

ELEVATED BLOOD PRESSURE IS NOT ASSOCIATED WITH ACCELERATED GFR DECLINE IN THE GENERAL NON-DIABETIC MIDDLE-AGED POPULATION

Bjørn O. Eriksen MD PhD^{1,3}, Vidar T. N. Stefansson MD¹, Trond G. Jenssen MD PhD^{1,4}, Ulla D. Mathisen MD PhD^{1,3}, Jørgen Schei MD¹, Marit D. Solbu MD PhD^{1,3}, Tom Wilsgaard PhD²,
Toralf Melsom MD PhD^{1,3}

¹Metabolic and Renal Research Group, ²Dept. of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway; ³Section of Nephrology, University Hospital of North Norway, Tromsø; ⁴Oslo University Hospital, Oslo, Norway

Corresponding author: Bjørn Odvar Eriksen, Phone: +47 466 82 780; e-

mail: bjorn.odvar.eriksen@unn.no

Word count: 3017

Sources of support: This study was funded by the Northern Norway Regional Health Authority, UiT The Arctic University of Norway and by a grant from Boehringer-Ingelheim.

Running headline: Blood pressure and GFR decline

Abstract

Although hypertension is a risk factor for end-stage renal disease, this complication develops in only a minority of hypertensive patients. Whether non-malignant hypertension itself is sufficient to cause reduced glomerular filtration rate (GFR) is unclear. We investigated whether elevated blood pressure (BP) was associated with accelerated GFR decline in the general population. The study was based on the Renal Iohexol-clearance Survey in Tromsø 6 (RENIS-T6), which included a representative sample of 1594 subjects aged 50 to 62 years from the general population without baseline diabetes, kidney or cardiovascular disease. GFR was measured as iohexol clearance at baseline and follow-up after a median observation time of 5.6 years. BP was measured according to a standardized procedure. The mean (standard deviation) GFR decline rate was 0.95 (2.23) mL/min/year. In multivariable adjusted linear mixed regressions with either baseline systolic or diastolic BP as the independent variable, there were no statistically significant associations with GFR decline. We conclude that elevated BP is not associated with accelerated mean GFR decline in the general middle-aged population. Additional genetic and environmental factors are probably necessary for elevated BP to develop manifest chronic kidney disease in some individuals.

Keywords: hyperfiltration, chronic kidney disease, cardiovascular disease, obesity

Introduction

Hypertension is a risk factor for end-stage renal disease (ESRD)¹⁻⁴ and is the second most important cause of ESRD in the U.S.⁵ However, the incidence of ESRD is low relative to the high prevalence of hypertension. This indicates that hypertensive individuals may have a different susceptibility for developing kidney failure. In people without baseline chronic kidney disease (CKD) or diabetes, randomized controlled trials have not shown an effect of antihypertensive treatments on renal outcomes.⁶⁻⁸

These observations have led some investigators to question whether non-malignant hypertension is indeed a sufficient cause of CKD, which would entail an association between elevated blood pressure (BP) and accelerated GFR decline at the population level.^{9, 10} The results of studies of the relationship between BP and the rate of glomerular filtration rate (GFR) decline in the general population have not been consistent. Although several studies have found that higher BP accelerated GFR decline,¹¹⁻¹⁷ some have found that hypertension was associated with elevated GFR or hyperfiltration.¹⁸⁻²³ The difficulty of measuring GFR in the near-normal range with sufficient precision is probably the most important explanation for the lack of evidence in this field.²⁴ Estimates of GFR based on creatinine or cystatin C are both inaccurate in the near-normal range and known to be confounded by non-GFR factors.²⁵⁻²⁷

Iohexol clearance is recognized as a precise method for measuring GFR.²⁸ We have previously measured GFR as iohexol clearance in a representative sample of the general middle-aged population in the Renal Iohexol-clearance Survey in Tromsø 6 (RENIS-T6). To our knowledge, this study has been the largest population-based cohort with GFR measurements.²⁹ These measurements have now been repeated in the same cohort as a part of the RENIS Follow-up Study (RENIS-FU). The aim of this longitudinal study was to investigate whether there was an

association between elevated baseline BP and accelerated decline in GFR between baseline and follow-up.

Results

In the present investigation, 1299 (81%) of the 1594 participants in the baseline cohort had a follow-up GFR measurement after a median (IQR) observation time of 5.63 years (5.23 – 6.03) (Figure 1). A total of 87 subjects had a repeated follow-up measurement of GFR. The mean coefficient of variation (95% confidence interval) for the intra-individual GFR variation was 4.2% (3.4% - 4.9%).

