ORIGINAL RESEARCH

Urine Albumin/Creatinine Ratio Below 30 mg/g is a Predictor of Incident Hypertension and Cardiovascular Mortality

Ki-Chul Sung, MD, PhD; Seungho Ryu, MD, PhD; Jong-Young Lee, MD, PhD; Sung Ho Lee, MD, PhD; EunSun Cheong, MD; Young-Youl Hyun, MD, PhD; Kyu-Beck Lee, MD, PhD; Hyang Kim, MD, PhD; Christopher D. Byrne, MBBCh, PhD

***Background*—**Microalbuminuria is associated with cardiovascular disease (CVD) mortality, but whether lower levels of urine albumin excretion similarly predict CVD is uncertain. We investigated associations between urine albumin:creatinine ratio (UACR) <30 mg/g, and incident hypertension, incident diabetes mellitus, and all-cause and CVD mortality, during a maximum of 11 years of follow-up.

***Methods and Results*—**Individuals (37 091) in a health screening program between 2002 and 2012 with baseline measurements of UACR were studied. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs for incident hypertension, incident diabetes mellitus, and mortality outcomes (lowest UACR quartile as reference) at follow-up. For linear risk trends, the quartile rank was used as a continuous variable in regression models. Nine-hundred sixty-three cases of incident hypertension, 511 cases of incident diabetes mellitus, and 349 deaths occurred during follow-up. In the fully adjusted models, there was a significant HR for the association between UACR and incident hypertension (highest UACR quartile HR 1.95 [95% CI 1.51, 2.53], *P*-value for trend across UACR quartiles $P<0.001$). In contrast, the association between UACR and incident diabetes mellitus was not significant (highest UACR quartile, HR 1.15 [95% CI 0.79, 1.66], *P*-value for trend $P=0.20$). For CVD mortality, with increasing UACR quartiles, there was a significant increase in HR across quartiles, $P=0.029$, (for all-cause mortality, $P=0.078$).

***Conclusions*—**Low levels of albuminuria, UACR below 30 mg/g, are associated with increased risk of incident hypertension and CVD mortality at follow-up, but are not associated with increased risk of incident diabetes mellitus. **(*J Am Heart Assoc*. 2016;5: e003245 doi: 10.1161/JAHA.116.003245)**

Key Words: albuminuria • cardiovascular disease risk factors • diabetes mellitus • hypertension • low-grade albuminuria • microalbuminuria heart failure • mortality

Chronic kidney disease is a costly disease, and the costs associated with the care of patients with end-stage renal disease are estimated to exceed US$1 trillion globally.[1]

From the Division of Cardiology, Departments of Medicine (K.-C.S., J.-Y.L., S.H.L., E.C.), Occupational and Environmental Medicine (S.R.), and the Division of Nephrology, Department of Medicine (Y.-Y.H., K.-B.L., H.K.), Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; Nutrition and Metabolism, Faculty of Medicine, University of Southampton and University Hospitals Southampton, UK (C.D.B.); Southampton National Institute for Health Research, Biomedical Research Centre, University Hospital Southampton, Southampton, UK (C.D.B.).

Correspondence to: Ki-Chul Sung, MD, PhD, Division of Cardiology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, #108, Pyung Dong, Jongro-Ku, Seoul 110-746, Korea. E-mail: kcmd.sung@samsung.com and Christopher D. Byrne, MBBCh, PhD, Nutrition and Metabolism Unit, IDS Building, Southampton General Hospital, University of Southampton, MP 887, Tremona Rd, Southampton SO166YD, UK. E-mail: c.d.byrne@soton.ac.uk

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Albuminuria or microalbuminuria, albumin excretion rate ≥30 mg/24 hours or albumin/creatinine ratio (ACR) ≥30 mg/g (≥3 mg/mmol), is used as a marker of renal damage and is used to define chronic kidney disease along with low estimated glomerular filtration rate (eGFR).[2] Albuminuria is not only a predictor of development and progression of diabetic[3] and nondiabetic[4] renal diseases, but is a marker of endothelial dysfunction.[5] In 1969, Keen and colleagues first showed that increased urinary albumin excretion (microalbuminuria) occurred in people with type 2 diabetes mellitus compared with controls during an oral glucose tolerance test.[6]

A recent meta-analysis based on more than 100 000 individuals with ACR data and 1.1 million participants with dipstick data from 21 general population cohorts demonstrated that albuminuria was associated with all-cause and cardiovascular mortality independently of each other and traditional cardiovascular risk factors.[7] These data from 21 studies from 14 countries of Asia, Europe, North America, and Oceania showed consistency in both continuous and categorical models for ACR across the different regional cohorts.

Both cardiovascular disease (CVD) and diabetes mellitus share many risk factors in common (the "common soil" hypothesis[8]), but whether urine albumin:creatinine ratio (UACR) below 30 mg/g similarly predicts mortality outcomes, hypertension, and diabetes mellitus in the same population is uncertain. It is well established that microalbuminuria is associated with all-cause and cardiovascular mortality, and microalbuminuria is associated with diabetes mellitus[9] and resistant hypertension.[10] However, although it has been shown that urinary albumin excretion predicts blood pressure progression in people without diabetes mellitus or hypertension, at levels of UACR below 30 mg/g,[9] it is less certain whether these levels are associated with CVD mortality, and increased risk of incident hypertension and incident diabetes mellitus.

The aim of the study was to test the hypothesis that UACR below 30 mg/g was associated with the following outcomes: incident hypertension, incident diabetes mellitus, and all-cause and CVD mortality during a maximum of 11 years of follow-up, in a middle-aged relatively healthy occupational cohort with exclusion of those with UACR >30 mg/g.

