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Original Investigation

Health-Related Quality of Life in Patients With Autosomal Dominant Polycystic Kidney Disease and CKD Stages 1-4: A Cross-sectional Study

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Background: In people with early autosomal dominant polycystic kidney disease (ADPKD), average total kidney volume (TKV) is 3 times normal and increases by an average of 5% per year despite a seemingly normal glomerular filtration rate (GFR). We hypothesized that increased TKV would be a source of morbidity and diminished quality of life that would be worse in patients with more advanced disease.

Study Design: Cross-sectional.

Setting & Participants: 1,043 patients with ADPKD, hypertension, and a baseline estimated GFR (eGFR) >20 mL/min/1.73 m^2.

Predictors: (1) eGFR, (2) height-adjusted TKV (htTKV) in patients with eGFR >60 mL/min/1.73 m^2.

Outcomes: 36-Item Short Form Health Survey (SF-36) and the Wisconsin Brief Pain Survey.

Measurements: Questionnaires were self-administered. GFR was estimated from serum creatinine using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. htTKV was measured by magnetic resonance imaging.

Results: Back pain was reported by 50% of patients, and 20% experienced it "often, usually, or always." In patients with early disease (eGFR >60 mL/min/1.73 m^2), there was no association between pain and htTKV, except in patients with large kidneys (htTKV $>1,000$ mL/m). Comparing across eGFR levels and including patients with eGFRs <60 mL/min/1.73 m^2, patients with eGFRs of 20-44 mL/min/1.73 m^2 were significantly more likely to report that pain impacted on their daily lives and had lower SF-36 scores than patients with eGFRs of 45-60 and $\geq$60 mL/min/1.73 m^2. Symptoms relating to abdominal fullness were reported by 20% of patients and were related significantly to lower eGFRs in women, but not men.

Limitations: TKV and liver volume were not measured in patients with eGFR <60 mL/min/1.73 m^2. The number of patients with eGFRs <30 mL/min/1.73 m^2 is small. Causal inferences are limited by cross-sectional design.

Conclusions: Pain is a common early symptom in the course of ADPKD, although it is not related to kidney size in early disease (eGFR >60 mL/min/1.73 m^2), except in individuals with large kidneys (htTKV $>1,000$ mL/m). Symptoms relating to abdominal fullness and pain are greater in patients with more advanced (eGFR, 20-45 mL/min/1.73 m^2) disease and may be due to organ enlargement, especially in women. More research about the role of TKV in quality of life and outcomes of patients with ADPKD is warranted.

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INDEX WORDS: Autosomal dominant polycystic kidney disease (ADPKD); quality of life (QoL); chronic kidney disease (CKD); patient-reported outcomes; extrarenal symptoms; renal disease; activities of daily life.

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Autosomal dominant polycystic kidney disease (ADPKD) is unique among forms of chronic kidney disease (CKD) for the growth of cysts and enlargement of the kidneys, which occur well before kidney function declines. Past studies show that >60% of adult patients and 35% of children with ADPKD report pain, often despite normal kidney function (ie, decades before they reach end-stage renal disease [ESRD]).[1,2] There are many causes of pain in ADPKD, including cyst expansion under the renal capsule, traction on the renal pedicle, compression of nearby structures by kidney or liver cysts, or mechanical back pain that arises from an exaggerated pelvic tilt and increased lumbar lordosis.[3] The average rate of kidney growth among individuals with early disease (estimated glomerular filtration rate [eGFR] > 60 mL/min/1.73 m^2) was estimated at 5.3% ± 4.0% per year in the Consortium for Radiologic Imaging for the Study of Polycystic Kidney Disease (CRISP) Study, and this has been consistent across studies.[4-6] The kidneys are estimated to double in size over 8 years.[7] Liver cysts are very common, found in 85% of individuals older than 30 years in the CRISP cohort at baseline,[8] and contribute further to abdominal distension and symptoms related to increased abdominal mass. The continuous enlargement of the kidneys and liver occurs well before reaching ESRD and can be the source of severe morbidity that is different from that associated with declining kidney function or its treatment.

Formal study of the impact of ADPKD on quality of life has been limited. Although some studies have described symptoms,[9-11] the impact on daily living and the changes that occur with disease progression have not been systematically characterized. The largest study to date consisted of 101 patients with preserved GFR (eGFR > 70 mL/min/1.73 m^2) who completed the 36-Item Short Form Health Survey (SF-36) and at the same time had total kidney volume (TKV) measured by magnetic resonance imaging.[12] Results showed that SF-36 scores were well preserved and much better than those of other patients with CKD, but did not correlate with TKV. However, this study was limited by its small sample size, use of a generic health-related quality of life (HRQoL) instrument only, and lack of selection for patients at high risk for progression to ESRD (eg, presence of hypertension).

The HALT PKD trials consist of 2 randomized clinical trials that are examining combination angiotensin-converting enzyme (ACE)-inhibitor/angiotensin receptor blocker use compared with ACE-inhibitor use alone in hypertensive patients with eGFRs > 60 mL/min/1.73 m^2 (study A) and eGFRs of 25-60 mL/min/1.73 m^2 (study B).[13] Participants completed the SF-36[14] and a modified[9] version of the Wisconsin Brief Pain Survey[15] at baseline, prior to intervention. This provides a unique opportunity to describe the symptoms and their interference with daily living at early through to more advanced stages of ADPKD. We hypothesized that symptoms, including pain and mass effects, would be worse in individuals with larger kidneys. Kidney volume was measured by magnetic resonance imaging at the time of questionnaire administration in study A patients only. Although TKV was not measured in study B patients, we hypothesized that there would be a relationship of pain and symptoms with disease severity (as defined by eGFR) in study B patients given the known strong inverse correlation of GFR with TKV.[7,16,17]

METHODS

Study Population

The design and implementation of the HALT-PKD trials and the baseline characteristics of this population have been reported in detail elsewhere.[13] Briefly, the HALT-PKD trials are 2 prospective, randomized, double-blind, placebo-controlled, multicenter, interventional trials testing whether multilevel blockade of the renin-angiotensin-aldosterone system using ACE-inhibitor plus angiotensin receptor blocker (lisinopril plus telmisartan) combination therapy will delay the progression of kidney disease compared with ACE-inhibitor (lisinopril plus placebo) monotherapy in studies A and B, and whether low blood pressure control (95-100/60-75 mm Hg) will delay progression compared with standard control (120-130/70-80 mm Hg) in study A. In study A, patients are aged 15-49 years with eGFRs > 60 mL/min/1.73 m^2, whereas in study B, patients are aged 18-64 years with eGFRs of 25-60 mL/min/1.73 m^2. All patients undergo a formal screening visit to verify eligibility, diagnosis of ADPKD, and assignment to study A or study B based on eGFR. All HALT-PKD participants have hypertension, defined as current use of antihypertensive medications for blood pressure control or systolic blood pressure >130 mm Hg and/or diastolic blood pressure >80 mm Hg on 3 separate readings within the past year.

