Overweight and Obesity Are Predictors of Progression in Early Autosomal Dominant Polycystic Kidney Disease

Kristen L. Nowak,1 Zhiying You,1 Berenice Gitomer,1 Godela Brosnahan,1 Vicente E. Torres,2 Arlene B. Chapman,3 Ronald D. Perrone,4 Theodore I. Steinman,5 Kaleab Z. Abebe,6 Frederic F. Rahbari-Oskoui,7 Alan S.L. Yu,8 Peter C. Harris,2 Kyongtae T. Bae,9 Marie Hogan,2 Dana Miskulin,4 and Michel Choncho1

1Division of Renal Diseases and Hypertension, University of Colorado Anschutz Medical Campus, Aurora, Colorado; 2Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota; 3Section of Nephrology, University of Chicago, Chicago, Illinois; 4Division of Nephrology, Tufts University Medical Center, Boston, Massachusetts; 5Department of Medicine and Renal Division, Beth Israel Deaconess Medical Center, Boston, Massachusetts; 6Center for Clinical Trials & Data Coordination, Division of General Internal Medicine, and 9Department of Radiology, University of Pittsburgh, Pittsburgh, Pennsylvania; 7Division of Renal Medicine, Emory University School of Medicine, Atlanta, Georgia; and 8Division of Nephrology and Hypertension, University of Kansas Medical Center, Kansas City, Kansas

ABSTRACT

The association of overweight/obesity with disease progression in patients with autosomal dominant polycystic kidney disease (ADPKD) remains untested. We hypothesized that overweight/obesity associates with faster progression in early-stage ADPKD. Overall, 441 nondiabetic participants with ADPKD and an eGFR > 60 ml/min per 1.73 m2 who participated in the Halt Progression of Polycystic Kidney Disease Study A were categorized on the basis of body mass index (BMI; calculated using nonkidney and nonliver weight) as normal weight (18.5 – 24.9 kg/m2; reference; n = 192), overweight (25.0 – 29.9 kg/m2; n = 168), or obese (≥ 30 kg/m2; n = 81). We evaluated the longitudinal (5-year) association of overweight/obesity with change in total kidney volume (TKV) by magnetic resonance imaging using linear regression and multinomial logistic regression models. Among participants, mean ± SD age was 37 ± 8 years, annual percent change in TKV was 7.4% ± 5.1%, and BMI was 26.3 ± 4.9 kg/m2. The annual percent change in TKV increased with increasing BMI category (normal weight: 6.1% ± 4.7%, overweight: 7.9% ± 4.8%, obese: 9.4% ± 6.2%; P < 0.001). In the fully adjusted model, higher BMI associated with greater annual percent change in TKV (β = 0.79; 95% confidence interval [95% CI], 0.18 to 1.39, per 5-unit increase in BMI). Overweight and obesity associated with increased odds of annual percent change in TKV ≥ 7% compared with < 5% (overweight: odds ratio, 2.02; 95% CI, 1.15 to 3.56; obese: odds ratio, 3.76; 95% CI, 1.81 to 7.80). Obesity also independently associated with greater eGFR decline (slope) versus normal weight (fully adjusted β = −0.08; 95% CI, −0.15 to −0.02). In conclusion, overweight and, particularly, obesity are strongly and independently associated with rate of progression in early-stage ADPKD.
have suggested that ADPKD is a state of defective glucose metabolism and metabolic reprogramming. Furthermore, mild-to-moderate food restriction slows disease progression in multiple mouse models of ADPKD, suggesting that changes in energy status may have a profound effect on ADPKD progression.

The Halt Progression of Polycystic Kidney Disease (HALT) Study A was a randomized, double-blind, placebo-controlled study in nondiabetic patients with early-stage ADPKD and is among the largest trials ever conducted in patients with ADPKD. In order to evaluate the association of overweight and obesity with ADPKD progression, we examined the longitudinal association of baseline BMI categories with the primary outcome in Study A (percent change in total kidney volume [TKV]). We hypothesized that categorization as overweight or obese would be independently associated with a greater rate of progression in early-stage ADPKD, as indicated by greater annual change in TKV. We also evaluated whether overweight and obesity were associated with decline in eGFR.

