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Hypertension

ORIGINAL ARTICLE

Albuminuria, renal dysfunction and circadian blood pressure rhythm in older men: a population-based longitudinal cohort study

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Abstract

Background: Both albuminuria and kidney dysfunction may affect circadian blood pressure (BP) rhythm, while exacerbating each other's effects. We investigated associations and interactions of these two risk factors with circadian BP rhythm variation and non-dipper pattern progression in community-dwelling older men.

Methods: This was a cross-sectional and longitudinal analyses in the third and fourth cycles of the Uppsala Longitudinal Study of Adult Men, including 1051 men (age 71 years) with assessments on urinary albumin excretion rate (UAER), 24-h ambulatory BP monitoring (ABPM) and cystatin-C-estimated glomerular filtration rate (eGFR). Of these, 574 men attended re-examination after 6 years. Study outcomes were ABMP changes and non-dipping BP pattern (prevalence and progression).

Results: UAER associated with circadian BP rhythm both cross-sectionally and longitudinally. Longitudinally, significant interactions were observed between UAER and kidney dysfunction (eGFR < 60 mL/min/1.73 m^2) in its association with the changes of both night-time systolic BP (SBP) and night–day SBP ratio. After stratification, UAER strongly predicted night–day SBP ratio change only in those with concurrent kidney dysfunction. At re-examination, 221 new cases of non-dipper were identified. In multivariable logistic models, high UAER associated with increased likelihood of non-dipper progression, but more strongly so among individuals with concurrent kidney dysfunction. These associations were evident also in the subpopulation of non-diabetics and in participants with normal range UAER.

Conclusions: UAER associates with circadian BP rhythm variation and non-dipper progression in elderly men. Concurrent renal dysfunction modifies and exacerbates these associations.

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Key words: albuminuria, ambulatory blood pressure monitoring, circadian BP rhythm, kidney dysfunction, non-dipper pattern

Introduction

Hypertension is highly prevalent among elderly individuals and a well-documented risk factor of cardiovascular disease (CVD) morbidity and mortality in the community [1, 2]. The kidneys play an essential role in the pathogenesis and maintenance of hypertension and circadian blood pressure (BP) rhythm [3, 4]. Both albuminuria [5, 6] and kidney dysfunction [3] associate with measures of BP in cross-section. Traditionally, albuminuria and kidney dysfunction are interpreted as a consequence of long-term poorly controlled hypertension. However, existing observational evidence allows the speculation that these associations may be bidirectional in nature, as some longitudinal studies link albuminuria with progression of hypertension [7–12]. We could recently report that both kidney dysfunction and albuminuria associate synergistically with the incidence of hypertension among the elderly [13].

The loss of the physiologic decline in nocturnal BP, termed non-dipping, is associated with worse CVD outcomes regardless of arterial BP during daytime or during 24 h [14, 15]. There is an emerging evidence that kidney dysfunction also affects circadian BP rhythm: cross-sectional studies have linked both albuminuria [16–18] and renal insufficiency [4] with non-dipping patterns, but factors that drive the appearance of circadian fluctuation in the kidney are not fully elucidated [19]. As a continuation of our preceding analysis [13], in this study, we address plausible associations between albuminuria, kidney dysfunction or both, on circadian BP rhythm change and progression to non-dipping pattern in community-dwelling older men.

Materials and methods

Participants

The present study is based on the Uppsala Longitudinal Study of Adult Men (http://www.pubcare.uu.se/ULSAM/), when participants were 70–71 years old (1991–95; $n = 1221$). We excluded 170 subjects who were missing albuminuria, serum cystatin C and/or 24-h ambulatory BP monitoring (ABPM) data, leaving 1051 men for the cross-sectional analysis. Of these 1051 individuals, 333 died or were lost to follow-up before a re-examination taking place 6 years later when the participants were ~77 years old. Of the 718 men who attended the re-examination, 144 were excluded due to missing ABPM records, leaving 574 men for the longitudinal analysis (Figure 1). No major characteristics differed between included and non-included participants at re-examination (Supplementary Table S1). All participants gave written consent, and the Ethics Committee of Uppsala University approved the study.

