# Pain and Obesity in Autosomal Dominant Polycystic Kidney Disease: A Post Hoc Analysis of the Halt Progression of Polycystic Kidney Disease (HALT-PKD) Studies

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**Rationale & Objective:** Pain is a frequent complication of autosomal dominant polycystic kidney disease (ADPKD) and includes back and abdominal pain. We hypothesized that in adults with early- and late-stage ADPKD, overweight and obesity are independently associated with greater self-reported back, abdominal, and radicular pain at baseline and that weight loss would be associated with decreased pain over a follow-up period.

**Study Design:** Post hoc analysis of pooled data from 2 randomized trials.

**Setting & Participants:** Participants in the HALT-PKD study A or B. 867 individuals were included in a cross-sectional analysis. 4,248 observations from 871 participants were included in a longitudinal analysis.

**Predictor:** Overweight and obesity (cross-sectional); annual change in weight as a time-varying predictor (longitudinal).

**Outcome:** Pain (Likert-scale responses; cross-sectional); annual change in pain (binary outcome of worsening pain or not worsening; longitudinal).

**Analytical Approach:** Multivariable ordinal logistic regression (cross-sectional); generalized estimating equation analysis (longitudinal).

**Results:** Participants were aged 42±10 years and baseline estimated glomerular filtration rate was 71±26 mL/min/1.73 m². Back, abdominal, and radicular pain were reported more frequently in individuals with increasing body mass index category (all *P* < 0.05 for trend). After multivariable adjustment, obesity was associated with increased odds of greater back and radicular pain, but not abdominal pain. Associations remained similar after further adjustment for baseline height-adjusted kidney and liver volume (study A only, n = 457); back pain: OR, 1.88 (95% CI, 1.15-3.08); and radicular pain: OR, 2.92 (95% CI, 1.45-5.91). Longitudinally (median follow-up, 5 years), weight loss (annual decrease in weight ≥ 4%) was associated with decreased adjusted odds of worsening back pain (OR, 0.87 [95% CI, 0.76-0.99]) compared with the reference group (stable weight).

**Limitations:** Post hoc, associative analysis.

**Conclusions:** In early- and late-stage ADPKD, obesity was associated with greater back and radicular pain independent of total kidney/liver volume. Mild weight loss was associated with favorable effects on back pain.

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease and among the most frequent causes of end-stage kidney disease.[1] It is characterized by the development of kidney cysts that progressively destroy the adjacent renal

parenchyma and massively enlarge the kidneys.[2] Pain is a frequent complication of ADPKD, afflicting most patients, and includes back and abdominal pain.[3]

Notably, the cause of chronic pain in ADPKD is often not definitive because patients experience a wide range of pain symptoms and intensity.[3] Within the general population, body mass index (BMI) and pain are positively associated, in part due to mechanical stress. Obesity is also linked to increased pain beyond increased mechanical load, including by metabolic and inflammatory mechanisms.[2,4] Interestingly, a glycolytic metabolic shift can

promote chronic pain.[5,6] Recent evidence also supports that ADPKD is characterized by metabolic reprogramming, including defective glucose metabolism (ie, the Warburg effect).[7,8]

Thus, although it is plausible that higher BMI is associated with greater pain in patients with ADPKD, this association has not been evaluated. The Halt Progression of Polycystic Kidney Disease (HALT-PKD) trials were randomized, double-blind, placebo-controlled studies in nondiabetic patients with early-stage (study A) or more advanced (study B) ADPKD.[9,10] Using data from HALT-PKD, we examined the cross-sectional association of baseline BMI categories with pain variables (back pain, radiating back pain, and abdominal pain), as well as the association of longitudinal changes in weight with changes in pain. We hypothesized that overweight and obesity would be independently associated with greater self-reported pain at baseline and that weight loss would be associated with reduced pain during the follow-up period.

### PLAIN-LANGUAGE SUMMARY

Pain is a frequent complication of autosomal dominant polycystic kidney disease (ADPKD) and includes back and abdominal pain. As a post hoc analysis of the HALT-PKD clinical trials, we evaluated the cross-sectional association of overweight and obesity with self-reported back, abdominal, and radiating back pain and the effect of mild weight loss on these pain variables during longitudinal follow-up of 5 years. We found that in individuals with early- and late-stage ADPKD, obesity was associated with greater likelihood of back and radiating back pain compared with normal-weight individuals independent of kidney size, liver size, and other factors. Additionally, mild weight loss was associated with favorable effects on back pain, suggesting that this may be a potential intervention to reduce back pain in ADPKD.

