UNIKLINIK KÖLN
Klinik II für Innere Medizin
Nephrologie, Rheumatologie, Diabetologie
und Allgemeine Innere Medizin

Interventions diététique: rationnel et résultats

Necker Seminars in Nephrology 2024

Roman-Ulrich Müller
Cologne Polycystic and Genetic Kidney Disease Center

colpkd G&K Genes & Kidney CECAD COLOGNE CMMC CESEK Centrum für Seltene Erkrankungen Köln

Conflicts of interest

- scientific advisory boards: Vifor, Alnylam, AICuris, GSK, Santa Barbara Nutrients, Ephyra
- research funding: Otsuka Pharmaceuticals, ThermoFisherScientific

Management of ADPKD – state of the art

- sufficient fluid intake (urine volume > 3 l/d)
- **limit salt intake**
- physical activity, avoid overweight
- healthy diet (e.g. mediterranean diet)
- blood pressure control !
- moderate coffee consumption, no smoking
- avoid estrogen supplementation

Müller and Benzing CKJ 2018

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Müller and Benzing CKJ 2018

Dietary salt restriction is beneficial in ADPKD

www.kidney-international.org clinical investigation

Dietary salt restriction is beneficial to the management of autosomal dominant polycystic kidney disease

Vicente E. Torres[1], Kaleab Z. Abebe[2], Robert W. Schrier[3], Ronald D. Perrone[4], Arlene B. Chapman[5], Alan S. Yu[6], William E. Braun[7], Theodore I. Steinman[8], Godela Brosnahan[3], Marie C. Hogan[1], Frederic F. Rahbari[9], Jared J. Grantham[6], Kyongtae T. Bae[2], Charity G. Moore[10] and Michael F. Flessner[11]

[1]Mayo Clinic College of Medicine, Rochester, Minnesota, USA; [2]University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA; [3]University of Colorado Health Sciences Center, Denver, Colorado, USA; [4]Tufts Medical Center, Boston, Massachusetts, USA; [5]University of Chicago, Chicago, Illinois, USA; [6]Kansas University Medical Center, Kansas City, Kansas, USA; [7]Cleveland Clinic, Cleveland, Ohio, USA; [8]Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA; [9]Emory University School of Medicine, Atlanta, Georgia, USA; [10]Carolinas HealthCare System, Charlotte, North Carolina, USA; and [11]National Institutes of Health, Bethesda, Maryland, USA

- 0.09 ml/min/year increase of eGFR loss per 1 gram of salt

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our approach: < 5-7 g sodium chloride per day

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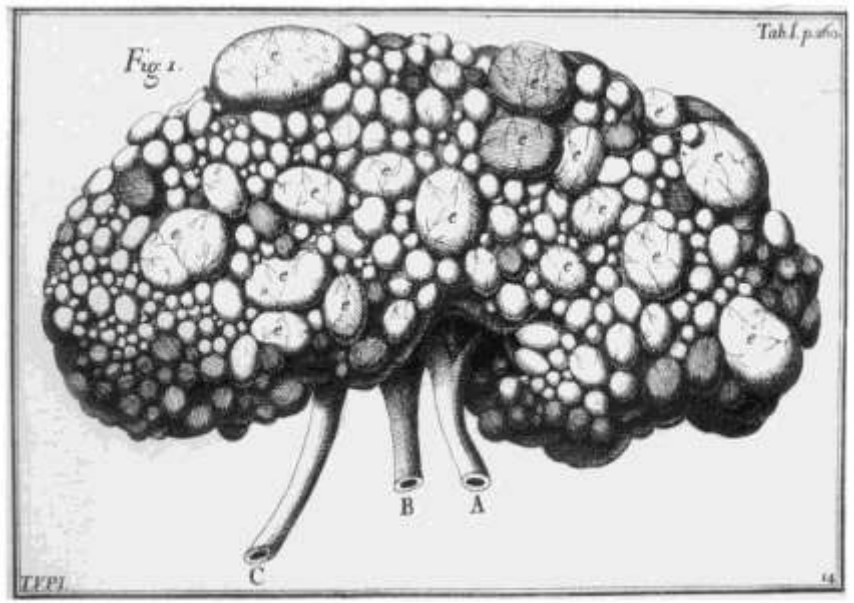
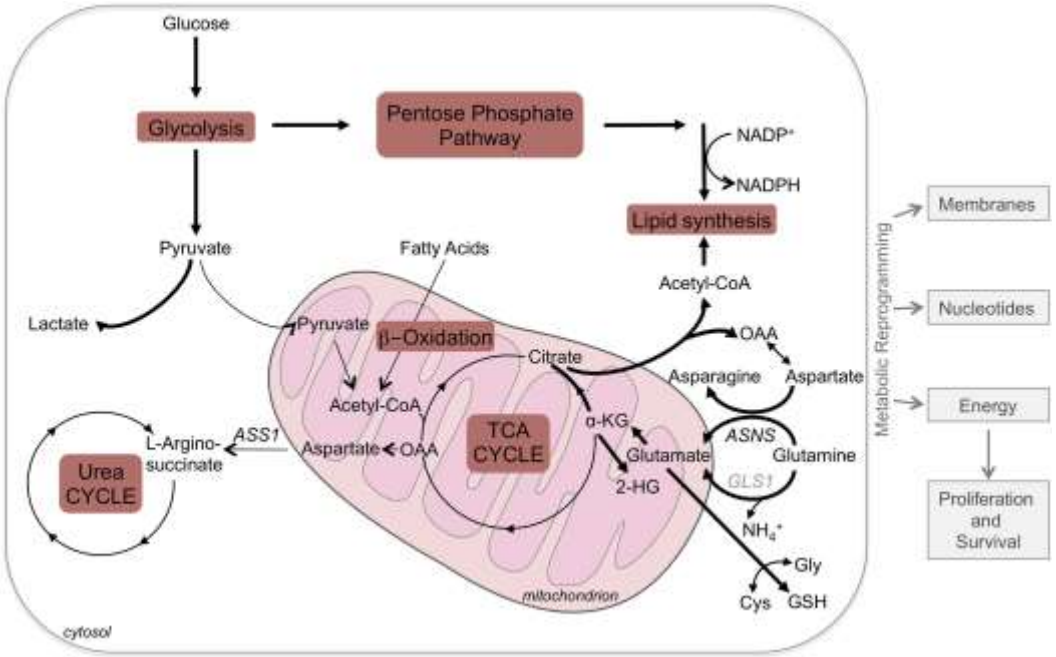
Müller and Benzing CKJ 2018



?

Domenico Gusmano Galeazzi (1757)

ADPKD is a metabolic disorder



- Warburg effect
- glutamine anaplerosis
- defective TCA cycle
- defective OXPHOS
- reduced FA oxidation
- enhanced FA biosynthesis

Podrini, Cassina and Boletta Cellular Signaling 2020
Haumann, Müller and Liebau IJMS 2020

Metabolism…

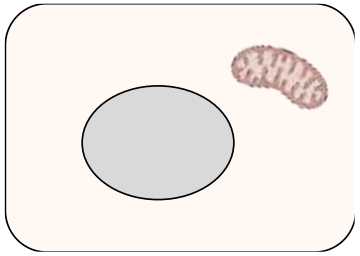
The main purposes of metabolism are:

1. the conversion of the energy in **food to energy** available to cells

2. the conversion of **food to building blocks**

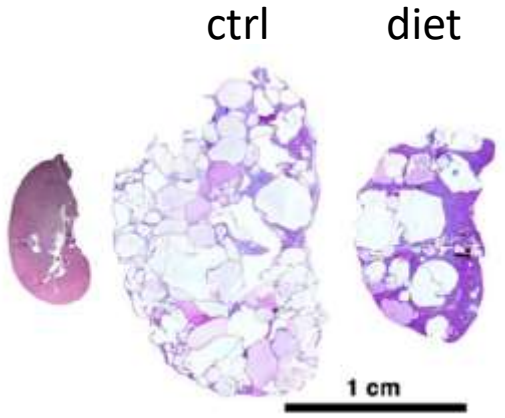
POLLUTING ENERGY
FINITE SOURCES

CLEAN ENERGY
RENEWABLE SOURCES

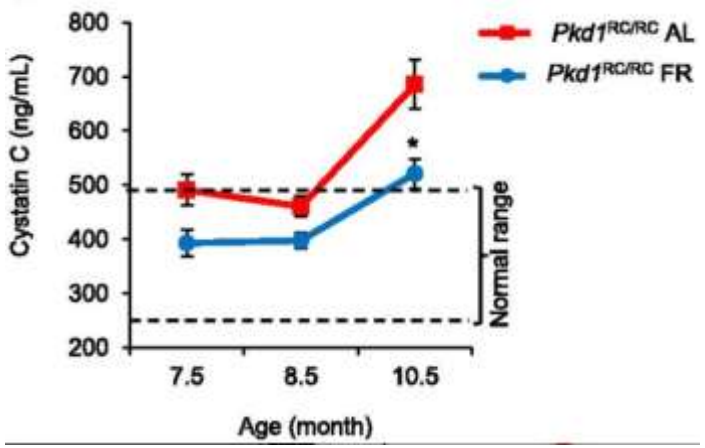


Caloric restriction reduces cyst growth

- 23% calorie restriction
- *PKD1*$^{cond/cond}$:Nes^{Cre}
- day 35 until day 84



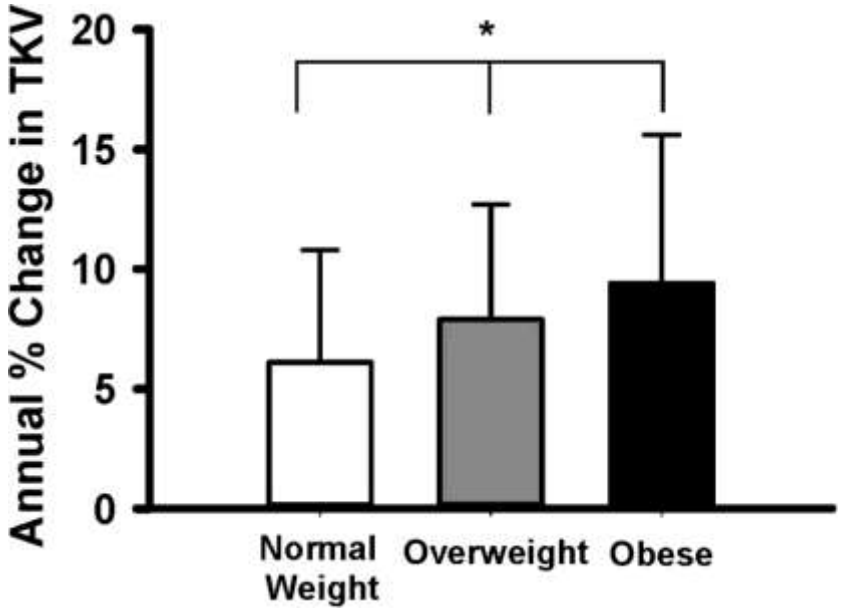
- 40% calorie restriction
- *PKD1*$^{RC/RC}$
- 5.5 months – 8.5 months



Kipp et al. Am J Physiol Renal Physiol. 2016 Apr 15; 310(8): F726–F731.
Warner et al. J Am Soc Nephrol. 2016 May;27(5):1437-47.

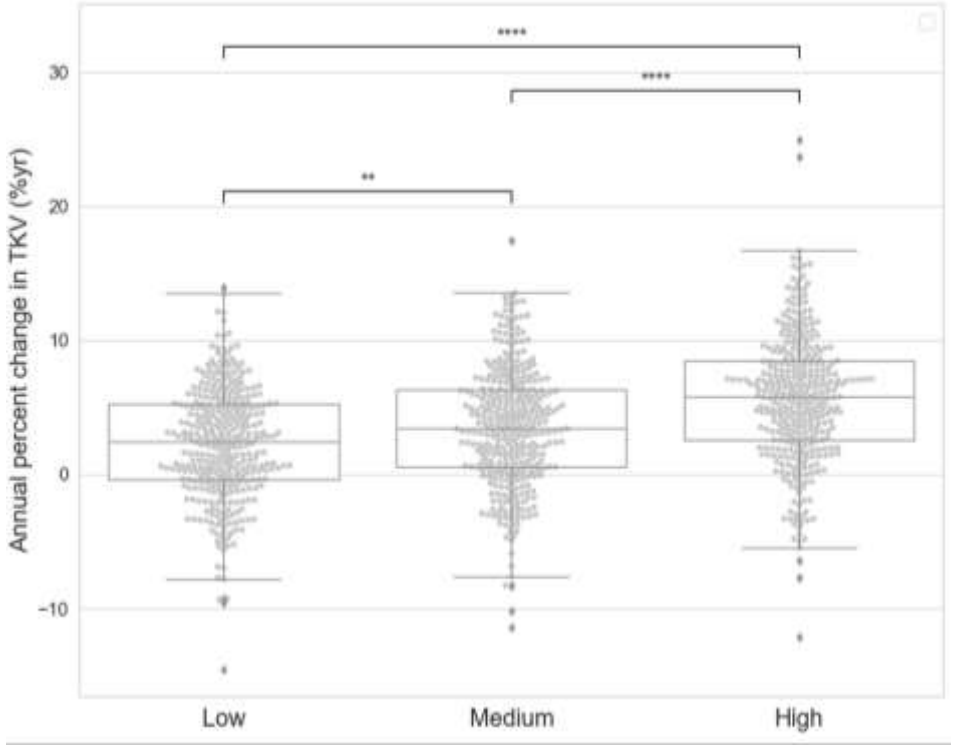
Overweight and obesity are associated with faster disease progression in ADPKD

- posthoc analysis HALT-PKD
- 441 patients



Nowak et al. JASN Feb 2018, 29 (2) 571-578

Visceral adiposity associates with more rapid kidney growth

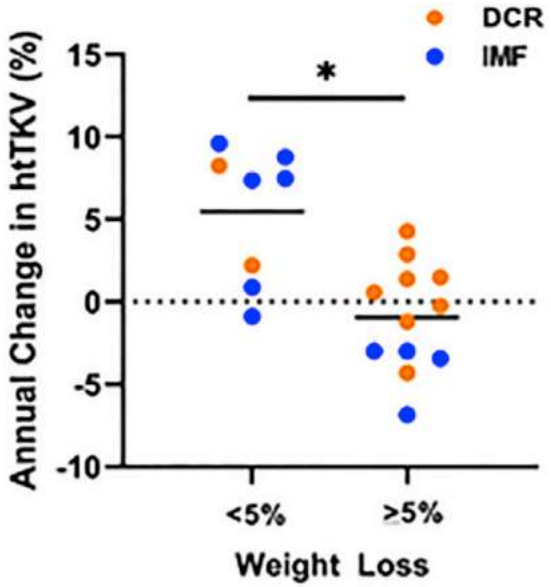


posthoc analysis TEMPO 3:4

Nowak et al. AJKD 2024
https://doi.org/10.1053/j.ajkd.2024.02.014

Weight reduction is associated with slower kidney growth in ADPKD

28 overweight or obese ADPKD patients
1 year dietary intervention
randomized daily caloric restriction vs. intermittent fasting



Hopp, … and Nowak
iScience 2022

Is it really all just about the amount of food?

