above baseline or a hospitalization (discharge or death) coded for chronic renal disease (International Classification of Diseases, Ninth Revision [ICD-9] codes 581-583 or 585-588), hypertensive renal disease (ICD-9 code 403), hypertensive heart and renal disease (ICD-9 code 404), unspecified disorder of kidney and ureter (ICD-9 code 593.9), diabetes with renal manifestations (ICD-9 code 250.4), kidney transplantation, renal dialysis, or adjustment/fitting of catheter (ICD-9 codes V42.0, V45.1, or V56), hemodialysis (ICD-9 code 39.95) or peritoneal dialysis (ICD-9 code 54.98), without acute renal failure (ICD-9 codes 584, 586, 788.9, and 958.5) as the pri-
mary or secondary hospitalization code. Serum creatinine was measured at baseline and at the 3-year (University of Minnesota) and 9-year (ARIC central laboratory, Houston) follow-up visits using a modified kinetic Jaffé method. Serum creatinine measurements were corrected for interlaboratory differences and calibrated indirectly to the Cleveland Clinic measurement standards. Assessment of short-term variability within ARIC participants revealed that 0.18 mg/dL (16 µmol/L) was the minimal change in creatinine at which 95% confidence existed that a true change had occurred (methodological variability, SD = 0.05 mg/dL [4.4 µmol/L]; and within-person variability, SD = 0.04 mg/dL [3.5 µmol/L]). An increase in serum creatinine was defined as a change of at least twice this amount (0.4 mg/dL [35 µmol/L]) as in previous analyses. Ancillary analyses compared association with CKD hospitalization and creatinine increase as separate outcomes as well as alternative definitions of CKD.

Statistical Analysis
Differences in baseline characteristics by race and CKD progression were assessed using t and χ² tests. Primary analysis evaluated associations of APOE variation with time to CKD progression, defined as time to the visit date at which the increase in serum creatinine occurred (creatinine-based CKD cases), date of hospitalization discharge or death date (hospitalization-based CKD cases), or the earlier of the date of last contact or January 1, 2003 (for noncases). Proportional hazards models were constructed to examine APOE variation as an independent predictor of CKD progression. Race-stratified analyses and assessments of interaction with race were performed. To determine excess risk of CKD in African Americans explained by APOE, the relative risk (RR) of CKD associated with race was compared in multivariate models with and without APOE. APOE variation was modeled as an additive model with number of ε2 and ε4 alleles and as an APOE summary score model. APOE alleles appear additive in effect in lipid modulation and in Alzheimer disease. Effects of APOE were also examined by genotype, with similar results (not shown). Because previous literature suggested that ε4 conferred protection while ε2 increased risk, a genotypic scoring system was devised that respectively assigned +1, 0, or −1 per ε2, ε3, or ε4 allele of an individual with genotypes (and scores) of: ε2/ε2 (+2), ε2/ε3 (+1), ε2/ε4(0), ε3/ε3 (0), ε3/ε4 (−1), and ε4/ε4 (−2). Summary scores have been demonstrated to increase power in modeling genetic exposures.

Variables thought to influence CKD risk were chosen as baseline covariates: sex, age, race, body mass index (BMI), diabetes mellitus, blood pressure, hypertensive medication use, CHD history, GFR, total cholesterol, LDL, HDL, and triglycerides. The likelihood ratio test was used to evaluate combined significance of APOE ε2 and ε4 terms in predicting risk in multivariate models and to assess significance of interaction terms. To verify consistency across high-risk subgroups, we also stratified by diabetes, hypertension, hypercholesterolemia (cholesterol ≥240 mg/dL [6.2 mmol/L]), and subnormal baseline kidney function (GFR <90 mL/min/1.73m²). Cross-sectional analyses of APOE and macroalbuminuria (albumin-to-creatinine ratio ≥300 µg/mg) at visit 4 used logistic regression methods, using STATA statistical software (version 8). A P value of <.05 was considered statistically significant.

