NIH Public Access
Author Manuscript
Am J Kidney Dis. Author manuscript; available in PMC 2011 November 1.

Published in final edited form as:
Am J Kidney Dis. 2010 November ; 56(5): 852–860. doi:10.1053/j.ajkd.2010.04.013.

Predictors of Incident Albuminuria in the Framingham Offspring Cohort

Conall M. O'Seaghdha, MD[1,2], **Shih-Jen Hwang, PhD**[2], **Ashish Upadhyay, MD**[3], **James B. Meigs, MD, MPH**[4], and **Caroline S. Fox, MD, MPH**[2,5]

[1]Renal Division, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

[2]National Heart, Lung and Blood Institute's Framingham Heart Study and the Center for Population Studies, Framingham, MA

[3]Division of Nephrology, Tufts Medical Center and Tufts University School of Medicine, Boston, MA

[4]General Medicine Division, Massachusetts General Hospital and Harvard Medical School, Boston, MA

[5]Division of Endocrinology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Abstract

Background—Predictors for incident albuminuria are not well-known in population based cohorts. The purpose of this study was to identify predictors of incident albuminuria in an unselected, middle-aged population.

Study Design—Observational cohort study

Setting and participants—Framingham Offspring Study participants who attended both the sixth (baseline; 1995–1998) and eighth (2005–2008) examination cycles.

Predictors—Standard clinical predictors were used. Predictors of incident albuminuria were identified by stepwise logistic regression analysis with age and sex forced into the model.

Outcomes and Measurements—Albuminuria was defined as urine albumin-creatinine ratio (UACR) ≥17 mg/g (men) or ≥ 25 mg/g (women). Individuals with albuminuria at baseline were excluded.

Results—1916 participants were available for analysis (mean age 56 years, 54% women). Albuminuria developed in 10.0% of participants (n=192) over 9.5 years. Age (odds ratio [OR], 2.09; p-value<0.001), baseline diabetes (OR, 1.93; p-value= 0.01), smoking (OR, 2.09; p-value <0.001) and baseline log UACR (OR per standard deviation increase in log UACR, 1.56; p-value <0.001) were associated with incident albuminuria in a stepwise model. An inverse relationship with female sex (OR, 0.53; p <0.001) and HDL cholesterol (OR, 0.80; p-value=0.007) was also observed. Results were similar when participants with baseline chronic kidney disease (n=102), defined as eGFR < 60 mL/min/1.73 m^2, were excluded from the model. Age, male sex, low HDL-

Corresponding author: Caroline S. Fox, MD, MPH, National Heart, Lung and Blood Institute's Framingham Heart Study, 73 Mt. Wayte Avenue Suite #2, Framingham, MA 01702, foxca@nhlbi.nih.gov, Phone : 508-935-3447; Fax : 508-626-1262.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Financial Disclosure: The authors declare that they have no relevant financial interests.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

cholesterol, smoking and log UACR continued to be associated with incident albuminuria when baseline diabetes (n= 107) was excluded. Age, male sex and log UACR correlated with incident albuminuria after participants with baseline hypertension were excluded (n= 651).

Limitations—Causality may not be inferred due to the observational nature of the study. One-third of participants did not return for follow-up, potentially attenuating the observed risks for albuminuria.

Conclusions—The known cardiovascular risk factors of increasing age, male sex, diabetes, smoking, low HDL cholesterol, and albuminuria within the "normal range" are correlates of incident albuminuria in the general population.

Index words

Microalbuminuria; albuminuria; proteinuria

Albuminuria, generally defined as levels of urinary albumin excretion above 30 mg/day, is an independent risk factor for cardiovascular disease.[1] The prevalence of albuminuria ranges from 5 to 7% in unselected individuals[2–4] to as high as 40% in patients with hypertension and diabetes.[5] However, the natural history of albuminuria is poorly defined in the "general" population and in patients with atherosclerotic cardiovascular or kidney disease, with the important exception of patients with type 1 diabetic nephropathy.

The pathophysiology of albuminuria is widely disputed. Traditionally, increased urinary albumin excretion is thought to occur as a consequence of localized kidney injury, as observed in diabetic nephropathy or atherosclerotic reno-vascular disease. Alternatively, urinary albumin leakage is believed to mirror systemic endothelial dysfunction, serving as the link between impaired endothelial function and the vascular leak of albumin.[6] Recent studies suggest that inter-individual variability in albumin excretion rates within the microalbuminuric range reflect endothelial phenotypic variation, determining later susceptibility to vascular disease and organ damage.[6] Albuminuria has also been shown to independently predict incident hypertension,[7, 8] heart failure,[9] chronic kidney disease (CKD)[10] and diabetes,[11] arguing against albuminuria occurring solely as a consequence of acquired disease.

In order to better characterize the natural history of albuminuria in the general population, we sought to identify clinical predictors in the Framingham Offspring Cohort.

