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ORIGINAL ARTICLE

Serum uromodulin is inversely associated with biomarkers of subclinical inflammation in the population-based KORA F4 study

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ABSTRACT

Background. Uromodulin is a kidney-specific glycoprotein synthesized in tubular cells of Henle's loop exerting nephroprotective and immunomodulatory functions in the urinary tract. A small amount of uromodulin is also released into the systemic circulation, where its physiological role is unknown. Serum uromodulin (sUmod) has been associated with metabolic risk factors and with cardiovascular events and mortality, where these associations were partly stronger in men than in women. In this study, we investigated the associations of sUmod with biomarkers of subclinical inflammation in a population-based sample of women and men.

Methods. Associations of sUmod with 10 biomarkers of subclinical inflammation were assessed in 1065 participants of the Cooperative Health Research in the Region of Augsburg (KORA) F4 study aged 62–81 years using linear regression models adjusted for sex, age, body mass index, estimated glomerular filtration rate and diabetes. Analyses were performed in the total study sample and stratified by sex.

Results. sUmod was inversely associated with white blood cell count, high-sensitive C-reactive protein, interleukin (IL)-6, tumour necrosis factor-α, myeloperoxidase, superoxide dismutase-3, IL-1 receptor antagonist and IL-22 after multivariable adjustment and correction for multiple testing ($P < 0.001$ for each observation). There was a trend towards a stronger association of sUmod with pro-inflammatory markers in men than in women, with a significant P for sex interaction (<0.001) regarding the relation of sUmod with IL-6.

Conclusions. sUmod was inversely associated with biomarkers of subclinical inflammation in older participants of the KORA F4 study. The association of sUmod with IL-6 differed between women and men. Future research should focus on whether the immunomodulatory properties of sUmod are one explanation for the association of sUmod with cardiovascular outcomes and mortality.

Keywords: immunology, immune marker, subclinical inflammation, serum uromodulin, uromodulin

INTRODUCTION

Uromodulin (Tamm–Horsfall protein) is a tissue-specific glycoprotein synthesized in tubular cells of the thick ascending limb of Henle's loop. Uromodulin is mostly secreted into the urinary tract, where it exerts anti-lithogenic, anti-infective and immunomodulatory functions [1–5], but a small amount is also secreted into the blood stream (serum uromodulin, sUmod) [6, 7].

The physiological function of sUmod is elusive to date, but epidemiological evidence indicates that sUmod levels are inversely associated with all-cause and cardiovascular mortality [8–11] as well as with cardio-metabolic risk factors, including diabetes [12, 13] and the metabolic syndrome [14]. Remarkably, these associations are largely independent of the estimated glomerular filtration rate (eGFR), indicating that sUmod itself may play a role in metabolic and cardiovascular health.

Immunomodulatory properties might link sUmod to metabolic and cardiovascular outcomes. Analogous to its role in the urinary tract, immune-regulative functions of sUmod in the systemic circulation are conceivable. Preclinical studies investigating this issue yielded inconsistent results. Increased neutrophil numbers in the kidney and the circulation were reported in uromodulin-deficient mice, which also displayed an increased bone marrow granulopoiesis [15]. Patras *et al.* [16] showed that uromodulin binds isolated human neutrophils *in vitro* and that this interaction reduced the generation of reactive oxygen species. Furthermore, uromodulin was shown to bind immunoglobulin G [17], tumour necrosis factor (TNF)-α [18] and complement 1q [19], and inhibited the activation of the classical complement pathway *in vitro* [20].

In contrast, other studies indicated a pro-inflammatory role of uromodulin. Isolated uromodulin was shown to bind and activate human granulocytes *in vitro*, enhancing their interleukin (IL)-8 expression [4]. Further studies showed that uromodulin activated myeloid dendritic cells via toll-like receptor-4 to acquire a fully mature dendritic cell phenotype [21] and isolated human monocytes to secrete pro-inflammatory cytokines including IL-1β [5].