Methods

Study Population

The study population consisted of individuals who participated in a comprehensive health screening program with UACR at Kangbuk Samsung Hospital, Seoul, Korea from 2002 to 2012 (N=44 964). The purpose of the screening program was to promote health through early detection of chronic diseases and their risk factors. Additionally, the Korean Industrial Safety and Health Law demands that working individuals participate in an annual or biennial health examination. Participants, who were employees or spouses of companies or local governmental organizations, registered individually for the program. For this analysis, we opportunistically investigated associations between low levels of albuminuria (below the threshold for defining microalbuminuria), and risks of incident hypertension, incident diabetes mellitus, and CVD mortality at follow-up. Incident hypertension was defined by the presence of new antihypertensive medication, self-reporting by the patient of hypertension, and a blood pressure at follow-up ≥140/90 mm Hg; incident diabetes mellitus was defined by new antidiabetic medication, self-reporting by the patient of diabetes mellitus, or a fasting glucose at follow-up ≥126 mg/dL. Subjects were excluded for 1 or more of the following reasons: UACR ≥30 mg/g, subjects with missing data for smoking, alcohol, or exercise at baseline; subjects with a history of cancer; and subjects with unknown mortality status. The total number of eligible subjects for testing associations with all-cause and CVD mortality was 37 091 (median follow-up [FU]: 5.13 years and mean [SD] FU: 4.99 [2.57] years). To test the effect of low-grade albuminuria for incident type 2 diabetes mellitus and hypertension, we studied 13 475 subjects who had baseline UACR and follow-up data on more than 1 occasion between 2002 and 2013. To analyze associations between UACR and incident hypertension, we additionally excluded the following: subjects with missing data for smoking, alcohol, or exercise at baseline; and subjects with hypertension at baseline; thus, the total number of eligible subjects for this analysis was 9102 (median FU: 2.68 years and mean [SD] FU: 3.52 [2.13] years). For testing associations between UACR and incident diabetes mellitus, data were available on 10 930 subjects (median FU: 2.98 years and mean [SD] FU: 3.47 [2.17]) years after excluding subjects for missing data and subjects with type 2 diabetes mellitus at baseline.

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital. Requirement for informed consent was waived as de-identified information was retrieved retrospectively.

Measurements

As part of the health screening program, individuals completed questionnaires related to their medical and social history and medication use. Individuals were asked about duration of education (years), frequency of exercise (none, less than once a week, at least once a week, ≥3 times per week [regular exercise]), smoking history (never, former, or current), and alcohol consumption (g/week).

Trained staff also collected anthropometric measurements and vital statistics. Body weight was measured in light clothing with no shoes to the nearest 0.1 kg using a digital scale. Height was measured to the nearest 0.1 cm. Body mass index was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured using standard mercury sphygmomanometers. Blood samples were collected after at least 10 hours of fasting and were analyzed in the same core clinical laboratory. The core clinical laboratory has been accredited and participates annually in inspections and surveys by the Korean Association of Quality Assurance for Clinical Laboratories.

Urinary albumin excretion was measured from an early-morning urine sample as the UACR. The urinary albumin concentration was determined by immunoradiometry (radioimmunological competition assay; Immunotech) and immunoturbidimetric assay (Roche Modular P800), and urinary creatinine concentration was measured by a modified Jaffe method. The UACR measured in a spot urine sample is highly correlated with the 24-hour urine albumin excretion.[11] All subjects with a UACR ≥30 mg/g were excluded from these analyses.

Ascertainment of Mortality

Deaths among participants were identified by matching the information to death records from the National Statistical Office using identification numbers assigned to subjects at birth. Causes of death were coded centrally by trained coders using the ICD-10 classification (International Classification of Diseases, 10th revision) and ICD 00-99 was considered to represent cardiovascular death.

Statistical Analyses

The statistical analysis was performed using STATA version 11.2 (StataCorp LP, College Station, TX). Reported *P*-values were 2-tailed, and <0.05 were considered statistically significant. The distribution of continuous variables was evaluated and transformations were conducted for nonparametric variables. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs for mortality in each quartile, compared with the lowest quartile as reference for urine ACR. For testing linear risk trends, we used the quartile rank as a continuous variable in the regression models. We checked the proportional hazards assumption by examining graphs of estimated log (−log) survival. The models were initially adjusted for age, sex, center, year of screening examination, smoking status, alcohol intake, regular exercise, and education level (model 1). In Model 2, the models were further adjusted for body mass index, hypertension, diabetes mellitus, and history of CVD. Model 3 includes adjustment for the same factors as Model 2 plus adjustment for eGFR. Associations were examined between urine ACR quartiles and all-cause and CVD mortality in clinically relevant subgroups.

For incident type 2 diabetes mellitus, models included adjustment for age, sex, center, year of screening examination, smoking status, alcohol intake, regular exercise, and education level (Model 1); Model 1 plus adjustment for fasting plasma glucose, family history of diabetes mellitus and body mass index (Model 2). Model 3 includes adjustment for the same factors as Model 2 plus adjustment for eGFR. For incident hypertension, Model 1 included adjustment for age, sex, center, year of screening examination, smoking status, alcohol intake, regular exercise, and education level (Model 1); Model 1 plus adjustment for systolic blood pressure and body mass index (Model 2). Model 3 includes adjustment for the same factors as Model 2 plus adjustment for eGFR. *P*<0.05 was considered significant.

