

Plasma copeptin as a predictor of kidney disease

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ABSTRACT

Background. Plasma copeptin, a marker of vasopressin, is associated with renal function decline in the general population. Our aim was to study the links between elevated copeptin and future risk of kidney disease.

Methods. Copeptin was measured in a sample of the Malmö Preventive Project (MPP) Reinvestigation ($n = 5158$) and in the Malmö Diet and Cancer Cardiovascular Cohort (MDC-CC) ($n = 5162$). According to national registers, 89 subjects in MPP and 180 in MDC-CC developed chronic kidney disease (CKD) during follow-up (8.7 and 19.6 years, respectively).

Results. After multivariate adjustment (gender, age, body mass index, smoking status, estimated glomerular filtration rate, prevalent diabetes, systolic blood pressure and prevalent antihypertensive treatment), copeptin (beta-coefficient per 1 standard deviation increment of ln copeptin) was independently associated with increased risk of CKD during follow-up in both cohorts (MPP: (HR) 1.46, 95% confidence interval (CI) 1.18–1.80, $P < 0.001$; MDC-CC: HR 1.25, 95% CI 1.02–1.54, $P = 0.03$) among subjects free from prevalent kidney disease at baseline. Furthermore, in MPP, elevated copeptin predicted a specified diagnosis of kidney disease other than CKD (HR 1.31, 95% CI 1.08–1.59, $P = 0.006$) after multivariate adjustment. In a corresponding analysis in MDC-CC, copeptin was associated with a 10% increased risk, which, however, was non-significant ($P = 0.25$). A meta-analysis of the MPP and MDC-CC data showed significant association between elevated copeptin and a specified diagnosis of kidney disease other than CKD (HR 1.18, 95% CI 1.05–1.34, $P = 0.008$).

Conclusion. An increased level of copeptin independently predicts development of both CKD and other specified kidney diseases, suggesting that copeptin can be used to identify individuals at risk for kidney disease development.

Keywords: copeptin, diagnosis, kidney disease, meta-analysis, vasopressin

INTRODUCTION

Around 10% of individuals worldwide suffer from chronic kidney disease (CKD), which is a growing problem [1]. Decreased renal function is associated with an increased risk for cardiovascular events and death [2].

The main role of the pituitary peptide vasopressin (VP) is to regulate water reabsorption by VP 2 Receptor (V2R)-mediated recruitment of aquaporins in the collecting ducts of the kidney, and thereby maintaining plasma osmolality within a narrow range [3, 4]. However, VP acts in many organs and has a variety of different physiological effects, and we and others previously established VP as an independent risk factor for diabetes, the metabolic syndrome, cardiovascular disease and death [5–10]. The VP 1a receptor (V1aR) is involved in vasoconstriction and platelet aggregation in the vessels [11, 12], and glycogenolysis and gluconeogenesis in the liver [13, 14], whereas the VP 1b receptor (V1bR) stimulates adrenocorticotrophic hormone (ACTH) release from the anterior pituitary gland and cortisol release from the adrenal gland [15, 16]. Furthermore, depending on the current glucose level in plasma, V1bR mediates insulin or glucagon release from the pancreas [17]. Thus, it is suggested that the V1aR and/or V1bR play a role in the pathophysiology behind VP-associated cardiometabolic risk.

VP is difficult to measure and most assays have relatively limited sensitivity [18]. An assay has been developed to quantify VP release by measurement of copeptin, the C-terminal part of the VP precursor protein, which correlates well with VP levels and can be determined reliably in plasma [19]. Recently, allelic variation in the human VP gene was associated with both elevated copeptin and increased risk of hyperglycaemia, supporting causal association between elevated copeptin and metabolic risk [20].

Several experimental studies in rats have shown that chronic infusion of a V2R-agonist (dDAVP) contributes to proteinuria and renal function decline [21, 22], and the reverse, that low

circulating VP level due to increased water intake, or V1a/V2-receptor antagonism, improves kidney function by reducing VP-mediated effects in the kidney [23, 24]. Furthermore, experiments in humans have shown that V2R-agonists increase urinary albumin excretion in healthy individuals, an effect that is absent in individuals with nephrogenic diabetes insipidus and thus no functional V2Rs in the collecting ducts of the kidney [22]. In addition, in population-based cohorts, the risk of CKD and decline in estimated glomerular filtration rate (eGFR) was inversely correlated with fluid intake and urine volume [25, 26]. In line with these findings, we and others recently showed that elevated copeptin was associated with microalbuminuria [8] as well as renal function decline, both in diabetics [27, 28] and in the general population [29, 30].

In this study, we investigate if elevated copeptin is associated with increased risk not only of CKD generally associated with metabolic disease, but also with other types of kidney disease.

