Dickkopf-3 (DKK3) - A novel kidney stress marker

58th ANZSN Annual Scientific Meeting

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Conflicts of interest

Consultant and speaker fees
Amgen, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, GSK, Novartis, Novo Nordisk, Sanofi, Vifor

Biomarkers in nephrology

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

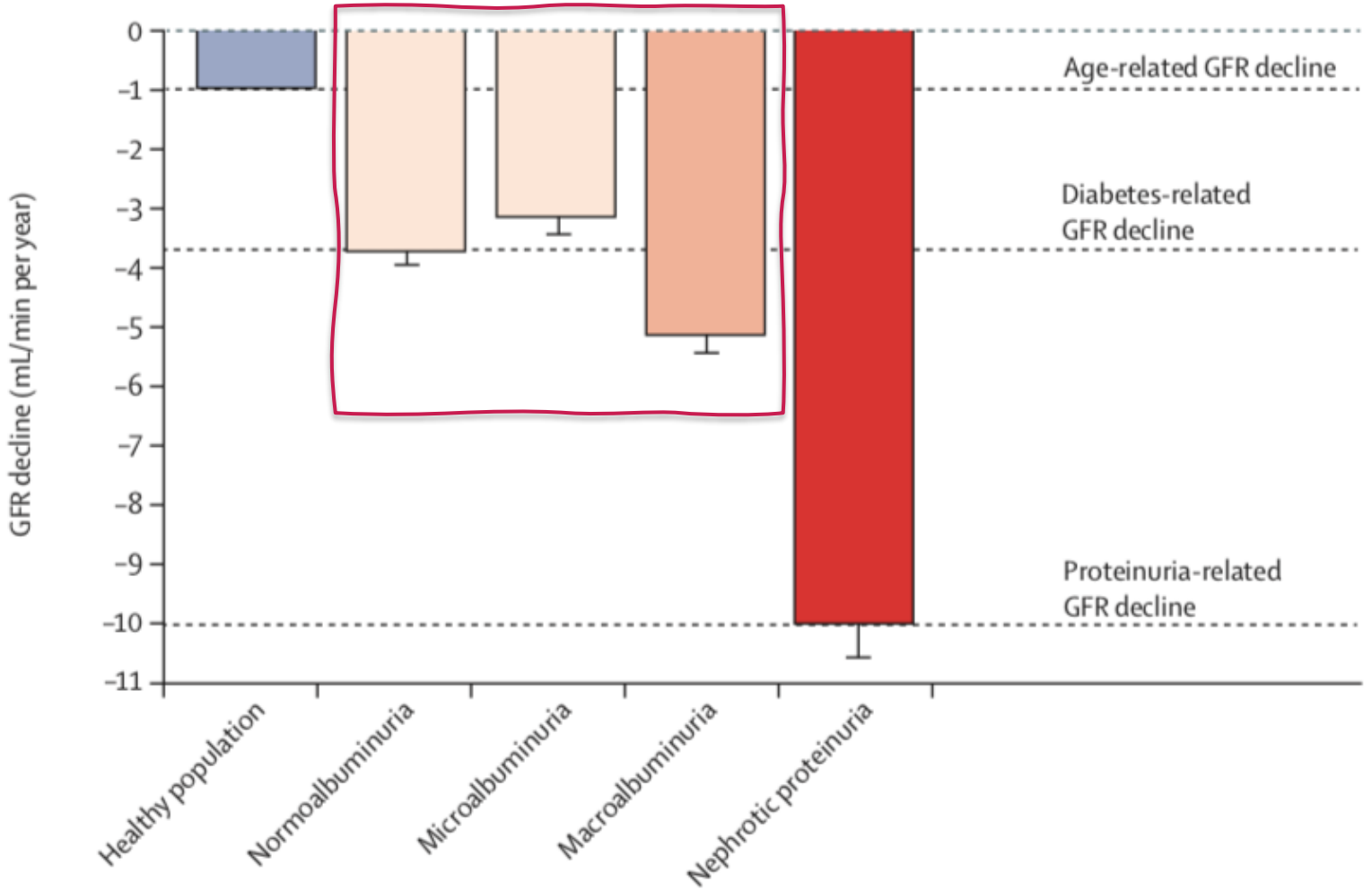
eGFR

Albuminuria

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

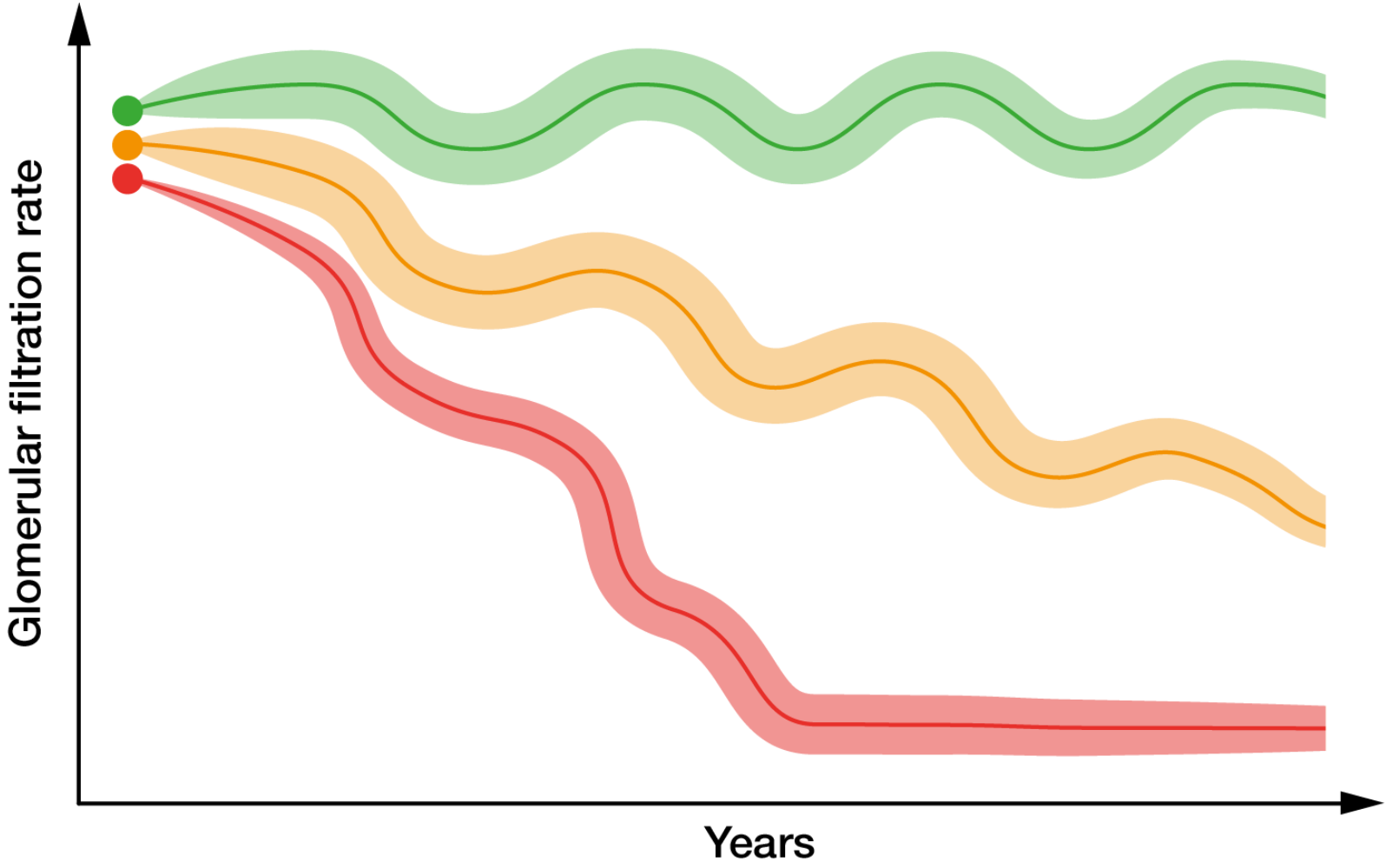
Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Progression of CKD in T2DM

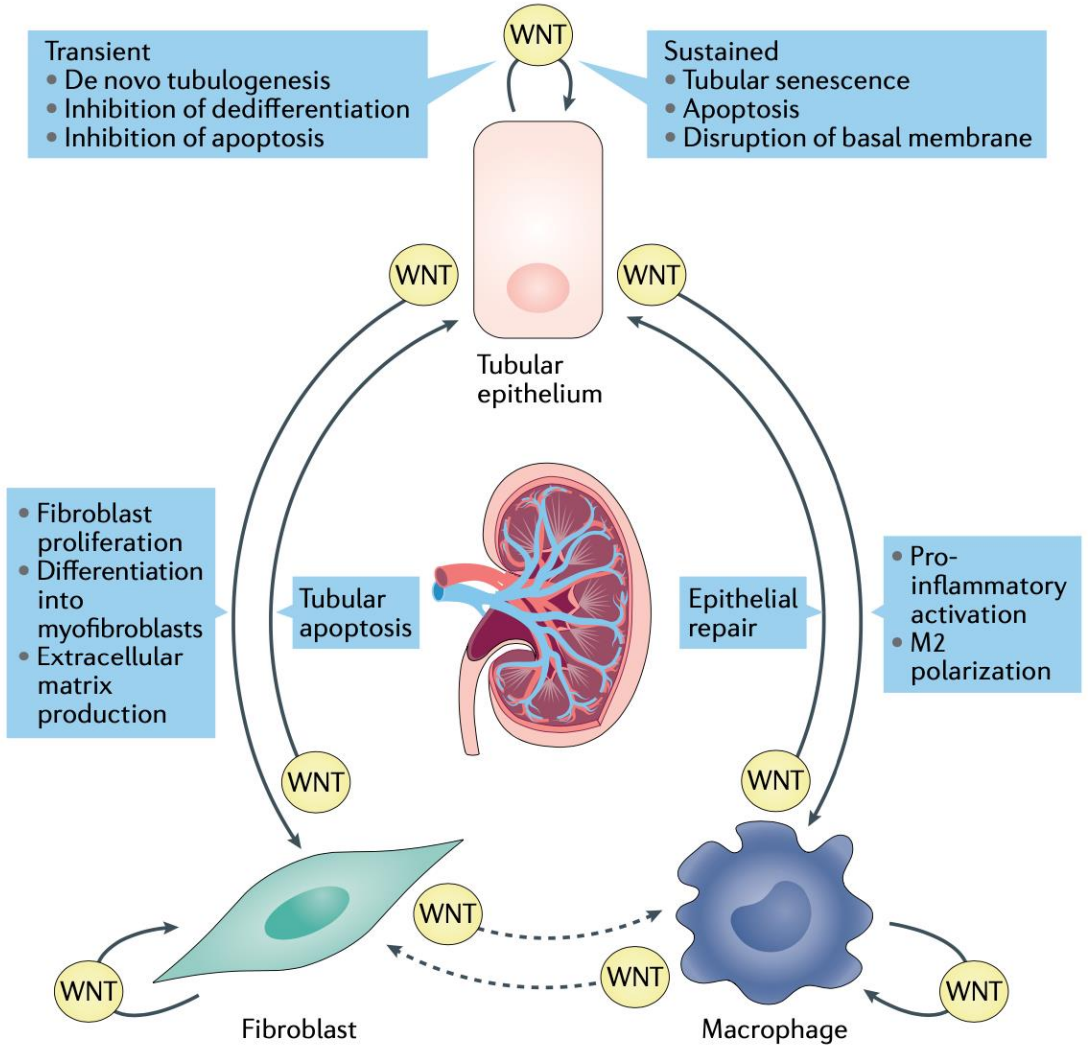


Porrini et al. Lancet Diab Endocrinol 2015

Individual course of CKD



Wnt/β-catenin signaling in kidney injury



Schunk,..,Speer. Nat Rev Nephrol 2021

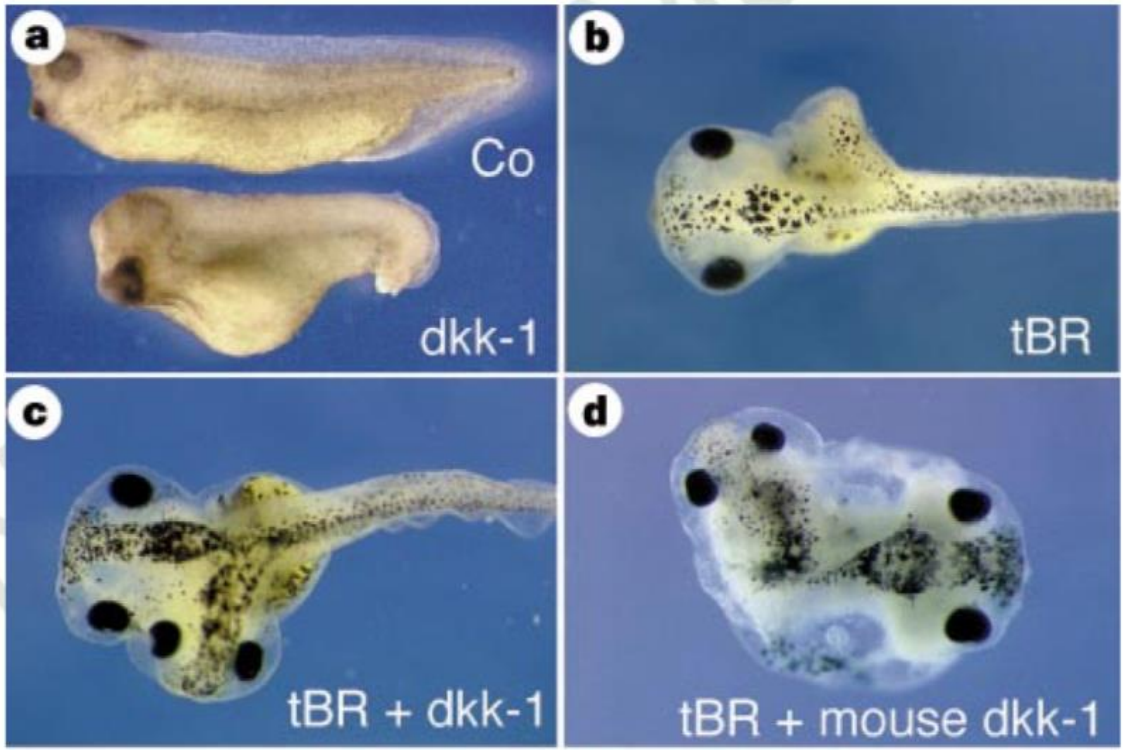
Dickkopf-protein family

Dickkopf-1 is a member of a new family of secreted proteins and functions in head induction

