10 Jahre GCKD – was haben wir gelernt ?

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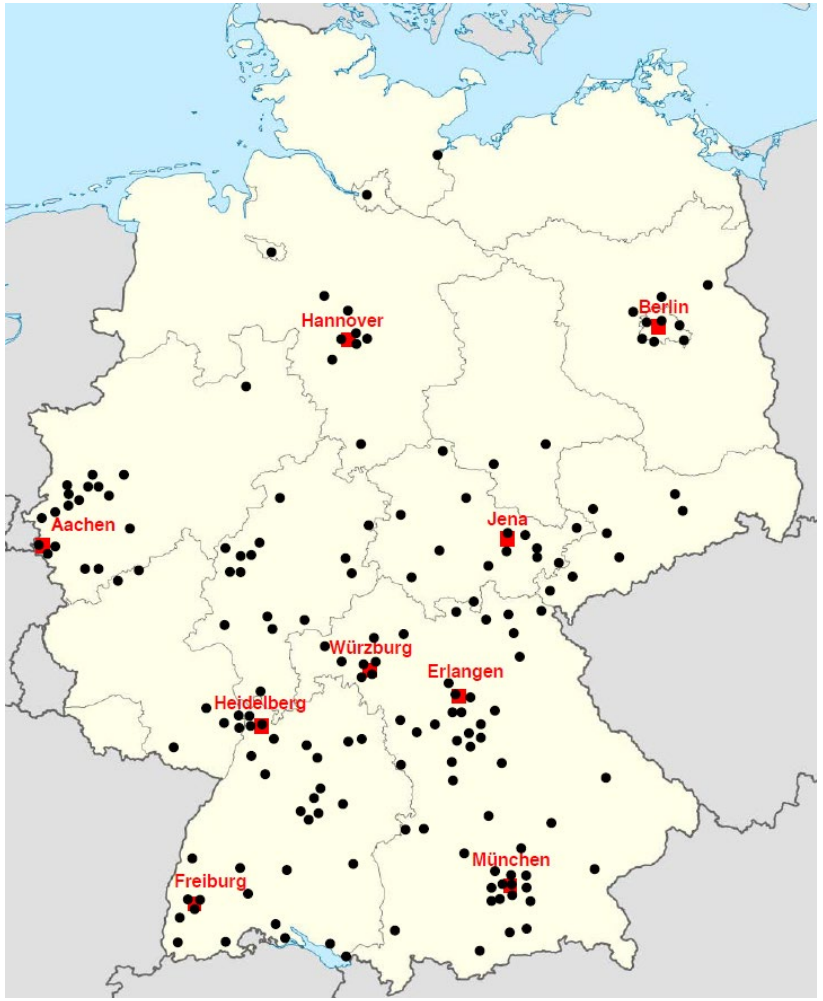
Aims and Network

- **Goal:** Longterm observation of patients with chronic kidney disease

- **Questions:**
  - Cause, course, consequences and complications of CKD
  - Causes of heterogeniety of disease course (“stable“ vs “progressive“)
  - Associations of biomarkers with clinically relevant endpoints



9 Regional Centers (RC) plus 2 Analytical Institutes (AI)

Erlangen
(RC; Coordinating Centre)

Aachen (RC)
Berlin (RC)
Freiburg (RC)
Hannover (RC)
Heidelberg (RC)
Jena (RC)
München (RC)
Würzburg (RC)

Regensburg (AI)
Innsbruck (AI)

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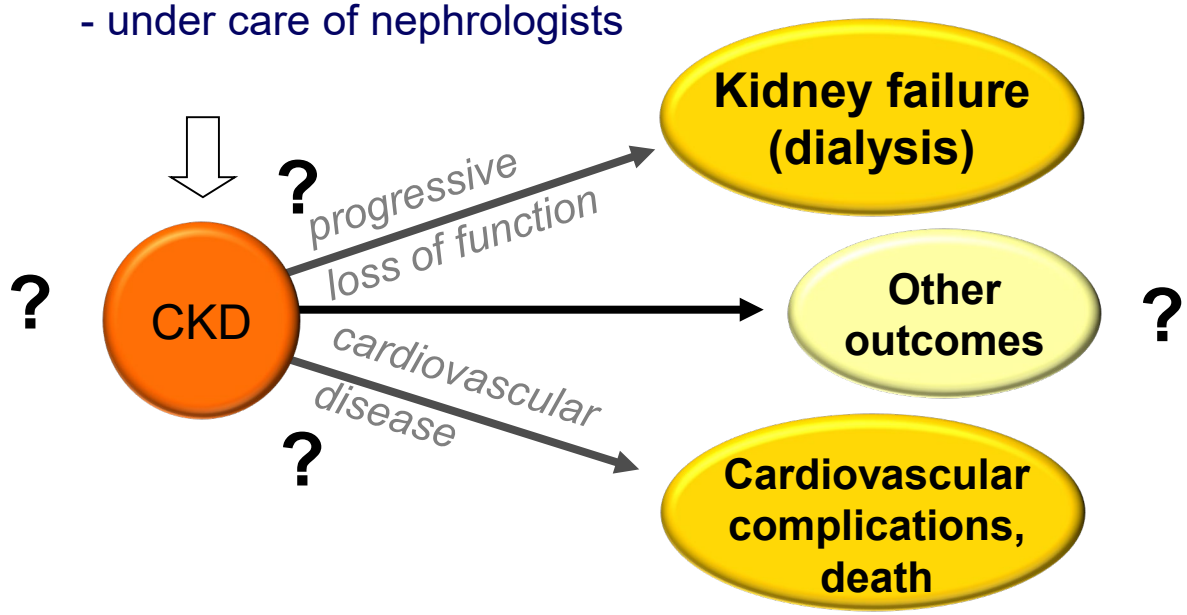
University of Regensburg
Institute of Functional Genomics
Peter Oefner, Wolfram Gronwald, PhD

Study Concept

- Diabetes mellitus
- Hypertension
- Glomerulonephritis
- Polycystic Kidney Disease
- Vasculitis
- others

5000 Patients
- CKD stage 3 (eGFR 30-60) *or* overt albuminuria
- under care of nephrologists



Clinical Phenotype

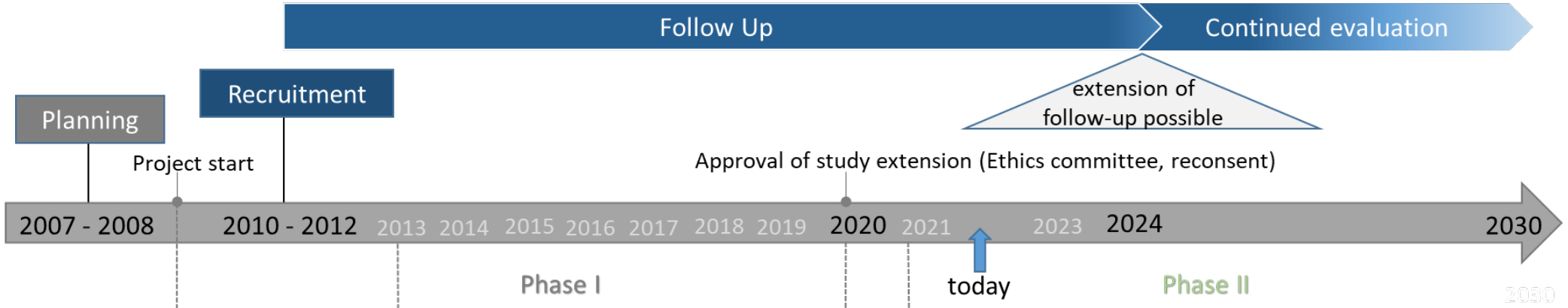
Biomaterials
- DNA
- Serum, Plasma
- Urine

Outcome

prospective follow-up (up to 10 years)