Methods

Study Sample

Details of the study design and methods of the Framingham Offspring cohort have been published previously.[12] Briefly, the Offspring cohort is a prospective cohort study composed of 5124 children, and spouses of children, of the original Framingham cohort.[13] Participants attended Framingham Heart Study clinic examinations approximately every 4 to 7 years. Each examination visit comprised a detailed medical history, physical examination including blood pressure measurements, anthropometry, and laboratory assessment of risk factors. Offspring cohort participants who were examined during the sixth examination cycle (1995–1998) were included in this study, as both serum creatinine and urinary albumin excretion were measured at that time. Of a total of 3532 attendees at the sixth examination cycle, 2318 returned for the eighth examination cycle (2005 to 2008). Of these, 57 were excluded due to missing serum creatinine values, 335 were excluded due to baseline albuminuria (defined as UACR ≥ 17 mg/g (men) or ≥ 25 mg/g (women)), and 10 were excluded due to missing covariates, resulting in a final study sample of 1916 participants.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

The Boston University Medical Center (Boston, MA) Institutional Review Board approved this study, and all participants supplied written informed consent.

Measurements and Definitions

Urinary albumin-creatinine ratio (UACR)[14] was measured on spot morning urine samples. UACR is a reliable measure of urinary albumin excretion, and is highly correlated with albumin excretion rates obtained from 24-hour collection.[15] Spot urine samples were obtained during the examination between February 1995 and September 1998, and kept at −20°C until quantification in October 1998 in Children's Hospital, Boston, MA. Urinary albumin concentration was measured using immunoturbidimetry (Tina-quant Albumin assay; Roche Diagnostics; www.roche-diagnostics.us/). Urinary creatinine was assessed using a modified Jaffé method; the intra-assay coefficient of variation varied from 1.7% to 3.8%. Albuminuria was defined using the sex-specific cut-points of UACR ≥ 17 mg/g (men) or ≥ 25 mg/g (women).[16]

CKD was defined according to the National Kidney Foundation's KDOQI clinical practice guidelines (ie, eGFR < 60 mL/min/1.73 m^2).[17] Glomerular filtration rate was estimated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation.[18] Serum creatinine assessment using the modified Jaffé method was performed during the participants' sixth examination cycle. To reduce potential inter-laboratory variability, a 2-step calibration process for serum creatinine was used: a correction factor of 0.23 mg/dL (20.33 umol/L) was applied to National Health and Nutritional Examination Survey III (NHANES III) creatinine values to align them with the Cleveland Clinic Laboratory. Our serum creatinine values were then calibrated to the age- and sex-specific mean values for serum creatinine levels from NHANES III as previously described.[19]

Covariate Assessment

Fasting blood samples were used for the measurement of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides and blood glucose. Systolic and diastolic blood pressure measurements were taken as the mean of 2 physician readings using a mercury sphygmomanometer during the sixth examination. Hypertension was defined as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, and/or use of antihypertensive medications. Self-reported use of medication for hypertension was recorded during the sixth examination. The pulse pressure was calculated as the systolic pressure minus the diastolic pressure. The mean arterial pressure was calculated as midpoint between the systolic and diastolic pressures. Body mass index was defined as an individual's weight in kilograms divided by their height in meters squared. Waist circumference was measured at the level of the umbilicus while the participant was standing. Diabetes was defined as fasting blood glucose of 126 mg/dL or greater (7 mmol/L) or use of medication for the treatment of diabetes. Impaired fasting glucose was defined as a fasting blood glucose of 100 mg/dL to 125 mg/dL among participants not being treated for diabetes.

Statistical Methods

The distribution of demographic characteristics and cardiovascular risk factors between the 192 participants who developed albuminuria over 9.5 years of follow-up and the 1724 participants who remained free of albuminuria over this same period was illustrated using standard descriptive statistics: chi-Square test for dichotomous and analysis of variance for continuous variables. We performed step-wise regression analysis with age and sex forced into the model to determine the most parsimonious set of predictors associated with incident albuminuria. Stepwise regression models were constructed that contained the following potential predictor variables: Systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse pressure, glucose, diabetes, impaired fasting glucose, total-, LDL- and HDL-

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

cholesterol, triglycerides, body mass index, waist circumference, waist to hip ratio, smoking status, baseline CKD and baseline urinary albumin-creatinine ratio levels. Inclusion of the preceding potential predictors in the final model required a p-value of <0.05.

Three separate subgroup analyses were performed where participants with baseline CKD, hypertension and diabetes were excluded from the model and the stepwise procedure was repeated as described above.

SAS, version 9.1 (SAS Institute, www.sas.com), was used to perform all analyses; a 2-tailed P<0.05 was considered statistically significant.

Results

Baseline participant characteristics

At baseline, the sample was on average 56 years of age and 54% were women. Participants who subsequently developed albuminuria tended to be older (61 vs. 56 years) and 60% were men. They were also more likely to have hypertension and diabetes (Table 1). UACR values ranged from 10 mg/g to 2901 mg/g and 8 people (0.4%) developed albuminuria >300mg/day during follow-up.

