# Traditional and Nontraditional Risk Factors Predict Coronary Heart Disease in Chronic Kidney Disease: Results from the Atherosclerosis Risk in Communities Study

Paul Muntner,*† Jiang He,*† Brad C. Astor,‡ Aaron R. Folsom,¶ and Josef Coresh‡§||

*Departments of *Epidemiology and †Medicine, Tulane University Health Sciences Center, New Orleans, Louisiana; Departments of ‡Epidemiology, §Medicine; and ||Biostatistics, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland; and ¶Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, Minnesota*

**Some risk factors for coronary heart disease (CHD) incidence in the general population are not associated with CHD incidence among patients with ESRD but have not been well characterized in chronic kidney disease (CKD). The association of several risk factors with CHD incidence was studied among participants with CKD in the population-based Atherosclerosis Risk in Communities (ARIC) Study. CHD risk factors and estimated GFR using serum creatinine were measured among 807 ARIC participants with CKD (estimated GFR between 15 and 59 ml/min per 1.73 m$^2$). The incidence of CHD during 10.5 yr of follow-up was 6.3, 8.5, and 14.4 per 1000 person-years among ARIC participants with an estimated GFR of ≥90, 60 to 89, and 15 to 59 ml/min per 1.73 m$^2$, respectively. After adjustment for age, race, gender, and ARIC field center, among those with CKD, the relative risk (95% confidence interval) of CHD was 1.65 (1.01 to 2.67) for current smoking, 2.02 (1.27 to 3.22) for hypertension, 3.06 (2.01 to 4.67) for diabetes, and 1.96 (1.14 to 3.36) for anemia. The comparably adjusted relative risks of CHD for each standard deviation higher total and HDL cholesterol were 1.50 (1.25 to 1.71) and 0.79 (0.62 to 1.01), respectively, and 1.38 (1.13 to 1.69), 1.24 (1.06 to 1.46), 0.65 (0.54 to 0.79), and 1.38 (1.19 to 1.59) for waist circumference, leukocyte count, serum albumin, and fibrinogen, respectively. CHD risk factors in the general population remain predictive among patients with CKD. Given the high risk for CHD among patients with CKD, control of these risk factors may have a substantial impact on their excess burden of CHD.**

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Coronary heart disease (CHD) has long been identified as a leading cause of death among patients with ESRD (1). Mortality among patients in the United States Renal Data System, a population-based registry of patients who are treated for ESRD, is 10 to 20 times higher than similarly aged individuals from the general U.S. population (2). More recently, compared with their counterparts without chronic kidney disease (CKD), a 1.5- to 3-fold increased risk for CHD has been reported among the population with CKD, before the need for dialysis therapy (3–8). Furthermore, several cross-sectional studies have identified a higher prevalence of traditional and nontraditional CHD risk factors among patients with CKD compared with people with normal kidney function (2,9–12). Analyses of the Third National Health and Nutrition Examination Survey (NHANES III) show a higher prevalence of hypertension; high blood cholesterol; diabetes; and elevated levels of fibrinogen, C-reactive protein, homocysteine, and several other CHD risk factors among noninstitutionalized patients with *versus* without CKD (12–14).

The extent to which traditional and nontraditional CHD risk factors are predictive of CHD in individuals with CKD is important for several reasons. First, many risk relationships are altered in the dialysis population, with both hypertension and cholesterol showing U-shaped relationships with the risk for CHD and mortality. Second, patients with CKD have been excluded from many cardiovascular clinical trials because of concerns regarding side effects and treatment complications. Third, a greater role of arteriolar stenosis, calcification, and cardiomyopathy in vascular disease among CKD patients may alter these risk relationships (15). Fourth, recent estimates indicate that between 10 and 20 million people in the United States have CKD (16). Finally, a number of studies have documented that CHD risk-reduction therapies are used less often among patients with CKD (17,18).

Identifying risk factors for CHD among patients with CKD will provide a scientific background for prevention. To date, National Kidney Foundation (NKF) guidelines for treating patients with CKD have, in part, relied on data from the general population (19). We used data from the population-based Atherosclerosis Risk in Communities (ARIC) Study to assess whether risk factors for CHD in the general population are

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**Address correspondence to:** Dr. Paul Muntner, Department of Epidemiology, Tulane University SPHTM, 1430 Tulane Avenue, SL-18, New Orleans, LA 70112. Phone: 504-988-1047; Fax: 504-988-1568; E-mail: pmuntner@tulane.edu



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associated with CHD incidence among individuals with CKD characterized by moderately decreased kidney function.

## Materials and Methods

### *Study Population and Data Collection*

The ARIC Study, a population-based prospective cohort study of atherosclerosis and its risk factors, has been described in detail previously (20). In brief, between 1986 and 1989, 15,792 study participants aged 45 to 64 yr were enrolled from four U.S. communities (Forsyth County, NC; Jackson, MS; the northwest suburbs of Minneapolis, MN; and Washington County, MD). Of permanent residents in the four study areas, potential participants were excluded when they were deemed, in the judgment of the interviewer, physically or mentally incapable of full participation in the study or were planning to relocate permanently. A baseline and three follow-up clinic examinations were conducted at 3-yr intervals. The current analysis was limited to white and black ARIC participants without a history of CHD (no history of a myocardial infarction or cardiac procedure) at baseline and with a valid baseline serum creatinine measurement. In addition, people with an estimated GFR <15 ml/min per 1.73 $m^2$ ($n$ = 17) were excluded, resulting in a final study population of 14,856.