Eckardt et al., *NDT 2011*

Project Overview



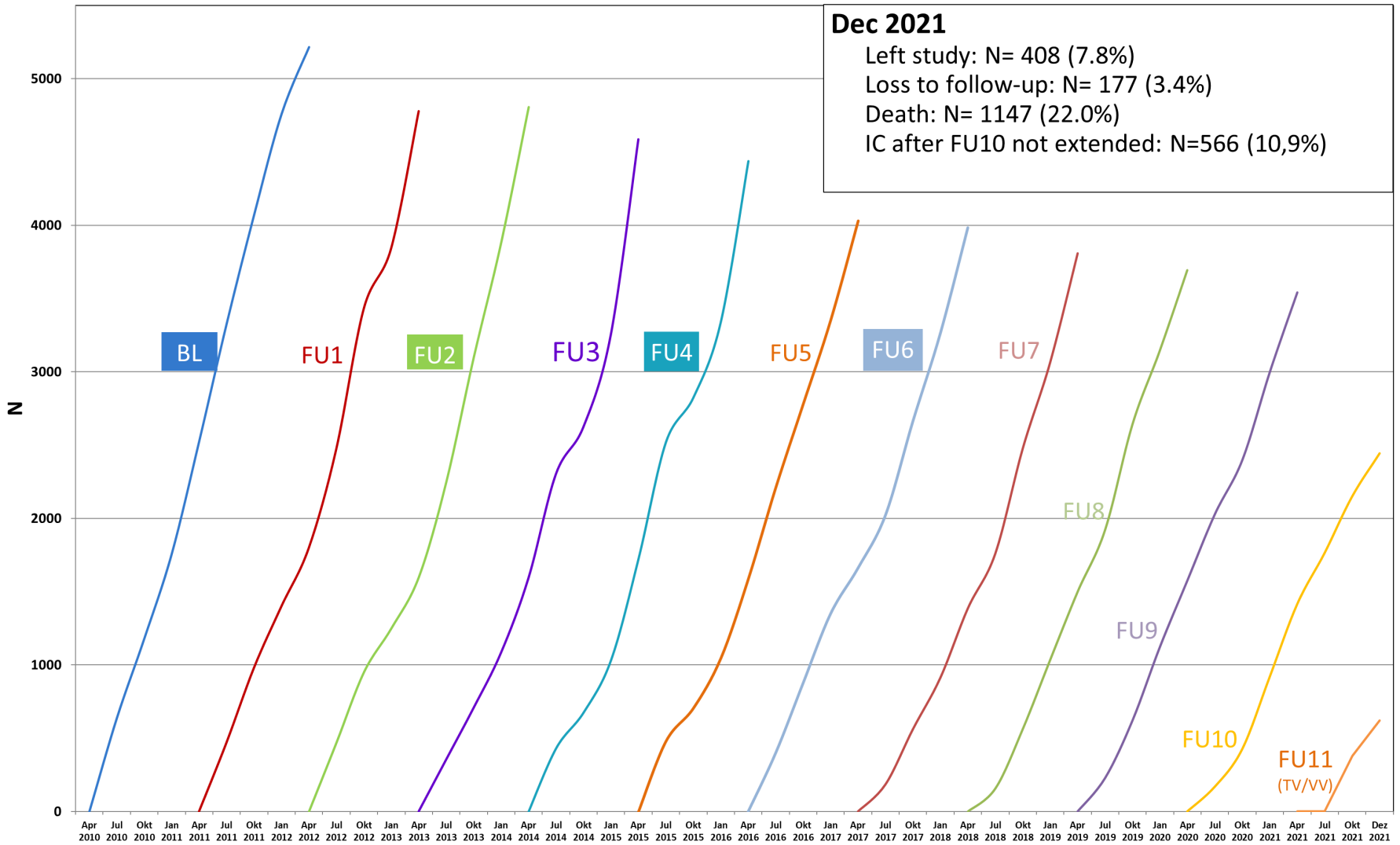
Study visits

	BL	FU1	FU2	FU3	FU4	FU5	FU6	FU7	FU8	FU9	ongoing FU10	FU11	FU12
in person (with biomaterials)	**100%**	-	**81%**	3%	**61%**	1%	**58%**	-	-	-	-	1%	
Telephone interview	-	**94%**	10%	**83%**	20%	**72%**	13%	**67%**	65%	**62%**	46%	12%	

Scientific value

Publications per year (n)	1	1	0	6	5	7	11	13	12	12
cum. Impact Factor	4.5	1.9	0	28	56.3	73.9	85.7	145.9	90.1	110.4

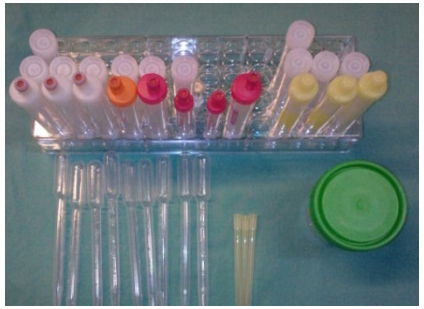
Recruitment and Follow-Up



To date 10 visits following baseline (BL), FU2, FU4, FU6, FU11 with biosampling

Biobanking

- **Biomaterial** collection, on-site sample management



	Primäry tubes	Aliquots
Serum	> 35.400	~ 56.000
Plasma	> 30.000	~ 80.000
Urin	> 37.000	~ 61.000
Total	> 300.000	