Data on the association of sUmod with markers of subclinical inflammation in a large epidemiological study are lacking. Therefore, we investigated the association of sUmod with markers that may increase in response to inflammatory stimuli, including white blood cell count, six pro-inflammatory biomarkers [high-sensitive C-reactive protein [hsCRP], IL-6, TNF-α, IL-18, soluble intercellular adhesion molecule-1 (sICAM-1) and myeloperoxidase (MPO)], and three anti-inflammatory markers [IL-1 receptor antagonist (IL-1RA), IL-22 and superoxide dismutase-3 (SOD-3)] in the population-based Cooperative Health Research in the Region of Augsburg (KORA) F4 study. Since women have significantly higher sUmod levels than men [12], we stratified the analyses by sex in addition to the analyses in the total study sample.

MATERIALS AND METHODS

Study participants

The KORA F4 study involved 3080 participants from the general community in the region of Augsburg, Southern Germany. KORA F4, which was the first follow-up examination of KORA S4 (1999–2001), was performed in 2006–08. Study design, recruitment and eligibility criteria, standardized sampling methods and data collection (medical history, medication, anthropometric and blood pressure measurements) have been described in detail elsewhere [22, 23]. All study participants gave written informed consent. The study was approved by the Ethics Committees of the Bavarian Medical Association in adherence to the declaration of Helsinki.

Criteria for clinically diagnosed diabetes mellitus were a validated medical diagnosis or current self-reported use of

glucose-lowering agents. All participants without clinically diagnosed diabetes underwent a standard 75 g oral glucose tolerance test. Newly diagnosed diabetes was defined according to the 1999 World Health Organization diagnostic criteria based on both fasting glucose and glucose values 2 h after intake of the 75 g glucose solution (diabetes: ≥7.0 mmol/L fasting and/or ≥11.1 mmol/L 2-h glucose). Participants with diabetes other than Type 2 diabetes ($n = 3$) or unknown glucose tolerance status ($n = 22$) were excluded from the current analysis.

sUmod was measured in 1119 participants aged 62–81 years of the KORA F4 study with available serum samples (from a total of 1161 participants in this age group). All variables necessary for the current analyses were available for 1065 participants.

Laboratory measurements

Blood samples were collected after an overnight fast of at least 8 h and were kept at room temperature until centrifugation. Plasma was separated immediately, serum after 30 min. Plasma and serum samples were assayed immediately or stored at −80°C. sUmod was measured with a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Euroimmun AG, Lübeck, Germany) with a lower detection limit of 2 ng/mL, an intra-assay coefficient of variation of 2.3% and inter-assay coefficients of variation of 4.4 and 9.5% for sUmod target values of 24.9 and 142.2 ng/mL, respectively. The measurement procedure was described by Steubl *et al.* [7]. hsCRP was determined in plasma with a high-sensitivity latex-enhanced nephelometric assay on a BN II analyser (Siemens, Erlangen, Germany). Serum levels of IL-6 and TNF-α were measured with Quantikine HS ELISA kits, IL-22, IL-1RA and -1 with Quantikine ELISA kits (R&D Systems, Wiesbaden, Germany) [24–26]. Plasma levels of IL-18 were determined using ELISA kits from MBL (Nagoya, Japan). Serum MPO concentrations were measured using the Human MPO Quantikine ELISA (R&D Systems, Wiesbaden, Germany). Serum SOD-3 concentrations were measured with an ELISA from Cloud-Clone Corp. (Houston, TX, USA) [27]. Intra-assay coefficients of variation for hsCRP, IL-1RA, IL-22, -1, IL-6, TNF-α, IL-18, MPO and SOD-3 were 2.7, 2.8, 5.5, 3.5, 7.2, 6.3, 7.6, 3.2 and 7.1%, respectively. Interassay coefficients were 6.3, 7.0, 9.3, 6.4, 11.8, 14.4, 9.4, 5.6 and 7.1%, respectively. For IL-22, 332 (31%) of the sera yielded values below the limit of detection (LOD; 3.9 pg/mL). Values below LOD were assumed to be evenly distributed between 0 and LOD and were assigned a value of 0.5× LOD. Blood glucose levels were assessed using the hexokinase method (GLU Flex; Dade Behring, Marburg, Germany). Serum creatinine was determined with a modified Jaffe test (Krea Flex; Dade Behring). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (2009) based on serum creatinine [28].