Overall, 34% of participants (n=1,214) did not return for the follow-up visit. These participants were generally older (63 vs. 57 years; p<0.001), had higher rates of hypertension (50 vs. 34 %; p=0.02) and hypertension treatment (35 vs. 22%; p=0.03), higher systolic blood pressure (133 vs. 126 mmHg; p-value=0.04) and were more likely to smoke (20 vs. 13 %; p<0.001). Their rates of diabetes (12 vs. 6 %; p-value=0.003) and chronic kidney disease (14 vs. 4 %; p-value=0.04) were also higher, their mean HDL-cholesterol concentrations were lower (49 vs. 52 mg/dL; p-value<0.001) and they were more likely to die during the examination interval (34 vs. 0 %; p-value<0.001).

Predictors of incident albuminuria

During a median follow-up period of 9.5 years, albuminuria developed in 10.0% (n=192) of the 1916 participants. Results of the stepwise regression model showed that baseline diabetes (odds ratio [OR], 1.93; p-value=0.01), current smoking (OR, 2.09; p-value<0.001) and baseline log UACR (OR per standard deviation increase in log UACR, 1.56; p-value <0.001) were associated with incident albuminuria (Table 2). An inverse relationship with HDL cholesterol was also observed (OR for each standard deviation increment in HDL cholesterol, 0.80; p-value<0.001). Results were similar when modeled to identify predictors of albuminuria as a continuous variable, and when participants who developed new-onset hypertension (n=473) or new-onset diabetes mellitus (n=127) during the follow-up period were excluded.

Subgroup analyses

In the first of three subgroup analyses, participants with diabetes at baseline were excluded from the model (n= 107). Age, male sex, smoking, HDL cholesterol and baseline UACR all continued to correlate with incident albuminuria (Table 3). In the second subgroup analysis, participants with hypertension at baseline were excluded (n = 651, Table 3). Log UACR continued to be associated with incident albuminuria, but the association with DM and HDL cholesterol was no longer significant in this subset. Finally, participants with baseline CKD, defined as an eGFR < 60ml/min/1.73 m^2, were excluded (n=102); DM, smoking, HDL cholesterol and baseline UACR all correlated with incident albuminuria (Table 3).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Discussion

We have identified increasing age, male sex, diabetes mellitus, smoking, urinary albumin excretion within the "normal range" and low HDL-cholesterol as predictors of incident albuminuria in the general population. These observations are consistent across sub-groups without diabetes and CKD.

Diabetic kidney disease is the most common cause of end-stage kidney disease in the United States, Europe and Japan,[20] and the first sign of kidney involvement in diabetes is often albuminuria. Observational studies estimate the prevalence of albuminuria amongst people with type 2 diabetes to be as high as 39%.[5] Furthermore, impaired glucose tolerance[21] and sub-diabetic glycemia[22] have been shown in association with increased prevalence of albuminuria in cross-sectional studies of the general population. Data from double-blind randomized controlled trials have demonstrated that pharmacologic interventions which lower levels of urinary albumin excretion are associated with delayed progression to diabetic nephropathy.[23, 24] In light of this, our results are consistent with the prior literature that diabetes is a predictor of incident albuminuria. Those individuals with diabetes at baseline were almost twice as likely to develop albuminuria after ten years of follow-up, although this odds ratio is lower than that reported for new-onset kidney disease[19] or ESRD.[25] This difference may be due in part to the fact that increased urinary albumin excretion is a common, but not universal finding in diabetic nephropathy.[26] Finally, predictors of incident albuminuria were similar after excluding prevalent chronic kidney disease from the analysis model, suggesting these two entities are etiologically distinct.

Low HDL cholesterol levels are associated with progression from microalbuminuria to macroalbuminuria in diabetes,[27] but the relationship at disease outset is less clear. A recent analysis of lipid abnormalities and incident kidney disease demonstrated higher total cholesterol, non-HDL-cholesterol, triacylglycerol, apolipoprotein AII (Apo-AII) and Apo-B and Apo-B/Apo-AI and triacylglycerol/HDL-cholesterol ratios (but not HDL-cholesterol alone) at baseline increased the risk of incident albuminuria in a prospective cohort of people with type 1 diabetes.[28] However, in multivariable analysis, high (not low) HDL subfraction 3 (HDL_3) was predictive of incident albuminuria. Similarly, low HDL cholesterol was not a correlate of incident albuminuria in a longitudinal study of dyslipidemia and abnormal urinary albumin excretion in adolescents with type 1 diabetes.[29] The present study contrasts with these findings, and extends our knowledge, in that it identifies low HDL cholesterol as an independent predictor of incident albuminuria in a community-based population, even after participants with diabetes were excluded from the analysis.