Andrei Glinka, Wei Wu, Hajo Delius*, A. Paula Monaghan†, Claudia Blumenstock & Christof Niehrs

*Division of Molecular Embryology, *Division of Applied Tumorvirology, and † Division of Molecular Biology of the Cell I, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany*

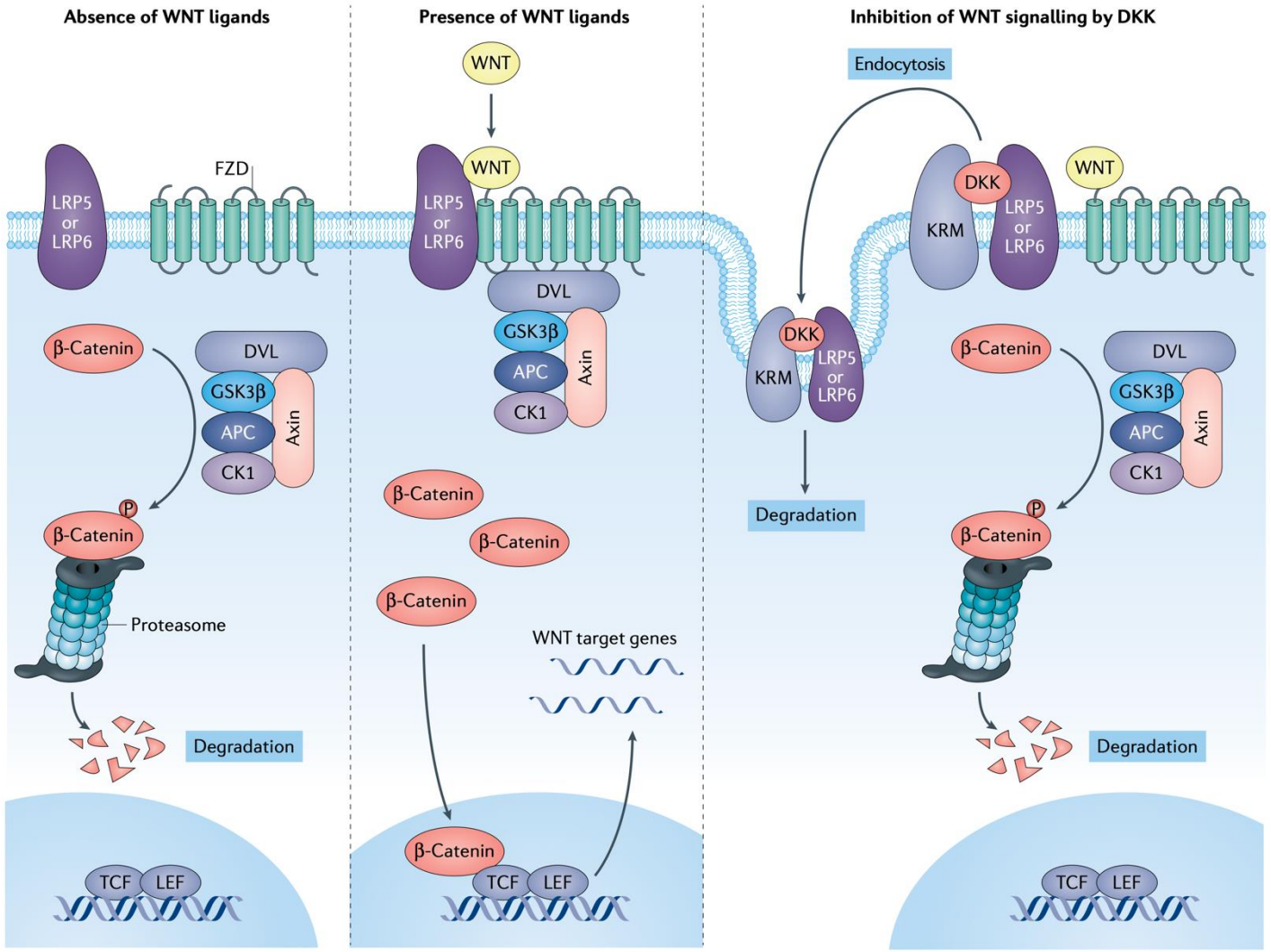
Dickkopf =
Bullhead or pighead



Overexpression of DKK1 in tadpoles

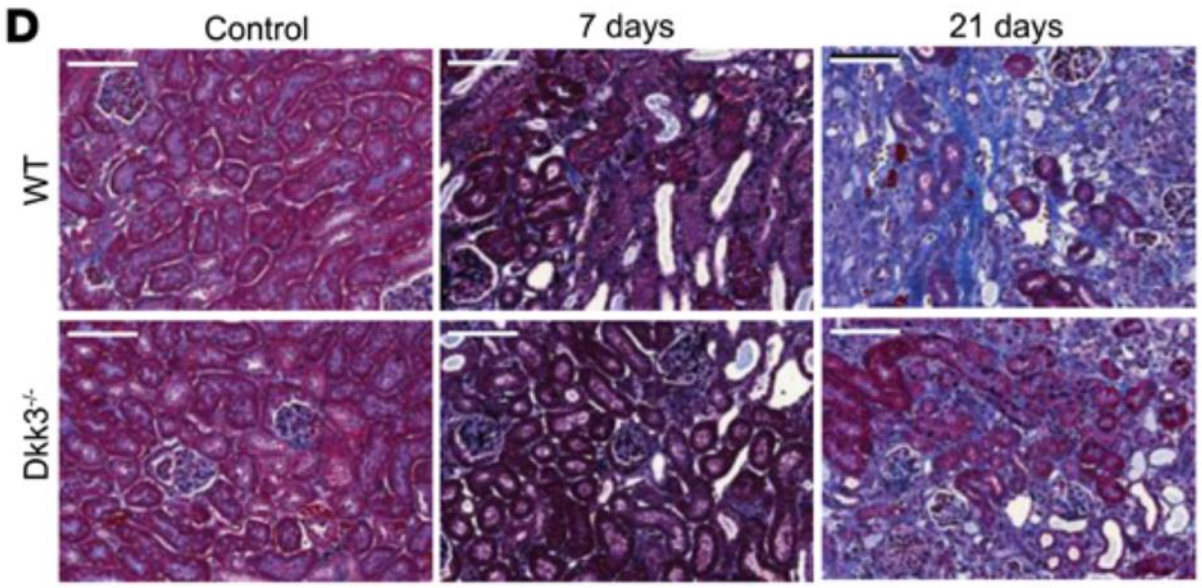
Glinka et al. Nature 1998

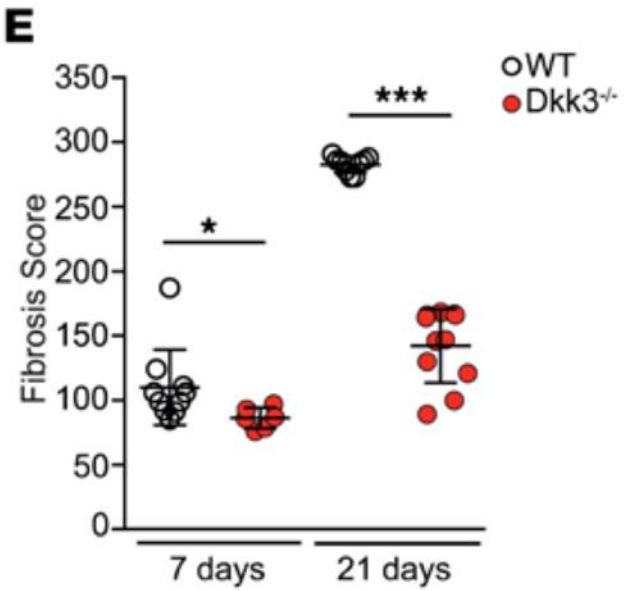
Dickkopf and Wnt/β-catenin signaling