HRQoL Measurement

Patients completed the SF-36[18] and a modified version[9] of the Wisconsin Brief Pain Survey[15] while attending the baseline visit. The pain questionnaire consisted of questions that asked about the location, frequency, and intensity of pain; treatments that had been used and their effectiveness in relieving pain; and the degree to which pain interfered with activities of daily life. Patients completed the questionnaires without assistance from study staff.

Statistical Analyses

Patients were categorized into 3 groups based on their baseline eGFRs. eGFR was estimated from the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation standardized for body surface area of 1.73 m^2. The cutoff values for eGFR subgroups were 20-44, 45-60, and >60 mL/min/1.73 m^2. The lowest strata includes eGFR < 25 mL/min/1.73 m^2 (the cutoff eGFR for study eligibility) because this study is based on eGFR at the baseline visit, which declined from the screening visit eGFR in some subjects. Individual items on the pain questionnaire were primarily dichotomous (yes/no) and were analyzed as such. For questions that had Likert-type answers (never, rarely, sometimes, often, usually, and always), the first 2 responses were consolidated, as well as the last 3, resulting in 3 distinct groups. Pain questionnaire items were compared across eGFR groups within sexes using Fisher exact test or Kruskal-Wallis test. SF-36 component scores were summarized by sample means and compared across the 3 eGFR groups within sexes using the Kruskal-Wallis test. The

Table 1. Baseline Characteristics Across eGFR Subgroups

	eGFR > 60 (n = 609)	eGFR 45-60 (n = 221)	eGFR 20-44 (n = 213)	*P*
Age (y)	37.3 ± 9.3	47.0 ± 7.8	49.1 ± 8.2	<0.001[a]
Years since diagnosis	9.3 ± 8.4	14.4 ± 10.1	15.5 ± 10.8	<0.001[a]
Male sex	303 (49.8)	113 (51.1)	107 (50.2)	0.9
Race				0.9
White	562 (92.7)	209 (94.6)	199 (93.9)	
African American	16 (2.6)	5 (2.3)	5 (2.4)	
Other	28 (4.6)	7 (3.2)	8 (3.8)	
Highest education level				0.03[a]
Some high school	18 (3.0)	1 (0.5)	2 (0.9)	
Completed high school/equivalent	69 (11.4)	20 (9.1)	28 (13.2)	
Some college	138 (22.8)	51 (23.1)	55 (25.9)	
Completed college	233 (38.5)	77 (34.8)	64 (30.2)	
Graduate studies	148 (24.4)	72 (32.6)	63 (29.7)	
Marital status				<0.001[a]
Single	168 (27.7)	23 (10.4)	23 (10.9)	
Married	384 (63.4)	166 (75.1)	158 (74.5)	
Divorced/separated/widowed/other	54 (8.9)	32 (14.4)	40 (18.8)	
Working status				<0.001[a]
Full-time employment	436 (72.2)	154 (71.0)	150 (71.1)	
Part-time employment	69 (11.4)	24 (11.1)	23 (10.9)	
Student	35 (5.8)	2 (0.9)	2 (1.0)	
Retired	10 (1.7)	14 (6.5)	15 (7.1)	
Disabled/other	26 (4.4)	6 (2.7)	10 (4.5)	
Exercise				0.2
Aerobic activity ≥3 d/wk	228 (37.6)	87 (39.7)	80 (37.9)	
Aerobic activity <3 d/wk	72 (11.9)	17 (7.8)	15 (7.1)	
No regular aerobic activity	307 (50.6)	115 (52.5)	116 (55.0)	
Family history of ADPKD	524 (86.0)	190 (86.0)	189 (88.7)	0.5
Baseline eGFR	84.7 ± 18.3	52.4 ± 4.5	36.8 ± 5.3	<0.001[a]
TKV (mL)	1,198.0 ± 711.1 (n = 524)	1,821.0 ± 1,041.3 (n = 15)[b]	—	0.002[a]
Height-adjusted TKV (mL/m)	685.6 ± 393.1 (n = 512)	1,058.8 ± 579.7 (n = 15)	—	0.002[a]
TLV (mL)	1,949.8 ± 799.6 (n = 530)	2,224.6 ± 789.7 (n = 16)	—	0.09
Height-adjusted TLV (mL/m)	1,119.7 ± 457.4 (n = 519)	1,330.1 ± 521.5 (n = 15)	—	0.04[a]

Note: eGFRs expressed in mL/min/1.73 m^2. Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation.

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; eGFR estimated glomerular filtration rate; TKV, total kidney volume; TLV, total liver volume.

[a] $P \leq 0.05$.

[b] A small number of patients with baseline eGFRs < 60 mL/min/1.73 m^2 underwent magnetic resonance imaging because eGFR was >60 mL/min at the screening visit (when study arm was assigned).

relationship between pain and height-adjusted TKV (htTKV) was quantified by computing the median htTKV for each answer of a particular pain question. Spearman rank correlations (r) were calculated between htTKV and each SF-36 component to investigate the relationship between quality of life and kidney enlargement. In addition, median SF-36 component scores were compared with age- and sex-matched median component scores from the general population. In addition to within-sex analyses, pain questionnaire responses were compared between sexes while collapsing across eGFR and htTKV categories. Due to the between-sex variability in htTKV, analyses of kidney volume were conducted within and across sexes. For analyses that compared more than 2 groups, Bonferroni-adjusted significance levels were used to account for pairwise comparisons.

RESULTS

Study Participants

The SF-36 questionnaire and pain survey were completed at baseline by 552 of 558 (98.9%) and 555 of 558 (99.5%) study A patients and 479 of 486

(98.6%) and 480 of 486 (98.8%) study B patients, respectively. Baseline characteristics of participants across eGFR levels are as described in Table 1 and in a prior publication.[17] Patients in the subgroup with eGFRs of 20-44 mL/min/1.73 m^2 were older, had a longer time since diagnosis of ADPKD, were more likely to be married and have a college education, and were a little more likely to be retired or disabled. Mean eGFRs in the eGFR strata of 20-44, 45-60, and >60 mL/min/1.73 m^2, respectively, were 36.8 ± 5.3 (SD), 52.4 ± 4.5, and 84.7 ± 18.3 mL/min/1.73 m^2.