### *Clinical Examinations*

Fasting blood samples were drawn from an antecubital vein into vacuum tubes, and analysis of serum chemistries, plasma lipids, and hemostatic factors were performed at ARIC centralized laboratories. At baseline (1986 to 1989) and the first follow-up (1990 to 1993) study visit, serum creatinine was measured using a modified kinetic Jaffe method at the University of Minnesota. Methodologic and day-to-day variability estimates (*i.e.*, SD) of creatinine measurements among ARIC participants were 0.049 and 0.043 mg/dl, respectively (21). Plasma total cholesterol, plasma triglycerides, and HDL cholesterol were determined using enzymatic methods. Glucose, apolipoproteins A-1 and B, lipoprotein(a) [Lp(a)], fibrinogen, hemoglobin, serum albumin, and leukocyte count were measured as described elsewhere (5). Diabetes was defined as a fasting glucose of ≥126 mg/dl, nonfasting glucose of ≥200 mg/dl, a self-reported history of diabetes, or use of glucose-lowering medications. Anemia was defined as hemoglobin <12 mg/dl for women and <13 mg/dl for men.

ARIC technicians, who were trained and certified in the use of a random-zero sphygmomanometer, took three blood pressure (BP) measurements following a standardized protocol; an average of the second and third measurements was used to estimate BP. The presence of hypertension was defined as a systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or the use of antihypertensive medications. Trained technicians measured height, weight, and waist circumference following a standardized protocol. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared, and obesity was defined as ≥30 kg/$m^2$. Current cigarette smoking and physical activity were determined through the use of standardized questionnaires. Participants who reported having smoked >400 cigarettes during their lifetime and responded affirmatively to, "Do you now smoke cigarettes?" were classified as current smokers. Physical activity was defined as participating in 1 h or more of sports per week for 10 mo or more during the previous year.

### *Definition of CKD*

GFR was estimated using a formula derived by the Modification of Diet in Renal Disease study group as follows: Estimated GFR = 186.3 × (serum creatinine)$^{-1.154}$ × age$^{-0.203}$ × (0.742 if female) × (1.21 if black) (22). For use in this formula, serum creatinine concentration was calibrated with Cleveland Clinic measurement standards by subtraction of 0.24 mg/dl. Estimated GFR was divided into three categories: ≥90, 60 to 89, and 15 to 59 ml/min per 1.73 $m^2$, and, following NKF guidelines, participants with an estimated GFR between 15 and 59 ml/min per 1.73 $m^2$ at baseline or visit 2 were defined as having CKD (19). People with an estimated GFR ≥90 ml/min per 1.73 $m^2$ at baseline and between 60 and 89 ml/min per 1.73 $m^2$ or 15 and 59 ml/min per 1.73 $m^2$ at visit 2 contributed follow-up time from baseline to visit 2 in the GFR ≥90 category and from visit 2 onward in the 60 to 89 ml/min per 1.73 $m^2$ or CKD categories, respectively. Analogously, people with an estimated GFR between 60 and 89 ml/min per 1.73 $m^2$ at baseline and between 15 and 59 ml/min per 1.73 $m^2$ at visit 2 contributed follow-up time in the 60 to 89 ml/min per 1.73 $m^2$ category from baseline through visit 2 and in the CKD category from the date of visit 2 to the end of follow-up.

### *Outcome Definition and Assessment*

The primary outcome for this analysis was the incidence of CHD from the baseline ARIC visit through December 31, 2000. Several methods were used to ascertain incident CHD events among ARIC participants. Participants were contacted annually via telephone to identify all hospitalizations and/or deaths. ARIC Study staff members also surveyed death certificates and discharge lists from local hospitals to identify additional CHD events. For hospitalizations of ARIC participants, the signs and symptoms at presentation and related clinical information were abstracted from charts by trained and certified study staff. Out-of-hospital deaths were validated using death certificate data and, when possible, interviews with next of kin and the participant's physician. When available, autopsy reports were used for further validation. For the current analysis, CHD incidence was defined as a definite or probable myocardial infarction, a definite CHD death, or coronary revascularization. An ARIC Morbidity and Mortality Classification Committee used published criteria to review and adjudicate all potential CHD events (23).

### *Statistical Analyses*

The incidence rate of CHD was calculated by level of estimated GFR (≥90, 60 to 89, and 15 to 59 ml/min per 1.73 $m^2$). Age-, race-, and gender-standardized means for continuous variables and prevalences for dichotomous variables were calculated by level of estimated GFR and for people who had CKD and did and did not subsequently develop CHD during follow-up. Risk factor levels were updated at visit 2 for participants who changed GFR categories. Levels and prevalence estimates were standardized to the population distribution of ARIC participants with CKD (an age of 56.1 yr, 33.0% male, and 21.8% black). The statistical significance of the difference in continuous and dichotomous risk factor levels across category of estimated GFR and for participants who did and did not develop CHD among those with CKD were determined using age-, race-, gender-, and field center–adjusted linear and logistic regression models, respectively, taking into account the repeated measurements.

With the use of Cox proportional hazards regression models, the adjusted hazard ratio of CHD for people with CKD were calculated for the presence of dichotomous risk factors (*e.g.*, cigarette smoking) and each SD higher continuous risk factor (*e.g.*, 20 mmHg systolic BP). Hazard ratios were initially adjusted for age, race, gender, and ARIC field center. Subsequent models additionally adjusted for traditional CHD risk factors, including current smoking, diabetes, hypertension, and total cholesterol. Deviations from a linear association between continuous risk factors (systolic BP, BMI, total cholesterol, HDL cholesterol, triglycerides, leukocyte count, serum albumin, and fibrinogen) and CHD incidence were assessed by including quadratic and cubic terms for the continuous risk factors in the regression models.

