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ORIGINAL ARTICLE

Ketogenic dietary interventions in autosomal dominant polycystic kidney disease—a retrospective case series study: first insights into feasibility, safety and effects

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ABSTRACT

Background. Our laboratory published the first evidence that nutritional ketosis, induced by a ketogenic diet (KD) or time-restricted diet (TRD), ameliorates disease progression in polycystic kidney disease (PKD) animal models. We reasoned that, due to their frequent use for numerous health benefits, some autosomal dominant PKD (ADPKD) patients may already have had experience with ketogenic dietary interventions (KDIs). This retrospective case series study is designed to collect the first real-life observations of ADPKD patients about safety, feasibility and possible benefits of KDIs in ADPKD as part of a translational project pipeline.

Methods. Patients with ADPKD who had already used KDIs were recruited to retrospectively collect observational and medical data about beneficial or adverse effects and the feasibility and safety of KDIs in questionnaire-based interviews.

Results. A total of 131 ADPKD patients took part in this study. About 74 executed a KD and 52 a TRD for 6 months on average. A total of 86% of participants reported that KDIs had improved their overall health, 67% described improvements in ADPKD-associated health issues, 90% observed significant weight loss, 64% of participants with hypertension reported improvements in blood pressure, 66% noticed adverse effects that are frequently observed with KDIs, 22 participants reported safety concerns like hyperlipidemia, 45 participants reported slight improvements in estimated glomerular filtration rate and 92% experienced KDIs as feasible while 53% reported breaks during their diet.

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Conclusions. Our preliminary data indicate that KDIs may be safe, feasible and potentially beneficial for ADPKD patients, highlighting that prospective clinical trials are warranted to confirm these results in a controlled setting and elucidate the impact of KDIs specifically on kidney function and cyst progression.

Keywords: autosomal dominant polycystic kidney disease, caloric restriction, intermittent fasting, ketogenic diet

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a common genetic disorder caused by mutations in the *PKD1* or *PKD2* genes [1]. ADPKD is characterized by slow but relentless bilateral cyst growth that leads to organ enlargement, fibrosis and a decline in kidney function, ultimately requiring dialysis or kidney transplantation in most cases [2, 3]. Tolvaptan, the only drug approved by the US Food and Drug Administration (FDA) for polycystic kidney disease (PKD), is only available to a fraction of patients, has significant adverse effects, high cost and only slows disease progression but cannot halt or reverse it [4–6]. There is a great need for more widely accessible, more effective and safer treatment options.

Recent research revealed that PKD cyst lining cells are metabolically inflexible and rely on glucose as an energy source, indicating that defects in energy metabolism underlie the pathogenesis of PKD [7–9]. We and others reported that mild reductions in food intake in orthologous *Pkd1* mouse models strongly decreased renal cyst growth [10, 11]. Recent work from our laboratory showed that the metabolic state of ketosis appeared to mediate the beneficial effects of food restriction. Ketosis induced by a time-restricted diet (TRD) or ketogenic diet (KD) significantly inhibited cyst growth, fibrosis and PKD-associated signaling pathways [12].

Ketosis represents the metabolic adaption to reduced blood glucose levels by utilizing fatty acid mobilization and synthesis of the ketone bodies acetoacetate and beta-hydroxybutyrate (BHB) as replacement energy sources [13, 14]. Ketogenic dietary interventions (KDIs) such as fasting, caloric restriction (CR) and a KD can result in physiological BHB levels of 0.5–7 mmol/L [13, 14]. Physiological ketosis must be distinguished from the pathological state of ketoacidosis, a metabolic dysregulation that primarily occurs in type 1 diabetes [15].

Classical KDs are characterized by high fat, low carbohydrate and moderate protein intake. The misconception that KDs must be high in protein actually often prevents robust ketosis [14, 16]. KDs are accepted clinical treatments for pediatric epilepsy or weight reduction and are emerging as potentially beneficial in several other diseases [17–20]. Nonetheless, adverse effects like hyperlipidemia, a higher risk for kidney stones and other temporary symptoms can occur and have been controversially discussed as safety concerns [21–23].

Since KDIs are widely used in the general population for numerous potential health benefits, we reasoned that PKD patients might already have tried self-initiated KDIs. We were able to recruit a sizeable number of PKD patients into this retrospective case series study with the aim of collecting patient-reported experiences about safety, feasibility and possible beneficial effects (Figure 1A). These observations indicate that KDIs may be feasible and safe for ADPKD patients and could be beneficial for their well-being, PKD-associated health issues (HIs), weight, arterial hypertension and kidney function.

MATERIALS AND METHODS

Study design

The study Experience of people with ADPKD with ketogenic diets—Implementation and effects was designed as an uncontrolled, unbalanced case series study that aimed to retrospectively collect and analyze patient-reported observations and self-reported medical data before and during the execution of KDIs (study cohort 'KDIs'; Figure 1A). Participants were recruited using a recruitment letter that was distributed in PKD-associated social media groups (https://www.facebook.com/groups/weimbslab, https://www.facebook.com/groups/720938791650358, https://www.facebook.com/groups/reversingpkd, https://www.facebook.com/groups/537045026874783, https://www.facebook.com/groups/4570435860, https://www.facebook.com/groups/274752693388309) and via patient advocacy groups in the USA and Germany (US PKD Foundation and the German Familiäre Zystennieren). All data were collected in questionnaire-based phone interviews (see Supplementary Material). The study was approved by the institutional review boards (IRBs) at the University of California, Santa Barbara and the University Hospital of Cologne (protocols: UC Santa Barbara, 3-20-0252; University of Cologne, 20-1359). Additionally, this article presents data from a second independent study, Questionnaire on eating habits and special diets in patients with ADPKD – identification of ADPKD patients following a special diet (study cohort Eating habits; Supplementary data, Figure S1A), which was approved by the IRB at the University Hospital of Cologne (protocol 19-1627) and collected data on eating habits and special diets using an online survey (see Supplementary Material) distributed by the German patient advocacy group Familiäre Zystennieren in PKD-associated social media groups. All participants agreed to participate by signing an informed consent form.

Participants

The study cohort KDIs includes 131 ADPKD patients who tried self-initiated KDIs in the past. KDIs include variations of KDs, TRDs and CR. Participants on dialysis, with kidney transplants or on dietary protocols that were not 'KDI conformable' were excluded. Baseline characteristics are shown in Table 1. A separate analysis of participants executing CR showed no significant differences to the other subcohorts. Due to the limited number of participants on CR, this subgroup is not separately displayed throughout the figures. A separate analysis of participants on tolvaptan (Table 1) revealed no significant differences in any endpoints besides the data on water consumption, so all other data include tolvaptan patients.

The survey study cohort Eating habits is separate from the KDI cohort and includes 210 ADPKD patients (147 females and 63 males) between 25 and 79 years of age.