Covariates

Smoking status was defined as current smoking versus non-smoking. Physical activity was defined as the reporting of exercise habits according to four physical activity categories (sedentary, moderate, regular and athletic) [20]. Previous CVD was defined as a history of any CVD as recorded in the Swedish Hospital Discharge Registry [International Classification of Diseases (ICD)-8 codes 390–458 or ICD-9 codes 390–459]. Hyperlipidaemia was defined as serum cholesterol >6.5 mmol/L, triglycerides >2.3 mmol/L or treatment with lipid-lowering medications. Diabetes was defined as fasting glucose ≥7.0 mmol/L, 2-h post-load glucose level ≥11.1 mmol/L or the use of oral hypoglycaemic agents or insulin [21]. Classification of antihypertensive was performed according to the, at that time, list of pharmaceutical specialties available in Sweden (FASS 1992/1993). All information about use of diuretics, α-blockers, β-blockers, calcium channel blockers and angiotensin-converting enzyme inhibitors was collected with a medical questionnaire. Because previous literature correlates sodium intake with circadian BP rhythm [4], we also considered dietary sodium intake after correction for total energy intake by the residual method [22] as derived from 7-day dietary records [23].

Kidney function and albuminuria measurements

Serum cystatin C was measured by latex-enhanced reagent (N Latex Cystatin C, Dade Behring, Deerfield, IL) with a Behring BN ProSpec analyser (Dade Behring). Estimated glomerular filtration rate (eGFR) was calculated from serum cystatin C concentrations (mg/L): $\text{eGFR} = 77.24 \times \text{cystatin C}^{-1.2623}$, which has been shown to be closely correlated with iohexol clearance in this specific population [24]. Kidney dysfunction was defined as cystatin-C eGFR < 60 mL/min/1.73 m^2 [25]. Urinary albumin excretion rate (UAER) was calculated on the amount of albumin in the urine collected during the night. The subjects were instructed to void immediately before going to bed and to record the time. All urine samples during the night and the first sample of urine in the morning after rising were collected and used for the analysis. The assay employed a commercially available radioimmunoassay kit (Albumin RIA 100, Pharmacia, Uppsala, Sweden). Normal range albuminuria was defined as UAER < 20 μg/min.

Circadian BP rhythm assessment

The ABPM device Accutracker II (Suntech Medical Instruments, Raleigh, NC) was used in both examinations and attached to the subjects' non-dominant arm by a skilled lab technician, and BP recordings were made every 20 min during 24 h (daytime: 06:00–23:00, night-time: 23:00–06:00). Data were edited to a limited extent omitting all readings of zero, all heart rate readings <30 beats/min, diastolic BP (DBP) readings >170 mmHg, systolic BP (SBP) > 270 and <80 mmHg, and all readings where the difference between SBP and DBP was <10 mmHg. Nocturnal BP change = $(\text{SBP}_{\text{day}} - \text{SBP}_{\text{night}})/\text{SBP}_{\text{day}} \times 100\%$, non-dipper BP pattern defined as nocturnal BP change <10% and hypertension was defined as either average daytime BP ≥135/85 mmHg or night-time BP ≥120/70 mmHg or 24-h daytime BP from ABPM ≥130/80 mmHg or intake of antihypertensive drugs, according to the new National Institute for Health and Care Excellence Guidance [26] and the Task Force for the management of arterial hypertension of the European Society of Hypertension and of the European Society of Cardiology [27].

Analyses

In cross-sectional analysis, multivariable linear regressions were calculated to determine independent associations between UAER and BP circadian rhythm measurements at baseline (daytime SBP, night-time SBP and nocturnal BP change). UAER was $\log_2$ transformed to improve its distribution towards normal. Confounders in adjusted models included body mass index (BMI), smoking status, physical activity, comorbidities (CVD,