Schunk,..,Speer. Nat Rev Nephrol 2021

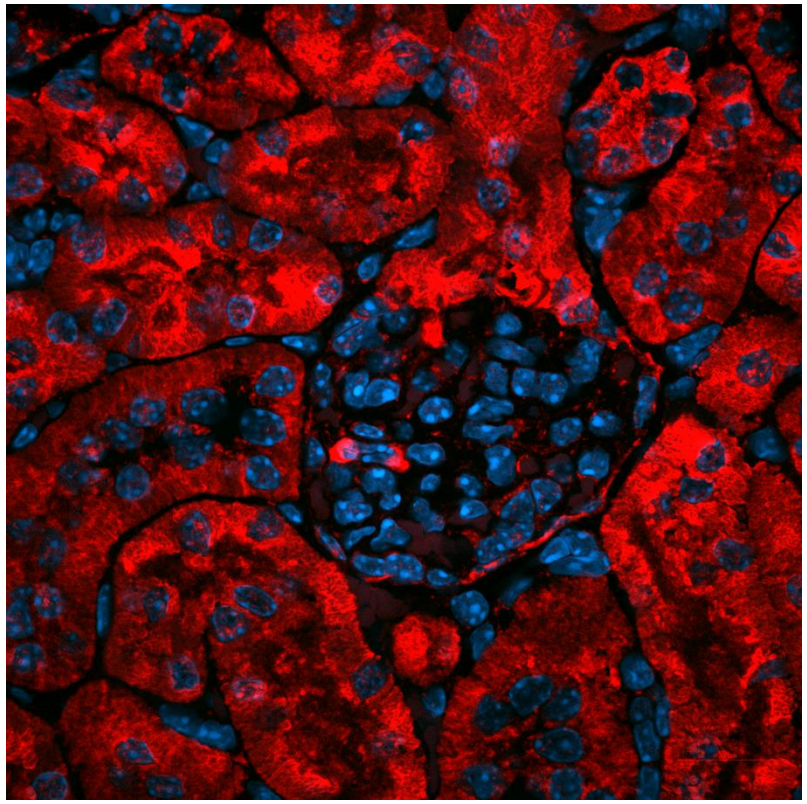
Dickkopf-3 and kidney fibrosis

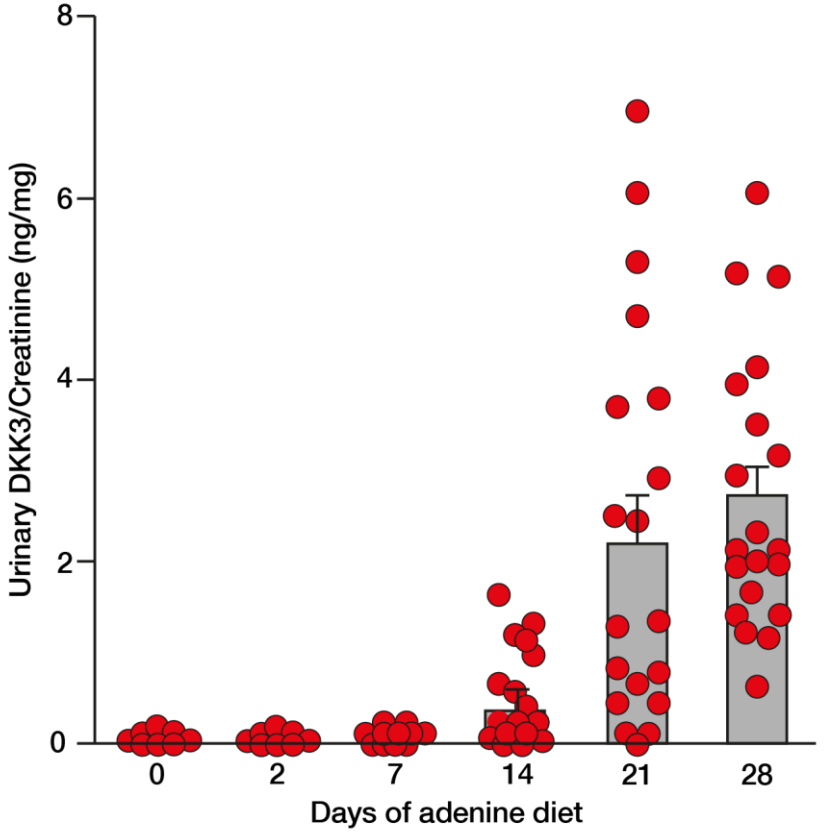




Federico et al. JCI Insight 2016

DKK3 can be detected in the urine

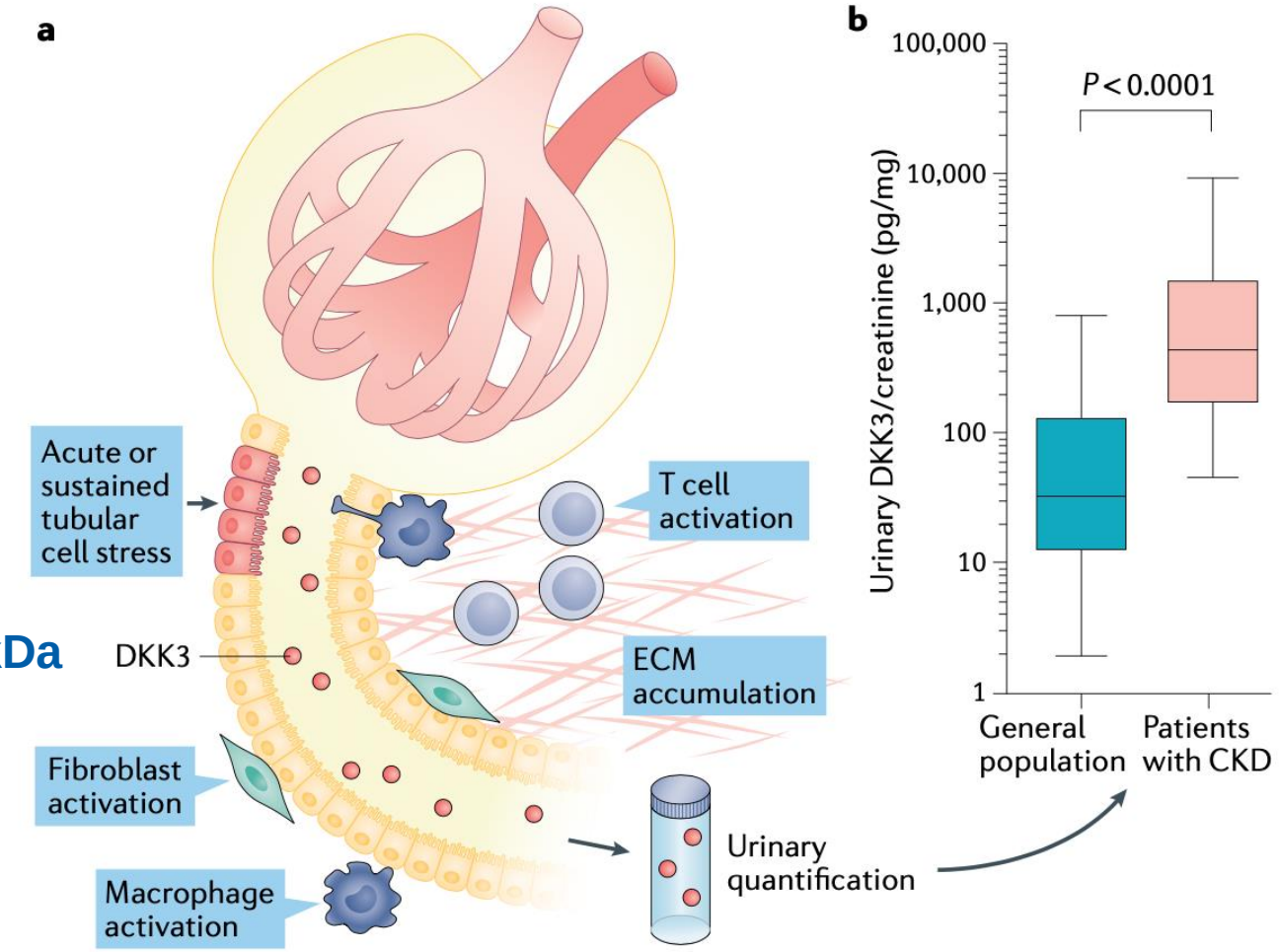




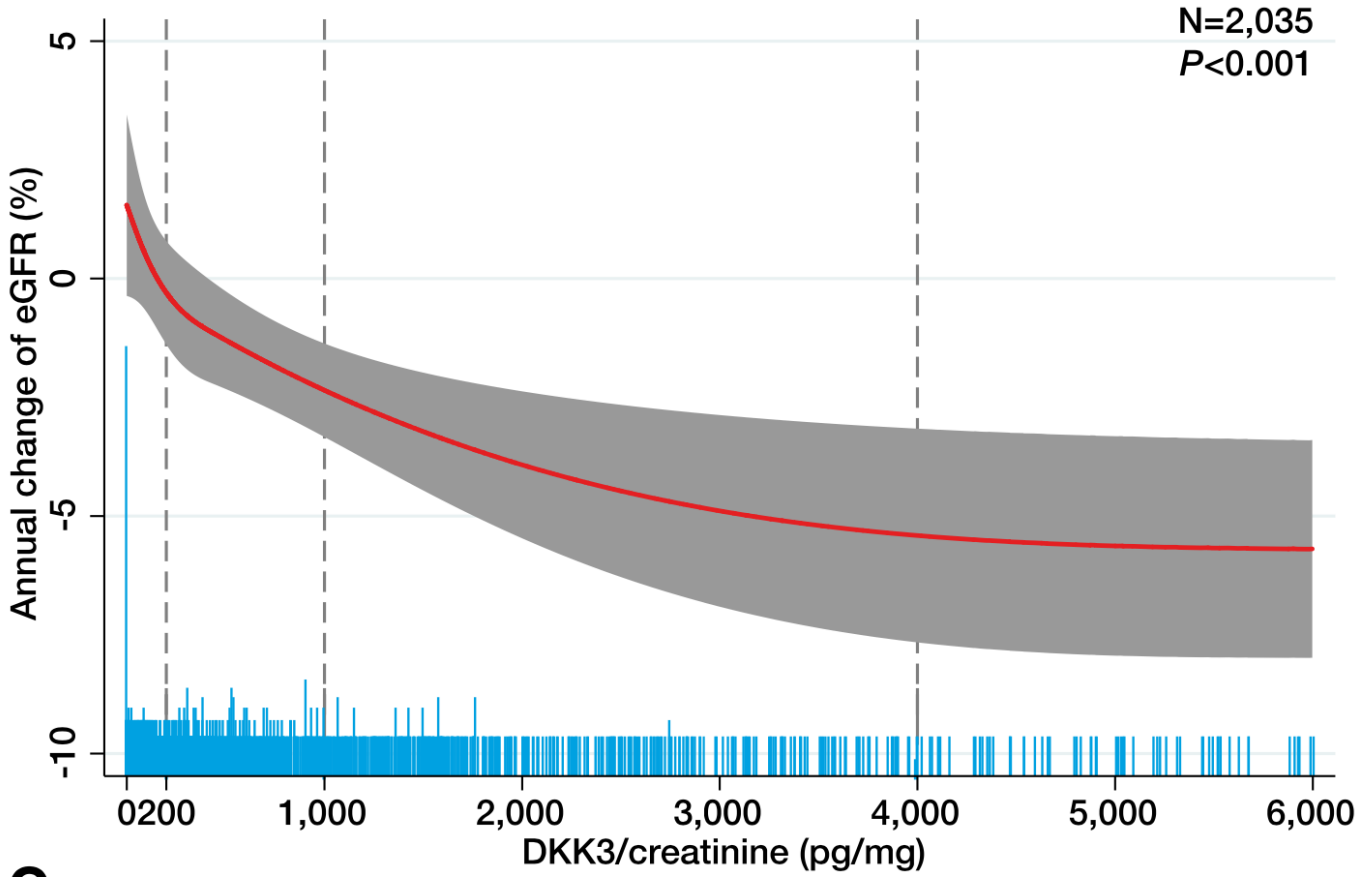
Federico et al. JCI Insight 2016

DKK3 is a tubular stress marker

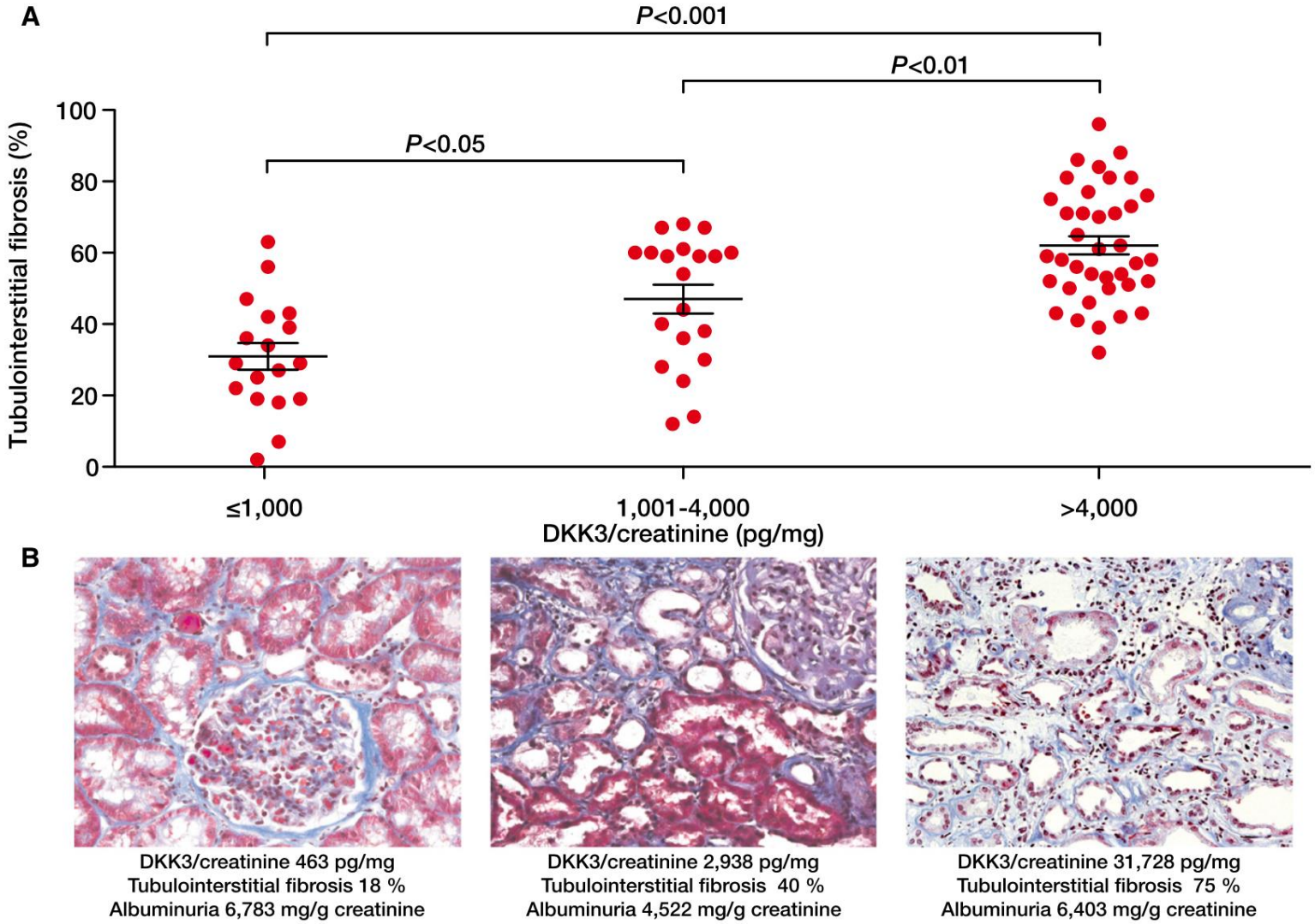
DKK3 38.4 kDa



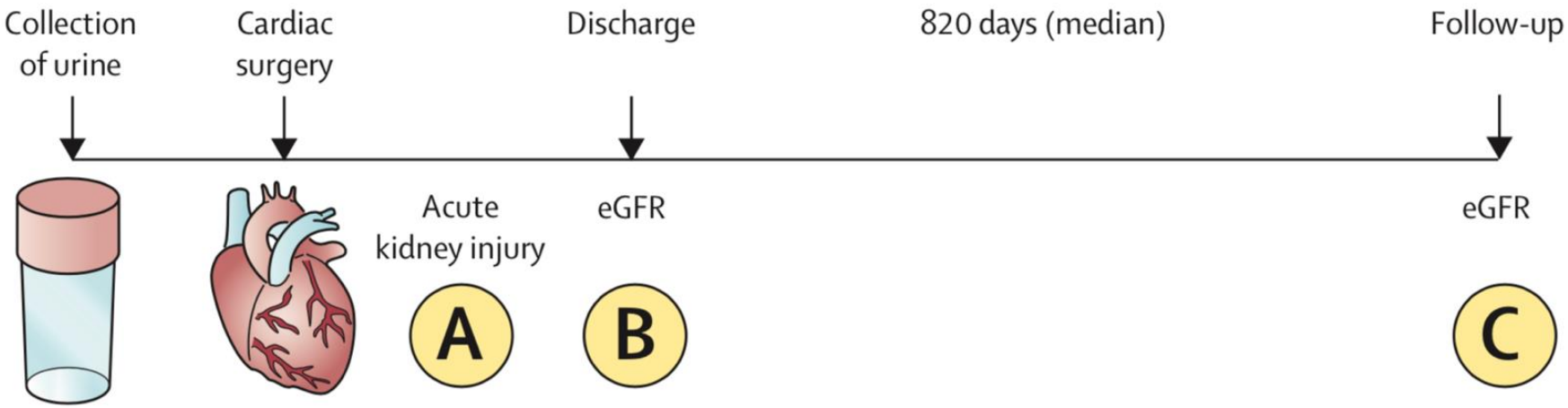
DKK3 and short-term CKD progression