Results

The baseline characteristics of the cohort according to death, CVD death, incident hypertension, and incident diabetes mellitus at follow-up are shown in Table 1. There were 349 deaths during follow-up and blood pressure and the proportion of subjects with hypertension and diabetes mellitus was higher in subjects who died during follow-up. UACR was increased at baseline in subjects who died during follow-up. To investigate associations between increasing UACR and risk factors for all-cause and cardiovascular mortality, we examined the trends across UACR quartiles and risk factors for all-cause and cardiovascular mortality. Table 2 shows the baseline characteristics of the cohort according to baseline UACR quartiles. Quartiles of UACR were for quartile 1: <3.4 mg/g (0.38 mg/mmol); quartile 2: 3.4 to 4.7 mg/g (0.38–0.53 mg/mmol); quartile 3: 4.7 to 7.4 mg/g (0.53–0.84 mg/mmol), and for the highest quartile ≥7.4 mg/g (0.84 mg/mmol). There was a significant increase in the proportion of people with diabetes mellitus, obesity, and hypertension across UACR quartiles. There were remarkably similar eGFR values across UACR quartiles, with eGFR varying by only 0.4 mL/min across UACR quartiles.

We investigated associations between baseline UACR quartiles and all-cause and CVD mortality. Table 3 shows the HRs for the associations between UACR quartiles and all-cause and CVD mortality. The fully adjusted models showed a significant trend with increasing UACR quartiles and CVD mortality. Adjustment for eGFR in these models had an impact on the strength of the association between UACR and all-cause mortality. Before adjustment for eGFR, there was a significant trend for the association between UACR and all-cause mortality, *P*=0.036, whereas after adjustment for eGFR, there was a decrease in the strength of the association between UACR and all-cause mortality, *P*=0.078.

As can be seen for CVD mortality with each increasing quartile of UACR, there was an increase in the HR for CVD mortality relative to Quartile 1, HR=1; Quartile 2, HR=1.45; Quartile 3, HR=2.05; Quartile 4, HR=3.38, *P*-value for the trend across increasing quartiles *P*=0.029.

Next we tested associations between baseline UACR and CVD mortality (Figure 1) and baseline UACR and all-cause mortality (Figure 2) in clinically relevant subgroups. These analyses investigated trends across UACR quartiles and interaction between subgroup and UACR. For CVD mortality there were significant interactions with age and vigorous exercise. For all-cause mortality no significant interactions with UACR were noted.

We investigated associations between baseline UACR and both incident hypertension and incident diabetes mellitus at follow-up. In the fully adjusted models there was a significant HR for the association between UACR and incident hypertension (highest UACR quartile HR 1.95 [95% CI 1.51, 2.53] and the *P*-value for the trend across UACR quartiles was *P*<0.001) (Table 4). In contrast, in the fully adjusted models there was a nonsignificant HR for the association between UACR and

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Table 1. Baseline Characteristics of the Cohort According to Vital and Disease Status at Follow-Up

Baseline Characteristics	Overall	No Death	New Death	*P*-Value	No CVD Death	New CVD Death	*P*-Value	No Incident Hypertension	Incident Hypertension	*P*-Value	No Incident Diabetes Mellitus	Incident Diabetes Mellitus	*P*-Value
Total number	37 091	37 091	37 091		37 091	37 091		9102	9102		10 930	10 930	
Number of event	37 091	36 742	349		37 041	50		8139	963		10 419	511	
N (%) Men	19 688 (53.1)	19 437 (52.9)	251 (71.9)		19 652 (53.1)	36 (72.0)		4187 (51.4)	665 (69.1)		5768 (55.4)	360 (70.5)	
Age, y	45.8 (11.9)	45.7 (11.9)	57.2 (12.0)	<0.001	45.8 (11.9)	58.9 (12.6)	<0.001	42.1 (10.1)	47.6 (10.2)	<0.001	43.7 (10.6)	49.6 (9.6)	<0.001
BMI, kg/m^2	23.6 (3.2)	23.6 (3.2)	23.9 (3.3)	0.109	23.6 (3.2)	24.0 (3.6)	0.402	23.0 (2.9)	24.6 (2.9)	<0.001	23.4 (3.0)	25.3 (2.8)	<0.001
Systolic BP, mm Hg	115.9 (14.9)	115.9 (14.8)	123.6 (16.8)	<0.001	115.9 (14.8)	127.4 (18.8)	<0.001	110.4 (10.8)	119.1 (9.9)	<0.001	114.7 (14.0)	121.8 (14.4)	<0.001
Diastolic BP, mm Hg	74.9 (9.9)	74.9 (9.9)	78.5 (9.8)	<0.001	74.9 (9.9)	81.2 (10.7)	<0.001	71.6 (7.8)	77.5 (6.7)	<0.001	74.5 (9.7)	79.2 (9.4)	<0.001
Higher education (%)*	11 046 (55.7)	10 964 (56.0)	82 (35.2)	<0.001	11 034 (55.8)	12 (35.3)	0.016	2927 (70.4)	316 (55.2)	<0.001	3710 (67.3)	134 (47.9)	<0.001
Regular exercise (%)†	7183 (19.4)	7122 (19.4)	61 (17.5)	0.370	7177 (19.4)	6 (12.0)	0.187	1475 (18.1)	213 (22.1)	0.003	1988 (19.1)	114 (22.3)	0.071
Current smoker (%)	9774 (26.4)	9654 (26.3)	120 (34.4)	0.001	9758 (26.3)	16 (32.0)	0.364	2111 (25.9)	289 (30.0)	0.007	2674 (25.7)	163 (31.9)	0.002
Alcohol intake ≥20 g/day (%)	7542 (20.3)	7457 (20.3)	85 (24.4)	0.061	7533 (20.3)	9 (18.0)	0.682	1459 (17.9)	272 (28.3)	<0.001	2076 (19.9)	170 (33.3)	<0.001
Fatty liver (%)	10 882 (29.3)	10 784 (29.4)	98 (28.1)	0.603	10 865 (29.3)	17 (34.0)	0.469	1960 (24.1)	378 (39.3)	<0.001	2809 (27.0)	299 (58.5)	<0.001
Obesity (%)	11 691 (31.5)	11 569 (31.5)	122 (35.0)	0.165	11 674 (31.5)	17 (34.0)	0.706	1976 (24.3)	407 (42.3)	<0.001	3064 (29.4)	271 (53.0)	<0.001
Hypertension (%)	8740 (23.6)	8594 (23.5)	146 (41.8)	<0.001	8714 (23.6)	26 (52.0)	<0.001				—	—	—
Diabetes mellitus (%)	2314 (6.2)	2254 (6.1)	60 (17.2)	<0.001	2305 (6.2)	9 (18.0)	0.001	—	—	—	1323 (12.7)	1443 (23.5)	<0.001
Hx of CVD (%)	3016 (8.1)	2978 (8.1)	38 (10.9)	0.058	37 041 (8.1)	9 (18.0)	0.011	—	—	—	—	—	—
Insulin, μIU/mL	8.01 (6.27–10.26)	8.01 (6.27–10.26)	8.23 (6.63–10.68)	0.001	8.01 (6.27–10.26)	8.32 (6.58–10.36)	0.411	4.69 (3.1–6.73)	5.5 (4.01–8.03)	0.002	4.8 (3.17–6.85)	6.15 (4.1–8.71)	0.007
Glucose, mg/dL	96.4 (17.8)	96.3 (17.7)	104.0 (27.3)	<0.001	96.4 (17.8)	101.8 (22.6)	0.033	93.4 (13.6)	99.1 (18.6)	<0.001	92.6 (8.7)	105.5 (10.9)	<0.001
Total cholesterol, mg/dL	195.9 (35.2)	195.9 (35.2)	193.5 (37.9)	0.202	195.9 (35.2)	200.2 (26.7)	0.383	193.2 (33.7)	202.1 (35.2)	<0.001	195.2 (34.1)	207.3 (35.7)	<0.001
LDL-C, mg/dL	115.6 (31.3)	115.6 (31.3)	111.0 (32.0)	0.006	115.6 (31.3)	119.5 (22.9)	0.380	113.2 (30.0)	120.5 (31.7)	<0.001	114.8 (30.4)	122.7 (32.8)	<0.001
HDL-C, mg/dL	55.7 (13.3)	55.7 (13.3)	55.0 (13.7)	0.317	55.7 (13.3)	55.2 (11.0)	0.767	56.9 (13.7)	54.2 (11.9)	<0.001	56.5 (13.4)	51.8 (11.0)	<0.001