MATERIALS AND METHODS

Population and cohort description

This study was conducted in the Malmö Preventive Project (MPP) cohort and the Malmö Diet and Cancer Cardiovascular Cohort (MDC-CC). The Malmö Diet and Cancer study is a Swedish population-based prospective cohort consisting of 30 447 individuals surveyed in 1991–96 with the aim of exploring the links between dietary patterns and cancer [31]. From the Malmö Diet and Cancer study, a random 50% were invited to a sub-study for the epidemiology of carotid artery disease. This sample is referred to as the MDC-CC and consists of 6103 individuals [32]. Copeptin was measured in the majority of MDC-CC participants ($n = 5252$) and complete data were available in 5162 individuals.

The MPP is also a Swedish population-based prospective cohort. It consists of 33 346 individuals recruited between 1974 and 1992 from the city of Malmö who are screened for traditional risk factors of all-cause mortality and cardiovascular disease. Between 2002 and 2006, all subjects who were alive were invited for a re-examination ($n = 18 240$). Cardiovascular risk factors were re-assessed and plasma was frozen to -80°C for later analyses. Among these 18 240 subjects, a random sample of 5410 individuals were chosen and fasting plasma copeptin was measured. The only exclusion criterium was prior participation in the MDC-CC. Complete data were available in 5158 individuals.

The research was conducted in accordance with the Helsinki Declaration and the study protocols were approved by the regional Ethics Committee of Lund University. All the participants provided written informed consent.

Ascertainment of endpoints and covariates

Cases of renal diseases were identified by the Swedish National Patient Register, which is a principal source of data for numerous research projects that cover >99% of all somatic and psychiatric hospital discharges and Swedish hospital-based outpatient care [33] and the Swedish Cause-of-Death Register, which comprises all deaths among Swedish residents occurring

in Sweden or abroad [34]. However, the Swedish National Patient Register did not cover hospital-based outpatient care until 2001 [35], which is why we calculated baseline eGFR and used a cut-off value of $<60\text{ mL/min/1.73 m}^2$ as a measure of prevalent kidney disease. Prevalent kidney disease was then defined as either eGFR $<60\text{ mL/min/1.73 m}^2$ or a register-based kidney diagnosis captured before the baseline investigation (Table 1).

CKD was defined as a diagnosis of any of the following International Classification of Diseases (ICD) 9 or ICD 10 codes: 585, 585.1–585.6, 585.9, N18.1–N18.5 or N18.9. Specified kidney disease other than CKD was defined as a diagnosis of any of the following ICD 9 or ICD 10 codes: 580–583, 7531, N10–N16 or Q61. A few cases of dialysis care (ICD 10 code Z49) were identified but not classified as renal disease if not associated with any other renal disease diagnosis.

The CKD diagnoses were validated in a two-step quality process in which two experienced specialists in nephrology independently analysed the patient records and laboratory data for 100 randomly selected patients following the ICD 9 and ICD 10 codes for CKD. The CKD diagnosis requires two GFR measurements with at least 3 months in between in order to fulfill the criteria. Diagnoses were divided according to degree of accuracy. Eighty-six cases were considered to be accurate at the first evaluation. The rest of the cases were considered to be either inaccurate, to have low probability of accuracy or insufficient information, or to have reasonably high probability of accurate diagnoses, and were all re-evaluated to receive a final degree of accuracy. The validation showed that 94% of the patients had a correct diagnosis of CKD.

Prevalent diabetes diagnosis was defined as a self-reported physician diagnosis of diabetes or use of antidiabetic medication or fasting plasma glucose $\geq 7.0\text{ mmol/L}$ (in MPP) or fasting blood glucose of $\geq 6.1\text{ mmol/L}$ (in MDC-CC). Furthermore, prevalent and incident diabetes cases were captured by six different national and regional diabetes registers as described in detail previously [9]. Finally, in MDC-CC, incident diabetes could be captured at the MDC-CC reinvestigation as described previously [9]. Blood pressure was measured with a mercury-column sphygmomanometer after 10 min of rest in the supine position. Hypertension was

Table 1. Baseline characteristics

Characteristics	MPP ($n = 5158$)	MDC-CC ($n = 5162$)
Age (years)	69.2 \pm 6.2	57.5 \pm 5.9
Gender, men, n (%)	3559 (69.9)	2110 (40.9)
Systolic blood pressure (mmHg)	145.7 \pm 20.6	141.4 \pm 19.0
Diastolic blood pressure (mmHg)	83.8 \pm 10.8	87.0 \pm 9.4
Antihypertensive treatment, n (%)	2013 (39.0)	873 (16.9)
eGFR (mL/min/1.73 m^2) ^a	66.5 \pm 15.6	76.1 \pm 13.8
Kidney disease, n (%) ^b	1820 (35.3)	589 (11.4)
Diabetes, n (%)	590 (11.4)	432 (8.4)
Copeptin (pmol/L) ^c	7.1 (4.3–12.0)	5.2 (3.2–8.2)

Mean \pm SD if not otherwise specified.

^aAccording to the 2009 CKD-EPI creatinine formula.

^bDiagnosis of any kidney disease at baseline or eGFR $<60\text{ mL/min/1.73 m}^2$.

^cExpressed as median (interquartile range).

defined as baseline systolic blood pressure of 140 mmHg or greater, diastolic blood pressure of 90 mmHg or greater or use of antihypertensive medication.