Is reducing calorie intake required for the effect?

What exactly happens in the metabolism of a mouse on a diet?

caloric restriction leads to ketogenesis

- if mice get less food, they eat everything at once

caloric restriction leads to ketogenesis

- if mice get less food, they eat everything at once

- and when there is nothing left…

  …time-restricted feeding is the consequence

caloric restriction leads to ketogenesis

- if mice get less food, they eat everything at once

- and when there is nothing left…

  …time-restricted feeding is the consequence

→ **the body starts burning fat instead of sugar**

→ **formation of „ketone bodies“**

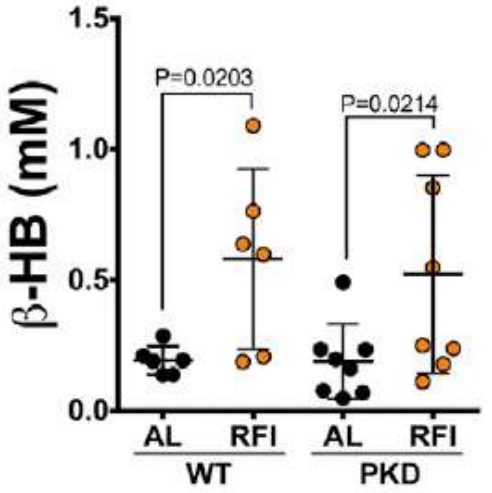
caloric restriction leads to ketogenesis

- if mice get less food, they eat everything at once

- and when there is nothing left…

  …time-restricted feeding is the consequence

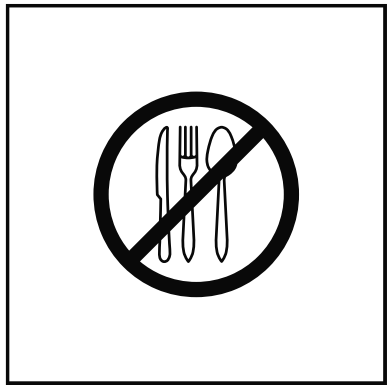
PKD1$^{cond/cond}$:Nes^{cre} mice
on caloric restriction



Torres et al. Cell Metabolism 2019

How can we reach a ketogenic state?

Time-restricted diet

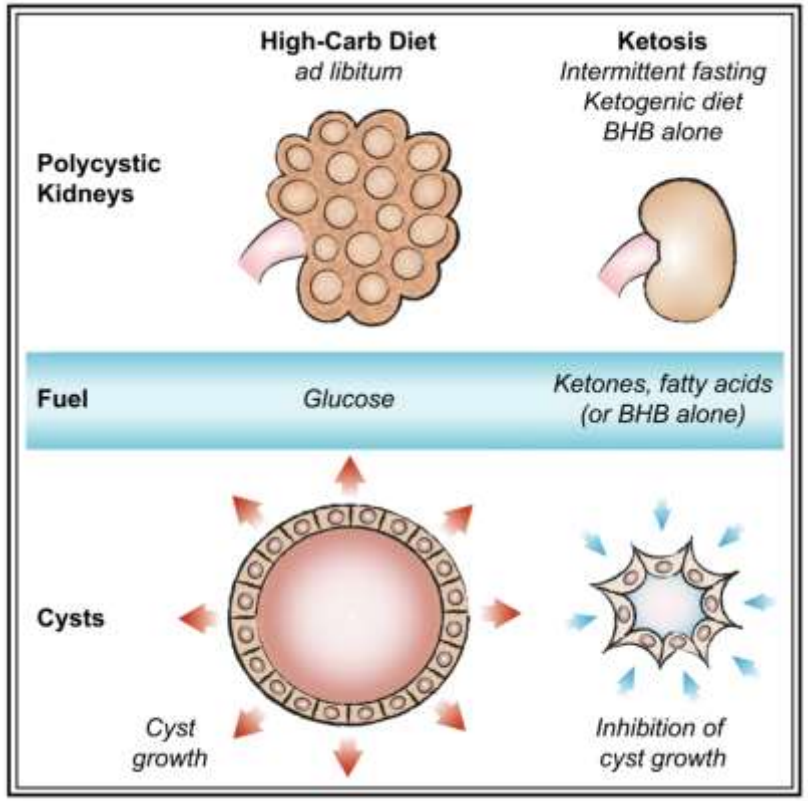


Intermittent fasting

ketogenic diet

- increase of fat intake
- massive reduction of carbohydrate intake (~20 g/d)
- normal protein intake

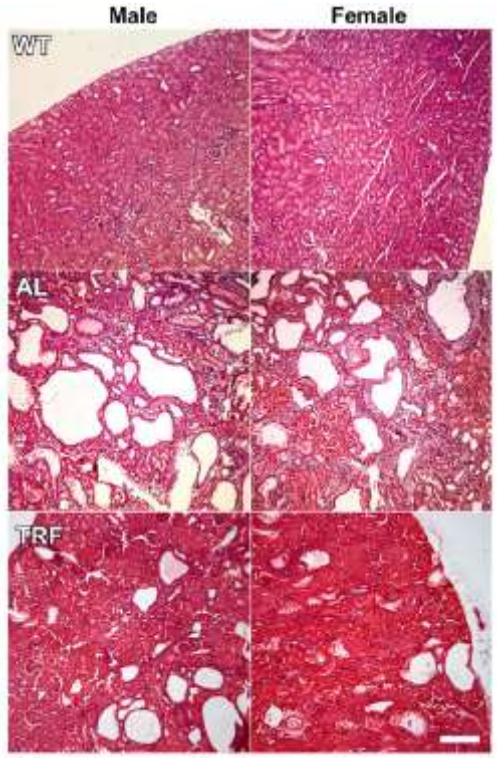
It’s indeed not only about calories…

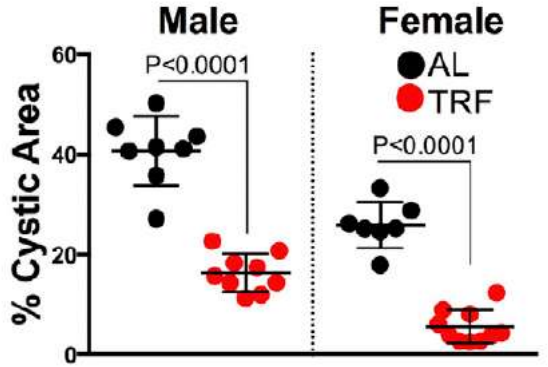


- caloric restriction induces ketone body formation
- ketogenic dietary interventions ameliorate PKD in animal models

Torres al. Cell Metabolism 2019

ketogenic dietary interventions inhibit cyst formation in animal models



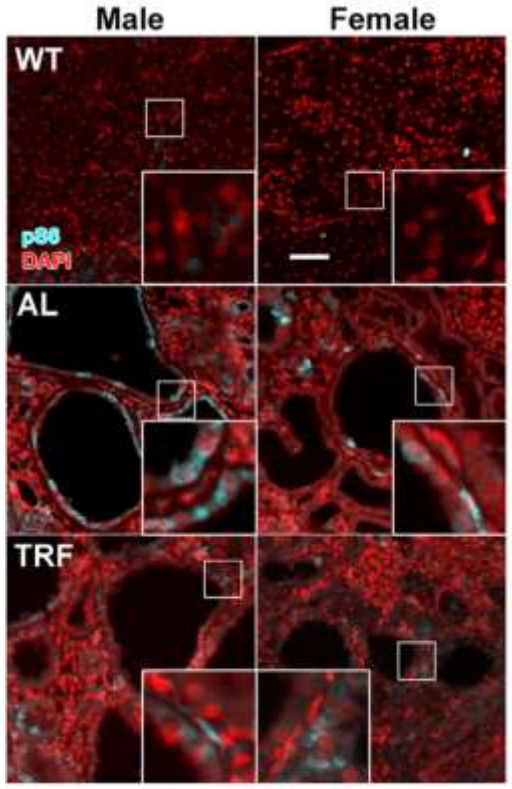


Han:SPRD rats
time-restricted feeding
5 weeks, from 3 wks of age

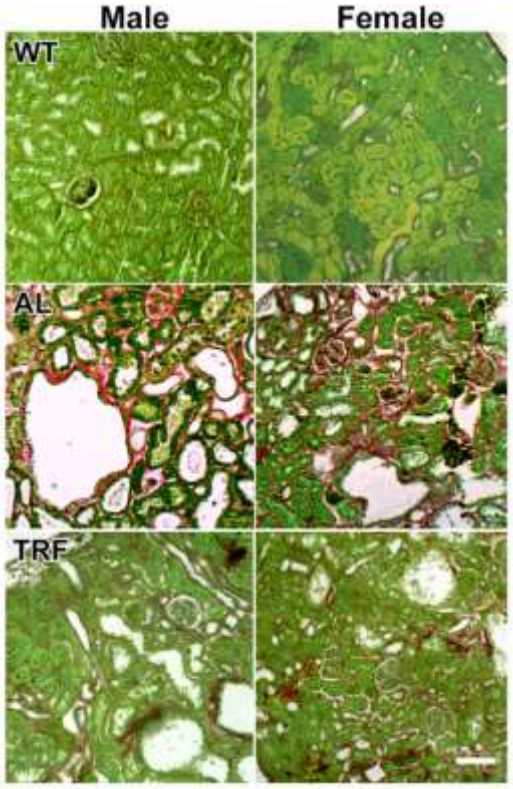
Torres, … and Weimbs
Cell Metabolism 2019

ketogenic dietary interventions reduce mTORC signaling and fibrosis

phospho S6



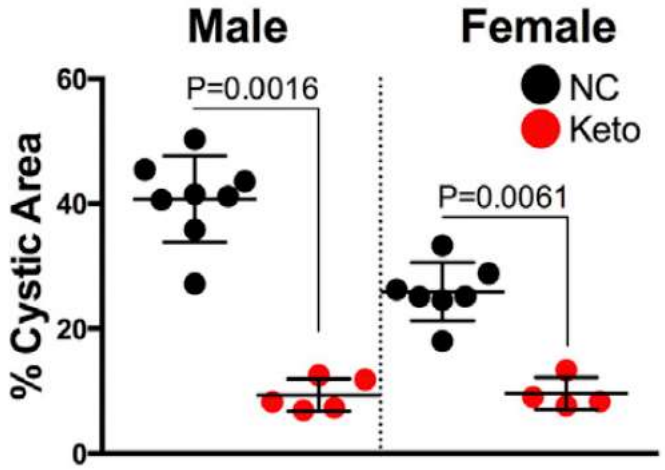
sirius red

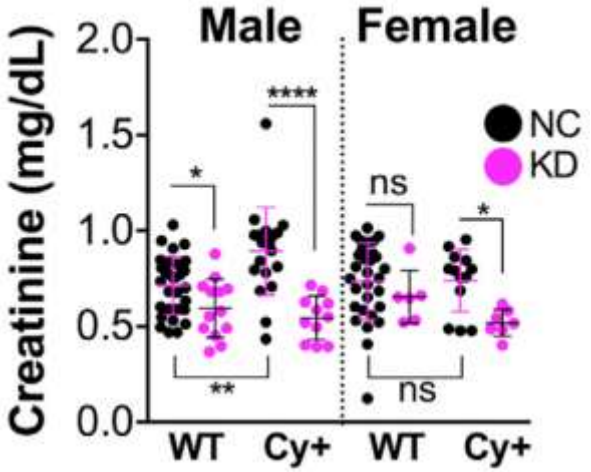


Han:SPRD rats
time-restricted feeding

Torres, … and Weimbs
Cell Metabolism 2019

ketogenic dietary interventions – impact on kidney function

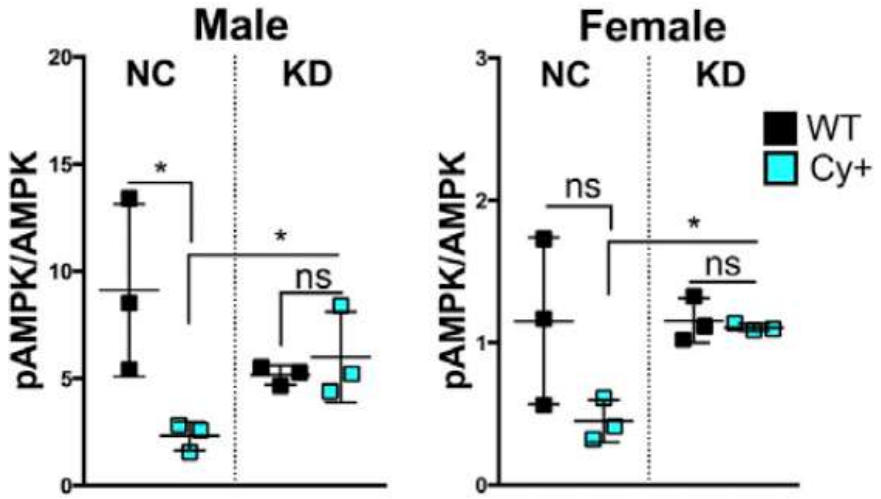




Han:SPRD rats
ketogenic diet
5 weeks, from 3 wks of age

Torres, … and Weimbs
Cell Metabolism 2019

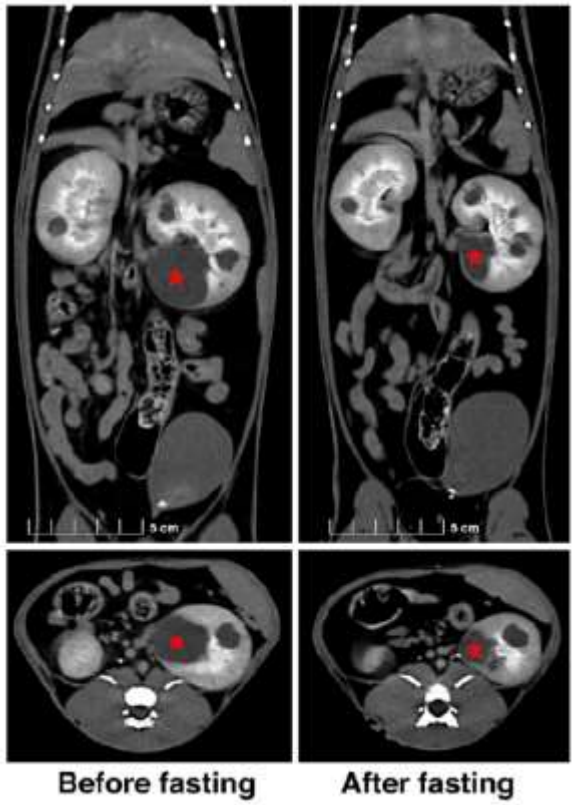
ketogenic dietary interventions restore AMPK activity