Serum, plasma, urine, blood

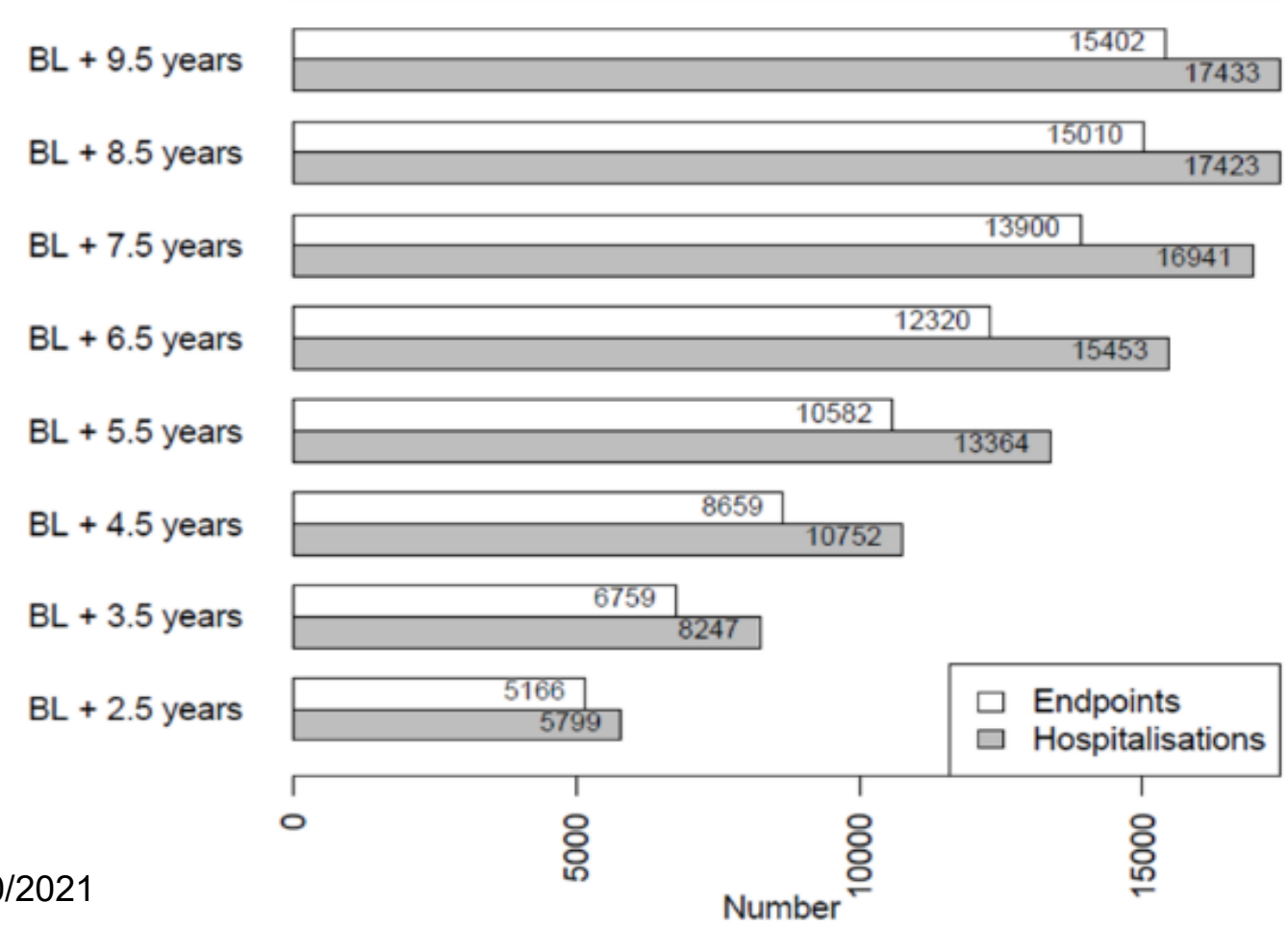
Erlangen

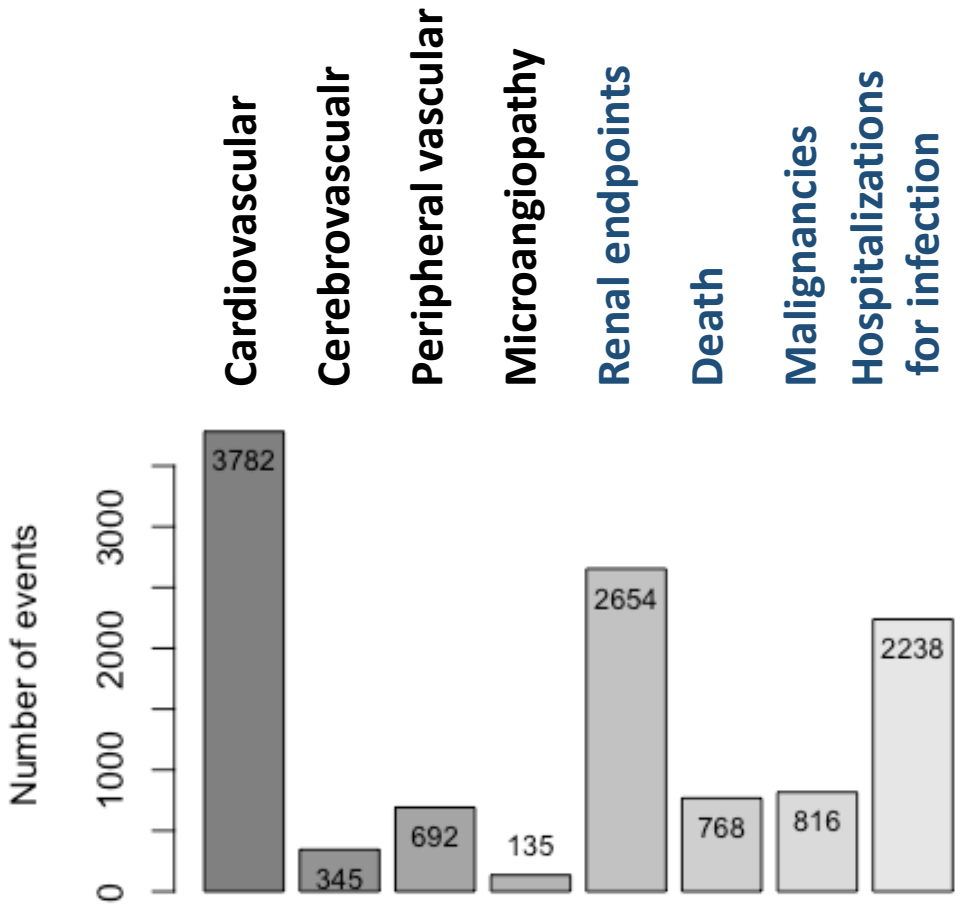
Central Lab

GCKD Biobank

Endpoints during Follow-Up

> 3300 patients have reached at least one endpoint





~ 650 mit chron. KF

German Chronic Kidney Disease Study

- Concept and Structure

What have we learned ?

German Chronic Kidney Disease Study

- Concept and Structure
- **Characteristics of a CKD population**
- **Opportunities**
- **Medication – good adherence despite high numbers**
- **Insights into pathomechanisms**
- **Risks for poor outcomes**
- **Contributions to large(r) efforts**

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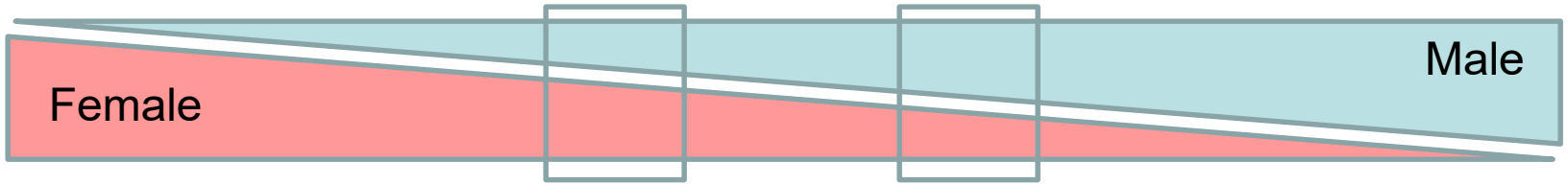
Cohort Composition

	eGFR 30-60 N = 4775	*overt proteinuria at eGFR > 60 N = 442*	*Total N = 5217*
Age (yrs)	61.3 ± 10.9	46.3 ± 13.9	60.1 ± 12.0
Male gender	2870 (60.1)	262 (59.3)	3132 (60)
Kidney function measures			
Serum creatinin (mg/dl)	1.56 ± 0.46	0.99 ± 0.3	1.51 ± 0.48
Serum cystatin C (mg/l)	1.57 ± 0.48	1.05 ± 0.3	1.52 ± 0.49
eGFR (MDRD) (ml/min x 1.73 m^2)	44.1 ± 12.6	79.3 ± 21.4	47.1 ± 16.7
U-albumin / creatinine ratio (UACR; mg/g)	39 (8-276)	624 (261-1338)	50.9 (9-392)
Renal biopsy	1094 (22.9)	272 (61.5)	1366 (26.2)
GN as dominant disease	745 (15.6)	233 (52.7)	978 (18.7)



Titze et al., *NDT 2014*

Baseline eGFR and Albuminuria

Proportions of patients in different categories (%)

		A1	A2	A3
		< 30 mg/g	30-300 mg/g	> 300 mg/g
G1	≥ 90	0	1	2
G2	60-89	6	3	4
G3 a	45-59	20	8	6
G3 b	30-44	19	13	8
G4	15-29	3	3	4
G5	< 15	0	0	0

Risk categories: 6 | 24 | 33 | 33 | 4

Based on

Levey et al., *Kidney Int 2010*

Titze et al., *NDT 2014*

CVD Burden at Baseline

- Coronary artery disease (20%)
- Cardiac valve replacement (2%)
- Cerebrovascular disease (10%)
- Peripheral vascular disease (9%)
- Heart failure (18-43%)

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Blood Pressure

N = 5217

Mean BP:
139.5 / 79.3 mmHg

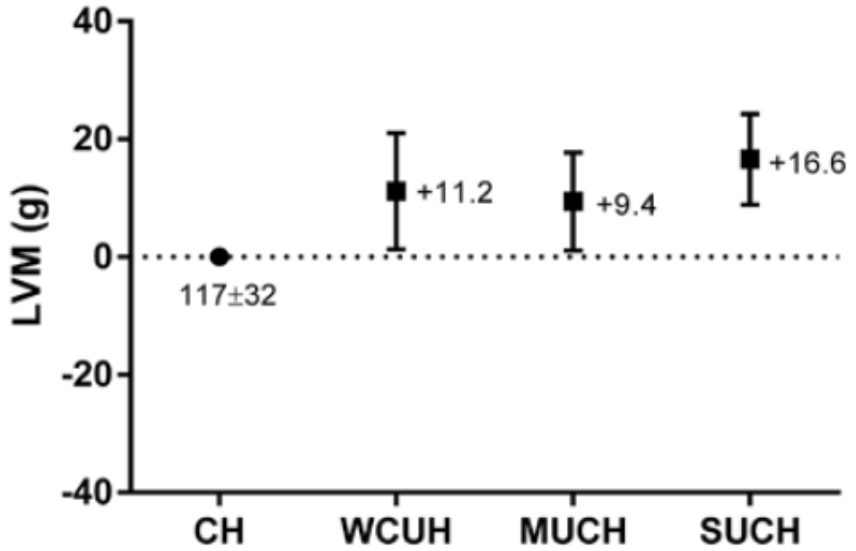
BP < 130/80: 26.5%

BP < 140/90: 52.1%

CARdio**V**ascular **I**n **D**epth **A**ssessment in Chronic Kidney Disease (CARVIDA) substudy of the GCKD study; N=305 patients with CKD