Analysis and statistics

All data were pseudonymized after collection and analyzed using Prism software (GraphPad Software, San Diego, CA, USA) as absolute or percentage values. Normally distributed medical data were

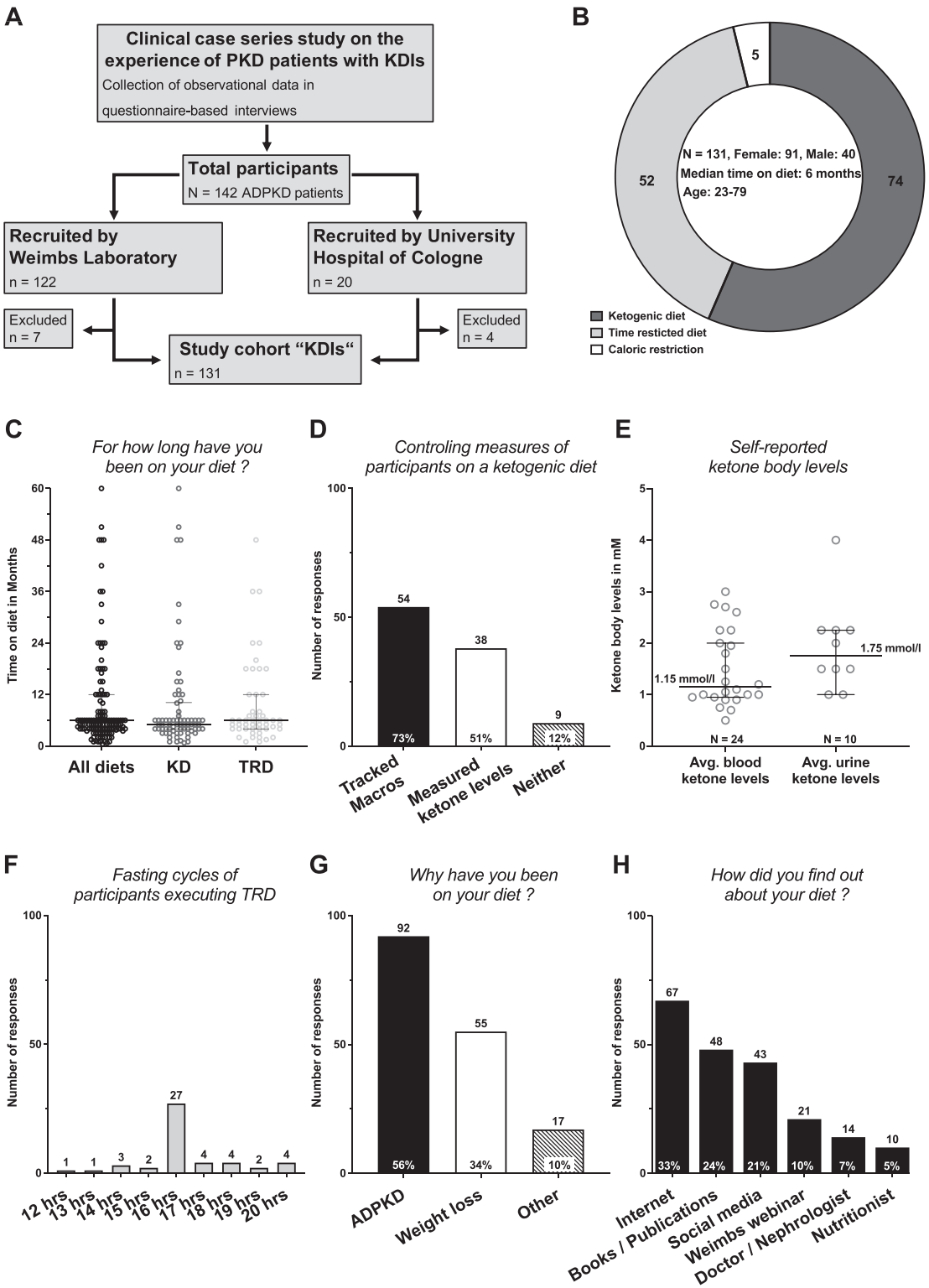

FIGURE 1: The study cohort KDIs. (**A**) Flow diagram of the case series study cohort KDIs. PKD patients were recruited by the Weimbs Laboratory and the University Hospital of Cologne to participate in questionnaire-based interviews about the experience of PKD patients with KDIs. (**B**) Description of the study cohort: distribution of age, sex and type of KDIs. (**C**) Average time on KDIs. Time on the diet is displayed as the median average. (**D**) Controlling measures of participants on a KD. Participants were asked how they control to reach ketosis. (**E**) Self-reported ketone body levels of participants who measured KB in the blood or urine. KB levels are displayed as the median average. N for KB in blood = 24. N for KB in urine = 10. (**F**) Fasting cycles used by participants executing a TRD. Participants were asked to specify their fasting cycle when practicing a TRD. $n = 48$. (**G**) Reason for experimenting with KDIs. Participants were asked why they started a KDI. (**H**) Resources used for starting a KDI. Participants were asked how they found out about KDIs in PKD.

Table 1. Baseline characteristics

Characteristics	Total cohort ($N = 131$)	KD cohort ($n = 74$)	TRD cohort ($n = 52$)	CR cohort ($n = 5$)
Age (years), median (IQR)	50 (20)	47 (18.25)	51 (19.75)	57 (24)
Gender, *n* (%)				
Female	91 (69.5)	52 (70.3)	36 (69.8)	3 (60)
Male	40 (30.5)	22 (29.7)	16 (30.8)	2 (40)
Time on diet (months), median (IQR)	6 (8)	5 (6.13)	6 (8)	8 (66.9)
Participants still on diet, *n* (%)	104 (79.4)	56 (75.7)	45 (86.5)	3 (60)
Weight (kg), median (IQR)	79.55 (25.91)	78.4 (25.46)	80.8 (20.06)	95.3 (61)
Patients on tolvaptan while on KDIs, *n* (%)	20 (15.4)	12 (16.2)	7 (13.5)	1 (20)
BMI, median (IQR)	26.2 (8.2)	25.65 (8.88)	26.36 (7.04)	32 (12.55)
Water consumption (L), median (IQR)	2.0 (1)	1.95 (1.05)	2 (1.25)	1.5 (1.5)
BP (mmHg), median (IQR)				
Systolic	132 (8.5)	131 (8.3)	135 (13)	130 (35)
Diastolic	85 (10)	85 (10)	80 (10)	90 (35)
eGFR (mL/min/1.73 m^2), median (IQR)	57 (32.5)	53.5 (28.5)	60 (46)	67 (0)

List of baseline characteristics of all participants, separated by KDIs.
IQR, interquartile range.