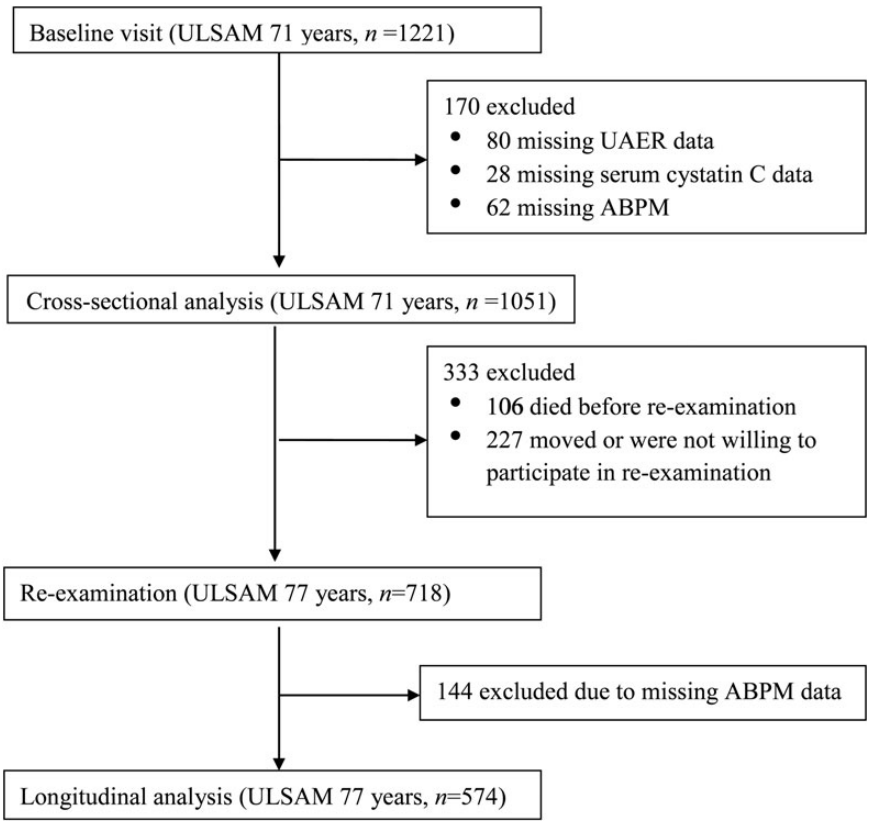

Fig. 1. Flowchart of the participants. Flow chart depicting the selection of individuals for the current investigation including causes for exclusion of participants. ULSAM, Uppsala Longitudinal Study of Adult Men; UAER, urinary albumin excretion rate; ABPM, ambulatory blood pressure monitoring.

diabetes and hyperlipidaemia), eGFR, number of antihypertensive drugs (1, 2 or ≥3 drugs) and sodium intake. Data are expressed as regression coefficients (β) and 95% confidence intervals (CIs).

In longitudinal analysis, two outcomes were defined *a priori*: (i) intra-individual BP changes, defined as changes in BP measurements (delta daytime BP, delta night-time BP and delta nocturnal BP change) from baseline to re-examination and (ii) progression to a non-dipper BP pattern. For the second outcome, participants with non-dipper BP pattern at baseline were excluded from the analyses. Multivariable linear regressions were used to examine the association between UAER and BP circadian rhythm changes described above. Multivariable logistic regression models were used to examine the association between UAER and the risks of *de novo* non-dipper BP pattern at re-examination. Covariance in adjusted models included BMI, smoking status, physical activity, comorbidities, eGFR, number of antihypertensive drugs at baseline and sodium intake. Results are shown as odds ratios and 95% CI.

We examined multivariable models that included interaction terms for UAER (as a continuous variable) and kidney function (as a binominal variable: eGFR ≥60 or <60 mL/min/1.73 m^2) and performed the analyses after stratification of individuals according to the presence/absence of kidney dysfunction. P-values for interaction were reported. In addition, because both diabetic nephropathy and micro-/macro-albuminuria *per se* may affect study outcomes, analyses were repeated in non-diabetics and in a subpopulation with normal range UAER (<20 μg/min). $P < 0.05$ was regarded as significant. All statistical analyses were performed using statistical software STATA version 12 (Stata Corporation, College Station, TX).

Results

Cross-sectional analysis

Baseline characteristics of the study population are presented in Table 1. Multivariable regression analyses were fitted to study cross-sectional associations of albuminuria with circadian BP rhythm (night-time SBP, daytime SBP and nocturnal BP change) by ABPM at baseline (Table 2). In fully adjusted models, albuminuria was considered an independent contributor to the variance of circadian BP rhythm measurements. The associations were similar, slightly improving in individuals with kidney dysfunction than in individuals without, but no statistically significant interaction terms were noted.

Longitudinal analysis

After 6 years, 574 individuals attended a re-examination and underwent 24-h ABPM assessment. In multivariable regression analyses, associations were observed between albuminuria and the change in both night-time SBP and nocturnal BP (Table 3). Significant interaction terms between albuminuria and the presence of kidney dysfunction on the prediction of changes of circadian BP rhythm were observed. After stratification, albuminuria appeared as an independent predictor of these changes in subjects with kidney dysfunction, but not in those without. Similar associations were observed in individuals without diabetes as well as in individuals with normal range UAER (<20 μg/min) (Supplementary Table S2).