RESULTS

Participant Characteristics at Baseline
Four hundred forty-one participants with early ADPKD who participated in HALT Study A were included in the analysis of the association of overweight and obesity with change in TKV. Among these participants, the mean ± SD age was 37 ± 8 years, 93.9% (n=426) were white, and the mean ± SD annual percent change in TKV was 7.4% ± 5.1%. Participants were categorized by baseline BMI (calculated from an adjusted weight removing the contribution of weight of the kidney and liver) as normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), or obese (≥30 kg/m²). The median BMI at baseline was 26.3 ± 4.9 kg/m². The median (interquartile range) baseline TKV was 1040 (808, 1552) ml. Individuals with a higher BMI were more likely to be men, had a higher systolic BP (SBP) and fasting serum glucose, and had a larger liver volume at baseline (Table 1).

Relation between Overweight and Obesity and Change in TKV
We first considered the initial and final TKV values from each participant in HALT Study A and calculated annual percent change in TKV. Using this approach, the annual percent change in TKV was greater with increasing BMI category (normal weight: 6.1% ± 4.7%, overweight: 7.9% ± 4.8%, obese: 9.4% ± 6.2%; P<0.001; Figure 1), with a mean ± SD follow-up period of 4.7 ± 0.8 years. In both unadjusted and adjusted analyses, obesity was associated with increased rate of change in TKV as compared with the normal weight group (Table 2). When BMI was considered as a continuous variable, higher BMI was also associated with greater annual percent change in TKV in the fully adjusted model (model 5: β=0.79; 95% confidence interval, 0.18 to 1.39, per 5-unit increase in BMI).

Because of a significant interaction term of BMI × sex in the linear regression model with an outcome of annual percent change TKV (P value for interaction=0.03) and previous analysis of baseline HALT Study A data which showed effect modification by sex, additional analyses were performed stratified by sex. In the final adjusted models, the association between BMI as a continuous variable and annual percent change in TKV was significant in both men and women, but quantitatively larger in men (men: β=1.71; 0.92 to 2.50; women: β=0.87; 0.34 to 1.39, per 5-unit increase in BMI).

Next, we considered three categories of annual percent change in TKV using the initial and final TKV measurements from each participant (<5% growth, 5%–7% growth, and ≥7% growth). In the fully adjusted model, compared with the normal weight group, the obese group had a 3.76 (1.81 to 7.80) greater odds of progressing at a rate of ≥7% compared with <5% TKV growth (Table 3). The odds of progressing at a rate ≥7% compared with <5% were also significantly greater in the overweight compared with normal weight group (odds ratio [OR], 2.02; 1.15 to 3.56). For every 5-unit increase in BMI, the odds of progressing at ≥7% was 1.89 (1.42 to 2.52) in the fully adjusted model.

As a sensitivity analysis, we also considered a clinically meaningful final TKV end point of >1500 ml. In the fully adjusted model, the odds of reaching the >1500 ml end point were significantly greater in the overweight (OR, 3.33; 1.12 to 9.97) and obese (OR, 3.52; 1.06 to 11.69) compared with normal weight group. For every 5-unit increase in BMI, the odds of reaching a final TKV>1500 ml were 1.89 (1.41 to 4.04) in the fully adjusted model.

Last, in a sensitivity analysis utilizing a linear mixed model approach incorporating all available time points where TKV was measured, there was a significant BMI × time interaction in the fully adjusted model (P<0.01), consistent with the results of the primary analysis. For every 5-unit increase in BMI, TKV increased by 32.0 (12.2, 51.8) ml at month 24, 71.6 (33.3, 109.9) ml at month 48, and 101.8 (30.5, 153.0) ml at month 60.

Relation between Overweight and Obesity and eGFR Slope
Four hundred forty-eight participants with early ADPKD who participated in HALT Study A were included in the analysis of
the association of overweight and obesity with slope of eGFR over the study duration. Baseline characteristics were very similar to the cohort included in the analysis of the TKV end point (Supplemental Table 1). The mean ± SD annual decline in eGFR (long-term phase) was \(-3.2 ± 3.1\) ml/min per 1.73 m\(^2\) per year. In the fully adjusted linear regression model incorporating all available measurements >4 months (to eliminate short-term hemodynamic effects), obesity was associated with greater decline in eGFR as compared with the normal weight group (Table 4). Results were similar when BMI was considered as a continuous variable (model 4: \(\beta = -0.03; -0.05\) to 0.00, per 5-unit increase in BMI).