Laboratory measurement

Copeptin was measured in fasting plasma samples stored at -80°C using a commercially available chemiluminescence sandwich immunoassay with coated tubes (B.R.A.H.M.S AG, Hennigsdorf, Germany) [19]. Measurement of P-creatinine was made according to standard procedures at the Department of Clinical Chemistry, Skåne University Hospital, Malmö, with the Jaffé method and traceable to the International Standardization with isotope dilution mass spectrometry. eGFR was calculated using the 2009 CKD Epidemiology Collaboration (CKD-EPI) creatinine formula [36].

Statistics

SPSS statistical software (version 24.0; SPSS Inc., Chicago, IL, USA) was used for all calculations except for the meta-analysis, where Stata statistical software (version 13.1; StataCorp, College Station, TX, USA) was used. The distribution of copeptin was skewed to the right and, therefore, transformed using the natural logarithm. Baseline copeptin was related to risk of development of renal disease using multivariate Cox proportional hazards models and Kaplan–Meier plots. An interaction term was introduced on top of all other covariates (copeptin \times diabetes status) to test for interaction on risk of CKD. A two-sided P-value of <0.05 was considered statistically significant.

RESULTS

At baseline of the MPP study, the mean age was 69 ± 6 years, 70% were males and the prevalence of kidney disease (diagnosis of any kidney disease at baseline or $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$) was 35%. At the MDC-CC baseline, the mean age was 58 ± 6 years, 41% were males and the prevalence of kidney disease was 11%.

In MPP, 89 subjects free from prevalent kidney disease developed CKD during a follow-up time [mean \pm standard deviation (SD)] of 8.7 ± 2.4 years, and in MDC-CC the corresponding numbers were 178 incident cases during a follow-up time of 19.6 ± 4.7 years (Table 2).

A 1 SD increment of ln-transformed copeptin was, after multivariate adjustment [gender, age, body mass index (BMI), smoking status, eGFR, prevalent diabetes, systolic blood pressure and prevalent antihypertensive treatment], associated with a 46% increased risk of CKD during follow-up in MPP, and a

Table 2. Incident register-based CKD in MPP and MDC-CC in subjects free from kidney disease^a at baseline

Disease/condition	MPP (<i>n</i> = 5158)	MDC-CC (<i>n</i> = 5162)
Number of subjects without prevalent kidney disease	3338	4573
Incident CKD	89	178

^aFree from all kinds of register-based renal disease at baseline and with baseline $\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$.

24% increased risk in MDC-CC (Table 3). Subjects who developed other defined kidney diseases than CKD during follow-up (according to Table 4) were censored in the analyses. A meta-analysis of the MPP and MDC-CC data further strengthened the significant association between copeptin and CKD development [hazard ratio (HR) 1.34, 95% confidence interval (95% CI) 1.16–1.56, $P < 0.001$] (Figure 1A). When dividing the subjects into tertiles of copeptin, the subjects in the top tertile had

Table 3. Plasma copeptin as a predictor of CKD

Population/subgroup	HR	95% CI	P-value
All			
CKD development MPP (<i>n</i> = 89/3338) ^a	1.46	1.18–1.80	<0.001
CKD development MDC-CC (<i>n</i> = 178/4573) ^a	1.24	1.01–1.53	0.04
Individuals with diabetes diagnosis ^b			
CKD development MPP (<i>n</i> = 34/736)	1.42	0.95–2.12	0.09
CKD development MDC-CC (<i>n</i> = 84/835)	1.23	0.89–1.70	0.22
Individuals without diabetes diagnosis			
CKD development MPP (<i>n</i> = 55/2602)	1.45	1.13–1.85	0.003
CKD development MDC-CC (<i>n</i> = 94/3738)	1.25	0.95–1.65	0.12

In subjects free from all kinds of kidney disease at baseline and with $\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$.

Cases of specified incident kidney diseases other than CKD disease (see Table 4) are censored in the analyses.

HRs expressed as per SD increment of ln-transformed copeptin.

Analyses adjusted for age, gender, BMI, smoking status, eGFR, systolic blood pressure and prevalent antihypertensive treatment.

^aAnalysis additionally adjusted for prevalent diabetes.

^bPrevalent or incident diabetes.

Table 4. Incident specified kidney diseases and conditions in MPP and MDC-CC in subjects free from kidney disease^a at baseline

Disease/condition	MPP (<i>n</i> = 5158)	MDC-CC (<i>n</i> = 5162)
Number of subjects without prevalent kidney disease	3338	4573
Acute glomerulonephritis	1	4
Rapidly progressive glomerulonephritis	7	6
Recurrent and persistent haematuria	1	2
Chronic glomerulonephritis	5	10
Nephrotic syndrome	4	0
Non-specified glomerulonephritis	4	0
Isolated proteinuria with specified morphological lesion	0	3
Hereditary nephropathy not classified elsewhere	0	0
Glomerular disorders	4	10
Acute nephritis/glomerulonephritis	0	1
Chronic glomerulonephritis	0	1
Acute tubulointerstitial nephritis	58	118
Chronic tubulointerstitial nephritis	2	6
Tubulointerstitial nephritis, not specified as acute or chronic	4	7
Hydronephrosis	41	61
Toxic nephropathy	0	3
Tubulointerstitial kidney disease	1	1
Tubulointerstitial kidney disease in diseases classified elsewhere	0	2
Cystic kidney disease	0	3
Specified kidney diseases pooled	118	213