Continued

Table 1. Continued

Baseline Characteristics	Overall	No Death	New Death	*P*-Value	No CVD Death	New CVD Death	*P*-Value	No Incident Hypertension	Incident Hypertension	*P*-Value	No Incident Diabetes Mellitus	Incident Diabetes Mellitus	*P*-Value
Triglycerides, mg/dL	103 (72–154)	103 (72–154)	114 (82–162)	<0.001	103 (72–154)	117 (82–167)	0.215	94 (67–140)	122 (86–177)	<0.001	100 (70–148)	152 (104–218)	<0.001
HOMA IR	1.87 (1.40–2.48)	1.86 (1.40–2.48)	2.05 (1.55–2.69)	<0.001	1.86 (1.40–2.48)	2.05 (1.60–2.48)	0.175	1.81 (1.36–2.34)	2.04 (1.60–2.70)	<0.001	1.84 (1.40–2.37)	2.42 (1.88–3.17)	<0.001
eGFR, mL/min	81.6 (14.4)	81.7 (14.4)	76.6 (13.0)	<0.001	81.6 (14.4)	72.9 (12.9)	<0.001	83.5 (14.4)	78.5 (12.0)	<0.001	82.1 (14.2)	77.5 (12.9)	<0.001

SI conversion factors (multiply the conversion factor to obtain SI unit): insulin, 6.945 (pmol/L); glucose, 0.0555 (mmol/L); total cholesterol, 0.0259 (mmol/L); LDL-C, 0.0259 (mmol/L); HDL-C, 0.0259 (mmol/L); triglycerides, 0.0113 (mmol/L). BMI indicates body mass index; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HOMA IR, homeostatic model assessment-insulin resistance; LDL-C, low-density lipoprotein cholesterol.

*≥College graduate.

†≥3 times per week.

incident diabetes mellitus (highest UACR quartile HR 1.15 [95% CI 0.79, 1.66] and the *P*-value for the trend across UACR quartiles was *P*=0.195) (Table 5).

Discussion

We show for the first time that UACR below 30 mg/g is associated with increased risk of incident hypertension and CVD mortality over 10 years of follow-up. Our results show there was a linear trend for increased risk of incident hypertension and CVD mortality, with very low-grade albuminuria defined by UACR, and these trends were independent of eGFR levels. eGFR only varied by 0.4 mL/min across UACR quartiles, and the HRs for the associations between UACR and each outcome were not materially affected by adjustment for eGFR in the regression models. The associations we observed are in a healthy, young occupational cohort without overt renal disease and although many of the risk factors for type 2 diabetes mellitus and hypertension are shared, it is important to note that there was no significant association between baseline UACR and incident diabetes mellitus. Importantly, our data add uniquely to current knowledge, since we show that very low levels of albuminuria are a risk factor for both incident hypertension and also CVD mortality and the linear increase in risk from 0 to <30 mg/g therefore suggests strongly that any albuminuria is a risk factor for vascular disease. Whether hypertension represents the intermediary causal link between UACR and increased CVD mortality is uncertain, as it is not possible to prove a causal link from this cohort study.

In general, urinary albumin excretion is classified as normoalbuminuria (<30 mg/day or UACR <30 mg/g), microalbuminuria (30–300 mg/day or UACR 30–300 mg/g), and macroalbuminuria (>300 mg/day or UACR >300 mg/g). Thus, it is important to note that all individuals included in this study in all quartiles of UACR would be classified has having normoalbuminuria. Consequently, our results strongly suggest that even within the normal range of urinary albumin excretion, an increase in UACR is associated with CVD mortality and increased risk of developing incident hypertension during follow-up.