In a sensitivity analysis utilizing a linear mixed model approach incorporating all available time points after month 4 where eGFR was measured, there was a significant BMI × time interaction in the fully adjusted model (\(P=0.03\), consistent with the results of the eGFR slope analysis. For every 5-unit increase in BMI, eGFR declined by \(-0.01 (-0.96, 0.93)\) ml/min per 1.73 m\(^2\) at month 24, \(-1.60 (-3.02, -0.19)\) ml/min per 1.73 m\(^2\) at month 48, and \(-1.71 (-3.17, -0.24)\) ml/min per 1.73 m\(^2\) at month 60.

**DISCUSSION**

We have demonstrated for the first time that overweight, and particularly obesity, are strongly associated with rate of progression of early-stage ADPKD, as measured by annual percent change in TKV and eGFR slope. In early-stage patients in HALT Study A, compared with normal weight individuals, obesity was associated with nearly four times greater adjusted odds of progressing at an annual rate of change in TKV of \(7\%\) compared with \(5\%\). The annual percent increase in TKV in obese individuals was >50% greater than in normal weight individuals. These findings cannot be accounted for by baseline kidney and liver size, because BMI was calculated after removing the contribution of weight from these organs. Furthermore, baseline TKV and liver volume were included in all final adjusted models. In sensitivity analyses, overweight and obesity were also associated with achieving a clinically meaningful final TKV >1500 ml, a volume at which risk of subsequent decline in eGFR is increased.\(^{16}\) Importantly, obesity was also associated with greater decline in eGFR as compared with the normal weight group.
In a previous cross-sectional analysis of the baseline data from HALT, body surface area but not BMI was independently associated with baseline height-adjusted TKV and eGFR.\(^{15}\) Body surface area was thought to reflect genetic and environmental factors influencing both birth weight and postnatal growth velocities in a manner associated with, but distinct from, body size. In unadjusted analyses only, BMI was significantly associated with height-adjusted TKV and eGFR in men but not women. Similarly, in the current analysis, the association of BMI with annual percent change in TKV was slightly stronger in men than women. Notably, these associations were significant after adjustment for potential confounders, unlike in the analysis of baseline HALT Study A data. It is not unusual for longitudinal data to differ from cross-sectional data because the latter considers only a single time point. The current results suggest that overweight and obesity may indeed be important contributors to rate of progression in ADPKD.

It is biologically plausible that common pathways may be implicated in both ADPKD and obesity. Obesity can increase the mechanistic target of rapamycin (mTOR) activity via activation by PI3K/Akt and reduced AMP-activated protein kinase (AMPK) activity.\(^{17−19}\) Overnutrition and obesity activate mTOR complex 1 and its downstream target S6 kinase (S6K) via elevated cellular amino acid, glucose, and ATP concentrations,\(^{20}\) whereas caloric restriction represses mTOR via AMPK activation in the presence of low glucose, high AMP/ATP ratios, and decreased amino acids.\(^{21,22}\) Overactivation of mTOR/S6K is also central to the progression of ADPKD, playing a major role in mediating hyperproliferation of the cystic epithelium.\(^{15,24}\) Additionally, AMPK negatively regulates both the cystic fibrosis transmembrane conductance regulator (CFTR), which promotes secretion of cyst fluid,\(^{25,26}\) as well as mTOR signaling.\(^{27,28}\) Metformin, a pharmacologic activator of AMPK, has been shown to slow cyst growth in vitro and ex vivo in models of cystogenesis via inhibition of the mTOR pathway and CFTR.\(^{29}\)

It has been proposed that obesity in the setting of a positive energy balance may increase cancer risk, in part due to inhibition of AMPK and activation of mTOR and downstream proliferative pathways.\(^{20}\) Additionally, mTOR inhibitors have been shown to block tumor-promoting effects of obesity in mouse models.\(^{18,30,31}\) Inflammation and oxidative stress are also increased in obesity, which may additionally promote

