DIETARY FACTORS ASSOCIATED WITH THE PROGRESSION OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

BY

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DIETARY FACTORS ASSOCIATED WITH THE PROGRESSION OF AUTOSOMAL DOMINANT
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ABSTRACT

Introduction: Dietary factors (sodium, protein, acid precursors, and fluid) have been observed to influence cyst growth in human and animal studies of autosomal dominant polycystic kidney disease (ADPKD). However, no studies have been conducted to control such dietary constituents. Body mass index (BMI) and high-density lipoprotein (HDL), factors associated with dietary behaviors, have also been reported to associate with ADPKD progression and warrant further examination. The following series of studies aimed to (1) determine whether patients could adhere to a low sodium, low protein, low acid precursor diet with increased fluid intake; (2) understand participants’ experiences and perspectives as they attempted to follow the diet; (3) reveal potential barriers that may reduce the likelihood of long-term adherence; (4) determine if data obtained from the electronic health record (EHR) can be used to identify risk factors associated with ADPKD progression (BMI and HDL).

Methods: A four-week dietary intervention was conducted to determine if a relatively complex dietary prescription targeting salt, protein, acid precursors, and fluid intake would be adopted by adult patients with ADPKD. Consecutive 24-hour urine collections were analyzed for sodium, urea, net acid excretion (NAE), urine volume, and osmolality. Three-day diet records were analyzed for sodium, protein, net endogenous acid production (NEAP), and fluid intake. A basic metabolic panel was obtained from blood samples. Blood pressure, height, and weight were obtained by a nurse at each visit. Outcomes were measured at baseline, two weeks, and four weeks. Following the dietary intervention, interviews and a Nutrition Hassles Questionnaire (NHQ) were conducted with participants to determine how difficult it was for them to follow the diet. Finally, we collected BMI and HDL levels from the EHRs of ADPKD patients seen at the University of Kansas Medical Center and determined their associations with the age of reaching kidney failure (estimated glomerular filtration rate (eGFR) ≤ 15ml/min/1.73m²).

Results: The dietary changes caused a decrease in daily sodium excretion (-20%), urea excretion (-28%), and NAE (-46%) while increasing urine volume 35% above baseline. Subjects eating the experimental diet reached the daily goals for sodium (≤ 1.5 mmol/kg), protein (≤ 1 g/kg), and fluid intake (mean 24h urine osmolality ≤ 285 mosm/kg) prescribed for each patient and were sustained for four weeks. NEAP
decreased 58 mEq/d from baseline. Only one participant reported hassles on the NHQ as “moderately severe” and no hassles were reported as “extremely severe”. The NHQ also showed that 10 out of 11 individuals were “somewhat confident” or “very confident” that they could manage the new diet. The interviews conducted following the dietary intervention found a general consensus that reducing portion sizes of meat and increasing intake of fruits and vegetables were the easiest components of the diet while keeping track of what they ate and reaching the prescribed goal amount for fruits and vegetables each day were the most difficult components. Participants met their fluid goal and believed it to be an attainable amount long-term. Travel and meals away from home made following and tracking the diet more difficult. Participants stated a cell phone app may have mitigated some of these issues. Data collected from the EHR did not show an association of BMI with age at kidney failure (p=0.69, HR=1.096, 95% CI 0.697-1.724). By contrast, those with a desirable HDL (Men & Women: ≥60 mg/dL) had a significantly slower disease progression compared to individuals with low (Men: <40 mg/dL; Women <50 mg/dL) (p=0.0147, HR=0.271, 95% CI 0.095-0.774) and acceptable (Men: 40-59 mg/dL; Women 50-59 mg/dL) HDL levels (p=0.0436, HR=0.319, 95% CI 0.105-0.968).

**Conclusion:** Dietary sodium, protein, and acid precursors can be effectively reduced while increasing fluid intake, and sustained for at least four weeks in patients with ADPKD. Eight out of twelve participants reported they could follow the diet over a much longer period of time. It is reasonable to suppose that our experimental diet could be used to ameliorate cyst growth in patients with ADPKD; however, long-term, adequately powered studies that evaluate structural and functional changes in kidney function need to be examined. Furthermore, participants reported that to move forward to a long-term dietary trial, the development of an app to help monitor and track dietary intake in individuals with ADPKD is necessary. Participants thought an app would help them be successful tracking and adhering to the diet long-term. The results of these studies provide new ways worthy of more robust, long-term testing to determine the efficacy of slowing disease progression. Additionally, analysis of ADPKD histories in the EHR confirms that HDL is positively associated with the age at kidney failure whereas BMI is not. Monitoring and improving HDL levels through dietary and lifestyle behaviors may provide
additional benefits when included as part of a comprehensive lifestyle intervention. Collaborative efforts that would permit the mining of EHR data from multiple centers would allow for assessment of large-scale laboratory and clinical measurements to determine if additional risk factors for ADPKD progression should be routinely monitored in patients. If successful, these modifiable risk factors could be targeted in clinical trials in an effort to halt disease progression through dietary, lifestyle, or behavioral modifications.
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CHAPTER ONE