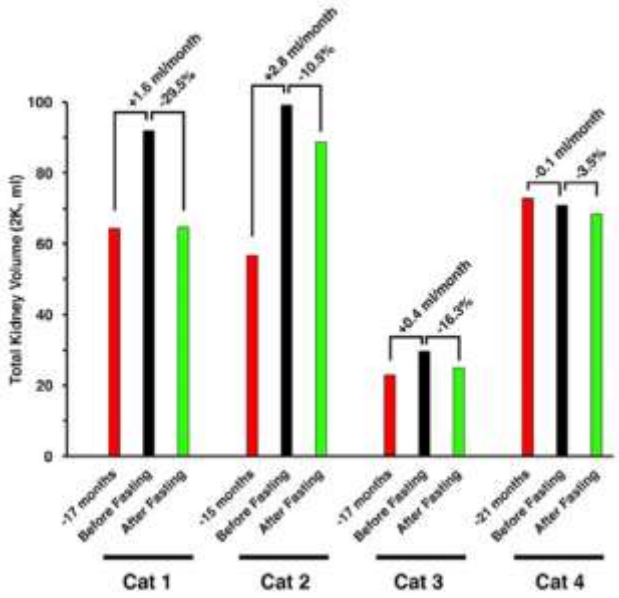


Han:SPRD rats
ketogenic diet
5 weeks, from 3 wks of age

Torres, … and Weimbs
Cell Metabolism 2019

fast-acting effects of ketosis





orthologous feline ADPKD model
fasting 72 hours

Torres, … and Weimbs
Cell Metabolism 2019

Ketogenic diets inhibit cyst formation in animal models…

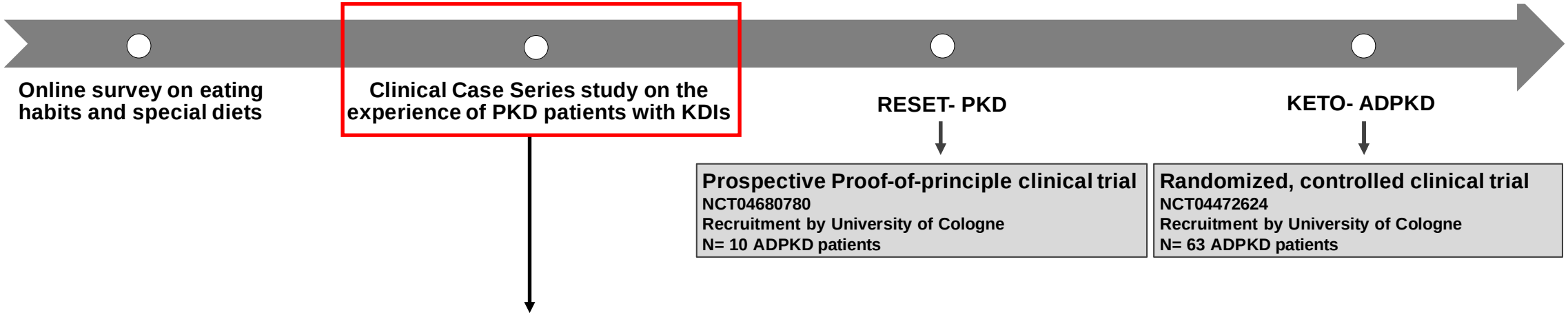
Should all ADPKD patients follow a ketogenic diet now?

Ketogenic diets inhibit cyst formation in animal models…

Should all ADPKD patients follow a ketogenic diet now?

No, data in humans are missing !

A translational pipeline for ketogenic interventions in ADPKD

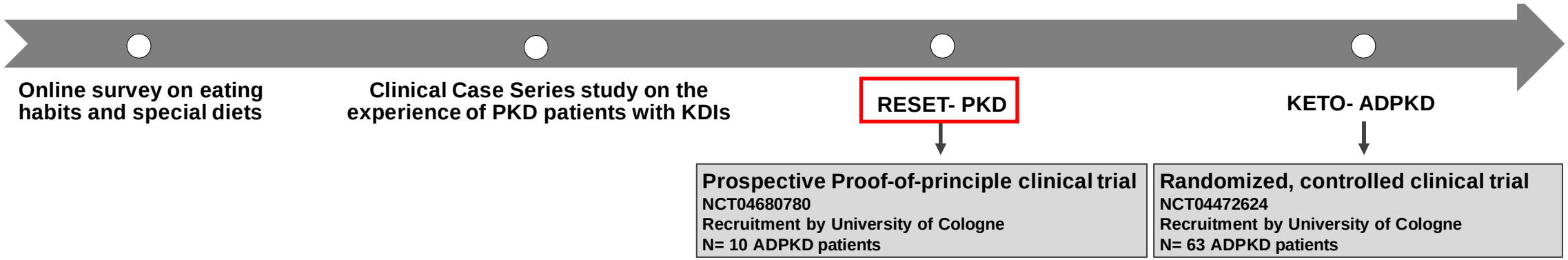


131 ADPKD patients that had already used ketogenic dietary interventions

questions about well-being, feasibility and potential (side) effects

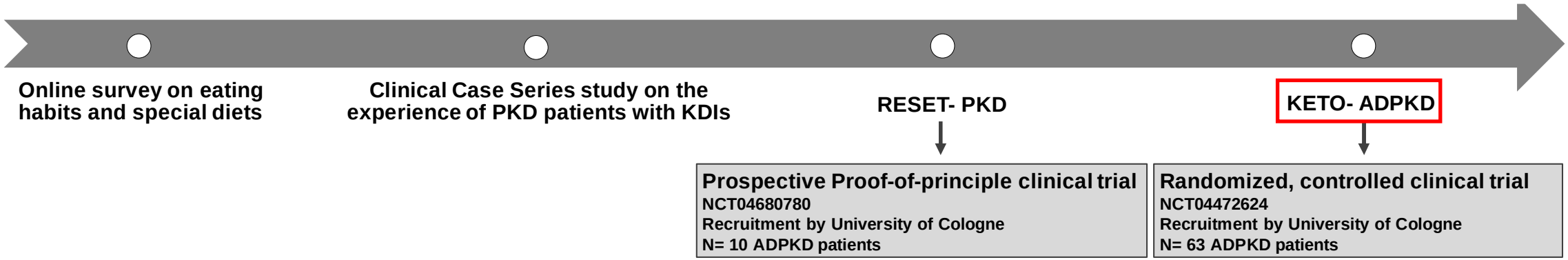
Strubl al. CKJ 2021

A translational pipeline for ketogenic interventions in ADPKD



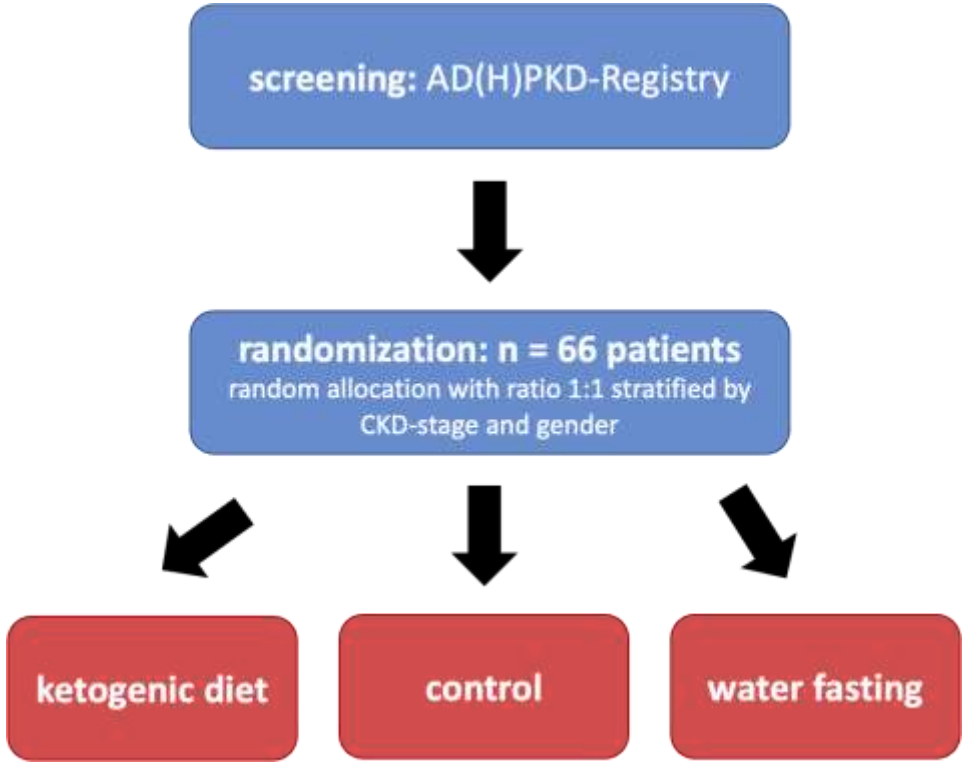
Strubl al. CKJ 2021; Oehm, Steinke et al. NDT 2022

A translational pipeline for ketogenic interventions in ADPKD



Strubl al. CKJ 2021; Oehm, Steinke et al. NDT 2022
Cukoski, Lindemann et al. Cell Reports Medicine 2023

KETO-ADPKD: randomized controlled trial



1) **balanced standard diet**

2) **ketogenic diet**

3) **3-day water fasting 1x/month**

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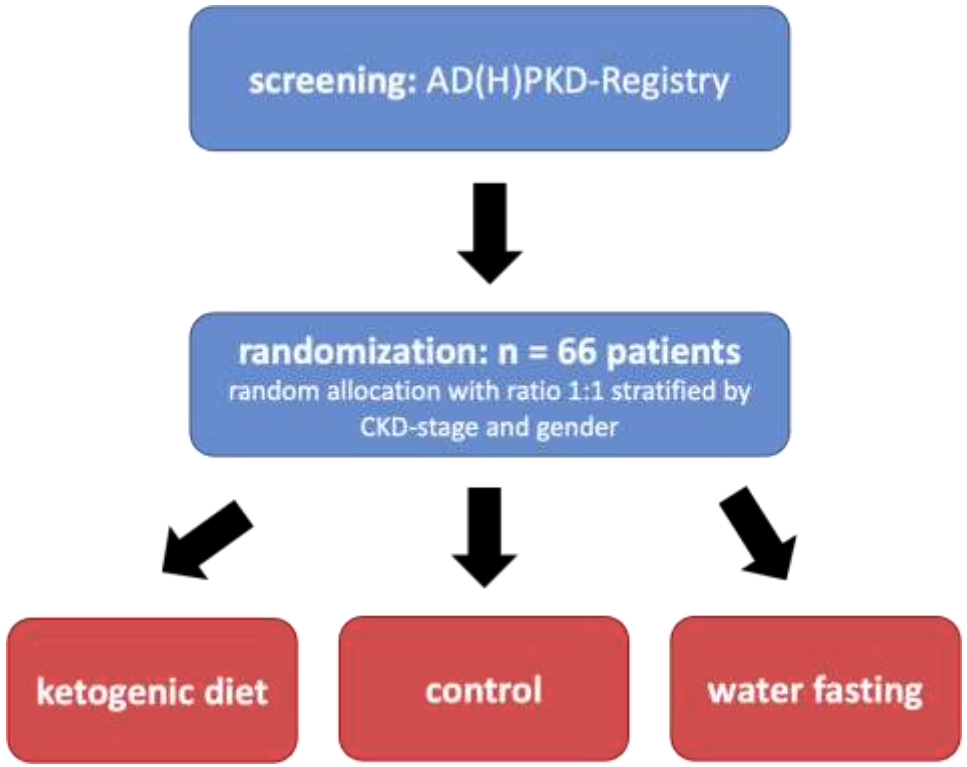
KETO-ADPKD: randomized controlled trial



PKD FOUNDATION
Polycystic kidney disease

KETO ADPKD

the importance of well-characterized cohorts:
rapid recruitment in a single center

AD(H)PKD
Zystennieren: Diagnose, Forschung, Therapie

n = 1500 patients

Cukoski, Lindemann et al. Cell Reports Medicine 2023

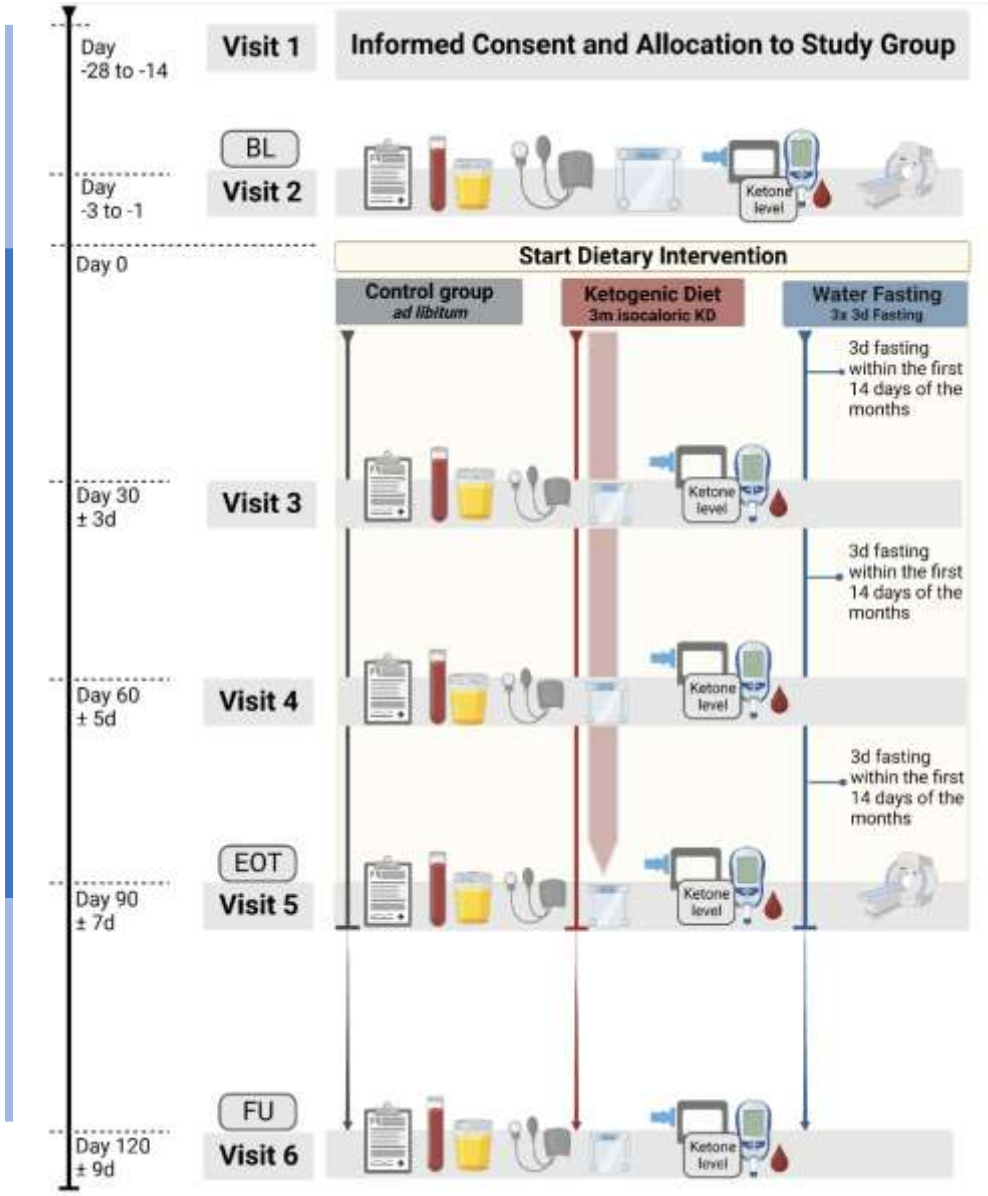
run-in phase
(1 month)