Cigarette smoking has been associated with development of persistent albuminuria[30, 31] as well as overt nephropathy[31] in people with diabetes. However, the relationship in those without diabetes is less clear. Cross-sectional analyses of individuals free of diabetes in Europe and Asia demonstrated an increased likelihood of albuminuria in cigarette smokers and suggested a dose-dependant relationship.[32–34] However, a subsequent longitudinal analysis in the PREVEND study demonstrated no association between smoking and progression of albuminuria, nor between smoking cessation and regression of albuminuria.[35] The present work helps better define the longitudinal relationship between smoking and incident albuminuria, demonstrating an association between the two, independent of the effect of diabetes. We observed that smoking pack years was also associated with increased albuminuria risk, indicating a dose-dependent relationship. Furthermore, former smokers were also at increased risk in the present analysis.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

In susceptible people with diabetes, urinary albumin excretion appears to occur along a continuum, with individuals in the "high-normal" range at increased risk of developing incident albuminuria in later life.[36, 37] There is less known of the natural history of urinary albumin excretion in those without diabetes, but the available literature suggests that rates of urinary albumin excretion remain stable over time.[35, 38] The present work challenges this hypothesis by demonstrating a relationship between baseline urinary albumin excretion within the normal range and the later development of incident albuminuria in among individuals without diabetes. This observation was also demonstrable when individuals with chronic kidney disease or hypertension were excluded from the model.

Smoking may induce albuminuria through the formation of advanced glycation end products,[39] compounds shown to increase vascular permeability[40] and promote pathological vascular changes.[41] An alternate explanation is insulin resistance: smoking has been linked to insulin resistance in individuals without diabetes,[42, 43] and a correlation between the latter and albuminuria is seen in observational studies.[44] Proteinuria in diabetic kidney disease has been shown to occur by several mechanisms, including glomerular hyperfiltration, endothelial cell injury, diminished endothelial glycocalyx, altered VEGF (vascular endothelial growth factor) signaling, decreased negative charge and irregular thickening of the glomerular basement membrane, podocytopenia and foot process widening and effacement due to disruption of the actin cytoskeleton.[45]

There are several important implications of this work. First, the finding that baseline UACR predicts incident albuminuria in individuals without diabetes challenges the view that intra-individual urinary albumin excretion rates are static. In some, urinary albumin excretion in the upper "normal range" may represent an early manifestation of pathological urinary albumin leakage, and the current cut-offs used for the definition of albuminuria may not be valid, as has been suggested elsewhere.[46] Second, the finding that smoking is longitudinally correlated with incident albuminuria independent of diabetes supports the existence of glycemia-independent mechanisms of pathological albumin leakage. Finally, the observation that low HDL-cholesterol predicts incident albuminuria argues against altered lipolysis due to kidney disease as the cause of this lipid abnormality,[47] and implies a possible role for dyslipidemia in the pathogenesis of albuminuria.

It is notable that hypertension or systolic blood pressure was not an independent risk factor for incident albuminuria in our study. Whereas hypertension is strongly associated with albuminuria in longitudinal series of individuals with diabetes,[30, 37, 48] this has not been borne out in follow-up studies of the general population.[38, 49] Cross-sectional studies demonstrate an association between hypertension and urinary albumin,[50] and the urinary albumin excretion rate also appears to correlate with incremental levels of systolic blood pressure.[51] These observations may be explained by acute, hypertension-mediated hemodynamic changes at the glomerular level, hyperfiltration and reduced proximal tubular resorption of albumin.[52] The finding that treatment of hypertension is strongly associated with reduction, and even normalization, of urinary albumin excretion is consistent with this hypothesis.[38, 53]

There are several strengths to this study, including the well-characterized participants from the Framingham Heart Study, well-defined cardiovascular disease risk factors, and UACR present at two points in time. However, there are also several limitations. First, UACR was assessed on only a single urine specimen in our sample. Previous studies suggest that urinary albumin levels exhibit considerable intra-individual variability,[54] which could lead to misclassification. Despite this, national practice guidelines recommend the use of spot specimens for UACR due to ease of use and robust correlation with 24-hour collections.[14] Also, urine was stored at −20°C, as opposed to − 80°C, for between 1 month and 3 ½ years.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Freezing samples *per se* can result in an underestimation of urinary albumin by as much as 30%,[55] and freezing at − 80°C is believed to attenuate this degradation. However, this is effect is most pronounced when using HPLC-based assays, being less pronounced when using immunoassays as in this analysis.[55] Second, our sample was predominantly of European ancestry, limiting the generalizability of our results. Third, we did not have information on insulin resistance for the baseline exam cycle. This is pertinent, as insulin resistance is associated with the development of albuminuria.[61] Fourth, nearly one-third of participants did not return for the eighth exam cycle, with indication of a survival bias, potentially attenuating the observed risks associated with albuminuria. Finally, the Framingham Heart Study is an observational cohort, and causality cannot be inferred.

In conclusion, the known cardiovascular risk factors of increasing age, male sex, diabetes, current smoking, low HDL cholesterol and albuminuria within the "normal range" are correlates of incident albuminuria in the general population. Further research is necessary to illuminate the underlying mechanisms of the observations, and to establish whether the identified factors form part of the causal pathway of albuminuria.