After exclusion of non-dippers at baseline ($n = 395$), 221 individuals progressed to non-dipper at re-examination. Albuminuria

Table 1. Baseline characteristics of study participants according to quartiles of UAER ($n = 1051$)

Parameters	Quartiles of UAER (range, μg/min)				P for trend
	Quartile 1 (0.5–3.3)	Quartile 2 (>3.3–5.3)	Quartile 3 (>5.3–11.7)	Quartile 4 (>11.7–1346)	
n	264	261	262	264	
eGFR (mL/min/1.73 m^2)	61.4 (53.4–70.1)	62.7 (54.9–70.9)	61.4 (53.8–70.1)	60.7 (50.5–70.1)	0.32
BMI (kg/m^2)	25.5 ± 3.2	25.9 ± 3.2	26.6 ± 3.3	27.0 ± 3.8	<0.001
Smokers, *n* (%)	35 (13)	52 (20)	55 (22)	62 (25)	0.002
Physical activity, *n* (%)					
Sedentary	5 (2)	5 (2)	13 (5)	10 (4)	0.04
Moderate	80 (32)	90 (36)	82 (33)	94 (37)	
Regular	149 (59)	144 (57)	144 (58)	135 (54)	
Athletic	18 (7)	14 (6)	11 (4)	13 (5)	
CVD, *n* (%)	68 (25)	83 (31)	81 (30)	97 (36)	0.02
Hyperlipidaemia, *n* (%)	96 (36)	80 (30)	91 (34)	111 (41)	0.14
Diabetes, *n* (%)	22 (8)	27 (10)	41 (15)	71 (26)	<0.001
Dietary sodium intake (mg/day)	2486 ± 358	2484 ± 371	2576 ± 356	2526 ± 382	0.05
Circadian BP assessment					
Daytime SBP (mmHg)	134 ± 15	136 ± 14	140 ± 16	145 ± 17	<0.001
Night-time SBP (mmHg)	115 ± 17	118 ± 17	122 ± 19	128 ± 21	<0.001
Nocturnal BP change	13.6 ± 8.5	12.9 ± 8.9	12.7 ± 8.7	11.8 ± 8.9	0.04
Non-dipper BP pattern, *n* (%)	69 (26)	86 (33)	94 (35)	103 (38)	0.002
Hypertension, *n* (%)	162 (61)	174 (67)	206 (79)	236 (89)	<0.001
Antihypertensive medication					
Number of drugs, *n* (%)					
1 drug	41 (16)	48 (18)	53 (20)	70 (27)	<0.001
2 drugs	21 (8)	21 (8)	32 (12)	45 (17)	
≥3 drugs	5 (2)	8 (3)	5 (2)	10 (4)	
ACEI use, *n* (%)	4 (2)	11 (4)	22 (8)	25 (10)	<0.001
CCB use, *n* (%)	22 (8)	24 (9)	31 (12)	54 (21)	<0.001
β-Blocker use, *n* (%)	49 (19)	43 (16)	44 (17)	69 (26)	0.03
α-Blocker use, *n* (%)	5 (2)	1 (0.4)	3 (1)	5 (2)	0.81
Diuretics use, *n* (%)	29 (11)	29 (11)	37 (14)	43 (16)	0.04

Data are expressed as mean ± SD, median (interquartile range) or number (percentage), as appropriate. Nocturnal BP change = ($SBP_{day} - SBP_{night}$)/SBP_{day} × 100% and non-dipper BP pattern defined as nocturnal BP change <10%. UAER, urinary albumin excretion rate; BMI, body mass index ; eGFR, estimated glomerular filtration rate; ABPM, ambulatory blood pressure monitoring; SBP, systolic blood pressure; ACEI, angiotensin-converting enzyme inhibitors; CCB, calcium channel blockers.