INTRODUCTION
AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Etiology

Polycystic Kidney Disease (PKD) is the most common inherited disorder of the kidneys (1). A form of PKD, known as autosomal dominant polycystic kidney disease (ADPKD), occurs in 1 in 400 to 1 in 1000 people (2). ADPKD is a monogenic disease meaning that only a single mutated gene is required to pass the disease from an affected parent to his/her offspring. This means that children of a parent with ADPKD have a 50% chance of inheriting the disease; however, there is a small subset of individuals with ADPKD (~5-10%) that appear to develop the disease through a spontaneous mutation (2-4). Since ADPKD is typically inherited, kidney damage occurs from birth and throughout their lifespan until kidney failure occurs and the use of chronic renal replacement therapies and kidney transplantation must be considered.

Diagnosis and Monitoring

ADPKD is characterized by cysts that develop in individual renal tubules and enlarge progressively throughout life causing kidney volume to increase (2). Therefore, ADPKD can be diagnosed using three primary clinical tests: ultrasound imaging, computed tomography (CT), or magnetic resonance imaging (MRI), all used to identify the growth of cysts.

Ultrasound imaging is most commonly used to screen for ADPKD because it is cost effective and does not require injected dyes or radiation, making it safe for all patients. Ultrasound detects cysts 1 cm or larger in diameter, which is sensitive enough to diagnose ADPKD in adults; however, during childhood cyst growth may not be large enough to be detected (5).

MRI and CT scans are more sensitive and can detect cysts as small as 3 mm in diameter, making it possible to detect cyst growth early in the course of the disease (6). MRI scans are preferred because
they do not involve radiation and contrast dyes than can be nephrotoxic; however, CT scans better detect both early cyst growth and development, and bleeding cysts (6).

**Current Treatments**

There is no cure for ADPKD, and current treatments consist of managing symptoms of the disease. Treatments include medications to control blood pressure, treating UTIs, and managing pain (1, 7).

**Recent Evidence**

Recent evidence shows that kidney volume predicts the likelihood of developing renal insufficiency in an 8-year period, evidence of a link between the growth of cysts and damage to kidney function (8). The evidence suggests that cysts injure key structures required to generate glomerular filtrate. This is followed by elevated filtration rates in the surviving glomeruli to compensate for loss of nephrons, known as compensatory hyperfiltration (9). Consequently, kidney damage occurs decades before a decline in glomerular filtration rate (GFR) can be measured. Eventually, the decline in kidney function results in kidney failure in ~50% of ADPKD patients (3). ADPKD is the fourth leading cause of kidney failure (10). Diet, obesity, and HDL are modifiable factors associated with disease progression (9, 11).

**MODIFIABLE FACTORS IN ADPKD PROGRESSION**

Data in humans and experimental animals with cystic kidneys indicate that the rate of kidney volume increase is hastened by excess dietary protein, salt, and total urinary solutes and slowed by increased water intake sufficient to lower plasma vasopressin levels (1, 9). Urinary acid excretion, which is affected by dietary acid intake, has also been shown to accelerate ADPKD progression in a rodent model (12). Dietary acids accelerate the progression of kidney disease in hypertensive nephropathy patients suggesting a diet lower in dietary acids could be beneficial in ADPKD (13-15). The harm that
dietary acids do to kidney function was also validated in a nationally representative cohort of individuals with chronic kidney disease (16). Lastly, elevated body mass index (BMI) and low levels of high-density lipoprotein (HDL) are associated with disease progression (9).

**Sodium, Total Solutes, High-Density Lipoprotein, and Body Mass Index**

The Consortium for Radiologic Imaging of Polycystic Kidney Disease (CRISP) is an ongoing (2001-2015), observational, multicenter study of 241 people that is being conducted to examine imaging techniques, follow disease progression, and evaluate treatment methods in ADPKD patients (9, 17). Subjects were examined at baseline and annually. Twenty-four hour urine collections (creatinine, urea nitrogen, sodium, and albumin excretion), anthropometric measurements (height, weight, BSA, and BMI), blood pressures, and blood samples (hemoglobin, electrolytes, liver enzymes, and lipids) were collected and analyzed at year 6. The results were compared to functional changes (GFR) and structural changes (Total Kidney Volume [TKV]) in the kidney over that time. High urinary sodium (a surrogate marker of salt intake), high urinary osmolality, low serum HDL, and higher BMI were correlated with increased kidney volume and decreased in GFR over a 6-year period. The restriction of sodium intake, increasing fluid consumption and moderating energy intake, as well as exercising to control weight, could slow the progression of ADPKD.

