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Letter to the Editor

LETTER TO THE EDITOR

Mediators of the association between albuminuria and incident cancer: the PREVEND study

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To the Editor,

Increased albuminuria, together with impaired estimated glomerular filtration rate (eGFR), is an essential marker of chronic kidney disease [1]. Although it has consistently been shown that there is an independent association between albuminuria and cancer incidence, mechanisms connecting albuminuria to cancer (particularly mechanisms beyond the role of kidney function) are largely unknown [2].

Determining potential mediators of the albuminuria-cancer link in epidemiological studies can provide key insights that will help shift from broad hypotheses to targeted mechanistic investigations. Currently, there is a paucity of knowledge on these mediators. This study therefore aimed to investigate in a prospective cohort study the extent to which a set of literature-based markers mediate the albuminuria cancer association.

For this investigation, we analysed data from the Prevention of Renal and Vascular End-stage Disease (PREVEND) study, a population-based cohort of 8592 Dutch men and women aged 28 to 75 years that by design was enriched for subjects with higher levels of albuminuria. Details of the PREVEND study have been reported previously [3]. Exclusion criteria were being on or having a history of dialysis, as well as missing values for kidney function and the mediator for the corresponding analysis.

Albuminuria was quantified as the average of two 24-hour urine albumin excretion (UAE) values of each subject obtained at baseline, and expressed as mg per 24 hours. Based upon prior literature, we chose to study markers as potential mediators in this study that are relevant to the mechanisms of systemic inflammation, oxidative stress, activation of the renin-angiotensin system, endothelial dysfunction, growth factors, comorbidities and osmotic effects (particularly for urinary tract cancer) (Fig. 1) [4]. Primary outcome was the incidence of overall cancer. We defined secondary outcomes as the incidence of urinary tract cancer (defined as the sum of urothelial cell carcinoma and kidney cancer) and lung cancer, as previous studies consistently demonstrated an association between albuminuria and these specific cancer types [5, 6]. Data on cancer incidence were retrieved by record linkage with the Dutch Pathology Registry (Palga) which has a virtually complete national coverage [7].

UAE was analysed as a continuous term on the log2-transformed scale (i.e. per doubling of urine albumin) and as a categorical term with a cut-off of 30 mg/24 h to define increased

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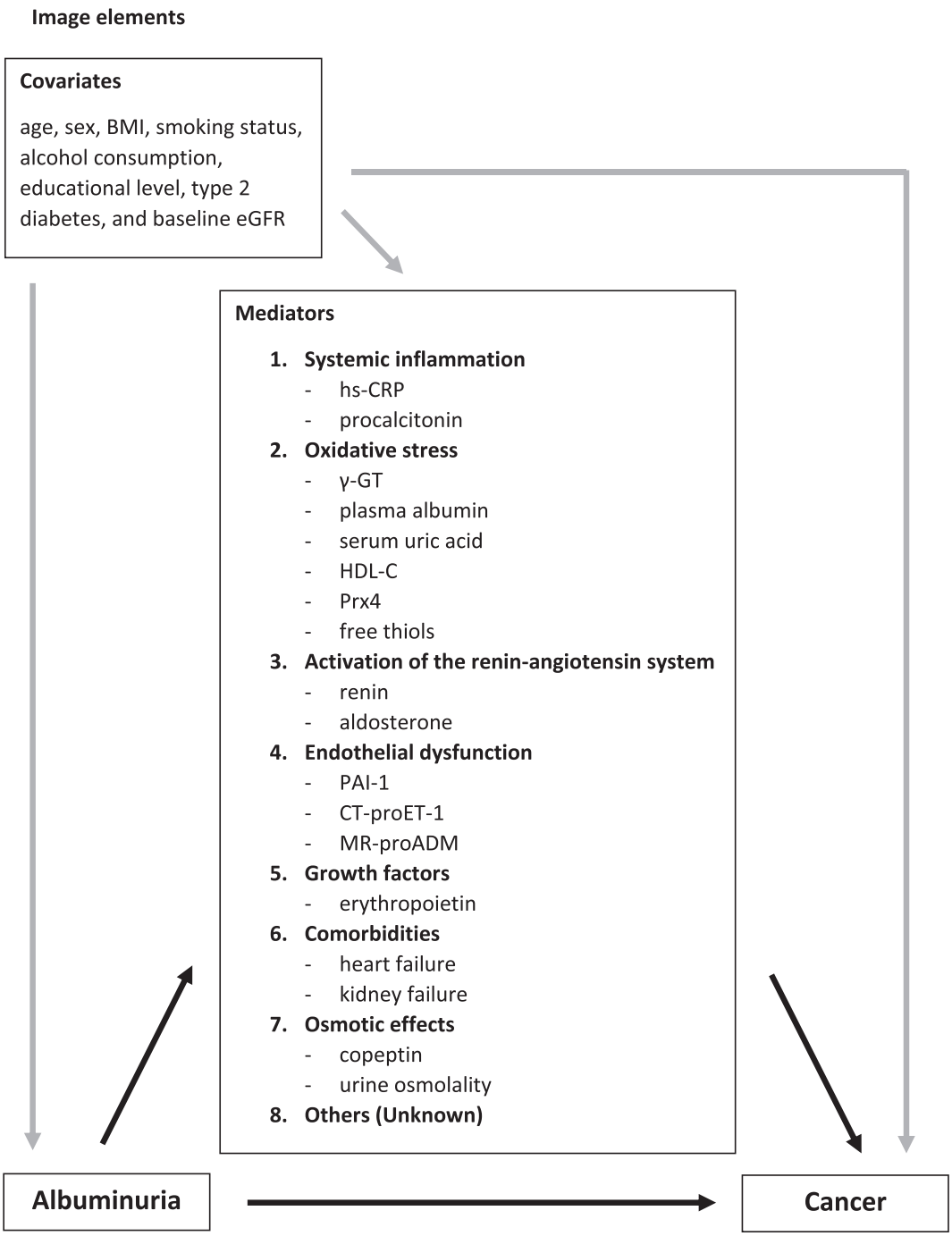