## METHODS

### Study Design

The HALT-PKD trials were 2 concurrent, prospective, randomized, double-blind, placebo-controlled, multi-center studies in participants with early- (study A) and late-stage (study B) ADPKD. The design of the studies has been described in detail previously.[9-11] Briefly, eligible participants were enrolled across 7 clinical sites between February 2006 and June 2009. All procedures were approved by the site institutional review boards, participants provided written informed consent, and the study adhered to the Declaration of Helsinki. Study A used a 2×2 factorial design and evaluated: (1) multilevel renin-angiotensin-aldosterone system blockade with an angiotensin-converting enzyme (ACE) inhibitor plus angiotensin receptor blocker (ARB) compared with ACE inhibitor plus placebo, and (2) low (95-110/60-75 mm Hg) compared with standard (120-130/70-80 mm Hg) blood pressure control. Study B randomly assigned participants to ACE inhibitor plus angiotensin receptor blocker compared with ACE inhibitor plus placebo. All participants in study B were also randomly assigned to a blood pressure goal of 110-130/70-80 mm Hg.

Participants in both studies had a known diagnosis of ADPKD, had either hypertension or high-normal blood pressure, and were nondiabetic. Study A participants were 15 to 49 years old with an estimated glomerular filtration rate (eGFR) > 60 mL/min/1.73 m$^2$ using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation. The primary outcome in study A was percent change in total kidney volume assessed by magnetic resonance imaging. Total kidney volume was assessed at baseline and 24, 48, and 60 months. Participants in study B were 18 to 64 years of age with eGFRs of 25 to 60 mL/min/1.73 m$^2$ using the MDRD Study equation. The

composite primary outcome in study B was time to death, end-stage kidney disease, or 50% reduction from baseline eGFR. Serum creatinine level was collected for calculation of eGFR at baseline, month 4, month 12, and every subsequent 6 months until the participant met an end point or was censored.

In the current post hoc analysis, we performed both a cross-sectional analysis of the association of baseline BMI with baseline self-reported pain and a longitudinal analysis of the association of annual change in weight with annual change in pain over the study duration. Of the 1,044 participants in the HALT-PKD trials (558 in study A and 486 in study B), 867 were included in cross-sectional analysis and 871 were included in the longitudinal analysis.

In the cross-sectional analysis, 22 were missing data for BMI, 3 were excluded due to classification of BMI as underweight (discussed later), 2 were missing data on self-reported pain, and an additional 150 were missing covariates (described next; the most frequently missing covariate was genotype [n = 84]), leaving 867 participants for the current analysis.

In the longitudinal analysis, 3 were excluded due to classification of BMI as underweight and an additional 161 were missing covariates (the most frequently missing covariate was genotype [n = 84]). We also identified 9 participants with errors in nonbaseline weight entries in the database that were not physiologically plausible and thus were excluded from the analysis (weight changed ≥30% annually, which could not be logically corrected by conversion of units [kg vs lb]; this correction was applied when logical). Thus, 871 participants were included in the longitudinal analysis.

Total kidney volume and total liver volume were assessed only in study A and were available for 457 participants in the cross-sectional analysis and 465 participants in the longitudinal analysis.

### Study Variables

Participants were categorized based on BMI as normal weight (18.5-24.9 kg/m$^2$), overweight (25.0-29.9 kg/m$^2$), or obese (≥30 kg/m$^2$) using the National Heart, Lung, and Blood Institute criteria.[12] A small number of participants classified as underweight (n = 3) were excluded from the analysis because underweight individuals may differ physiologically from those of normal weight.

Study participants completed a modified version of the Wisconsin Brief Pain Survey at their baseline study visit and then annually throughout the study.[13] Included in the pain questionnaire were questions about the location and frequency of "nagging or chronic" pain during the past 3 months. In the current analysis, we focused on the frequency of back, abdominal, and radicular (back pain radiating to the buttock, hips, or legs) pain as dependent variables. These questions had Likert-type answers (never,

rarely, sometimes, often, usually, and always). We consolidated the responses into 3 categories: (1) never or rarely, (2) sometimes, and (3) often, usually, or always, consistent with the reporting of the baseline pain data from HALT-PKD.[13] The questionnaire also evaluated pain medication use; we provided these descriptive results according to BMI category but did not consider this to be a confounding variable. For the cross-sectional analysis, we also performed a stratified analysis according to baseline pain medication use (none vs over the counter or prescription).

Confounders related to BMI and the dependent variables, all measured at baseline, were selected a priori as potential covariates. Race was categorized as White and non-White, as determined by self-report. Education, marital status, employment, and exercise were also determined by self-report. eGFR was calculated throughout the study using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation using serum creatinine concentrations measured by a central laboratory (Cleveland Clinic Foundation Reference Laboratory).[9,10] Mutation analysis was performed previously, with mutation class categorized as PKD1 truncating mutations, PKD1 nontruncating mutations, PKD2 mutations, and no mutation detected/other disease gene.[14] In study A, magnetic resonance imaging was performed at each study site using a protocol developed by the HALT PKD Imaging Subcommittee to determine total kidney volume (as well as total liver volume).[11,15]

### Statistical Analyses

In the cross-sectional analysis, the baseline association of overweight and obesity with frequency of self-reported pain (back, abdominal, and radicular) was assessed using multivariable ordinal logistic regression models. Participants were classified into 3 categories according to BMI as described (normal weight, overweight, and obese). The outcome was 3 categories of pain (never/rarely, sometimes, and often/usually/always). Odds ratios were calculated with the normal-weight group serving as the reference.