Pain and Effects on Daily Living Across eGFR Subgroups

Back pain was present in 51% of patients in the past 3 months, of whom 30% experienced it sometimes and 21% experienced it often, usually, or always (Table 2). Back pain frequency during the past 3 months did not vary by eGFR subgroup in men or women. Abdominal pain was reported as often, usually, or always by 14.6%, 11.2%, and 5.6% of men with eGFRs of 20-44, 45-60, and >60 mL/min/1.73 m^2 ($P = 0.05$), respectively; there was no difference in women by eGFR subgroups. The intensity of back, radicular, and abdominal pain on average or at their worst (data not shown) also was not associated with eGFR. Eighty of 450 (18%) patients treated for pain were "completely or very dissatisfied" with their physical ability to do what they wanted and this also did not vary by level of kidney function. However, pain was more likely to interfere with daily life among those with lower compared with higher eGFRs. More men with eGFRs of 20-44 mL/min/1.73 m^2 compared with men with eGFRs of 45-60 and >60 mL/min/1.73 m^2, respectively, reported that pain interfered moderately to extremely with work (14.0% vs 3.8% vs 10.2%; $P = 0.04$), strenuous activity (25.5% vs 14.2% vs 14.3%; $P = 0.02$), and social activities (12.5% vs 1.9% vs 7.5%; $P = 0.02$). More women with eGFRs of 20-44 mL/min/1.73 m^2 reported moderate to extreme interference with walking due to pain than women with eGFRs of 45-60 and >60 mL/min/1.73 m^2 (22.8% vs 18.3% vs 12.3%, respectively; $P = 0.03$). Over-the-counter and prescription pain medications were not used with increased frequency by patients with lower versus higher eGFRs. Women were more likely than men to experience pain, pain was more likely to interfere with daily activities, and use of pain medication was higher in women than men.

Early Satiety and Abdominal Fullness Across eGFR Subgroups

Approximately 20% of participants (varied across items) experienced symptoms relating to abdominal fullness (Fig 1A-D; Table S1, available as online supplementary material). Women experienced more abdominal fullness symptoms than men at all levels of eGFR. Women in the subgroup with eGFRs of 20-44 mL/min/1.73 m^2 were more likely than those in the subgroups with eGFRs of 45-60 and >60 mL/min/1.73 m^2 to report that their abdomens had gotten bigger in the past year (49.0%, 44.0%, and 33.8%, respectively; $P = 0.01$) and that they ate less sometimes, often, usually, or always due to abdominal fullness (39.2%, 30.3%, and 24.2%, respectively; $P = 0.05$). More men in the subgroup with eGFRs of 20-44 mL/min/1.73 m^2 compared with the subgroups with eGFRs of 45-60 and >60 mL/min/1.73 m^2 reported that abdominal fullness interfered with usual activities somewhat, often, usually, or always (20.6%, 15.3%, and 11.1%, respectively; $P = 0.2$) and reported early satiety (22.8%, 17.5%, and 13.9%, respectively; $P = 0.2$), but these differences did not reach statistical significance.

SF-36 Scores by eGFR

SF-36 scores were lower for patients with eGFRs of 20-44 mL/min/1.73 m^2 than patients with higher eGFRs for Physical Functioning, Role–Physical, General Health, Vitality, and the Physical Component Summary scores (Table 3). As shown in Fig 2, SF-36 scores in patients with ADPKD with eGFRs > 60 mL/min/1.73 m^2 were the same as or higher than the age-matched general population for all except the General Health domain. The same pattern was found for SF-36 scores for patients with ADPKD with eGFRs of 45-60 and 20-44 mL/min/1.73 m^2 compared with the age-matched general population.

Relationship of htTKV With Pain and Effects on Daily Living in Early Disease

Among patients with eGFRs > 60 mL/min/1.73 m^2, htTKV was not related to the frequency or intensity of back, abdominal, or radicular pain in females or males (Table S2). A relatively large proportion of patients reported that pain interfered with mood (17%), relations with others (11%), walking ability (11%), sleep (20%), work (13%), strenuous physical activity (18%), social activities (12%), and enjoyment of life (13%), although htKTV was not higher among those who reported these interferences compared with those who did not. Findings were consistent in males and females.

There were 101 of 540 (19%) patients with eGFRs > 60 mL/min/1.73 m^2 and htTKV > 1,000 mL/m, 70% of whom were male. We found that more of these patients reported back pain in the past 3 months than in the full population with eGFRs > 60 mL/min/1.73 m^2, although a sizable proportion (~40%) never or rarely experienced it. As shown in Table 4, htTKV was greater in patients experiencing more frequent back pain (1,373 vs 1,167 mL/m for often-always vs never-rarely, respectively; $P = 0.08$), experiencing