### Table 2. Associations (β-estimates [95% confidence intervals]) of BMI categories with annual percent change in TKV

<table>
<thead>
<tr>
<th>Model</th>
<th>Normal Weight (BMI 18.5–24.9 kg/m²) (n=192)</th>
<th>Overweight (BMI 25–29.9 kg/m²) (n=168)</th>
<th>Obese (BMI ≥30 kg/m²) (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>Ref</td>
<td>1.84 (0.79 to 2.88)</td>
<td>3.39 (2.08 to 4.71)</td>
</tr>
<tr>
<td>Model 1</td>
<td>Ref</td>
<td>1.36 (0.34 to 2.38)</td>
<td>3.05 (1.80 to 4.29)</td>
</tr>
<tr>
<td>Model 2</td>
<td>Ref</td>
<td>1.33 (0.30 to 2.35)</td>
<td>3.05 (1.81 to 4.29)</td>
</tr>
<tr>
<td>Model 3</td>
<td>Ref</td>
<td>0.93 (−0.11 to 1.96)</td>
<td>2.71 (1.46 to 3.95)</td>
</tr>
<tr>
<td>Model 4</td>
<td>Ref</td>
<td>1.05 (0.02 to 2.07)</td>
<td>2.84 (1.59 to 4.08)</td>
</tr>
<tr>
<td>Model 5</td>
<td>Ref</td>
<td>0.82 (−0.22 to 1.87)</td>
<td>2.70 (1.45 to 3.95)</td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, sex, and race/ethnicity. Model 2: adjusted for model 1+randomization group and SBP. Model 3: model 2+eGFR (CKD-EPI equation), urinary albumin excretion, and serum glucose. Model 4: model 3+baseline TKV and liver volume. Model 5: model 4+mutation class. Mutation class is unavailable in n=12.

### Table 3. Associations (OR [95% confidence intervals]) of BMI categories with categories of annual percent change in TKV

<table>
<thead>
<tr>
<th>End Point (Annual %Δ in hTKV)</th>
<th>Model</th>
<th>Normal Weight (BMI 18.5–24.9 kg/m²) (n=192)</th>
<th>Overweight (BMI 25–29.9 kg/m²) (n=168)</th>
<th>Obese (BMI ≥30 kg/m²) (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%–7% versus &lt;5%</td>
<td>Unadjusted</td>
<td>Ref</td>
<td>2.10 (1.12 to 3.93)</td>
<td>2.22 (0.95 to 5.20)</td>
</tr>
<tr>
<td></td>
<td>Model 1</td>
<td>Ref</td>
<td>1.92 (1.00 to 3.67)</td>
<td>2.16 (0.92 to 5.12)</td>
</tr>
<tr>
<td></td>
<td>Model 2</td>
<td>Ref</td>
<td>2.00 (1.03 to 3.89)</td>
<td>2.26 (0.94 to 5.44)</td>
</tr>
<tr>
<td></td>
<td>Model 3</td>
<td>Ref</td>
<td>1.55 (0.79 to 3.07)</td>
<td>1.97 (0.81 to 4.81)</td>
</tr>
<tr>
<td></td>
<td>Model 4</td>
<td>Ref</td>
<td>1.62 (0.81 to 3.21)</td>
<td>2.16 (0.87 to 5.38)</td>
</tr>
<tr>
<td></td>
<td>Model 5</td>
<td>Ref</td>
<td>1.66 (0.82 to 3.38)</td>
<td>2.32 (0.91 to 5.91)</td>
</tr>
<tr>
<td>≥7% versus &lt;5%</td>
<td>Unadjusted</td>
<td>Ref</td>
<td>2.39 (1.50 to 3.83)</td>
<td>3.54 (1.89 to 6.64)</td>
</tr>
<tr>
<td></td>
<td>Model 1</td>
<td>Ref</td>
<td>2.20 (1.33 to 3.64)</td>
<td>3.45 (1.80 to 6.63)</td>
</tr>
<tr>
<td></td>
<td>Model 2</td>
<td>Ref</td>
<td>2.31 (1.38 to 3.85)</td>
<td>3.72 (1.91 to 7.23)</td>
</tr>
<tr>
<td></td>
<td>Model 3</td>
<td>Ref</td>
<td>1.92 (1.11 to 3.07)</td>
<td>3.29 (1.67 to 6.51)</td>
</tr>
<tr>
<td></td>
<td>Model 4</td>
<td>Ref</td>
<td>2.03 (1.19 to 3.48)</td>
<td>3.70 (1.84 to 7.45)</td>
</tr>
<tr>
<td></td>
<td>Model 5</td>
<td>Ref</td>
<td>2.02 (1.15 to 3.56)</td>
<td>3.76 (1.81 to 7.80)</td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, sex, and race/ethnicity. Model 2: adjusted for model 1+randomization group and SBP. Model 3: model 2+eGFR (CKD-EPI equation), urinary albumin excretion, and serum glucose. Model 4: model 3+baseline TKV and liver volume. Model 5: model 4+mutation class. Mutation class is unavailable in n=12.
tumorigenesis.20,32 Because ADPKD is characterized by many features that align with the hallmarks of cancer,33 it is tempting to speculate that obesity may contribute to cystogenesis. Consistent with this hypothesis, mild-to-moderate food restriction was recently shown to slow progression in multiple mouse models of ADPKD, concomitant with suppressed mTOR signaling and AMPK activation.12,13