The initial model was unadjusted, then multivariable-adjusted models were performed to include age, sex, race/ethnicity, education, marital status, employment status, and exercise (model 1), model 1 plus eGFR (CKD-EPI) (model 2), and model 2 plus mutation class (model 3). Height-corrected total kidney volume and total liver volume were added to model 3 (model 4) for participants from study A with the information available (n = 457).

In the longitudinal analysis, a generalized estimating equation analysis was used to evaluate the association of change in weight with change in pain over the study duration. The predictor variable was annual change in weight (calculated using weight measured in a given year [collected annually] as compared with the previous year's weight), classified as decreasing by ≥4%, increasing by ≥4%, or remaining stable (change of <4%). A change in

weight of 4% was selected because 5% weight loss is typically the threshold for moderate weight loss in the general population,[16] and relaxing this threshold to 4% greatly increased the number of observations that could be included as a weight increase or decrease in this cohort, increasing power. Importantly, mild weight loss (<5%) still has significant clinical benefits.[17-19] We also considered change in BMI as a continuous variable.

The dependent variable was change in pain, classified as changing between never/rarely/sometimes and often/usually/always, and was defined as a binary outcome variable of pain worsening or not. A binary outcome was selected to simplify the clinical interpretation of the results, as opposed to an ordinal outcome variable, and to ensure high enough frequency of all cells in the models.

It was assumed that the association between change in weight during the past year and change in pain during the year is constant and that weight can change over time. This assumption was confirmed by correlation between the 2 variables over time using the raw data. Because the correlation at 96 months increased slightly for back pain and abdominal pain compared with other time points, we performed analysis with data at 96 months excluded and found that all conclusions were unchanged. We also noted that the number of participants remaining at 96 months was much smaller than earlier time points (29 vs 212 to 772); thus, the higher correlation could be just because of random error. Thus, the assumption of constant association could be considered approximately met and results from analyses including all data (ie, all participants with at least 2 measurements of the predictor and outcome variables, and necessary covariates) were presented.

All baseline covariates and their interactions with change in weight (ie, increase, decrease, and stable) were included in the full model. Time-varying covariates were not included in the model because not all covariates were updated throughout the course of the study. The initial model was unadjusted, then multivariable-adjusted models were performed to include age, sex, race/ethnicity, education, marital status, employment status, exercise, and randomly assigned study group (model 1), model 1 plus eGFR (CKD-EPI; model 2), and model 2 plus mutation class (model 3). Height-corrected total kidney volume and total liver volume could not be included as covariates because the models failed to converge. Stable weight was considered as the reference group.

In all analyses, baseline characteristics were summarized by BMI categories and presented as mean ± standard deviation or median with interquartile range for continuous variables and number and percentage for categorical variables. Comparisons across BMI categories were made using a $\chi^2$ test for categorical data and analysis of variance for continuous variables.

Two-tailed $P < 0.05$ was considered statistically significant for all analyses. All statistical analyses were performed using SAS, version 9.4 (SAS Institute).

**Table 1.** Baseline Characteristics of Study Participants From HALT-PKD Study A and B Included in the Cross-sectional Analysis According to BMI Category