Table 2. Safety concerns

Safety concerns	Responses, *n*	Comments
Increased cholesterol levels	10	
Increased heart rate	3	2 of 3 responses reported a normalization over time
Strong side effects	2	Brain fog, 'keto flu'
Increase in creatinine	2	2 of 2 responses reported a return back to levels before starting the diet
New incidence of kidney stones	1	Incidental finding
Increase in serum uric acid	1	
Increased serum bilirubin levels	1	Normalized over time
Decreased international normalized ratio levels	1	Participant on warfarin therapy prior to the start of the diet. Warfarin dose was adjusted accordingly
Decreased vitamin B levels	1	
Decline in BP	1	Consecutive dizziness. Normalized after adjusting BP medication

Full list of changes on KDIs that have raised safety concerns for the participants or their doctors.

statistically analyzed using the Mann–Whitney U-test, paired Student's *t*-test, Wilcoxon signed rank test or Spearman's rank correlation. Analysis of blood pressure (BP) was based on self-reported values of participants who measured BP on a regular basis and could confirm no changes in BP medication during this time.

RESULTS

The Case series study cohort 'Ketogenic dietary interventions (KDIs)'

An online survey about eating habits and diets in PKD patients in Germany suggested significant interest in dietary interventions as PKD treatment and indicated that some patients might already have tried KDIs (Supplementary data, Figure S1). We were able to recruit 131 PKD patients, mainly based in the USA, of which 74 followed a KD, 52 a TRD and 5 CR. More than half of the KD subgroup additionally executed a TRD ($n = 35$) or CR ($n = 5$). Participants followed KDIs for an average of 6 months (Figure 1B and C). Participants on KDs typically controlled their diets by tracking macronutrients and set target levels, while 38 participants measured ketone levels in their blood, urine or breath, which averaged ~1.15 mmol/L in the blood and ~1.75 mmol/L in the urine, indicating successful ketosis (Figure 1D and E). Participants executing TRD mostly adhered to the 16:8 regimen (8-h eating window per day; Figure 1F). The majority started their diet because of ADPKD and learned about KDIs through the internet and social media (Figure 1G and H).

KDIs reportedly improve overall health and PKD-related symptoms

We first analyzed whether participants experienced any general changes on KDIs. Surprisingly, 80% of participants reported improvements in their well-being (Figure 2A). Furthermore, participants were asked whether they observed changes in

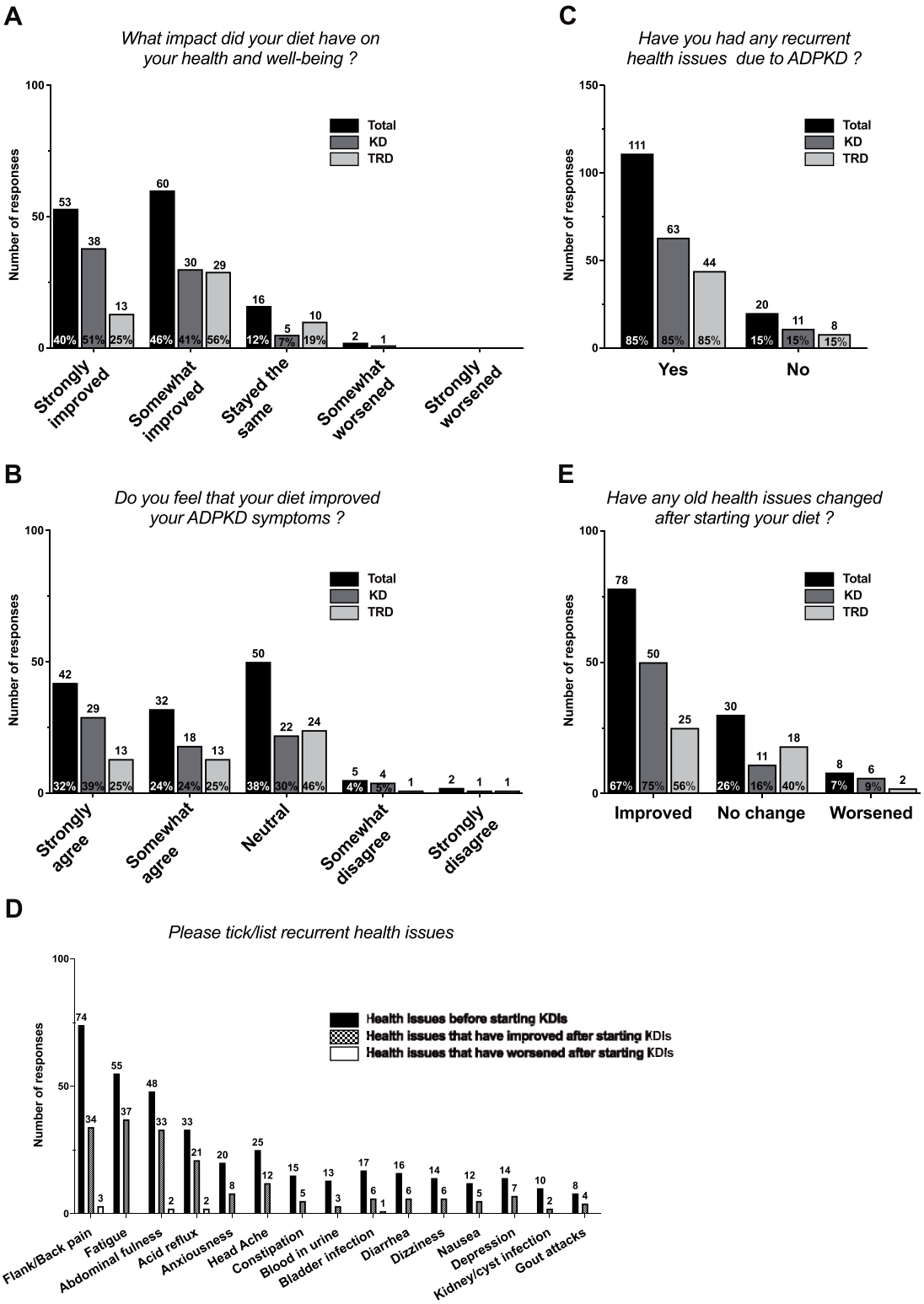

FIGURE 2: Dietary impact on health and well-being and PKD-related HIs. (**A**) Impact of KDIs on personal health and well-being. Participants were asked whether their diet had an impact on their overall health and well-being. (**B**) Impact of KDIs on ADPKD symptoms. Participants were asked whether their diet improved personal ADPKD symptoms. (**C**) Presence of recurrent HIs commonly associated with PKD. Participants were asked whether they experienced any recurrent HIs related to PKD before starting their diet. (**D**) Specification of recurrent HIs and their improvements. Participants were asked to specify recurrent HIs before starting their diet and respective improvements after starting KDIs using a list of common PKD-associated symptoms. (**E**) Impact of KDIs on recurrent HIs associated with PKD. Participants were asked whether any old recurrent HIs have changed after starting their diet. Five participants reported both improvement and worsening of old recurrent HIs.