Except for body weight, fasting triglycerides, mean arterial pressure (MAP) and the use of “other antihypertensives”, all of the characteristics changed between the baseline and follow-up investigations ($p < 0.05$) (Table 1). The most important changes were increases in the percentages of subjects receiving antihypertensives (from 17.5 to 31.2%) or lipid lowering treatments (from 6.1 to 17.0%). Comparisons of the baseline characteristics of those included in the follow-up study and those lost to follow-up are shown in Supplementary Table S1. The differences were small, except for the percentage of current smokers (18 vs. 28, $p < 0.001$).

The unadjusted mean (SD) rate of change for the absolute GFR in the study period was -0.95 (2.23) mL/min/year and was -0.84 (2.00) mL/min/1.73 m²/year for the GFR standardized to body surface area. A negative change signifies a decline in GFR. The unadjusted change rates according to change in MAP (lower or unchanged vs. higher) and change in antihypertensive medication (yes/no) are shown in Table 2. Subjects with an increase in MAP from baseline to follow-up had a slower unadjusted decline in GFR ($p = 0.007$). The unadjusted GFR decline was steeper in participants using antihypertensive treatments both at baseline and follow-up than in participants who had never used antihypertensive medication ($p = 0.006$) (Table 2). Subjects with lower or unchanged MAP had a mean (SD) body weight loss of 1.1 (4.8) kg between baseline and follow-up (from a mean body weight of 81.2 to 80.1 kg), whereas those with an increase in

MAP had a mean weight gain of 0.8 (4.2) kg (from a mean body weight of 77.5 to 78.4 kg) ($p < 0.001$ for the difference in weight change between the MAP groups).

When the GFR change rate was assessed in the linear mixed model using baseline values of BP and the adjustment variables, none of the BP components was associated with GFR decline (Table 3). There were no statistically significant non-linear relationships between the BP components and GFR rate of change when fractional polynomial transformations were tested in the fully adjusted models.

Subgroup analyses for subjects with hypertension at baseline and/or follow-up, with normotension at both baseline and follow-up, without self-reported heart disease, without albuminuria (ACR less than 1.92 mg/mmol for men and 2.83 mg/mmol for women) or with GFR greater than 60 ml/min/1.73 m² were performed (Supplementary Table S2 and S3). The results were essentially the same as shown in Model 2 in Table 3, i.e. there was no statistically significant association between BP components and GFR decline in any of these subgroups.

The relationships between baseline BP components and GFR decline assessed by body-surface adjusted measured GFR (GFR_{BSA}), $eGFR_{crea}$ and $eGFR_{cys}$ are shown in Supplementary Table S4. The same models and adjustments as in Table 3 were used. In the fully adjusted models, there were statistically significant negative relationships between baseline SBP, DBP and MAP and change in $eGFR_{crea}$, but not $eGFR_{cys}$ or GFR_{BSA} .

Discussion

We did not find an association between accelerated GFR decline and elevated baseline BP (Table 3). To our knowledge, the present study is the first investigation of the association between BP and the GFR change rate in the general population using actual measurements of GFR. However, several investigators have studied changes in serum creatinine, estimated GFR or creatinine clearance.^{11-17, 30} The results across these trials have not been consistent. Most of them have found a faster GFR decline with higher BP, but there has been considerable variation in which BP components have been reported.¹¹⁻¹⁷ In fully adjusted models, the present study also found statistically significant negative associations between baseline BP components and the eGFR_{crea} change rate, which were not confirmed when change rates were calculated from eGFR_{cys} or iohexol clearance (Table S4). Few of previous studies excluded subjects with cardiovascular disease or diabetes, or presented analyses that adjusted for these conditions.^{11, 13, 15, 16} None of the studies adjusted for individual classes of antihypertensive medications.