| Variable | Normal Weight (BMI 18.5-24.9 kg/m²) (n = 294) | Overweight (BMI 25-29.9 kg/m²) (n = 319) | Obese (BMI ≥ 30 kg/m²) (n = 254) | Entire Cohort (n = 867) | P |
|---|---|---|---|---|---|
| Age, y | 42 ± 11 | 43 ± 10 | 42 ± 10 | 42 ± 10 | 0.13 |
| Male sex | 104 (35.4%) | 193 (60.5%) | 133 (52.4%) | 430 (49.6%) | <0.001 |
| White race | 272 (92.5%) | 303 (95.0%) | 240 (94.5%) | 815 (94%) | 0.41 |
| Education | | | | | 0.02 |
| ≤High school | 31 (10.5%) | 43 (13.5%) | 39 (15.4%) | 113 (13%) | |
| Some college | 52 (17.7%) | 77 (24.1%) | 73 (28.7%) | 202 (23.3%) | |
| College | 127 (43.2%) | 115 (36.1%) | 85 (33.5%) | 327 (37.7%) | |
| Graduate school | 84 (28.6%) | 84 (26.3%) | 57 (22.4%) | 225 (26.0%) | |
| Marital status | | | | | 0.03 |
| Single | 68 (23.1%) | 53 (16.6%) | 48 (18.9%) | 169 (19.5%) | |
| Married | 188 (63.9%) | 236 (74.0%) | 166 (65.4%) | 590 (68.1%) | |
| Divorced, widowed, separated, or other | 38 (12.9%) | 30 (9.4%) | 40 (15.7%) | 108 (12.5%) | |
| Employment | | | | | <0.001 |
| Full-time | 176 (59.9%) | 243 (76.2%) | 180 (70.9%) | 599 (69.1%) | |
| Part-time | 38 (12.9%) | 26 (8.2%) | 17 (6.7%) | 81 (9.3%) | |
| Student | 31 (10.5%) | 8 (2.5%) | 16 (6.3%) | 55 (6.3%) | |
| Retired | 11 (3.7%) | 11 (3.4%) | 13 (5.1%) | 35 (4.0%) | |
| Homemaker, disabled, or other | 38 (12.9%) | 31 (9.7%) | 28 (11.0%) | 97 (4.0%) | |
| Exercise | | | | | <0.001 |
| ≤2 d/wk | 223 (75.9%) | 217 (68.0%) | 161 (63.4%) | 601 (69.3%) | |
| 3-4 d/wk | 52 (17.7%) | 70 (21.9%) | 46 (18.1%) | 168 (19.4%) | |
| ≥5 d/wk | 19 (6.5%) | 32 (10.0%) | 47 (18.5%) | 98 (11.3%) | |
| Pain medications | | | | | 0.003 |
| None | 182 (61.9%) | 203 (63.6%) | 123 (48.4%) | 508 (58.6%) | |
| Over the counter | 78 (26.5%) | 91 (28.5%) | 91 (35.8%) | 260 (30.0%) | |
| Prescription | 23 (7.8%) | 17 (5.3%) | 27 (10.6%) | 67 (7.7%) | |
| Not reported | 11 (3.7%) | 8 (2.5%) | 13 (5.1%) | 32 (3.7%) | |
| BMI, kg/m² | 22.4 ± 1.6 | 27.4 ± 1.4 | 34.3 ± 3.8 | 27.7 ± 5.3 | <0.001 |
| CKD-EPI eGFR, mL/min/1.73 m² | 74.9 ± 26.4 | 70.8 ± 25.5 | 67.0 ± 26.4 | 71.1 ± 26.2 | 0.002 |
| Height-corrected TKV, mL/m | 562 [390-858] | 568 [398-916] | 646 [448-864] | 587 [402-870] | 0.20 |
| Height-corrected liver volume, mL/m | 932 [825-1,060] | 1,043 [947-1,155] | 1,165 [1,044-1,360] | 1,035 [903-1,195] | <0.001 |
| Mutation class | | | | | 0.14 |
| PKD1 truncating | 166 (56.5%) | 154 (48.3%) | 115 (45.3%) | 435 (50.2%) | |
| PKD1 nontruncating | 71 (24.1%) | 92 (28.8%) | 76 (29.9%) | 239 (27.6%) | |
| PKD2 | 37 (12.6%) | 54 (16.9%) | 40 (15.7%) | 131 (15.1%) | |
| No mutation detected | 20 (6.8%) | 19 (6.0%) | 23 (9.1%) | 62 (7.2%) | |

*Note:* Data are mean ± standard deviation, number (percent), or median [interquartile range]. TKV and total liver volume were measured only in HALT-PKD study A (n = 457).
Abbreviations: BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HALT-PKD, Halt Progression of Polycystic Kidney Disease; TKV, total kidney volume.