DKK3 and tubulointerstitial fibrosis



DKK3 and acute kidney injury



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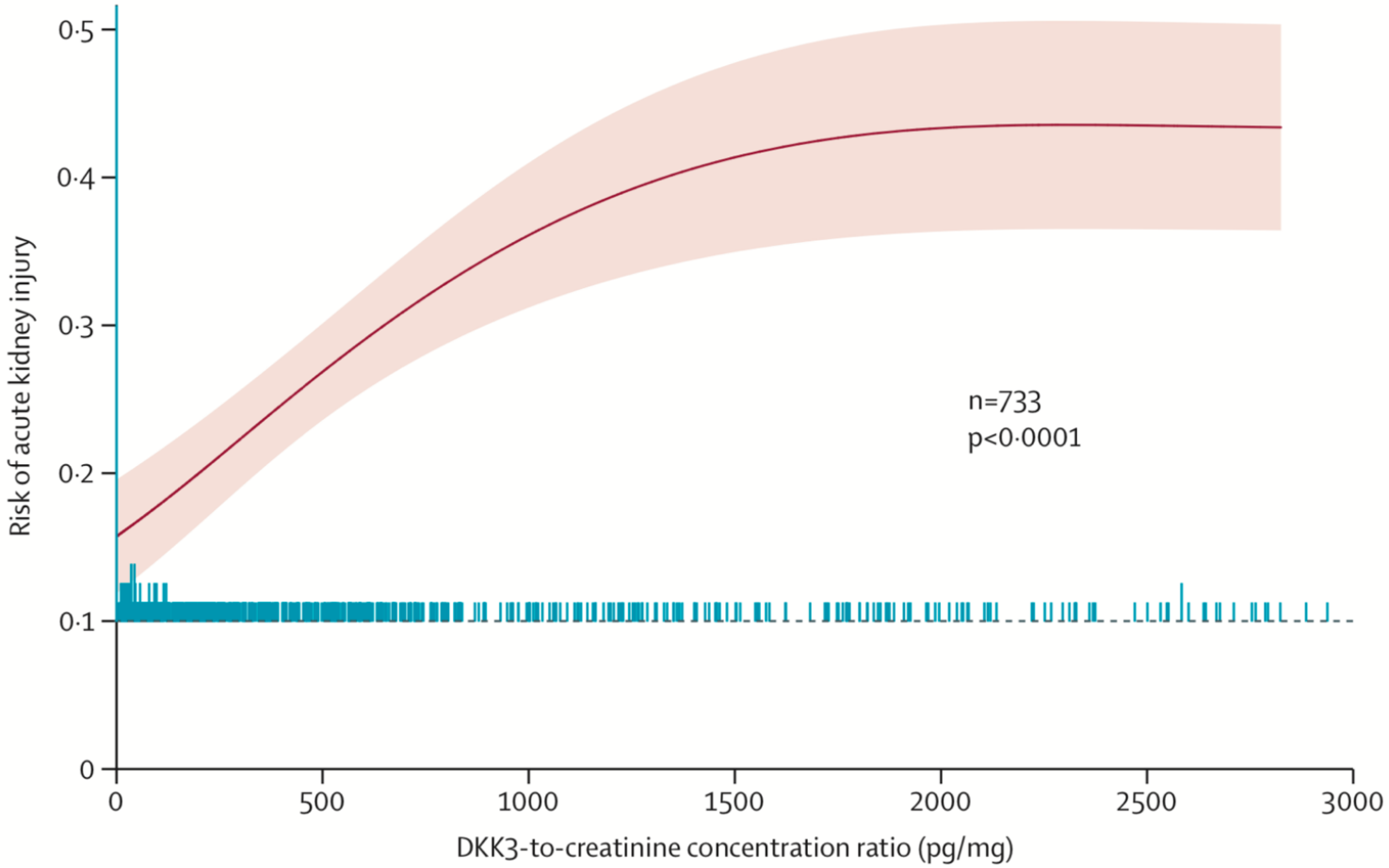
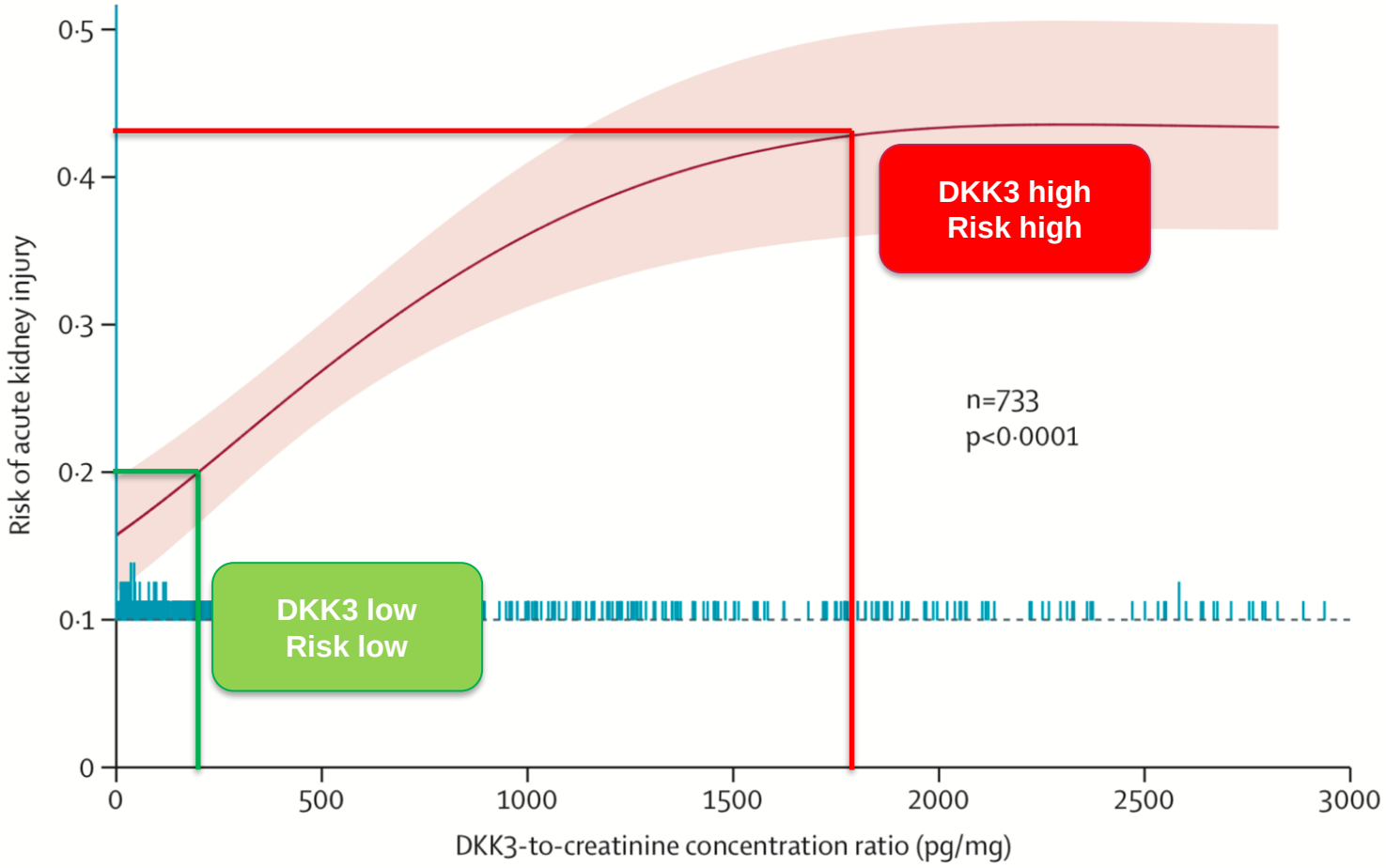


Schunk,...,Speer. Lancet 2019

DKK3 and acute kidney injury



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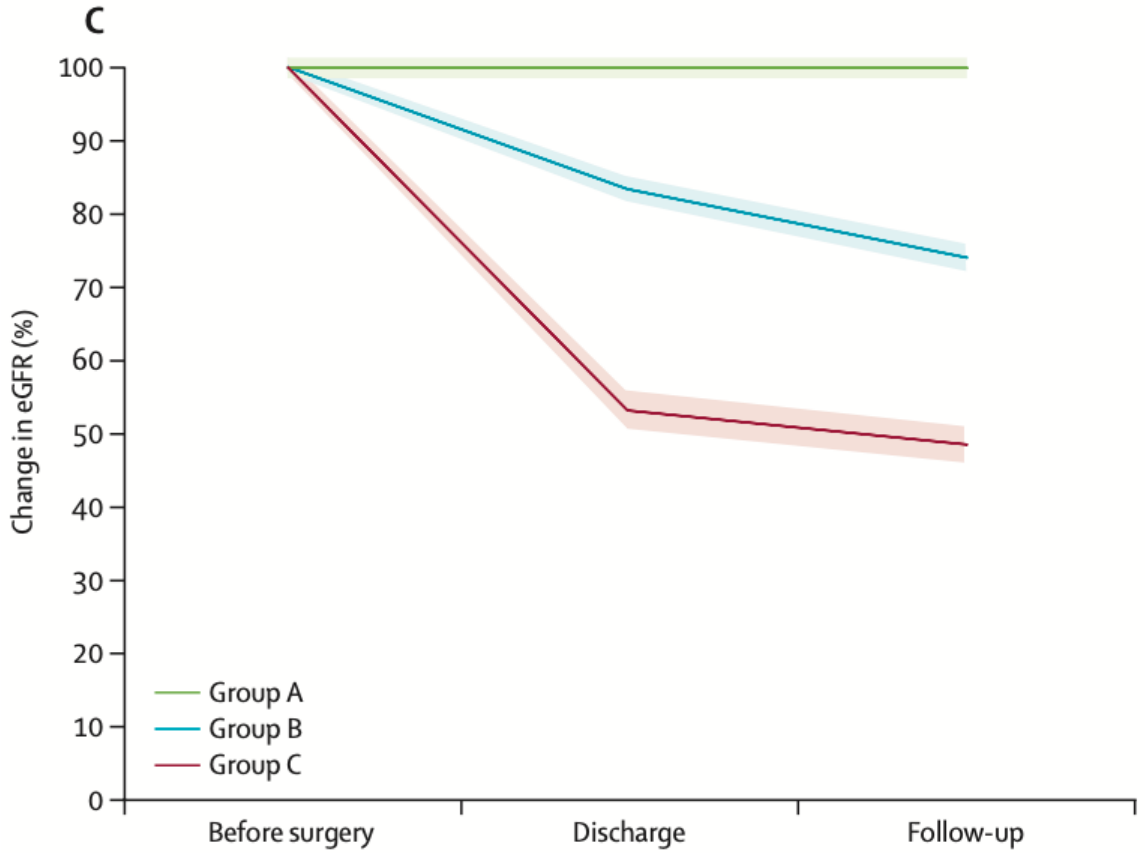
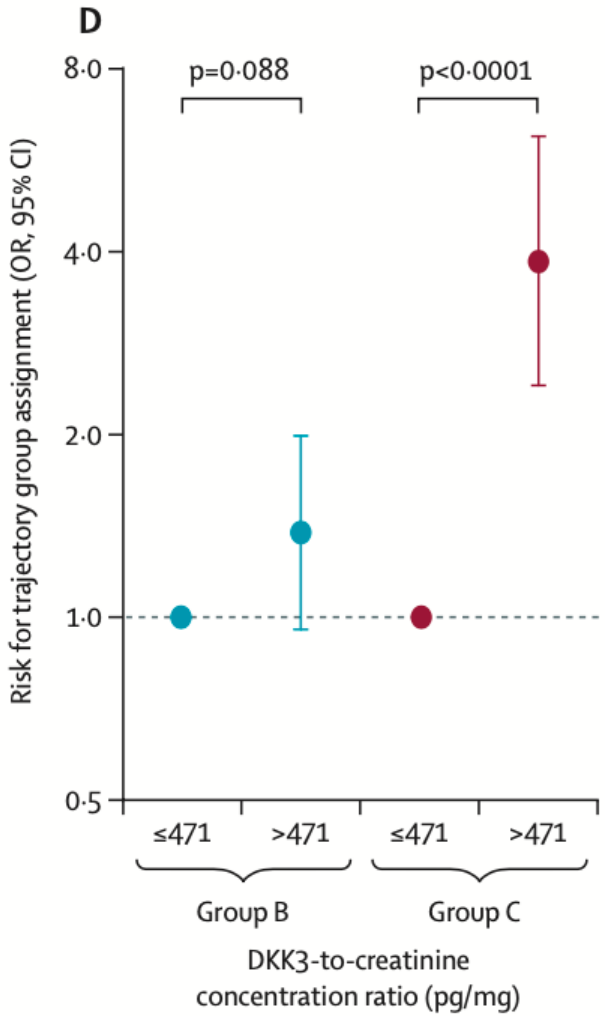
DKK3 and AKI CKD transition





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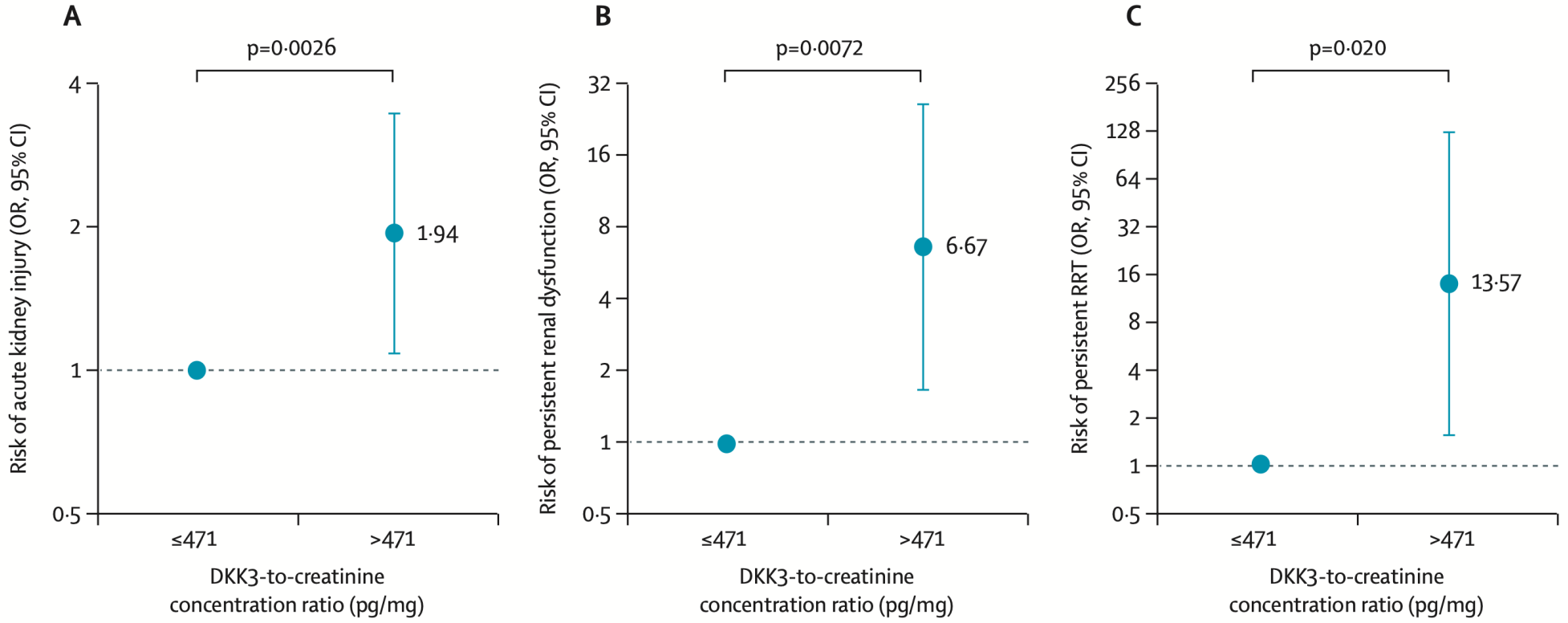