RESULTS

CKD Progression Risk Factors
TABLE 1 summarizes baseline characteristics by race and incident CKD progression status of participants without severe baseline kidney dysfunction. Chronic kidney disease risk factors were predominantly worse in African Americans, with more prevalent diabetes mellitus and hypertension. However, African Americans had better baseline GFR and comparable lipid profiles compared with whites. Persons who had incident CKD progression were older, more likely to be men or African American; to have a history of diabetes, hypertension, or CHD; to have lower GFR and HDL levels; and to have higher BMI, total cholesterol, triglycerides, and LDL levels. Genotypic frequencies for African Americans and whites were consistent with previously published estimates, and APOE variation was in Hardy-Weinberg equilibrium in each racial group. When combined, the 3 common genotypes—ε2/ε3, ε3/ε3, and ε4/ε4—constituted 93.4% of all participants; 89.3% of African Americans and 94.9% of whites.

Incident CKD Progression
During a median follow-up of 14 years, CKD progression developed in 1,060 individuals (incidence rates per 1,000 person-years: 5.5 overall; 8.8 in African Americans and 4.4 in whites). Of cases, 55.7% were hospitalized or died with a CKD diagnosis code (n = 590), 27.9% were identified by an increase in serum creatinine (n = 296), and 16.4% were established by both criteria (n = 174). Consistent with the hypothesis of increased CKD risk for ε2 and decreased risk for ε4, cases of CKD progression tended to have greater frequency of ε2 and a lower frequency of ε4 compared with cases without progression (ε2: 9.7% vs 8.8%; ε4: 15.8% vs 16.8%; χ² P value = .24), particularly among cases identified by an increase in serum creatinine (n = 470 cases; ε2: 11.7% vs 8.8%; ε4: 16.1% vs 16.8%; χ² P value = .007).

APOE genotype-specific incidence rates of CKD progression (FIGURE 1) suggest a dose-response relationship in African Americans (P for trend = .11). With ε3/ε3 as the reference, the incidence rate increased with the number of ε2 alleles and decreased with the number of ε4 alleles. The relationship was less significant in whites (P for trend = .26 for all genotypes and .08 for the common genotypes ε2/ε3, ε3/ε3, and ε4/ε4). APOE genotype-specific incidence rates of CKD progression identified by an increase in serum creatinin
nine were also similar, and the dose-response relationship was more evident in African Americans (P for trend = .02).

**Multivariate Analyses**

Risk of CKD progression for African Americans was 2.31 (95% CI, 2.04-2.61) times that of whites, after adjustment for age and sex. Further inclusion of APOE in the model showed that it did not explain the excess risk of CKD in African Americans (APOE-adjusted RR, 2.36; 95% CI, 2.09-2.68). There were no differential effects of APOE variation by race. Race-stratified analyses demonstrated that effects of APOE alleles on CKD progression were slightly stronger in African Americans but not significantly different by racial group (Table 2, model 1; P for interaction = .27). Therefore, analyses were performed in the full cohort, adjusting for race.

Multivariate analysis of APOE alleles and CKD progression among all participants were consistent with race-stratified findings (Table 2). e2 increased risk by 1.04 (95% CI, 0.90-1.20) and e4 decreased risk by 0.85 (95% CI, 0.75-0.96), independent of age, sex, and race (likelihood ratio test, \( P = .02 \)). In model 2, e2 conferred risk (RR, 1.07; 95% CI, 0.93-1.24) and e4 was protective (RR, 0.87; 95% CI, 0.77-0.98), independent of major CKD risk factors (likelihood ratio test, \( P = 0.03 \)) including hypertension and diabetes. Similar results were shown by the APOE summary score, with increasing scores (ie, more e2 and fewer e4 alleles) associated with higher risk of CKD progression (\( P<.01 \)).