Statistical analyses

Characteristics of the study participants were compared between women and men using *t*-tests in case of approximately normally distributed variables and Mann–Whitney U-tests for variables with skewed distributions. Binomial proportions were compared with Chi-square tests. The associations of sUmod (independent variable) with biomarkers of subclinical inflammation were assessed with linear regression models. Continuous variables were transformed to a Gaussian distribution by probability integral transformation followed by inverse transform sampling. β coefficients and their respective standard error from linear regression models are given per standard deviation of sUmod. The main model was adjusted for the potential confounders sex, age, eGFR, body mass index (BMI) and diabetes, since these factors may influence subclinical inflammation and have previously been shown to be associated with sUmod [12, 14]. Active smoking, which potentially induces subclinical inflammation, was not related to sUmod ($\beta = -0.02 \pm 0.12$, $P = 0.85$) and therefore not included in the models. Analyses were computed in the total study sample, as well as in women and men separately. An alpha level of 0.05 (two-sided) was considered statistically significant. To account for multiple testing (10 parameters in 3 subgroups = 30 tests), we also reported the significance of the results setting the threshold at a $P < 0.00167$ ($0.05 \div 30$). We tested for sex interaction in order to assess differences between women and men. For the interaction terms, an alpha level of 0.1 was considered statistically significant [$P < 0.010$ after correction for multiple testing accounting for 10 tests ($0.1 \div 10$]). Calculations were performed using R, version 3.6.0.

RESULTS

Study population characteristics

Table 1 displays the characteristics of the study population. Whereas the eGFR did not differ significantly between women and men, sUmod was higher in women ($P < 0.001$). The white blood cell count and several proinflammatory biomarkers (IL-6, TNF-α, IL-18 and MPO), as well as the anti-inflammatory markers IL-22 and SOD-3, were higher in men. sICAM-1 did not differ between men and women. hsCRP and the anti-inflammatory IL-1RA were higher in women.

Association of sUmod with biomarkers of inflammation

Supplementary data, Figure S1 shows the plots of the biomarkers of subclinical inflammation in dependence of sUmod. The results of the regression models are given in Table 2. In the crude analysis in the total cohort, sUmod was inversely associated with all assessed biomarkers of subclinical inflammation. The association with sICAM-1 lost significance after adjustment for confounders, and the association with IL-18 was no longer significant after additional correction for multiple testing. All other biomarkers remained significantly inversely associated with sUmod in the total cohort after adjustment for sex, age, BMI, eGFR and diabetes, and correction for multiple testing ($P < 0.001$ for each observation).

Sensitivity analyses

Due to the functional relationship of TNF-α with IL-6 and of IL-6 with hsCRP, we additionally adjusted the association of sUmod with IL-6 for TNF-α, which only weakly affected the result ($\beta = -0.12 \pm 0.03$; $P < 0.001$), and the association of sUmod with hsCRP for IL-6, which moderately attenuated the effect (β: -0.10 ± 0.03; $P < 0.001$). Since IL-22 and IL-1RA are functionally related, we included IL-22 in the fully adjusted regression model for the association of sUmod with IL-1RA, which had a modest effect on the regression coefficient ($\beta = -0.11 \pm 0.03$; $P < 0.001$). To evaluate the possible influence of white blood cell count on the association of sUmod with IL-6, IL-22 and MPO, we included white blood cell count in the respective fully adjusted regression models. The results were only weakly attenuated and remained significant ($\beta = -0.12 \pm 0.04$ for the association of sUmod with IL-6, $\beta = -0.13 \pm 0.04$ for the association of sUmod with IL-22, $\beta = -0.12 \pm 0.03$ for the association of sUmod with

Table 1. Characteristics of the study participants[a]