		Office BP	
		< 140/90	≥ 140/90
24h BP	< 130/80	**CH** 41%	**WCUH** 11%
	≥ 130/80	**MUCH** 18%	**SUCH** 30%

CH - Controlled Hypertension
WCUH - White Coat Uncontrolled Hypertension
MUCH - Masked Uncontrolled Hypertension
SUCH - Sustained Uncontrolled Hypertension



(adjusted for clinical factors)

→ Office BP misclassifies in ~ 1/3 of cases

→ All categories of hypertension are associated with end organ damage

Titze et al., *NDT 2014*

Scheppach et al., *Hypertension 2018*

Diet

European Journal of Clinical Nutrition (2021) 75:1389–1397
https://doi.org/10.1038/s41430-020-00849-3

ARTICLE

Nutrition in acute and chronic diseases

Low adherence to CKD-specific dietary recommendations associates with impaired kidney function, dyslipidemia, and inflammation

Food frequency questionnaire
European Prospective Investgation into Cancer and Nutrition (EPIC)

3283/4754 participants of FU 2 (2012-14) returned (69.1%)

Development of CKD diet score based on KDIGO recommendations

?

Component	1 Point	2 Points	3 Points	4 Points	5 Points
Sodium/1000 kcal	>1.22 g	1.1–1.22 g	1.0–1.09 g	0.88–0.99 g	<0.88 g
Potassium/ 1000 kcal	<1.13 g	1.13–1.24 g	1.25–1.36 g	1.37–1.52 g	>1.53 g
Fiber/1000 kcal	<7.42 g	7.42–8.59 g	8.60–9.73 g	9.74–11.1 g	>11.1 g
Total protein/ 1000 kcal	>39.82 g	36.08–39.82 g	33.14–36.07 g	30.04–33.13 g	<30.04 g
Sugar/1000 kcal	>64.91 g	53.67–64.90 g	44.85–53.66 g	36.11–44.84 g	<36.11 g
Cholesterol/ 1000 kcal	>183.9 mg	164.73–183.9 mg	147.62–164.72 mg	127.95–147.61 mg	<127.95 mg

Table 3 Associations between adherence to CKD-specific dietary recommendations and characteristics of participants of the German Chronic Kidney Disease (GCKD) observational cohort study 2012–2014 as obtained from multivariable ordinal regression.

Effect	OR[a] (95 % CI)
Age (per 1-SD increase)	0.78 (0.72, 0.85)
BMI (per 1-SD increase)	1.14 (1.06, 1.23)
Gender (male vs. female)	2.18 (1.86, 2.55)
Smoking (vs. non-smoker)	
Smoker	1.42 (1.13, 1.77)
Former smoker	0.95 (0.82, 1.12)
Alcohol (≥3×/week vs. <1–2×/week)	0.66 (0.55, 0.79)
Physical activity for 30 min (vs. >5×/week)	
<1×/week	1.48 (1.17, 1.87)
1–2×/week	1.05 (0.87, 1.27)
3–5×/week	1.11 (0.93, 1.33)
German school education (vs. ≥12th grade)	
≤9th grade	1.51 (1.24, 1.85)
10th grade	1.32 (1.07, 1.63)
Diabetes mellitus (yes vs. no)	1.04 (0.88, 1.23)
eGFR (per 1-SD increase)	0.92 (0.85, 1.0)
UACR (per 1-SD increase)	1.02 (0.94, 1.1)
Intake of lipid-lowering medication	1.01 (0.87, 1.17)
Intake of anti-hypertensive medication	0.93 (0.71, 1.22)
Intake of anti-gout medication	1.09 (0.93, 1.28)

Kaeseler et al., *Europ J Clin Nutr 2021*

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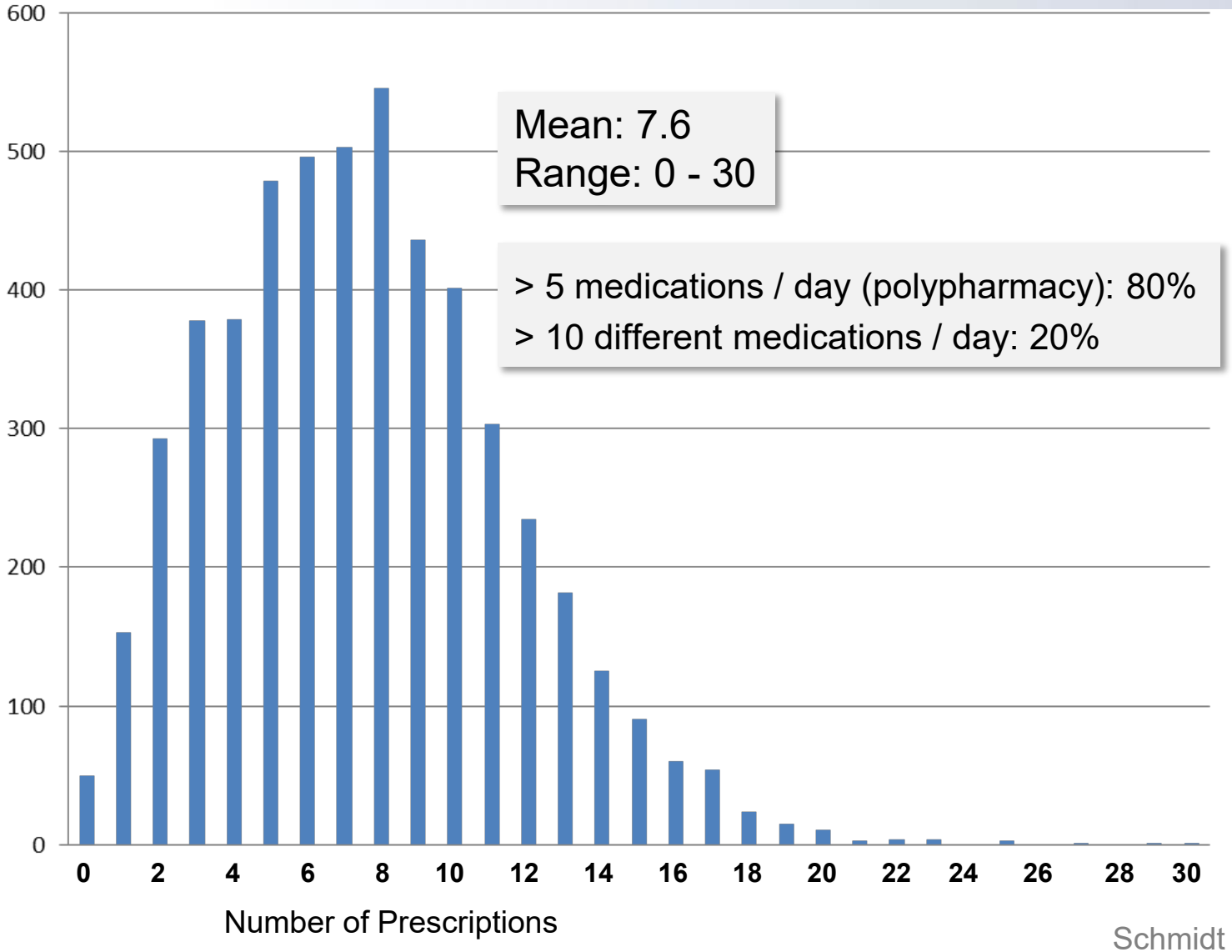
Prescribed Medication



Schmidt et al., *Clin Kid J 2019*

Prescribed Medication – Top Twelve

Drug Class	n	%
Beta-Blockers (BB)	2875	55%
ACE-Inhibitors (ACE-I)	2721	52%
HMG-CoA-Reductase-Inhibitors	2490	48%
Loop-Diuretics	2022	39%
Ca Chanel-Blockers (Dihydropyridin type)	1983	38%
Platelet Aggregation Inhibitors	1942	37%
Vitamins	1821	35%
Ang II - Receptorantagonists (ARB)	1769	34%
Uric acid lowering drugs	1654	32%
Thiazides	1573	30%
Insulin and derivatives	1539	30%
Proton Pump Inhibitors (PPI)	1444	28%