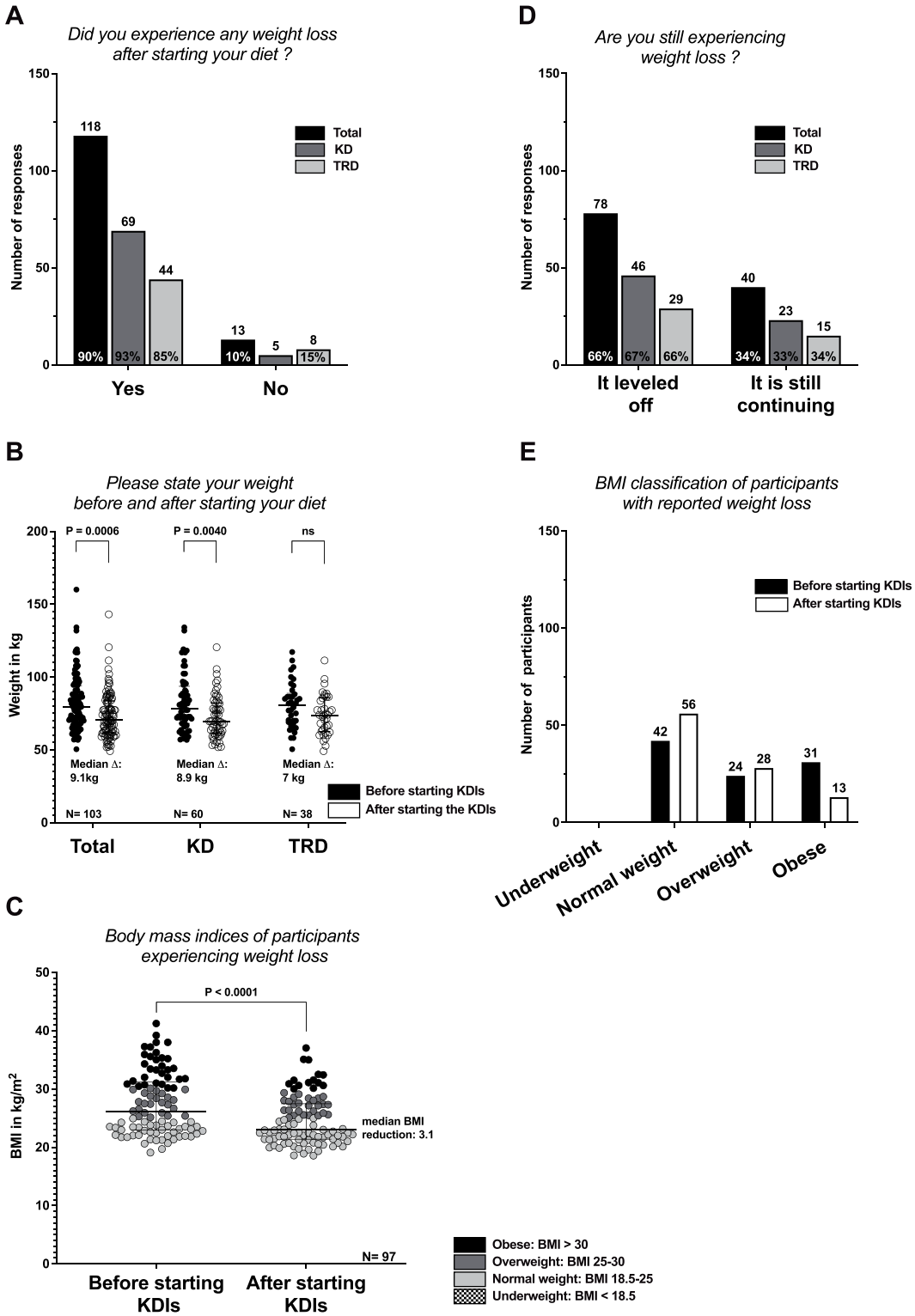

FIGURE 3: Impact on weight. (**A**) Weight loss upon the start of KDIs. Participants were asked whether they experienced any weight loss after starting their diet. (**B**) Median average weight loss. Participants experiencing weight loss were asked for their starting weight and average weight loss. Total $n = 103$, KD $n = 60$, TRD $n = 38$. (**C**) Analysis of BMIs before and after starting KDIs of participants experiencing weight loss. $n = 97$. Dots are color-coded according to the BMI classifications. (**D**) Course of weight loss. Participants who experienced weight loss were asked whether weight loss has leveled off or was continuing over time. (**E**) BMI classification of participants experiencing weight loss before and after starting KDIs. $n = 97$. Statistical analyses by Mann–Whitney U-test. Error bars represent the median average with interquartile range.

recurrent PKD-associated HIs (Figure 2B). Therefore participants were asked to specify how such HIs affected their well-being before and after starting the diet. A total of 111 participants reported recurrent HIs before starting KDIs (Figure 2C), of which flank/back pain, fatigue and abdominal fullness were most common (Figure 2D). Most notably, 67% of participants with HIs reported improvements after starting KDIs (Figure 2E). More than 50% of all HIs were reportedly improved (Figure 2D). The KD cohort reported a more profound effect than the TRD cohort (Figure 2A and E). These observations indicate that KDIs could be beneficial for PKD-associated HIs and the overall well-being of PKD patients.

KDIs lead to a reduction in body weight and BMI in PKD patients

About 90% of participants reported weight loss on KDIs (Figure 3A). On average, participants reported 9.1 kg of weight reduction, reducing their body mass index (BMI) by 3.1 points (Figure 3B and C). A KD led to more weight reduction than a TRD. Participants described rapid weight loss within the first weeks, which then leveled off for 66% after a few months (Figure 3D). A total of 34% reported continued weight loss. Several participants could downgrade their BMI classification. No participant reported BMI levels of underweight (Figure 3C and E). While the interpretation of unadjusted BMI in ADPKD is limited [24, 25], these results indicate that KDIs appear to be effective for weight management in this cohort.

KDIs may improve arterial hypertension in PKD patients

Since arterial hypertension can accelerate PKD disease progression and KDIs reportedly improve hypertension [2, 26], we analyzed the study cohort for possible changes in BP. A total of 74% of participants reported having hypertension (Figure 4A). Most notably, 64% of those participants described improvements in BP on KDIs (Figure 4B). Self-provided BP values revealed a considerable decrease in BP averages, from 132/85 to 118/76 mmHg (Figure 4C and D), which is consistent with previous studies in individuals without PKD [27, 28]. A total of 23 participants additionally reported a decrease in BP medication on KDIs.

Impact of KDIs on water consumption

A total of 58% of participants not taking tolvaptan reported increased water intake by ~1.5 L (Figure 4E and F) and 42% did not experience any changes, which may be explained by the higher baseline consumption. This may be due to participants' adherence to PKD treatment guidelines [1, 2]. Both subgroups did not display differences in beneficial or adverse effects (data not shown). Participants on tolvaptan mostly reported no changes in water intake. Taken together, KDIs may go along with increased water intake in PKD patients.