Table 2. Pain and Impact on Daily Living Within the Past 3 Months by eGFR Level

		Males (n = 517)					Females (n = 526)				
	All (N = 1,043)	eGFR > 60 (n = 303)	eGFR 45-60 (n = 108)	eGFR 20-44 (n = 106)	All	*P*[a]	eGFR > 60 (n = 306)	eGFR 45-60 (n = 113)	eGFR 20-44 (n = 107)	All	*P*[a]
Back pain frequency						0.6					0.2
Never-rarely	491 (49.0)	155 (54.0)	64 (59.8)	54 (52.4)	273 (54.9)		138 (47.1)	40 (36.7)	40 (38.8)	218 (43.2)	
Sometimes	298 (29.7)	85 (29.6)	29 (27.1)	28 (27.2)	142 (28.6)		83 (28.3)	40 (36.7)	33 (32.0)	156 (30.9)	
Often-usually-always	213 (21.3)	47 (16.4)	14 (13.1)	21 (20.4)	82 (16.5)		72 (24.6)	29 (26.6)	30 (29.1)	131 (25.9)	
Back pain intensity on average[b]	2.0 [1.0-3.0] (n = 775)	1.0 [1.0-3.0] (n = 218)	2.0 [1.0-3.0] (n = 79)	2.0 [1.0-3.0] (n = 80)	2.0 [1.0-3.0] (n = 377)	0.3	2.5 [1.0-4.0] (n = 222)	2.0 [1.0-4.0] (n = 85)	2.0 [1.0-4.0] (n = 91)	2.0 [1.0-4.0] (n = 398)	0.4
Back pain associated with gross hematuria	39 (5.0)	12 (5.5)	5 (6.2)	4 (4.9)	21 (5.5)	0.9	10 (4.5)	3 (3.6)	5 (5.5)	18 (4.5)	0.8
Radiculopathy frequency						0.08					0.1
Never-rarely	814 (81.9)	244 (85.3)	94 (90.4)	88 (86.3)	426 (86.6)		229 (79.0)	82 (74.5)	77 (75.5)	388 (77.3)	
Sometimes	125 (12.6)	29 (10.1)	9 (8.7)	14 (13.7)	52 (10.6)		39 (13.5)	14 (12.7)	20 (19.6)	73 (14.5)	
Often-usually-always	55 (5.5)	13 (4.5)	1 (1.0)	0 (0.0)	14 (2.8)		22 (7.6)	14 (12.7)	5 (4.9)	41 (8.2)	
Radicular pain intensity[b] on average	3.0 [1.0-5.0] (n = 336)	3.0 [1.0-5.0] (n = 84)	2.0 [1.0-3.0] (n = 28)	3.5 [1.5-6.5] (n = 32)	3.0 [1.0-5.0] (n = 144)	0.08[c]	4.0 [2.0-6.0] (n = 105)	4.0 [1.0-7.0] (n = 41)	4.0 [2.0-6.0] (n = 46)	4.0 [2.0-6.0] (n = 192)	0.9
Abdominal pain frequency						0.05[c]					0.8
Never-rarely	716 (72.0)	239 (83.9)	85 (79.4)	81 (78.6)	405 (81.8)		181 (62.4)	70 (64.2)	60 (59.4)	311 (62.2)	
Sometimes	160 (16.1)	30 (10.5)	10 (9.3)	7 (6.8)	47 (9.5)		62 (21.4)	25 (22.9)	26 (25.7)	113 (22.2)	
Often-usually-always	119 (12.0)	16 (5.6)	12 (11.2)	15 (14.6)	43 (8.7)		47 (16.2)	14 (12.8)	15 (14.8)	76 (15.2)	
Abdominal pain intensity[b] on average	2.0 [1.0-3.0] (n = 480)	2.0 [1.0-3.0] (n = 97)	1.0 [1.0-3.0] (n = 39)	2.0 [1.0-3.0] (n = 47)	2.0 [1.0-3.0] (n = 183)	0.4	2.0 [1.0-3.0] (n = 175)	2.0 [1.0-4.0] (n = 56)	2.0 [1.0-4.0] (n = 66)	2.0 [1.0-4.0] (n = 297)	0.9
Treatment for pain											
No treatment	586 (56.5)	195 (64.6)	75 (70.1)	66 (62.9)	336 (65.4)	0.4	147 (48.4)	54 (47.8)	49 (46.2)	250 (47.8)	0.9
OTC Medications	305 (29.4)	62 (20.5)	26 (24.3)	30 (28.6)	118 (23.0)	0.2	110 (36.2)	39 (34.5)	38 (35.9)	187 (35.8)	0.9
Prescription pain medications	125 (12.0)	28 (9.3)	6 (5.6)	11 (10.5)	45 (8.7)	0.4	40 (13.2)	20 (17.7)	20 (18.9)	80 (15.3)	0.2
Acupuncture, heat or cold, massage therapy	113 (10.8)	23 (7.6)	7 (6.5)	6 (5.7)	36 (7.0)	0.8	45 (14.7)	17 (15.0)	15 (14.0)	77 (14.6)	0.9
Surgical procedure	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0)	—	2 (0.7)	0 (0.0)	2 (1.9)	4 (0.8)	0.2
Pain affected physical ability to do what you want to						0.2					0.4
Completely/very dissatisfied	80 (17.8)	16 (16.2)	9 (25.7)	8 (19.5)	33 (18.9)		27 (17.1)	10 (17.2)	10 (16.9)	47 (17.1)	
Somewhat dissatisfied	79 (17.6)	13 (13.1)	5 (14.3)	12 (29.3)	30 (17.1)		23 (14.6)	11 (19.0)	15 (25.4)	49 (17.8)	
Somewhat satisfied	96 (21.3)	20 (20.2)	6 (17.1)	8 (19.5)	34 (19.4)		39 (24.7)	9 (15.5)	14 (23.7)	62 (22.5)	
Completely/very satisfied	195 (43.3)	50 (50.5)	15 (42.9)	13 (31.7)	78 (44.6)		69 (43.7)	28 (48.3)	20 (33.9)	117 (42.5)	

(Continued)

Table 2 (Cont'd). Pain and Impact on Daily Living Within the Past 3 Months by eGFR Level

	All	Males (n = 517)					Females (n = 526)				
	(N = 1,043)	eGFR > 60 (n = 303)	eGFR 45-60 (n = 108)	eGFR 20-44 (n = 106)	All	P[a]	eGFR > 60 (n = 306)	eGFR 45-60 (n = 113)	eGFR 20-44 (n = 107)	All	P[a]
Pain interfered moderately to extremely with:											
Mood	159 (16.0)	41 (14.4)	8 (17.5)	14 (14.1)	63 (12.9)	0.1	55 (18.8)	19 (17.4)	22 (21.8)	96 (19.1)	0.7
Relations with others	103 (10.4)	22 (7.7)	5 (4.7)	8 (8.0)	35 (7.19)	0.5	41 (14.0)	11 (10.0)	16 (15.8)	68 (13.5)	0.4
Walking ability	120 (12.1)	25 (8.8)	4 (3.8)	12 (12.0)	41 (8.4)	0.1	36 (12.3)	20 (18.3)	23 (22.8)	79 (15.7)	0.03[c]
Sleep	206 (20.8)	48 (16.9)	13 (12.4)	19 (19.2)	80 (16.4)	0.4	70 (23.9)	29 (26.6)	27 (26.7)	126 (25.1)	0.7
Work	129 (13.1)	29 (10.2)	4 (3.8)	14 (14.0)	47 (9.6)	0.04[c]	47 (16.5)	15 (13.9)	20 (20.2)	82 (16.7)	0.4
Strenuous physical activity	198 (21.1)	38 (14.2)	15 (14.3)	25 (25.5)	78 (16.6)	0.02[c]	60 (22.4)	29 (28.4)	31 (32.3)	120 (25.7)	0.1
Social activities or hobbies	107 (11.5)	20 (7.5)	2 (1.9)	12 (12.5)	34 (7.3)	0.02[c]	43 (16.0)	13 (12.9)	17 (18.1)	73 (15.8)	0.6
Enjoyment of life	140 (14.2)	34 (12.0)	10 (9.4)	13 (13.1)	57 (11.7)	0.6	41 (14.1)	19 (17.4)	23 (22.8)	83 (16.6)	0.1

Note: eGFRs expressed in mL/min/1.73 m^2. Values for categorical variables are given as number (percentage); values for continuous variables, as median [interquartile range], with numbers of participants with data indicated.

Abbreviations: eGFR, estimated glomerular filtration rate; OTC, over the counter.

[a]P values across eGFR groups. [b]Pain intensity score is based on a visual analogue scale with 0 as no pain and 10 as pain as bad as you can imagine.

[c]$P \leq 0.05$.

greater intensity of back pain (1,349 vs 1,073 mL/m^2 for 3 vs 0 pain on a Likert scale, respectively; $P = 0.03$), and/or reporting that pain interfered moderately to extremely with their mood (1,471 vs 1,246 mL/m for yes vs no, respectively; $P = 0.007$) and/or relations with others (1,496 vs 1,282 mL/m for yes vs no, respectively; $P = 0.02$) than those who do not have these symptoms or interferences. For other pain questions, patients experiencing greater pain or pain impact had greater htTKV, but these findings were not statistically significant.

Relationship of htTKV With Symptoms of Abdominal Fullness in Early Disease

In early disease (eGFR > 60 mL/min/1.73 m^2), htTKV was higher (1,011 mL/m) for men reporting that abdominal fullness interfered often, usually, or always with usual activities and eating compared with those reporting less (624.2 mL/m) or no interference (692.6 mL/m), but the number of severely affected men was small and differences were not statistically significant (Table S3). No associations were found between htTKV and symptoms relating to abdomen fullness in women with eGFRs > 60 mL/min/1.73 m^2. When restricted to individuals with htTKV > 1,000 mL/m, there were no differences in the statistical significance of relationships of htTKV and abdominal fullness symptoms from those shown in the full population with eGFRs > 60 mL/min/1.73 m^2 (data not shown).