MRI #1

intervention phase
(3 months)

MRI #2

washout phase
(1 month)



Cukoski, Lindemann et al. *Cell Reports Medicine* 2023

KETO-ADPKD: balanced at baseline

	Overall (n=63)	Control Group (n=19)	Ketogenic Diet (n=23)	Water Fasting (n=21)
Male	32 (50.79)	10 (52.63)	11 (47.83)	11 (52.38)
Age, years	41.41(±9.55)	41.26(±10.49)	41.26(±9.94)	41.71(±8.67)
BMI	25.65(±3.86)	25.14(±4.28)	25.85(±3.78)	24.98(±3.34)
htTKV, ml/m	958.04(±651.57)	838.04(±424.85)	896.47(±511.77)	1134.05(±902.75)
htTLV, ml/m	1305.55(±825.91)	1394.75(±1047.96)	1106.49(±514.93)	1442.87(±872.72)
Mayo Class 1A-B	11 (17.46)	3 (15.79)	5 (21.74)	3 (14.29)
Mayo Class 1C-E	52 (82.54)	16 (84.21)	18 (78.26)	18 (85.71)
eGFR ml/min/1.73 m²	84.01(±24.00)	82.24(±22.62)	85.77(±22.56)	83.66(±27.52)
CKD1	25 (41.27)	6 (31.58)	10 (43.48)	9 (42.86)
CKD2	24 (38.09)	9 (47.37)	8 (34.78)	7 (33.33)
CKD3a	9 (14.29)	2 (10.53)	4 (17.39)	3 (14.29)
CKD3b	5 (79.37)	2 (10.53)	1 (4.35)	2 (9.52)
Urological complications <35 years	26 (41.27)	6 (31.58)	10 (43.47)	10 (47.62)
Arterial hypertension <35 years	53 (84.13)	14 (73.68)	20 (86.95)	19 (90.48)

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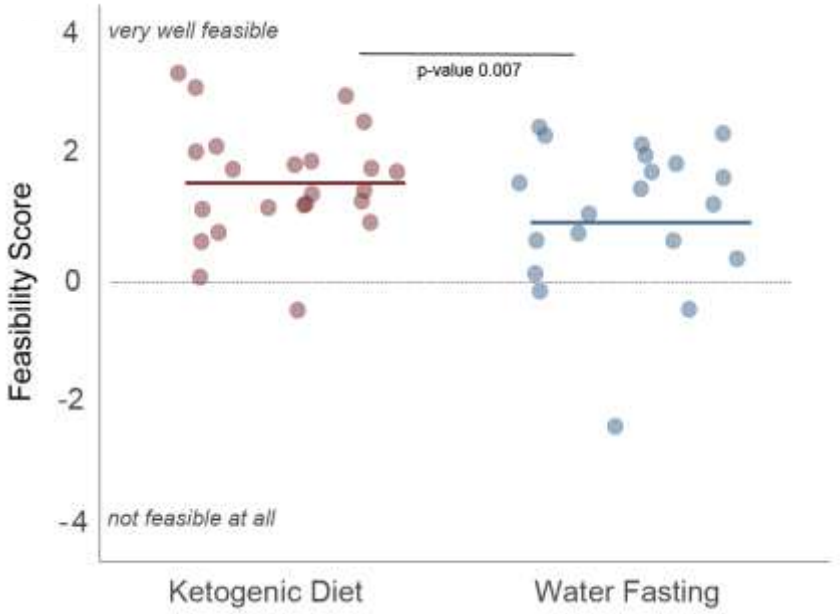
KETO-ADPKD: Feasible, but not always easy…

PRO questionnaire



+4 = no problem at all
-4 = not feasible at all

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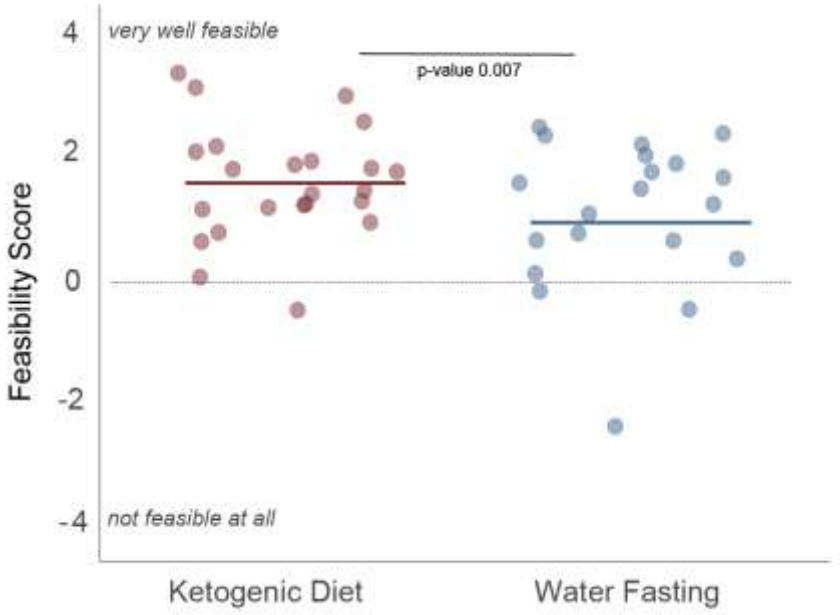
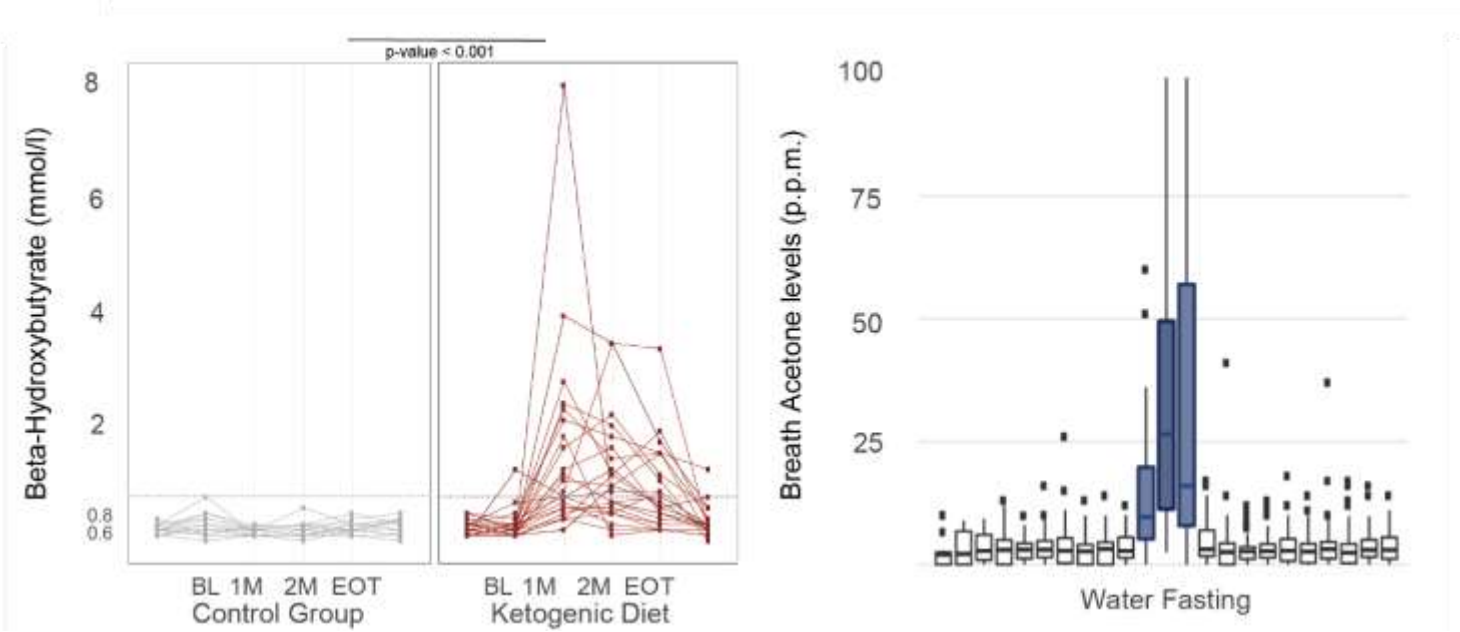
KETO-ADPKD: Feasible, but not always easy…

PRO questionnaire + adherence? → ketone bodies





+4 = no problem at all
-4 = not feasible at all

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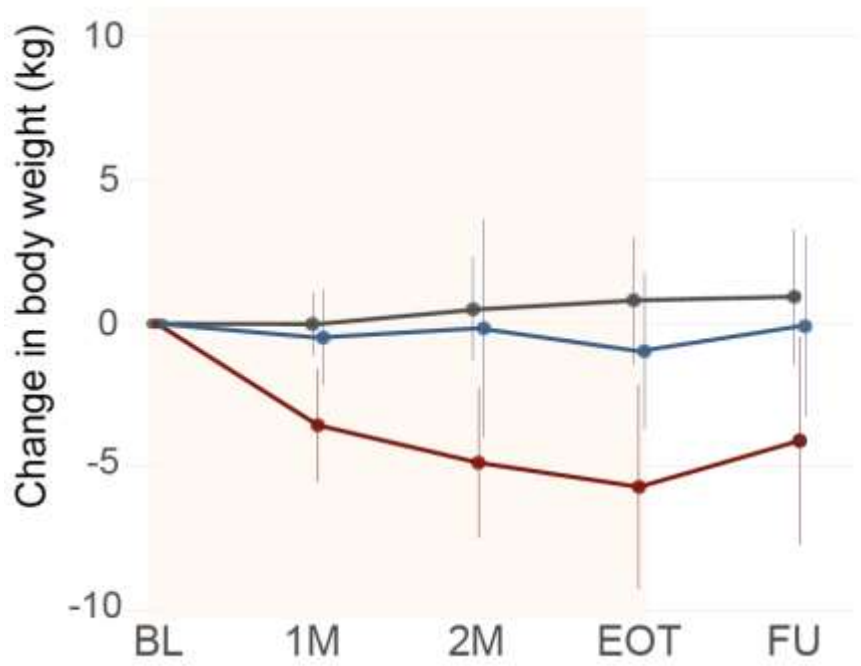
KETO-ADPKD: Body weight…mainly fat mass



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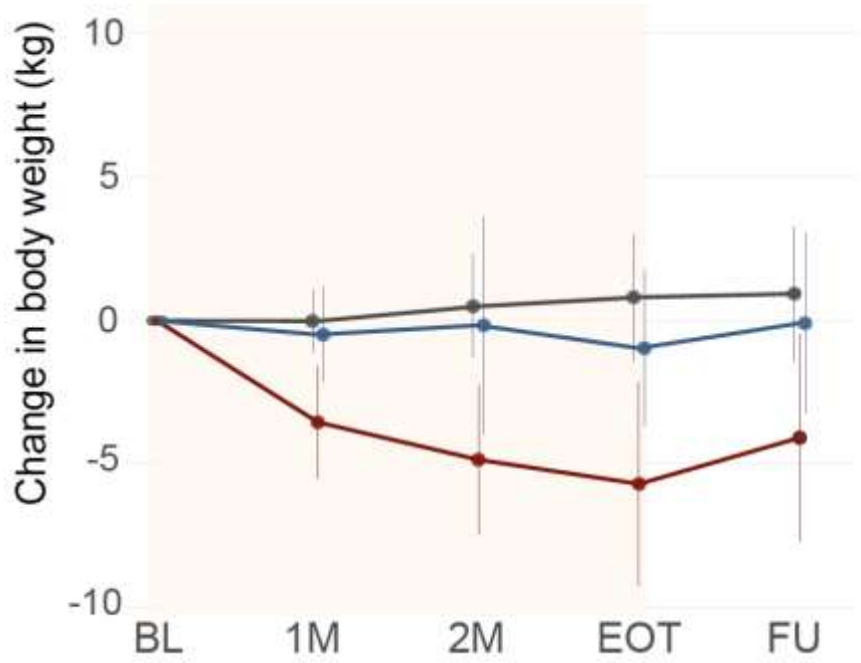
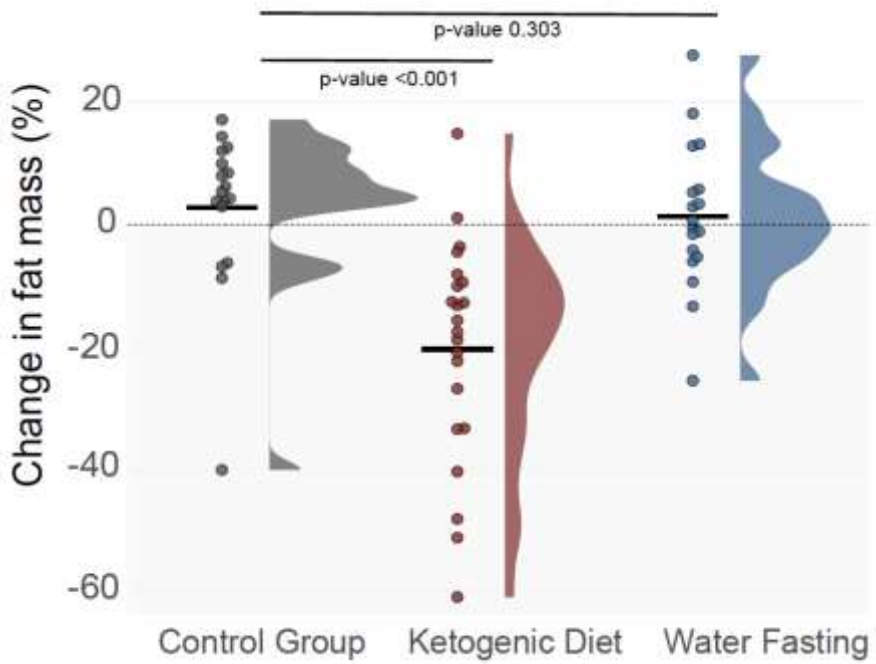
KETO-ADPKD: Body weight…mainly fat mass