Table 2. Cross-sectional associations between UAER and circadian BP in the whole cohort and after stratification by the presence of kidney dysfunction ($n = 1051$)

Log$_2$ UAER (μg/min)	β Coefficient (95% CI)			
	Total ($n = 1051$)	eGFR < 60 mL/min/1.73 m^2 ($n = 465$)	eGFR ≥ 60 mL/min/1.73 m^2 ($n = 586$)	P for interaction
Night-time SBP (mmHg)	2.51*** (1.79, 3.23)	2.94*** (1.86, 4.03)	2.13*** (1.14, 3.11)	0.62
Daytime SBP (mmHg)	2.04*** (1.42, 2.65)	2.08*** (1.22, 2.93)	2.04*** (1.13, 2.94)	0.74
Nocturnal BP change	−0.51** (−0.86, −0.16)	−0.79** (−1.31, −0.27)	−0.24 (−0.73, 0.24)	0.36

Nocturnal BP change = ($SBP_{day} - SBP_{night}$)/SBP_{day} × 100%. Adjusted models included BMI, smoking status, physical activity, CVD, diabetes, hyperlipidaemia, eGFR, number of antihypertensive drugs and energy-adjusted sodium intake. UAER, urinary albumin excretion rate; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; CI, confidence interval.
**P < 0.01, ***P < 0.001.

was associated with this non-dipper progression (Table 4). Again, multiplicative interactions were observed between albuminuria and the presence of kidney dysfunction in the prediction of this progression (P = 0.03). After stratification, albuminuria was an independent predictor of non-dipper progression in subjects with kidney dysfunction, but not in those without. Similar associations were observed in individuals without diabetes, as well as in individuals with normal range albuminuria (Supplementary Table S3).

Discussion

The main finding of our study is the longitudinal association between UAER, circadian BP rhythm changes and progression to non-dipper BP pattern in elderly men. In addition, the presence of concurrently impaired renal function exacerbated these associations.

Our data confirm previous 'cross-sectional' surveys showing a positive association between albuminuria and circadian pattern

Table 3. Longitudinal associations between UAER and circadian BP variation 6 years apart, in the whole cohort and after stratification by the presence of kidney dysfunction ($n = 574$)

	β Coefficient (95% CI)			
Log_2 UAER (μg/min)	Total ($n = 574$)	eGFR < 60 mL/min/1.73 m^2 ($n = 245$)	eGFR ≥ 60 mL/min/1.73 m^2 ($n = 329$)	P for interaction
Delta night-time SBP (mmHg)	1.02** (0.23, 1.82)	2.51*** (1.19, 3.84)	−0.25 (−1.22, 0.73)	0.002
Delta daytime SBP (mmHg)	0.48 (−0.22, 1.19)	1.22* (0.08, 2.36)	−0.09 (−0.98, 0.80)	0.05
Delta nocturnal BP change	−0.37* (−0.76, 0.00)	−0.99** (−1.62, −0.36)	0.13 (−0.37, 0.64)	0.03

Nocturnal BP change = $(SBP_{day} - SBP_{night})/SBP_{day} \times 100\%$. Adjusted models included BP measured at baseline (night-time SBP, daytime SBP and nocturnal BP change, respectively), BMI, smoking status, physical activity, CVD, diabetes, hyperlipidaemia, eGFR, number of antihypertensive drugs and energy-adjusted sodium intake. UAER, urinary albumin excretion rate; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; CI, confidence interval.
*P < 0.05, **P < 0.01, ***P < 0.001.

Table 4. Logistic regression models for progression to non-dipper at re-examination among non-dipper-free individuals ($n = 395$)

Log_2 UAER (μg/min)	Events/ total	Model A OR (95% CI)	Model B OR (95% CI)
Total	221/395	1.16 (1.00, 1.35)	1.16 (1.01, 1.35)
eGFR < 60 mL/min/ 1.73 m^2	89/159	1.43 (1.10, 1.87)	1.43 (1.10, 1.87)
eGFR ≥ 60 mL/min/ 1.73 m^2	132/236	0.98 (0.80, 1.20)	0.98 (0.80, 1.21)
P for interaction		0.03	0.03

Non-dipper BP pattern incidence defined as nocturnal BP change $[(SBP_{day} - SBP_{night})/SBP_{day} \times 100\%] < 10\%$ at re-examination. Model A included BMI, smoking status, physical activity, CVD, diabetes, hyperlipidaemia, eGFR and number of antihypertensive drugs. Model B included BMI, smoking status, physical activity, CVD, diabetes, hyperlipidaemia, eGFR, number of antihypertensive drugs and energy-adjusted sodium intake. UAER, urinary albumin excretion rate; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; OR, odds ratio.