Figure 1: Graph of potential mediating pathways between albuminuria and cancer. Black arrows indicate possible causal pathways, and grey arrows indicate potential confounding pathways. eGFR was investigated as mediator, but also used to adjust for when investigating the potential mediating role of other markers. BMI, body mass index; CT-proET-1, C-terminal pro-endothelin-1; eGFR, estimated glomerular filtration rate; γ-GT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitive C-reactive protein; MR-proADM, mid-regional pro-adrenomedullin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAI-1, plasminogen activator inhibitor-1; Prx4, peroxiredoxin 4.

albuminuria. Cox regression models were first used to investigate the association of UAE with time to cancer incidence. We continued with linear regression analyses to identify potential mediators associated with UAE. In case significant associations were found, we conducted Cox regression models that were additionally adjusted for potential mediators and performed mediation analyses to examine whether and how much these potential mediators explain the association between UAE and cancer incidence. We used the *mediation* R-package to estimate mediation within the counterfactual framework described by Imai *et al.* [8]. All regression analyses were adjusted for clinically important confounders, including baseline eGFR (assessed by the 2012 combined creatinine cystatin C-based CKD-EPI equation) [9]. eGFR was investigated as a mediator, but also used to

Table 1: Mediators of the association between urine albumin excretion and the incidence of overall, urinary tract, and lung cancer.