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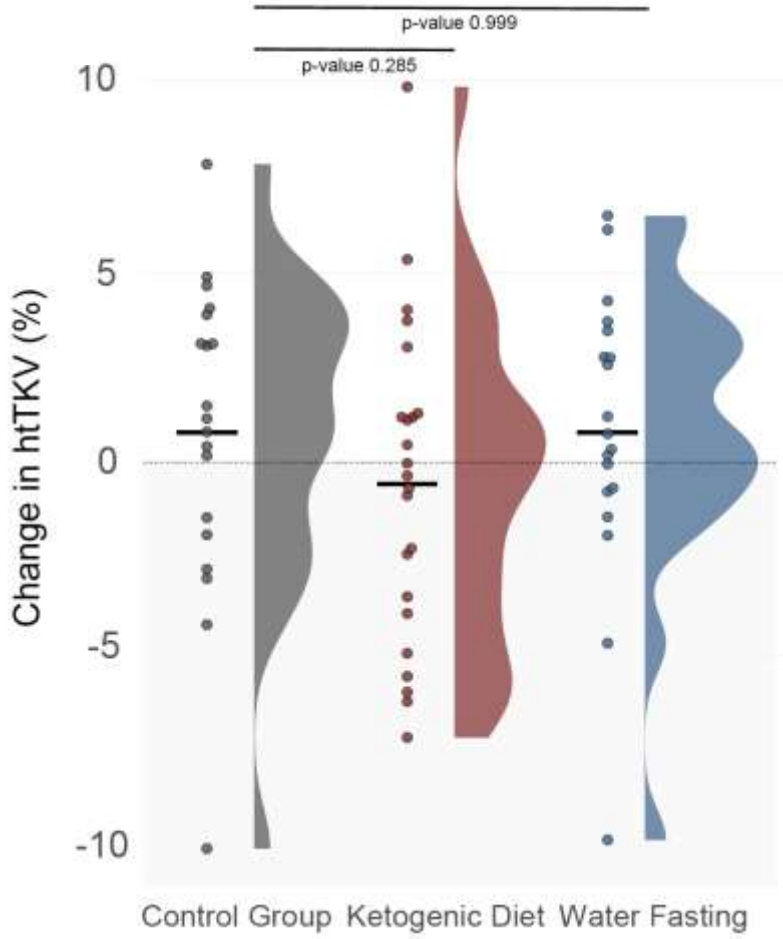
KETO-ADPKD: Total kidney volume



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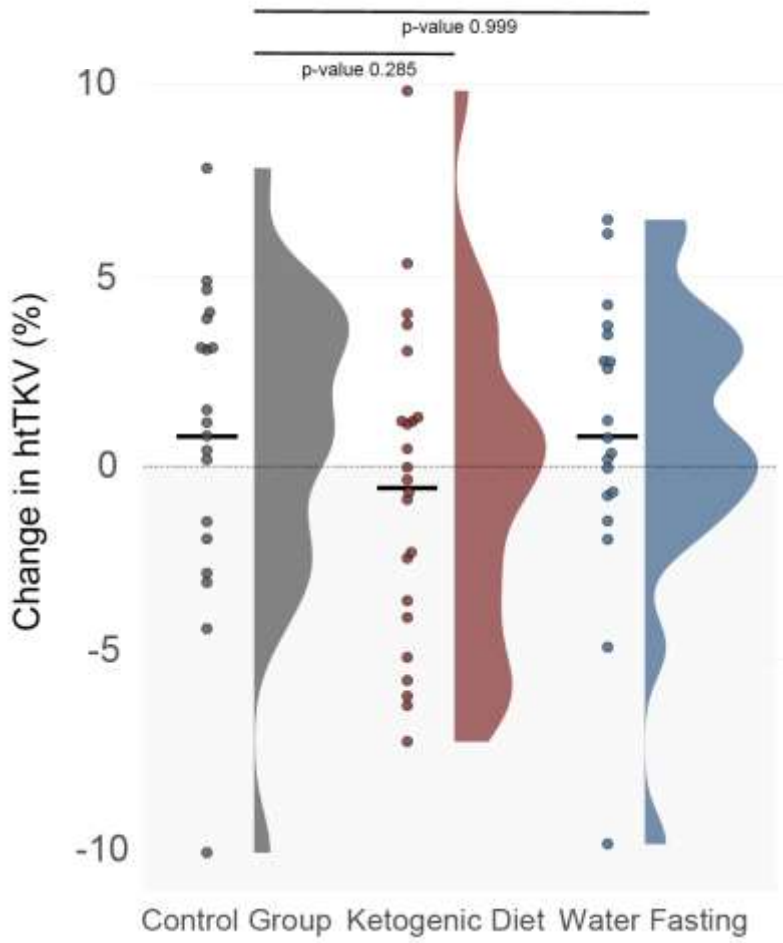
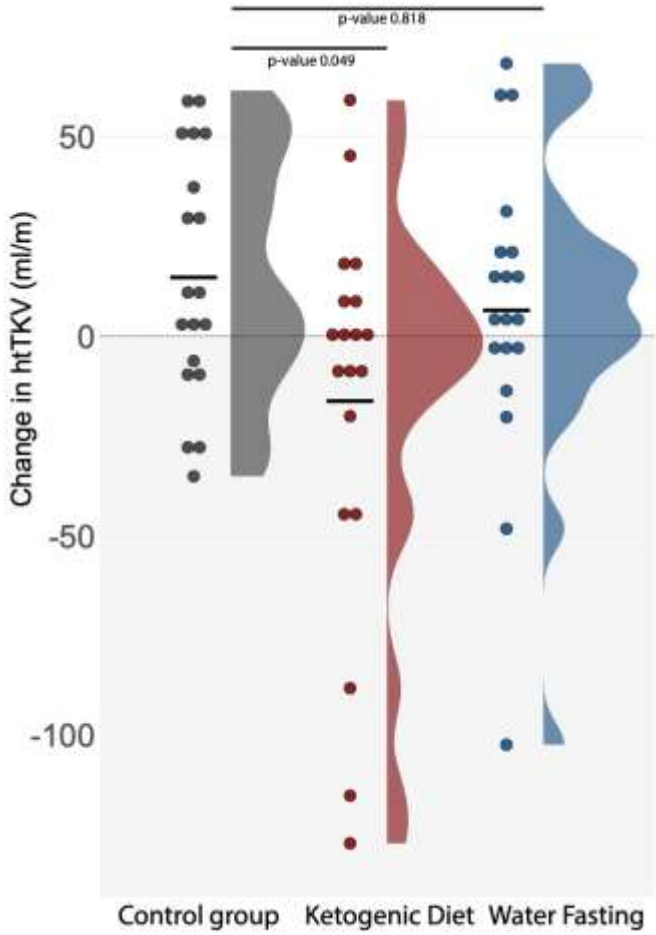
KETO-ADPKD: Total kidney volume





unpublished posthoc analysis

KD: patients with BHB ≥ 0.5mmol/l at 2/3 visits

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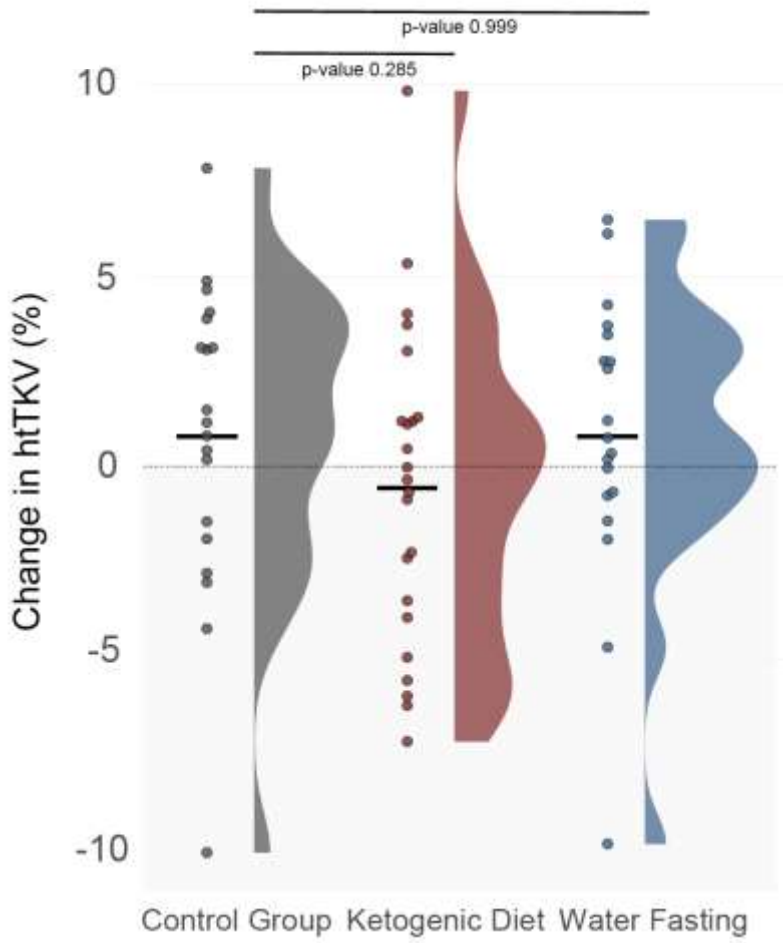
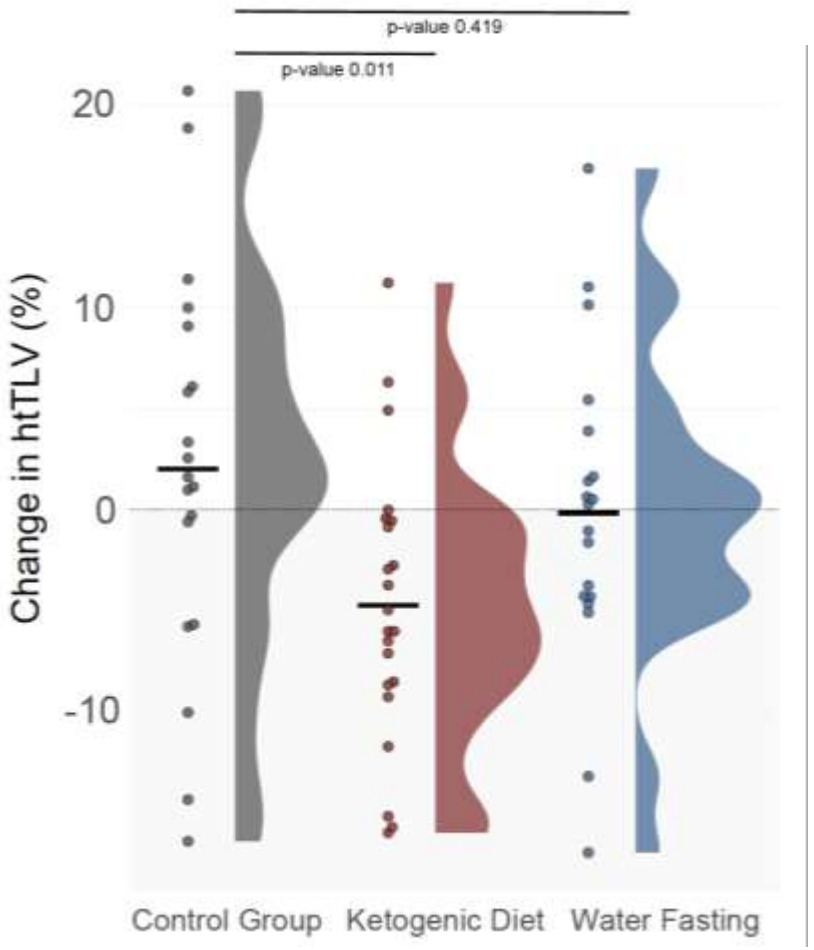
KETO-ADPKD: Kidney and liver volume





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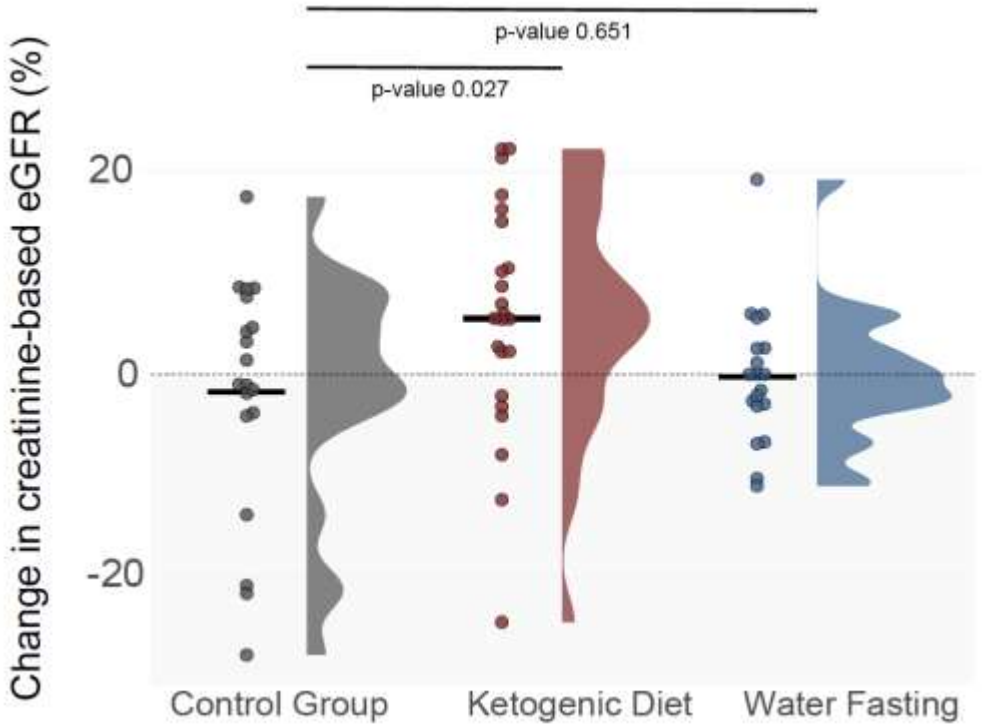
KETO-ADPKD: Kidney function



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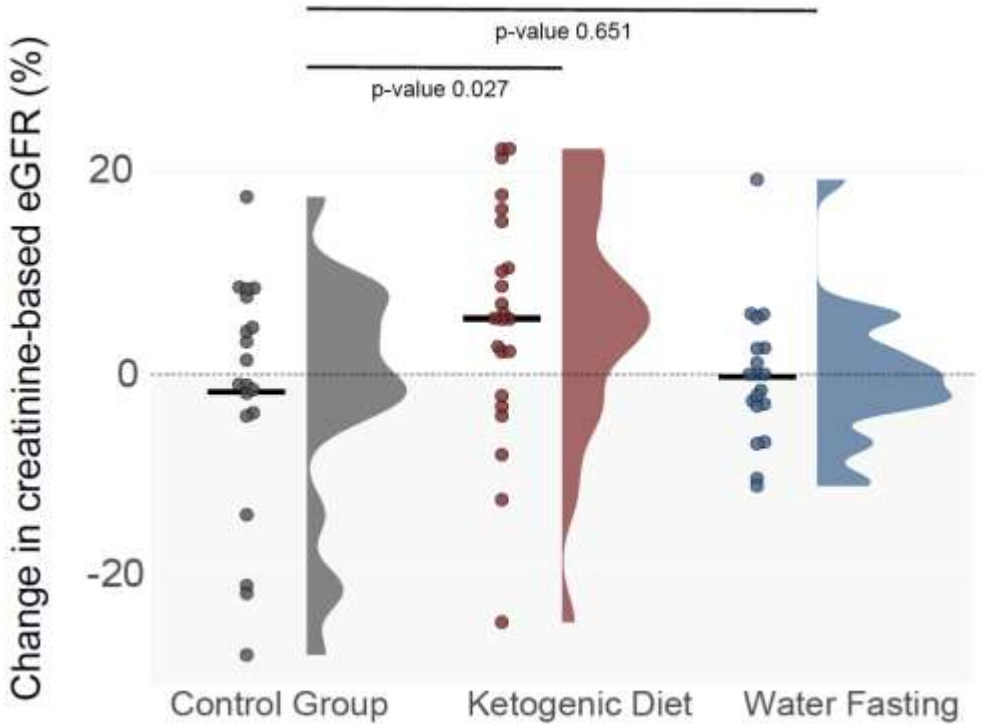

muscle mass?

meat intake?