of BP both in the community- and disease-specific populations [16–18]. Furthermore, we now expand this evidence by demonstrating, we believe for the first time, coherent 'longitudinal' associations and increased albuminuria-associated risk of non-dipper progression. Of interest, these associations were also evident at UAER levels within the normal range, adding to previous studies suggesting harm for albuminuria below currently proposed thresholds [28, 29]. In addition, renal dysfunction directly correlated with a non-dipper phenotype in our study, much like a previous publication showing that non-dipping status was associated with both the presence of chronic kidney disease (CKD) and proteinuria [17]. Non-dipper pattern among diabetics was also suggested to be a risk factor for the progression to manifest albuminuria and latent nephropathy [30]. These two above-mentioned studies explored the potential interaction between albuminuria and kidney function on non-dipper pattern as secondary outcome, however, offering mixed results [17, 30]. In our sample, we had a large proportion (nearly 50%) of individuals with CKD, as expected perhaps from the age range of the population sampled. In this setting, we report a consistent effect modification by underlying kidney disease in the longitudinal association between UAER, circadian BP changes and progression to non-dipper. Adding to the traditional view that albuminuria and GFR reduction may be the result of hypertension and non-dipper BP pattern and therefore signal an unfavourable prognosis [31], our study allows us to speculate on the alternative sequential pathway that could also be encountered in clinical practice. Although observational, our longitudinal design provides additional support to the hypothesis that these associations may be causal in nature. Nevertheless, interventional studies are warranted to evaluate the clinical relevance of our findings.

Various mechanisms may contribute to explaining the possible role of albuminuria and renal function in maintaining normal circadian BP. Albuminuria is regarded as a surrogate marker of not only glomerular but also systemic vascular damage, such as vascular endothelial dysfunction and abnormal vascular permeability [32]. Furthermore, reduction in the number of nephrons (via glomerular hyperfiltration in the residual nephrons) followed by elevated intra-glomerular pressure, glomerular injury and the concomitant incomplete absorption by proximal tubular cells may also provide a link between higher albumin excretion and the circadian BP pattern [33]. Salt handling by the kidney has long been recognized as a critical determinant of BP and abnormal circadian BP, while in kidney hypertension, inappropriate sodium transport is frequently observed [19]. Because glomerular filtration capability is one of the major factors determining sodium sensitivity, as GFR is reduced, night/day BP ratios, natriuresis and proteinuria will increase [4]. In addition, the circadian BP rhythm can be affected by sodium intake in patients with hypertension: in salt-sensitive patients with hypertension, a non-dipper nocturnal BP pattern transformed into a dipper pattern after sodium restriction [34]. Unfortunately, our cohort does not have data on urinary sodium excretion, but energy-adjusted sodium intake was correlated, as one would expect, with non-dipper pattern in cross-section. Altogether, we speculate that a decline in renal function could exaggerate the aforementioned mechanisms with regard to albumin excretion and that this may explain the interaction observed in our analysis.

Strengths of this study include the relatively large, community-based sample, the prospective data collection and its longitudinal design with ABPM visits 6 years apart. Another strength is that urinary albumin excretion was assessed from timed urine samples collected overnight rather than from a spot sample. Finally, we had a careful and rich consideration of confounders, and we confirmed our findings in normal-range albuminuria and in non-diabetics. The rationale for the latter is that diabetic nephropathy usually progresses with albuminuria, reduced eGFR and hypertension, potentially influencing our findings. We acknowledge, however, several limitations. The first one is that, although the inclusion of elderly men with identical age, ethnicity and geographical distribution reduced important confounding, these results may not necessarily be extrapolated to women or other age categories. A considerable number of individuals did not participate in the re-examination, which may introduce selection bias. Reasons for not attending re-examination were death in approximately a third of the cases of this elderly

population. The remaining individuals, at the age of 77, refused to undergo the thorough questionnaires and clinical assessment of this study. UAER was measured only once while current recommendations suggest two consecutive measurements to diagnose micro-/macro-albuminuria [25]. Regardless, potential misclassifications would result in an underestimation of the true risk reported here. Finally, residual confounding by unknown or unmeasured factors, a problem nevertheless inherent to observational studies.

Conclusions

Urinary albumin excretion was associated with negative changes of circadian BP rhythm and with progression to a non-dipper BP pattern in community-dwelling older men. The presence of concurrently impaired renal function amplified these associations.

Supplementary data

Supplementary data is available online at http://ndt.oxfordjournals.org.

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Conflicts of interest statement

B.L. is affiliated with Baxter Healthcare Corporation. None of the other authors declare any conflict of interest.

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