^aIn subjects free from all kinds of register-based kidney disease at baseline and with $\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$.

an 8–10% risk of CKD diagnosis compared with around 2% risk in the bottom tertile (Figure 2). There was no significant interaction between diabetes status and copeptin on the risk of CKD in either the MPP or the MDC-CC cohort (data not shown). These negative findings were concordant with the findings of the performed subanalyses in non-diabetic and diabetic individuals, respectively, in which the only result that remained significant was the association between elevated copeptin and risk of CKD among non-diabetic individuals in the MPP population (Table 3).

Among subjects free from prevalent kidney disease, 118 subjects in MPP and 213 subjects in MDC-CC received a specified diagnosis of kidney disease other than only CKD diagnosis during follow-up (as listed in Table 4). Within this group, by far the most frequent diagnoses in both cohorts were acute tubulointerstitial nephritis and hydronephrosis. In MPP, 1 SD

increment of ln-transformed copeptin was, after multivariate adjustment (gender, age, BMI, smoking status, eGFR, prevalent diabetes, systolic blood pressure and prevalent antihypertensive treatment), associated with a 31% increased risk of receiving any of these specified kidney diseases other than CKD (Table 5). In MDC-CC, there was a 10% increased risk which was, however, not significant ($P = 0.25$) (Table 5). Subjects who first had a diagnosis of CKD during follow-up (according to Table 2) were censored in the analyses. A meta-analysis of the MPP and MDC-CC data showed a significant association between copeptin and specified kidney diseases other than CKD (HR 1.18, 95% CI 1.05–1.34, $P = 0.008$) (Figure 1B). When dividing the subjects into tertiles of copeptin, the subjects in the top tertile had an 8–10% risk of these specified other kidney disease diagnosis compared with around 2–4% risk in the bottom tertile (Figure 3).