To examine lipid-independent effects of APOE, we assessed models adjusting only for lipid level (total cholesterol, HDL, LDL, or triglycerides) singly or in combination; the findings were comparable (results not shown). Independent of both major CKD risk factors and lipids (model 3), e2 increased risk of CKD progression without reaching statistical significance by 1.08 (95% CI, 0.93-1.25) and e4 decreased risk in a statistically significant manner by 0.85 (95% CI, 0.75-0.95) compared with e3 (likelihood

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**Table 1. Characteristics of 14 520 Adults Aged 45 to 64 Years, by Race and Incidence of CKD Progression**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (n = 14 520)</th>
<th>African American (n = 3859)</th>
<th>White (n = 10 661)</th>
<th>Absent (n = 13 460)</th>
<th>Present (n = 1080)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>54.2 (5.8)</td>
<td>53.5 (5.8)</td>
<td>54.4 (5.7)</td>
<td>54.0 (5.7)</td>
<td>56.6 (5.4)</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>8029 (55.3)</td>
<td>2397 (61.4)</td>
<td>5600 (53.1)</td>
<td>7544 (56.1)</td>
<td>485 (45.8)</td>
</tr>
<tr>
<td>African Americans, No. (%)</td>
<td>3859 (26.6)</td>
<td>3431 (25.5)</td>
<td>428 (40.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prevalent disease, No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1635 (11.3)</td>
<td>723 (18.7)</td>
<td>912 (6.6)</td>
<td>1296 (9.6)</td>
<td>340 (32.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5588 (38.5)</td>
<td>2172 (56.3)</td>
<td>3416 (32.0)</td>
<td>4897 (36.4)</td>
<td>691 (65.2)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>719 (5.0)</td>
<td>166 (4.3)</td>
<td>553 (5.2)</td>
<td>582 (4.3)</td>
<td>137 (12.9)</td>
</tr>
<tr>
<td>Lipids, mean (SD), mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>214.4 (41.4)</td>
<td>214.7 (44.7)</td>
<td>214.3 (40.1)</td>
<td>214.0 (40.9)</td>
<td>219.8 (46.7)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>124.7 (64.4)</td>
<td>109.1 (54.9)</td>
<td>130.3 (66.6)</td>
<td>123.0 (63.4)</td>
<td>145.9 (72.3)</td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td>51.9 (17.0)</td>
<td>55.1 (17.4)</td>
<td>50.8 (16.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>137.5 (39.2)</td>
<td>137.7 (42.8)</td>
<td>137.4 (37.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerular filtration rate, mL/min/1.73m²</td>
<td>93.2 (20.5)</td>
<td>103.3 (23.8)</td>
<td>89.6 (17.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, mean (SD)†</td>
<td>27.7 (5.4)</td>
<td>29.6 (6.1)</td>
<td>27.0 (4.9)</td>
<td>27.5 (5.3)</td>
<td>29.2 (5.9)</td>
</tr>
<tr>
<td>APOE genotype, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e2/e2</td>
<td>129 (0.9)</td>
<td>50 (1.3)</td>
<td>79 (0.7)</td>
<td>120 (0.9)</td>
<td>0 (0.9)</td>
</tr>
<tr>
<td>e2/e3</td>
<td>1869 (12.9)</td>
<td>531 (13.8)</td>
<td>1338 (12.6)</td>
<td>1713 (12.7)</td>
<td>156 (14.7)</td>
</tr>
<tr>
<td>e2/e4</td>
<td>445 (3.1)</td>
<td>191 (5.0)</td>
<td>254 (2.4)</td>
<td>414 (3.1)</td>
<td>31 (2.9)</td>
</tr>
<tr>
<td>e3/e3</td>
<td>8055 (55.5)</td>
<td>1730 (44.8)</td>
<td>6325 (59.3)</td>
<td>7472 (55.5)</td>
<td>583 (55.0)</td>
</tr>
<tr>
<td>e3/e4</td>
<td>3634 (25.0)</td>
<td>1185 (30.7)</td>
<td>2449 (23.0)</td>
<td>3376 (25.1)</td>
<td>258 (24.3)</td>
</tr>
<tr>
<td>e4/e4</td>
<td>388 (2.7)</td>
<td>172 (4.5)</td>
<td>216 (2.0)</td>
<td>365 (2.7)</td>
<td>23 (2.2)</td>
</tr>
</tbody>
</table>

**Figure 1. Incidence Rates of Chronic Kidney Disease Progression by APOE Genotype and Race**

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Table 2. Adjusted Relative Risk of CKD Progression by APOE Alleles, Summary Score, and Race*