# RESULTS

## Cross-sectional Analysis

### Participant Characteristics at Baseline for the Cross-sectional Analysis

A total of 867 participants with ADPKD who participated in HALT-PKD study A or B were included in the cross-sectional analysis of the association of baseline overweight and obesity with pain. Individuals with overweight or obesity were more likely to be men, work full-time, and exercise regularly and less likely to have higher education (Table 1). Overweight individuals were more likely to be married. CKD-EPI eGFR was lower and height-corrected liver volume was greater with increasing BMI category.
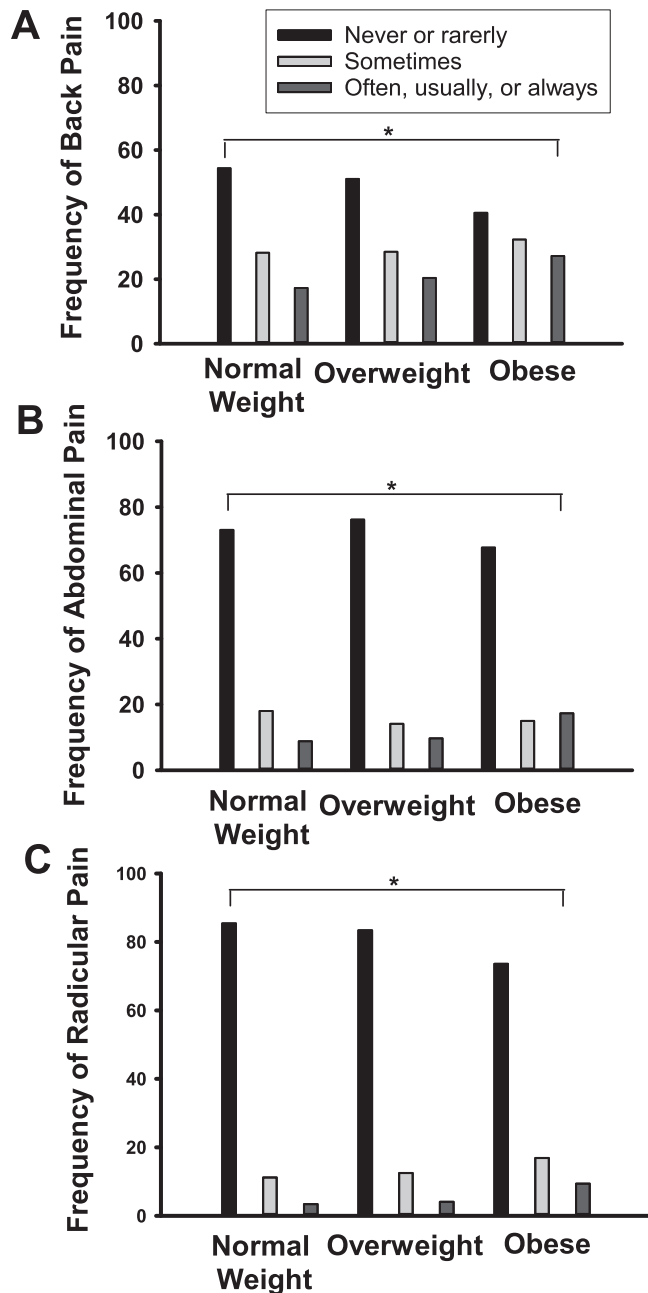
**Figure 1.** Increased frequency of back, abdominal, and radicular pain in autosomal dominant polycystic kidney disease (ADPKD) with overweight and obesity. Frequency of back, abdominal, and radicular pain were all greater with increasing body mass index category in participants in the Halt Progression of Polycystic Kidney Disease (HALT-PKD) study A and B. *$P < 0.05$ by $\chi^2$ test.

## Frequency of Pain and Pain Medication Use at Baseline According to BMI Category

Back, abdominal, and radicular pain were reported more frequently with increasing BMI category, with the greatest frequencies of pain reported in the obese group ($P < 0.05$ for trend; Fig 1). Use of over-the-counter and prescription pain medications was greatest in individuals with obesity (Table 1).

## Association of Overweight and Obesity With Pain at Baseline

After adjustment for age, sex, race/ethnicity, education, marital status, employment status, exercise, CKD-EPI eGFR, and mutation class, obesity was associated with increased odds of back pain and radicular pain compared with the normal-weight group (Table 2). There was no difference in odds of abdominal pain according to BMI category. Results were similar when BMI was considered as a continuous variable: odds ratios per 5-unit increase in BMI: 1.19 (95% CI, 1.050 1.35; back pain), 1.06 (95% CI, 0.92-1.23; abdominal pain), and 1.36 (95% CI, 1.16-1.60; radicular pain). After further adjustment for height-corrected total kidney volume and height-corrected liver volume (study A only), the association of obesity with increased back and radicular pain was similar (Table 2).

Analyses were also stratified according to baseline pain medication use. There was no statistical interaction between BMI category and pain medication use for any pain outcomes ($P \geq 0.10$). However, in individuals who reported no pain medication use, obese individuals had a greater odds of back pain (1.88 [95% CI, 1.12-3.15]), but not radicular (2.25 [95% CI, 0.89-5.66]) or abdominal pain (0.70 [95% CI, 0.35-1.42]), compared with the normal-BMI category (model 3). In contrast, among individuals who reported over-the-counter or prescription pain medication use, obesity was associated with greater odds of radicular pain (2.59 [95% CI, 1.39-4.83]) but not back (1.25 [95% CI, 0.74-2.11] or abdominal pain (1.68 [95% CI, 0.96-2.94]) compared with the normal-BMI category (model 3).

## Longitudinal Analysis

### Participant Characteristics at Baseline for the Longitudinal Analysis

A total of 871 participants with ADPKD who participated in HALT-PKD study A or B were included in the analysis of change in weight with change in pain over the study duration. The median follow-up period was 60 (interquartile range, 48-72) months. Baseline characteristics were very similar to the cohort included in the cross-sectional analysis (Table S1). Of note, it is not possible to categorize participants according to annual change in weight because this was calculated on an annual basis in the generalized estimating equation model. Thus, an individual participant could fall into multiple change in weight categories (ie, loss ≥4%, no change, and gain ≥4%) across the study duration. There were 4,768 observations of annual change in weight and pain. Of these, 615 were of decreased weight (13%), 3,362 were of stable weight (71%), and 791 (17%) were of increased weight.