Acknowledgments

Support: The Framingham Heart Study is supported by the National Heart, Lung, and Blood Institute (N01-HC-25195). Dr Meigs is supported by Career Development Awards from the American Diabetes Association Research Grant and the American Diabetes Association. Urinary albumin excretion assay reagents were donated by Roche Diagnostics Inc.

References

1. Hillege HL, Fidler V, Diercks GF, et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation. 2002 Oct 1; 106(14):1777–1782. [PubMed: 12356629]
2. Atkins RC. The epidemiology of chronic kidney disease. Kidney Int Suppl. 2005 Apr.(94):S14–S18. [PubMed: 15752232]
3. Hillege HL, Janssen WM, Bak AA, et al. Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. J Intern Med. 2001 Jun; 249(6):519–526. [PubMed: 11422658]
4. Romundstad S, Holmen J, Hallan H, Kvenild K, Ellekjaer H. Microalbuminuria and all-cause mortality in treated hypertensive individuals: does sex matter? The Nord-Trondelag Health Study (HUNT), Norway. Circulation. 2003 Dec 2; 108(22):2783–2789. [PubMed: 14623803]
5. Parving HH, Lewis JB, Ravid M, Remuzzi G, Hunsicker LG. Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: a global perspective. Kidney Int. 2006 Jun; 69(11):2057–2063. [PubMed: 16612330]
6. de Zeeuw D, Parving HH, Henning RH. Microalbuminuria as an early marker for cardiovascular disease. J Am Soc Nephrol. 2006 Aug; 17(8):2100–2105. [PubMed: 16825327]
7. Brantsma AH, Bakker SJ, de Zeeuw D, de Jong PE, Gansevoort RT. Urinary albumin excretion as a predictor of the development of hypertension in the general population. J Am Soc Nephrol. 2006 Feb; 17(2):331–335. [PubMed: 16434504]
8. Forman JP, Fisher ND, Schopick EL, Curhan GC. Higher levels of albuminuria within the normal range predict incident hypertension. J Am Soc Nephrol. 2008 Oct; 19(10):1983–1988. [PubMed: 18579639]
9. Bahrami H, Bluemke DA, Kronmal R, et al. Novel metabolic risk factors for incident heart failure and their relationship with obesity: the MESA (Multi-Ethnic Study of Atherosclerosis) study. J Am Coll Cardiol. 2008 May 6; 51(18):1775–1783. [PubMed: 18452784]
10. Verhave JC, Gansevoort RT, Hillege HL, Bakker SJ, De Zeeuw D, de Jong PE. An elevated urinary albumin excretion predicts de novo development of renal function impairment in the general population. Kidney Int Suppl. 2004 Nov.(92):S18–S21. [PubMed: 15485409]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

11. Brantsma AH, Bakker SJ, Hillege HL, de Zeeuw D, de Jong PE, Gansevoort RT. Urinary albumin excretion and its relation with C-reactive protein and the metabolic syndrome in the prediction of type 2 diabetes. Diabetes Care. 2005 Oct; 28(10):2525–2530. [PubMed: 16186291]
12. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham offspring study. Am J Epidemiol. 1979 Sep; 110(3): 281–290. [PubMed: 474565]
13. Dawber TR, Meadors GF, Moore FE Jr. Epidemiological approaches to heart disease: the Framingham Study. Am J Public Health Nations Health. 1951 Mar; 41(3):279–281. [PubMed: 14819398]
14. Eknoyan G, Hostetter T, Bakris GL, et al. Proteinuria and other markers of chronic kidney disease: a position statement of the national kidney foundation (NKF) and the national institute of diabetes and digestive and kidney diseases (NIDDK). Am J Kidney Dis. 2003 Oct; 42(4):617–622. [PubMed: 14520612]
15. Nathan DM, Rosenbaum C, Protasowicki VD. Single-void urine samples can be used to estimate quantitative microalbuminuria. Diabetes Care. 1987 Jul–Aug; 10(4):414–418. [PubMed: 3622198]
16. Mattix HJ, Hsu CY, Shaykevich S, Curhan G. Use of the albumin/creatinine ratio to detect microalbuminuria: implications of sex and race. J Am Soc Nephrol. 2002 Apr; 13(4):1034–1039. [PubMed: 11912263]
17. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002 Feb; 39 Suppl 1(2):S1–S266. [PubMed: 11904577]
18. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999 Mar 16; 130(6):461–470. [PubMed: 10075613]
19. Fox CS, Larson MG, Leip EP, Culleton B, Wilson PW, Levy D. Predictors of new-onset kidney disease in a community-based population. JAMA. 2004 Feb 18; 291(7):844–850. [PubMed: 14970063]
20. Boddana P, Caskey F, Casula A, Ansell D. UK Renal Registry 11th Annual Report (December 2008): Chapter 14 UK Renal Registry and international comparisons. Nephron Clin Pract. 2009; 111 Suppl 1:c269–c276. [PubMed: 19542702]
21. Franciosi M, Pellegrini F, Sacco M, et al. Identifying patients at risk for microalbuminuria via interaction of the components of the metabolic syndrome: a cross-sectional analytic study. Clin J Am Soc Nephrol. 2007 Sep; 2(5):984–991. [PubMed: 17702724]
22. Meigs JB, D'Agostino RB Sr, Nathan DM, Rifai N, Wilson PW. Longitudinal association of glycemia and microalbuminuria: the Framingham Offspring Study. Diabetes Care. 2002 Jun; 25(6):977–983. [PubMed: 12032102]
23. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001 Sep 20; 345(12): 861–869. [PubMed: 11565518]
24. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001 Sep 20; 345(12):870–878. [PubMed: 11565519]
25. Brancati FL, Whelton PK, Randall BL, Neaton JD, Stamler J, Klag MJ. Risk of end-stage renal disease in diabetes mellitus: a prospective cohort study of men screened for MRFIT. Multiple Risk Factor Intervention Trial. JAMA. 1997 Dec 17; 278(23):2069–2074. [PubMed: 9403420]
26. Thomas MC, Macisaac RJ, Jerums G, et al. Nonalbuminuric renal impairment in type 2 diabetic patients and in the general population (national evaluation of the frequency of renal impairment cO-existing with NIDDM [NEFRON] 11). Diabetes Care. 2009 Aug; 32(8):1497–1502. [PubMed: 19470839]
27. Tolonen N, Forsblom C, Thorn L, et al. Lipid abnormalities predict progression of renal disease in patients with type 1 diabetes. Diabetologia. 2009 Oct 10.
28. Tolonen N, Forsblom C, Thorn L, et al. Lipid abnormalities predict progression of renal disease in patients with type 1 diabetes. Diabetologia. 2009 Dec; 52(12):2522–2530. [PubMed: 19816673]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