Low levels of eGFR are associated with renal impairment and albuminuria, but our results show clearly that the association between low-grade albuminuria and mortality outcomes and incident hypertension were independent of eGFR levels. A previous cohort study undertaken in North and South America and Europe that followed individuals aged ≥55 years for a median 4.5 years showed that any degree of albuminuria was a risk factor for CV events.[11] Another multicenter cohort study involving patients with hypertension and left ventricular hypertrophy also showed an association

Table 2. Baseline Characteristics of Study Subjects by UACR Quartile

Characteristics	Overall	ACR Quartiles				*P* for Trend
		Q1 (<3.4 mg/g)	Q2 (3.4–4.7 mg/g)	Q3 (4.7–7.4 mg/g)	Q4 (≥7.4 mg/g)	
N=37 091		9273	9274	9272	9272	
Age, y	45.8 (11.9)	42.6 (10.7)	44.5 (11.3)	46.6 (11.9)	49.5 (12.5)	<0.001
BMI, kg/m^2	23.6 (3.2)	23.7 (2.9)	23.3 (3.0)	23.4 (3.2)	24.0 (3.5)	<0.001
Systolic BP, mm Hg	115.9 (14.9)	113.5 (12.5)	113.7 (13.7)	115.8 (14.8)	120.7 (16.9)	<0.001
Diastolic BP, mm Hg	74.9 (9.9)	73.8 (9.0)	73.7 (9.5)	74.8 (9.9)	77.5 (10.7)	<0.001
Higher education (%)*	11 046 (55.7)	3138 (68.3)	2893 (58.9)	2651 (52.7)	2364 (44.8)	<0.001
Regular exercise (%)†	7183 (19.4)	1796 (19.4)	1798 (19.4)	1799 (19.4)	1790 (19.3)	0.925
Current smoker (%)	9774 (26.4)	3566 (38.5)	2448 (26.4)	1914 (20.6)	1846 (19.9)	<0.001
Alcohol intake ≥20 g/day (%)	7542 (20.3)	2447 (26.4)	1865 (20.1)	1535 (16.6)	1695 (18.3)	<0.001
Obesity (%)	11 691 (31.5)	2881 (31.1)	2611 (28.2)	2732 (29.5)	3467 (37.4)	<0.001
Hypertension (%)	8740 (23.6)	1363 (14.8)	1708 (18.5)	2180 (23.6)	3489 (37.7)	<0.001
Diabetes mellitus (%)	2314 (6.2)	246 (2.7)	378 (4.08)	551 (5.9)	1139 (12.3)	<0.001
Hx of CVD (%)	3016 (8.1)	593 (6.4)	732 (7.9)	810 (8.7)	881 (9.5)	<0.001
Insulin, μIU/mL	8.01 (6.27–10.26)	7.69 (5.8–9.83)	8.0 (6.36–10.09)	8.1 (6.4–10.34)	8.29 (6.47–10.84)	<0.001
Glucose, mg/dL	96.4 (17.8)	93.9 (11.6)	94.4 (14.6)	96.0 (16.8)	101.2 (24.6)	<0.001
Total cholesterol, mg/dL	195.9 (35.2)	193.6 (33.5)	194.1 (34.2)	196.2 (35.4)	199.8 (37.3)	<0.001
LDL-C, mg/dL	115.6 (31.3)	116.0 (30.1)	114.2 (30.6)	114.8 (31.3)	117.5 (33.0)	0.001
HDL-C, mg/dL	55.7 (13.3)	54.3 (12.8)	56.2 (13.3)	56.8 (13.7)	55.6 (13.4)	<0.001
Triglycerides, mg/dL	103 (72–154)	105 (75–152)	99 (70–146)	99 (69–149)	111 (76–169)	<0.001
HOMA IR	1.87 (1.40–2.48)	1.75 (1.29–2.31)	1.84 (1.40–2.40)	1.88 (1.43–2.49)	2.01 (1.48–2.74)	<0.001
eGFR, mL/min	81.6 (14.4)	81.7 (13.4)	81.6 (14.1)	81.8 (14.6)	81.4 (15.5)	0.309

SI conversion factors (multiply the conversion factor to obtain SI unit): insulin, 6.945 (pmol/L); glucose, 0.0555 (mmol/L); total cholesterol, 0.0259 (mmol/L); LDL-C, 0.0259 (mmol/L); HDL-C, 0.0259 (mmol/L); triglycerides, 0.0113 (mmol/L). BMI indicates body mass index; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HOMA IR, homeostatic model assessment-insulin resistance; Hx, history; LDL-C, low-density lipoprotein cholesterol; UACR, urine albumin: creatinine ratio.

*≥College graduate.

†≥3 times per week.

between UACR and increased cardiovascular morbidity and mortality with no threshold of UACR contributing to increased risk.[12] These results are in keeping with our results and with our previous study in which we showed an association between different cardiovascular risk factors and low-grade albuminuria.[13] However, the baseline characteristics of subjects in these studies were very different from the baseline characteristics of subjects in the present study. In these previous studies, there was inclusion of subjects with recognized cardiovascular risk factors at baseline, such as diabetes,[11] hypertension with left ventricular hypertrophy,[12] and coronary artery disease.[13] Furthermore, baseline UACR was notably higher in these previous studies than in the presented data. Consequently, the presented data are novel and this is the first study to show that UACR below 30 mg/g is associated with increased risk of CVD mortality.