**Protein**

High dietary protein intake has been demonstrated to accelerate the progression of ADPKD. In a study conducted in Han:SPRD-cy rats, a rodent model of ADPKD, Ogborn and Sareen examined the effects of dietary protein intake on ADPKD progression (18). Animals were randomized to a low or high-protein diet, 8% and 20% energy from protein, respectively, and their kidney function and kidney volume were measured for four months. The low-protein diet was associated with significantly smaller kidney volume when compared to the high-protein diet after adjusting for differences in body weight (p=0.027).
In addition, cysts were significantly smaller on the low-protein diet compared to the high-protein diet (p<0.0001), evidence that dietary protein intake plays a role in the progression of cyst development and kidney volume enlargement. Larger cyst size and kidney volume are associated with accelerated kidney function decline in a rodent model and have been confirmed by others (12). In humans, there is also evidence to suggest that protein affects ADPKD progression. A study examining the effects of protein on individuals with ADPKD found that a protein restricted diet (0.6g/kg/day) slowed disease progression compared to a diet without protein restriction (19). The evidence is consistent with the possibility that protein intake may increase ADPKD progression and suggests that restricting protein intake could slow ADPKD progression.

**Dietary Acids**

Acid-base homeostasis is vital for all living organisms. Loss of homeostasis affects a wide range of processes from an individual’s capacity for high-intensity exercise to growth in infants (20-22). When acid/base status fluctuates in the human body, the kidneys and lungs compensate to keep in acid/base homeostasis. The kidneys achieve this by up-regulating urinary acid excretion. The effects of increased urinary acid excretion through diet and acidic compounds accelerate ADPKD progression in animal models, indicating that dietary acid precursors play an important role in ADPKD progression (12, 23).

Cowley et al. showed that administration of ammonium chloride, increased dietary protein (casein), or severe potassium depletion increased the rate of disease progression in rats with ADPKD (12). This suggests that protons may have an adverse effect on this disease. Tanner and colleagues validated the effects of ammonium chloride in the rodent model of ADPKD and have shown that the administration of alkalinizing salts ameliorates disease progression (23). Unfortunately, studies examining these factors in animal models with PKD1 or PKD2, two variations of ADPKD, and humans have yet to be conducted. However, a recent study has demonstrated that reduced urinary acid excretion through the addition of either dietary fruits and vegetables or orally administered sodium bicarbonate/sodium citrate can attenuate kidney injury markers and preserve GFR in hypertensive nephropathy patients (13-15).
Additionally, these findings were recently validated in a nationally representative cohort of individuals with chronic kidney disease showing that individuals with higher dietary acid intake progress to kidney failure more rapidly than their low dietary acid consuming peers (16). These studies indicate that excreted H+ ions are capable of injuring renal tubules and contribute to the rate of kidney function decline. The specific mechanisms by which excess protons injure renal tissue is unknown, but under active study. Diet plays a role in establishing acid/base balance and certain dietary components actuate the production of H+ ions, raising the possibility that dietary acid precursors will adversely affect polycystic kidneys (24).

**Fluids**

When individuals are dehydrated, the production of cyclic adenosine monophosphate (cAMP) and arginine vasopressin (AVP) increases which promotes the kidneys to concentrate urine and conserve fluid in the body. Unfortunately, the production of cAMP is believed to stimulate cell proliferation and net fluid secretion, two key factors in cyst growth and development in ADPKD. AVP exacerbates cyst enlargement in animals with renal cystic diseases and is slowed with administration of an arginine vasopressin V2 receptor (AVP-V2) inhibitor (25). Given these factors, it is reasonable to believe that increased fluid intake could slow ADPKD progression by reducing the production of AVP and stopping a cascade of events leading to cysts growth.

Wang et al. demonstrated that prescribing fluid intake decreased urine osmolality, a factor that would halt the production of AVP (26). Participants were prescribed a goal fluid intake needed to reduce urine osmolality to the level of plasma (285 mosm/kg), while eating their normal diets. The amount of additional water prescribed each day was 788 +/- 344 mL/day. Mean urine output of participants increased to 2.35 L/d and urine osmolality decreased to a mean of 325 mosm/kg, a 35% reduction. Because increased fluid intake may slow the growth of cysts, it will should be monitored and discussed as a component of dietary interventions that may benefit this patient population.
CONCLUSION

ADPKD is a slow progressing disease that results in kidney failure in 50% of individuals by the age of 53. Dietary and behavioral factors have been observed to influence cysts growth in human and animal studies (9, 11, 12, 23). Medical therapeutic diets are often prescribed to prevent or treat diseases such as diabetes and cardiovascular disease in the early stages of the condition. For individuals with kidney disease a diet is often not prescribed until late in the disease process. In ADPKD, data suggest that sodium, protein, dietary acids, and fluids play a role in the progression of the disease indicating that the course and outcome of the disease could be altered by diet therapy. Since certain dietary constituents likely play a role in the progression of ADPKD, incorporating these components into a single dietary intervention is the next logical step in PKD research. However, no studies have been done to determine the extent to which such dietary constituents would affect disease outcomes in individuals with ADPKD. BMI and HDL have also been shown to be associated with ADPKD progression observationally and warrant further examination (9). Along with diet, moderation of calorie intake and maintaining desirable HDL levels may prove worthy as a lifestyle intervention for individuals with ADPKD.