Next, continuous CHD risk factors for all ARIC participants were divided into four levels on the basis of the quartile cutoffs from the population with CKD. Using the lowest quartile of the risk factor as the reference category, the age-, race-, gender-, and ARIC field center–adjusted hazard ratio of CHD incidence during follow-up was calculated for the upper three quartiles by level of kidney function, separately, using Cox proportional hazards regression models. To ascertain effect modification of reduced kidney function and CKD (estimated GFR of 60 to 89 and of 15 to 59 ml/min, respectively) on the relationship of risk factors with CHD incidence, we used a Cox proportional hazards model that included all ARIC Study participants and adjusted for age, race, gender, and ARIC field center. For these analyses, main effects were included for each level of kidney function and quartile of CHD risk factor for each continuous risk factor and risk factor presence for dichotomous risk factor, and the product of these main effects that represents the difference in CHD risk associated with the respective CHD risk factor across level of kidney function. Associations between risk factors and CHD incidence were also determined stratified by gender and race, separately, and for people with CKD at the ARIC baseline visit *versus* those who developed CKD at ARIC visit 2.

The proportionality assumption of the Cox model was confirmed using Schoenfeld residuals. All data management and analysis were conducted using SAS 8.1 (Cary, NC) and Stata 7.0 software (College Station, TX).

## Results

At baseline, 391 (2.6%) participants had and 14,465 did not have CKD. An additional 416 participants developed CKD by visit 2. Therefore, 807 (5.4%) participants met the definition for CKD at some point during follow-up. Of these, 108 had an incident CHD event during 7516 yr of follow-up. The incidence of CHD was 14.4 per 1000 person-years among participants with CKD, compared with 8.5 (903 CHD events during 106,155 yr of follow-up) and 6.3 (329 CHD events during 52,066 yr of follow-up) per 1000 person-years among their counterparts with an estimated GFR between 60 and 89 ml/min per 1.73 $m^2$ and ≥90 ml/min per 1.73 $m^2$, respectively.

People with lower levels of estimated GFR were older and less likely to be male or black (Table 1). In addition, participants with lower estimated GFR were less likely to be current smokers and more likely to be physically active and obese and have hypertension, diabetes, and anemia. In addition, higher mean levels of BMI, glucose, total cholesterol, triglycerides, waist circumference, Lp(a), apolipoprotein-B, and leukocyte count were present at lower levels of GFR. In contrast, HDL cholesterol and apolipoprotein-A1 were lower among participants with lower levels of estimated GFR.

Among participants with CKD, those who subsequently had a CHD event during follow-up ($n = 108$) were older and more likely to be male, black, and current smokers and have hypertension and diabetes (all $P < 0.05$; Table 2). In addition, levels of BMI, systolic BP, glucose, total cholesterol, triglycerides, waist circumference, apolipoprotein-B, leukocyte count, and fibrinogen were higher at the visit at which CKD was first noted among people who developed CHD, *versus* their counterparts with CKD who did not develop CHD, during follow-up. In contrast, among participants with CKD, baseline serum albumin levels were lower among those who subsequently developed *versus* those who did not develop CHD ($P = 0.005$).

After age, race, gender, and field center adjustment, current smoking, hypertension, obesity, diabetes, and anemia each were associated with an elevated risk of CHD (Table 3). In addition, after identical adjustment, higher levels of systolic BP, BMI, glucose, total cholesterol, log triglycerides, waist circumference, apolipoprotein-B, leukocyte count, and fibrinogen were associated with an increased CHD risk. In contrast, higher levels of serum albumin were associated with a decreased CHD risk. Further adjustment for current smoking, diabetes, hypertension, and total cholesterol attenuated the association of obesity, HDL cholesterol, log triglycerides, and leukocyte count with CHD incidence. In models that included quadratic and cubic terms, deviations from linear trends were not found to be present for any of these risk factors (each $P > 0.10$).

Higher levels of systolic BP, BMI, total cholesterol, triglycerides, waist circumference, leukocyte count, and fibrinogen were associated with an increased risk for CHD at each level of kidney function (Table 4). Also, higher serum albumin levels were associated with a decreased risk for CHD. Although higher levels of HDL cholesterol were associated with a lower risk for CHD for people with an estimated GFR ≥90 and 60 to 89 ml/min per 1.73 $m^2$ (each $P < 0.001$), this trend was NS for people with CKD ($P = 0.127$). The relative hazard of CHD for each quartile higher level of these risk factors and for current smoking, anemia, and diabetes is presented in Figure 1 by level of estimated GFR: ≥90, 60 to 89, and 15 to 59 ml/min per 1.73 $m^2$. The relationship between higher risk factor levels and CHD incidence was similar for ARIC participants with an estimated GFR ≥90 and 60 to 89 ml/min per 1.73 $m^2$ for all risk factors except serum albumin. Specifically, the relative hazard (95% confidence interval [CI]) of CHD for each quartile higher serum albumin was 0.80 (0.72 to 0.89) for people with an estimated GFR ≥90 ml/min per 1.73 $m^2$ and 0.95 (0.89 to 1.02) for their counterparts with an estimated GFR between 60 and 89 ml/min per 1.73 $m^2$ ($P = 0.011$ for interaction). A similar relationship across quartiles of each continuous risk factor and CHD incidence was present for people with an estimated GFR ≥90 ml/min per 1.73 $m^2$ and their counterparts with an estimated GFR between 15 and 59 ml/min per 1.73 $m^2$, with the exception of HDL cholesterol. For each quartile higher HDL cholesterol, the relative hazard (95% CI) of CHD was 0.63 (0.56 to 0.70) for people with an estimated GFR ≥90 ml/min per 1.73 $m^2$, 0.68 (0.63 to 0.73) for those with an estimated GFR between 60 and 89 ml/min per 1.73 $m^2$, and 0.86 (0.71 to 1.04) for their counterparts with an estimated GFR of 15 to 59 ml/min per 1.73 $m^2$ ($P = 0.012$ for interaction, comparing the relative hazards for people with an estimated GFR 15 to 59 ml/min per 1.73 $m^2$ *versus* ≥90 ml/min per 1.73 $m^2$). In addition, the relative hazard of CHD associated with anemia was greater (1.96 [95% CI 1.14 to 3.36], respectively) among people with CKD compared with their counterparts with an estimated GFR 60 to 89 ml/min per 1.73 $m^2$ and ≥90 ml/min per 1.73 $m^2$ (1.46 [95% CI 1.12 to 1.89] and 0.97 [95% CI 0.67 to 1.40], respectively; $P = 0.001$ for interaction).