Our finding of a lack of association between elevated baseline BP and a steeper GFR decline runs contrary to the results of observational studies that have demonstrated that hypertension is a risk factor for both ESRD^{1, 2} and less severe CKD.³¹⁻³⁵ There are at least two possible explanations for this apparent paradox. First, there may not be a contradiction between the lack of an association between BP and the mean GFR change rate and its association with progressive nephropathy in a minority. There is little doubt that elevated BP is an important contributing risk factor for progressive CKD, but additional genetic or environmental factors are probably necessary. Secondly, there is evidence that renal hyperfiltration, i.e., abnormally elevated GFR, is an early phase of hypertensive nephropathy, similar to what is observed in diabetic nephropathy. Cross-sectional studies have found associations between BP and elevated GFR both in hypertensive patients¹⁸⁻²¹ and in the general population.²² A longitudinal study found a

greater increase in serum creatinine after 6 years in hypertensive patients with the highest creatinine clearance at baseline.²³

The most important strength of the present study is its use of measured GFR in a population representative of the general middle-aged population rather than using GFR estimated from creatinine or cystatin C. The conclusions of this study would have been different if it had been based on $eGFR_{crea}$ instead of measured GFR (Table S4). The different results from $eGFR_{crea}$ may have been caused by the influence of non-GFR factors on creatinine or from reduced precision of $eGFR_{crea}$ in the normal range.²⁵⁻²⁷ Another strength was that confounding from comorbid conditions was limited by excluding subjects with diabetes or cardiovascular disease at baseline. Because we obtained three GFR measurements from a random subset of subjects, state-of-the-art linear mixed models rather than ordinary linear regression could be used for the analyses.³⁶ The intraindividual variation in the GFR measurements calculated from this subset was lower than in most previous studies and indicates a low level of measurement error.^{25, 37} The repeated follow-up measurements were included in the linear mixed models and allowed adjustment for intraindividual variation in the analyses.³⁸ However, only two measurements for most of the subjects limit the precision of estimates and preclude the study of individual non-linear GFR trajectories. The study design was chosen as a compromise between the need to use actual measurements of GFR and the willingness of subjects to undergo repeated time-consuming examinations during the six year follow-up.

Since assessment of GFR change depends critically on the repeatability of the measurement method over time, we reanalyzed frozen samples to correct for drift (see Methods). The process of obtaining samples, preanalytic procedures and HPLC-analysis involves several steps that could have changed slightly over nearly six years. We calibrated the baseline measurements, but cannot exclude the possibility that the drift may have introduced random error which may have diluted our estimates and reduced statistical power.

The principal limitation of the study was that it is not possible to draw firm conclusions about causality from an observational study. However, our results do not support the hypothesis that elevated BP causes a steeper mean GFR decline in the general population. In addition to showing no statistically significant associations, the lower limits of the confidence intervals for the baseline BP regression coefficients in the fully adjusted models were greater than most estimates reported in previous studies (Table 3).^{11, 13, 14, 16, 17}

Because only middle-aged Caucasians were included, caution should be exercised when generalizing the results to other age groups and ethnic groups.

We conclude that elevated BP is not associated with an accelerated mean GFR decline in the general middle-aged population, and that our findings do not support the hypothesis of non-malignant high BP as a sufficient cause of faster GFR decline. Additional risk factors are probably necessary for the development of manifest hypertensive nephropathy. Studies with an even longer observation period and repeated measurements of GFR are needed to fully evaluate the effect of BP on kidney function.

Methods

Study population

This investigation is a follow-up study of RENIS-T6.²⁹ RENIS-T6 included a representative sample of 1627 people between 50 and 62 years of age from the general population without self-reported kidney disease, myocardial infarction, stroke or diabetes in the municipality of Tromsø in Northern Norway. Baseline GFR was measured by iohexol-clearance between October 2007 and June 2009. The cohort has been previously described in detail.²⁹ In the present investigation, 33 subjects who satisfied biochemical criteria for diabetes (fasting glucose ≥ 7.0 mmol/L and/or hemoglobin A1c $\geq 6.5\%$) at baseline were excluded, leaving 1594 subjects. Ten subjects with missing data for baseline hemoglobin A1c who all had fasting glucose < 7.0 mmol/L, were not excluded. RENIS-FU included subjects with a follow-up measurement of GFR between September 2013 and January 2015. All of the participants in the baseline study were invited except for 23 subjects who had died and 7 who had suffered a possible delayed allergic reaction to iohexol at baseline, leading to 1564 total people eligible (Figure 1). A random sample was invited to a repeated follow-up investigation to obtain a subset of subjects with three GFR measurements, necessary for analysis with a linear mixed regression model with random intercept and slope. This study was approved by the Norwegian Data Inspectorate and the Regional Committee for Medical and Health Research Ethics of North Norway. The study adhered to the Declaration of Helsinki, and all subjects provided written consent.

Data

Both of the baseline and follow-up investigations were conducted in the Clinical Research Unit at the University Hospital of North Norway. On both occasions, the assessments included a health questionnaire with questions on alcohol and tobacco use and all current medications.