<table>
<thead>
<tr>
<th>Model†</th>
<th>Relative Risk per APOE Allele (95% CI)</th>
<th>Relative Risk Per Unit Increase in APOE Summary Score (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ε3</td>
<td>ε2</td>
<td>ε4</td>
</tr>
<tr>
<td>Both races</td>
<td>Age, sex, and race adjusted (model 1)</td>
<td>1.00 (0.90-1.20)</td>
<td>0.85 (0.75-0.96)§</td>
</tr>
<tr>
<td>Risk factor adjusted (model 2)</td>
<td>1.00 (0.93-1.24)</td>
<td>0.87 (0.77-0.98)§</td>
<td>1.12 (1.03-1.22)</td>
</tr>
<tr>
<td>Risk factor and lipid adjusted (model 3)</td>
<td>1.00 (0.93-1.25)</td>
<td>0.85 (0.75-0.95)§</td>
<td>1.14 (1.05-1.24)</td>
</tr>
<tr>
<td>African American</td>
<td>Age and sex adjusted (model 1)</td>
<td>1.00 (0.94-1.42)</td>
<td>0.91 (0.77-1.08)</td>
</tr>
<tr>
<td>Risk factor adjusted (model 2)</td>
<td>1.00 (0.93-1.41)</td>
<td>0.90 (0.76-1.07)</td>
<td>1.12 (0.99-1.27)</td>
</tr>
<tr>
<td>Risk factor and lipid adjusted (model 3)</td>
<td>1.00 (0.95-1.45)</td>
<td>0.88 (0.74-1.05)</td>
<td>1.15 (1.01-1.31)</td>
</tr>
<tr>
<td>White</td>
<td>Age and sex adjusted (model 1)</td>
<td>1.00 (0.77-1.16)</td>
<td>0.80 (0.67-0.94)§</td>
</tr>
<tr>
<td>Risk factor adjusted (model 2)</td>
<td>1.00 (0.83-1.24)</td>
<td>0.84 (0.71-0.99)</td>
<td>1.12 (0.99-1.26)</td>
</tr>
<tr>
<td>Risk factor and lipid adjusted (model 3)</td>
<td>1.00 (0.82-1.24)</td>
<td>0.82 (0.69-0.97)</td>
<td>1.13 (1.00-1.27)</td>
</tr>
</tbody>
</table>

Abbreviations: APOE, apolipoprotein E; CI, confidence interval; CKD, chronic kidney disease.
*No interaction by race for any of the models (P > .05).
†Model 2 includes covariates age, sex, race, body mass index, type 2 diabetes, systolic blood pressure, diastolic blood pressure, antihypertensive medication use, prevalent coronary heart disease, and glomerular filtration rate. Model 3 includes model 2 covariates plus lipid levels (high- and low-density lipoproteins, triglycerides).
‡APOE summary score assigned +1, 0, or −1 risk units for each ε2, ε3, or ε4 allele of an individual with genotypes (scores) of: ε2ε2 (ε2), ε2ε3 (1), ε2ε4 (0), ε3ε3 (0), ε3ε4 (−1), ε4ε4 (−2). Reference group: ε3ε3 with summary score = 0. §The combined significance of the APOE ε2 and ε4 terms were evaluated by a likelihood ratio test. Those marked were significant at P < .01.

Figure 2. Chronic Kidney Disease Progression Overall and in Subgroups for a Unit Change in APOE Summary Score

Table: Adjusted Relative Risk of CKD Progression Overall and in Subgroups for a Unit Change in APOE Summary Score