Validation in RenalRIP

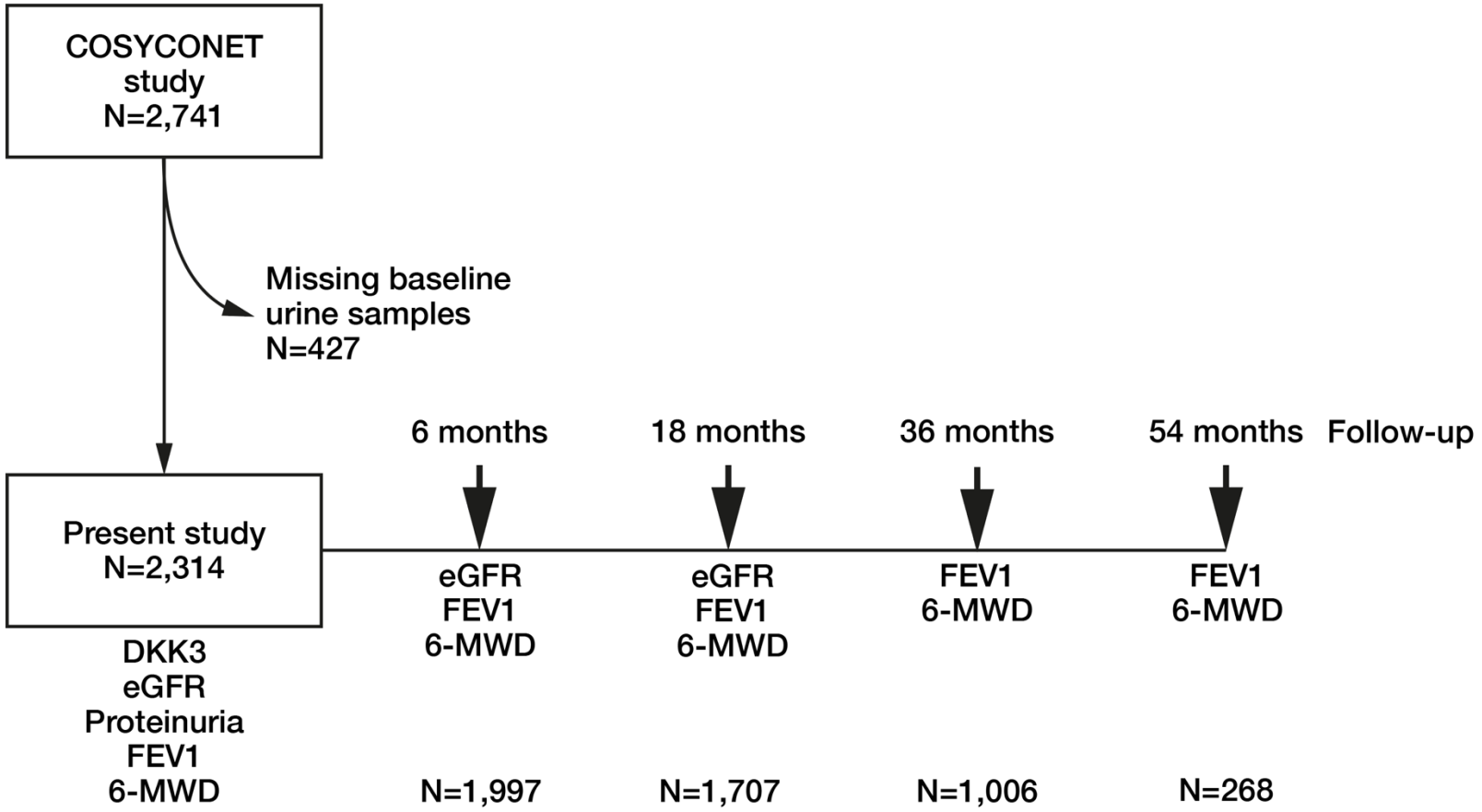
Schunk,...,Speer. Lancet 2019

DKK3 in Non-CKD patients

Characteristic	Total cohort (N = 2314)	Urinary DKK3 ≤ 200 pg/mg creatinine (n = 1048)	Urinary DKK3 > 200 pg/mg creatinine (n = 1266)	P
Age, yr	65.0 ± 8.6	64.2 ± 8.5	65.3 ± 8.7	0.001
Sex, % male	59.1	60.2	58.2	0.328
Body mass index, kg/m^2	27.1 ± 5.4	27.5 ± 5.4	26.8 ± 5.4	0.001
GOLD grade 0	15.0	16.3	13.9	0.047
GOLD grade 1	10.4	10.7	10.1	
GOLD grade 2	37.8	36.8	38.7	
GOLD grade 3	29.6	27.7	31.1	
GOLD grade 4	7.2	8.4	6.1	
FEV_1, % predicted	55.0 (30.0)	55.0 (32.0)	55.0 (29.0)	0.469
TLCO, % predicted	53.7 (29.7)	55.2 (29.1)	53.5 (29.5)	0.235
Smoking	92.4	92.6	92.2	0.915
Pack-years	42.0 (42.5)	43.0 (41.5)	42.5 (44.3)	0.824
Hypertension	55.4	54.4	56.3	0.377
Heart failure	10.3	9.3	11.1	0.339
IDDM	5.1	5.0	5.2	0.850
NIDDM	9.2	8.8	9.6	0.564
Corticosteroid therapy	11.3	9.9	12.6	0.141
Serum creatinine, mg/dl	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.991
eGFR, ml/min per 1.73 m^2	82.0 ± 16.4	82.5 ± 16.0	81.3 ± 16.7	0.119
Urinary DKK3, pg/mg creatinine	227 (414)	77 (119)	467 (493)	<0.001
Proteinuria, mg/g creatinine	5.0 (6.0)	4.0 (4.0)	5.0 (7.0)	<0.001

UNCORRECTED

DKK3 in Non-CKD patients



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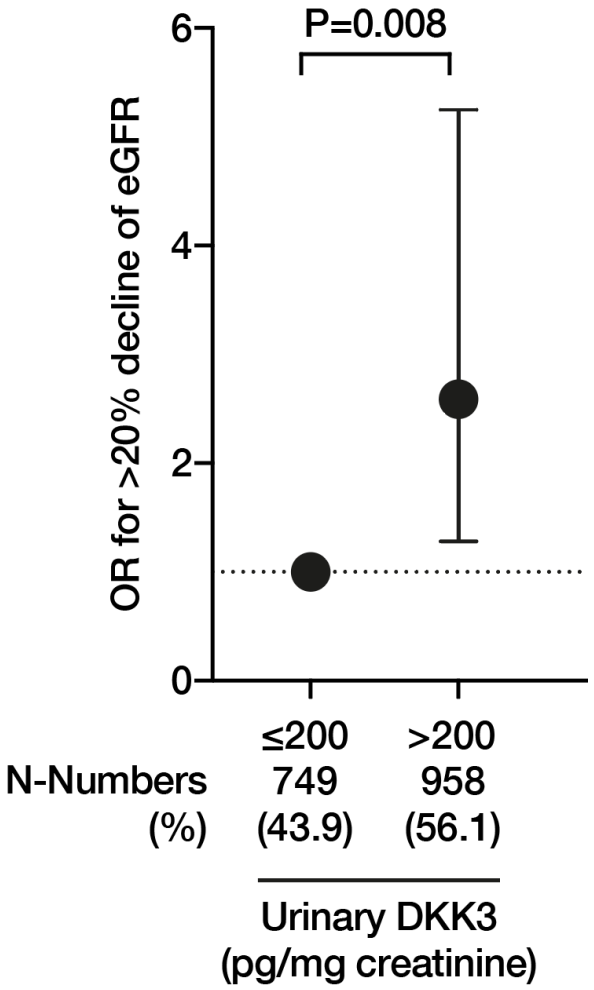

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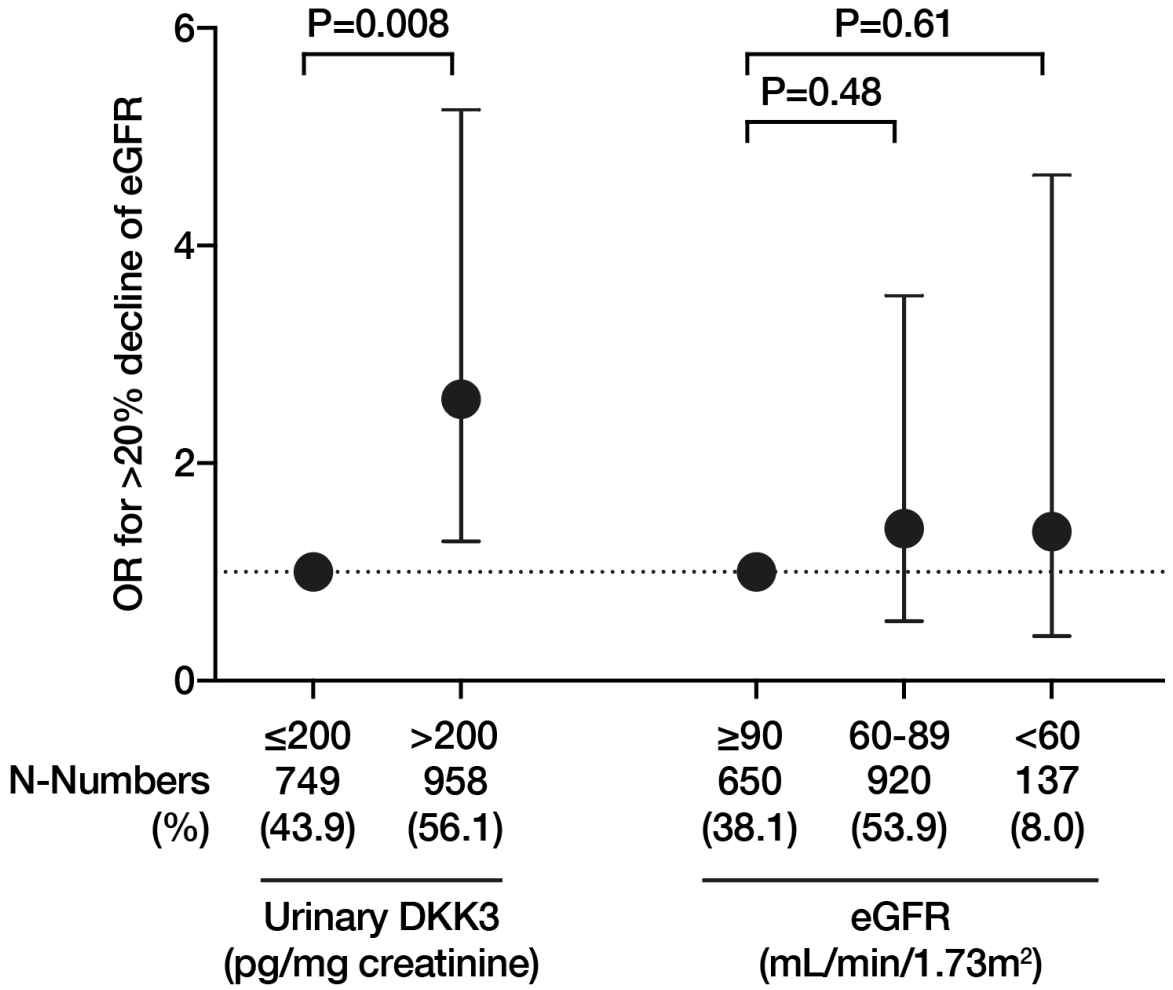

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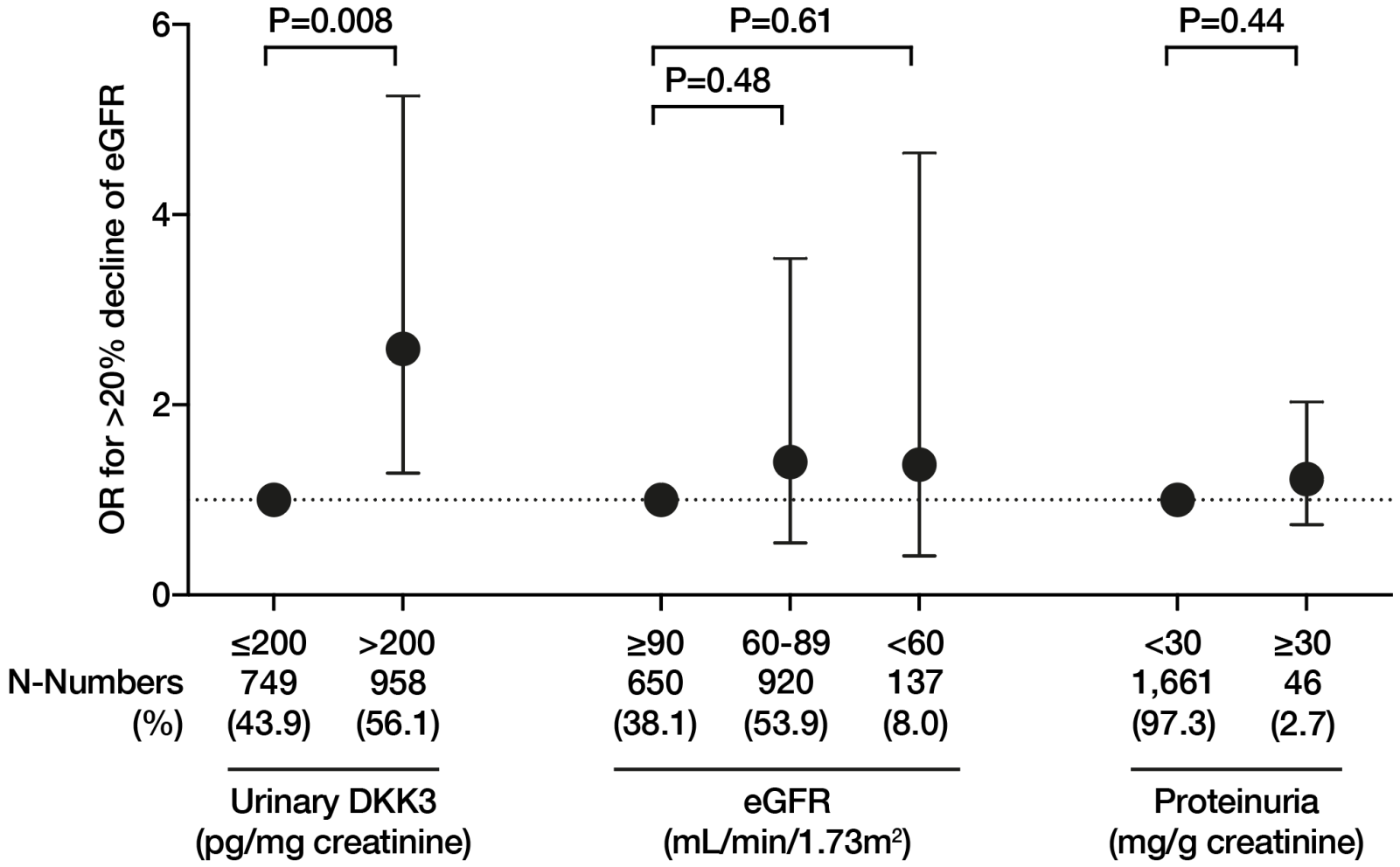