Parameter	All participants	Women	Men	P-value[b]
N	1065	519	546	–
Age, years	70.3 ± 5.5	70.2 ± 5.4	70.3 ± 5.6	0.888[c]
BMI, kg/m^2	28.7 ± 4.5	29.1 ± 5.0	28.4 ± 3.9	0.021[c]
Type 2 diabetes, %	207 (19)	81 (16)	126 (23)	0.003[e]
eGFR, mL/min/1.73 m^2	77.9 (67.3–87.7)	76.8 (66.0–87.8)	79.5 (68.2–87.4)	0.349[d]
sUmod, ng/mL	152.3 (110.6–207.7)	169.9 (120.9–223.8)	138.3 (103.3–188.5)	<0.001[d]
White blood cell count/nL	5.7 (4.9–6.8)	5.6 (4.8–6.8)	5.8 (4.9–7.1)	0.003[d]
hsCRP, mg/L	1.53 (0.79–3.18)	1.67 (0.91–3.44)	1.44 (0.72–2.99)	0.019[d]
IL-6, pg/mL	1.61 (1.12–2.45)	1.53 (1.08–2.31)	1.67 (1.14–2.60)	0.034[d]
TNF-α, pg/mL	2.01 (1.47–2.89)	1.90 (1.43–2.75)	2.05 (1.51–2.98)	0.038[d]
IL-18, pg/mL	318.0 (251.0–416.0)	290.0 (228.0–370.5)	354.5 (275.5–440.0)	<0.001[d]
sICAM-1, ng/mL	229.8 (199.7–262.7)	231.0 (200.1–264.6)	229.4 (198.2–260.8)	0.630[d]
MPO, ng/mL	146.3 (95.1–211.5)	138.4 (92.3–198.0)	154.6 (96.5–226.3)	0.005[d]
IL-1RA, pg/mL	307.4 (236.4–409.7)	316.2 (245.6–419.0)	299.4 (230.4–393.4)	0.044[d]
IL-22, pg/mL	6.56 (1.95–13.20)	4.64 (1.95–9.07)	9.34 (4.69–16.67)	<0.001[d]
SOD-3, ng/mL	126.2 (111.3–142.4)	122.0 (109.6–140.4)	128.5 (113.9–144.9)	<0.001[d]

[a]Data are presented as mean ± standard deviation, median (first–third quartile) or absolute numbers (%).
[b]The P-value is related to the null hypothesis of no differences between women and men.
[c]t-test;
[d]Mann–Whitney U-test;
[e]Chi-square test.

Table 2. Associations between sUmod and biomarkers of inflammation in the total cohort and stratified by sex: β coefficients ± standard error from linear regression models are given per standard deviation of sUmod

	Total study $n = 1065$	Women $n = 519$	Men $n = 546$	Total study $n = 1065$	Women $n = 519$	Men $n = 546$	P interaction[a]
	Without adjustment			Adjustment for (sex), age, BMI, eGFR and diabetes			
Pro-inflammatory biomarkers							
White blood cell count	−0.17 ± 0.03***	−0.14 ± 0.04***	−0.19 ± 0.05***	**−0.12 ± 0.03*** **	−0.09 ± 0.04*	**−0.16 ± 0.05****	0.53
hsCRP	−0.21 ± 0.03***	−0.19 ± 0.04***	−0.28 ± 0.04***	**−0.16 ± 0.03*** **	−0.13 ± 0.04**	**−0.20 ± 0.05****	0.07
IL-6	−0.27 ± 0.03***	−0.17 ± 0.04***	−0.37 ± 0.04***	**−0.15 ± 0.03*** **	−0.06 ± 0.04	**−0.25 ± 0.04****	**<0.001**
TNF-α	−0.18 ± 0.03***	−0.13 ± 0.04**	−0.22 ± 0.04***	**−0.12 ± 0.03*** **	−0.08 ± 0.05	**−0.15 ± 0.05****	0.13
IL-18	−0.18 ± 0.03***	−0.13 ± 0.04**	−0.16 ± 0.04***	−0.08 ± 0.03**	−0.07 ± 0.05	−0.10 ± 0.04*	0.62
sICAM-1	−0.08 ± 0.03**	−0.06 ± 0.04	−0.13 ± 0.04**	−0.03 ± 0.03	0.01 ± 0.04	−0.07 ± 0.05	0.25
MPO	−0.18 ± 0.03***	−0.21 ± 0.04***	−0.11 ± 0.04*	**−0.14 ± 0.03*** **	**−0.20 ± 0.04****	−0.08 ± 0.05	0.08
Anti-inflammatory biomarkers							
SOD-3	−0.21 ± 0.03***	−0.21 ± 0.04***	−0.18 ± 0.04***	**−0.13 ± 0.03*** **	**−0.15 ± 0.04****	−0.12 ± 0.05*	0.41
IL-1RA	−0.23 ± 0.03***	−0.26 ± 0.043***	−0.23 ± 0.04***	**−0.12 ± 0.03*** **	**−0.14 ± 0.04****	−0.10 ± 0.04*	0.60
IL-22	−0.22 ± 0.03***	−0.20 ± 0.04***	−0.16 ± 0.04***	**−0.13 ± 0.03*** **	**−0.14 ± 0.04****	**−0.14 ± 0.04****	0.34