Impact of KDIs on renal function

Our laboratory showed that KDIs improve renal function and total kidney volume (TKV) in PKD animal models [12]. To obtain insights in PKD patients, we collected estimated glomerular filtration rate (eGFR) data from before and after starting KDIs. Of 70 participants providing data, 45 reported improvement, 8 no change and 17 a decline in eGFR (Figure 5A). A paired analysis indicated stabilization of eGFR with small increases of 3.6 mL/min/1.73 m^2 in the mean average (Figure 5B). Participants with documented ketosis had greater increases by 7.3 mL/min/1.73 m^2, which positively correlated with the corresponding average serum BHB levels (Figure 5B and C).

Side effects and safety considerations of KDIs in PKD patients

While one-third of participants did not report any new HIs, 66% observed on average 2.6 new symptoms on KDIs. Participants on a KD reported new HIs more frequently than those on a TRD (Figure 6A). Fatigue, hunger and 'keto flu' were most common (Figure 6B), in line with expected side effects of KDIs [22, 23]. A total of 55% reported that most HIs subsided over time, while 12% reported persistence of most HIs. In total, 76% of all new HIs reportedly resolved over time (Figure 6B and C).

Furthermore, 22 participants reported changes that raised safety concerns (Figure 6D and Table 2). The most commonly reported safety concern was the increase in cholesterol levels. Self-reported data indicated an average increase in total cholesterol of 13 mg/dL and in LDL levels of 8.5 mg/dL, which was significantly higher in the KD cohort (Figure 6E). Triglycerides and high-density lipoprotein (HDL) cholesterol seemed largely unchanged. No participant reported the concomitant start of hyperlipidemia treatment, one participant reported findings of kidney stones and two participants reported an increase in serum creatinine.

Feasibility of KDIs for PKD patients

A total of 76% of participants experienced the implementation of KDIs as manageable (Figure 7A). The food preparation time seemed not to be negatively affected (Figure 7B). Most participants described their diet as relatively easy to execute and would recommend it to others (Figure 7C and D). A totla of 50% of participants reported adhering to their diet every day, while 42% skipped several times a month (Figure 7E). A total of 40% of participants reported breaks due to practical difficulties, indicating that the adherence to KDIs might still be challenging (Figure 7F). In particular, a KD was reported to be more demanding than a TRD. These observations indicate that KDIs appeared feasible for PKD patients in this study, with manageable implementation and adherence.

DISCUSSION

Our laboratory recently showed that KDIs inhibit renal cyst growth, preserve renal function and reverse existing cyst burden in PKD animal models [12]. This is consistent with the emerging consensus that PKD cyst lining cells rely on glucose as an energy source due to defective fatty acid metabolism. Our findings indicated that PKD cysts cannot adapt to the metabolic changes in ketosis, which could potentially be exploited therapeutically.

In this study we recruited a sizeable number of PKD patients who had already tried self-initiated KDIs. Participants executed variable dietary protocols and the majority could not provide measured ketone levels as evidence of ketosis. Since all data were self-reported in an uncontrolled, unbalanced (gender imbalance) and retrospective setting, the reliability and interpretation of the data are clearly limited but can serve as an initial resource of ADPKD patients' experiences with KDIs for future translation into clinical and real-life settings and to inform future clinical trials.

The observations indicate that PKD patients could benefit from KDIs, as most participants reported improvements in PKD-