	Overall cancer			Urinary tract cancer			Lung cancer		
Potential mediators	No. of cancer events/subjects	Percentage mediated (%, 95% CI)	*P* value	No. of cancer events/subjects	Percentage mediated (%, 95% CI)	*P* value	No. of cancer events/subjects	Percentage mediated (%, 95% CI)	*P* value
hs-CRP, mg/L	1 268/7 836	**8.4 (2.8, 20.4)**	**<0.01**	167/8 065	**12.0 (2.9, 36.3)**	**<0.01**	219/8 076	**16.9 (6.6, 71.2)**	**<0.01**
Procalcitonin, ng/mL	-	-	-	-	-	-	-	-	-
γ-GT, U/L	915/6 486	3.3 (−3.3, 18.8)	0.22	115/6 507	1.1 (−11.3, 15.9)	0.74	159/6 524	7.8 (−52.8, 99.1)	0.18
Plasma albumin, g/L	1 169/7 134	1.7 (0.0, 4.7)	0.06	146/7 348	2.3 (−8.6, 18.9)	0.35	203/7 353	0.4 (−5.0, 6.5)	0.81
Serum uric acid, µmol/L	1 312/8 050	−1.0 (−5.4, 2.5)	0.52	175/8 291	1.0 (−6.1, 9.8)	0.72	229/8 300	2.5 (−6.9, 17.6)	0.44
HDL-C, mmol/L	-	-	-	-	-	-	-	-	-
Prx4, U/L	1 286/7 900	0.9 (−3.4, 5.4)	0.65	171/8 134	3.1 (−5.3, 17.2)	0.39	225/8 142	6.7 (−0.7, 27.8)	0.08
Serum free thiols (adjusted for protein), µmol/g	834/6 045	0.8 (−8.6, 14.5)	0.63	114/6 110	0.2 (−25.9, 23.3)	0.95	146/6 114	8.8 (−99.6, 133.9)	0.26
Renin, μIU/mL	-	-	-	-	-	-	-	-	-
Aldosterone, pg/mL	-	-	-	-	-	-	-	-	-
PAI-1, ng/ml	-	-	-	-	-	-	-	-	-
CT-proET-1, pmol/L	1 205/7 592	0.4 (−0.9, 3.2)	0.49	153/7 813	−1.3 (−10.6, 2.6)	0.36	208/7 823	**2.5 (0.1, 9.9)**	**<0.05**
MR-proADM, nmol/L	1 206/7 596	1.2 (−0.5, 4.7)	0.19	153/7 817	−1.4 (−15.5, 7.3)	0.47	209/7 827	**3.4 (0.6, 12.1)**	**<0.05**
Erythropoietin, IU/L	939/6 624	**9.6 (2.5, 57.2)**	**<0.05**	138/6 697	3.8 (−2.3, 17.8)	0.16	161/6 699	−2.0 (−37.9, 34.0)	0.68
NT-proBNP, ng/L	1 311/8 051	**14.3 (6.6, 29.4)**	**<0.001**	175/8 292	2.2 (−10.4, 19.8)	0.67	229/8 301	**16.5 (2.9, 65.1)**	**<0.05**
eGFR, mL/min/1.73 m^2	1 341/8 218	**5.2 (1.5, 12.8)**	**<0.01**	177/8 465	0.7 (−9.4, 11.1)	0.84	231/8 474	−3.0 (−23.8, 8.6)	0.50
Copeptin, pmol/L	-	-	-	144/7 616	6.4 (−1.5, 28.5)	0.07	-	-	-
Urine osmolality, mOsm/kg	-	-	-	-	-	-	-	-	-

hs-CRP, γ-GT, Prx4, erythropoietin, NT-proBNP, and copeptin were log2 transformed for analyses. eGFR was estimated using the 2012 CKD-EPI equation using creatinine as well as cystatin C.

Results from causal mediation analyses. Effects are reported as percentage mediated of the association between UAE (<30 versus ≥30 mg/24 h) and the incidence of overall, urinary tract, and lung cancer. The significance of the mediation effect was tested by the quasi-Bayesian Monte Carlo method with 1000 simulations. Bold *P* values indicate statistical significance. Estimates are adjusted for age, sex, BMI, smoking, alcohol, educational level, type 2 diabetes, and baseline eGFR. Models in which eGFR was analysed as a mediator were not adjusted for baseline eGFR.

BMI, body mass index; CI, confidence interval; CT-proET-1, C-terminal pro-endothelin-1; eGFR, estimated glomerular filtration rate; γ-GT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitive C-reactive protein; MR-proADM, mid-regional pro-adrenomedullin; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAI-1, plasminogen activator inhibitor-1; Prx4, peroxiredoxin 4; UAE, urinary albumin excretion.

adjust for when investigating the potential mediating role of other markers. More details of the methodology are provided in the supplementary materials.

The study population consisted of 8490 subjects, that were predominantly whites, 50% were female, and their mean age was 49.8 ± 12.7 years. Median baseline UAE was 9.4 (IQR, 6.3–17.8) mg/24 h and their mean baseline eGFR was 94.6 ± 17.2 mL/min/1.73 m^2 (Table S1, see online supplementary material).

During a median follow-up of 17.7 years, 1341 subjects developed cancer. In Cox regression analyses, higher UAE was associated with a higher risk of overall cancer incidence (Table S2, model 1, see online supplementary material). Linear regression analyses showed that UAE was significantly associated with hs-CRP, γ-GT, plasma albumin, serum uric acid, Prx4, serum free thiols, CT-proET-1, MR-proADM, erythropoietin, NT-proBNP, eGFR and copeptin (Table S3, see online supplementary material). After additionally adjusting for these mediators, the association between UAE and overall cancer incidence was slightly attenuated, suggesting possible mediation by these markers (Table S2, model 2, see online supplementary material). The mediation analyses showed that hs-CRP, erythropoietin, NT-proBNP, and eGFR explained 8.4% (95% CI, 2.8%-20.4%), 9.6% (95% CI, 2.5%-57.2%), 14.3% (95% CI, 6.6%-29.4%), and 5.2% (95% CI, 1.5%-12.8%), respectively, of the association between UAE and overall cancer incidence (Table 1). Regarding potential mediators of the association between UAE and the incidence of urinary tract cancer and lung cancer, we found that the associations for urinary tract cancer and lung cancer were also partly explained by hs-CRP, and for lung cancer also by CT-proET-1, MR-proADM, and NT-proBNP, respectively. The contribution of these mediators was independent of kidney function.