Schmidt et al., *Clin Kid J 2019*

Statin Prescription – Gap to Guideline

New Guideline 2014:
Instead of LDL-"titration" CVD risk- orientated therapy:
→ All CKD patients ≥ 50 yrs. should be treated
→ CKD patients < 50 yrs. with add. risk factors should be treated

	GCKD Baseline		Application of new guideline		
Age group	With statin	w/o statin	Additional condition required	Newly eligible for statin	Total
≥50 yrs N=4224 (81%)	2196	2028	*none*	2028	4224
18-49 yrs N=992 (19%)	277	715	add risk factors	130	407
Total	2473 ***47 %***	2743 *53 %*		2158 *41 %*	4631 ***89 %***

88% of patients > 50 yrs not yet treated with a statin have 10 year CVE risk > 7.5%

Schneider et al., *Kidney Int 2015*

Prescribed Medication

CLINICAL EPIDEMIOLOGY www.jasn.org

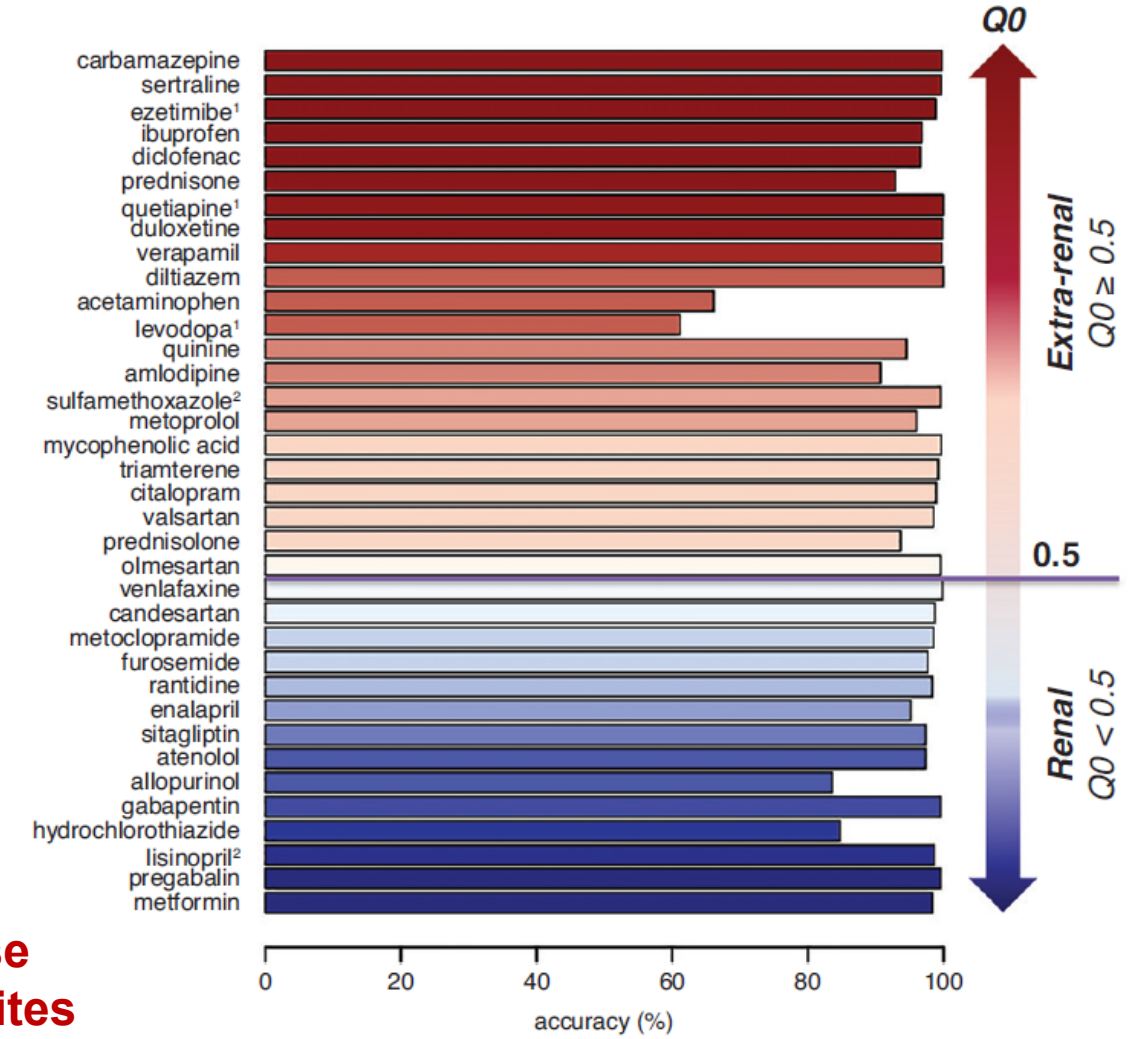
Self-Reported Medication Use and Urinary Drug Metabolites in the German Chronic Kidney Disease (GCKD) Study

All active ingredients of self reported medications extracted (ATC – Classification System);
158 analyzed substances (reported by >20 patients)
41 drug groups

Metabolites quantified from spot urine samples (Metabolon); 1487 metabolites in cleaned data set, including 90 drug metabolites

→ **108 medication metabolite pairs (MMPs)**

- **High agreement between reported medication use and measurement of drug and/or drug metabolites**
- **Higher than reported use of OTC analgesics**



Kotsis et al., *JASN 2021*

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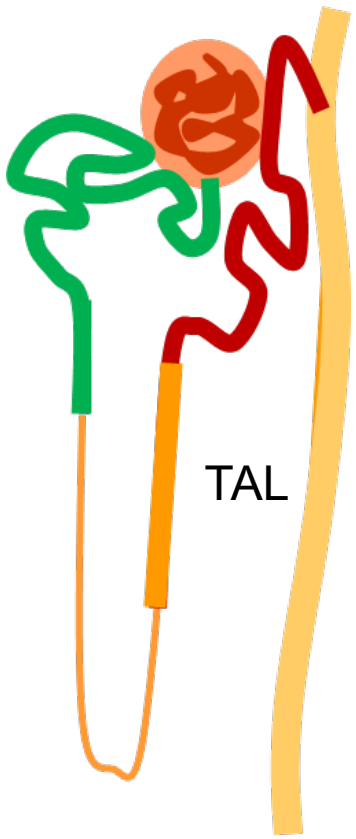
Tamm Horsfall Protein = Uromodulin



- Exclusively produced in the Thick Ascending Limb (TAL) of the kidney
- Most abundant protein in normal urine
- Involved in
  - salt transport
  - protection against urinary tract infection and kidney stones
- *UMOD* gene involved in monogenic (ADTKD) and polygenic CKD
- **Primarily secreted into urine, but to a much smaller extent also into blood**

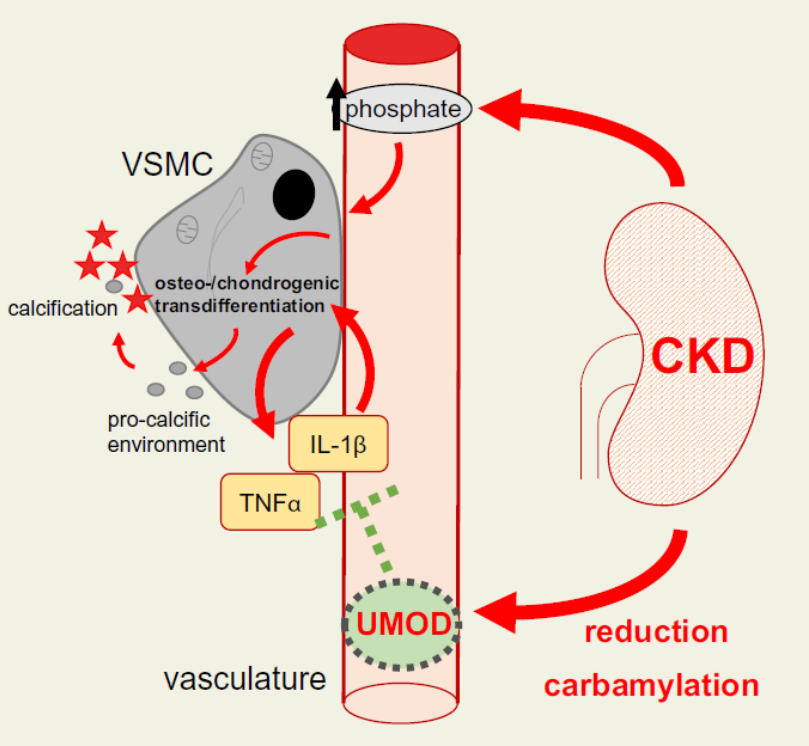
UMOD in Serum

Association of Serum Uromodulin with Death, Cardiovascular Events, and Kidney Failure in CKD