Relationship of Total Liver Volume With Pain and Abdominal Fullness in Early Disease

There were 69 of 540 (13%) patients with eGFRs > 60 mL/min/1.73 m^2 and total liver volume (TLV) > 2,500 mL, 34 (49%) of whom were female. We found no relationship of TLV with responses to pain items in these patients (data not shown). Similarly, there were no differences in the relationship of TLV with abdominal mass symptoms (data not shown) from those found with htTKV (Table S3), with the exception that for "ate less due to abdominal fullness" in males, there was a statistically significant relationship of increasing TLV ($P = 0.03$), whereas it was borderline significant with htTKV ($P = 0.06$).

Correlation of htTKV With SF-36 Scores in Early Disease

Correlations between htTKV values and SF-36 domain scores were weak and none was statistically significant within men or women with eGFRs > 60 mL/min/1.73 m^2 (Table S4).

DISCUSSION

To our knowledge, this is the largest comprehensive study of the experiences in daily living among

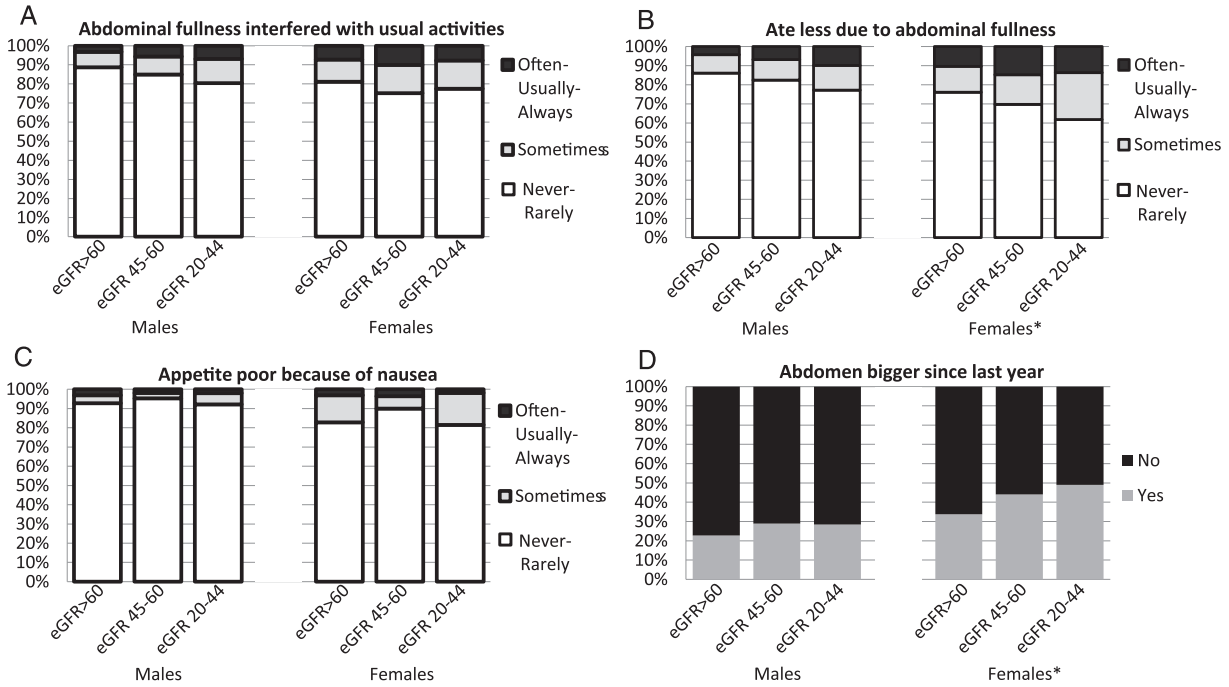

Figure 1. Reports from patients with autosomal dominant polycystic kidney disease of frequency of abdominal symptoms. (A) There were no statistically significant differences in the frequency at which abdominal fullness interfered with usual activities across estimated glomerular filtration rate (eGFR) strata in men or women. (B) Women with eGFRs of 20-44 mL/min/1.73 m^2 were more likely than women with eGFRs of 45-60 or >60 mL/min/1.73 m^2 to report that they ate less due to abdominal fullness ($P = 0.05$). No differences by eGFR were seen in men. *Significant $P < 0.05$ when comparing across eGFR groups. (C) There were no statistically significant differences in the frequency at which patients reported that their appetite was poor due to abdominal fullness across eGFR strata in men or women. (D) Women with eGFRs of 20-44 mL/min/1.73 m^2 were more likely than women with eGFRs of 45-60 or >60 mL/min/1.73 m^2 to report that their abdomen had gotten bigger over the past year ($P = 0.01$). No differences by eGFR were seen in men. *Significant $P < 0.05$ when comparing across eGFR groups.

individuals with ADPKD and eGFRs > 20 mL/min/1.73 m^2, with comparisons across htTKV and eGFR levels. As has been reported previously, pain is common, and even early in disease (eGFR > 60 mL/min/1.73 m^2), pain affects a relatively high proportion of patients with basic activities, such as walking (11%) and sleep (20%). However, we found that pain is not related to kidney size in early disease, except in individuals with the largest kidneys (htTKV > 1,000 mL/m). Our findings show that pain interferes with daily activities more in patients with eGFRs < 45 mL/min/1.73 m^2 compared with patients at higher eGFRs. Moreover, we observed that symptoms relating to abdominal fullness are greater for patients at lower versus higher eGFRs, but this was statistically significant only in women. The implication of these findings for research is that a minimum htTKV should be part of the eligibility criteria for clinical trials testing cyst-reducing therapies in early disease because effects on pain and HRQoL will be more likely to be found in patients with larger kidneys. Both pain and symptoms of abdominal fullness are correlated with eGFR at lower eGFR levels (20-44 mL/min/1.73 m^2). If organ enlargement is the reason for these symptoms, a therapy that reduces cyst growth, if applied early enough in the course of disease, may reduce the later development of these symptoms.