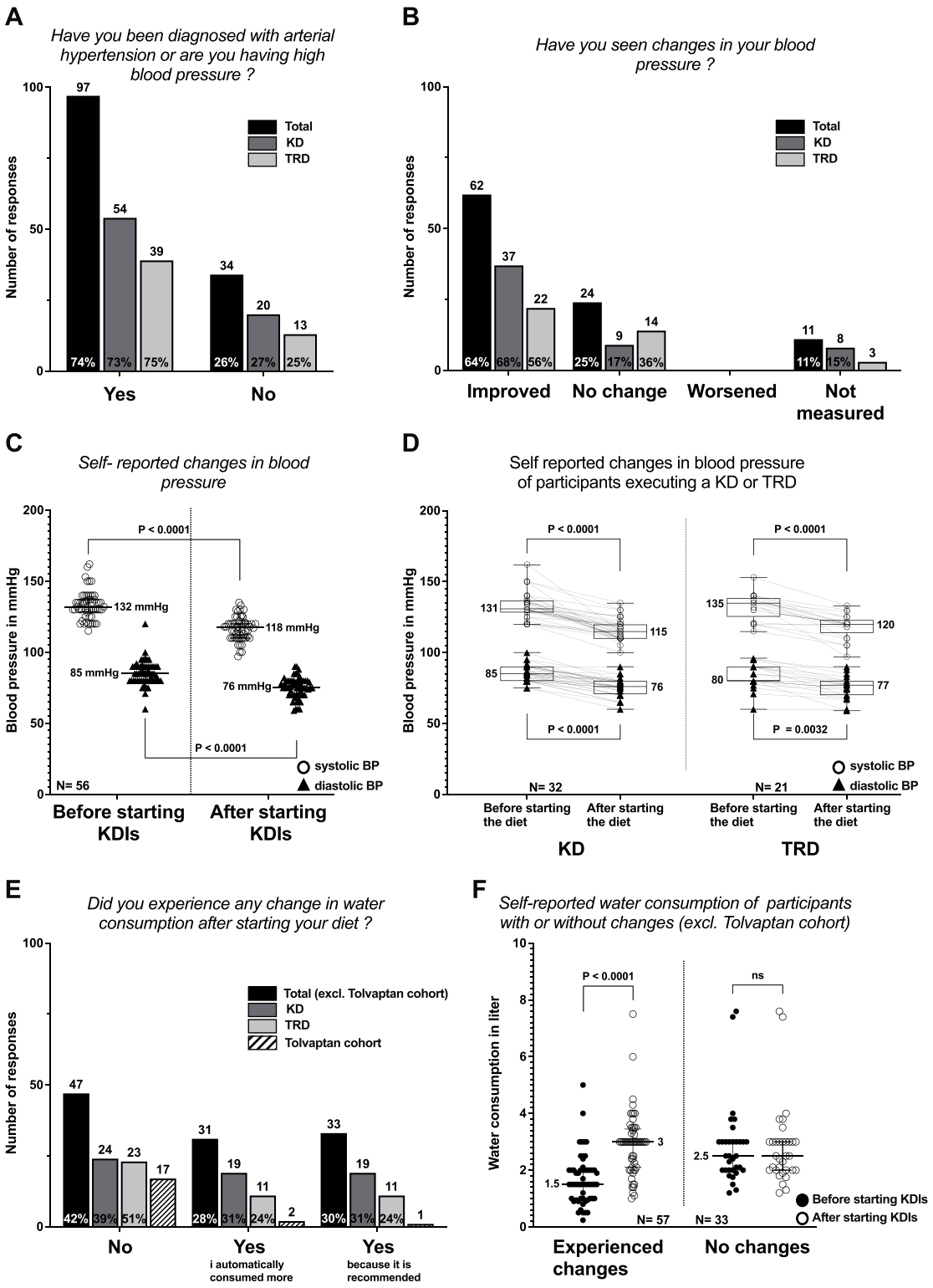

FIGURE 4: Impact on hypertension and water consumption. (**A**) Presence of arterial hypertension. Participants were asked whether they were diagnosed with hypertension or have problems with high BP. (**B**) Impact on BP on the start of KDIs. Participants with hypertension were asked whether they experienced any changes in BP after starting their diet. (**C**) Analysis of self-reported BP values from participants with hypertension before and after starting KDIs. $n = 56$. Error bars represent the median average with interquartile range. (**D**) Separate analysis for KD and TRD of self-reported BP values from participants with hypertension. KD $n = 32$, TRD $n = 21$. Box and whisker error bars represent median average with minimum to maximum. Statistical analysis by Mann–Whitney U-test. (**E**) Impact on water consumption. Participants were asked whether they experienced changes in water intake after starting KDIs. Since tolvaptan treatment significantly alters water consumption, participants on tolvaptan were analyzed separately. (**F**) Analysis of self-reported water consumption before and after starting KDIs. Since tolvaptan treatment significantly alters water consumption, participants on tolvaptan were excluded from this analysis. The cohort was analyzed separately based on whether participants reported changes or no changes in water consumption. Statistical analysis by Mann–Whitney U-test. Error bars represent the median average with interquartile range. n (experienced changes) = 57; n (no changes) = 33.

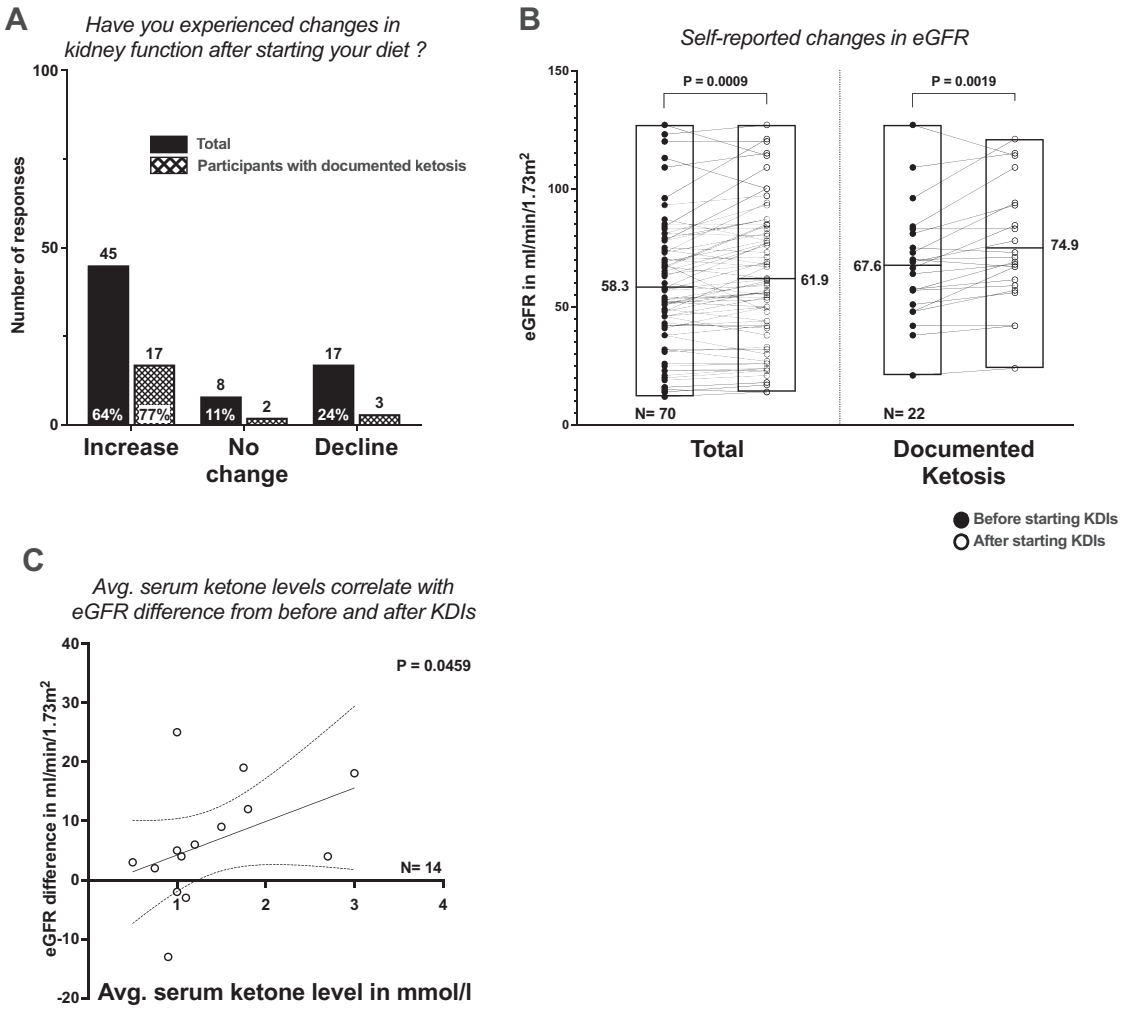

FIGURE 5: Impact on kidney function. (**A**) Impact on kidney function. Participants were asked whether they experienced changes in kidney function after starting KDIs. Total $n = 70$. Participants with documented ketosis = 22. (**B**) Paired analysis of self-reported changes in eGFR before and after starting KDIs. Total $n = 70$, participants with documented ketosis = 22. Statistical analysis by paired *t*-test. Error bars represent the mean average with standard deviation. (**C**) Correlation analysis between eGFR difference before and after starting the diet with corresponding mean serum BHB levels reveals a positive correlation. Number of participants with both self-reported eGFR values and serum BHB levels = 14. Statistical analysis by nonparametric Spearman correlation. Line represents best fit and dotted lines represent 95% confidence intervals. P = 0.0459.

associated HIs and overall well-being. However, the retrospective setting could have facilitated biased data reports attracting more participants with positive rather than negative experiences. Additionally, most participants described considerable improvements in arterial hypertension. Whether those beneficial observations are due to the significant weight loss or other mechanistic considerations of KDIs remains unknown. Furthermore, participants might have changed other lifestyle factors besides their diet that could have affected results. Nonetheless, since overweight seems to be strongly associated with TKV progression in PKD [25, 29], effective weight management should be regarded as important for PKD management.

Several participants reported increases in eGFR on KDIs, which is consistent with previous reports in individuals with mild CKD [30, 31]. However, since our observations are based on single values obtained in a non-controlled fashion and eGFR values can fluctuate in individuals, the reliability of these data is limited [32–34]. While a slight eGFR increase might indicate a stabilization in renal function, it can also be interpreted as a sign of glomerular hyperfiltration [35]. Although classic KDs are not high in protein, this could be caused by increased protein intake associated with some KD variants, which has been considered to affect kidney health negatively [36, 37].