N=5143 GCKD participants; 4 yrs of Fu

www.cjasn.org Vol 15 May, 2020

Outcome	Events	Hazard Ratio (95% CI)			
		Univariable	Model 1[a]	Model 2[b]	Model 3[c]
All-cause mortality					
HR per SD higher serum uromodulin	335/5143	0.61 (0.52 to 0.71)	0.67 (0.57 to 0.78)	0.75 (0.63 to 0.89)	0.80 (0.66 to 0.96)
Quartile 1 (≤55.6 ng/ml)		1 (reference)	1 (reference)	1 (reference)	1 (reference)
Quartile 2 (>55.6–83.4 ng/ml)		0.63 (0.48 to 0.82)	0.69 (0.52 to 0.90)	0.76 (0.57 to 1.01)	0.80 (0.60 to 1.07)
Quartile 3 (>83.4–125.3 ng/ml)		0.48 (0.36 to 0.65)	0.53 (0.39 to 0.71)	0.62 (0.45 to 0.86)	0.70 (0.50 to 0.97)
Quartile 4 (>125.3 ng/ml)		0.31 (0.22 to 0.44)	0.40 (0.28 to 0.57)	0.50 (0.34 to 0.75)	0.57 (0.38 to 0.87)
Kidney failure					
HR per SD higher serum uromodulin	229/5143	0.30 (0.24 to 0.39)	0.31 (0.25 to 0.40)	0.61 (0.46 to 0.80)	0.61 (0.46 to 0.81)
Quartile 1 (≤55.6 ng/ml)		1 (reference)	1 (reference)	1 (reference)	1 (reference)
Quartile 2 (>55.6–83.4 ng/ml)		0.50 (0.37 to 0.68)	0.50 (0.37 to 0.68)	0.73 (0.53 to 0.99)	0.73 (0.52 to 1.01)
Quartile 3 (>83.4–125.3 ng/ml)		0.27 (0.19 to 0.40)	0.28 (0.19 to 0.42)	0.64 (0.43 to 0.96)	0.65 (0.43 to 0.99)
Quartile 4 (>125.3 ng/ml)		0.07 (0.03 to 0.14)	0.06 (0.03 to 0.13)	0.27 (0.12 to 0.59)	0.24 (0.10 to 0.55)
MACE					
HR per SD higher serum uromodulin	417/5143	0.68 (0.60 to 0.77)	0.74 (0.65 to 0.84)	0.80 (0.70 to 0.92)	0.87 (0.77 to 1.02)
Quartile 1 (≤55.6 ng/ml)		1 (reference)	1 (reference)	1 (reference)	1 (reference)
Quartile 2 (>55.6–83.4 ng/ml)		0.73 (0.57 to 0.93)	0.75 (0.59 to 0.96)	0.76 (0.59 to 0.99)	0.85 (0.66 to 1.11)
Quartile 3 (>83.4–125.3 ng/ml)		0.61 (0.47 to 0.79)	0.64 (0.49 to 0.83)	0.70 (0.53 to 0.93)	0.78 (0.58 to 1.03)
Quartile 4 (>125.3 ng/ml)		0.35 (0.26 to 0.48)	0.43 (0.32 to 0.59)	0.49 (0.35 to 0.69)	0.63 (0.45 to 0.90)



sUMOD = *marker* of tubular function / mass (beyond eGFR)

Could low sUMOD also be a risk factor ?

Steubl et al., C*JASN 2020*

Alesutan et al., Cardiovasc Res *2020*

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Educational Attainment and CV Outcomes

Educational Attainment is Associated with Kidney and Cardiovascular Outcomes in Chronic Kidney Disease

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Longitudinal Cohort Study

German CKD Study
n=5095

eGFR 30-60 mL/min/1.73m^2
and/or
UACR >300 mg/g

CASMIN* classification of education attained
(1, 2, or 3 from lowest to highest level)

Follow-up 6.5 years

	Age	Never Smoker	BMI	Diabetes	CVD
53.3% CASMIN 1	63.2 ± 9.8	**38.5%**	29.9	**41.4%**	**19.7%**
31.1% CASMIN 2	55 ± 13.3	41.7%	28.1	28.9%	6.8%
15.5% CASMIN 3	59.8 ± 12	46.8%	27.4	30.5%	3.9%

CASMIN 1 (lowest education) compared to CASMIN 3 (highest)

	CKD ETIOLOGY		ADVERSE OUTCOMES		
	DKD	CKD AFTER AKI	DEATH	MACE	MAKE
OR or HR (95% CI)	**1.65 (1.36-2.0)**	**1.56 (1.03-2.35)**	**1.48 (1.16-1.90)**	**1.37 (1.02-1.83)**	**1.54 (1.15-2.05)**

*Comparative Analysis of Social Mobility in Industrialized Nations

MACE, major adverse cardiovascular events; MAKE, major adverse kidney events

KI REPORTS
Kidney International Reports

Winitzki D, 2022

Visual abstract by:
Jade Teakell, MD PhD
@JMTeakell

Conclusion Low educational attainment is associated with CKD etiology and adverse outcomes. Lifestyle habits and biomarkers mediate associations between low educational attainment and mortality.

Winitzki et al.,
Kid Int Reports 2022

Metabolic Syndrome

JIM Original Article

doi: 10.1111/joim.13355

Association of the metabolic syndrome with mortality and major adverse cardiac events: A large chronic kidney disease cohort

Table 1. *Baseline characteristics of 5110 patients available for analysis by the presence or absence of metabolic syndrome*

	Total ($N = 5110$)	No metabolic syndrome ($N = 1826$)	Metabolic syndrome ($N = 3284$)	p-Value
Age, years	60.1 ± 12.0	56.0 ± 13.6	62.3 ± 10.2	<0.001
Sex (female)	2050 (40.1%)	834 (45.6%)	1216 (37.0%)	<0.001
Body mass index (BMI; kg/m^2)	29.8 ± 6.0	26.1 ± 4.5	32.0 ± 5.7	<0.001
Waist circumference (cm)	103.6 ± 15.8	92.2 ± 12.7	110.1 ± 13.6	<0.001
	104 [93, 114]	93 [83, 100]	109 [102, 118]	
Current smokers	819 (16.1%)	311 (17.1%)	508 (15.5%)	0.15
Statin use	2442(47.8%)	659(36.1%)	1783(54.3%)	<0.001
Metabolic syndrome components				
Triglyceride component	2518 (49.6%)	250 (13.7%)	2268 (69.7%)	<0.001
HDL cholesterol component	1845 (36.3%)	98 (5.4%)	1747 (53.7%)	<0.001
Blood pressure component	5000 (97.8%)	1728 (94.5%)	3272 (99.7%)	<0.001
Glucose component	2600 (51.3%)	266 (14.7%)	2334 (71.6%)	<0.001
Waist component	3392 (67.6%)	529 (29.5%)	2863 (88.9%)	<0.001
Total number of metabolic syndrome components	3.0 ± 1.33 [2, 4]	1.6 ± 0.52 [1, 2]	3.8 ± 0.84 [3, 4]	<0.001

6.5 yrs follow-up

Table 3. *Association of metabolic syndrome with all cause-mortality, 3-point MACE and 4-point MACE during the prospective follow-up of 6.5 years using Cox proportional hazards regression models with various adjustments for confounders. For 3-point MACE and 4-point MACE, both cause-specific hazard ratio (HR) and subdivision HR (SHR) are given*