[a]In the fully adjusted model.
*P < 0.05;
**P < 0.01;
***P < 0.001.
Bold indicates statistical significance in the fully adjusted model after correcting for multiple testing (corresponding to a P < 0.00167 for the linear regression models and to a P < 0.010 for the sex interaction term).

MPO, P < 0.001 for all observations), indicating largely independent associations of sUmod with the respective markers of subclinical inflammation.

Sex differences of the association of sUmod with biomarkers of inflammation

In women, sUmod was significantly inversely related to 6 out of the 10 assessed biomarkers (white blood cell count, hsCRP, MPO, IL1-RA, IL-22 and SOD-3) after multivariable adjustment. After additional correction for multiple testing, MPO, IL-1RA, IL-22 and SOD-3 remained significantly associated with sUmod. Interestingly, three of these four biomarkers have primarily anti-inflammatory functions. The interaction term indicated a stronger association of sUmod with MPO in women than in men, which, however, lost significance after correction for multiple testing.

In men, sUmod was inversely associated with 8 out of the 10 biomarkers after multivariable adjustment, and with 5 biomarkers after additional correction for multiple testing. These five biomarkers were white blood cell count, hsCRP, IL-6, TNF-α and IL-22, four of which have primarily pro-inflammatory properties. The interaction term showed a stronger association of sUmod with hsCRP and IL-6 in men compared with women, and

remained significant for the association of sUmod with IL-6 after correction for multiple testing.

DISCUSSION

In the population-based KORA F4 study, we found an inverse association of sUmod with all assessed biomarkers of subclinical inflammation except for sICAM-1 and IL-18, which lost significance after multivariable adjustment and correction for multiple testing. Remarkably, the associations were largely independent of the eGFR and do therefore not seem to primarily depend on kidney function and renal filtration of the inflammation markers. The inverse associations of sUmod with the inflammation markers may indicate an immunoregulatory effect of sUmod. Possible mechanisms reported from preclinical studies are binding of these serum components [17–20], downregulation of immune cells [15, 16], inhibiting the c-Jun N-terminal kinase signalling in proximal epithelial cells [29], a pathway that may also be involved in the release of cytokines, and enhancing the clearance of cytokines as a renal ligand for systemic cytokine clearance [30, 31]. Concerning the primarily anti-inflammatory biomarkers, also indirect effects may play a role, since all three investigated anti-inflammatory markers display reactive elevations in response to pro-inflammatory stimuli and cardio-metabolic risk factors.

Association of sUmod with pro-inflammatory biomarkers

hsCRP, IL-6 and TNF-α are general biomarkers of subclinical inflammation and are functionally related [32]. TNF-α activates the transcription factor nuclear factor-κB, thereby inducing IL-6 expression [33], whereas IL-6 stimulates CRP generation in the liver [34]. Inclusion of TNF-α in the regression model hardly influenced the association of sUmod with IL-6. However, adjustment for IL-6 weakened the association of sUmod with hsCRP, which nevertheless remained significant. These data indicate that the association of sUmod with pro-inflammatory biomarkers may partly be influenced by each other.