Schunk,...,Speer. Kidney Int 2021

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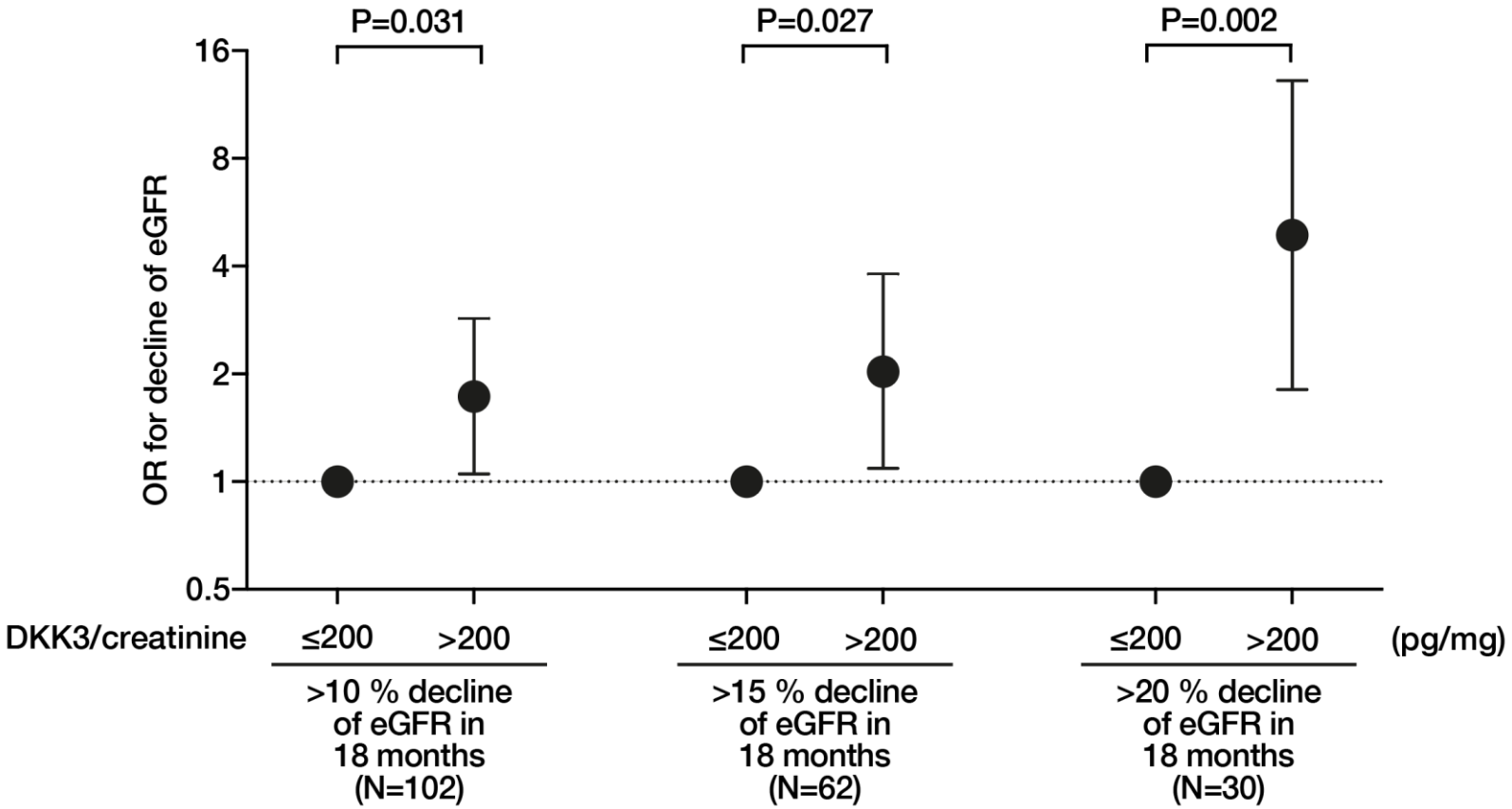
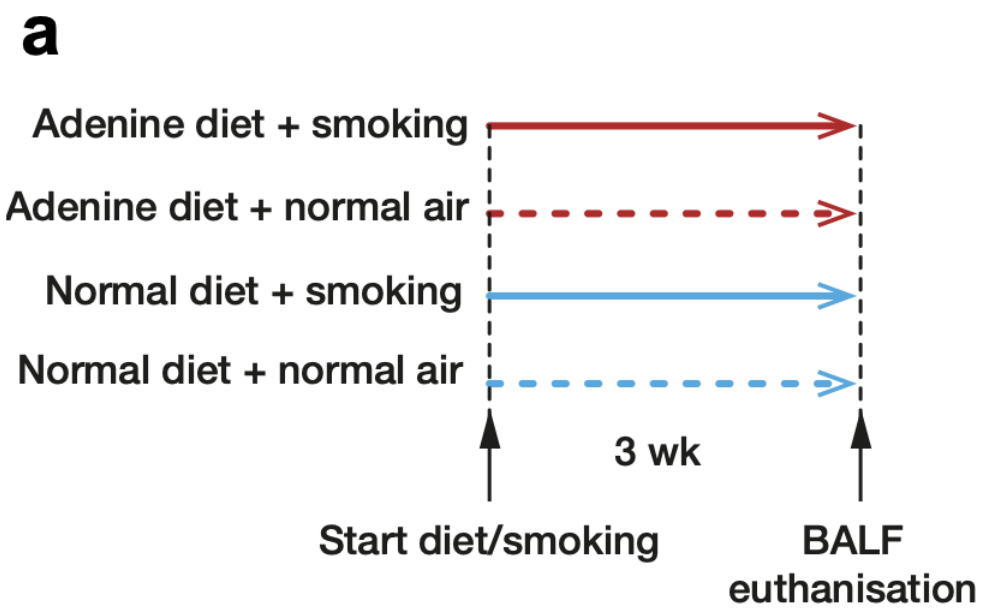


eGFR
≥90 mL/min/1.73m2
and
Proteinuria
<30 mg/g creatinine

Schunk,...,Speer. Kidney Int 2021

DKK3 and combined kidney/lung injury



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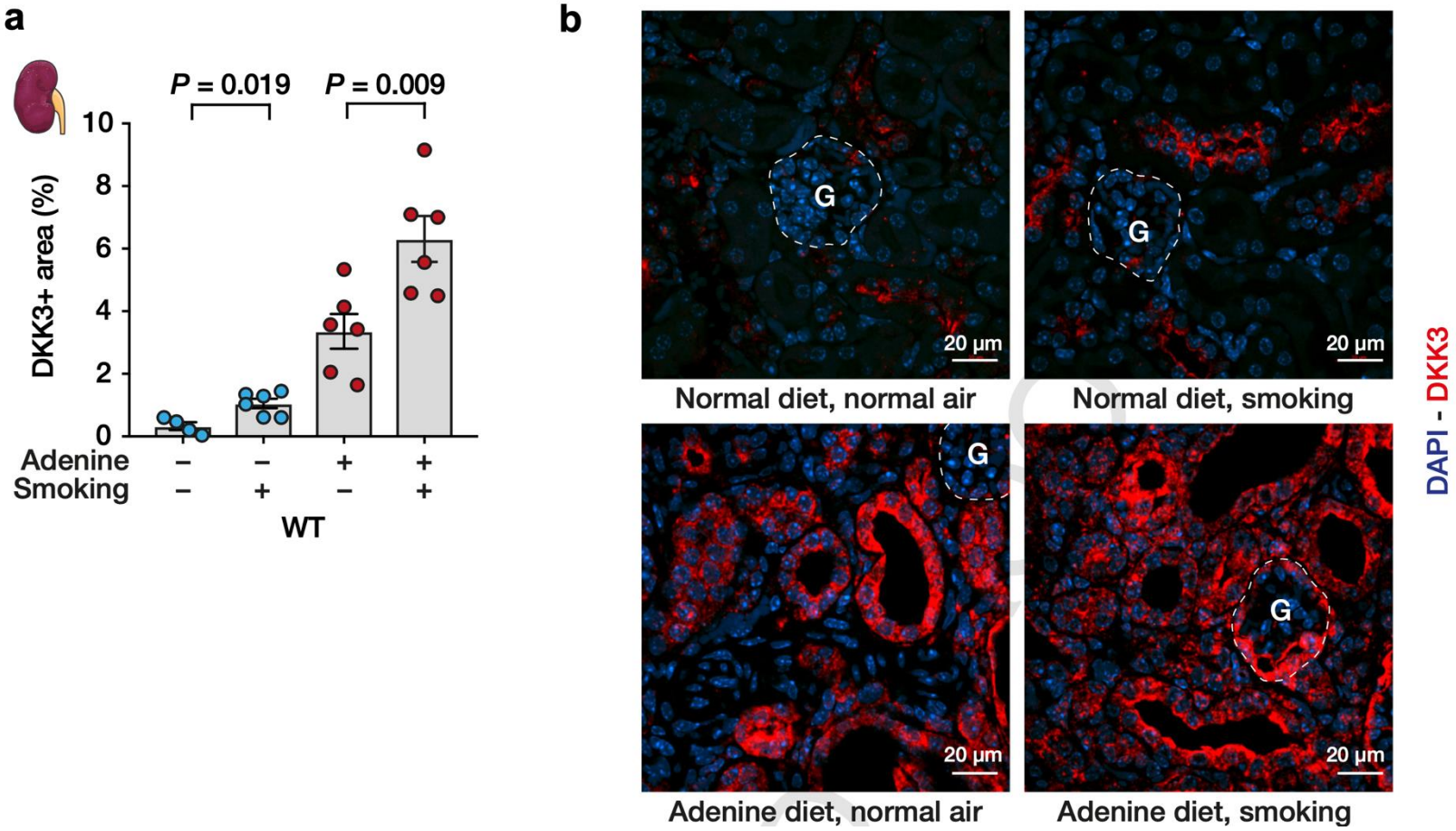

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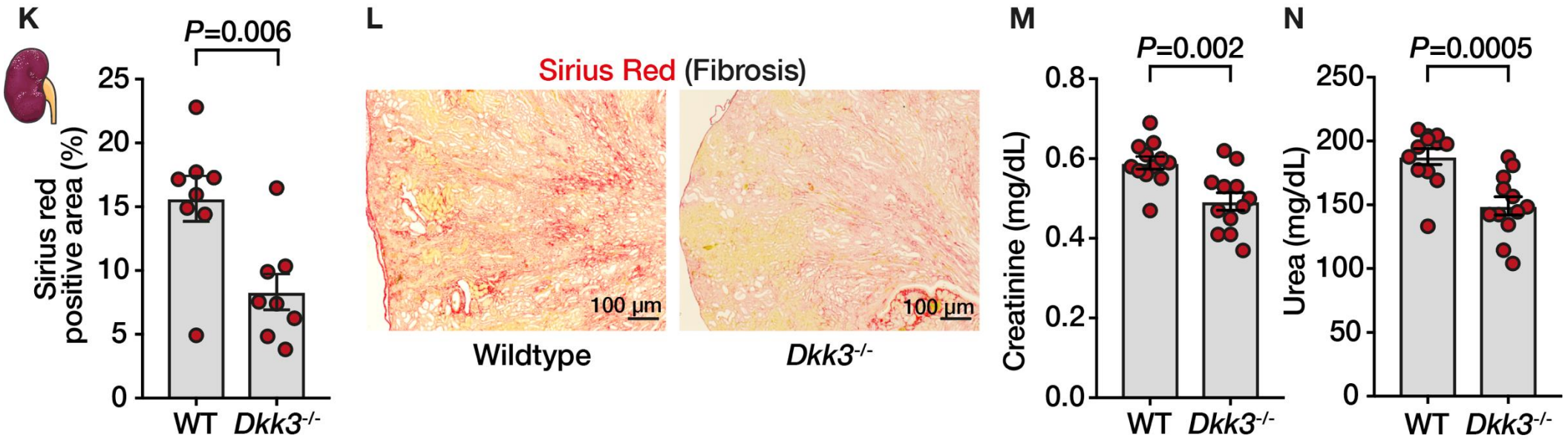
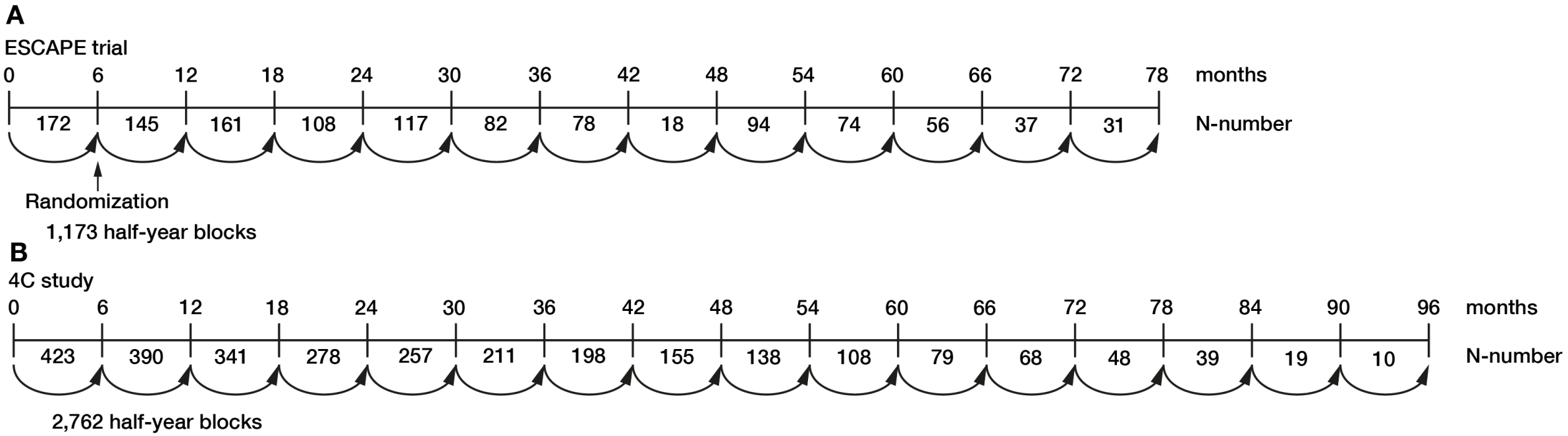