Why is low-grade albuminuria, UACR below 30 mg/g, associated with increased CVD mortality and incident hypertension? Increased albumin excretion is the net result of glomerular filtration and tubular resorption, and it is suggested that in normal physiological conditions there is little filtration. When irreversible increases in albumin excretion occur it is assumed that there is increased glomerular hydraulic pressure, increased glomerular filtration coefficient, and change in size and charge selectivity of the glomerular membrane.[7] The mechanisms linking increased albuminuria and cardiovascular mortality are uncertain, but it is likely that increased urinary albumin excretion reflects widespread vascular endothelial cell dysfunction,[5,14] and it is plausible that this might predispose to increased accumulation of atherogenic lipoproteins within the subendothelial cell space.[15] Thus, increased albuminuria might reflect glomerular and/or systemic vascular endothelial dysfunction that precedes development of hypertension in humans.[16] In previous cross-sectional studies, increased urinary albumin excretion was associated with increased blood pressure in subjects with

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Table 3. Risk of All-Cause and CVD Mortality According to Baseline UACR Quartiles

ACR Quartiles, mg/g	Person-Years	Number of Events	Mortality Rate (100 000 Person-Year)	Age-Sex Adjusted HR (95% CI)	Multivariate HR*(95% CI)			
					Model 1	Model 2	Model 3	Model 4
All-cause mortality								
Q1 (<3.4 mg/g)	42 971.8	63	146.6	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (3.4–4.7 mg/g)	47 491.7	67	141.1	0.93 (0.66–1.32)	0.77 (0.49–1.20)	0.76 (0.49–1.18)	0.74 (0.48–1.15)	0.74 (0.47–1.15)
Q3 (4.7–7.4 mg/g)	47 411.1	89	187.7	1.13 (0.81–1.57)	1.05 (0.69–1.58)	1.04 (0.69–1.56)	0.99 (0.66–1.50)	0.98 (0.65–1.48)
Q4 (≥7.4 mg/g)	47 135.7	130	275.8	1.33 (0.97–1.83)	1.37 (0.93–2.03)	1.33 (0.89–1.98)	1.25 (0.83–1.86)	1.25 (0.84–1.87)
P for trend				0.025	0.019	0.036	0.078	0.069
CVD mortality								
Q1 (<3.4 mg/g)	42 971.8	7	16.3	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (3.4–4.7 mg/g)	47 491.7	11	23.2	1.35 (0.52–3.51)	1.42 (0.34–6.00)	1.40 (0.33–5.90)	1.45 (0.34–6.15)	1.43 (0.94–6.05)
Q3 (4.7–7.4 mg/g)	47 411.1	10	21.1	1.09 (0.41–2.94)	1.97 (0.51–7.61)	1.93 (0.50–7.50)	2.05 (0.53–7.96)	2.03 (0.52–7.90)
Q4 (≥7.4 mg/g)	47 135.7	22	46.7	1.89 (0.77–4.61)	3.46 (0.97–12.35)	3.14 (0.86–11.48)	3.38 (0.92–12.39)	3.37 (0.92–12.36)
P for trend				0.163	0.020	0.038	0.029	0.028

SI units for ACR: divided by 8.84, mg/mmol. ACR indicates albumin/creatinine ratio; BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; UACR, urine albumin:creatinine ratio.

*Model 1: adjustment for age, sex, center, year of screening examination, smoking status, alcohol intake, regular exercise, education level; Model 2: Model 1 adjustments plus adjustment for BMI, hypertension, diabetes mellitus, and history of CVD; Model 3: Model 2 adjustments plus adjustment for eGFR; Model 4: Model 3 adjustments plus adjustment for HDL and LDL.