PURPOSE OF DISSERTATION

Research examining whether a diet designed to lower sodium, protein, dietary acids, and increase fluids can be followed and adherence confirmed with dietary and urinary markers needs to be tested before moving to larger scale trials. Additionally, the examination of BMI and HDL as risk factors for ADPKD progression from regularly obtained clinical measurements, stored in the electronic health record (EHR), is a novel approach that has not been reported in the literature of ADPKD. The goals of this project were (1) to determine whether patients could adhere to a low sodium, low protein, low acid precursor diet with increased fluid intake; (2) to understand participants’ experiences and perspectives as they attempted to follow the diet; (3) to reveal potential barriers that may reduce the likelihood of long-term adherence; (4) to determine if data obtained from the electronic health record (EHR) can be used to identify risk factors associated with ADPKD progression (BMI and HDL).
CHAPTER TWO

Individuals with Polycystic Kidney Disease are Able to Successfully Adhere to a Low Sodium, Low Protein, Low Acid Diet Augmented with Water that is Designed to Ameliorate Disease Progression
Abstract

Introduction: Dietary sodium, protein, acid precursors, and water have been linked to cyst growth in polycystic kidney disease; yet, no studies in patients have examined the feasibility of using a dietary intervention to control these factors. Therefore, our goal was to determine if a diet, appropriate for persons of most ages, reduces the excretion of sodium, urea, acid, and decreases mean urine osmolality while gaining acceptance by patients with autosomal dominant polycystic kidney disease (ADPKD).

Methods: Twelve adults with ADPKD enrolled in a pre-post feasibility study and served as their own controls. Individuals consumed their usual diet for one week then for four weeks followed an isocaloric diet lower in sodium and protein and higher in fruits, vegetables, and water. Three-day diet records and two 24-hour urine samples were collected at baseline, week 2, and week 4 visits; blood pressure, weight, and serum were obtained at all three visits. A modified nutrition hassles questionnaire (NHQ) was completed on the last visit.

Results: During the dietary intervention, subjects (n=11) consumed less sodium, protein, and dietary acid precursors 36%, 28%, and 99%, respectively, and increased fluid intake by 42%. Urinary sodium, urea, net acid excretion, osmoles, and osmolality decreased 20%, 28%, 20%, 37%, and 15%, respectively, and volume increased 35%. Changes were in accord with the diet record. Ninety-one percent of participants reported that none of the dietary hassles on the NHQ were worse than “somewhat severe”, and most participants were “somewhat confident” or “very confident” that they could manage the new diet.

Conclusions: Dietary sodium, protein, and acid precursors can be effectively reduced while increasing fluid intake, and sustained for at least four weeks in patients with ADPKD. Controlling these dietary constituents may ameliorate cyst growth in patients with ADPKD; however, long-term, adequately powered studies that evaluate structural and functional changes in kidney function need to be examined. This trial was registered at clinicaltrials.gov as NCT01810614.
Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disorder that affects ~600,000 individuals in the United States and ~12.5 million people worldwide (6). The clinical hallmark of ADPKD is the development of cysts in individual renal tubules that enlarge progressively throughout life. Although cysts begin forming during fetal development, the glomerular filtration rate (GFR) usually stays within an apparently normal range for several decades owing to compensatory hyperfiltration (27). Meanwhile, cysts increase in number and volume, causing serious injury to blood vessels and renal tubules. Recent evidence indicates that kidney volume predicts the likelihood of developing renal insufficiency over time, suggesting that the growth of cysts is linked to declining kidney function (8).

The disease phenotype is highly variable causing differing rates of cyst growth even among members of the same family (28). Dietary factors appear to account for some of the variability in this rate of renal enlargement; a process that appears to be hastened by the excessive intake of salt and animal-sourced protein (9, 12). Additionally, increased urinary acid excretion accelerates cyst growth in experimental animals and leads to a more rapid decline in kidney function in patients with moderately advanced chronic progressive renal diseases, including ADPKD (12, 13, 15, 16, 23, 29-32). Acid excretion is largely driven by high intakes of animal-sourced dietary protein, but can be reduced by base-producing fruits and vegetables (33). Increasing fluid intake has also been shown to reduce kidney weight (% of total body weight) by 27-30% by lowering plasma levels of arginine vasopressin (AVP); a result achieved when reaching a urine osmolality of <290 mosm/kg H$_2$O (25). In view of this evidence, we aimed to determine if adult patients with ADPKD would meaningfully adopt a relatively complex dietary prescription targeting dietary salt, protein, acid precursors, and fluid intake.
Methods