Since it is well-established that ADPKD is relentlessly progressive, eGFR values are not expected to stabilize or increase on average over time on a cohort basis, as observed in this study [38–40]. While it is still controversially discussed whether GFR can even be reversed and improved in CKDs, there are data to support this [41]. Mechanistically, of course, no new nephrons will develop in affected kidneys. However, one may speculate that relieving pressure due to inhibiting cyst expansion may beneficially affect the function of healthy, adjacent nephrons. Our observations indicate that KDIs might not have negative, but rather positive outcomes in PKD. Thus it suggests that prospective clinical trials utilizing more standardized diets are warranted to elucidate the specific impact of KDIs on well-being, BP, weight, renal function and TKV of PKD patients.

This study further indicates that KDIs can trigger new HIs in PKD patients, which are commonly associated with KDIs and are likely to resolve over time [22, 23]. A few participants

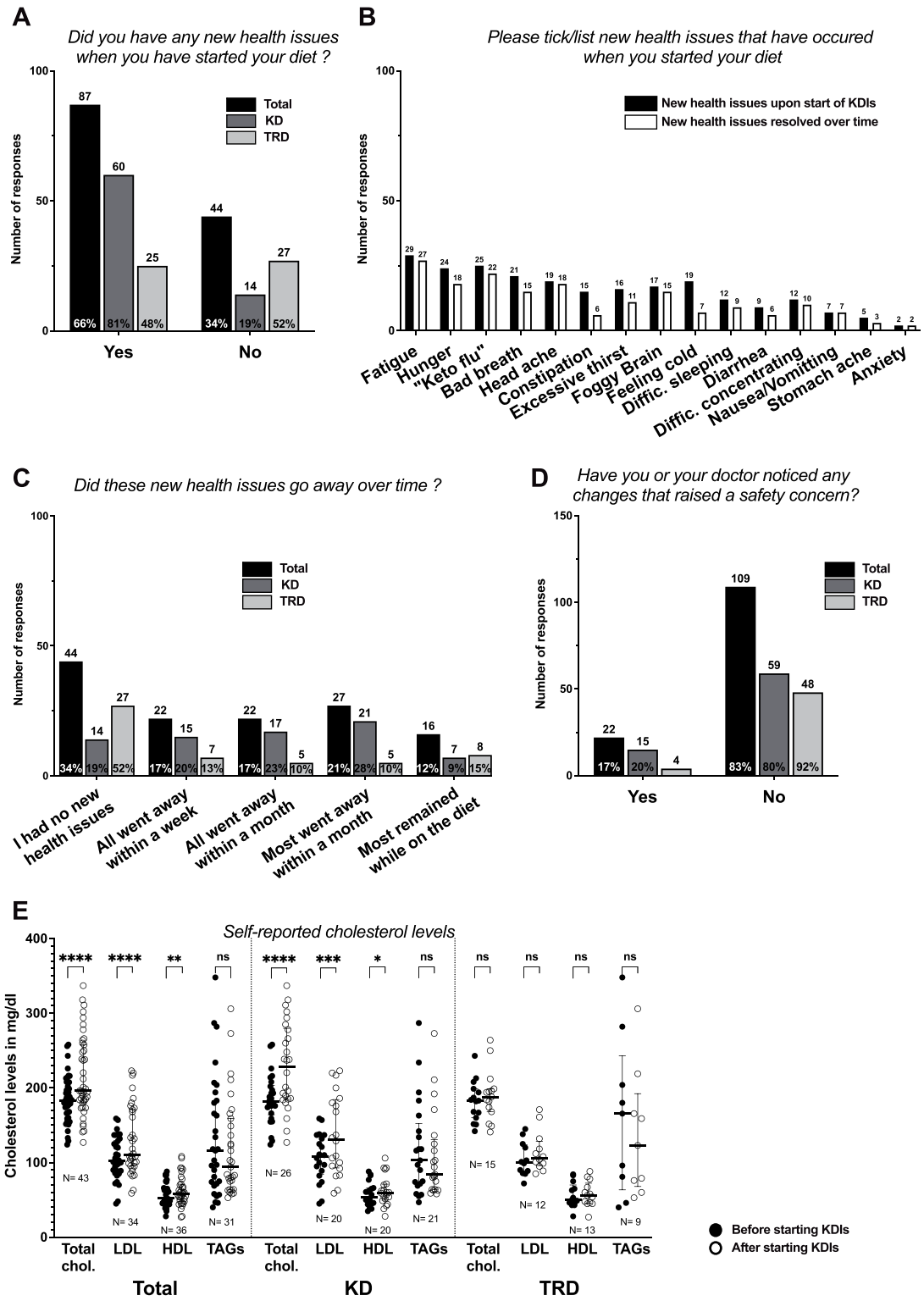

FIGURE 6: Side effects and safety concerns. (**A**) New HIs on the start of KDIs. Participants were asked whether they experienced new HIs after starting their diet. (**B**) Specification of side effects on the start of KDIs. Participants were asked to specify those new side effects and their resolution over time using a list of common symptoms associated with KDIs. (**C**) Persistence of side effects. Participants were asked whether new side effects were resolving over time. (**D**) Safety concerns upon the start of KDIs. Participants were asked whether they or their doctors noticed changes that raised safety concerns. (**E**) Analysis of self-reported cholesterol levels before and after starting KDIs. Statistical analysis by Wilcoxon matched pairs signed rank test. Error bars represent the median average with interquartile range. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P \leq 0.0001$.