Alcohol use was coded as 1 for the use of alcohol more than once a week and 0 otherwise.

Tobacco use was coded as the number of cigarettes currently smoked daily.

Measurements

Iohexol Clearance

GFR was measured at baseline and follow-up using single-sample plasma clearance of iohexol.

This method has been validated against gold standard methods for measuring GFR.^{37, 39-41} The procedure used in RENIS-FU was the same as in the baseline RENIS-T6, which has previously been described in detail²⁹. The investigation was rescheduled for subjects suffering from any acute illness.

To adjust for a possible drift in the method between baseline and follow-up, a 6% random sample of blood samples from the baseline investigation previously frozen at -80° C were thawed. The older iohexol samples were randomly distributed among the newer RENIS-FU samples throughout the study period and were simultaneously analyzed. The mean difference in the GFR between follow-up and baseline was 2.28 mL/min/1.73 m² (95% confidence interval 1.05 to 3.51). All of the baseline GFR measurements reported in this study were adjusted by adding this constant to the original measurements. In a linear regression model with the GFR difference as the dependent variable and the baseline variables of the fully adjusted model described below (Model 2) as the independent variables, there was no statistically significant relationship between the difference and these variables ($F_{19,84} = 1.12$, $p=0.35$).

To investigate intra-individual variation in the GFR measurements, we obtained a repeated measurement after two weeks and within two months from a 5.5% random sample of the subjects in the follow-up study.

Other measurements

The procedure for BP measurements has been described previously.⁴² Subjects with systolic BP (SBP) ≥ 140 mmHg, diastolic BP (DBP) ≥ 90 mmHg, or using antihypertensive medications were categorized as having hypertension. Mean pulse pressure (PP) was defined as SBP minus DBP. Mean arterial pressure (MAP) was defined as DBP plus one-third of the PP. Fasting serum glucose, creatinine, cystatin C, triglycerides, and LDL- and HDL-cholesterol, hemoglobin A1C and the urine albumin-creatinine ratio (ACR) were measured with standard methods as described previously.^{42, 43} Serum creatinine was measured using an enzymatic assay standardized to the isotope dilution mass spectroscopy method (CREA Plus, Roche Diagnostics, GmbH, Mannheim, Germany). Cystatin C was measured by a particle-enhanced turbidimetric immunoassay (Gentian, Moss, Norway) and calibrated to the international reference ERM-DA471/IFCC as previously described.⁴⁴ Estimated GFR (eGFR) was calculated from creatinine or cystatin C using the Chronic Kidney Disease Epidemiology Collaboration equations (eGFR_{crea} and eGFR_{cys}).²⁴

Statistical methods

Mean (standard deviation (SD)) or median (interquartile range (IQR)) for skewed variables were used for descriptive statistics. Differences between subjects in the follow-up investigation and those lost to follow-up were tested with two-sample t-tests, Wilcoxon rank-sum tests, two-sample tests of proportions or Fisher's exact test, as appropriate. Differences between baseline and follow-up were assessed with the paired t-test or Wilcoxon signed-rank test for continuous variables and McNemar's test for paired dichotomous variables.

The GFR measurements were analyzed in a linear mixed regression model with random intercept and slope.⁴⁵ The subjects had from one to three GFR measurements (baseline, follow-up and/or repeated follow-up). Absolute GFR in mL/min was used as the dependent variable. Observation

time from baseline was used as the independent time variable. Effects of the baseline BP components (SBP, DBP, PP and MAP) on the rate of change in GFR were assessed by including two-way interaction terms between the BP variable in question and the time variable. Separate regression analyses were performed for each BP component.

All of the linear mixed regression analyses were conducted with the following two sets of baseline adjustment variables: Model 1 (age; sex; body weight; height; individual dichotomous variables for the use of ACE-inhibitors, A2-receptor blockers, beta-blockers, calcium-blockers, diuretics and other antihypertensives) and model 2 (same variables as model 1 while also including LDL-cholesterol, HDL-cholesterol, fasting triglycerides, fasting glucose, ACR, pulse frequency, number of cigarettes currently smoked, and a dichotomous variable for the alcohol use). Subjects with missing data for alcohol use (n=6), ACR (n=5) or triglycerides (n=4) at baseline were excluded from the analyses. There were no missing data for the other independent variables or for GFR.