DKK3 in children with CKD



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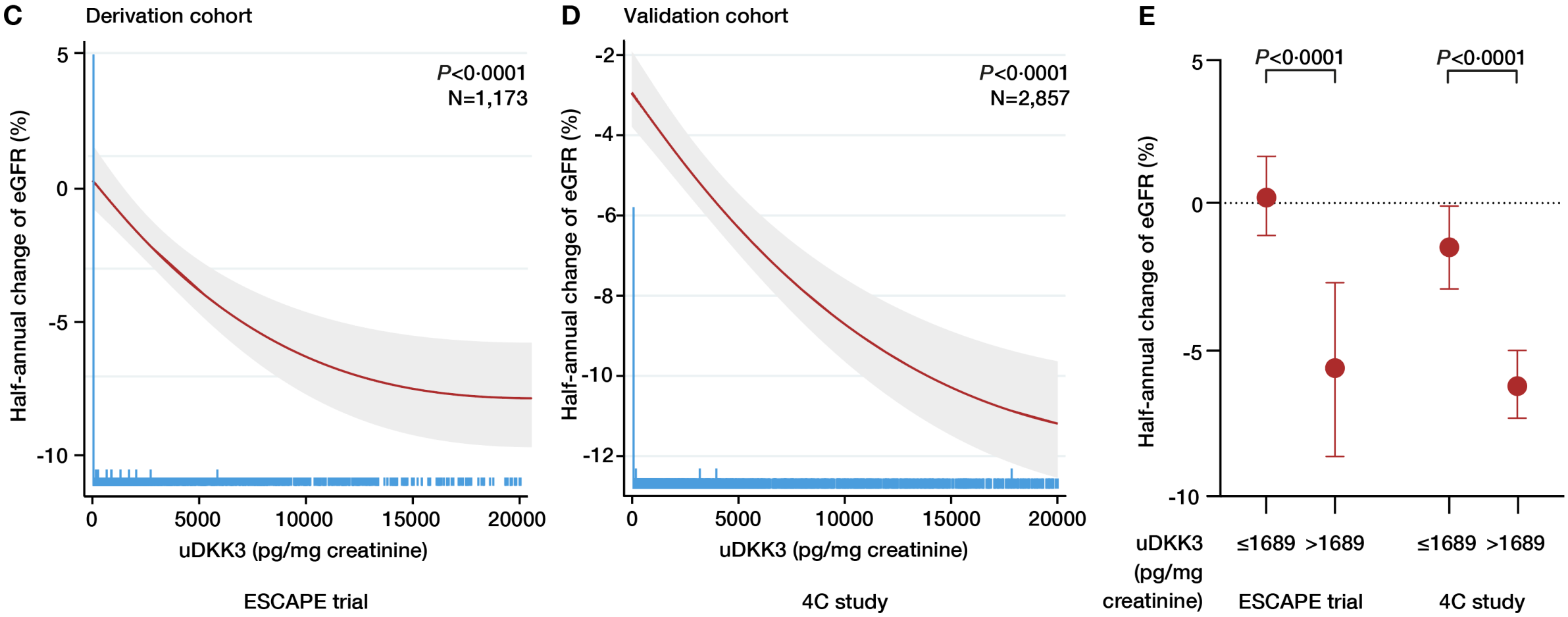

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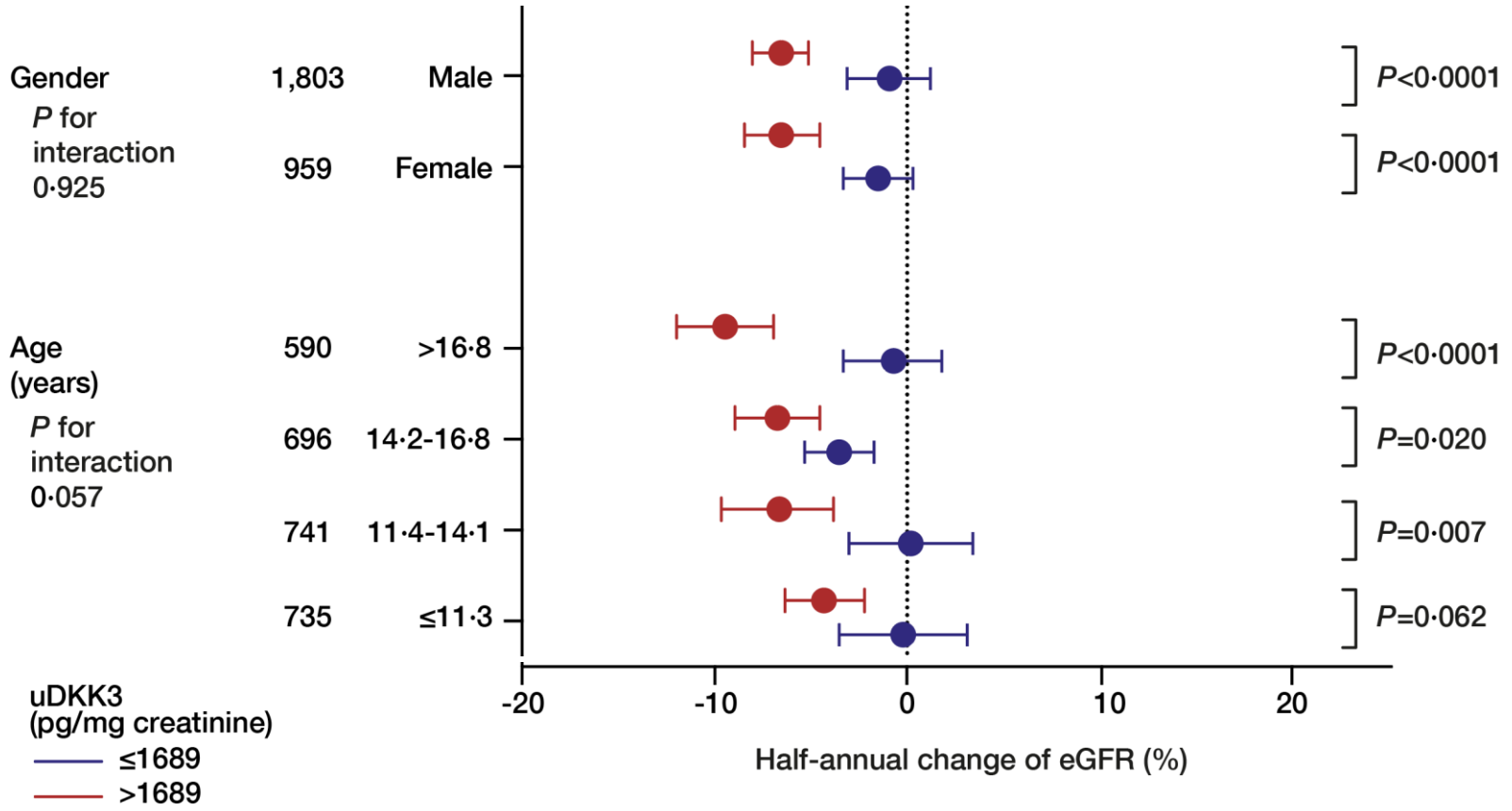

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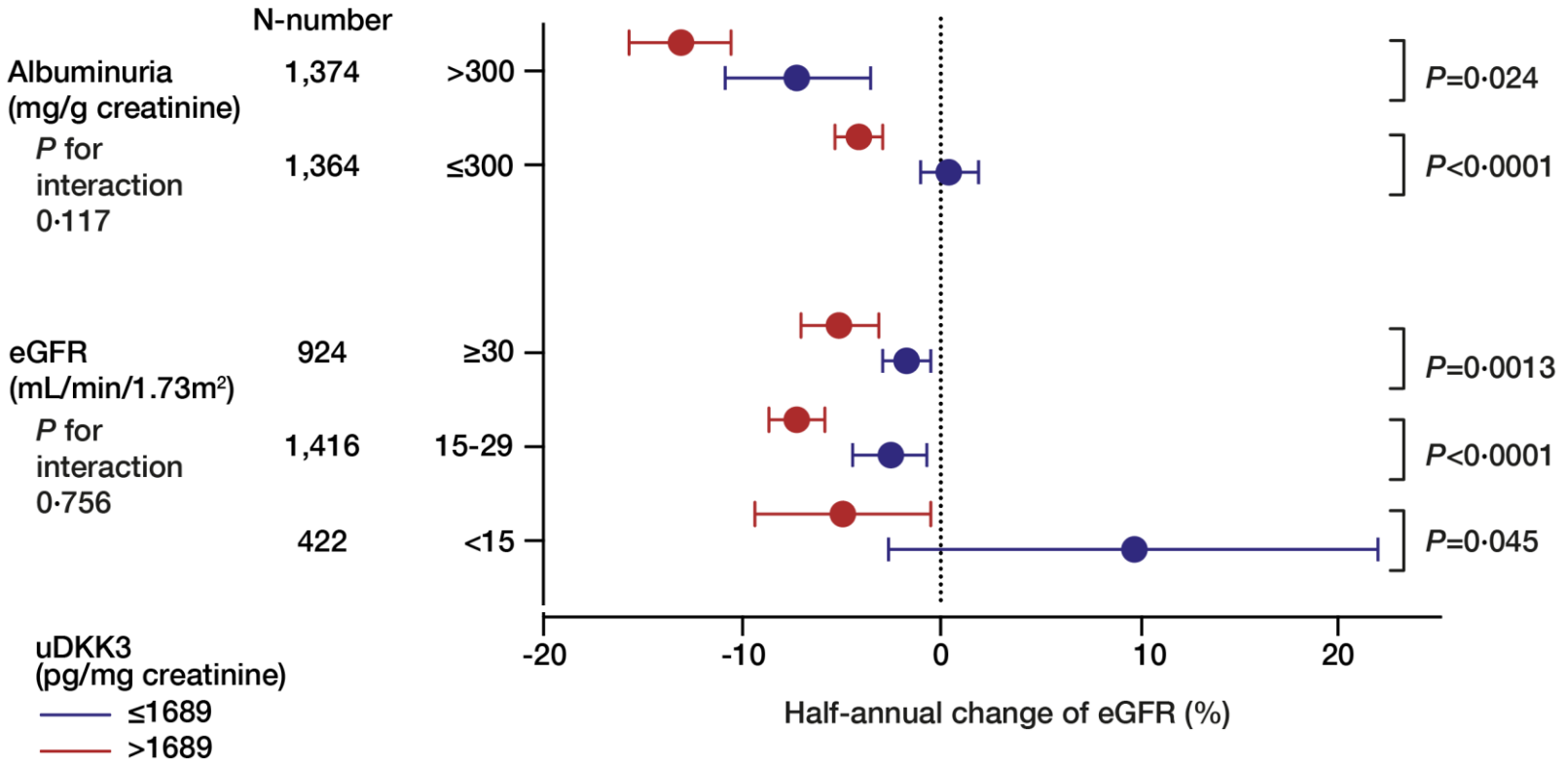

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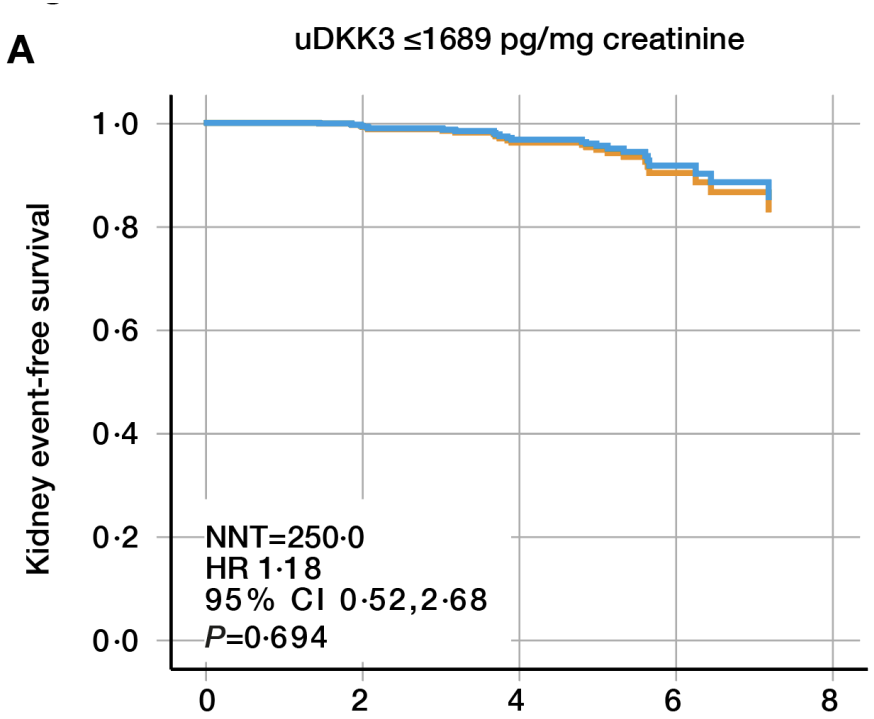
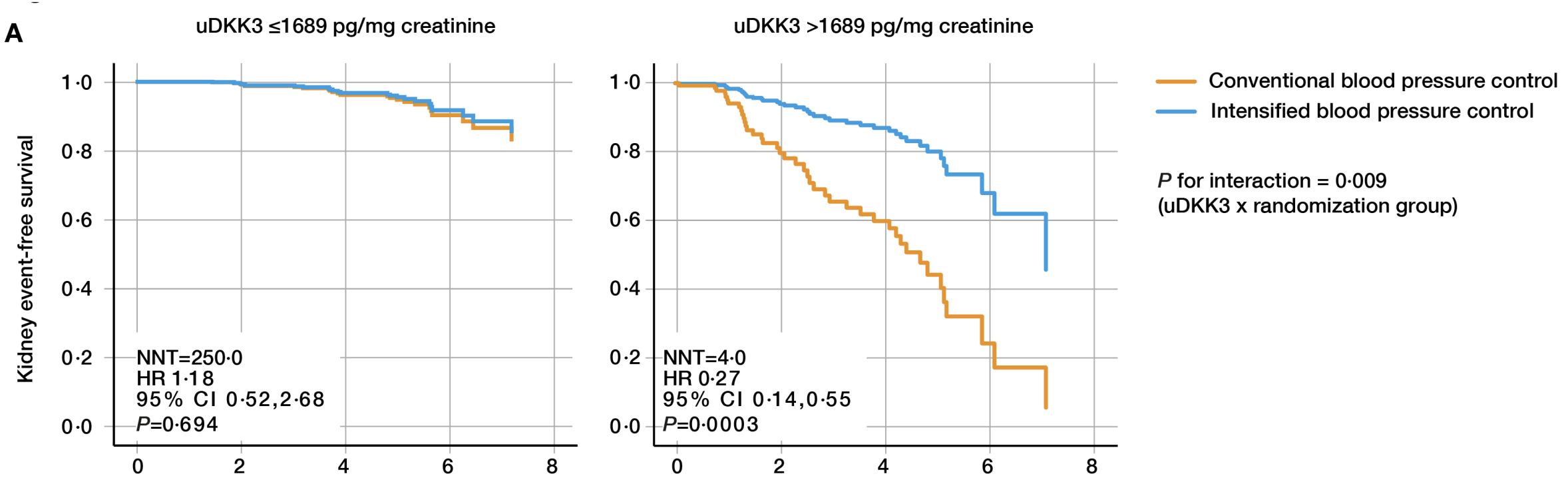


Conventional blood pressure control
Intensified blood pressure control

P for interaction = 0·009
(uDKK3 x randomization group)