Participants

Twelve subjects with a certain diagnosis of ADPKD confirmed by family history, magnetic resonance, computed tomography or ultrasound imaging were enrolled (6). Subjects were recruited from the University of Kansas Medical Center Polycystic Kidney Disease clinic during routine visits between May 2013 and January 2014. Inclusion in the study required a blood pressure <135/85 mmHg, stable weight and clinical biochemistry, a diet history of >30 mEq/day of net endogenous acid production (NEAP), and an estimated GFR (eGFR) of >30ml/min/1.73m² based on the MDRD-EPI equation (34). Subjects were excluded if they used pharmaceuticals or dietary restrictions/enhancements for preexisting medical conditions not associated with standard of care for ADPKD or if they had been prescribed medications that affect acid/base status. A physical examination was performed by a physician to confirm medical appropriateness to participate. Written informed consent was obtained prior to study enrollment. This study was approved by the Human Subject Committee at the University of Kansas Medical Center. This trial was registered at clinicaltrials.gov (NCT01810614). A physician co-investigator monitored data and safety.

Design

Subjects were enrolled for a five-week study that included an enrollment visit, three study visits (baseline, 2 weeks, 4 weeks) and two follow-up phone calls (Figure 2.1). Study visits occurred in the clinical and translational science unit. Each subject submitted a three-day diet record (three days prior to study visits regardless of weekday or weekend), two consecutive 24-hour urine collections (two days prior to study visit), and a study nurse recorded blood pressures, anthropometrics, and drew blood samples at each visit. All subjects received instructions on how to modify their diet and served as their own controls in this pre-post feasibility study.
Three-day Diet Records

Diet records included a detailed accounting of all food and beverages consumed, the amounts consumed, the method of food preparation, and, if homemade, the recipe that was used. The amount of food consumed was measured by weight on an electronic food scale or by typical volumetric household measures. If neither of these methods of measurement were available, participants were asked to estimate portion sizes using picture books that were provided. Diet records were analyzed at each visit using the Nutrition Data for System Research (NDSR version 2012) (35). To improve collection of dietary data, probing techniques and a multiple pass system were used during study visits to gather information that subjects may have omitted or recorded incorrectly (36).

Figure 2.1 Diagram of the study protocol, study visit days, and data collected at visits. PKD, polycystic kidney disease.

Three-day Diet Records
Urine Measurements

Participants were instructed at the enrollment visit on how to collect 24-hour urine samples. Instructions included detailed methods for properly recording start and stop times and when to switch to the second 24-hour collection. Written instructions were also provided. Timed 24-hour urine collections were completed on the two days prior to each visit and coincided with the last two days of the diet record. Urine collections were kept on ice or placed in a refrigerator throughout the duration of each timed collection. Urine volume was determined from the weight of the collected sample. Aliquots of urine were centrifuged, and stored immediately at -20° C for the later measurement of urinary acid excretion (37). The remaining urine was sent immediately to the University of Kansas Hospital lab for analysis of electrolytes, urea, creatinine, bicarbonate, and osmolality.

Other measurements

Height was measured without shoes using a stadiometer. Weight was recorded to the nearest 0.1 kg and measured without shoes in street clothes. Subjects were supine for the measurement of blood pressure. Electrolytes, blood urea nitrogen (BUN), creatinine, uric acid, glucose, and bicarbonate were determined in serum samples by the hospital laboratory.

Diet Calculations

Three-day diet records were used to calculate net endogenous acid production from the formula \( \text{NEAP} = \text{PRAL} + \text{organic acids (OA)} \) and the mean recorded. NEAP is used to predict the amount of acid excreted in the urine (38, 39). The first term, PRAL, estimates the potential net acid or base contribution a food or liquid would make when combusted by whole body metabolism (40). The daily PRAL was calculated from all food and drink consumed over the day by estimating the dietary intake of anions (phosphorus and sulfur) and cations (potassium, calcium, and magnesium) from diet records using nutrient profiles from NDSR; sulfur was estimated based on the normative content of methionine and cysteine derived from protein in the diet. The fractional absorption of nutrients by the intestines, the
dissociation of phosphate, and ionic valences are all taken into account in Remer’s method for determining PRAL (38, 40). Daily consumption of these anions and cations was entered into an excel program developed by the research team that accounts for the variables listed in Remer’s equation to generate the daily PRAL of the diet. The second component of the equation, OA, is estimated from body surface area according to Berkemeyer and Remer (41). Given the time frame and stable body weight in this study, we assumed that OA excretion was also stable.

**Urine calculations**

Net acid excretion (NAE) is a direct measure of acid/alkali excretion in the urine and is determined from the sum of titratable acid + ammonium – bicarbonate (33). NEAP predicts acid in the urine and should approximate NAE. NAE was measured within 3 months of sample collection using standard methods (37).