Though largely unknown, accumulating evidence suggests that the mechanism linking albuminuria to cancer should at least in part go beyond the role of kidney function [5, 6]. This is concordant with our results that eGFR only partly mediates the association between albuminuria and overall cancer incidence, and that other mediating pathways we found significant in this study remained significant after controlling for eGFR. Of the various mediators tested in this study, hs-CRP, an acute-phase protein characterizing systemic inflammation, is the only marker that consistently mediates the association between albuminuria and the incidence of cancer (overall, urinary tract as well as lung cancer). This suggests that systemic inflammation serves as a potent shared mediating pathway for various cancer types. Several considerations are crucial for us to position inflammation as a potential mediator of the albuminuria cancer association. First, while inflammation can pathologically promote albuminuria, it is also plausible that albuminuria reflects a leakage of albumin and other plasma macromolecules (e.g. low-density lipoproteins) in the interstitial space which can stimulate pro-inflammatory processes [10], leading to a carcinogenic micro-milieu [11]. Second, the mediating effects of inflammation should be cautiously interpreted because of potential lead time bias (e.g. urinary tract infection increases the chance of screening for urinary tract cancer). However, we found no strong evidence for such type of bias because our 1-year landmark analysis (in which a diagnosis of cancer within the first year after the baseline screening was deleted from the analyses) showed essentially similar results (Table S4, see online supplementary material).

Notably, our findings also indicate that the associations of albuminuria with the incidence of different cancer types are mediated by distinct markers, representing unique pathways. For example, markers relevant to endothelial dysfunction (i.e. CT-proET-1 and MR-proADM) and comorbid heart failure (i.e. NT-proBNP) mediate the association for lung cancer incidence, which did not hold for the associations for the incidence of overall or urinary tract cancer. Although this might be a power issue, an alternative explanation is that pathways linking albuminuria to cancer can vary across different cancer types. For instance, comorbid heart failure may exclusively mediate the association for lung cancer, based on the assumption that pulmonary vascular remodeling secondary to heart failure may exert localized stimuli on developing pro-carcinogenic milieu in the lungs [12, 13]. Still, we cannot rule out the possible contribution of the pathways that we did not find significant evidence for in this study, given that potential mediators investigated in the present study are yet to characterize relevant pathways fully. This study therefore also provides implications for future studies to explore other potential mediators. Other implications of this study include the need for further investigations to corroborate the pathways suggested in the present study and examine the interplays of these mediators (i.e. how they may causally connect to one another) [4, 14].

Our study has several strengths and limitations. To our knowledge, this is the first study investigating potential mediators of the albuminuria cancer association. Albuminuria and eGFR were quantified in the best manner available (i.e. two 24-hour UAE measurements and creatinine cystatin C-based eGFR). Other strengths include a long follow-up and pathologically verified cancer outcomes. Limitations contain possible residual confounding due to the observational nature of PREVEND as in all observational studies.

In conclusion, this study found that several markers, especially hs-CRP as a marker of systemic inflammation, mediate the albuminuria cancer association independent of kidney function. Our data provide a rationale for targeted investigations into mechanisms underlying the albuminuria-cancer association in future studies.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

All authors conceived and designed the study. L.M.K., B.v.d.V., E.G.G., S.J.L.B., R.A.d.B., N.S., and R.T.G. contributed to data acquisition. L.L. and P.V. conducted data analysis. All authors contributed to the interpretation of the data. L.L. and R.T.G. drafted

the manuscript. All authors revised the article. L.M.K. and R.T.G. supervised the work. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

R.A.d.B. has received research grants and/or fees from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals GmbH, Ionis Pharmaceuticals, Inc., Novo Nordisk, and Roche; and has had speaker engagements with Abbott, AstraZeneca, Bayer, Bristol Myers Squibb, Novartis, and Roche. B.v.d.V. reports research grants and/or (speaker) fees received by UMCG from AstraZeneca, Daiichi Sankyo, MSD, Philips, Visiopharm, Owkin, Diaceutics and personal consultancy fees from DEKRA. All are unrelated to the submitted work. Other authors have none to declare.

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