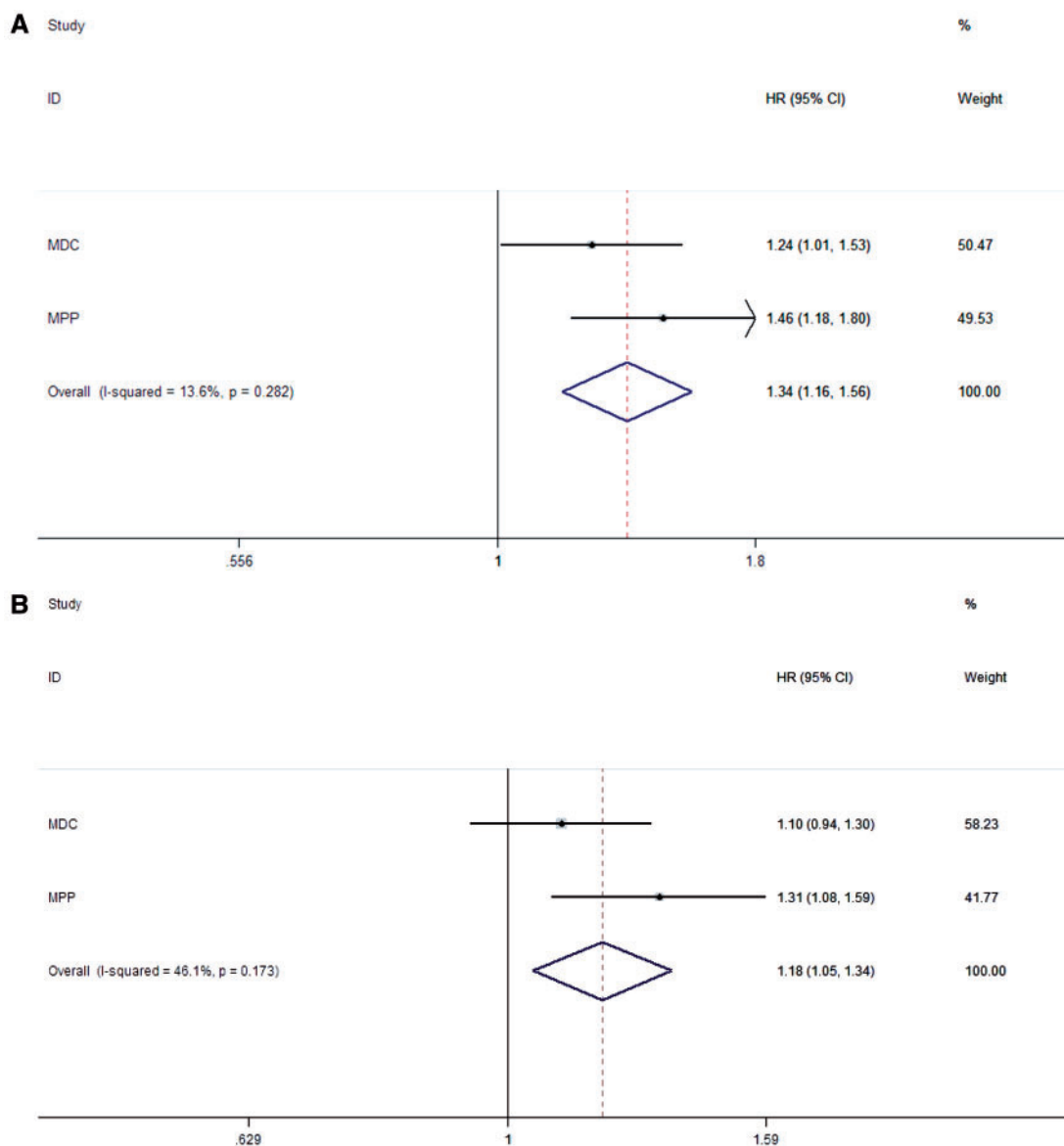


FIGURE 1: Meta-analysis of the MPP and MDC-CC data on the association between copeptin (beta-coefficient per 1 SD increment of ln copeptin) and CKD development (A) and Meta-analysis of the MPP and MDC-CC data on the association between copeptin (beta-coefficient per 1 SD increment of ln copeptin) and development of specified kidney disease other than CKD (B).

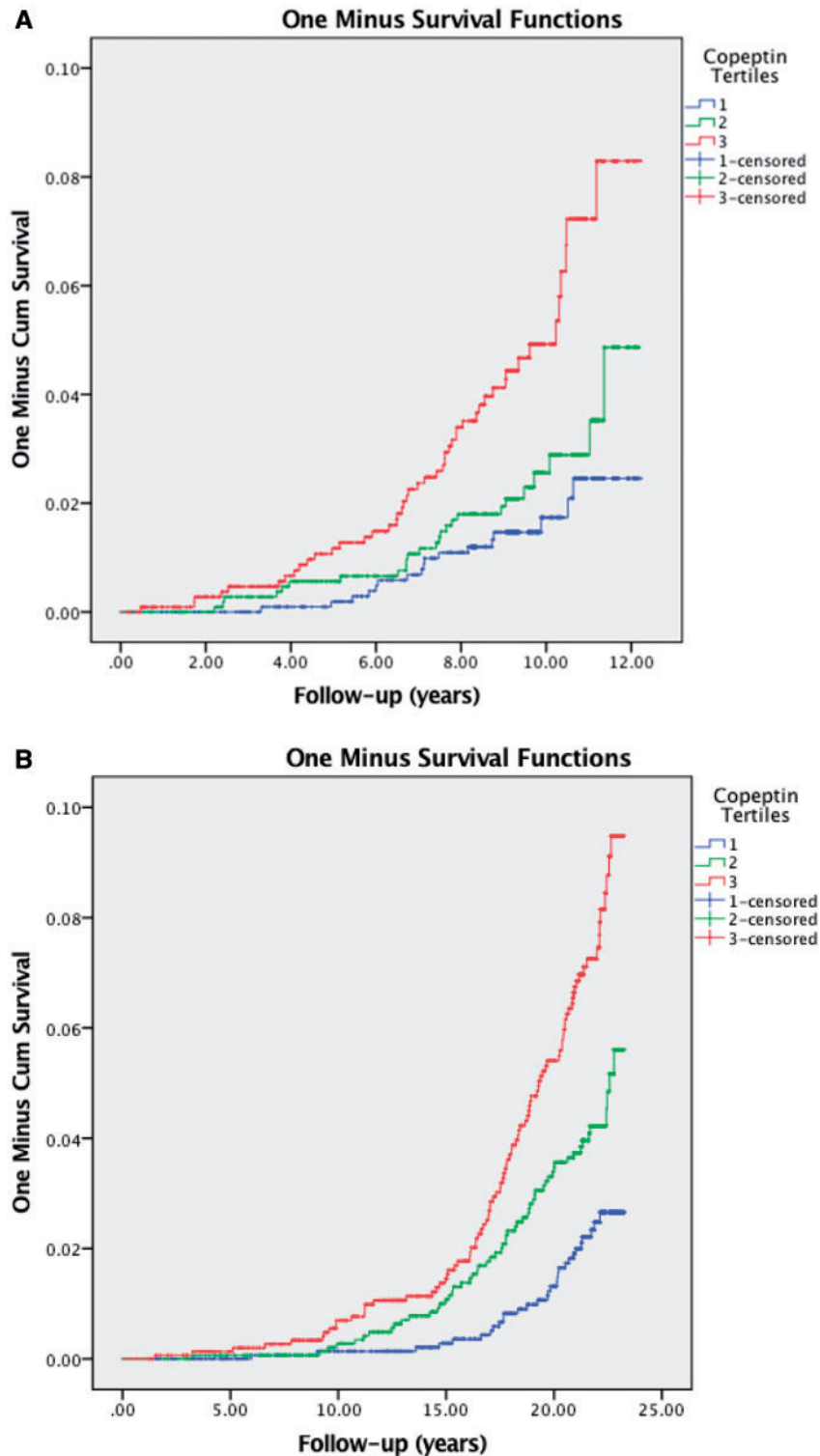


FIGURE 2: Increased risk of CKD diagnosis in the highest tertile of copeptin in MPP (A) and MDC-CC (B), among subjects without diagnosis of prevalent kidney disease and with baseline eGFR (CKD-EPI 2009) ≥ 60 mL/min/1.73 m². Cases of specified kidney disease are censored.