The association between each risk factor studied and CHD incidence was similar for men and women and for white and

*Table 1*. Characteristics[a] of Atherosclerosis Risk in Communities (ARIC) Study participants by level of estimated GFR (≥90, 60 to 89, and 15 to 59 ml/min per 1.73 $m^2$)[b]

| Risk Factor | Estimated GFR (ml/min per 1.73 $m^2$) | | | *P* Trend |
|---|---|---|---|---|
| | ≥90 (*n* = 7213) | 60–89 (*n* = 9878) | 15–59 (*n* = 807) | |
| Age (yr) | 53.4 | 54.3 | 56.1 | <0.001 |
| Men (%) | 41.9 | 44.1 | 33.0 | <0.001 |
| Black (%) | 38.6 | 17.3 | 21.8 | <0.001 |
| Traditional risk factors | | | | |
| current smoking (%) | 27.8 | 21.1 | 16.3 | <0.001 |
| physically active (%) | 23.8 | 25.8 | 25.7 | 0.001 |
| hypertension (%) | 31.1 | 35.2 | 57.2 | <0.001 |
| systolic BP (mmHg) | 122.0 | 121.4 | 125.1 | 0.217 |
| BMI (kg/$m^2$) | 27.4 | 27.7 | 28.6 | <0.001 |
| obesity (BMI ≥30 kg/$m^2$) | 24.7 | 26.7 | 33.0 | <0.001 |
| glucose (mg/dl) | 108.9 | 108.8 | 123.0 | <0.001 |
| diabetes (%) | 11.5 | 10.2 | 19.6 | 0.001 |
| total cholesterol (mg/dl) | 215.9 | 217.5 | 221.5 | 0.002 |
| HDL cholesterol (mg/dl) | 55.7 | 53.8 | 49.9 | <0.001 |
| log triglycerides, log (mg/dl) | 4.71 | 4.73 | 4.86 | <0.001 |
| Nontraditional risk factors | | | | |
| waist circumference | 96.4 | 96.8 | 99.5 | <0.001 |
| log Lp(a), log (mg/L) | 3.98 | 4.03 | 4.15 | <0.001 |
| apolipoprotein-A1 (mg/dl) | 136.7 | 134.8 | 129.5 | <0.001 |
| apolipoprotein-B (mg/dl) | 92.8 | 95.3 | 99.6 | <0.001 |
| anemia (%) | 7.9 | 6.7 | 13.9 | 0.023 |
| leukocyte count ($10^9$ cells/L) | 6.17 | 5.98 | 6.34 | 0.004 |
| serum albumin (mg/dl) | 3.85 | 3.87 | 3.82 | 0.358 |
| fibrinogen (mg/dl) | 306.4 | 303.3 | 322.2 | 0.249 |

[a]Prevalence and levels for all variables except age, gender, and race are standardized to the ARIC population with CKD (age, 56.1 yr; gender, 33.0% male; and 21.8% black race).

[b]Participants were permitted to be in two groups if they changed level of GFR at visit 2 (*e.g.*, someone with an estimated GFR ≥90 ml/min per 1.73 $m^2$ at baseline and between 60 and 89 at visit 2 is counted in both the ≥90 and 60 to 89 ml/min per 1.73 $m^2$ categories of this table with updated covariates at visit 2). At the ARIC baseline visit, 7213, 7252, and 391 ARIC participants had an estimated GFR ≥90, 60 to 89, and 15 to 59 ml/min per 1.73 $m^2$, respectively. Of those with an estimated GFR ≥90 at visit 1, 2626 participants had an estimated GFR between 60 and 89 at visit 2, and 416 participants with an estimated GFR ≥60 ml/min per 1.73 $m^2$ at visit 1 had an estimated GFR <60 ml/min per 1.73 $m^2$ at visit 2. ARIC, Atherosclerosis Risk in Communities; BMI, body mass index.

black ARIC participants with the exception of glucose, diabetes, and anemia (data not shown). Each of these risk factors showed stronger associations with CHD incidence in blacks compared with whites ($P < 0.05$ for interaction). Finally, associations were consistent for people with prevalent CKD (estimated GFR between 15 and 59 ml/min per 1.73 $m^2$) at baseline and those who developed CKD at ARIC visit 2.