Obesity is a well-established independent risk factor for incident CKD,6,34,35 ESRD,7,8 and decline in eGFR in the general population.36 In individuals with prevalent CKD, obesity is associated with a decline in eGFR in some8,37 but not in other studies.38–40 The association of obesity with decline in renal function in an ADPKD cohort has not been evaluated previously. We found an independent association between categorization as obese, but not overweight, and decline in eGFR in early-stage ADPKD. This finding is notable, because in the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease study, an observational study of early-stage ADPKD, the decline in eGFR over a 3-year period was significant only in individuals with baseline TKV>1500 ml.16 Additionally, in HALT Study A, the low BP group had a significantly lower annual percent increase in TKV compared with the standard BP group with no differences in rate of change in eGFR,14 highlighting that HALT Study A participants were indeed in an early stage of a slowly progressing disease. Thus, a greater rate of decline in eGFR in patients with early-stage ADPKD with obesity is clinically significant.

There are several limitations to this study. We are only able to demonstrate an association of overweight and obesity with ADPKD progression, rather than causation, and there may be residual confounding. Although BMI is commonly used to classify overweight and obesity, it is unable to distinguish between fat and muscle mass. Additionally, only baseline BMI and covariates were used in the statistical models. The major strength of this study is that we demonstrated a strong association of overweight and obesity with ADPKD progression, which is a novel and clinically relevant finding. Our results were consistent across various statistical approaches and accounted for any contribution of baseline kidney and liver weight to BMI classification. Last, progression was evaluated longitudinally with approximately 5 years of follow-up, and covariates were well characterized in the setting of a clinical trial.

These results pose an interesting and clinically relevant question of whether weight loss may be an effective strategy to slow progression in patients with ADPKD. The prevalence of overweight and obesity in the HALT study was over half of participants, thus an effective intervention could affect a large number of individuals. Given well known difficulties with weight loss adherence and the life-long nature of ADPKD, targeting prevention of the development of overweight and obesity early in life could potentially be a novel approach. Future research should evaluate the association of overweight and obesity with ADPKD progression in other cohorts, including late-stage patients, and whether weight loss or prevention of weight gain may slow disease progression.

**CONCISE METHODS**

**Study Design**

The design of the HALT PKD Study A has been described in detail previously.14,15,41 Briefly, the study was a prospective, randomized, double-blind, placebo-controlled, multicenter trial. Eligible participants were enrolled across seven clinical sites between February of 2006 and June of 2009. All participants provided written informed consent and the study adhered to the Declaration of Helsinki. Study A employed a 2×2 factorial design and evaluated the effect of (1) multilevel renin angiotensin aldosterone system blockade with an angiotensin converting enzyme inhibitor (ACEi) + angiotensin receptor blocker (ARB) compared with ACEi + placebo, and (2) low (95–110/60–75 mm Hg) compared with standard (120–130/70–80 mm Hg) BP control.

All participants had a known diagnosis of ADPKD and either hypertension or high-normal BP. All participants were free from diabetes. Participants in HALT Study A were 15–49 years of age with an eGFR>60 ml/min per 1.73 m² using the four-variable Modification of Diet in Renal Disease equation. The primary outcome in HALT Study A was percent change in TKV assessed by magnetic resonance imaging. TKV was assessed at baseline, 24, 48, and 60 months.