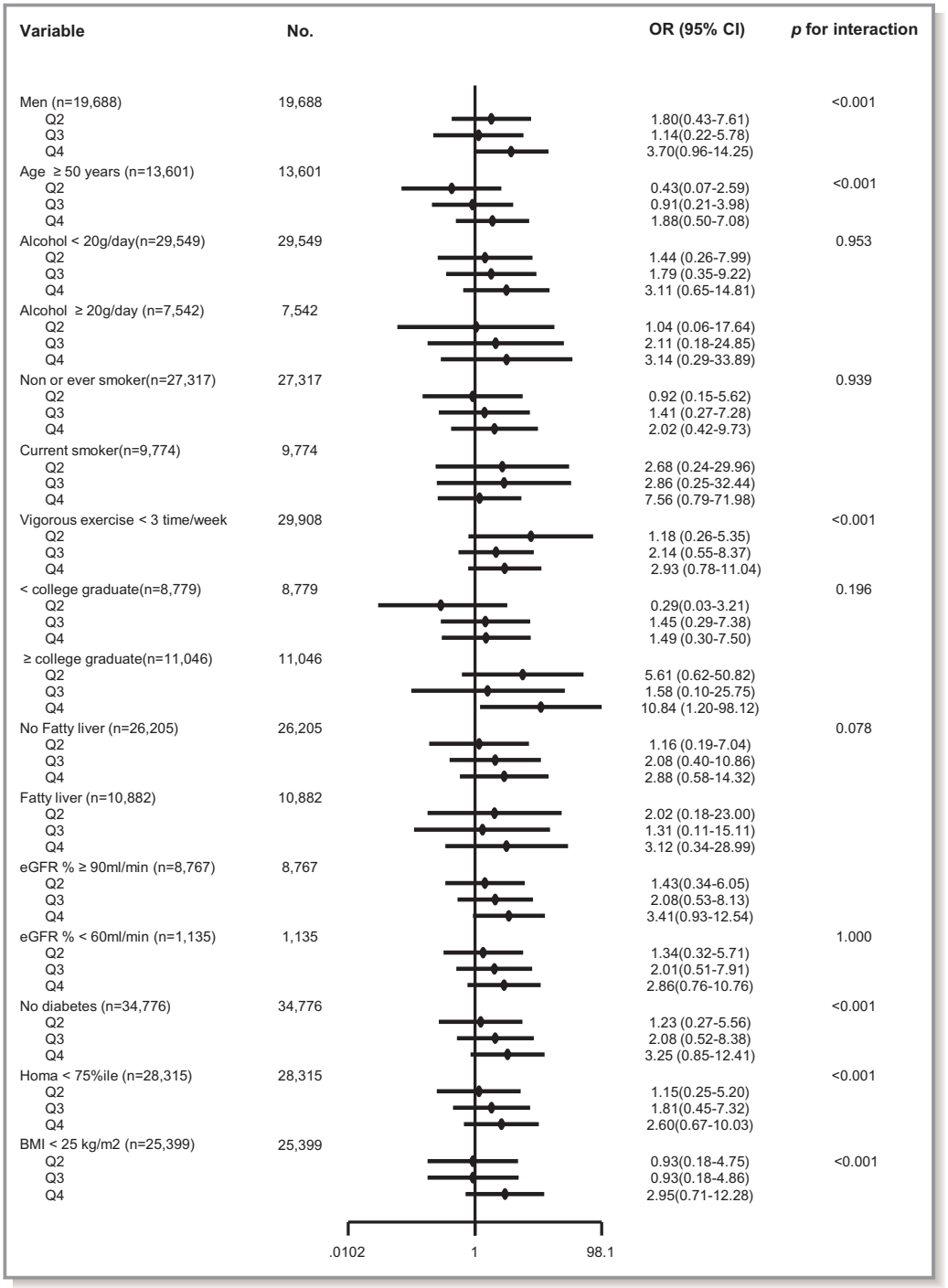

Figure 1. Risk of CVD mortality according to subgroup and quartiles of ACR concentration. ACR indicates albumin/creatinine ratio; BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; Homa, homeostatic model assessment; OR, odds ratio.

hypertension[17,18] and in the general population,[19] suggesting that the increased level of urinary albumin excretion in the present study could be in part due to an increase in blood pressure below levels to diagnose hypertension.

Although CVD and diabetes mellitus share many risk factors in common (the "common soil" hypothesis[8]) and as discussed above microalbuminuria occurs in people with diabetes mellitus and CVD, our data suggest a disconnect between diabetes and CVD, since in contrast to CVD mortality and hypertension, low-grade albuminuria was not significantly associated with any marked increase in incident diabetes mellitus. Thus, we suggest that these data lend credence to the notion that microalbuminuria/albuminuria occurs as a consequence of vascular dysfunction in diabetes mellitus,

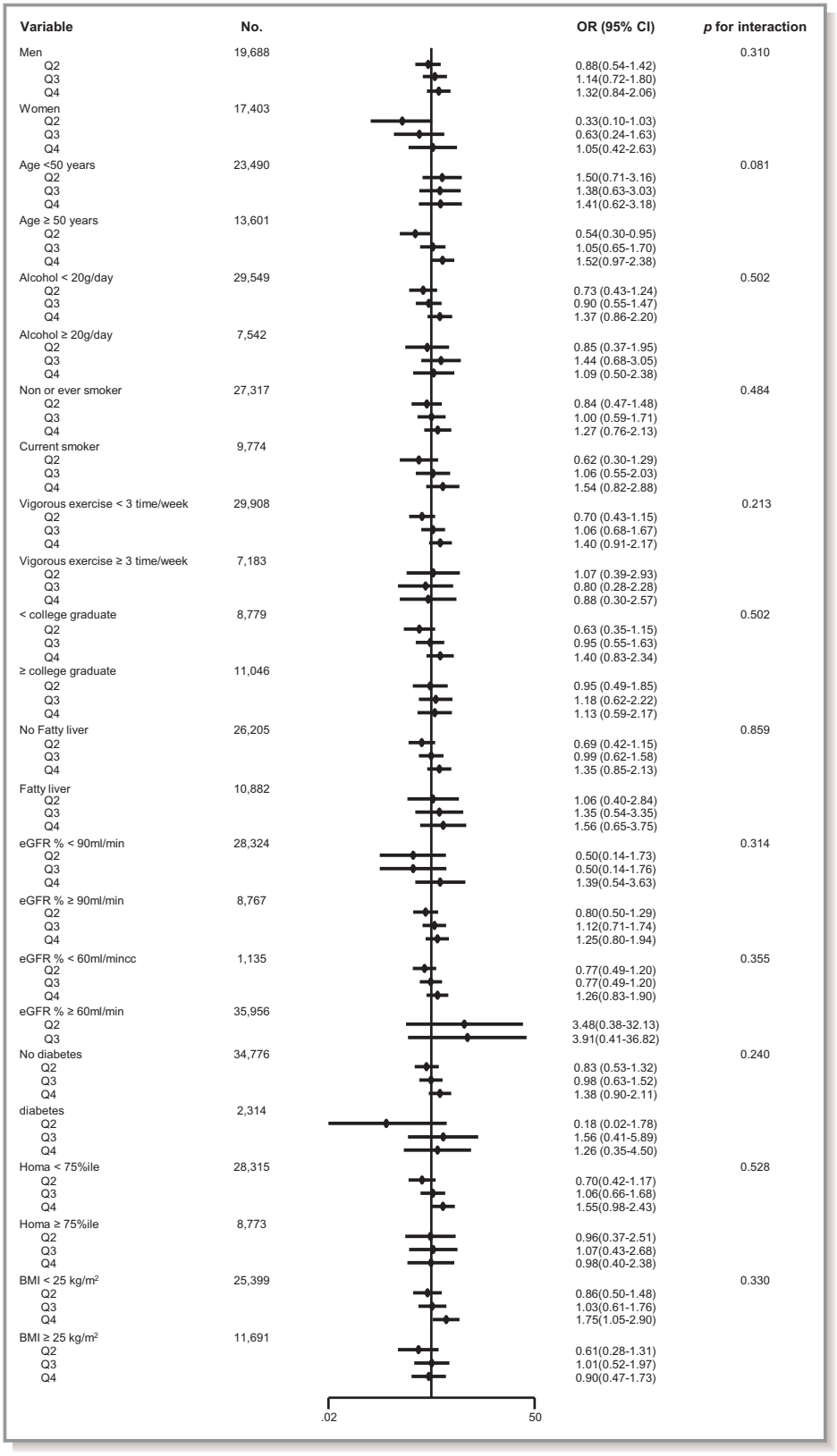

Figure 2. Risk of all-cause mortality according to subgroup and quartiles of ACR concentration. ACR indicates albumin/creatinine ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; Homa, homeostatic model assessment; OR, odds ratio.