## Association of Change in Weight With Change in Pain Over Time

Using generalized estimating equation models incorporating all available weight and pain measurements, the

**Table 2.** Associations (by Ordinal Logistic Regression) of BMI Categories With Greater Pain at Baseline

| Model | Normal Weight (BMI 18.5-24.9 kg/m$^2$) (n = 294) | Overweight (BMI 25-29.9 kg/m$^2$) (n = 319) | Obese (BMI ≥30 kg/m$^2$) (n = 254) |
|---|---|---|---|
| Back pain | | | |
| Unadjusted | Reference | 1.16 (0.86-1.57) | 1.75 (1.28-2.41) |
| Model 1 | Reference | 1.34 (0.97-1.85) | 1.80 (1.29-2.51) |
| Model 2 | Reference | 1.34 (0.97-1.85) | 1.80 (1.28-2.52) |
| Model 3 | Reference | 1.35 (0.98-1.87) | 1.80 (1.29-2.53) |
| Model 4 | Reference | 1.40 (0.89-2.21) | 1.88 (1.15-3.08) |
| Abdominal pain | | | |
| Unadjusted | Reference | 0.88 (0.61-1.26) | 1.40 (0.98-2.02) |
| Model 1 | Reference | 1.03 (0.69-1.52) | 1.42 (0.96-2.09) |
| Model 2 | Reference | 1.03 (0.69-1.52) | 1.42 (0.96-2.10) |
| Model 3 | Reference | 1.03 (0.70-1.53) | 1.42 (0.96-2.12) |
| Model 4 | Reference | 0.72 (0.41-1.26) | 0.88 (0.49-1.58) |
| Radicular pain | | | |
| Unadjusted | Reference | 1.13 (0.72-1.77) | 2.11 (1.36-3.26) |
| Model 1 | Reference | 1.44 (0.90-2.30) | 2.40 (1.52-3.78) |
| Model 2 | Reference | 1.44 (0.90-2.30) | 2.45 (1.55-3.88) |
| Model 3 | Reference | 1.44 (0.90-2.31) | 2.55 (1.60-4.04) |
| Model 4 | Reference | 2.31 [1.20, 4.47] | 2.92 [1.45, 5.91] |

*Note:* Values are odds ratio (95% CI). Cross-sectional analysis of HALT Study A and Study B, n = 867. Radicular pain refers to back pain radiating into the buttocks, hips, or legs. Model 1, adjusted for age, sex, race/ethnicity, education, marital status, employment status, and exercise. Model 2, model 1 plus estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration equation). Model 3, model 2 plus mutation class. Model 4, model 3 plus baseline height-adjusted total kidney volume and liver volume. Total kidney volume and liver volume were measured in only HALT-PKD study A (n = 457)
Abbreviation: BMI, body mass index; HALT-PKD, Halt Progression of Polycystic Kidney Disease.

association of change in weight with change in pain was evaluated across the study duration. In the fully adjusted model, an annual decrease in weight ≥4% was associated with reduced odds of worsening back pain compared with the reference group (stable weight), as reflected by changes in self-reported pain using Likert-scale responses (Table 3). Results were slightly attenuated when BMI was considered as a continuous variable (BMI change × time, P = 0.15; model 3), consistent with the differential effects of weight loss versus weight gain in the categorical analysis. There was no difference across groups (weight decrease ≥ 4%, stable weight, and weight increase ≥ 4%) in change in abdominal and radicular pain. Results were similar when change in BMI was considered as a continuous variable (interaction P = 0.23 and P = 0.69, respectively).

## DISCUSSION

We have reported for the first time that back, abdominal, and radicular pain occur more frequently in individuals with ADPKD with obesity and that the association of obesity with back and radicular pain is independent of other covariates. Notably, these associations were independent of height-corrected total kidney volume and total liver volume, suggesting that potentially modifiable factors (eg, musculoskeletal issues) may contribute to pain in these regions. Although there was no statistical interaction between BMI and pain medication use for any pain outcomes, the association of obesity with back pain was observed only in individuals not using pain medications,

whereas the association of obesity with radicular pain was observed only in individuals using pain medications. Additionally, modest weight loss over time was independently associated with reduced odds of worsening back pain as compared with weight stability. Although these findings are not entirely unique to a population of patients with ADPKD, contributing mechanisms may be in part ADPKD specific. Additionally, because pain is a common affliction in patients with ADPKD,[3] these findings are of important clinical relevance to this population.

Chronic back and/or abdominal pain are reported by more than half the patients with ADPKD and is the most frequent symptom that leads to the diagnosis of ADPKD.[20] It occurs early and continues throughout the course of the disease.[3] The baseline pain data from the HALT-PKD study have been reported previously and indicated a high prevalence of back pain (50% of participants), consistent with prior literature.[13] Notably, there was no association between pain and height-corrected total kidney volume, with the exception of individuals with large kidneys (height-corrected total kidney volume > 1,000 mL/m), although symptoms related to abdominal fullness and abdominal pain were greater in individuals with more advanced disease (lower eGFR). This suggests that factors other than kidney size alone are contributing to pain in patients with ADPKD and is consistent with our current finding that the association of obesity with back pain was independent of height-corrected total kidney volume and height-corrected liver volume.