**Diet prescription**

The experimental diet was tailored for individual subjects based on their baseline dietary intake of sodium, protein and NEAP (derived from three-day diet records) and measurements of urine osmolality and urine volume obtained from two 24-hour urine collections (Table 2.1)(26, 35, 39). The test diet was followed for the next four-weeks. At baseline, subjects received detailed instruction from a registered dietitian about limiting the intake of salt and protein while increasing the intake of fruits, vegetables, and fluid.
The daily limit for sodium in the test diet (1 – 1.5 mEq/kg) was apportioned over the course of the day based on the number of meals and snacks a participant typically ate. Each subject’s diet was uniquely modified in this manner to change his or her usual dietary pattern as little as possible. Subjects were informed of the sources of sodium in their diet, how to read food labels, and how to access nutrition information from restaurants and food companies online. Educational materials from the American Heart Association were provided to help educate subjects about dietary sodium (42).

Protein intake was limited to 0.8 – 1.0 g/kg body weight/day. To ease tracking, a protein point system was developed. Protein points were assigned to all protein-rich foods (meat, beans, dairy, protein-rich grains); one protein point was equal to approximately seven grams of protein (i.e., one ounce of meat, one cup of milk, or ½ cup dried beans). Participants were also taught how to convert food labels listing grams of protein to protein points. Participants were encouraged to make the majority of reductions in protein intake by eating less animal based protein sources.

<table>
<thead>
<tr>
<th>Table 2.1</th>
<th>Diet prescription†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet Component</td>
<td>Target level</td>
</tr>
<tr>
<td>Dietary Acids</td>
<td>Reduce NEAP by 50% (minimum 40 mEq / d)</td>
</tr>
<tr>
<td>Protein</td>
<td>0.8-1.0 g / kg body weight / d</td>
</tr>
<tr>
<td>Sodium</td>
<td>1-1.5 mmol / kg body weight</td>
</tr>
<tr>
<td>Fluid</td>
<td>Reduce urine osmolality to 285 mosm / kg H₂O</td>
</tr>
</tbody>
</table>

†NEAP, net endogenous acid production
The amount of fruits and vegetables prescribed was calculated to reduce NEAP by 50% (minimum 40 mEq/day) after accounting for their baseline fruit and vegetable intake. Because changes in NEAP are driven by changes in PRAL in adults with stable body weight, increasing the intake of fruits and vegetables decreases PRAL. Nutrient profiles from NDSR were used to calculate the PRAL per 100g of food according to Remer (40). These values were converted into the amount of PRAL reduction per serving of fruit or vegetable and given as a handout to the participants so they could track their intake (i.e., adding 40 points of fruits and vegetables per day is equivalent to reducing PRAL by 40 mEq). Participants were instructed on the number of points to eat daily from fruits and vegetables.

Since the goal was to reduce the urine osmolality to that of plasma or below, we used baseline mean 24-hour urine osmolality excretion to determine the total fluid intake that would be needed to decrease the mean urine osmolality to ≤ 285 mosm/kg H₂O/d; an additional 20% was added to correct for insensible losses (26). Assuming 1 kg fluid = 1000 ml of fluid, the daily fluid goal (mL/d) =

\[\text{((24-hr urine mosm/kg H}_2\text{O} / 285 \text{ mosm/kg H}_2\text{O}) \times \text{total urine volume (mL/d))} \times 1.2.\]

For patients with baseline mean urine osmolality equal to plasma or less we prescribed sufficient water to maintain urine osmolality at baseline levels.

*Nutrition Hassles Questionnaire analysis*

This diet is formulated for lifetime use so understanding the participants’ views about the extent of daily stress associated with nutritional issues is important. We adapted the Nutrition Hassles Questionnaire (NHQ) to flesh out particular aspects of the diet, such as concerns about the prescribed diet, planning menus, and eating the proper amounts, as well as issues related to the manner in which the diet was tracked by participants, that might impede wide acceptance (43). The NHQ is a set of 33 items designed to assess the perception of stress associated with the diet and is divided into 3 sections: hassles, uplifts, and self-efficacy. The hassles section includes 15 questions related to following the diet, each rated on a 0-3 scale (0 = no hassle and 3 = severe hassle). It includes questions aimed at uncovering
issues associated with planning meals, preparing meals, and tracking intake of dietary components. The uplifts section includes 6 questions about events that made the participant feel good while following the diet and is rated on a 0-3 scale (0 = never and 3 = very often). The self-efficacy section includes 12 questions about how confidently a person identifies and selects appropriate foods for meals and snacks, prepares appropriate foods, and their ability to follow the diet prescription. This section is rated on a 5 point scale (1 = not confident at all and 5 = very confident).

*Statistical analyses*

A paired samples t-test was used to compare two week and four week visit data to baseline measurements. Mean results of the three day diet records, 24-hour urine collections, and blood pressures were analyzed with SPSS software (44). Data were managed by REDCap (CTSA Award # UL1TR000001). Differences were considered statistically significant at p ≤ 0.05.