## Discussion

Data from the population-based ARIC Study indicate that risk factors for CHD in the general population also are associated with an increased risk for CHD among the population with CKD. Specifically, risk factors such as diabetes and hypertension each were related to a higher risk for CHD among participants with and without CKD. Furthermore, systolic BP, BMI, total cholesterol, leukocyte count, and fibrinogen each maintained similar risk relationships in ARIC participants with and without CKD. In contrast, the association of anemia with CHD incidence was greater and HDL cholesterol with CHD incidence was weaker among people with CKD.

Although the direct impact of interventions aimed at lowering risk factors among patients with CKD cannot be assessed with certainty in an observational epidemiologic study, such as the ARIC Study, we simulated the reduction in CHD incidence that would be expected from an SD reduction in systolic BP (20 mmHg), serum glucose (40 mg/dl), or total cholesterol (43 mg/dl) or if 50% of current cigarette smokers quit using a Poisson regression model. Population-wide reductions in systolic BP of 20 mmHg and serum glucose of 40 mg/dl were projected to be associated with reductions in CHD incidence of 18.0 and 8.9%, respectively. In addition, a 43-mg/dl reduction in total cholesterol and a 5-kg/$m^2$ reduction in BMI at the population level were associated with 19.7 and 10.6% reductions in CHD incidence, respectively. If 50% of smokers were to

*Table 2.* Characteristics[a] of ARIC Study participants with CKD who did and did not develop a major CHD event[b] during 10.5 yr of follow-up

| Risk Factor | No CHD ($n$ = 699) | Incident CHD during Follow-up[b] ($n$ = 108) | $P$ Value |
|---|---|---|---|
| Age (yr) | 55.8 | 58.0 | <0.001 |
| Men (%) | 29.5 | 54.7 | <0.001 |
| Black (%) | 9.8 | 22.5 | <0.001 |
| Traditional risk factors | | | |
| current smoking (%) | 15.1 | 24.4 | 0.026 |
| physically active (%) | 26.4 | 21.2 | 0.278 |
| hypertension (%) | 28.4 | 29.8 | 0.023 |
| systolic BP (mmHg) | 31.8 | 41.2 | 0.075 |
| BMI (kg/m$^2$) | 124.3 | 130.4 | 0.007 |
| obesity (BMI ≥30 kg/m$^2$) | 55.3 | 70.1 | 0.013 |
| glucose (mg/dl) | 118.9 | 150.0 | <0.001 |
| diabetes (%) | 17.2 | 36.3 | <0.001 |
| total cholesterol (mg/dl) | 218.8 | 239.9 | <0.001 |
| HDL cholesterol (mg/dl) | 50.2 | 47.7 | 0.154 |
| log triglycerides, log (mg/dl) | 4.84 | 5.05 | <0.001 |
| Nontraditional risk factors | | | |
| waist circumference | 99.0 | 102.9 | 0.009 |
| log Lp(a), log (mg/L) | 4.12 | 4.31 | 0.125 |
| apolipoprotein-A1 (mg/dl) | 129.8 | 127.3 | 0.408 |
| apolipoprotein-B (mg/dl) | 98.2 | 108.8 | 0.003 |
| anemia (%) | 13.2 | 18.9 | 0.124 |
| leukocyte count ($10^9$ cells/L) | 6.27 | 6.84 | <0.001 |
| serum albumin (mg/dl) | 3.84 | 3.75 | 0.005 |
| fibrinogen (mg/dl) | 317.9 | 350.8 | <0.001 |

[a]Prevalence and levels reflect the visit at which CKD was first noted (visit 1 for 391 participants and visit 2 for 416 participants) and are standardized for all variables except age, gender, and race to the ARIC population with CKD (age, 56.1; gender, 33.0% male; and 21.8% black race).

[b]CHD events include myocardial infarction incidence, fatal CHD, or coronary revascularization. CKD, chronic kidney disease; CHD, coronary heart disease.

quit, then the incidence of CHD would be reduced by 5.0%. A combined improvement in all of the above factors among ARIC participants with CKD would result in a 48.2% reduction in the incidence of CHD in this group.

The burden of traditional and nontraditional CHD risk factors is substantially higher among patients with CKD compared with the general population. However, the burden of these risk factors, including those reported in the current study, varies considerably depending on patient characteristics, including degree of renal dysfunction and cause of kidney disease. The prevalence of hypertension among patients with CKD reported in previous studies has ranged from 60 to 100%, depending on the study population and cause and level of renal dysfunction (24–26). Analysis of the NHANES III data indicates a prevalence of hypertension of 68% among participants with CKD. Also, on the basis of analysis of NHANES III, approximately 63% of the U.S. population with CKD have high blood cholesterol. Also, >27.6% of patients with CKD have diabetes (13). Astor *et al.* (14) reported the prevalence of anemia of 9% among the population with an estimated GFR of 30 ml/min per 1.73 m$^2$. The prevalence of nontraditional cardiovascular disease risk factors has also been reported to be more common among patients with CKD. For example, data from NHANES III indicate that after adjustment for age, race-ethnicity, and gender, people with CKD are 2.20, 1.90, and 7.93 times more likely to have elevated C-reactive protein, high fibrinogen, and high homocysteine levels, respectively (12). However, NHANES III is a cross-sectional study, which precludes ascertaining the relationship between these risk factors and the subsequent development of CHD.