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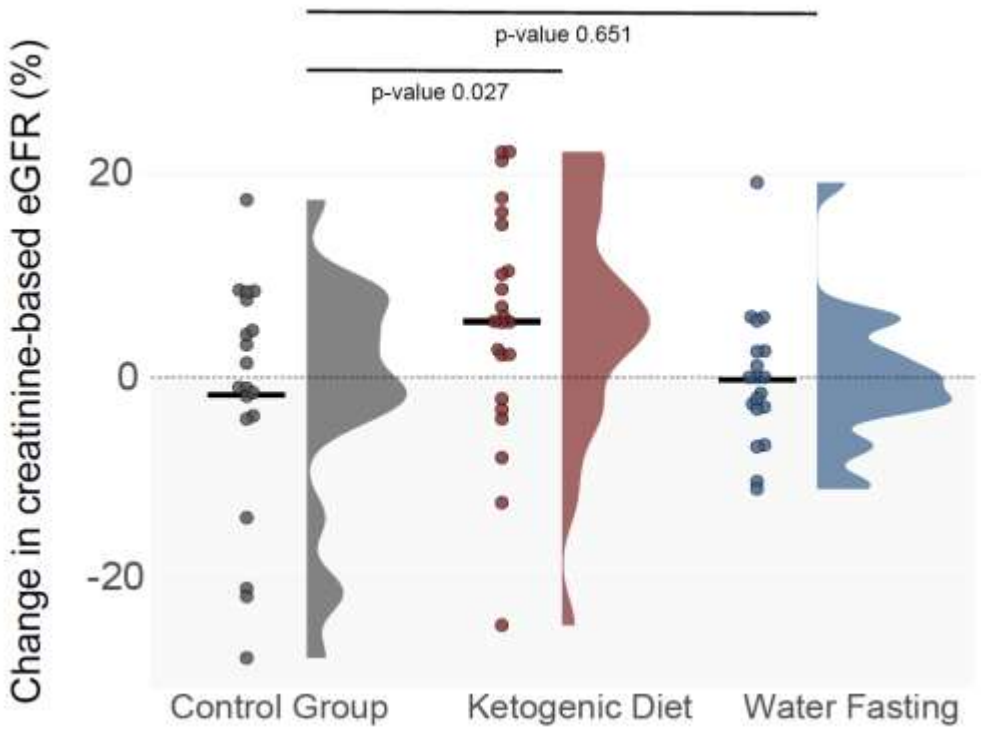
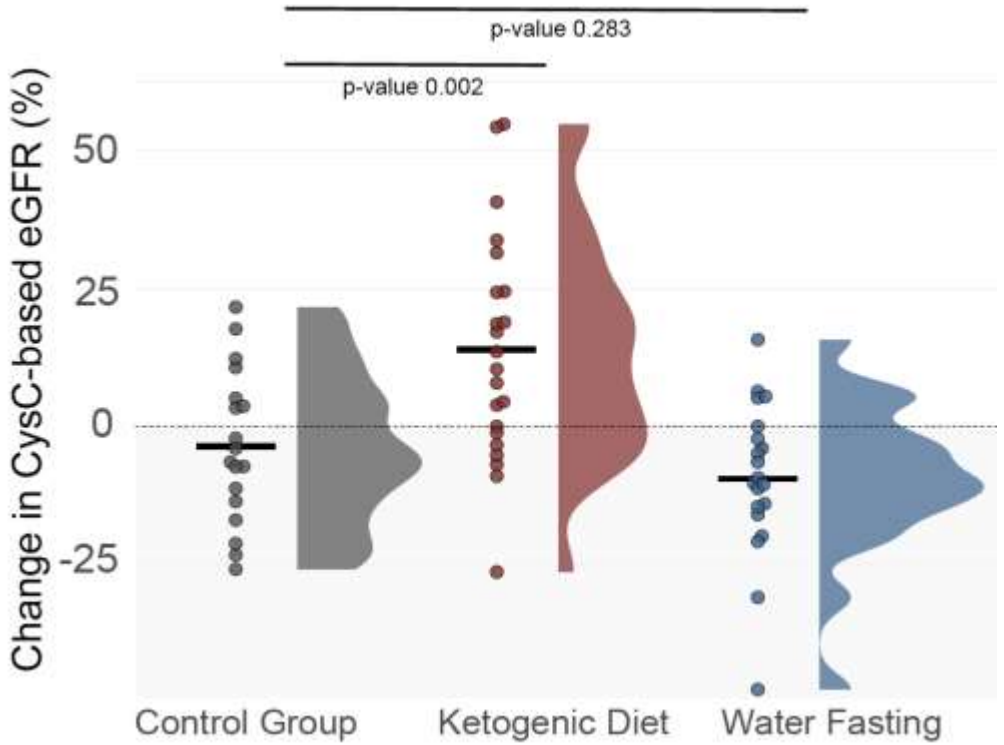
KETO-ADPKD: Kidney function





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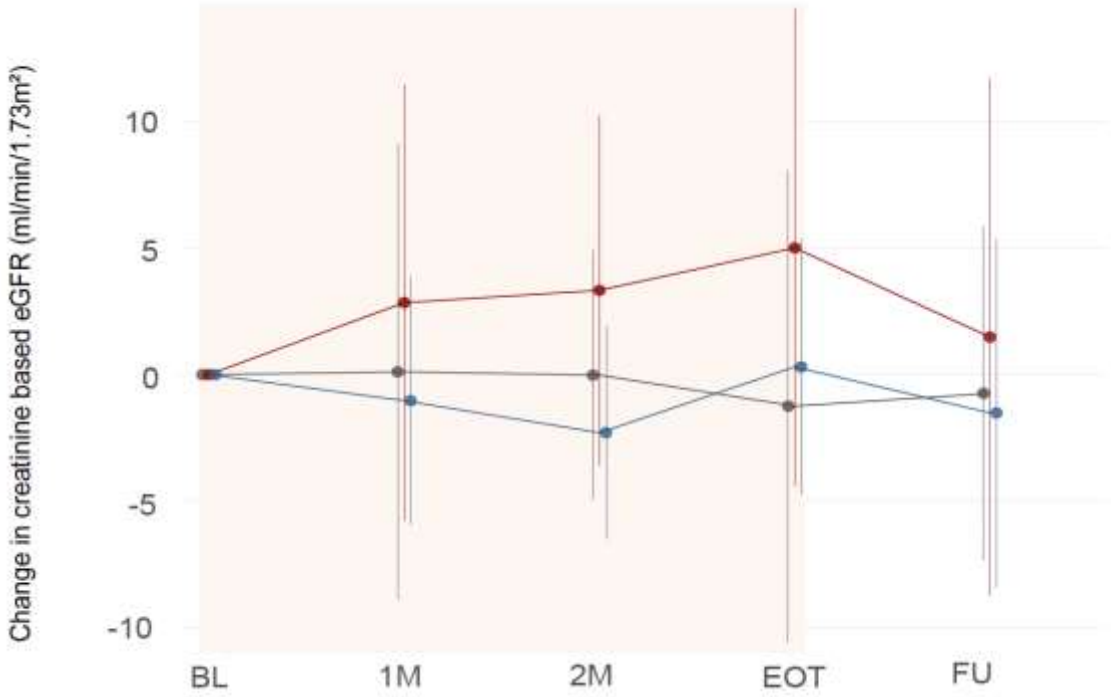
KETO-ADPKD: Kidney function

delta KD/ctrl	6.25	2.23	ml/min



pval KD/ctrl	0.01	0.31

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KETO-ADPKD: Open questions regarding kidney function

Side effects?

Hyperfiltration?

Long-term effects?

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KETO-ADPKD: Side effects?

	Description	KD n(%)	WF n(%)	Control n(%)
AST/ALT	>ULN - 3.0x ULN (>50 - 150 U/l)	1(4)	0	1(5)
	>3.0x - 5.0x ULN (>150 - 250 U/l)	0	0	0
Creatinine	up to 1.5 x increase baseline	0	0	0
	>1.5 - 3.0 x increase baseline	0	0	0
Uric Acid	>ULN without gout specific symptoms (>7 mg/dl)	4(17)	1(5)	1(5)
	>ULN with gout specific symptoms (>7 mg/dl)	0	0	0
Triglycerides	150 - 300 mg/dL	1(4)	3(16)	1(5)
	>300 - 500 mg/dL	2(8)	0	1(5)
Cholesterol	>ULN (200 mg/dl) - 300 mg/dl	3(13)	0	0
	>300 - 400 mg/dL	1(4)	0	0
Events probably related to the intervention	Orthostatic symptoms	4(17)	4(21)	0
	Keto flu associated	10(43)*	3(16)	0
	Reflux symptoms	0	1(5)	0
Safety relevant event with hospitalisation	Appendicitis	1(4)	0	0
	Cyst infection	0	0	1(5)
	Nephrolithiasis	1(4)	0	0

transient Keto flu

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KETO-ADPKD: Side effects?

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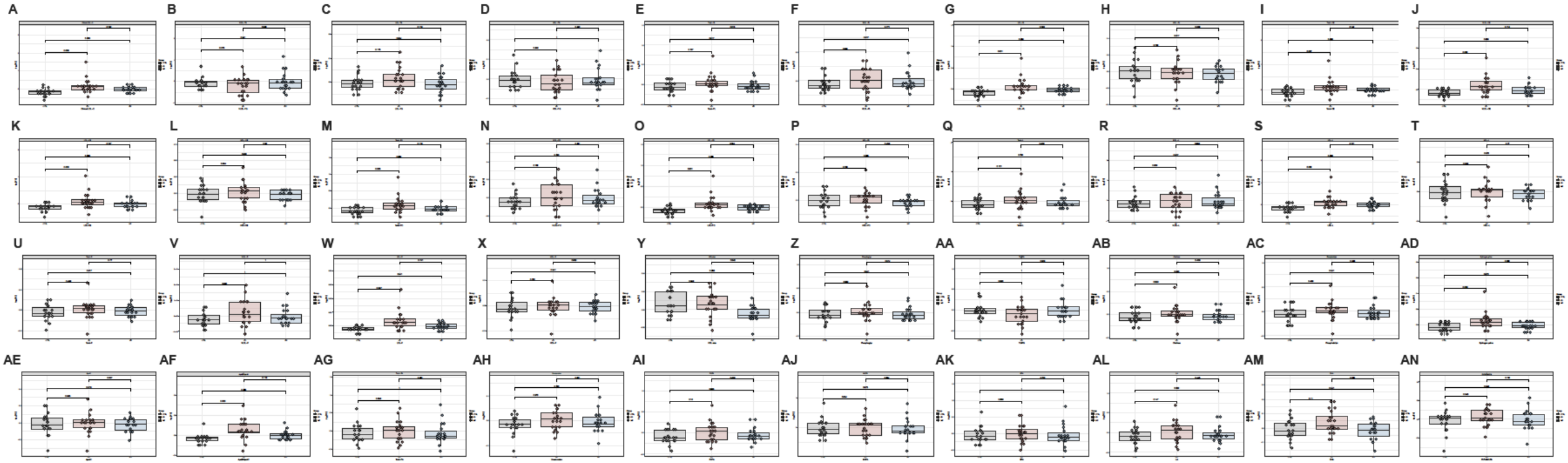
KETO-ADPKD: Distinct effects on cholesterol

NMR lipidomics to obtain an in-depth view on cholesterol metabolism in ADPKD patients on ketogenic diets.