*Results*

Baseline demographics data are listed in Table 2.2. Of the 50 individuals approached about participation in this diet intervention, twelve subjects signed consents and were enrolled. No subjects withdrew from this study and no adverse events were reported. This cohort is a cross-section of middle-aged, ADPKD patients with well-preserved eGFR.
Compliance

Of the 12 subjects enrolled, one subject failed to record 3-day diet records and improperly collected 24-hour urine samples and was considered a failure, because data were unavailable or unreliable. The remaining 11 subjects attended every study visit and brought completed diet records and urine collections with them to each visit. Creatinine excretion at the two week and four week visits was ~7% below baseline; however, this decrease is likely related to the reduced intake of animal protein in the test diet and not incomplete collection of 24-hour urine samples (45).

Baseline outcomes

Diet records revealed that the subjects at baseline were already eating reasonably well-balanced amounts of protein, carbohydrates, and fat (Table 2.3); however, energy intake was slightly more than recommended based on body size. Intake of sodium and protein was somewhat higher than commonly recommended for ADPKD subjects, but meat is a prominent component of most diets in the Midwest. The intake of other mineral cations, including potential protons, was moderate except for potassium which was relatively low. Due to the relatively high animal-sourced protein and low potassium intake, baseline NEAP was acidic in all subjects (mean = 58 mEq/d) (Figure 2.2). Baseline fluid intake was

<table>
<thead>
<tr>
<th>Table 2.2</th>
<th>Baseline descriptive features&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>Value&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Number of participants, n (M/F)</td>
<td>11 (4/7)</td>
</tr>
<tr>
<td>Age, y</td>
<td>47 ± 15</td>
</tr>
<tr>
<td>Caucasian, % (n)</td>
<td>91 (10)</td>
</tr>
<tr>
<td>African American, % (n)</td>
<td>9 (1)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>169.9 ± 9.5</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>71.3 ± 12.4</td>
</tr>
<tr>
<td>BMI, kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>24.9 ± 5.1</td>
</tr>
<tr>
<td>Systolic Blood Pressure, mmHg</td>
<td>129 ± 11</td>
</tr>
<tr>
<td>Diastolic Blood pressure, mmHg</td>
<td>77 ± 7</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>84 ± 25</td>
</tr>
</tbody>
</table>

<sup>1</sup>BMI, Body Mass Index; eGFR, estimated glomerular filtration rate.
<sup>2</sup>all results either mean ± SD or % (n), unless otherwise indicated.
variable averaging 3.2 liters a day which is in the upper range of conventional intake but not uncommon in ADPKD patients who are encouraged to drink extra water (Figure 2.3) (11, 46-48).
### Table 2.3
Dietary intake in 11 individuals with ADPKD by study visit

<table>
<thead>
<tr>
<th>Nutrient intake</th>
<th>Recommended&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Baseline</th>
<th>2 weeks</th>
<th>4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy Intake, kcal</td>
<td>1782-2138</td>
<td>2334 ± 416</td>
<td>2355 ± 425</td>
<td>2107 ± 399</td>
</tr>
<tr>
<td>Fat, % of energy</td>
<td>20-35%</td>
<td>34.6 ± 5.4</td>
<td>26.8 ± 7.2**</td>
<td>25.2 ± 6.0***</td>
</tr>
<tr>
<td>Cholesterol, mg/d</td>
<td>NE</td>
<td>327 ± 138</td>
<td>185 ± 82**</td>
<td>192 ± 76*</td>
</tr>
<tr>
<td>Carbohydrates, % of energy</td>
<td>45-65%</td>
<td>47.4 ± 7.9</td>
<td>59.1 ± 8.2***</td>
<td>61.6 ± 8.7***</td>
</tr>
<tr>
<td>Fiber, g/d</td>
<td>21-38</td>
<td>20.4 ± 4.5</td>
<td>32.5 ± 7.4***</td>
<td>28.4 ± 6.8***</td>
</tr>
<tr>
<td>Protein, % of energy</td>
<td>10-35%</td>
<td>17.0 ± 4.1</td>
<td>12.3 ± 2.7***</td>
<td>13.7 ± 4.3***</td>
</tr>
<tr>
<td>Protein, g/d</td>
<td>Based on body weight</td>
<td>97.8 ± 25.9</td>
<td>70.9 ± 12.9**</td>
<td>69.9 ± 18.4**</td>
</tr>
<tr>
<td>Animal Protein, g/d</td>
<td>NE</td>
<td>68.5 ± 24.7</td>
<td>37.5 ± 15.2***</td>
<td>40.9 ± 20.3**</td>
</tr>
<tr>
<td>Plant Protein, g/d</td>
<td>NE</td>
<td>29.3 ± 7.2</td>
<td>33.3 ± 14.4</td>
<td>29.0 ± 6.8</td>
</tr>
<tr>
<td>Protein, g/kg</td>
<td>0.8</td>
<td>1.39 ± 0.40</td>
<td>1.01 ± 0.19**</td>
<td>0.99 ± 0.25**</td>
</tr>
<tr>
<td>Fruits and vegetables, g/d</td>
<td>NE</td>
<td>441 ± 258</td>
<td>1201 ± 355***</td>
<td>1214 ± 389***</td>
</tr>
</tbody>
</table>