In the general population, greater BMI and in particular central obesity are associated with greater pain intensity,

**Table 3.** Associations by a Generalized Estimating Equation Analysis of Changing Weight (≥4% per year) With Worsening Pain Over Time

| Model | Weight Decreased ≥4% Annually | Weight Stable | Weight Increased ≥4% Annually |
|---|---|---|---|
| **Increased back pain** | | | |
| Unadjusted | 0.88 (0.80-1.02) | Reference | 1.04 (0.93-1.16) |
| Model 1 | 0.86 (0.76-0.99) | Reference | 1.02 (0.91-1.14) |
| Model 2 | 0.87 (0.76-0.99) | Reference | 1.02 (0.91-1.14) |
| Model 3 | 0.87 (0.76-0.99) | Reference | 1.02 (0.91-1.14) |
| **Increased abdominal pain** | | | |
| Unadjusted | 1.08 (0.96-1.22) | Reference | 1.03 (0.92-1.15) |
| Model 1 | 1.07 (0.94-1.21) | Reference | 1.01 (0.90-1.23) |
| Model 2 | 1.07 (0.94-1.22) | Reference | 1.01 (0.90-1.25) |
| Model 3 | 1.07 (0.94-1.22) | Reference | 1.00 (0.89-1.12) |
| **Increased radicular pain** | | | |
| Unadjusted | 0.98 (0.85-1.12) | Reference | 1.02 (0.90-1.15) |
| Model 1 | 0.95 (0.82-1.10) | Reference | 0.97 (0.85-1.11) |
| Model 2 | 0.94 (0.81-1.09) | Reference | 0.97 (0.81-1.11) |
| Model 3 | 0.95 (0.81-1.10) | Reference | 0.97 (0.85-1.11) |

*Note:* Values are odds ratio (95% CI). Longitudinal analysis of the Halt Progression of Polycystic Kidney Disease study A and study B, n = 871. Analysis was performed using a generalized estimating equation model incorporating all available weight and pain measurements. Change in weight was calculated annually, thus the number per category of weight change varies from year to year. Radicular pain refers to back pain radiating into the buttocks, hips, or legs. Model 1 adjusted for age, sex, race/ethnicity, education, marital status, employment status, exercise, and randomization groups. Model 2, model 1 plus estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration equation). Model 3, model 2 plus mutation class.

chronic pain, and less pain relief from treatment.[2,21-25] Greater fat mass, but not lean mass, as evaluated by dual radiograph absorptiometry, has been linked to higher levels of low back pain.[26] Reduced back pain has been reported following bariatric surgery in individuals with obesity.[27,28] Obesity can be associated with pain across various locations in the body, suggesting that pain is not driven solely by musculoskeletal factors.[4,22,29] Interestingly, behavioral weight loss treatment also reduces pain interference in overweight and obese women with fibromyalgia,[30,31] as well as levels of circulating inflammatory markers (ie, C-reactive protein and interleukin 6).[31] Similarly, weight loss has been shown to reduce osteoarthritis[32] and migraine[33] pain.

Mechanistically, increased abdominal girth resulting from enlarged kidneys in ADPKD and/or increased adiposity can promote increased lumbar lordosis (ie, pelvic tilt), accelerating degenerative changes in the spine.[34] This can lead to lumbodorsal muscle hypertrophy, which suggests a mechanical form of back pain that tends to get worse over time.[34] Lumbodorsal muscle hypertrophy was not measured in the HALT-PKD study; however, the assessment of this parameter and evaluation of its association with pain in a large cohort of patients with ADPKD is an interesting future direction. Various approaches to treat ADPKD-associated mechanical back pain have been described previously.[34] Additionally, in the general population, reductions in body fat can reduce pain by alleviating mechanical stress.[35]

Greater BMI can also promote pain through mechanisms beyond musculoskeletal factors. A metabolic hypothesis of pain in obesity has gained increasing support as an important mechanism contributing to pain.[4] The presence of metabolic syndrome is independently associated with higher pain scores in older adults.[25] Overlapping metabolic pathways have also been noted for obesity and migraines.[36] Interestingly, a metabolic shift toward glycolysis promotes chronic pain in mouse models through inflammatory mechanisms.[5,6] Because recent evidence also indicates metabolic reprogramming in ADPKD, including defective glucose metabolism favoring aerobic glycolysis,[8] it is biologically plausible that these processes could promote pain symptoms in ADPKD.