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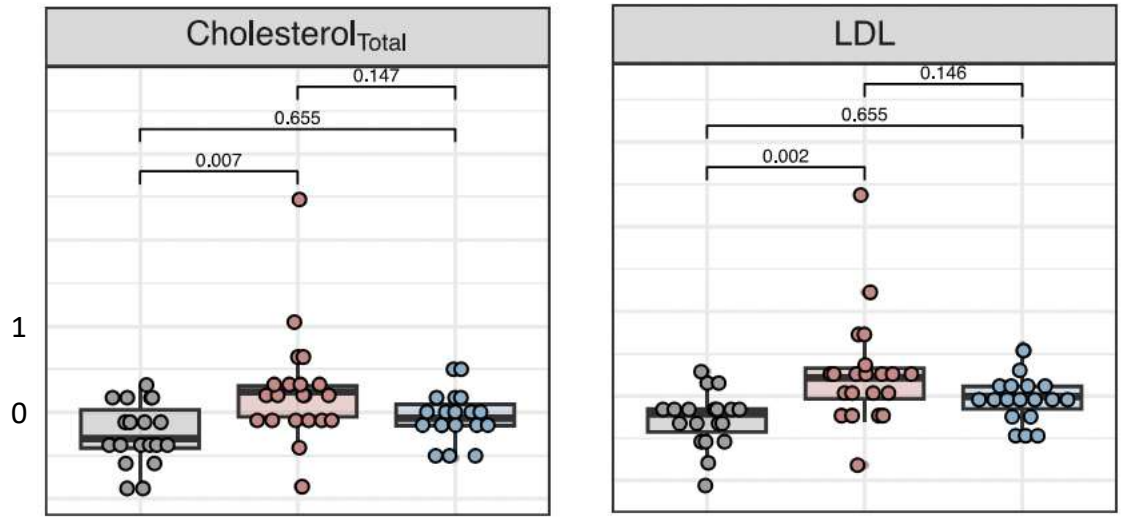
KETO-ADPKD: Distinct effects on cholesterol

log2 fold change
baseline to end-of-treatment



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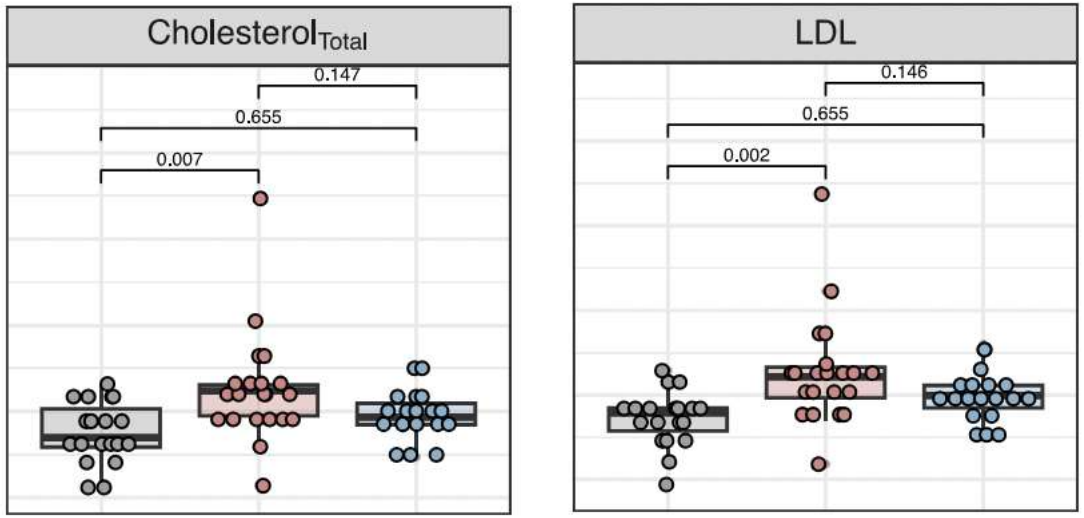
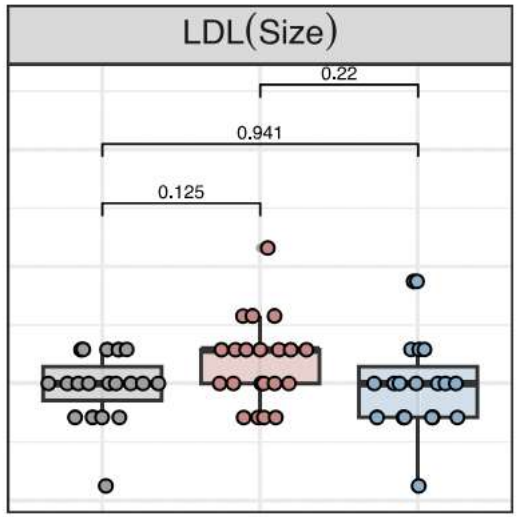
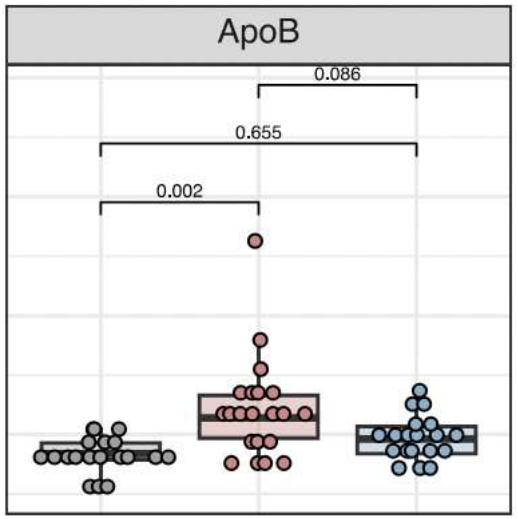
KETO-ADPKD: Distinct effects on cholesterol







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KETO-ADPKD: And now…?

What do the results mean?

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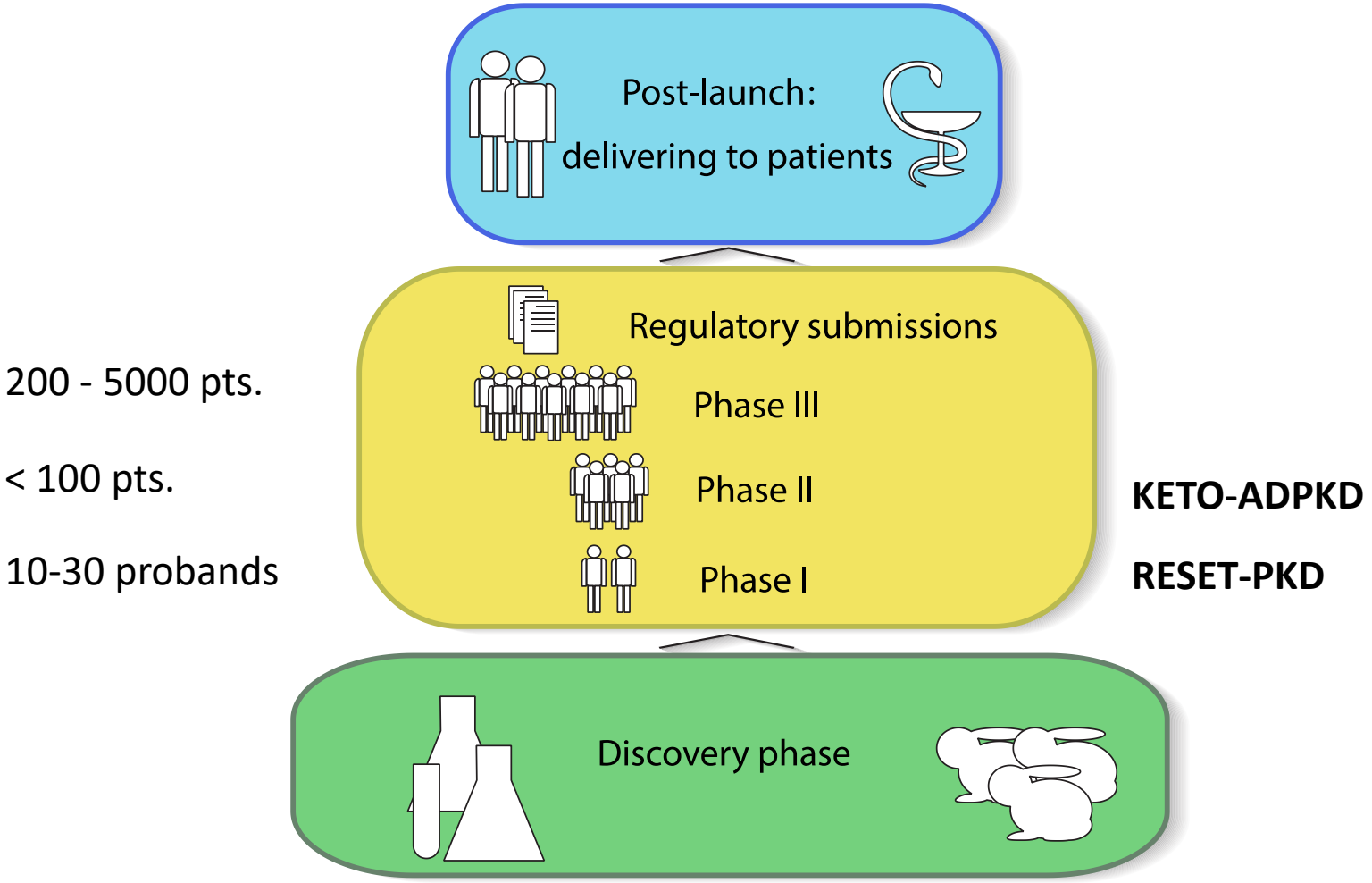
KETO-ADPKD: And now…?



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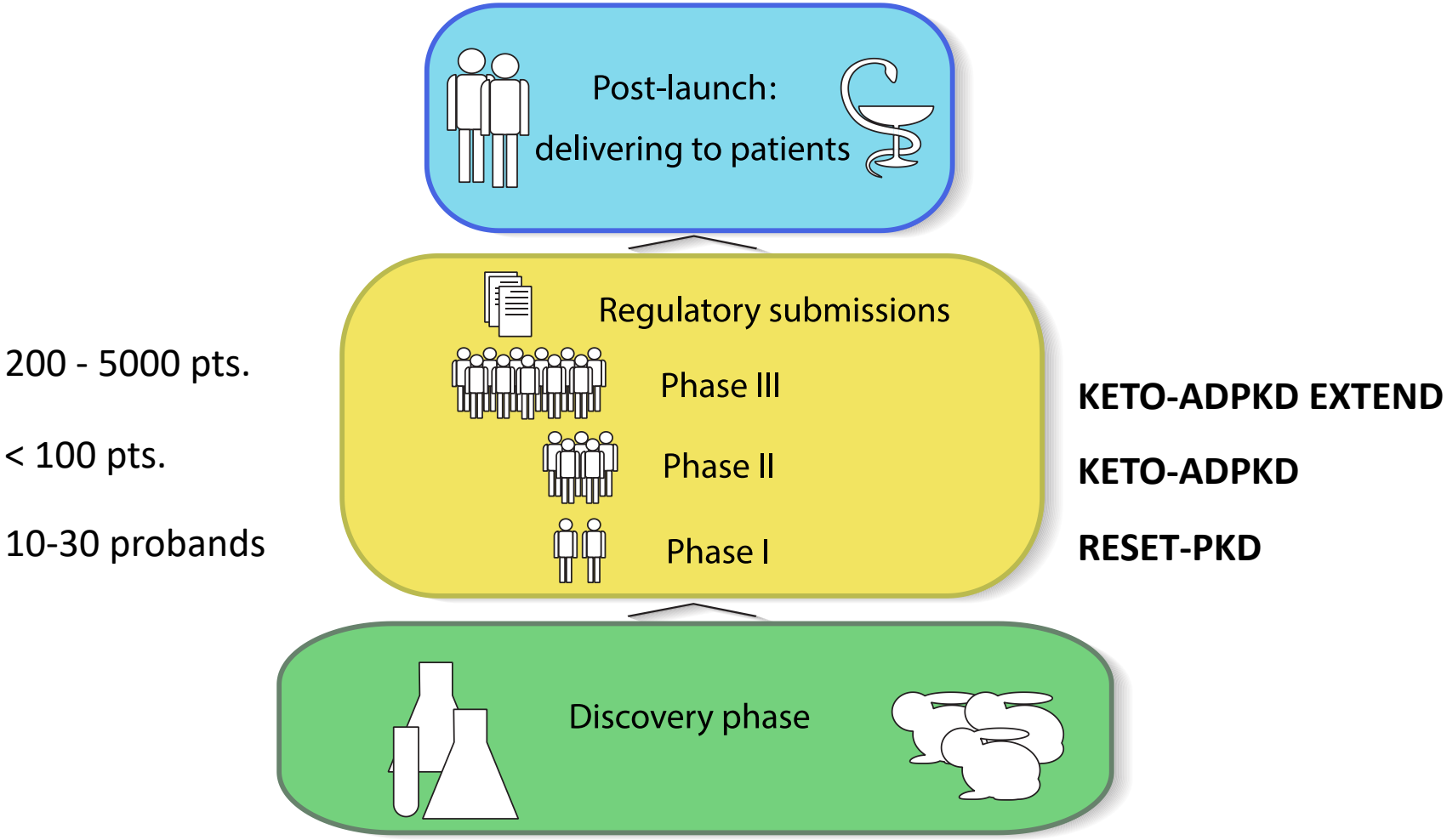
KETO-ADPKD: And now…?



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KETO-ADPKD: And now…?

We are not there yet to provide a recommendation…

But we will get there together.

Higher beta-hydroxybutyrate ketone levels associated with a slower kidney function decline in ADPKD

Is BHB associated with disease progression in ADPKD?

Methods

521 patients with ADPKD from DIPAK consortium

Plasma BHB measurement on baseline with NMR spectroscopy

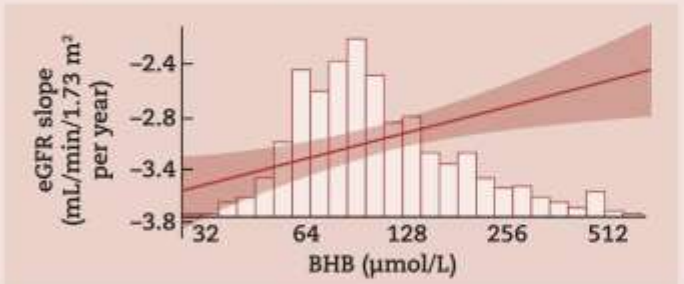
Exclusion criteria:
Diabetes type 2
Disease-modifying drugs
Not-fasting

Results

Doubling of BHB concentration associated with improvement of kidney function slope of

0.33 (0.09–0.57)

ml/min/1.73 m² per year (p=0.008) adjusted for potential confounders



Participant characteristics

BHB (µmol/L)	94 (68–147)
Age (years)	47 ± 12
Sex (female)	61%
htTKV (mL/m)	834 (495–1327)
eGFR (ml/min/1.73 m²)	63 ± 29