Incident cases of specified kidney diseases other than CKD were subdivided into either glomerulonephritis or tubulointerstitial diseases. Diagnoses of hydronephrosis and cystic kidney diseases were included in the latter as these conditions are associated with tubulointerstitial degradation [37, 38]. In MPP, 1 SD increment of ln-transformed copeptin was, after

multivariate adjustment (gender, age, BMI, smoking status, eGFR, prevalent diabetes, systolic blood pressure and prevalent antihypertensive treatment), associated with a 34% increased risk of receiving any specified tubulointerstitial kidney disease diagnosis (Table 5). In MDC-CC there was an 8% increased risk, which was not significant ($P = 0.40$) (Table 5). There was

Table 5. Plasma copeptin as a predictor of specified kidney diseases

Groups of specified disease diagnoses	HR	95% CI	P-value
All specified kidney diseases and conditions MPP (<i>n</i> = 118/3338) ^a	1.31	1.08–1.59	0.006
All specified kidney diseases and conditions MDC-CC (<i>n</i> = 213/4573) ^a	1.10	0.93–1.30	0.25
Glomerulonephritis diagnoses pooled MPP (<i>n</i> = 23/3338) ^b	1.24	0.79–1.92	0.35
Glomerulonephritis diagnoses pooled MDC-CC (<i>n</i> = 38/4573) ^b	1.28	0.82–2.00	0.28
Tubulointerstitial disease, hydronephrosis and cystic disease diagnoses pooled MPP (<i>n</i> = 99/3338) ^c	1.34	1.08–1.65	0.007
Tubulointerstitial disease, hydronephrosis and cystic disease diagnoses pooled MDC-CC (<i>n</i> = 180/4573) ^c	1.08	0.91–1.28	0.40

In subjects free from all kinds of kidney disease at baseline and with eGFR ≥ 60 mL/min/1.73 m².

^aIncident cases of CKDs (see Table 2) are censored in the analyses.

^bIncident cases of CKDs (see Table 2) as well as cases of tubulointerstitial disease, hydronephrosis and cystic diseases (see Table 4) are censored in the analyses.

^cIncident cases of CKDs (see Table 2) as well as cases of glomerulonephritis diseases (see Table 4) are censored in the analyses.

HRs expressed as per SD increment of ln-transformed copeptin.

Adjusted for age, gender, BMI, smoking status, eGFR, systolic blood pressure, prevalent antihypertensive treatment and prevalent diabetes.

no significant association between copeptin increment and risk of the pooled glomerulonephritis endpoint in either MPP or MDC-CC (Table 5).

There was a significant overlap of CKD diagnoses and other specified kidney disease diagnoses in both populations. In MPP, 21% of the subjects with incident CKD (Table 2) also had incident specified kidney disease other than CKD (as listed in Table 4), and 27% of those with incident specified kidney disease other than CKD had incident CKD. The corresponding numbers in MDC-CC were 24 and 20%, respectively.

DISCUSSION

In the present study, the key finding is that elevated baseline copeptin is independently associated with increased risk of CKD development in two separate cohorts from the Swedish general population followed for 9 and 20 years, respectively. Furthermore, in the MPP cohort, and in a meta-analysis of the MPP and MDC-CC cohorts, association between elevated copeptin and increased risk of specified kidney diseases other than CKD is observed.

Our current data extend our previous finding that increased levels of copeptin independently predict decline in eGFR [30], and suggest that copeptin can be used to identify individuals at higher risk for development of CKD. Whether the relationship between VP (measured as copeptin) and disease development is causal or due to covariation is unknown. Together with previous experiments in humans and animals, showing progressive renal function decline during VP exposure [21, 22], as well as beneficial effects on kidney function as a result of genetic lack of VP [21, 39], VP receptor antagonism [24] and increased water intake [23], our current data point at a possible causal role of elevated VP in the progression of CKD. Assuming causality between VP and CKD development, lowering of circulating VP level, for example by increased water intake or pharmacological manipulation, would represent a promising treatment target. Our data further implicate beneficial effects of lower circulating VP concentrations/increased hydration in the progression of specific other renal diseases.