Some risk factors clearly maintain similar relationships in the general population and the population with ESRD. For example, diabetes and cigarette smoking both maintain a strong relationship with cardiovascular disease and mortality among patients who are on dialysis therapy (27,28). However, the association of other risk factors with CHD that have been accepted in the general population may not be present in dialysis patients (29,30). In patients with ESRD, BMI, elevated lipid levels, and higher BP are not consistently associated with CHD risk or all-cause mortality (31–33). However, confounding by malnutrition, metabolic abnormalities, and kidney replacement treatment is present among patients who receive dialysis ther-

*Table 3.* Adjusted relative risks of a major CHD event (myocardial infarction incidence, fatal coronary heart disease, or coronary revascularization) associated with selected CHD risk factors among ARIC study participants with CKD

| Risk Factor | Adjusted Relative Risk (95% CI[a]) | |
|---|---|---|
| | Age, Race, Gender[b] | Multivariate Model[c] |
| Age, 5 yr | 1.42 (1.20–1.68) | 1.33 (1.11–1.60) |
| Male gender | 2.68 (1.81–3.96) | 3.96 (2.52–6.21) |
| Black | 2.06 (0.67–6.36) | 1.79 (0.55–5.85) |
| Traditional risk factors | | |
| current smoking | 1.65 (1.01–2.67) | 1.91 (1.16–3.15) |
| physical activity | 0.79 (0.48–1.28) | 0.79 (0.48–1.31) |
| hypertension | 2.02 (1.27–3.22) | 1.79 (1.11–2.89) |
| systolic BP, 20 mmHg | 1.33 (1.13–1.57) | 1.26 (1.05–1.51) |
| BMI, 5 $kg/m^2$ | 1.25 (1.05–1.49) | 1.16 (0.97–1.39) |
| obese | 1.52 (1.02–2.28) | 1.23 (0.82–1.86) |
| glucose, 40 mg/dl | 1.31 (1.20–1.43) | 1.26 (1.15–1.39) |
| diabetes | 3.06 (2.01–4.67) | 2.88 (1.85–4.47) |
| total cholesterol, 43 mg/dl | 1.50 (1.25–1.79) | 1.46 (1.25–1.70) |
| HDL cholesterol, 17 mg/dl | 0.79 (0.62–1.01) | 0.93 (0.73–1.19) |
| log triglycerides, 0.5 log (mg/dl) | 1.38 (1.15–1.65) | 1.12 (0.94–1.33) |
| Nontraditional risk factors | | |
| waist circumference, 13 cm | 1.38 (1.13–1.69) | 1.24 (1.00–1.55) |
| log Lp(a), 1.2 log (mg/L) | 1.24 (0.98–1.58) | 1.20 (0.94–1.53) |
| apolipoprotein-A1, 31 mg/dl | 0.88 (0.70–1.12) | 0.99 (0.78–1.26) |
| apolipoprotein-B, 29 mg/dl | 1.33 (1.13–1.56) | 1.28 (1.10–1.49) |
| anemia | 1.96 (1.14–3.36) | 2.01 (1.19–3.42) |
| leukocyte count, $1.9 \times 10^9$ cells/L | 1.24 (1.06–1.46) | 1.10 (0.91–1.34) |
| serum albumin, 0.332 mg/dl | 0.65 (0.54–0.79) | 0.76 (0.63–0.92) |
| fibrinogen, 69 mg/dl | 1.38 (1.19–1.59) | 1.23 (1.07–1.41) |

[a]CI, confidence interval.
[b]Adjusted for age, race, gender, and field center.
[c]Additionally adjusted for current smoking, diabetes, hypertension, and total cholesterol.

apy. For example, a recent analysis of serum cholesterol with total and cardiovascular mortality in dialysis patients showed that the association is strongly influenced by the high prevalence of malnutrition and inflammation (34). In that study, a strong, graded, positive association of total cholesterol with overall and cardiovascular disease mortality was reported among incident ESRD patients without inflammation or malnutrition (34). The associations in the current study should not be generalized to the population with ESRD. However, similar to the population without known renal disease, strong associations between higher levels of traditional and nontraditional risk factors with CHD incidence was present among ARIC Study participants with CKD.

The results of the current study provide supporting evidence for the recommendations of the NKF's Task Force on Cardiovascular Disease in Chronic Renal Disease (35) and the Kidney Disease Outcome Quality Initiative Chronic Kidney Disease guidelines (19). Specifically, these reports advocate CHD risk factor reduction among patients with CKD. Treatment recommended for patients with CKD includes the control of hyperglycemia, high BP, and dyslipidemia; participating in physical activity; and the cessation of tobacco use. The data that we report are especially important given that the development of the NKF guidelines, in part, relied on the extrapolation of results from the general population to the population with CKD.

Although the current study provides important data regarding the relationship between traditional and nontraditional risk factors and CHD incidence among patients with CKD, the results should be interpreted within the context of the study's limitations. Specifically, GFR was not measured directly but was estimated using a serum creatinine measurement. The formula that we used to estimate GFR adjusts serum creatinine for age, race, and gender of the patient. However, measuring GFR directly is not feasible in large epidemiologic studies or in the routine clinical setting. Therefore, our findings might have direct implications on clinical and public health practice. Additional limitations of the current study include the lack of urinary protein excretion data for identifying patients with kidney disease, and some participants may have developed CKD after ARIC visit 2. These people may have been misclassified as not having CKD, limiting the power to detect interac-