Chronic low-grade inflammation can also lower the pain threshold, causing or exacerbating pain.[37] Animal studies support that Western or high-fat diets can promote hypersensitivity to pain, mediated in part by increased levels of proinflammatory cytokines.[38,39] Additionally, excess adiposity can promote the release of leptin and proinflammatory cytokines, exacerbating states of pain.[40] This is consistent with evidence in humans that obesity is associated with increased pain sensitivity.[41] Even mild weight loss is associated with reduced concentrations of proinflammatory biomarkers.[17,42] Notably, chronic inflammation is evident in individuals with ADPKD, even at early stages.[43]

Of note, obesity may additionally contribute to pain through behavioral and psychosocial factors, such as reduced exercise and increased depression.[4] Perhaps surprisingly, individuals with obesity in the HALT-PKD study self-reported more frequent exercise than normal-weight individuals. Exercise and pain are likely complexly related because exercise could potentially alleviate pain, whereas pain could also inhibit exercise. Depression, which is also common in ADPKD,[44] has a high prevalence in obesity and may play a role in facilitating comorbid pain.[45]

The major strength of this study is the large sample size of participants with ADPKD assessed in the setting of a clinical trial with comprehensive characterization of covariates. The clinical relevance of the research questions addressed is an additional important strength because the association of obesity with pain in ADPKD has not previously been investigated. Furthermore, our longitudinal assessment of the association of changes in weight with changes in pain to complement our cross-sectional findings enhances the clinical relevance of our results.

There are also several limitations. This was a post hoc associative analysis and 17% of participants from the HALT-PKD studies were missing covariates and thus were excluded from the current analysis. There may also be residual confounding. Total kidney volume was not measured in HALT-PKD study B, and likely as a result of the smaller number with assessment of total kidney volume, the longitudinal models failed to converge; thus, height-corrected total kidney volume could not be included as a covariate. Likewise, we did not examine the associations separately in HALT-PKD study A and study B to maximize power. We have reported previously that HALT-PKD participants with eGFRs of 20 to 44 mL/min/1.72 m$^2$ were more likely to experience pain symptoms.[13] It is possible that weight loss also promotes slowed kidney growth, which in turn reduces pain symptoms. An ongoing pilot trial of behavioral weight loss interventions will be able to provide insight into this question (NCT03342742). Relatedly, changes in pain (such as beginning an exercise program to reduce pain) may have led to changes in weight, which we cannot discern in this analysis. BMI has inherent limitations because it does not necessarily reflect adiposity, and in particular, abdominal adiposity. Additionally, we were unable to examine mechanisms contributing to pain in this study, such as the role of proinflammatory cytokines or the role of additional potentially confounding comorbid conditions, such as recent injury or health conditions associated with pain.

In conclusion, we have demonstrated that in early- and late-stage participants in the HALT-PKD studies, obesity was associated with greater back and radiating back pain, independent of total kidney volume and total liver volume. Additionally, mild weight loss was associated with reduced odds of worsening back pain. Consequently, weight loss may be an effective approach to reduce back pain in individuals with ADPKD. Pain is a frequent complication of ADPKD that can lead to patient frustration, as well as suboptimal management.[2] Our findings suggest a possible strategy to reduce back pain in ADPKD.

## SUPPLEMENTARY MATERIAL

### Supplementary File (PDF)

**Table S1:** Baseline characteristics of study participants from HALT-PKD study A and B included in the longitudinal analysis according to body-mass index category.

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## Is obesity associated with greater pain in patients with autosomal dominant polycystic kidney disease?

**Kidney Medicine**

### METHODS AND COHORT

**Pooled Data from HALT-PKD A and B**

**PREDICTORS USED:**

Overweight / Obesity (cross-sectional)  Annual Weight Change (longitudinal)

**Wisconsin Brief Pain Survey**

**Post hoc analysis**

### RESULTS

**Cross-sectional Analysis (N=867)**

| | Overweight (N=319) (BMI 25-29.9 kg/m²) | Obese (N=254) (BMI ≥30 kg/m²) |
|---|---|---|
| Back Pain | OR 1.4 (0.89 – 2.21) | OR 1.88 (1.15 – 3.08) |
| Abdominal Pain | OR 0.72 (0.41 – 1.26) | OR 0.88 (0.49 – 1.58) |
| Radicular Pain | OR 2.31 (1.20 – 4.47) | OR 2.92 (1.45 – 5.91) |

**Longitudinal Analysis (N=871)**

| | Weight Decreased ≥4% Annually | Weight Increased ≥4% Annually |
|---|---|---|
| Increased Back Pain | OR 0.87 (0.76 – 0.99) | OR 1.02 (0.91 – 1.14) |
| Increased Abdominal Pain | OR 1.07 (0.94 – 1.22) | OR 1.00 (0.89 – 1.12) |
| Increased Radicular Pain | OR 0.95 (0.81 – 1.10) | OR 0.97 (0.85 – 1.11) |

**Conclusion:** In early- and late-stage ADPKD, obesity was associated with greater back and radicular pain, independent of total kidney/liver volume. Mild weight loss was associated with favorable effects on back pain.

**Reference:** Nowak KL, Murray K, You Z et al. Pain and obesity in autosomal dominant polycystic kidney disease: a post hoc analysis of the HALT-PKD studies. *Kidney Medicine*, 2021.

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