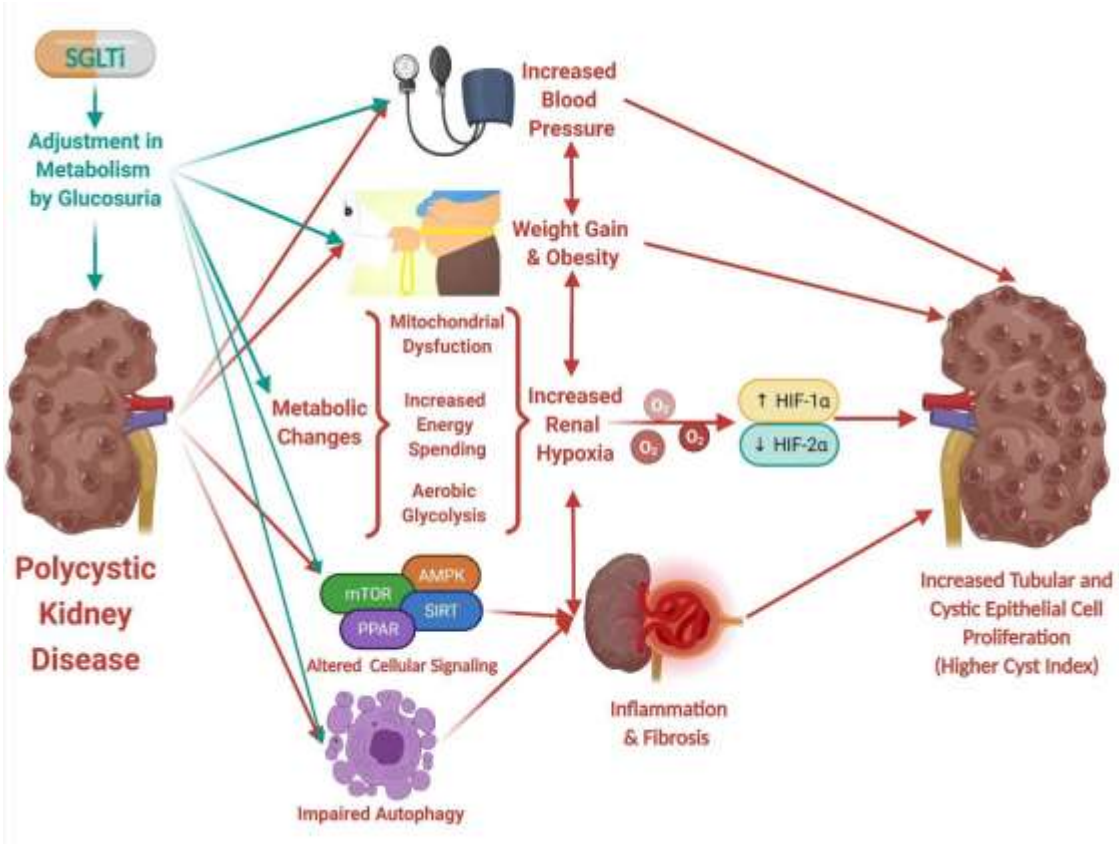
Cross-sectional associations
Linear regression analyses
Kidney function: BHB not significant
Kidney volume: BHB not significant

Longitudinal associations
Linear mixed model analyses
Kidney growth: BHB not significant
Kidney function slope: BHB significant

Knol, M.G.E. *et al.*
NDT (2023)
@NDTSocial

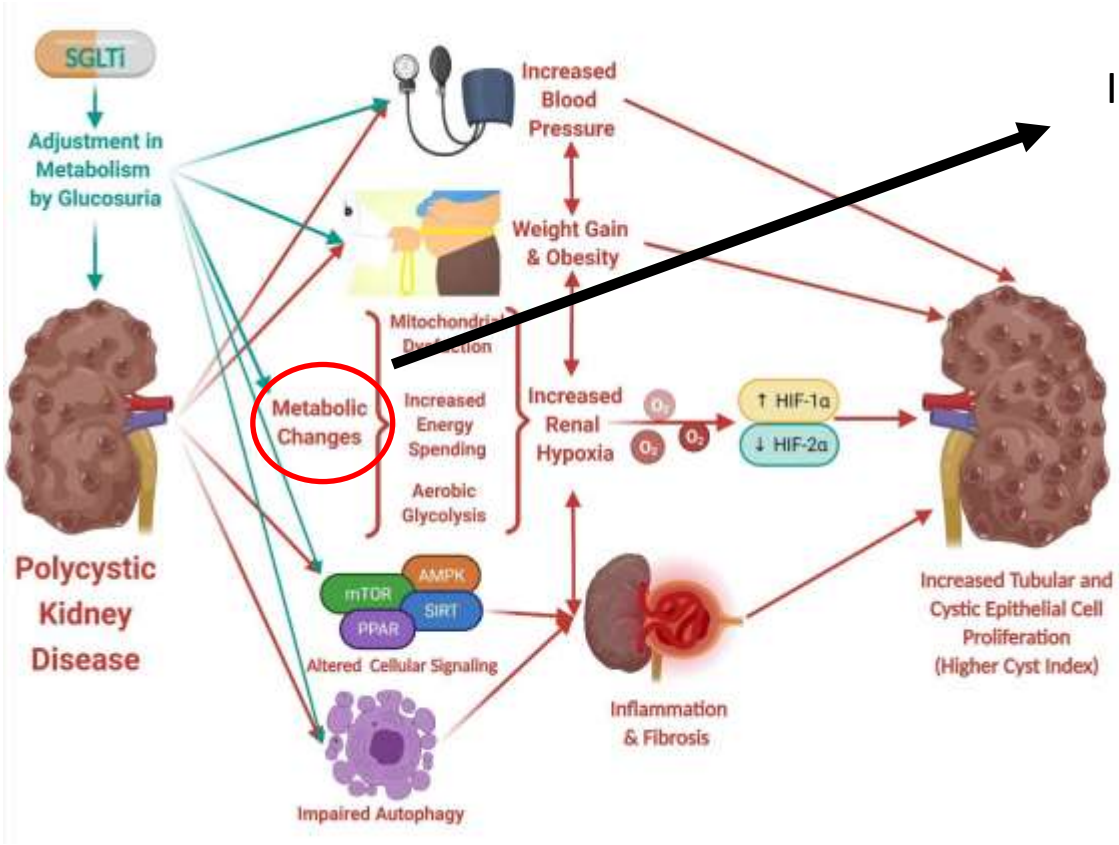
Although BHB was not associated with kidney volume, a higher BHB concentration was associated with an improvement in kidney function slope. This result supports the hypothesis that ketogenic interventions may offer an effective treatment for individuals with ADPKD.

SGLT2-inhibition: many good arguments in ADPKD



Afsar et al. CKJ 2022

SGLT2-inhibition: many good arguments in ADPKD



Increase in ketone bodies

Afsar et al. CKJ 2022

Great! So should we use SGLT2i in ADPKD now?

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Unfortunately, the answer is no….

Great! So should we use SGLT2i in ADPKD now?

Unfortunately, the answer is no….

- ADPKD was an exclusion criterion in the CKD trials
- the preclinical data in PKD models are heterogenous

preclinical data on SGLT2i in PKD are inconclusive

study	model	SGLT2i	kidney function	kidney weight	other findings
Wang et al. KI 2013	Han:SPRD rat	phlorizin	↑	↓	albuminuria ↓
Rodriguez Kidney Blood Press Res 2015	Han:SPRD rat	dapagliflozin	↑	↑	albuminuria ↓
Kapoor PLoSOne 2015	PCK rat	dapagliflozin	?	↑	albuminuria ↑
Leonhard et al. eBioMedicine 2019	*Pkd1*$^{fl/fl}$ inducible	canagliflozin	↔	-	-

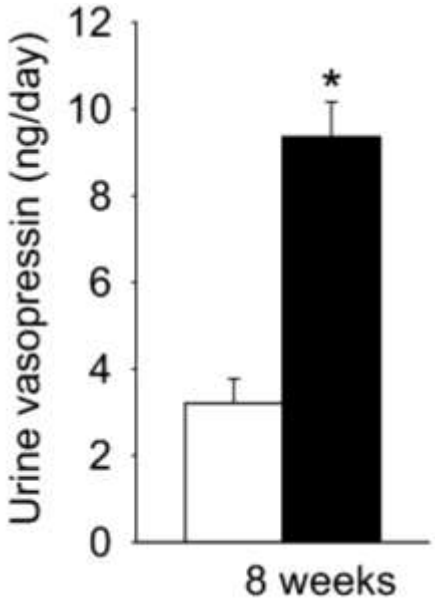
Great! So should we use SGLT2i in ADPKD now?

Unfortunately, the answer is no….

- ADPKD was an exclusion criterion in the CKD trials
- the preclinical data in PKD models are heterogenous
- Could there be safety concerns (vasopressin)?

SGLT2i increases vasopressin in both animals and humans without PKD

rats



Masuda et al. Physiol Rep 2020

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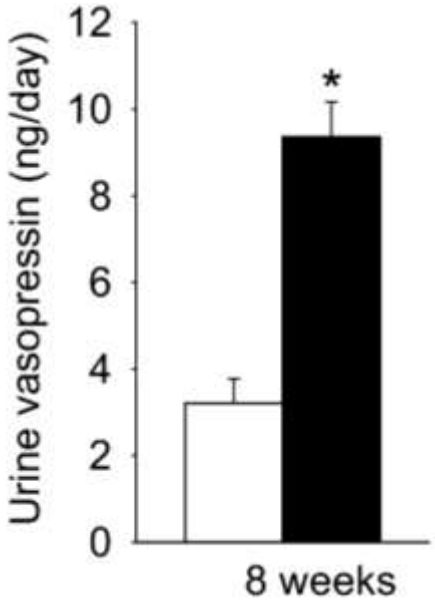
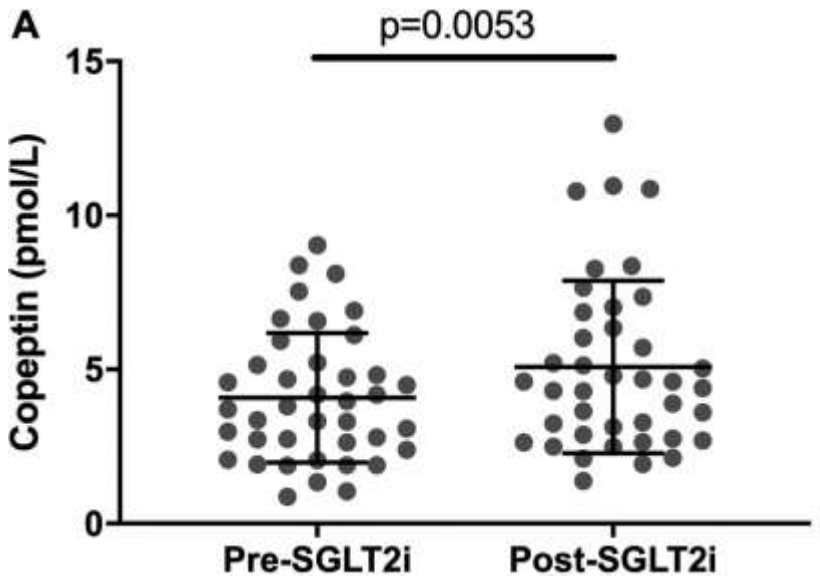
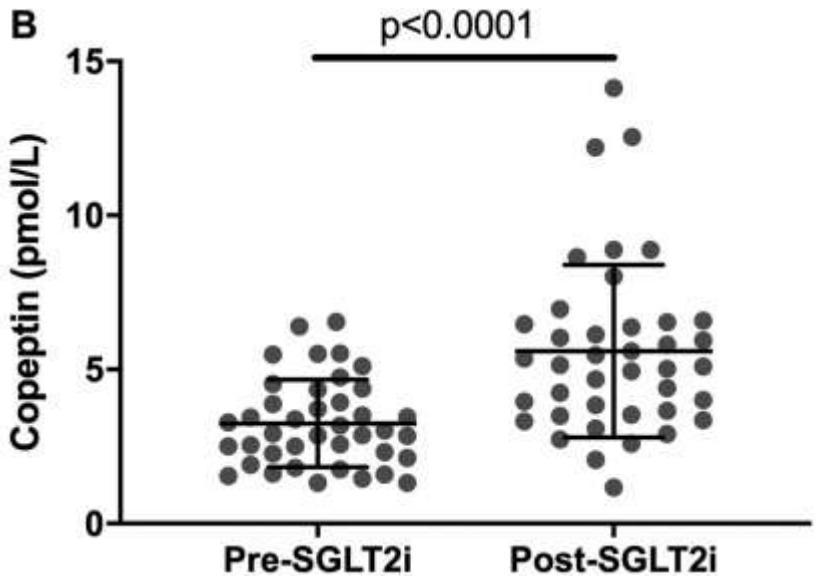


Masuda et al. Physiol Rep 2020

clamped euglycemic conditions



hyperglycemic conditions



Lytvyn et al. Diabetes Metab. 2020

Sen et al Diabetes Obes Metab 2022

Great! So should we use SGLT2i in ADPKD now?

Unfortunately, the answer is no….

- ADPKD was an exclusion criterion in the CKD trials
- the preclinical data in PKD models are heterogenous
- Could there be safety concerns (vasopressin)?

Clinical trial urgently required.

Last message: **KETO ≠ KETO**

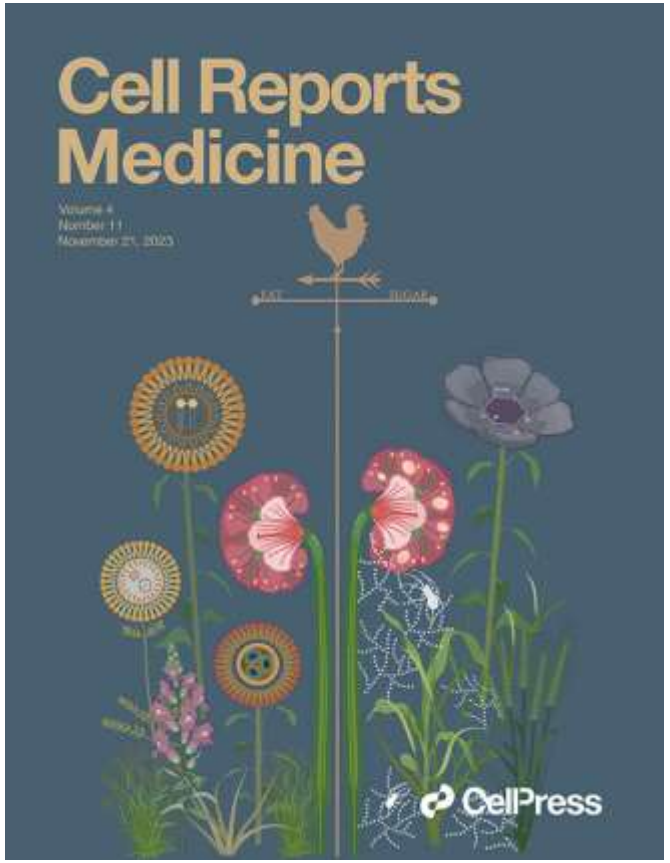
UNIKLINIK KÖLN
Department II of Internal Medicine, Nephrology, Rheumatology, Diabetes and General Internal Medicine
University Hospital of Cologne

colpkd

Franziska Grundmann
Sadrija Cukoski
Christoph Lindemann
Theresa Brecht
Adrian Kühn
Simon Oehm
Sita Arjune
Polina Todorova
Cornelia Böhme
Sebastian Strubl
Johannes Schmidt
Philipp Antczak
Hande Aydogan
+ all of the ADPKD team Cologne

All the patients participating in the trials.

Thanks very much.



Any more questions? nephrologie-adpkd@uk-koeln.de

Marga und Walter Boll-Stiftung
PKD FOUNDATION Polycystic kidney disease
AD(H)PKD
KETO ADPKD