DKK3 in children with CKD



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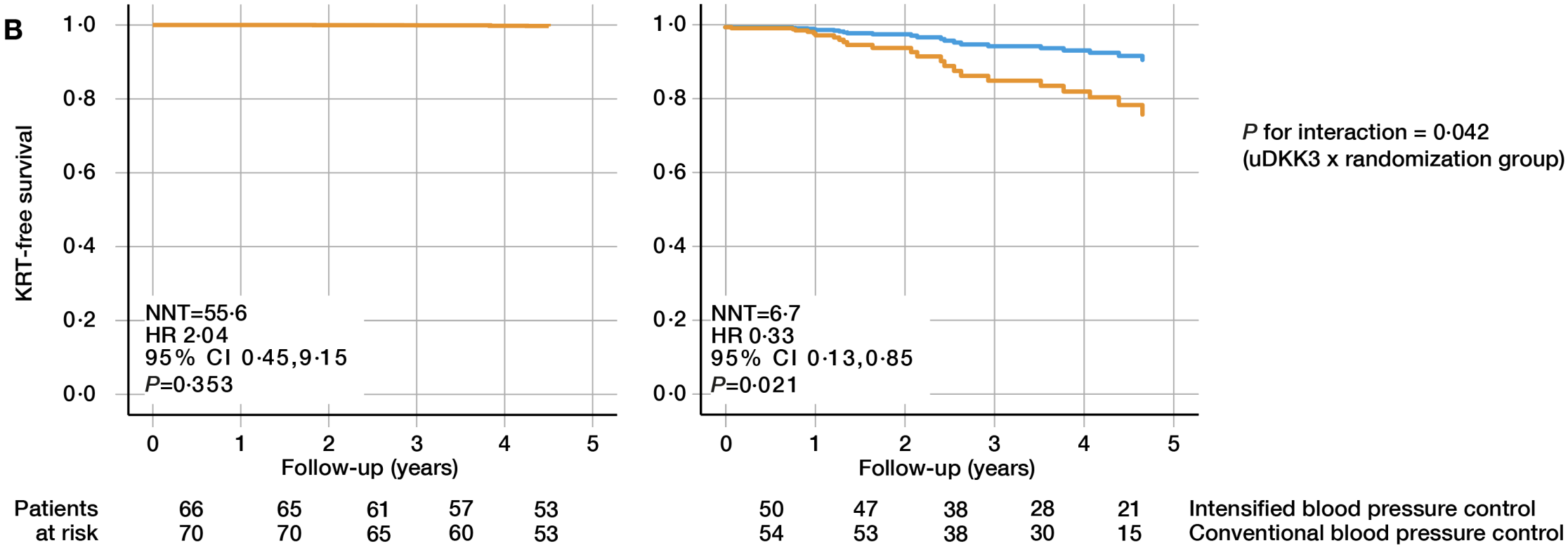
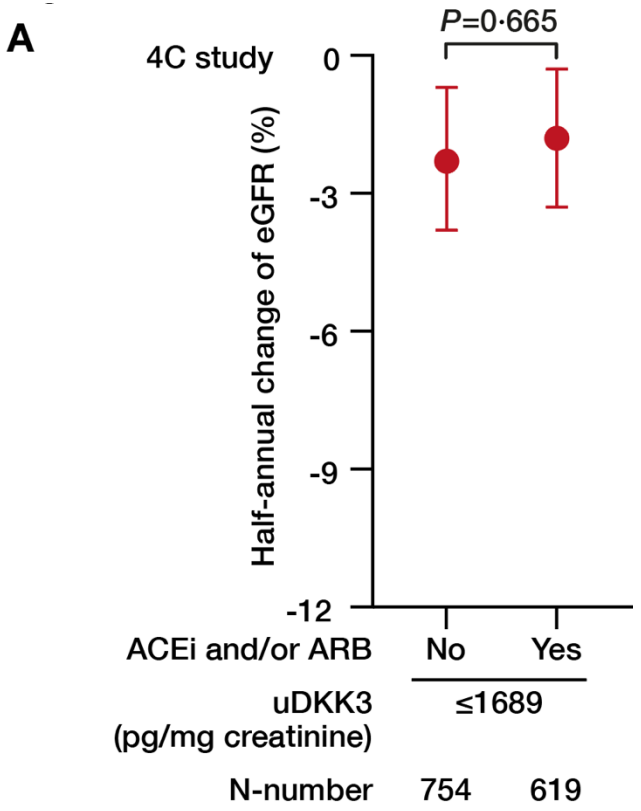
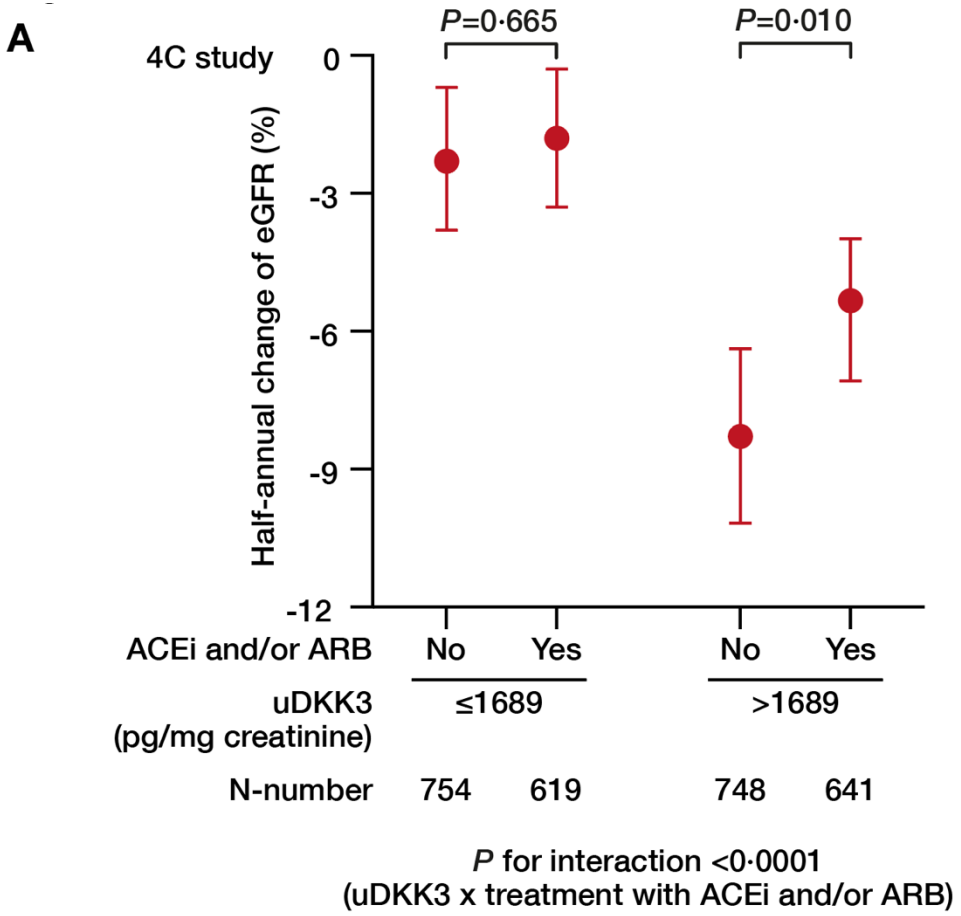


P for interaction = 0·042
(uDKK3 x randomization group)

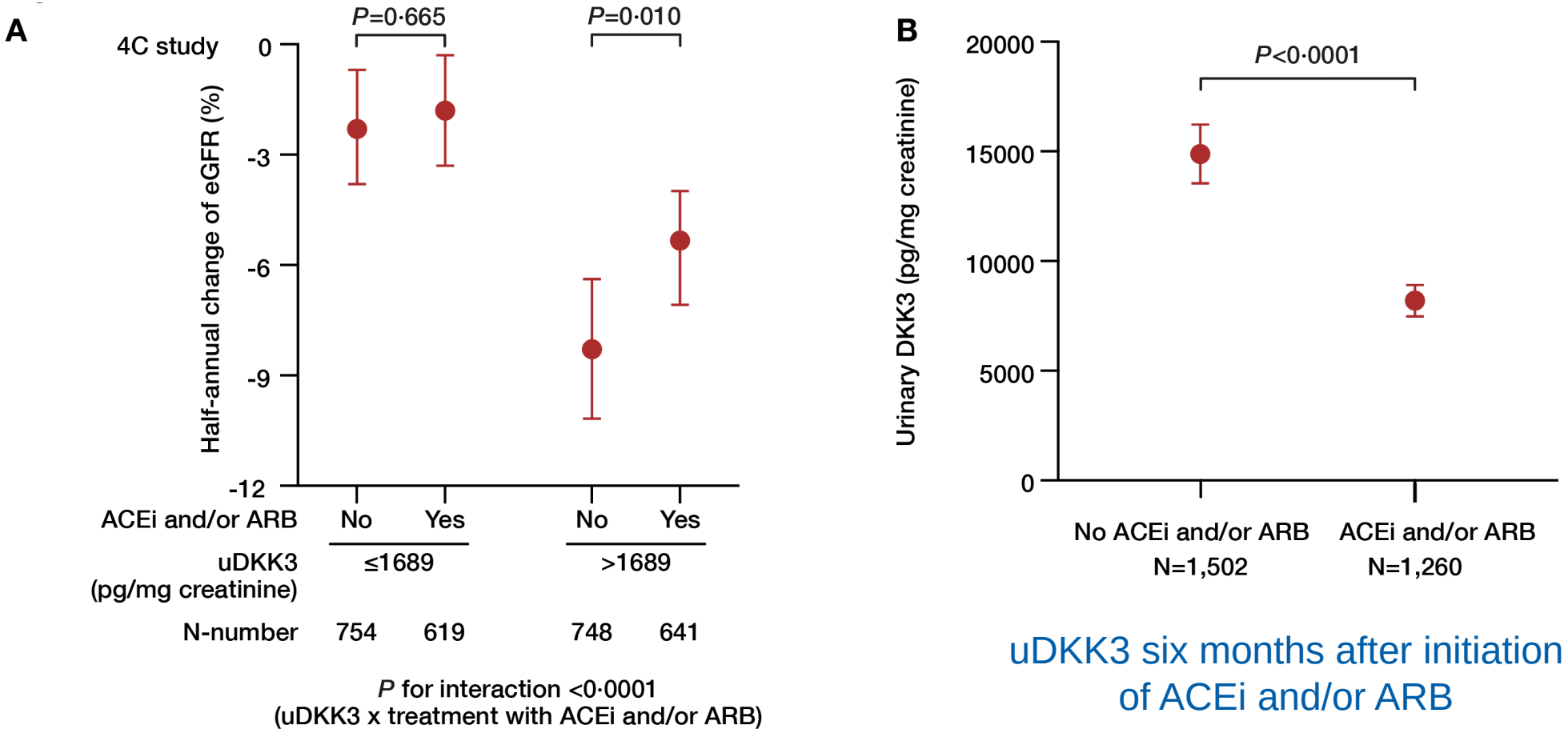
DKK3 in children with CKD



DKK3 in children with CKD



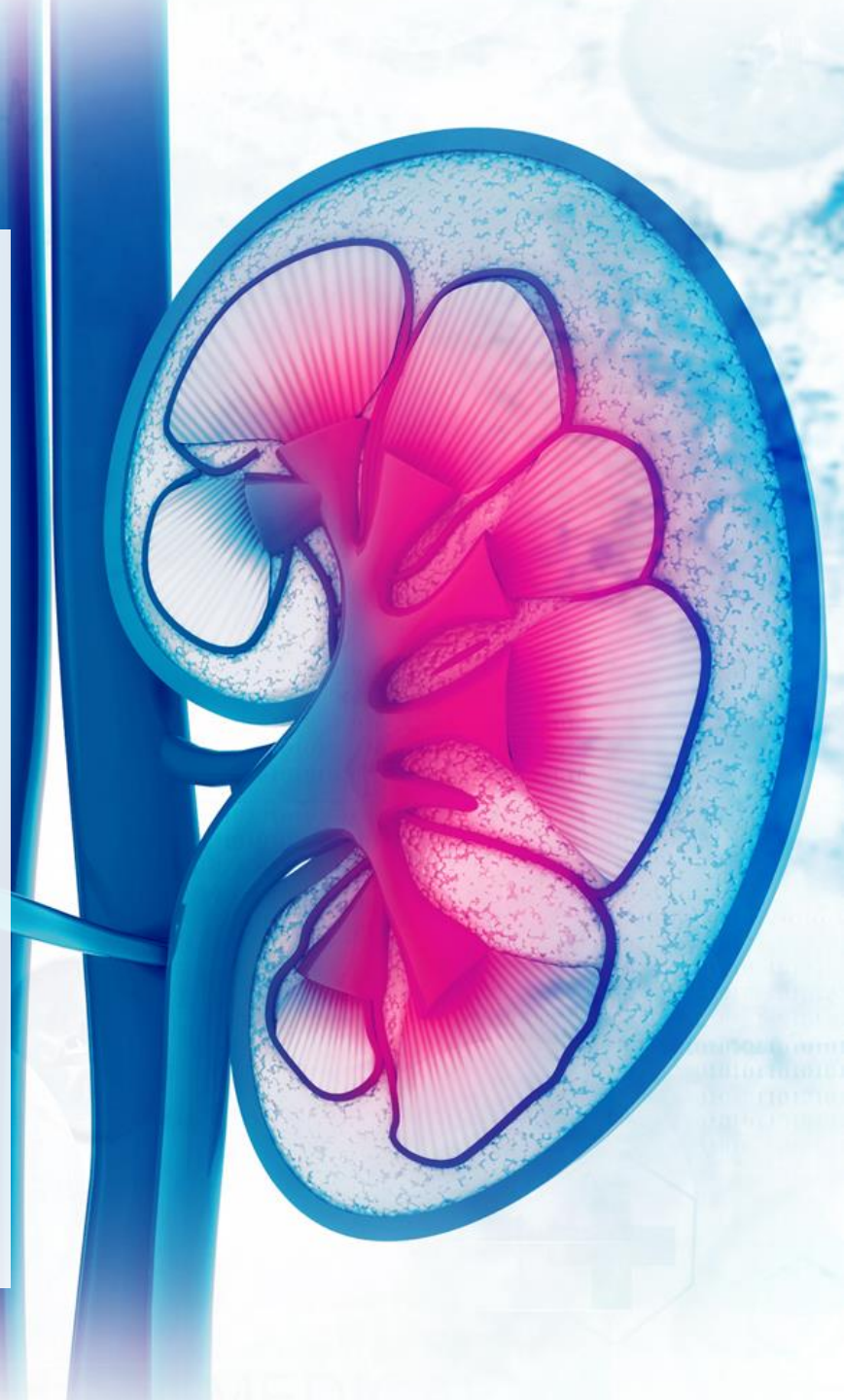
DKK3 in children with CKD



uDKK3 six months after initiation of ACEi and/or ARB

Summary

- **DKK3** is a tubular stress marker
- **DKK3** identifies patients at high risk for short-term decline of eGFR
- **DKK3** is independent of eGFR and albuminuria
- **DKK3** identifies patients at high risk for AKI-CKD transition
- **DKK3** identifies patients, who particularly benefit from nephroprotective therapies



Thank you