The absence of a strong association between kidney size and pain in early disease is unexpected, but is consistent with a prior study that showed no relationship of TKV with SF-36 Bodily Pain scores in a cohort of individuals with a mean eGFR of 65.1 ± 33.1 mL/min/1.73 m^2.[3] One possible explanation for this is that cyst size and location are more important than total number of cysts or total kidney size in causing pain. It also is possible that more patients experience pain, but do not recognize it until after they have had cyst reduction surgeries. Our study includes nearly 500 individuals with eGFRs < 60 mL/min/1.73 m^2 who would be expected to have higher htTKVs than those represented in the prior study, given the strong inverse correlation between eGFR and TKV.[7,16,17] We still do not find a strong relationship of disease stage (defined by eGFR) with patients' reports of pain frequency at eGFRs < 60 mL/min/1.73 m^2, although we observed an increase in reported interference by pain on daily activities in those with eGFRs of 20-44 versus 45-60 and >60 mL/min/1.73 m^2. This might suggest that patients are

Table 3. SF-36 Scores by eGFR Level

	All (N = 1,043)	Males (n = 517)					Females (n = 526)				
		eGFR > 60 (n = 303)	eGFR 45-60 (n = 108)	eGFR 20-44 (n = 106)	All	*P*[a]	eGFR > 60 (n = 306)	eGFR 45-60 (n = 113)	eGFR 20-44 (n = 107)	All	*P*[a]
Physical Functioning	89.66 ± 17.99 (n = 1,032)	91.57 ± 17.79 (n = 301)	90.66 ± 16.96 (n = 105)	90.13 ± 16.28 (n = 105)	91.09 ± 17.30 (n = 511)	0.03[b]	90.14 ± 17.31 (n = 303)	86.23 ± 21.17 (n = 113)	85.04 ± 18.56 (n = 105)	88.27 ± 18.56 (n = 521)	<0.001[b]
Role–Physical	88.37 ± 21.19 (n = 1,026)	91.31 ± 20.35 (n = 300)	91.65 ± 18.77 (n = 104)	88.16 ± 18.98 (n = 104)	90.74 ± 19.77 (n = 508)	0.006[b]	88.18 ± 20.87 (n = 302)	85.04 ± 23.22 (n = 112)	80.89 ± 24.38 (n = 104)	86.04 ± 22.27 (n = 518)	0.002[b]
Bodily Pain	77.09 ± 21.85 (n = 1,029)	80.44 ± 20.65 (n = 300)	82.98 ± 18.94 (n = 105)	77.24 ± 22.88 (n = 105)	80.30 ± 20.84 (n = 510)	0.2	75.27 ± 22.25 (n = 301)	72.83 ± 21.83 (n = 113)	71.28 ± 23.21 (n = 105)	73.93 ± 22.38 (n = 519)	0.1
General Health	64.77 ± 19.92 (n = 1,032)	66.90 ± 19.79 (n = 301)	67.76 ± 19.01 (n = 105)	62.00 ± 19.11 (n = 105)	66.07 ± 19.57 (n = 511)	0.05[b]	64.35 ± 19.99 (n = 303)	66.58 ± 18.98 (n = 113)	57.69 ± 21.08 (n = 105)	63.49 ± 20.20 (n = 521)	0.004[b]
Vitality	62.19 ± 19.63 (n = 1,030)	64.42 ± 18.43 (n = 300)	68.51 ± 18.16 (n = 105)	64.40 ± 17.49 (n = 105)	65.26 ± 18.23 (n = 510)	0.04[b]	59.81 ± 20.88 (n = 302)	61.67 ± 20.12 (n = 113)	54.64 ± 19.17 (n = 105)	59.17 ± 20.49 (n = 520)	0.01[b]
Social Functioning	87.69 ± 19.88 (n = 1,030)	89.75 ± 18.91 (n = 300)	92.62 ± 15.76 (n = 105)	88.33 ± 18.20 (n = 105)	90.05 ± 18.18 (n = 510)	0.1	86.13 ± 21.07 (n = 302)	85.07 ± 21.77 (n = 113)	83.57 ± 20.9 (n = 105)	85.38 ± 21.17 (n = 520)	0.3
Role–Emotional	90.84 ± 18.32 (n = 1,026)	91.56 ± 17.66 (n = 299)	93.02 ± 14.67 (n = 105)	92.94 ± 14.74 (n = 105)	92.14 ± 16.49 (n = 509)	0.8	89.31 ± 19.73 (n = 300)	89.82 ± 21.21 (n = 113)	89.98 ± 19.09 (n = 104)	89.56 ± 19.90 (n = 517)	0.4
Mental Health	78.27 ± 14.69 (n = 1,030)	78.44 ± 14.18 (n = 300)	81.43 ± 14.10 (n = 105)	78.81 ± 14.84 (n = 105)	79.13 ± 14.32 (n = 510)	0.1	76.44 ± 15.61 (n = 302)	79.53 ± 14.94 (n = 113)	77.98 ± 13.02 (n = 105)	77.42 ± 15.00 (n = 520)	0.06
PCS	51.33 ± 7.88 (n = 1,028)	52.70 ± 7.28 (n = 300)	52.58 ± 7.33 (n = 105)	50.87 ± 7.34 (n = 105)	52.29 ± 7.32 (n = 510)	0.02[b]	51.45 ± 7.85 (n = 301)	49.85 ± 8.05 (n = 113)	47.87 ± 9.24 (n = 104)	50.38 ± 8.30 (n = 518)	<0.001[b]
MCS	51.39 ± 8.90 (n = 1,028)	51.58 ± 8.26 (n = 300)	53.48 ± 7.85 (n = 105)	52.23 ± 7.72 (n = 105)	52.11 ± 8.09 (n = 510)	0.07	50.18 ± 9.81 (n = 301)	51.78 ± 10.02 (n = 113)	50.92 ± 8.38 (n = 104)	50.68 ± 9.59 (n = 518)	0.02[b]

Note: eGFRs expressed in mL/min/1.73 m^2. Values are given as mean ± standard deviation, with numbers of participants with data indicated.
Abbreviations: eGFR, estimated glomerular filtration rate; MCS, mental component summary; PCS, physical component summary; SF-36, 36-Item Short Form Health Survey.
[a] *P* value across eGFR groups.
[b] $P \leq 0.05$.