*Table 4.* Relative risk[a] (95% CI) of a major CHD event[b] among ARIC study participants associated with quartile of CHD risk factor by level of kidney function (estimated GFR ≥90, 60 to 89, and 15 to 59 ml/min per 1.73 m$^2$)

| | Quartile | | | | *P* Value for Trend |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | |
| Systolic BP (mmHg) | <111 | 112–122 | 123–138 | ≥139 | |
| GFR ≥90 | 1.00 | 1.26 (0.89–1.78) | 1.93 (1.41–2.63) | 2.21 (1.56–3.13) | <0.001 |
| 60–89 | 1.00 | 1.07 (0.87–1.32) | 1.73 (1.44–2.07) | 2.39 (1.96–2.91) | <0.001 |
| 15–59 | 1.00 | 1.52 (0.82–2.83) | 1.08 (0.57–2.05) | 2.37 (1.33–4.21) | 0.011 |
| BMI (kg/m$^2$) | <24.7 | 24.7–27.5 | 27.6–31.4 | ≥31.4 | |
| GFR ≥90 | 1.00 | 1.32 (0.98–1.79) | 1.67 (1.23–2.26) | 1.38 (0.99–1.92) | 0.008 |
| 60–89 | 1.00 | 1.17 (0.97–1.41) | 1.36 (1.13–1.65) | 1.62 (1.32–1.98) | <0.001 |
| 15–59 | 1.00 | 1.14 (0.60–2.17) | 1.33 (0.72–2.45) | 1.78 (0.97–3.25) | 0.052 |
| Total Cholesterol (mg/dl) | <190 | 191–217 | 218–244 | ≥245 | |
| GFR ≥90 | 1.00 | 1.44 (1.04–1.99) | 1.73 (1.24–2.42) | 2.04 (1.50–2.79) | <0.001 |
| 60–89 | 1.00 | 1.19 (0.97–1.45) | 1.50 (1.22–1.84) | 2.22 (1.84–2.67) | <0.001 |
| 15–59 | 1.00 | 1.29 (0.68–2.45) | 1.98 (1.08–3.61) | 2.25 (1.27–3.99) | 0.002 |
| HDL cholesterol (mg/dl) | <40 | 40–49 | 50–61 | ≥62 | |
| GFR ≥90 | 1.00 | 0.77 (0.59–1.00) | 0.44 (0.32–0.61) | 0.23 (0.16–0.35) | <0.001 |
| 60–89 | 1.00 | 0.58 (0.50–0.69) | 0.53 (0.44–0.64) | 0.27 (0.21–0.35) | <0.001 |
| 15–59 | 1.00 | 0.72 (0.43–1.23) | 0.73 (0.42–1.30) | 0.62 (0.34–1.14) | 0.127 |
| Triglycerides (mg/dl) | <87 | 87–124 | 125–181 | ≥182 | |
| GFR ≥90 | 1.00 | 1.53 (1.12–2.08) | 1.77 (1.29–2.44) | 2.51 (1.85–3.42) | <0.001 |
| 60–89 | 1.00 | 1.47 (1.20–1.80) | 1.82 (1.49–2.22) | 2.47 (2.02–3.03) | <0.001 |
| 15–59 | 1.00 | 1.84 (0.92–3.67) | 1.74 (0.91–3.29) | 2.73 (1.46–5.10) | 0.002 |
| Waist circumference (cm) | <90 | 91–99 | 100–108 | ≥109 | |
| GFR ≥90 | 1.00 | 1.51 (1.09–2.07) | 1.70 (1.23–2.35) | 1.81 (1.29–2.54) | <0.001 |
| 60–89 | 1.00 | 1.35 (1.09–1.66) | 1.45 (1.18–1.79) | 1.98 (1.59–2.46) | <0.001 |
| 15–59 | 1.00 | 0.82 (0.40–1.65) | 1.26 (0.67–2.35) | 1.77 (0.97–3.23) | 0.013 |
| Leukocyte count ($10^9$ cells/L) | <4.9 | 5.0–6.0 | 6.1–7.2 | ≥7.3 | |
| GFR ≥90 | 1.00 | 1.55 (1.10–2.19) | 1.66 (1.15–3.38) | 2.67 (1.93–3.68) | <0.001 |
| 60–89 | 1.00 | 1.16 (0.95–1.43) | 1.66 (1.35–2.05) | 2.42 (1.99–2.95) | <0.001 |
| 15–59 | 1.00 | 1.84 (0.94–3.63) | 2.09 (1.04–4.21) | 3.31 (1.74–6.32) | <0.001 |
| Serum albumin (mg/dl) | | | | | |
| GFR ≥90 | 1.00 | 0.62 (0.45–0.84) | 0.67 (0.50–0.89) | 0.46 (0.33–0.65) | <0.001 |
| 60–89 | 1.00 | 0.68 (0.55–0.85) | 0.81 (0.67–1.00) | 0.75 (0.61–0.93) | 0.147 |
| 15–59 | 1.00 | 0.57 (0.33–0.99) | 0.52 (0.29–0.92) | 0.38 (0.20–0.70) | 0.003 |
| Fibrinogen (mg/dl) | <270 | 271–310 | 311–358 | ≥359 | |
| GFR ≥90 | 1.00 | 1.32 (0.95–1.83) | 1.80 (1.31–2.48) | 2.77 (2.02–3.80) | <0.001 |
| 60–89 | 1.00 | 1.52 (1.27–1.82) | 2.06 (1.71–2.48) | 2.54 (2.08–3.09) | <0.001 |
| 15–59 | 1.00 | 1.46 (0.67–3.20) | 3.68 (1.80–7.52) | 4.27 (2.09–8.71) | <0.001 |

[a]Adjusted for age, race, gender, and ARIC field center.
[b]Myocardial infarction incidence, fatal coronary heart disease, or coronary revascularization.

tion between CKD and CHD risk factors with CHD incidence. Another limitation of the current study is that several nontraditional CHD risk factors (*e.g.*, C-reactive protein, homocysteine) are not available for the full ARIC cohort and could not be used in the current analysis. Furthermore, the mean estimated GFR of participants with CKD was 53 ml/min per 1.73 m$^2$ and thus reflects primarily the experience of patients at the higher end of the 15- to 60-ml/min per 1.73 m$^2$ range. Finally, the sample size was too small to analyze using more narrow categories of estimated GFR.