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Events/Total No.</th>
<th>Adjusted Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1060/15,452</td>
<td>1.14 (1.05-1.24)</td>
<td>.003</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>428/3869</td>
<td>1.15 (1.01-1.31)</td>
<td>.047</td>
</tr>
<tr>
<td>White</td>
<td>632/10,661</td>
<td>1.13 (1.00-1.27)</td>
<td>.03</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>340/1635</td>
<td>1.01 (0.87-1.18)</td>
<td>.88</td>
</tr>
<tr>
<td>No</td>
<td>720/12,885</td>
<td>1.18 (1.06-1.31)</td>
<td>.002</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>691/5588</td>
<td>1.13 (1.01-1.26)</td>
<td>.03</td>
</tr>
<tr>
<td>No</td>
<td>369/8932</td>
<td>1.14 (0.99-1.32)</td>
<td>.08</td>
</tr>
<tr>
<td>GFR, mL/min/1.73 m2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>629/7556</td>
<td>1.19 (1.06-1.33)</td>
<td>.003</td>
</tr>
<tr>
<td>≥60</td>
<td>431/6964</td>
<td>1.07 (0.94-1.23)</td>
<td>.29</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
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<tr>
<td>&lt;240</td>
<td>325/3561</td>
<td>1.14 (0.93-1.33)</td>
<td>.11</td>
</tr>
<tr>
<td>≥240</td>
<td>735/10,959</td>
<td>1.13 (1.02-1.25)</td>
<td>.02</td>
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APOE (apolipoprotein E) summary score assigned +1, 0, or −1 risk units for each ε2, ε3, or ε4 allele of an individual with genotype scores of the following: ε2ε2 (2), ε2ε3 (1), ε2ε4 (0), ε3ε3 (0), ε3ε4 (−1), ε4ε4 (−2). Data adjusted for baseline age, sex, race, diabetes, body mass index, coronary heart disease, antihypertensive use, systolic and diastolic blood pressure, glomerular filtration rate (GFR), high-density lipoprotein, low-density lipoprotein, and triglycerides. There were no significant interactions of APOE and chronic kidney disease risk categories on disease progression (all P interaction > .05). To convert cholesterol to mmol/L, multiply values by 0.0259.

The association between APOE alleles and CKD progression was consistent across race and risk groups (Figure 2), and no interactions between APOE and high-risk subgroups were significant (all P values for interaction > .05). The association of APOE with CKD risk was statistically significant in nondiabetic individuals (P = .002) while it was not in those with type 2 diabetes. However, a test of interaction was not significant (P = .20). Similarly, association between APOE and CKD progression appeared stronger among individuals with an estimated baseline GFR of less than 90 mL/min/1.73 m² (RR, 1.19; 95% CI, 1.06-1.33), but this could be due to random variation as well (P for interaction = .29).

Subsidiary Analyses

The association of APOE and CKD was robust across several definitions of CKD progression (including those defined by serum creatinine, GFR, and urine albumin), though the data suggested that the association of ε4 was evident for both early (increase in serum creatinine, change in GFR) and late (hospitalization, ESRD, and death) manifestations of kidney disease, whereas the association with ε2 was stronger with early manifestations of kidney disease. For an increase in serum creatinine of at least 0.4 mg/dL (3.5 μmol/L), ε2 increased risk by 1.25 (95% CI, 1.02-1.53) and ε4 decreased risk by 0.84 (95% CI, 0.70-1.01). For a hospitalization or death with CKD or ESRD, in the fully adjusted model ε2 increased risk by only 1.03 (95% CI, 0.87-1.23) and ε4 decreased risk by 0.83 (95% CI, 0.71-0.95). Per unit increase in the APOE summary score, RR was 1.21 (95% CI, 1.07-1.38) for an increase in serum creatinine and 1.13 (95% CI, 1.02-1.26) for hospitalization or death with CKD.

Results were also similar when we examined the incidence of moderately decreased kidney function (GFR <60 mL/min/1.73 m²) instead of an increase in serum creatinine. Individuals with moderately decreased kidney function at baseline were less likely to carry the ε4 allele.
allele (odds ratio, 0.77; 95% CI, 0.63-0.94). For incidence of decreased kidney function during follow-up, ε2 increased risk by 1.06 (95% CI, 0.91-1.23) and ε4 decreased risk by 0.86 (95% CI, 0.76-0.97) with APOE alleles significantly associated (likelihood ratio test, P = .03). Per unit increase in the APOE summary score, the RR was 1.12 (95% CI, 1.03-1.23).

The RR of the APOE summary score for a hospitalization with an ESRD code was similar as well, and it was statistically significant after adjustment for demographics and nonlipid risk factors (RR, 1.29; 95% CI, 1.05-1.59). In this analysis, the protective effect for ε4 on subsequent ESRD was stronger (RR, 0.60; 95% CI, 0.43-0.84) than for CKD progression in general, while the excess risk with ε2 was not observed (RR, 0.97; 95% CI, 0.68-1.38), but the number of ESRD cases was relatively small (n = 175).