IL-18 is a pro-inflammatory molecule of the IL-1 family and was moderately inversely associated with sUmod in our cohort, but the association lost significance after correction for multiple testing. sICAM-1 represents a marker of vascular inflammation. Elevated levels of cell adhesion molecules including sICAM-1 in the circulation result from increased expression and/or shedding of these proteins from the surface of endothelial cells due to endothelial cell activation [35]. sUmod was not associated with sICAM-1 after multivariable adjustment, thereby giving no hint for direct vasoprotective effects of sUmod.

MPO is a member of the superfamily of haem peroxidases and catalyses the conversion of H_2O_2 to reactive oxygen species. MPO is associated with inflammation, oxidative stress, multiple cardio-metabolic risk factors and incident cardiovascular events [36–38]. MPO is mainly expressed in neutrophils and monocytes [39]. In line with the inverse association of sUmod with MPO in our cohort, Delgado *et al.* [11] showed a lower percentage of neutrophils with increasing sUmod values in their cohort of patients admitted for coronary angiography. Correspondingly, we here show an inverse association of sUmod with white blood cell count although we cannot provide a differential leucocyte count.

Association of sUmod with anti-inflammatory biomarkers

Extracellular SOD-3 is a major antioxidant enzyme in the circulation catalysing the dismutation of superoxide radicals (O_{2^-} to H_2O_2). Gene variants associated with lower SOD-3 levels are related to a higher cardiovascular risk [40]. However, SOD-3 appears to undergo reactive elevation in cardio-metabolic risk situations [41] and is produced in response to reactive oxygen species and pro-inflammatory cytokines. Interestingly, a recent preclinical study reported increased oxidative stress in uromodulin-deficient mice [29], a possible mechanism mediating increased SOD-3 expression.

IL-1RA represents an anti-inflammatory cytokine from the IL-1 family. IL-1RA inhibits the action of IL-1β, one of the most potent inducers of innate immunity, by blocking its receptor [42]. In experimental studies, IL-1RA deficiency fuelled arterial inflammation and atherosclerosis [43, 44]. On the other hand, IL-1RA levels may increase secondary to IL-1β-related processes [42] and were shown to be elevated in individuals with metabolic risk factors, such as obesity, insulin resistance and Type 2 diabetes [45, 46]. Therefore, despite protective properties, higher circulation IL-1RA levels may indicate a higher risk for Type 2 diabetes [47] and cardiovascular disease [25].

Similarly, IL-22 may be increased secondarily to cardio-metabolic risk factors. IL-22 is a member of the IL-10 cytokine family produced by different leucocyte subsets and limits systemic inflammation [48]. Nonetheless, IL-22 was positively associated with cardiovascular risk parameters (male sex, current smoking and lower high density lipoprotein) [26] and may thus represent a biomarker for a systemic response against cardio-metabolic risk situations. IL-22 is implicated in the production of IL-1RA [49], suggesting that IL-22 may contribute to higher IL-1RA levels. Furthermore, the proinflammatory cytokine IL-1β is not only a positive regulator of IL-1RA, but also of IL-22 [48]. However, inclusion of IL-22 into the model only weakly influenced the association of sUmod with IL-1RA, indicating no major interference.

Potential sex differences in the association of sUmod with biomarkers of inflammation

We observed sex differences in the associations of sUmod with various immune biomarkers. Overall, women showed more and stronger inverse associations of sUmod with anti-inflammatory than with pro-inflammatory biomarkers, except for MPO, which was the only analysed pro-inflammatory biomarker displaying a stronger association with sUmod in women than in men. In men, the inverse associations of sUmod were more pronounced with pro-inflammatory biomarkers. Men displayed a stronger association of sUmod with hsCRP and IL-6 than women with a highly significant P-value for interaction regarding IL-6. White blood cell count, TNF-α and IL-18 also showed a stronger inverse association with sUmod in men, although the sex interaction term was not significant for these parameters.