According to previous studies on underlying causes of CKD development, the main CKD risk factors are metabolic diseases such as diabetes and hypertension [40, 41]. As we previously

found links between elevated copeptin and incident diabetes and hypertension [5, 7], we suspected that part of the association between elevated copeptin and CKD during follow-up would be driven by new-onset metabolic disease. However, this could not explain the observed association between copeptin and risk of developing other specified kidney diseases such as acute tubulointerstitial nephritis or hydronephrosis. Furthermore, there was no significant interaction between diabetes status and copeptin on the risk of CKD in either of the cohorts, and in sub-analyses of diabetic and non-diabetic individuals, respectively, the association between copeptin and CKD remained only in the subgroup of non-diabetic individuals in the MPP population (Table 3). Thus, it is likely that other pathophysiological mechanisms are involved.

In the kidney, the main role of VP is to mediate antidiuresis. The antidiuretic action of VP mainly depends on three V2R-mediated effects in the renal collecting duct that all contribute to an increased urine osmolality: water permeability (through recruitment of aquaporin 2), urea permeability and sodium reabsorption [42]. Furthermore, VP exhibits V1aR-mediated actions in the collecting duct that tend to reduce the V2 effects by activation of prostaglandin synthesis [42, 43]. The mechanisms that underlie VP-associated development of CKD are not fully unraveled, but it is hypothesized that the VP-induced increase in renal plasma flow and GFR (hyperfiltration) is at least partially involved [39, 44]. The mechanisms behind VP-mediated hyperfiltration are probably indirect [44]. It is suggested that a decrease in sodium and urea excretion, due to increase in V2R-mediated urine concentration activity, may lead to a compensatory rise in GFR [44, 45], which thus aggravates the risk of glomerular ageing [46].

In autosomal dominant polycystic kidney disease, VP exerts direct effects on the cysts and plays an important role in the disease progression [47]. These mechanisms thus differ from the pathophysiology behind VP-induced progression of CKD. In the current study, there were altogether only three individuals receiving the diagnosis cystic kidney disease, and cyst growth is, therefore, expected to play a minor role in the findings of the current study.

As the composite endpoint of any specified kidney disease diagnoses other than CKD consisted of a set of widely diverse diagnoses, and as most VP effects in the kidney are known to be