Of the 558 participants randomized in Study A, 487 had at least two measurements of TKV. One was missing data for BMI, 14 were excluded due to classification of BMI as underweight (see below), and an additional 31 were missing covariates (described below), leaving 441 participants for the current analysis. Twenty-four months data were used as baseline for n=2 participants who were missing baseline

---

**Table 4.** Associations (β [95% confidence interval]) of BMI categories with eGFR slope

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal Weight (BMI 18.5–24.9 kg/m²) (n=206)</th>
<th>Overweight (BMI 25–29.9 kg/m²) (n=168)</th>
<th>Obese (BMI≥30 kg/m²) (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>Ref</td>
<td>–0.03 (–0.08 to 0.03)</td>
<td>–0.08 (–0.15 to –0.02)</td>
</tr>
<tr>
<td>Model 1</td>
<td>Ref</td>
<td>–0.03 (–0.08 to 0.02)</td>
<td>–0.09 (–0.15 to –0.02)</td>
</tr>
<tr>
<td>Model 2</td>
<td>Ref</td>
<td>–0.02 (–0.07 to 0.03)</td>
<td>–0.08 (–0.14 to –0.01)</td>
</tr>
<tr>
<td>Model 3</td>
<td>Ref</td>
<td>–0.03 (–0.08 to 0.03)</td>
<td>–0.08 (–0.14 to –0.02)</td>
</tr>
<tr>
<td>Model 4</td>
<td>Ref</td>
<td>–0.02 (–0.08 to 0.03)</td>
<td>–0.08 (–0.15 to –0.02)</td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, sex, race/ethnicity, and randomization group. Model 2: adjusted for model 1+randomization group and SBP. Model 3: Model 2+eGFR (CKD-EPI equation), urinary albumin excretion, and serum glucose. Model 4: model 3+mutation class. Mutation class is unavailable in n=11.
TKV data. Of the 558 participants in HALT Study A, 529 also had at least two measurements of eGFR, 14 were excluded due to classification of BMI as underweight, and an additional 67 were missing covariates or TKV/liver volume for calculation of adjusted BMI, leaving 448 participants for the analysis of change in eGFR.

**Study Variables**
An adjusted body weight was calculated by subtracting out kidney and liver weight, assuming a tissue density equal to that of water (1 g/cm³), thus removing the contribution of kidney and liver size to BMI classification. BMI was then calculated using baseline adjusted body weight in kilograms divided by baseline height in meters squared (measured at clinical research clinics) and rounded to the nearest tenth. Participants were categorized on the basis of BMI as normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), or obese (≥30 kg/m²) using the National Heart, Lung, and Blood Institute’s criteria.43 Fourteen participants had an adjusted BMI<18.5 kg/m² (i.e., underweight) and were thus excluded from analyses, because underweight individuals may differ physiologically from those of normal weight. Magnetic resonance imaging was performed at each study site using a protocol developed by the HALT PKD Imaging Subcommittee to determine TKV (as well as total liver volume).15,41 Following acquisition, images were reviewed locally and transferred electronically to the Image Analysis Center at the University of Pittsburgh for analysis.

Baseline and follow-up eGFR were calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.44 Two blood samples were drawn a minimum of 1 hour apart and sent to the central laboratory (Cleveland Clinic Foundation Reference Laboratory) for measurement of serum creatinine.41 Consistency (<20% variation) was required, with a second set of samples drawn for repeat analysis if this requirement was not met.

Confounders related to BMI and the primary outcomes were selected a priori as potential covariates, and all were measured at baseline. Race was categorized as white or nonwhite, as determined by self-report. SBP was measured in the clinical research clinics with the participant seated quietly in a chair for at least 5 minutes, feet on the floor, and arm supported at heart level. Three measurements were taken with at least 30 seconds between each measurement and the last two readings were repeated if there was a >10 mm Hg difference. The last two readings were averaged and reported.41 Urinary albumin excretion was determined from 24-hour urine collections.43 Glucose level was measured in fasted serum samples during screening using standard methodology. Liver volume was measured as described above. Mutation analysis was performed previously, with mutation class categorized as *PKD1* truncating mutations, *PKD1* nontruncating mutations, *PKD2* mutations, and no mutation detected.44

**Statistical Analyses**
The association of overweight and obesity with change in TKV was assessed using linear regression and multinomial logistic regression models. Participants were classified into three categories according to BMI as described above (normal weight, overweight, and obese), with the normal weight category serving as the reference group in all analyses. In the linear regression models, the dependent variable was annual percent change in TKV calculated from the first and last available measurements. On the basis of analyses of baseline associations in HALT Study A,15 we tested for a statistical interaction between BMI and sex as a predictor of annual percent change in TKV. We performed stratified analyses on the basis of a significant interaction term (p < 0.05) with BMI as a continuous variable only. There was no significant interaction with study randomization group (ACEi/angiotensin receptor blocker versus ACEi/placebo or low versus standard BP target).