These observations may indicate that sUmod might have a stronger immunoregulatory effect in men than in women, despite the higher sUmod levels in women. Interestingly, the inverse association of sUmod with all-cause and cardiovascular mortality and with Type 2 diabetes was only present in men in our cohort [8, 12]. Hypothetically, different sUmod properties in women and men are conceivable, with hormonal factors playing a role. For example, uromodulin isolated from the urine of pregnant women has different immunomodulatory properties

compared with uromodulin from men and non-pregnant women, probably due to an altered uromodulin glycosylation state [50]. Whether such differences are also detectable in sUmod and may also account for postmenopausal women (as were included in the current study) remains to be clarified.

Study strengths and limitations

Strengths of our study are the population-based design with a large, well-characterized population-based study sample. However, only participants aged 62–81 years were included. Therefore, the associations of sUmod with biomarkers of inflammation remain to be confirmed in a younger population. Due to the observational nature of our study, we are not able to provide data on causal relationships and mechanistic links and cannot exclude reverse causation, i.e. inflammatory reactions decreasing sUmod.

CONCLUSIONS

sUmod was independently inversely associated with multiple biomarkers of subclinical inflammation in older adults from a general population. The data strengthen the view that uromodulin in addition to its renal functions also has systemic immunomodulatory effects. The associations partly differed between women and men with a trend towards stronger inverse associations of sUmod with anti-inflammatory biomarkers in women and with pro-inflammatory biomarkers in men. Future studies will clarify whether immunomodulatory properties of sUmod are responsible for its inverse association with cardiovascular events and mortality, and whether the differences in the associations of sUmod with biomarkers of inflammation between sexes are one explanation of the divergent associations of sUmod with all-cause and cardiovascular mortality and with Type 2 diabetes in women and men.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

DATA AVAILABILITY

The data are subject to national data protection laws and restrictions were imposed by the Ethics Committee of the Bavarian Chamber of Physicians to ensure data privacy of the study participants. Therefore, data cannot be made freely available in a public repository. However, data can be requested through an individual project agreement with KORA via the online portal KORA.passt (https://epi.helmholtz-muenchen.de/).

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AUTHORS' CONTRIBUTIONS

Conception and design of the study was done by C.T., B.T., C.M., C.Herder, C.Huth, M.R., M.H., A.P., W.K., W.R., M.S., H.M., T.M., J.Scherberich and J.Seissler; collection of data by B.T., C.T., C.M., C.Herder, C.Huth, M.R., M.H., A.P., W.K., W.R., A.L., M.S., T.M., J.Scherberich and J.Seissler; data analysis, interpretation of results, writing of the manuscript was by C.T., H.T., A.L., J.Scherberich and J.Seissler; all authors revised the manuscript critically for intellectual content and approved the final version.

CONFLICT OF INTEREST STATEMENT

C.Herder reports grants and personal fees from Sanofi and Lilly. W.K. reports personal fees from AstraZeneca, Novartis, Pfizer, The Medicines Company, from DalCor, Kowa, Amgen, Corvidia, Daiichi-Sankyo, Berlin-Chemie, Sanofi and Bristol-Myers Squibb, and grants and non-financial support from Singulex, Abbott, Roche Diagnostics and Beckmann. M.R. reports personal fees from Eli Lilly, Poxel S.A. Société, Boehringer-Ingelheim Pharma, Terra Firma, Sanofi US, Servier Laboratories, PROSCIENTO, Inc., Novo Nordisk, Fishawack Group, Novartis Pharma GmbH, Target Pharmasolutions, Gilead Sciences, Kenes Group, Bristol-Myers Squibb, Intercept Pharma. Inventiva, Astra Zeneca and Allergan GmbH. J.Scherberich has a patent at the University Charite Berlin pending. The reported disclosures are not directly related to this manuscript. The other authors declare that they have no conflict of interest associated with this manuscript.

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