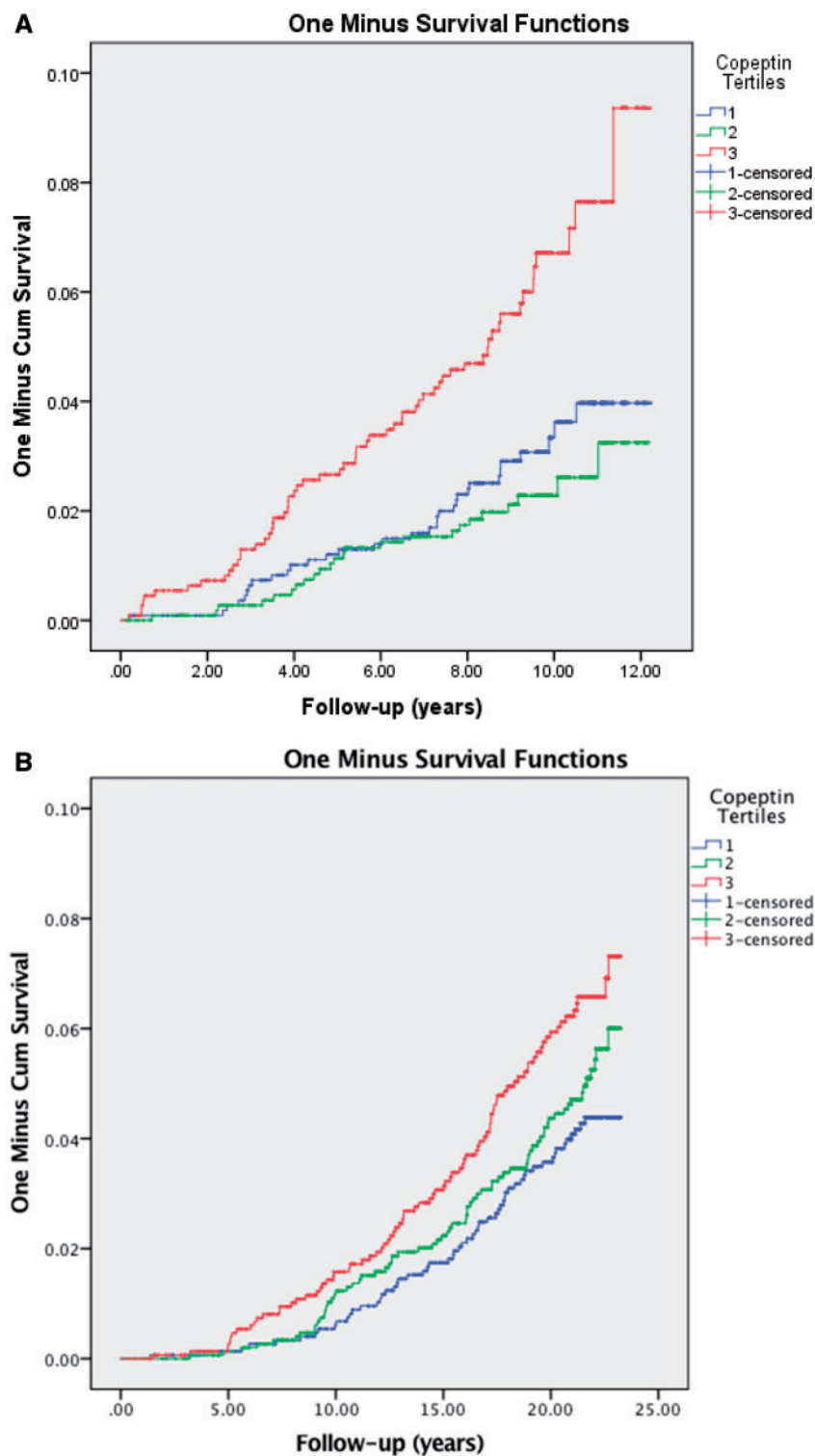


FIGURE 3: Increased risk of specified kidney diseases in the highest tertile of copeptin in MPP (A) and MDC-CC (B), among subjects without diagnosis of prevalent kidney disease and with baseline eGFR (CKD-EPI 2009) ≥ 60 mL/min/1.73 m². Cases of CKD are censored.

mediated through the V2R situated in the collecting ducts, we found it reasonable to divide our incident specified kidney disease cases into subgroups of either glomerulonephritis or tubulointerstitial disease (Table 5). Hydronephrosis and cystic kidney diseases are conditions associated with tubulointerstitial degradation [37, 38], which is why these diagnoses were included in the tubulointerstitial diagnoses. In these subanalyses,

we found that the association between elevated copeptin and increased risk of specified kidney disease in MPP was mainly driven by the risk of tubulointerstitial kidney disease (Table 5), a finding that may be linked to the fact that the V2R are localized in the tubuli. However, one may argue that hydronephrosis is not a disease diagnosis but a condition following obstruction, which is why a subanalysis without incident hydronephrosis

was performed in the MPP cohort. This analysis showed that the association between (1 SD increment of ln-transformed) copeptin and a pooled variable of only tubulointerstitial and cystic kidney diseases ($n = 63$) remained significant (HR 1.38, 95% CI 1.07–1.78, $P = 0.01$).

VP mediates ACTH release and elevates glucocorticoid level in plasma upon stressful stimuli [15, 16]. This VP-induced ACTH release has been reported to be resistant to glucocorticoid feedback in contrast to the corticotropin-releasing hormone-induced ACTH release [48], suggesting that excessive VP release, induced by for example, relative dehydration, stress or genetical predisposition, overstimulates the hypothalamic-pituitary adrenal (HPA) axis and elevates glucocorticoid levels, leading to development of a mild Cushing-like phenotype with overweight, obesity and insulin resistance [49]. Interestingly, chronic exposure to elevated glucocorticoids in patients with Cushing's syndrome causes a decreased GFR [50], and one may, therefore, speculate on the possibility that excessive VP release followed by overstimulation of the HPA axis may not only be linked to development of components of the metabolic syndrome, as described above, but also to renal function decline.

Limitations

It is likely that our study has underestimated new-onset cases of kidney disease due to physicians failing to register mild forms of CKD ($eGFR \geq 60 \text{ mL/min/1.73 m}^2$). This assumption is supported by the fact that the majority of CKD diagnoses were either classified as Stages 3 and 4 ($eGFR < 60 \text{ mL/min/1.73 m}^2$) or not specified as any specific stage at all. Furthermore, to achieve a kidney disease diagnosis, individuals had to actively seek healthcare. These factors would be expected to bias our results towards the null.

In this study, we did not have access to data on kidney transplantation. However, we believe that any subjects receiving a kidney transplant would most likely also have a diagnosis of the underlying kidney disease. The finding that copeptin predicts specified kidney disease diagnoses, which is suggested to mainly be driven by the association to tubulointerstitial diseases, needs to be confirmed in other cohorts. Moreover, the specified disease diagnoses were, in contrast to the CKD diagnoses, not validated, which further stresses the need for replication of this finding.

Finally, we cannot exclude that there is competing risk of mortality on the copeptin-associated risk of CKD. However, we performed Cox regressions with the combined endpoint CKD + all-cause mortality, as well as with the combined endpoint CKD + cardiovascular mortality, using the same multivariate adjustment model as in Table 3, and found that the HRs for the combined endpoints decreased in both cohorts when compared with using the CKD endpoint solely (data not shown), suggesting that there is no major competing risk of mortality.

CONCLUSION

Our results point at copeptin, a measure of VP, as a marker for development of renal diseases. In selected groups of patients, copeptin may in the future assist in detection of individuals that are at higher risk for developing renal diseases and its cardiovascular complications and who might benefit from preventive

therapy such as hydration and pharmacological blockade of the VP system.

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AUTHORS' CONTRIBUTIONS

All authors have contributed substantially to the conception, design and data interpretation of the study. S.E. and O.M. wrote the manuscript and made the statistical analyses. A.C. provided intellectual content of critical importance to the work.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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