Finally, quantitative data on albuminuria was available only at the last study visit. Using logistic regression, associations with prevalence of macroalbuminuria (odds ratios: APOE ε2, 1.20 [95% CI, 0.84-1.71]; ε4, 0.96 [95% CI, 0.71-1.31]; summary score: 1.10 [95% CI, 0.89-1.38]) were similar to those of the creatinine-based outcome but nonsignificant in this limited cross-sectional examination of albuminuria.

An alternative explanation for the inverse association seen with APOE and CKD could be that it is an artifact due to a survival effect. Specifically, individuals with ε4 may be lost to follow-up at a higher rate due to vascular events and mortality, thus artificially increasing CKD incidence in those with the ε2 allele. However, in this cohort, loss to follow-up did not differ by APOE genotype (P = .63 among African Americans, P = .83 among whites). Although ε4 may lead to increased mortality, this association was very weak in this cohort and could not account for the observed protective association with CKD. During follow-up, there were 2083 deaths in our cohort. When we examined the effect of APOE on CKD only among the 2083 mortality events, the adjusted effect of ε4 on CKD (n = 414 cases) was similar to that seen in the entire cohort (RRs, 0.85 and 0.85, respectively).

COMMENT

APOE allelic variation is a risk factor for CKD progression in the general US adult population but does not explain the excess risk of CKD in African Americans. Risk is lower for those with the ε4 allele and may increase with ε2, consistent with previous diabetic nephropathy studies, and the risk is of comparable magnitude but in the opposite direction to the association of APOE with CHD. The APOE association with CKD progression is not explained by established CKD risk factors, including diabetes and hypertension. Furthermore, the CKD risk association with APOE alleles is not directly mediated through lipid levels. Additionally, the relationship between APOE and CKD risk is not an artifact due to the association of APOE with serum lipid levels, vascular events, and mortality.

To our knowledge, this is one of the first large population-based prospective studies of the association between APOE and CKD progression. Our results confirm a recent cross-sectional study of 158 type 2 diabetic patients (51 overt nephropathy cases) that found increased risk with ε2 (odds ratio, 10.2 [95% CI, 1.18-87.93]) and protection with ε4 (odds ratio, 0.13 [95% CI, 0.03-0.49]). Notably, our results are more conservative, consistent with findings that larger prospective studies such as ours produce results of smaller magnitude with greater precision compared with those of smaller studies. A few studies demonstrated no significant association between APOE alleles and diabetic kidney disease, but positive studies consistently find ε2 to be a risk factor and ε4 to be protective. Although ε4 has “tradi- tionally” been seen as a risk allele due to associations with CHD and Alzheimer disease, our findings of ε4 as protective for CKD progression are consistent with the literature. Similar to previous studies, our results demonstrate ε2 to increase risk of early manifestations of kidney disease (increases in serum creatinine and a trend for macroalbuminuria) with little risk of CKD hospitalization and ESRD, whereas ε4 is associated with a lower risk of both early and late manifestations of kidney disease. No study of diabetic kidney disease has demonstrated that the ε4 allele increases risk.

This is the only study of APOE and CKD in African Americans, a population at particularly high risk of kidney disease. The APOE and CKD association is not weaker in African Americans, in further contrast to the Alzheimer disease association.

This study of APOE and kidney disease has the largest sample to date, which afforded more precise estimates of the effect of APOE on CKD progression and a detailed analysis examining alleles, genotypes, and subgroups not possible in smaller studies.