29. Marcovecchio ML, Dalton RN, Prevost AT, et al. Prevalence of abnormal lipid profiles and the relationship with the development of microalbuminuria in adolescents with type 1 diabetes. Diabetes Care. 2009 Apr; 32(4):658–663. [PubMed: 19171721]
30. Microalbuminuria Collaborative Study Group, United Kingdom. Risk factors for development of microalbuminuria in insulin dependent diabetic patients: a cohort study. BMJ. 1993 May 8; 306(6887):1235–1239. [PubMed: 8499853]
31. Rossing P, Hougaard P, Parving HH. Risk factors for development of incipient and overt diabetic nephropathy in type 1 diabetic patients: a 10-year prospective observational study. Diabetes Care. 2002 May; 25(5):859–864. [PubMed: 11978681]
32. Ishizaka N, Ishizaka Y, Toda E, et al. Association between cigarette smoking and chronic kidney disease in Japanese men. Hypertens Res. 2008 Mar; 31(3):485–492. [PubMed: 18497468]
33. Pinto-Sietsma SJ, Mulder J, Janssen WM, Hillege HL, de Zeeuw D, de Jong PE. Smoking is related to albuminuria and abnormal renal function in nondiabetic persons. Ann Intern Med. 2000 Oct 17; 133(8):585–591. [PubMed: 11033585]
34. Cirillo M, Senigalliesi L, Laurenzi M, et al. Microalbuminuria in nondiabetic adults: relation of blood pressure, body mass index, plasma cholesterol levels, and smoking: The Gubbio Population Study. Arch Intern Med. 1998 Sep 28; 158(17):1933–1939. [PubMed: 9759691]
35. Brantsma AH, Atthobari J, Bakker SJ, de Zeeuw D, de Jong PE, Gansevoort RT. What predicts progression and regression of urinary albumin excretion in the nondiabetic population? J Am Soc Nephrol. 2007 Feb; 18(2):637–645. [PubMed: 17215442]
36. Murussi M, Campagnolo N, Beck MO, Gross JL, Silveiro SP. High-normal levels of albuminuria predict the development of micro- and macroalbuminuria and increased mortality in Brazilian Type 2 diabetic patients: an 8-year follow-up study. Diabet Med. 2007 Oct; 24(10):1136–1142. [PubMed: 17561963]
37. The Microalbuminuria Collaborative Study Group. Predictors of the development of microalbuminuria in patients with Type 1 diabetes mellitus: a seven-year prospective study. Diabet Med. 1999 Nov; 16(11):918–925. [PubMed: 10588521]
38. Solbu MD, Kronborg J, Eriksen BO, Jenssen TG, Toft I. Cardiovascular risk-factors predict progression of urinary albumin-excretion in a general, non-diabetic population: a gender-specific follow-up study. Atherosclerosis. 2008 Dec; 201(2):398–406. [PubMed: 18405901]
39. Cerami C, Founds H, Nicholl I, et al. Tobacco smoke is a source of toxic reactive glycation products. Proc Natl Acad Sci U S A. 1997 Dec 9; 94(25):13915–13920. [PubMed: 9391127]
40. Vlassara H, Fuh H, Makita Z, Krungkrai S, Cerami A, Bucala R. Exogenous advanced glycosylation end products induce complex vascular dysfunction in normal animals: a model for diabetic and aging complications. Proc Natl Acad Sci U S A. 1992 Dec 15; 89(24):12043–12047. [PubMed: 1465438]
41. Brownlee M, Cerami A, Vlassara H. Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. N Engl J Med. 1988 May 19; 318(20):1315–1321. [PubMed: 3283558]
42. Janzon L, Berntorp K, Hanson M, Lindell SE, Trell E. Glucose tolerance and smoking: a population study of oral and intravenous glucose tolerance tests in middle-aged men. Diabetologia. 1983 Aug; 25(2):86–88. [PubMed: 6354814]
43. Facchini FS, Hollenbeck CB, Jeppesen J, Chen YD, Reaven GM. Insulin resistance and cigarette smoking. Lancet. 1992 May 9; 339(8802):1128–1130. [PubMed: 1349365]
44. Forsblom CM, Eriksson JG, Ekstrand AV, Teppo AM, Taskinen MR, Groop LC. Insulin resistance and abnormal albumin excretion in non-diabetic first-degree relatives of patients with NIDDM. Diabetologia. 1995 Mar; 38(3):363–369. [PubMed: 7758885]
45. Jefferson JA, Shankland SJ, Pichler RH. Proteinuria in diabetic kidney disease: a mechanistic viewpoint. Kidney Int. 2008 Jul; 74(1):22–36. [PubMed: 18418356]
46. Forman JP, Brenner BM. 'Hypertension' and 'microalbuminuria': the bell tolls for thee. Kidney Int. 2006 Jan; 69(1):22–28. [PubMed: 16374419]
47. Lee DM, Knight-Gibson C, Samuelsson O, Attman PO, Wang CS, Alaupovic P. Lipoprotein particle abnormalities and the impaired lipolysis in renal insufficiency. Kidney Int. 2002 Jan; 61(1):209–218. [PubMed: 11786103]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