Table 4. Risk of Incident Hypertension According to Baseline ACR Quartiles

ACR Quartiles, mg/g	Person-Years	Number of Events	Incidence Rate (1000 Person-Years)	Age-Sex Adjusted HR (95% CI)	Multivariate HR*(95% CI)			
					Model 1	Model 2	Model 3	Model 4
N=9102								
Q1 (<3.4 mg/g)	7171.4	167	23.3	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (3.4–4.7 mg/g)	7657.3	198	25.9	1.33 (1.08–1.64)	1.23 (0.93–1.63)	1.17 (0.88–1.55)	1.18 (0.89–1.56)	1.17 (0.89–1.56)
Q3 (4.7–7.4 mg/g)	7655.3	241	31.5	1.72 (1.40–2.11)	1.61 (1.23–2.12)	1.46 (1.11–1.92)	1.48 (1.12–1.94)	1.50 (1.14–1.97)
Q4 (≥7.4 mg/g)	7134.9	357	50.0	2.54 (2.10–3.08)	2.42 (1.88–3.13)	1.94 (1.50–2.50)	1.95 (1.51–2.53)	1.97 (1.52–2.55)
P for trend				<0.001	<0.001	<0.001	<0.001	<0.001

SI units for ACR: divided by 8.84, mg/mmol. ACR indicates albumin/creatinine ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; SBP, systolic blood pressure.

*Model 1: adjustment for age, sex, center, year of screening examination, smoking status, alcohol intake, regular exercise, and education level; Model 2: Model 1 plus adjustment for SBP and BMI; Model 3: Model 2 plus adjustment for eGFR; Model 4: model 3 adjustments plus adjustment for HDL and LDL.

rather than albuminuria/vascular dysfunction being a causal factor in the pathogenesis of diabetes mellitus.

Our study does have some limitations that should be discussed. UACR measurement was only available from a single measurement and since UACR can vary from day to day, this will result in imprecision in the UACR measurement. Moreover, although the absolute variability in ACR decreases with the magnitude of albuminuria, on the other hand a percentage of baseline ACR variability increases.[20] However, there is a considerable amount of evidence showing that a simple single-voided test is reliable and useful in screening for disease and follow-up of patients, and this methodology avoids the problems associated with a 24-hour urine collection.[20–24] Despite the potential imprecision associated with a single voided measurement of UACR, we have studied a large number of subjects in this cohort and any imprecision in the measurement of UACR would bias results towards the null. Although our subjects predominantly have normal renal function, it is possible that eGFR values are underestimated since it is known that the MDRD Study equation underestimates measured GFR when GFR is ≥60 mL/min per 1.73 m^2 in healthy individuals.[25] Furthermore, it is possible that development of diabetes mellitus or hypertension during follow-up has influenced our results, although our study design has limited this possibility by exclusion of these subjects at baseline. Although the follow-up time was a little different for studying the associations between baseline UACR and incident diabetes mellitus and incident hypertension, compared to studying associations with mortality outcomes, it should be noted that there were similar associations between baseline UACR and incident hypertension and CVD mortality, in contrast to the (lack of an) association between baseline UACR and incident diabetes mellitus. Thus, it seems unlikely that the shorter period of

Table 5. Risk of Incident Diabetes Mellitus According to Baseline ACR Quartiles

ACR Quartiles, mg/g	Person-Years	Number of Events	Incidence Rate (1000 Person-Years)	Age-Sex Adjusted HR (95% CI)	Multivariate HR*(95% CI)			
					Model 1	Model 2	Model 3	Model 4
N=10 930								
Q1 (<3.4 mg/g)	9064.2	100	11.0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (3.4–4.7 mg/g)	9754.9	106	10.9	1.07 (0.81–1.41)	1.01 (0.68–1.51)	0.83 (0.56–1.25)	0.83 (0.55–1.24)	0.84 (0.56–1.26)
Q3 (4.7–7.4 mg/g)	9792.8	130	13.3	1.33 (1.02–1.74)	1.52 (1.05–2.20)	1.06 (0.73–1.55)	1.05 (0.72–1.53)	1.03 (0.71–1.51)
Q4 (≥7.4 mg/g)	9337.3	175	18.7	1.70 (1.32–2.20)	1.83 (1.28–2.62)	1.16 (0.81–1.68)	1.15 (0.79–1.66)	1.14 (0.78–1.64)
P for trend				<0.001	<0.001	0.174	0.195	0.240

SI units for ACR: divided by 8.84, mg/mmol. ACR indicates albumin/creatinine ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein.

*Model 1: adjustment for age, sex, center, year of screening examination, smoking status, alcohol intake, regular exercise, education level; Model 2: Model 1 plus adjustment for glucose, family history of diabetes mellitus and BMI; Model 3: Model 2 plus adjustment for eGFR; Model 4: Model 3 adjustments plus adjustment for HDL and LDL.

follow-up for incident diabetes mellitus has influenced our results.

In summary, our results show for the first time that in a young predominantly healthy occupational cohort, UACR below 30 mg/g is an independent risk factor for incident hypertension and CVD mortality during a maximum of 11 years of follow-up. In contrast, low-grade albuminuria was not a risk factor for incident diabetes during the same period of follow-up. Whether hypertension represents the intermediary causal link between UACR and increased CVD mortality is uncertain, as it is not possible to prove a causal link from this cohort study.

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Disclosures

None.

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