In the multinomial logistic regression models, the outcome was three categories of annual TKV growth (<5%, 5%–7%, and ≥7%), again calculated from the first and last available measurements. ORs were calculated with the <5% annual TKV growth, normal weight group serving at the reference. There were no significant interaction terms between BMI/BMI category and either sex or randomization group, thus stratified analyses were not performed.

In both approaches, the initial model was unadjusted, then multivariable adjusted models were performed to include age, sex, and race/ethnicity (model 1), model 1 plus randomization group and SBP (model 2), model 2 plus eGFR (CKD-EPI) and urinary albumin excretion (model 3), and model 3 plus baseline TKV, baseline liver volume, and serum glucose (model 4). Mutation class was added to model 4 (model 5) for those with the information available (n=429). We additionally considered BMI as a continuous predictor variable. The interaction term was included in model 2 for the linear regression model, considering BMI as a continuous variable. As a sensitivity analysis, we also evaluated achieving a final TKV>1500 ml as a clinically meaningful end point.16 The same covariates were included in these models as described previously.

Linear regression models were also used to evaluate the association of BMI categories with eGFR slope, which was obtained by fitting a linear regression model to all eGFR measurements from an individual participant obtained at ≥4 months (i.e., long-term phase14). The initial model was unadjusted, then multivariable adjusted models were performed to include age, sex, race/ethnicity, and randomization group (model 1), model 1 plus SBP (model 2), and model 2 plus eGFR (CKD-EPI) and urinary albumin excretion (model 3). Mutation class was added to model 3 (model 4) for those with the information available (n=437). Annual change in eGFR was calculated using the final and month 5 eGFR values. There were no significant interaction terms between BMI/BMI category and either sex or randomization group, thus stratified analyses were not performed.

Last, as sensitivity analyses, we performed linear mixed model analysis incorporating all available measurements (with the exception of month 90 and 96 eGFR, which caused model failure due to a low number of measurements), with BMI as a continuous predictor variable and (1) TKV and (2) eGFR as continuous end points. Results were similar when the variable TKV was log-transformed. The same covariates were used as described above.

In all analyses, baseline characteristics were summarized by BMI categories and presented as mean±SD or median (interquartile range) for continuous variables and n (%) for categoric variables. Comparisons across BMI categories were made using a chi-squared or Wilcoxon score test for categoric data and ANOVA for continuous variables.
Two-tailed values of \( P<0.05 \) were considered statistically significant for all analyses. All statistical analyses were performed using SAS version 9.4.

ACKNOWLEDGMENTS

K.L.N. is supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), K01 DK103678. The Halt Progression of Polycystic Kidney Disease studies were supported by the NIDDK grants U01 DK062402, U01 DK062410, U01 CK082230, U01 DK062408, and U01 DK062401; the National Center for Research Resources General Clinical Research Centers (RR00039 to Emory University, RR000585 to the Mayo Clinic, RR000554 to Tufts Medical Center, RR000551 to the University of Colorado, RR023940 to the University of Kansas Medical Center, and RR001032 to Beth Israel Deaconess Medical Center); the National Center for Advancing Translational Sciences Clinical and Translational Science Awards (RR025008 and TR000454 to Emory University, RR024150 and TR00135 to the Mayo Clinic, RR025752 and TR001064 to Tufts University, RR025780 and TR001082 to the University of Colorado, RR025758 and TR001012 to Beth Israel Deaconess Medical Center, RR033179 and TR000001 to the University of Kansas Medical Center, and RR024989 and TR000439 to Cleveland Clinic); by funding from the Zell Family Foundation (to the University of Colorado); and by a grant from the Polycystic Kidney Disease Foundation.

The funding agencies had no direct role in the conduct of the study; the collection, management, analyses, and interpretation of the data; or preparation or approval of the manuscript.

DISCLOSURE

None.

REFERENCES


This article contains supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2017070819/-/DCSupplemental.