48. Xu J, Lee ET, Devereux RB, et al. A longitudinal study of risk factors for incident albuminuria in diabetic American Indians: the Strong Heart Study. Am J Kidney Dis. 2008 Mar; 51(3):415–424. [PubMed: 18295057]

49. Pascual JM, Rodilla E, Gonzalez C, Perez-Hoyos S, Redon J. Long-term impact of systolic blood pressure and glycemia on the development of microalbuminuria in essential hypertension. Hypertension. 2005 Jun; 45(6):1125–1130. [PubMed: 15897369]

50. Janssen WM, Hillege H, Pinto-Sietsma SJ, Bak AA, De Zeeuw D, de Jong PE. Low levels of urinary albumin excretion are associated with cardiovascular risk factors in the general population. Clin Chem Lab Med. 2000 Nov; 38(11):1107–1110. [PubMed: 11156337]

51. Verhave JC, Hillege HL, Burgerhof JG, Navis G, de Zeeuw D, de Jong PE. Cardiovascular risk factors are differently associated with urinary albumin excretion in men and women. J Am Soc Nephrol. 2003 May; 14(5):1330–1335. [PubMed: 12707402]

52. Lazzara MJ, Deen WM. Model of albumin reabsorption in the proximal tubule. Am J Physiol Renal Physiol. 2007 Jan; 292(1):F430–F439. [PubMed: 16954345]

53. Asselbergs FW, Diercks GF, Hillege HL, et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation. 2004 Nov 2; 110(18):2809–2816. [PubMed: 15492322]

54. Cohen DL, Close CF, Viberti GC. The variability of overnight urinary albumin excretion in insulin-dependent diabetic and normal subjects. Diabet Med. 1987 Sep–Oct; 4(5):437–440. [PubMed: 2959434]

55. Brinkman JW, de Zeeuw D, Lambers Heerspink HJ, et al. Apparent loss of urinary albumin during long-term frozen storage: HPLC vs immunonephelometry. Clin Chem. 2007 Aug; 53(8):1520–1526. [PubMed: 17573417]