The prevailing explanation for the association between APOE and diabetic nephropathy focuses on its lipid transport role, with subsequent effects on renal function. Glomerulosclerosis and atherosclerosis may share similar pathophysiologic parameters in progression. Triglyceride-rich lipoproteins initiate glomerular injury in experimental studies and in this cohort. APOE variation may affect CKD progression through 2 different pathways: modulation of circulating lipid levels and separately through nonlipid mechanisms, such as a direct effect on kidney remodeling. The influence of APOE could extend beyond lipid effects, as with ε4, β-amyloid, and Alzheimer disease. APOE is expressed in the kidney, and its isoforms differentially inhibit mesangial cell proliferation through induction of matrix heparan sulfate proteoglycan (HSPG). ε2 possesses the least competent antiproliferative effect. Additionally, among patients with IgA nephropathy, more severe histological damage has been associated with the ε2 allele. The role of ε2 on renal remodeling merits further study.
Our results corroborate findings that ε4 protects persons with diabetes from progressing to ESRD.21 The ε4 allele is associated with higher levels of HDL and lower levels of triglycerides,3 a lipid profile that decreases risk of CKD.1 In addition, the protein produced by ε4 shows far less intracellular accumulation than that of ε2 or ε3.41 Perhaps higher extracellular levels of the ε4 protein can hinder the cycle of further renal tissue deterioration through induction of matrix HSPG. The relationship of APOE and CKD mirrors that of APOE and age-related maculopathy in which ε4 also demonstrates a protective effect while ε2 increases risk.44

This study has several limitations. Because CKD is heterogeneous, the influence of APOE on specific kidney disease etiologies may not be directly inferred. However, the degree of sensitivity afforded by our definition provides sufficient power to examine the disease in a longitudinal, community-based setting that demonstrates that APOE affects overall CKD risk, not just hypertensive or diabetic kidney disease. While creatinine-based definitions of CKD progression can be insensitive, they should be specific and show the expected association with traditional risk factors.4 Additionally, the relationship of APOE with CKD is consistent across the various renal disease outcomes examined in our subsidiary analyses. Hospitalization or death with a CKD diagnosis code does not allow for quantification of the amount of kidney disease progression. However, among individuals without hypercreatinemia at baseline, such a diagnosis likely denotes a substantial increase in serum creatinine. Treating these events as outcomes also decreases bias due to censoring, since sick individuals are less likely to return for a subsequent clinic visit.

Another limitation is that the APOE and CKD association could be due to differential losses to follow-up by genotype, specifically due to increased mortality and nonrenal vascular events associated with the ε4 allele. However, the association with CKD was neither due to genotype-specific losses to follow-up, nor could it be explained by increased CHD risk among those with ε4. The magnitude of the association cannot be compared directly with previous studies due to variation in design and outcome definition. However, whenever an association of APOE alleles with CKD was found, directions have been remarkably consistent. Finally, the use of the APOE summary score may be oversimplifying. This score assumes a codominant model with opposite but equal effects for ε2 and ε4, which is supported by the data in this study, and provides a more powerful test of the overall impact of APOE genetic variation. However, the power to test deviations from these assumptions, particularly for rare genotypes such as ε2ε2, ε2ε4, and ε4ε4, is limited. In our study, risk associated with ε2ε4 is least certain, but exclusion of this genotype had no impact on our results.

In summary, APOE variation affects CKD progression, independent of major CKD risk factors and independent of the well-described effect of APOE variation on serum cholesterol and triglycerides. The modest size of the risk associated with APOE variation limits utility for screening, risk stratification, and individualized therapy. However, if multiple genes of small and moderate effect on CKD are identified, they may compose panels for risk assessment. Consistency of the finding across participants with and without diabetes and hypertension supports the hypothesis that much of CKD is multifactorial with common pathways across different diagnostic settings. Studying the pathways mediating this association, which has consistently been in the opposite direction to the CHD and Alzheimer disease associations, may shed light on novel pathways and therapeutic targets in the pathophysiology of CKD.

**Author Contributions:** Dr Coresh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. **Study concept and design:** Hsu, Kao, Coresh. **Acquisition of data:** Coresh, Boerwinkle, Bray. **Analysis and interpretation of data:** Hsu, Kao, Coresh, Pankow, Marsh-Manzi. **Drafting of the manuscript:** Hsu. **Critical revision of the manuscript for important intellectual content:** Hsu, Kao, Coresh, Pankow, Marsh-Manzi, Boerwinkle, Bray. **Statistical analysis:** Hsu, Kao, Marsh-Manzi. **Obtained funding:** Hsu, Coresh, Marsh-Manzi, Bray, Boerwinkle. **Administrative, technical, or material support:** Kao, Coresh, Pankow, Boerwinkle, Bray. **Study supervision:** Kao, Coresh.

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