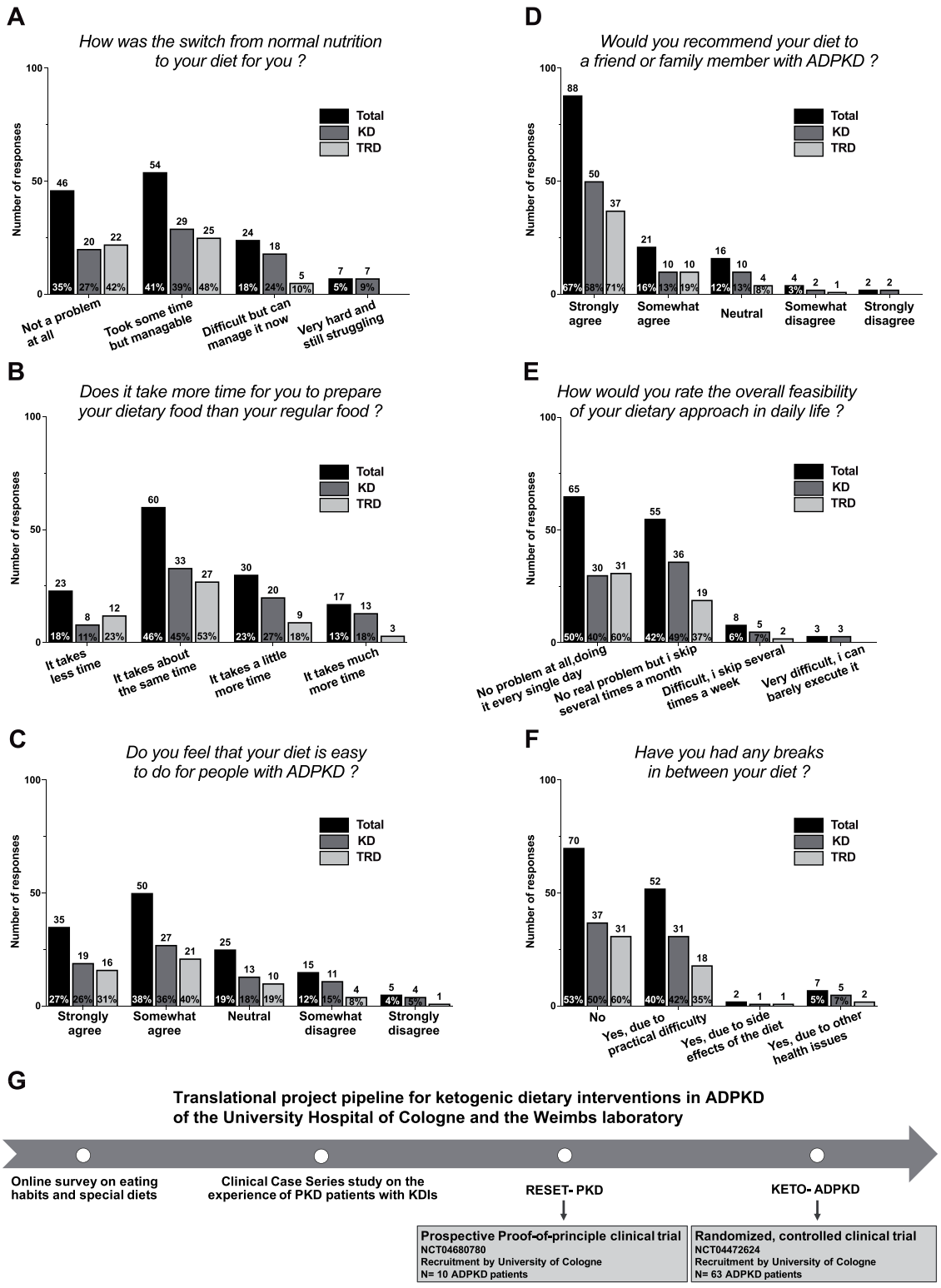

FIGURE 7: Feasibility of KDIs and translational project pipeline. (**A**) Implementation of KDIs. Participants were asked how they experienced the switch from 'standard' nutrition to KDIs. (**B**) Implementation of KDIs. Participants were asked whether food preparation for KDIs takes more time than 'standard' food. $n = 130$. (**C**) Feasibility of KDIs. Participants were asked whether their diet is easy to do for people with ADPKD. $n = 130$. (**D**) Feasibility of KDIs. Participants were asked whether they would recommend their diet to friends or family members with ADPKD. (**E**) Adherence to KDIs. Participants were asked to rate the overall feasibility and adherence of their diet in daily life. (**F**) Adherence to KDIs. Participants were asked whether they had a break in between their diets. (**G**) Flow diagram showing the translational project pipeline of the University Hospital Cologne and the Weimbs Laboratory to translate KDIs into the clinical setting of ADPKD. The first results from these trials are expected in 2021 and early 2022.

reported new HIs that raised safety concerns. One participant reported the finding of kidney stones, which has been associated with KDIs [21]. Kidney stones are also common in PKD [42], and it is unclear whether they were related to the KDI in this case. Two participants reported an increase in serum creatinine as a safety concern, but increases in serum creatinine are also part of the natural course of disease progression in ADPKD. Nonetheless, the occurrence of new HIs underscores the importance of supervision by qualified healthcare practitioners.

The most common safety concern raised by our participants was the increase in total cholesterol and LDL levels. In the past, nutritional trials have suggested that dietary intake of cholesterol increases the risk for cardiovascular diseases (CVDs) [43]. However, this hypothesis could not be substantiated, which has led to the removal of a recommended dietary cholesterol limit in the Dietary Guidelines for Americans [44]. Nevertheless, the fear of the possibility of increased CVD risk with increased cholesterol persists, especially since ADPKD patients are already at higher risk [45]. Recent research suggests that KDIs might even have a beneficial effect on CVD risk. Several positive effects of KDIs, like improvements in body weight, body fat, BP, HDL or inflammation markers, could outweigh the possible adverse effect of increased cholesterol/LDL on CVD risk [26, 46–49]. Furthermore, transient increases in cholesterol/LDL are a well-reported and necessary effect of KDIs, indicating the successful depletion of adipose lipid stores, and have been shown to normalize again over time [50, 51]. The conclusive evaluation of any possible—positive or negative—impact of KDIs on CVD risk in ADPKD patients will require more long-term prospective trials.

Finally, our observations suggest that KDIs could be feasible for PKD patients. Most participants reported manageable implementation and good adherence to KDIs, taking into account that participants started their diet without medical/nutritional support. This is also consistent with a pilot study using a modified Atkins diet in three PKD patients [52]. However, since participants have elected, on their own, to experiment with KDIs, indicating a high motivation to succeed, the study cohort is likely unbalanced and may not be representative of the average PKD population. Breaks due to practical difficulty were commonly reported and not all participants executed their diet every single day, which further limits the interpretation of the data and indicates that the execution of KDIs can still be challenging in daily life. Professional assistance and regular monitoring will be important measures for prospective trials to ensure a high rate of dietary adherence. Predictions of more long-term effects or rebound effects after stopping KDIs cannot currently be made since participants only executed KDIs for an average of 6 months and most participants were still on the diet during data collection (Table 1).

Taken together, in this study we observed that 131 PKD patients on self-initiated KDIs experienced such diets as overall beneficial, safe and feasible, indicating that prospective trials are warranted to confirm these findings in a controlled setting to elucidate the specific impact of KDIs on overall well-being, weight, BP, kidney function and cyst progression in individuals with ADPKD. The Weimbs laboratory and the University Hospital of Cologne established a clinical project pipeline to translate KDIs into the clinical setting of ADPKD (Figure 7G). The first results from these trials are expected in 2021 and early 2022.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

The results presented in this article have not been published previously in whole or part, except in abstract form. T.W. and J.A.T are inventors on issued and pending patents filed by the University of California, Santa Barbara related to discoveries reported in this article. T.W. is a shareholder and president and J.A.T. is a shareholder of Santa Barbara Nutrients. T.W. is on the scientific advisory board of Chinook Therapeutics, receives research funding from Chinook Therapeutics and is an inventor on a patent application by the University of California, Santa Barbara on a discovery unrelated to this article. R.U.M. is on the advisory board of Santa Barbara Nutrients.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its online supplementary material.

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