Non-linear effects of the baseline BP components on the GFR rate of change were explored by including second-degree fractional polynomial transformations of the BP components in the interactions with time in the linear mixed regression models.⁴⁶ Separate analyses were performed for each BP component. Absolute GFR (mL/min) was used as the dependent variable and the same independent variables as in Model 2. The Royston and Altman model-selection algorithm was used.⁴⁶ The algorithm performs a selection of fractional polynomial terms of the independent variables with exponents chosen from the set -2, -1, -0.5, 0, 0.5, 1, 2 and 3. The exponent zero is defined as the logarithm of the independent variable. The difference in deviance defined as minus twice the log-likelihood was used for choosing between models.

The same linear mixed regression analyses as described above were performed with change in eGFR assessed by eGFR_{crea} or eGFR_{cys} as the dependent variable in separate analyses.

Statistical significance was set at 0.05. All of the statistical analyses were performed in STATA/MP 13.1 (www.stata.com).

Disclosure of Competing Financial Interests

None.

References

1. Klag MJ, Whelton PK, Randall BL, *et al.* Blood pressure and end-stage renal disease in men. *N Engl J of Med* 1996; **334**: 13-18.
2. Hsu CY, McCulloch CE, Darbinian J, *et al.* Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. *Arch Intern Med* 2005; **165**: 923-928.
3. Haroun MK, Jaar BG, Hoffman SC, *et al.* Risk factors for chronic kidney disease: a prospective study of 23,534 men and women in Washington County, Maryland. *J Am Soc Nephrol* 2003; **14**: 2934-2941.
4. Munkhaugen J, Lydersen S, Wideroe TE, *et al.* Prehypertension, obesity, and risk of kidney disease: 20-year follow-up of the HUNT I study in Norway. *Am J Kidney Dis* 2009; **54**: 638-646.
5. United States Renal Data System. 2014 Annual Data Report: Epidemiology of Kidney Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, 2014.
6. Hsu CY. Does treatment of non-malignant hypertension reduce the incidence of renal dysfunction? A meta-analysis of 10 randomised, controlled trials. *J Hum Hypertens* 2001; **15**: 99-106.
7. Daien V, Duny Y, Ribstein J, *et al.* Treatment of Hypertension With Renin-Angiotensin System Inhibitors and Renal Dysfunction: A Systematic Review and Meta-Analysis. *Am J Hypertens* 2012; **25**: 126-132.
8. The SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med* 2015; **0**: null.
9. Hsu CY. Does non-malignant hypertension cause renal insufficiency? Evidence-based perspective. *Curr Opin Nephrol Hypertens* 2002; **11**: 267-272.
10. Freedman BI, Iskandar SS, Appel RG. The link between hypertension and nephrosclerosis. *Am J Kidney Dis* 1995; **25**: 207-221.
11. Kronborg J, Solbu M, Njolstad I, *et al.* Predictors of change in estimated GFR: a population-based 7-year follow-up from the Tromso study. *Nephrol Dial Transplant* 2008; **23**: 2818-2826.

12. Halbesma N, Jansen DF, Stolk RP, *et al.* Changes in renal risk factors versus renal function outcome during follow-up in a population-based cohort study. *Nephrol Dial Transplant* 2010; **25**: 1846-1853.
13. Rifkin DE, Katz R, Chonchol M, *et al.* Blood pressure components and decline in kidney function in community-living older adults: the Cardiovascular Health Study. *Am J Hypertens* 2013; **26**: 1037-1044.
14. Hirayama A, Konta T, Kamei K, *et al.* Blood Pressure, Proteinuria, and Renal Function Decline: Associations in a Large Community-Based Population. *Am J Hypertens* 2015; **28**: 1150-1156.
15. Wang Q, Xie D, Xu X, *et al.* Blood pressure and renal function decline: a 7-year prospective cohort study in middle-aged rural Chinese men and women. *J Hypertens* 2015; **33**: 136-143.
16. Peralta CA, Jacobs DR, Jr., Katz R, *et al.* Association of pulse pressure, arterial elasticity, and endothelial function with kidney function decline among adults with estimated GFR >60 mL/min/1.73 m²: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Kidney Dis* 2012; **59**: 41-49.
17. Lindeman RD, Tobin JD, Shock NW. Association between blood pressure and the rate of decline in renal function with age. *Kidney Int* 1984; **26**: 861-868.
18. Palatini P, Dorigatti F, Saladini F, *et al.* Factors Associated With Glomerular Hyperfiltration in the Early Stage of Hypertension. *Am J Hypertens* 2012; **25**: 1011-1016.
19. Harrap SB, Cumming AD, Davies DL, *et al.* Glomerular hyperfiltration, high renin, and low- extracellular volume in high blood pressure. *Hypertension* 2000; **35**: 952-957.
20. Kotchen TA, Piering AW, Cowley AW, *et al.* Glomerular hyperfiltration in hypertensive African Americans. *Hypertension* 2000; **35**: 822-826.
21. Mimran A, Ribstein J, DuCailar G, *et al.* Hyperfiltration in lean essential hypertension. *Contrib Nephrol* 1996; **119**: 98-102.
22. Okada R, Yasuda Y, Tsushita K, *et al.* Glomerular hyperfiltration in prediabetes and prehypertension. *Nephrol Dial Transplant* 2012; **27**: 1821-1825.
23. Schmieder RE, Veelken R, Gatzka CD, *et al.* Predictors for Hypertensive Nephropathy - Results of a 6-Year Follow-up-Study in Essential-Hypertension. *J Hypertens* 1995; **13**: 357-365.