Despite these limitations, the current study has several strengths. This study provides data from a population-based sample of people with CKD. A broad range of traditional and nontraditional CHD risk factors were measured following a standardized protocol and stringent quality control procedures. The ARIC Study has thorough and complete data on CHD incidence for participants during a mean of 10.5 yr of follow-up.

In conclusion, results from the ARIC Study show that traditional and nontraditional risk factors maintain strong associations with the incidence of CHD among people with CKD. With the exception of HDL cholesterol, which showed a weaker

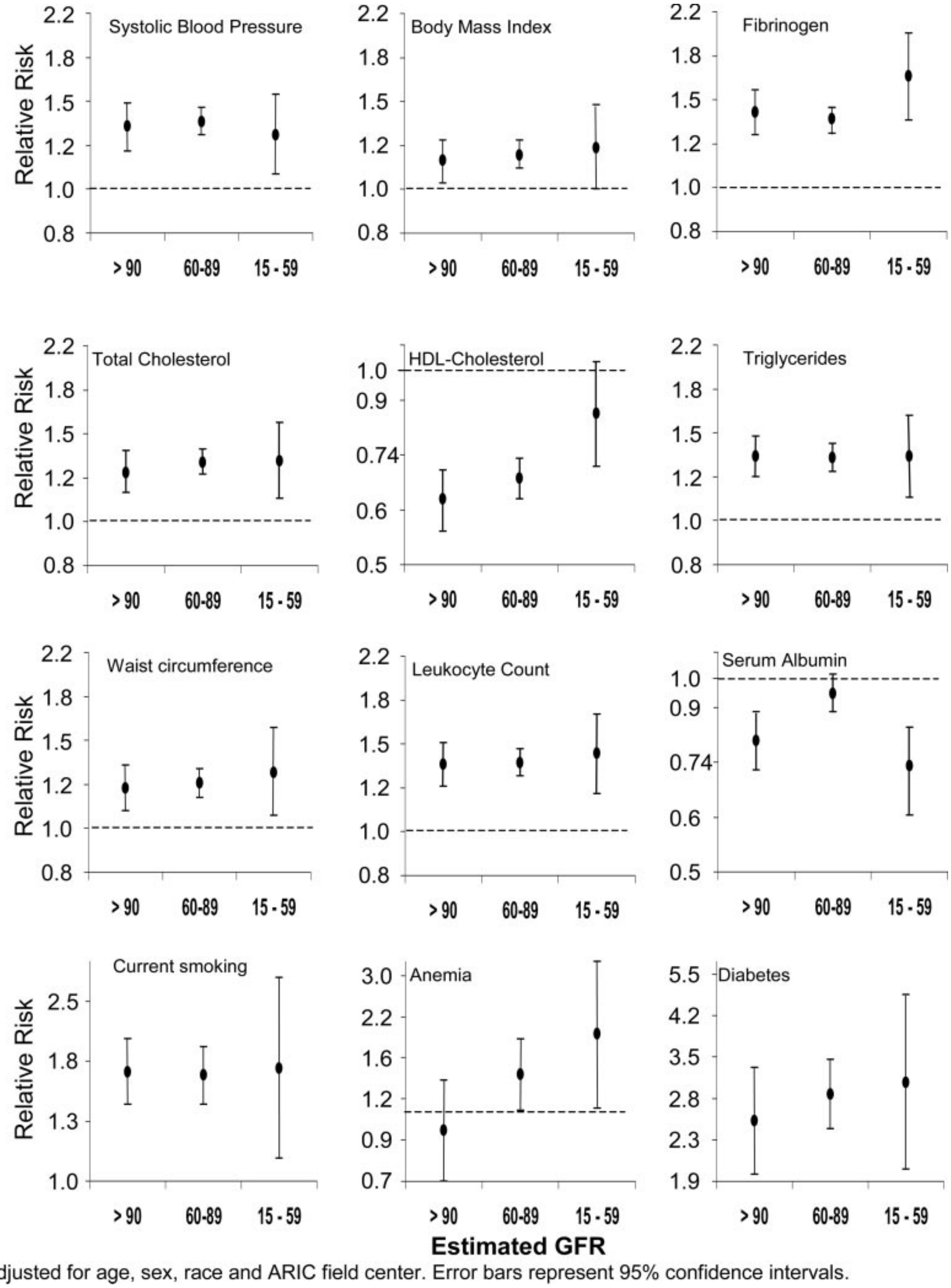


**Figure 1.** Relative risk of a major coronary heart disease event (myocardial infarction incidence, fatal coronary heart disease, or coronary revascularization) for each quartile increase in systolic blood pressure, body mass index, fibrinogen, total and HDL-cholesterol and triglycerides, waist circumference, leukocyte count, serum albumin, and for current smoking, anemia, and diabetes, by level of kidney function (estimated GFR ≥90, 60 to 89, and 15 to 59 ml/min). Adjusted for age, sex, race and Atherosclerosis Risk in Communities (ARIC) Study field center. Error bars represent 95% confidence intervals.

association, and anemia, which showed a stronger association, the relationship of CHD risk factors was similar for people with and without CKD. As such, the reduction of CHD risk factors may decrease the burden of CHD in CKD. Identification and correction of risk factors to prevent CHD among the 10 to 20 million patients in the United States with CKD should be given a high priority.

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