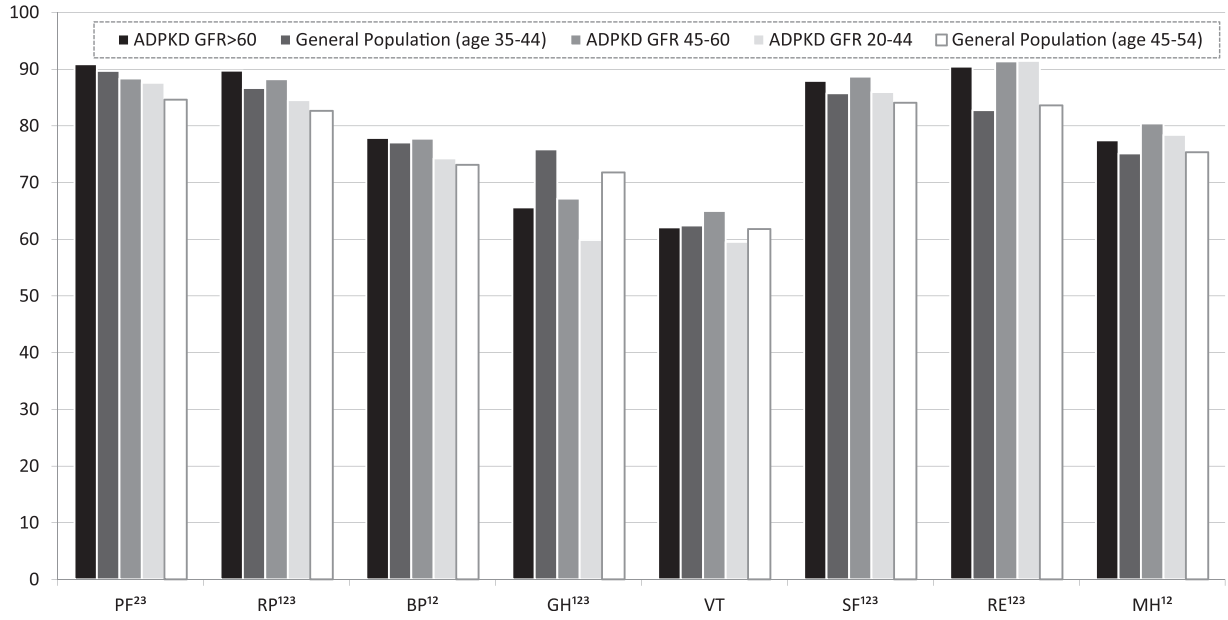

Figure 2. The 36-Item Short Form Health Survey (SF-36) scores in patients with autosomal dominant polycystic kidney disease (ADPKD) compared with age-matched healthy controls. SF-36 scores in patients with ADPKD with estimated glomerular filtration rates (eGFRs) > 60 mL/min/1.73 m^2 were the same as or higher than the age-matched general population for all except General Health (GH). The same pattern was found for SF-36 scores among those with eGFRs of 45-60 and 20-44 mL/min/1.73 m^2 compared with the age-matched general population. Abbreviations: BP, Bodily Pain; MH, Mental Health; PF, Physical Functioning; RE, Role–Emotional; RP, Role–Physical; SF, Social Functioning; VT, Vitality. [1]Significant difference between general population (aged 35-44 years) and patients with ADPKD with eGFRs > 60 mL/min/1.73 m^2; [2]significant difference between general population (aged 45-54 years) and patients with ADPKD with eGFRs of 45-60 mL/min/1.73 m^2; [3]significant difference between general population (aged 45-54 years) and patients with ADPKD with eGFRs of 20-44 mL/min/1.73 m^2. General population scores are based on respondents of the 1989 and 1990 General Social Survey (GSS), conducted by the National Opinion Research Center.[14]

restricting their activities, but they do not realize that it is because of pain. We believe that the increase in interference with daily activities with lower eGFRs is a reflection of symptoms due to organ enlargement (pain plus abdominal fullness symptoms) and an extension of the relationship of htTKV and pain found in patients with early disease (eGFR > 60 mL/min/1.73 m^2) and htTKV > 1,000 mL/m. Another possible explanation, other than organ enlargement, is that a patient's ability to cope with pain or abdominal fullness symptoms is reduced because of older age and/or reduced kidney function.

The finding of a relationship of abdominal fullness symptoms with lower eGFRs in females but not males may be due to larger liver size in females, which has been observed previously and is attributed to estrogen responsiveness of liver cysts.[8] Unfortunately, we cannot confirm this hypothesis because liver volumes were not measured in patients with eGFRs < 60 mL/min/1.73 m^2. That the enlarged organs as opposed to reduced kidney function are the cause of symptoms is supported by studies that show dramatic relief of symptoms and improvement in HRQoL after organ reduction therapy or removal.[19-22] Even modest reductions in liver volume (4.95% ± 6.77%) with 1-year treatment with octreotide in a blinded study led to improvements in Bodily Pain and Role–Emotional scales of the SF-36.[23] More recently, a large randomized trial involving patients with eGFRs > 60 mL/min/1.73 m^2 has shown that treatment with tolvaptan was associated with a significant reduction in the rate of htTKV growth (2.8% vs 5.5% per year) and episodes of severe pain (defined as need for hospitalization, narcotics, or surgical intervention).[6] The prevalence of less severe pain and quality of life at baseline or in response to treatment (to compare with this study) were not reported.

Our study would suggest that at the stages of disease represented here (largely CKD stages 1-3), most patients have symptoms, but they do not interfere greatly with daily living. The absence of an effect on HRQoL, despite the high frequency of pain, suggests that in most patients, these symptoms are mild or that patients have a tremendous resilience to adapt to their physical discomfort. This may be because they are comparing themselves to their family members with ADPKD who are on dialysis therapy or have died and thus view their current life circumstances favorably relative to them. The experience among individuals with CKD stage 4, which is not well represented here, and beyond has not been systematically studied. Case reports of patients referred for organ reduction

Table 4. Median htTKV Values by Pain Survey Responses in Participants With eGFR > 60 mL/min/1.73 m^2 and htTKV > 1,000 mL/m