24. Inker LA, Schmid CH, Tighiouart H, *et al.* Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012; **367**: 20-29.
25. Rule AD, Bailey KR, Lieske JC, *et al.* Estimating the glomerular filtration rate from serum creatinine is better than from cystatin C for evaluating risk factors associated with chronic kidney disease. *Kidney Int* 2013; **83**: 1169–1176.
26. Mathisen UD, Melsom T, Ingebretsen OC, *et al.* Estimated GFR is associated with cardiovascular risk factors independently of measured GFR. *J Am Soc Nephrol* 2011; **22**: 927-937.
27. Knight EL, Verhave JC, Spiegelman D, *et al.* Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. *Kidney Int* 2004; **65**: 1416-1421.
28. Soveri I, Berg UB, Björk J, *et al.* Measuring GFR: A Systematic Review. *Am J Kidney Dis* 2014; **64**: 411–424.
29. Eriksen BO, Mathisen UD, Melsom T, *et al.* Cystatin C is not a better estimator of GFR than plasma creatinine in the general population. *Kidney Int* 2010; **78**: 1305-1311.
30. Perneger TV, Nieto FJ, Whelton PK, *et al.* A prospective study of blood pressure and serum creatinine. Results from the 'Clue' Study and the ARIC Study. *JAMA* 1993; **269**: 488-493.
31. Schaeffner ES, Kurth T, Bowman TS, *et al.* Blood pressure measures and risk of chronic kidney disease in men. *Nephrol Dial Transplant* 2008; **23**: 1246-1251.
32. Fox CS, Larson MG, Leip EP, *et al.* Predictors of New-Onset Kidney Disease in a Community-Based Population. *JAMA* 2004; **291**: 844-850.
33. Kanno A, Kikuya M, Asayama K, *et al.* Night-time blood pressure is associated with the development of chronic kidney disease in a general population: the Ohasama Study. *J Hypertens* 2013; **31**: 2410-2417.
34. Yamagata K, Ishida K, Sairenchi T, *et al.* Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. *Kidney Int* 2007; **71**: 159-166.
35. Obermayr RP, Temml C, Knechtelsdorfer M, *et al.* Predictors of new-onset decline in kidney function in a general middle-european population. *Nephrol Dial Transplant* 2008; **23**: 1265-1273.

36. Boucquemont J, Heinze G, Jager K, *et al.* Regression methods for investigating risk factors of chronic kidney disease outcomes: the state of the art. *BMC Nephrology* 2014; **15**: 45.
37. Stevens LA, Levey AS. Measured GFR as a confirmatory test for estimated GFR. *J Am Soc Nephrol* 2009; **20**: 2305-2313.
38. Singer JD, Willett JB. *Applied Longitudinal Data Analysis. Modelling Change and Event Occurrence*. Oxford University Press, Inc.: Oxford, 2003.
39. Rydstrom M, Tengstrom B, Cederquist I, *et al.* Measurement of glomerular filtration rate by single-injection, single-sample techniques, using ⁵¹Cr-EDTA or iohexol. *Scand J Urol Nephrol* 1995; **29**: 135-139.
40. Brandstrom E, Grzegorzcyk A, Jacobsson L, *et al.* GFR measurement with iohexol and ⁵¹Cr-EDTA. A comparison of the two favoured GFR markers in Europe. *Nephrol Dial Transplant* 1998; **13**: 1176-1182.
41. Eriksson CG, Kallner A. Glomerular filtration rate: a comparison between Cr-EDTA clearance and a single sample technique with a non-ionic contrast agent. *Clin Biochem* 1991; **24**: 261-264.
42. Mathisen UD, Melsom T, Ingebretsen OC, *et al.* Ambulatory blood pressure is associated with measured glomerular filtration rate in the general middle-aged population. *J Hypertens* 2012; **30**: 497-504.
43. Solbu MD, Kronborg J, Eriksen BO, *et al.* Cardiovascular risk-factors predict progression of urinary albumin-excretion in a general, non-diabetic population: a gender-specific follow-up study. *Atherosclerosis* 2008; **201**: 398-406.
44. Eriksen BO, Lochen ML, Arntzen KA, *et al.* Estimated and Measured GFR Associate Differently with Retinal Vasculopathy in the General Population. *Nephron* 2015.
45. Leffondre K, Boucquemont J, Tripepi G, *et al.* Analysis of risk factors associated with renal function trajectory over time: a comparison of different statistical approaches. *Nephrol Dial Transplant* 2014; **30**: 1237-1243.
46. Royston P, Sauerbrei W. *Multivariable Model-building*. John Wiley & Sons Ltd.: Chichester, 2008.