	HR*	95% CI	p-Value	SHR*	95% CI	p-Value
All-cause mortality						
Model 1	1.47	[1.21–1.78]	<0.0001	–	–	–
Model 2	1.37	[1.13–1.67]	0.002	–	–	–
Model 3	1.26	[1.04–1.54]	0.021	–	–	–
Model 4	1.11	[0.91–1.35]	0.325	–	–	–
3-Point MACE						
Model 1	1.68	[1.35–2.10]	<0.0001	1.66	[1.32–2.07]	<0.0001
Model 2	1.59	[1.27–1.98]	<0.0001	1.57	[1.25–1.97]	<0.0001
Model 3	1.43	[1.14–1.79]	0.002	1.42	[1.13–1.78]	0.003
Model 4	1.31	[1.04–1.64]	0.020	1.32	[1.05-1.66]	0.019
4-Point MACE						
Model 1	1.74	[1.44–2.10]	<0.0001	1.72	[1.42–2.08]	<0.0001
Model 2	1.67	[1.38–2.02]	<0.0001	1.66	[1.37–2.01]	<0.0001
Model 3	1.48	[1.22–1.79]	0.0001	1.47	[1.21-1.78]	0.0001
Model 4	1.36	[1.12–1.65]	0.0022	1.36	[1.12-1.66]	0.002

*HR: Hazard ratios derived from Cox models; SHR: Subdivision HR, derived from competing for risk regression.
Model 1: adjusted for sex and age; Model 2: Model 1 + eGFR, log(urine albumin-creatinine ratio); Model 3: Model 2 + current smoking, prevalent cardiovascular disease, log(LDL cholesterol); Model 4: Model 3 + log(hs-CRP).
For definitions of 3-point MACE and 4-point MACE, see footnotes of Table 2.

3-Point MACE: CV death, ischaemic stroke, AMI
4-Point MACE: plus peripheral arterial disease events

Pammer et al., *J Int Medicine 2021*

Urine Metabolites

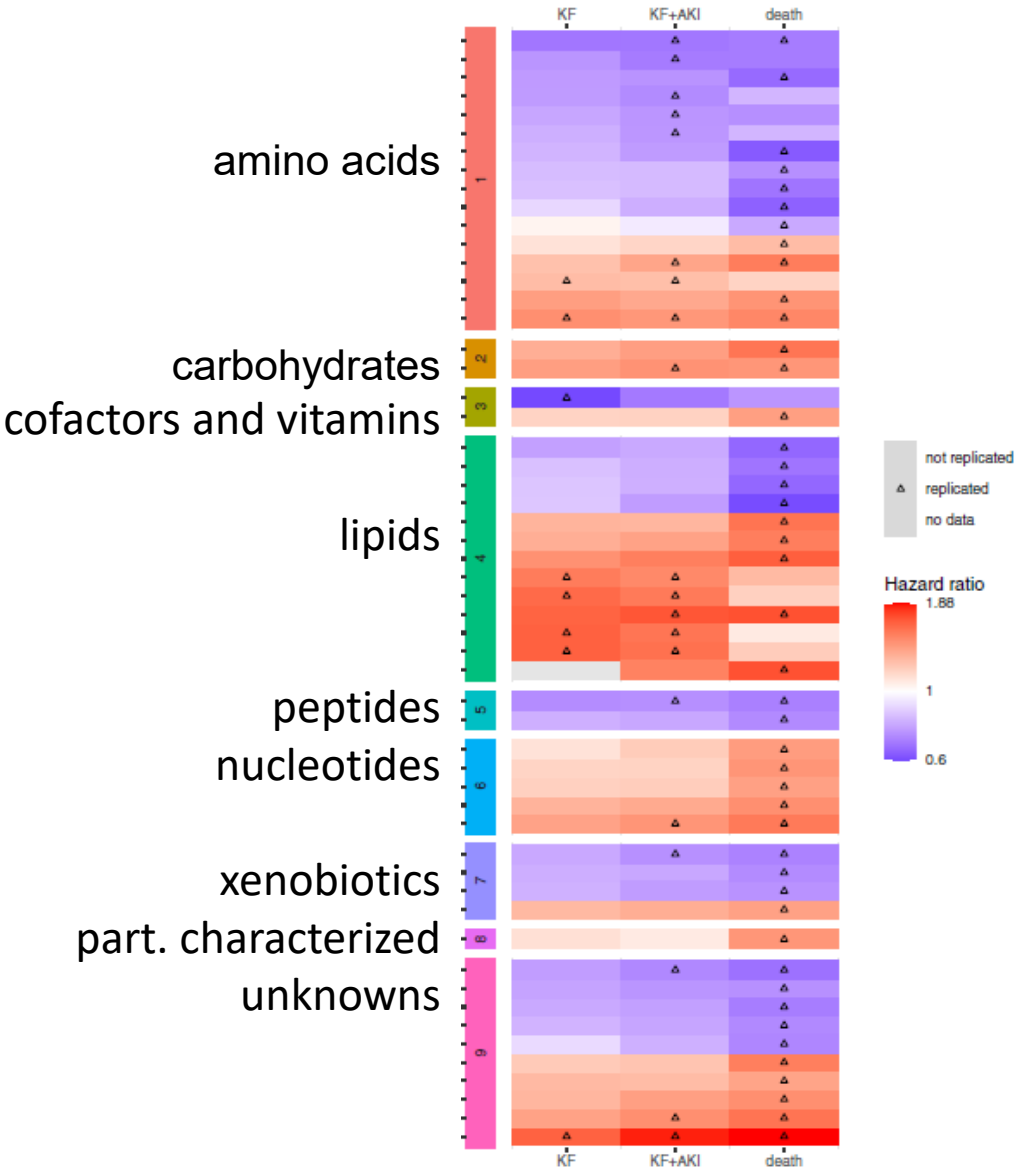
Original Investigation AJKD

Urine Metabolite Levels, Adverse Kidney Outcomes, and Mortality in CKD Patients: A Metabolome-wide Association Study

5087 patients

metabolites quantified from spot urine samples (Metabolon); 1487 metabolites in cleaned data set

- **55 metabolites identified, the levels of which were significantly associated with adverse kidney outcomes (AKI, KF) and / or mortality over 4 yrs.**



Steinbrenner et al., *AJKD 2021*

German Chronic Kidney Disease Study

- Concept and Structure
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- **Contributions to large(r) efforts**

(Epi)Genetic Basis of GFR / UAC

nature genetics

ARTICLES

https://doi.org/10.1038/s41588-019-0407-x

A catalog of genetic loci associated with kidney function from analyses of a million individuals

N = 1.046.070

Wuttke et al., *Nature Genetics 2019*

ARTICLE

https://doi.org/10.1038/s41467-019-11576-0 OPEN

Genome-wide association meta-analyses and fine-mapping elucidate pathways influencing albuminuria

N = 356.257; N = 192.168

Teumer et al., *Nature Commun 2019*

ARTICLE

https://doi.org/10.1038/s41467-021-27234-3 OPEN

Meta-analyses identify DNA methylation associated with kidney function and damage

N = 33605 (GFR); N = 15068 (UACR)

Schlosser et al., *Nature Commun 2021*

ARTICLE

https://doi.org/10.1038/s41467-020-15383-w OPEN

Check for updates

The genetic architecture of membranous nephropathy and its potential to improve non-invasive diagnosis

N = 3782 (cases); N = 9038 (controls)

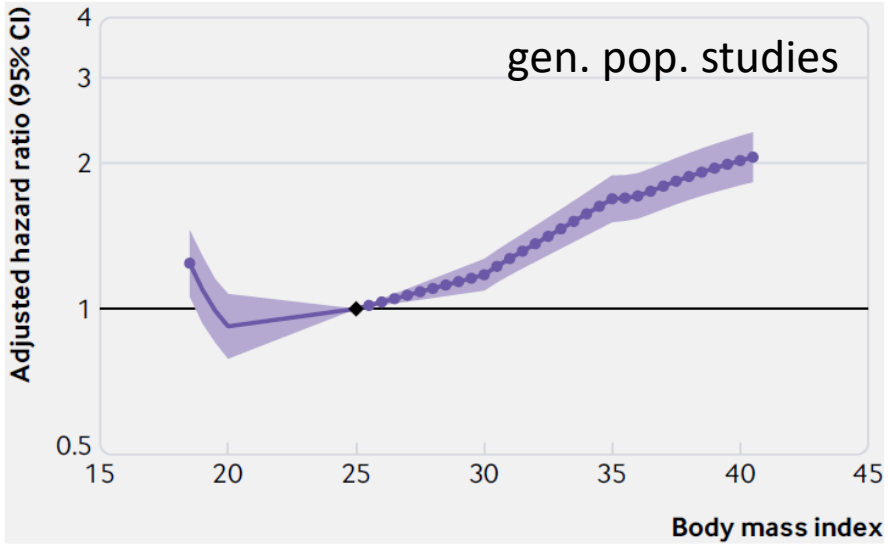
Xie et al., *Nature Comm 2020*

GFR Decline

Adiposity and risk of decline in glomerular filtration rate: meta-analysis of individual participant data in a global consortium