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 1

Baseline characteristics of study participants by albuminuria at follow-up*

Characteristic	Albuminuria at follow-up**		P value***
	No (n=1724)	Yes (n=192)	
Age (years)	56 (9)	61 (9)	<0.001
% Women	55.1 (949)	40.1 (77)	<0.001
Hypertension (%)	32.7 (563)	45.8 (88)	0.4
Systolic BP (mmHg)	125(17)	132(20)	0.07
Diastolic BP (mmHg)	75	76	0.4
Mean arterial pressure, mmHg	92	95	0.1
Pulse pressure, mmHg	50	55	0.07
Hypertension treatment (%)	20.9 (361)	32.8 (63)	0.2
Diabetes status (%)	4.8 (83)	12.5 (24)	0.008
Fasting glucose	99 (19)	107 (30)	0.002
Impaired fasting glucose(%)	30	35	0.9
Total Cholesterol, (mg/dl)	206	205	0.6
HDL Cholesterol (mg/dl)	52(16)	47(15)	0.004
LDL Cholesterol, (mg/dl)	127	130	0.6
Triglycerides§, (mg/dl)	111(78,164)	127(90,187)	0.3
Current smoking (%)	12.7 (218)	17.2 (33)	0.001
Former smokers (%)§§	38	48	0.3
Smoking, pack years	12.7	23.5	<0.001
Body mass index	27.7(5.0)	28.6(5.0)	0.08
Waist circumference, (cm)	38	39	0.3
Waist-to-hip ratio	0.92	0.96	0.2
Baseline UACR (mg/g)§	4.7 (2.1, 8.8)	6.1 (2.9, 12.1)	<0.001
Baseline eGFR ml/min/1.73m^2	90(23)	89(29)	0.07
Baseline CKD (%)	4.9 (84)	9.4 (18)	0.1

*Data presented mean with standard deviation in parenthesis for continuous variables or percent (no.) for categorical data

**Albuminuria defined using the sex-specific cut-points of UACR >17 mg/g (men) or > 25 mg/g (women)

***Age and sex adjusted, except age (which is sex adjusted) and sex (which is age adjusted)

Conversion factors for units: LDL, total, and HDL cholesterol in mg/dL to mmol/L, × 0.02586; triglycerides in mg/dL to mmol/L, × 0.01129; eGFR mL/min/1.73 m^2 to mL/s/1.73 m^2, × 0.01667; glucose in mg/dL to mmol/L × 0.055

§Data shown as median (25th, 75th percentiles)

BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein; UACR, urinary albumin-creatinine ratio

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 2

Correlates of incident albuminuria after 9.5 years of follow-up*

Characteristic	OR (95% CI)	P-value
Age (per decade increase)	2.09 (1.73, 2.53)	<0.001
Sex (Women vs Men)	0.53 (0.39, 0.73)	<0.001
Diabetes status (yes vs. no)	1.93 (1.15, 3.23)	0.01
HDL cholesterol (per 1 SD increase)**	0.80 (0.68, 0.94)	0.007
Current smoking (yes vs. no)	2.09 (1.36, 3.22)	<0.001
Log UACR (per 1-SD increase)***	1.56 (1.26, 1.92)	<0.001

* Step-wise analysis included: Systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse pressure, diabetes, impaired fasting glucose, glucose, Total-, LDL- and HDL-cholesterol, triglycerides, body mass index, waist circumference, waist to hip ratio, smoking status, baseline CKD and baseline urinary albumin-creatinine ratio (UACR) levels; table presents results with p-value < 0.05

** Sex-specific HDL standard deviation is 15.8 mg/dl in women and 12.1 mg/dl in men

*** Sex-specific SD for log UACR was 1.3 in women and 1.5 in men

Conversion factors for units: HDL cholesterol in mg/dL to mmol/L, × 0.02586;

Abbreviations: CI, confidence interval; HDL, high density lipoprotein; OR, Odds Ratio; UACR, urinary albumin-creatinine ratio; LDL, low-density lipoprotein

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 3

Subgroup analyses of incident albuminuria

Characteristic	OR (95% CI)	P-value
No diabetes at baseline (n=1809; 168 cases)		
Age (per 10 year increase)	2.01 (1.65, 2.45)	<0.001
Sex (Women vs men)	0.56 (0.40, 0.78)	<0.001
HDL cholesterol (per 1 SD increase)*	0.78 (0.65, 0.93)	0.006
Current smoking (Yes vs. no)	1.91 (1.21, 2.99)	0.005
Log UACR (per 1 SD increase)**	1.45 (1.17, 1.79)	<0.001
No hypertension at baseline (n=1265; 104 cases)		
Age (per 10 year increase)	1.86 (1.47, 2.37)	<0.001
Sex (Women vs men)	0.60 (0.40, 0.91)	0.02
Log UACR (per 1 SD increase)**	1.51 (1.15, 1.98)	0.003
No CKD at baseline (n=1814; 174 cases)		
Age (per 10 year increase)	2.08 (1.70, 2.54)	<0.001
Sex (Women vs men)	0.52 (0.37, 0.72)	<0.001
Diabetes (Yes vs. no)	2.05 (1.21, 3.49)	0.008
HDL cholesterol (per 1 SD increase)*	0.72 (0.60, 0.86)	<0.001
Current smoking (Yes vs. no)	2.12 (1.35, 3.33)	0.001
Log UACR (per 1 SD increase)**	1.52 (1.22, 1.89)	<0.001

* Sex-specific HDL standard deviation is 15.8 mg/dl in women and 12.1 mg/dl in men

** Sex-specific SD for log UACR was 1.3 in women and 1.5 in men

Abbreviations: CKD, chronic kidney disease; CI, confidence interval; HDL, high density lipoprotein; OR, Odds Ratio; UACR, urinary albumin-creatinine ratio