	All (N = 101)			Males (n = 70)			Females (n = 31)		
	No. (%)	Median htTKV (mL/m)	*P*	No. (%)	Median htTKV (mL/m)	*P*	No. (%)	Median htTKV (mL/m)	*P*
Back pain frequency			0.08			0.7			0.04[a]
Never-rarely	41 (42.3)	1,167		27 (40.9)	1,296		14 (45.2)	1,111	
Sometimes	34 (35.1)	1,330		26 (39.4)	1,316		8 (25.8)	1,371	
Often-usually-always	22 (22.7)	1,373		13 (19.7)	1,365		9 (29.0)	1,496	
Back pain intensity on average			0.03[a]			0.04[a]			0.3
0	8 (11.0)	1,073		8 (15.4)	1,073		0 (0.00)	—	
1-2	37 (50.7)	1,305		31 (59.6)	1,327		6 (28.6)	1,134	
≥3	28 (38.4)	1,349		13 (25.0)	1,318		15 (71.4)	1,380	
Radiculopathy frequency			0.3			0.4			0.7
Never-rarely	74 (77.9)	1,242		49 (76.6)	1,282		25 (80.7)	1,167	
Sometimes	14 (14.7)	1,363		11 (17.2)	1,360		3 (9.7)	1,443	
Often-usually-always	7 (7.4)	1,318		4 (6.3)	1,367		3 (9.7)	1,315	
Abdominal pain frequency			0.2			0.8			0.1
Never-rarely	73 (75.3)	1,296		53 (80.3)	1,326		20 (64.5)	1,112	
Sometimes	16 (16.5)	1,314		10 (15.2)	1,289		6 (19.4)	1,356	
Often-usually-always	8 (8.3)	1,587		3 (4.6)	1,381		5 (16.1)	1,793	
Abdominal pain intensity on average			0.2			0.3			0.08
0	5 (10.9)	1,282		5 (19.2)	1,282		0 (0.0)	—	
1-2	24 (52.2)	1,336		13 (50.0)	1,427		11 (55.0)	1,167	
≥3	17 (37.0)	1,380		8 (30.8)	1,373		9 (45.0)	1,380	
Medications for pain									
OTC pain medications			0.5			0.9			0.3
No	75 (75.0)	1,296		52 (75.4)	1,300		23 (74.2)	1,171	
Yes	25 (25.0)	1,340		17 (24.6)	1,340		8 (25.8)	1,310	
Prescription pain medications			0.3			0.9			0.09
No	93 (93.0)	1,296		64 (92.8)	1,307		29 (93.55)	1,171	
Yes	7 (7.0)	1,381		5 (7.3)	1,305		2 (6.45)	1,801	
Acupuncture, heat or cold, massage			0.3			0.7			0.3
No	87 (86.1)	1,282		61 (87.1)	1,296		26 (83.9)	1,169	
Yes	14 (13.9)	1,339		9 (12.9)	1,318		5 (16.1)	1,443	
Pain affected physical ability to do what you want to[b]			0.9			0.5			0.8
Completely/very satisfied	13 (31.7)	1,222		6 (21.43)	1,212		7 (53.85)	1,332	
Somewhat satisfied	12 (29.3)	1,297		10 (35.71)	1,297		2 (15.38)	1,417	
Somewhat dissatisfied	6 (14.6)	1,317		4 (14.29)	1,367		2 (15.38)	1,243	
Completely/very dissatisfied	10 (24.4)	1,354		8 (28.57)	1,354		2 (15.38)	1,406	
Pain interfered moderately to extremely with:									
Mood			0.007[a]			0.1			0.02[a]
No	78 (81.3)	1,246		54 (83.1)	1,296		24 (77.4)	1,130	
Yes	18 (18.8)	1,471		11 (16.9)	1,446		7 (22.6)	1,496	
Relations with others			0.02[a]			0.4			0.02[a]
No	85 (88.5)	1,282		61 (93.9)	1,305		24 (77.4)	1,130	
Yes	11 (11.5)	1,496		4 (6.2)	1,596		7 (22.6)	1,496	
Walking ability			0.4			0.8			0.2
No	84 (87.5)	1,303		57 (87.7)	1,326		27 (87.1)	1,167	
Yes	12 (12.5)	1,310		8 (12.3)	1,300		4 (12.9)	1,405	
Sleep			0.5			0.5			0.09
No	74 (77.1)	1,296		49 (75.4)	1,326		25 (80.6)	1,167	
Yes	22 (22.9)	1,338		16 (24.6)	1,269		6 (19.4)	1,618	

(Continued)

Table 4 (Cont'd). Median htTKV Values by Pain Survey Responses in Participants With eGFR > 60 mL/min/1.73 m^2 and htTKV > 1,000 mL/m

	All (N = 101)			Males (n = 70)			Females (n = 31)		
	No. (%)	Median htTKV (mL/m)	*P*	No. (%)	Median htTKV (mL/m)	*P*	No. (%)	Median htTKV (mL/m)	*P*
Work			0.1			0.7			0.08
No	81 (84.4)	1,282		55 (84.6)	1,296		26 (83.9)	1,153	
Yes	15 (15.6)	1,360		10 (15.4)	1,339		5 (16.1)	1,496	
Strenuous physical activity			0.3			0.5			0.1
No	73 (82.0)	1,259		49 (80.3)	1,318		24 (85.7)	1,130	
Yes	16 (18.0)	1,332		12 (19.7)	1,332		4 (14.3)	1,485	
Social activities or hobbies			0.1			0.1			0.3
No	83 (91.2)	1,259		57 (91.9)	1,296		26 (89.7)	1,153	
Yes	8 (8.8)	1,371		5 (8.1)	1,381		3 (10.3)	1,315	
Enjoyment of life			0.6			0.5			0.09
No	80 (86.0)	1,289		54 (84.4)	1,315		26 (89.7)	1,153	
Yes	13 (13.9)	1,318		10 (15.6)	1,307		3 (10.3)	1,793	

Note: P value is for difference in htTKVs between questionnaire response categories.
Abbreviations: eGFR, estimated glomerular filtration rate; htTKV, height-adjusted total kidney volume; OTC, over-the-counter.
[a]$P \leq 0.05$.
[b]This question is filled out only by subset of subjects who reported they required treatment for pain in prior question.

therapies or removal (most of whom have reached ESRD) indicate a high degree of morbidity from the enlarged organs, including reduced mobility, imbalance, dyspnea, and progressive anorexia.[21,22] The number of patients who experience severe morbidity and have not reached the need for renal replacement therapy is unknown because we do not have large studies of the natural history, but if significant, would justify a medical therapy that reduced cyst growth even if it had no effect on the rate of kidney function decline.

A final observation that warrants brief comment is the finding that females had more pain and reported greater interference with daily life than males for almost all the pain questionnaire items. Numerous studies have shown differences in pain perception across sexes exposed to the same painful stimulus, with results showing that pain tolerance is greater in men.[24,25] An alternate explanation is that women experience more pain and abdominal fullness symptoms, which again may be due to larger total organ mass (liver plus kidney). Another possibility is that symptoms experienced with monthly menstrual cycles (bloating, cramps, and pain) may be heightened by the presence of enlarged ADPKD organs.

A major limitation of this study is that it is based on participants of a clinical trial who may not be representative of the ADPKD population at large. Prior kidney cyst reduction surgery was an exclusion criterion and patients with pain and debility generally do not involve themselves in clinical trials, particularly when travel is involved. Thus, these results may underestimate the true incidence of pain. We did not have TKV or TLV measurements for patients with eGFRs < 60 mL/min/1.73 m^2 and thus are unable to be certain whether the increase in abdominal fullness symptoms and pain interference at lower versus higher eGFRs is due to organ enlargement. The pain questionnaire used in this study has not been validated previously in an ADPKD population. If this instrument lacks reliability and validity in this population, stronger relationships of pain with htTKV and eGFR may exist than were reported here. Patients who did not speak English were not enrolled in the study; thus, these results may not generalize to non–English-speaking patients. The cohort largely represents patients with early disease. Individuals with eGFRs < 20 mL/min/1.73 m^2, including patients who have reached ESRD, are excluded from this study and it is likely that much more significant morbidity is seen in these patients. Finally, the cross-sectional nature of the data precludes making causal inferences.

In conclusion, in patients with early disease (GFR > 60 mL/min/1.73 m^2), pain is common, although it is not related to htTKV except at htTKV > 1,000 mL/m. Symptoms relating to abdominal fullness were greater for patients with reduced eGFRs, especially women, and may be related to organ enlargement. Further studies with measurement of htTKV and htTLV in people with eGFRs < 60 mL/min/1.73 m^2 are needed to better understand the role of organ enlargement in ADPKD with symptoms and HRQoL.

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SUPPLEMENTARY MATERIAL

Table S1: Symptoms of abdominal fullness in past 3 months by eGFR.

Table S2: htTKV values by pain survey responses in participants with eGFR > 60.

Table S3: htTKV values and symptoms of abdominal fullness in participants with eGFR > 60.

Table S4: Spearman correlations of SF-36 with htTKV overall and by sex.

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