Alex R Chang,[1] Morgan E Grams,[2] Shoshana H Ballew,[2] Henk Bilo,[3] Adolfo Correa,[4] Marie Evans,[5] Orlando M Gutierrez,[6,7] Farhad Hosseinpanah,[8] Kunitoshi Iseki,[9,10] Timothy Kenealy,[11] Barbara Klein,[12] Florian Kronenberg,[13] Brian J Lee,[14] Yuanying Li,[15] Katsuyuki Miura,[16] Sankar D Navaneethan,[17] Paul J Roderick,[18] Jose M Valdivielso,[19] Frank L J Visseren,[20] Luxia Zhang,[21] Ron T Gansevoort,[22] Stein I Hallan,[23,24] Andrew S Levey,[25] Kunihiro Matsushita,[2] Varda Shalev,[26] Mark Woodward,[2,27,28] On behalf of the CKD Prognosis Consortium (CKD-PC)

N = 5.459.014



BMJ 2019

clinical investigation www.kidney-international.org

Meta-analysis uncovers genome-wide significant variants for rapid kidney function decline

Check for updates

see commentary on page 805

OPEN

Mathias Gorski[1,2,120], Bettina Jung[2,120], Yong Li[3,120], Pamela R. Matias-Garcia[4,5,6,120], Matthias Wuttke[3,7], Stefan Coassin[8], Chris H.L. Thio[9], Marcus E. Kleber[10], Thomas W. Winkler[1], Veronika Wanner[1], Jin-Fang Chai[11], Audrey Y. Chu[12], Massimiliano Cocca[13], Mary F. Feitosa[14], Sahar Ghasemi[15,16], Anselm Hoppmann[3], Katrin Horn[17,18], Man Li[19], Teresa Nutile[20], Markus Scholz[17,18], Karsten B. Sieber[21], Alexander Teumer[15,16], Adrienne Tin[22,23], Judy Wang[14], Bamidele O. Tayo[24], Tarunveer S. Ahluwalia[25], Peter Almgren[26], Stephan J.L. Bakker[27], Bernhard Banas[2], Nisha Bansal[28,29], Mary L. Biggs[30,31], Eric Boerwinkle[32], Erwin P. Bottinger[33,34], Hermann Brenner[35,36], Robert J. Carroll[37], John Chalmers[38,39,40], Miao-Li Chee[41], Miao-Ling Chee[41], Ching-Yu Cheng[41,42,43], Josef Coresh[40], Martin H. de Borst[27], Frauke Degenhardt[44], Kai-Uwe Eckardt[45,46], Karlhans Endlich[16,47], Andre Franke[44], Sandra Freitag-Wolf[48], Piyush Gampawar[49], Ron T. Gansevoort[27], Mohsen Ghanbari[50,51], Christian Gieger[4,5,52], Pavel Hamet[53,54,55], Kevin Ho[56,57], Edith Hofer[58,59], Bernd Holleczek[35], Valencia Hui Xian Foo[41], Nina Hutri-Kähönen[60,61], Shih-Jen Hwang[62,63], M. Arfan Ikram[50], Navya Shilpa Josyula[64], Mika Kähönen[65,66], Chiea-Chuen Khor[41,67], Wolfgang Koenig[68,69,70], Holly Kramer[24,71], Bernhard K. Krämer[72], Brigitte Kühnel[4], Leslie A. Lange[73], Terho Lehtimäki[74,75], Wolfgang Lieb[76]; Lifelines Cohort Study[77], Regeneron Genetics Center[77]: Ruth J.F. Loos[33,78], Mary Ann Lukas[79], Leo-Pekka Lyytikäinen[74,75], Christa Meisinger[80,81], Thomas Meitinger[69,82,83], Olle Melander[84], Yuri Milaneschi[85], Pashupati P. Mishra[74,75], Nina Mononen[74,75], Josyf C. Mychaleckyj[86], Girish N. Nadkarni[33,87], Matthias Nauck[16,88], Kjell Nikus[89,90], Boting Ning[91], Ilja M. Nolte[9], Michelle L. O'Donoghue[92,93], Marju Orho-Melander[26], Sarah A. Pendergrass[94], Brenda W.J.H. Penninx[85], Michael H. Preuss[33], Bruce M. Psaty[95,96], Laura M. Raffield[97], Olli T. Raitakari[98,99,100], Rainer Rettig[101], Myriam Rheinberger[2,102], Kenneth M. Rice[31], Alexander R. Rosenkranz[103], Peter Rossing[25], Jerome I. Rotter[104], Charumathi Sabanayagam[41,42], Helena Schmidt[49], Reinhold Schmidt[58], Ben Schöttker[35,36], Christina-Alexandra Schulz[26], Sanaz Sedaghat[50,105], Christian M. Shaffer[37], Konstantin Strauch[106,107], Silke Szymczak[48], Kent D. Taylor[104], Johanne Tremblay[53,55,54], Layal Chaker[50,108], Pim van der Harst[109,110,111], Peter J. van der Most[9], Niek Verweij[109], Uwe Völker[16,112], Melanie Waldenberger[4,5,69], Lars Wallentin[113,114], Dawn M. Waterworth[21], Harvey D. White[115], James G. Wilson[116], Tien-Yin Wong[41,42], Mark Woodward[38,39,40], Qiong Yang[91], Masayuki Yasuda[41,117], Laura M. Yerges-Armstrong[21], Yan Zhang[35], Harold Snieder[9], Christoph Wanner[118], Carsten A. Böger[2,102,121], Anna Köttgen[3,40,121], Florian Kronenberg[8,121], Cristian Pattaro[119,121] and Iris M. Heid[1,121]

N > 270.000 *Kidney International 2021*

Genetic Basis of Lipid Metabolism

Article

The power of genetic diversity in genome-wide association studies of lipids

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A list of authors and their affiliations appears online.

Increased blood lipid levels are heritable risk factors of cardiovascular disease with varied prevalence worldwide owing to different dietary patterns and medication use[1]. Despite advances in prevention and treatment, in particular through reducing

N = 1.650.000

Graham et al., *Nature 2021*

Di Maio *et al. Genome Medicine* (2020) 12:74
https://doi.org/10.1186/s13073-020-00771-0

Genome Medicine

RESEARCH Open Access

Investigation of a nonsense mutation located in the complex KIV-2 copy number variation region of apolipoprotein(a) in 10,910 individuals

Check for updates

N = 10.910

Di Maio et al., *Genome Medicine 2020*

(Epi)Genetic Basis of Urate Metabolism

nature genetics

ARTICLES

https://doi.org/10.1038/s41588-019-0504-x

Target genes, variants, tissues and transcriptional pathways influencing human serum urate levels

N = 457.690; N = 334.880

Tin et al., *Nature Genetics 2019*

ARTICLE

https://doi.org/10.1038/s41467-021-27198-4 OPEN

Check for updates

Epigenome-wide association study of serum urate reveals insights into urate co-regulation and the *SLC2A9* locus

N = 12.474; N = 5522

Tin et al., *Nature Commun 2021*

Risk Scores

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Research Paper

Incorporating kidney disease measures into cardiovascular risk prediction: Development and validation in 9 million adults from 72 datasets

N ~ 9 Millionen

Matsushita et al., *EClinicalMedicine 2020*

Original Investigation

AJKD

A Predictive Model for Progression of CKD to Kidney Failure Based on Routine Laboratory Tests

N = 4915; N = 3063

Zacharias et al., *AJKD 2022*

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- Insights into pathomechanisms
- Risks for poor outcomes
- Contributions to large(r) efforts

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www.gckd.org