Acknowledgments

We thank Britt-Ann Winther Eilertsen, Bjørg Skog Høgset, Saskia van Heusden, and the staff at the Clinical Research Unit (University Hospital of North Norway) for assistance in planning the study, performing the procedures and collecting data according to the GCP standard. We also thank Harald Strand and the staff at the Department of Medical Biochemistry (University Hospital of North Norway) for HPLC analyses of iohexol. We are grateful to all the participants in the RENIS-T6 cohort for making this study possible.

RENIS-FU was funded by the Northern Norway Regional Health Authority, UiT The Arctic University of Norway and by a grant from Boehringer-Ingelheim. None of the sponsors had any role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

This study was presented in abstract form at the 2015 Kidney Week of the American Society of Nephrology in San Diego.

Figure Legend

Figure 1. Inclusion of subjects in the RENIS Follow-Up Study (RENIS-FU). Subjects had from one to three GFR measurements: at baseline, at follow-up and/or at a repeated follow-up investigation.

Table 1. Study population characteristics at baseline and follow-up. The RENIS-FU Study.

	Baseline measurements		P-value for change between baseline and follow-up for subjects included in follow-up
	All	Included in follow-up study	
N (%)	1594 (100 %)	1299 (81 %)	1299 (81 %)
Male gender, n(%)	0	0	
Age, years	781 (49 %)	643 (49 %)	643 (49 %)
Height, cm	58.1 (3.8)	58.0 (3.9)	63.6 (4.0)
Body weight, kg	170.6 (8.7)	170.8 (8.6)	170.6 (8.7)
Body mass index, kg/m ²	27.2 (4.0)	27.1 (3.8)	27.1 (4.0)
Waist-hip ratio	0.91 (0.07)	0.91 (0.07)	0.93 (0.07)
Current smoker, n(%)	322 (20 %)	240 (18 %)	173 (13 %)
Use of alcohol more than 2-4 times a month, n(%)	434 (27 %)	366 (28 %)	431 (33 %)
LDL cholesterol, mmol/L	3.67 (0.86)	3.67 (0.85)	3.58 (0.90)
HDL cholesterol, mmol/L	1.54 (0.42)	1.54 (0.42)	1.63 (0.46)
Fasting triglycerides, mmol/L	1.00 (0.80 to 1.50)	1.00 (0.80 to 1.40)	1.00 (0.80 to 1.30)
Fasting glucose, mmol/L	5.30 (5.00 to 5.60)	5.30 (5.00 to 5.60)	5.40 (5.10 to 5.80)
Hemoglobin A1c, %	5.50 (5.30 to 5.80)	5.50 (5.30 to 5.70)	5.60 (5.40 to 5.80)
Urinary albumin-creatinine ratio, mg/mmol	0.23 (0.10 to 0.54)	0.22 (0.10 to 0.53)	0.34 (0.10 to 0.58)
Hypertension ^a , n(%)	674 (42 %)	539 (41 %)	672 (52 %)
Systolic BP, mmHg	129.4 (17.5)	129.1 (17.4)	130.5 (16.9)
Diastolic BP, mmHg	83.4 (9.8)	83.3 (9.8)	81.9 (9.3)
Pulse pressure, mmHg	46.1 (11.4)	45.8 (11.4)	48.6 (12.2)
Mean arterial BP, mmHg	98.7 (11.7)	98.6 (11.7)	98.1 (10.9)
Pulse frequency, beats/min	66.6 (9.8)	66.3 (9.7)	64.5 (9.2)
Antihypertensive medication, n(%)	289 (18 %)	227 (17 %)	405 (31 %)
ACE inhibitor, n(%)	28 (1.8 %)	26 (2.0 %)	48 (3.7 %)
A2 blocker, n(%)	132 (8.3 %)	105 (8.1 %)	201 (15.5 %)
Betablocker, n(%)	67 (4.2 %)	47 (3.6 %)	93 (7.2 %)
Calcium blocker, n(%)	80 (5.0 %)	62 (4.8 %)	126 (9.7 %)
Diuretic, n(%)	140 (8.8 %)	107 (8.2 %)	203 (15.6 %)
Other antihypertensives, n(%)	1 (0.1 %)	0 (0.0 %)	5 (0.4 %)
Lipid lowering medication, n(%)	100 (6.3 %)	79 (6.1 %)	221 (17.0 %)
Absolute GFR, mL/min	103.8 (19.9)	103.6 (19.6)	98.2 (19.8)
GFR, mL/min/1.73m ²	93.8 (14.3)	93.7 (14.2)	88.9 (14.5)

Abbreviations: RENIS-FU Study, the Renal Iohexol-clearance Survey Follow-up Study; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BP, blood pressure; GFR, glomerular filtration rate.

Estimates are given as mean (standard deviation), median (interquartile range) or percent.

^aSystolic BP >=140, diastolic BP >=90 or antihypertensive medication.

Table 2. Unadjusted mean GFR change rates according to change in mean arterial pressure and antihypertensive medication between baseline and follow-up. The RENIS-FU Study.

Antihypertensive medication		Change in mean arterial pressure from baseline to follow-up. N (%) and DGFR (SD), mL/min/year		
Baseline	Follow-up	Lower or unchanged	Higher	Total
No	No	374 (57) -1.10 (2.00)	508 (79) -0.69 (2.02)	882 (68) -0.86 (2.02)
No	Yes	145 (22) -1.05 (2.79)	45 (7) -0.91 (2.00)	190 (15) -1.02 (2.62)
Yes	No	6 (1) 0.23 (1.76)	6 (1) -1.79 (0.99)	12 (1) -0.78 (1.72)
Yes	Yes	129 (20) -1.76 (2.61)	86 (13) -0.48 (2.55)	215 (17) -1.25 (2.65)
Total		654 (100) -1.21 (2.34)	645 (100) -0.69 (2.09)	1299 (100) -0.95 (2.23)

Abbreviations: GFR, glomerular filtration rate; DGFR, change in GFR; RENIS-FU Study, the Renal Iohexol-clearance Survey Follow-up Study; SD, standard deviation.

Negative DGFR indicates a decline in GFR from baseline to follow-up

P-values for the effects of change in antihypertensive medication, change in MAP and the interaction between these two were 0.006, 0.007 and 0.009, respectively.

Table 3. The associations between baseline blood pressure and GFR change rates in linear mixed regression analyses. The RENIS-FU Study

BP component	Model 1 ^a			Model 2 ^b		
	Beta (mL/min/yr)	95 % confidence interval	P-value	Beta (mL/min/yr)	95 % confidence interval	P-value
Systolic BP per 10 mmHg	-0.05	-0.12 to 0.03	0.21	-0.02	-0.09 to 0.06	0.69
Diastolic BP per 10 mmHg	-0.04	-0.17 to 0.09	0.56	0.02	-0.11 to 0.16	0.72
Pulse pressure per 10 mmHg	-0.07	-0.18 to 0.03	0.17	-0.05	-0.15 to 0.06	0.41
Mean arterial pressure per 10 mmHg	-0.05	-0.16 to 0.06	0.34	0.00	-0.12 to 0.12	1.00

Abbreviations: RENIS-FU Study, the Renal Iohexol-clearance Survey Follow-up Study; BP, blood pressure
Each horizontal section in the table corresponds to one linear mixed regression model. Negative coefficients indicate a steeper GFR decline; positive coefficients a slower decline.

^a Model 1 adjusted for age; sex; body weight; height; individual dichotomous variables for the use of ACE-inhibitors, A2-receptor blockers, beta-blockers, calcium-blockers, diuretics and other antihypertensives.

^b Adjusted as model 1 and in addition LDL-cholesterol, HDL-cholesterol, fasting triglycerides, fasting glucose, urinary ACR, pulse frequency, number of cigarettes currently smoked, a dichotomous variable for the weekly use of alcohol or not.