**Fluids**

| Fluids                        | 2700-3700                | 3229 ± 573      | 4628 ± 855***   | 4575 ± 1076**   |

**Solute Intake**

| Sodium, mEq/d                | 57-65                    | 155.8 ± 45.7    | 102.8 ± 23.5**  | 99.0 ± 25.8**   |
| Sodium, mEq/kg               | -                        | 2.26 ± 0.87     | 1.45 ± 0.29**   | 1.41 ± 0.37**   |
| Potassium, mEq/d             | 120                      | 74 ± 14         | 116 ± 21***     | 111 ± 24***     |
| Calcium, mEq/d               | 50-60                    | 63 ± 26         | 68 ± 34         | 64 ± 32         |
| Magnesium, mEq/d             | 25.5-34.5                | 30 ± 7          | 39 ± 17         | 36 ± 17         |
| Phosphorus, mEq/d            | 45                       | 94 ± 18         | 81 ± 13         | 75 ± 10**       |
| Sulfur, mEq/d                | NE                       | 9 ± 3           | 6 ± 1***        | 6 ± 2***        |
| OA, mEq/d                    | NE                       | 43.1 ± 3.8      | 43.0 ± 3.7      | 43.1 ± 3.7      |

**Dietary Acids**

| PRAL, mEq/d                  | NE                       | 14.9 ± 20.0     | -44.0 ± 24.0*** | -41.7 ± 27.9*** |
| NEAP, mEq/d                  | NE                       | 57.9 ± 21.4     | -1.0 ± 23.6***  | 1.4 ± 28.0***   |

<sup>1</sup> Values are means ± SDs. ADPKD, autosomal dominant polycystic kidney disease; AI, adequate intake; AMDR, acceptable macronutrient dietary range; DRI, dietary recommended intake; NE, Not established; NEAP, net endogenous acid production; OA, organic acids; PRAL, potential renal acid load.

<sup>2</sup> Acceptable Macronutrient Dietary Range, Adequate Intake (ranges based on gender and age ranges), or Recommended Dietary Allowances (ranges based on gender and age ranges) as appropriate.

<sup>3</sup> Based on 25-30 kcal/kg actual body weight

*p ≤ 0.05 compared to baseline.

**p ≤ 0.01 compared to baseline.

***p ≤ 0.001 compared to baseline.
Figure 2.2 Box plots of dietary intake and excretion in 11 ADPKD patients. (A) Sodium estimated from diet records compared to (B) sodium excretion in urine collections at baseline, 2 weeks, and 4 weeks. (C) Protein intake estimated from diet records compared to (D) protein calculated from urea in urine collections at baseline, 2 weeks, and 4 weeks. (E) Net endogenous acid production (NEAP) estimated from diet records compared to (F) net acid excretion.
excretion (NAE) in urine collections at baseline, 2 weeks, and 4 weeks. The bottom and top of the boxes span the 25th and 75th percentile of data points. The dark bar within the box indicates the 50th percentile or median. The whiskers indicate 1.5 times the interquartile range from the lower and upper quartiles. *p ≤ 0.05 versus respective baseline, ^p ≤ 0.01 versus respective baseline, *p ≤ 0.001 versus respective baseline. o indicates outliers. *protein intake was calculated from urea excretion (49). ADPKD, autosomal dominant polycystic kidney disease; NEAP, net endogenous acid production; OA, organic acids; PRAL, potential renal acid load.

Figure 2.3  Box plots of fluid intake and excretion in 11 ADPKD patients. (A) Fluid intake predicted from diet records compared to (B) daily urine volumes at baseline, 2 weeks, and 4 weeks. (C) Mean 24h urine osmolality at baseline, 2 weeks, and 4 weeks; goal of ≤ 285 mosm/kg H$_2$O was reached by all but one participant. The bottom and top of the boxes span the 25th and 75th percentile of data points. The dark bar within the box indicates the 50th percentile or median. The whiskers indicate 1.5 times the interquartile range from the lower and upper quartiles. *p ≤ 0.05 versus respective baseline, ^p ≤ 0.01 versus respective baseline, *p ≤ 0.001 versus respective baseline. ADPKD, autosomal dominant polycystic kidney disease.
The extent to which the diet records reported what was actually consumed was examined in the urine recovery of key solutes at baseline (Tables 2.3, 2.4). We did not expect perfect correspondence, because subjects were expected to make timed collections and record diet consumption; however, the recoveries of sodium (95.9%), urea (85.4%), and potassium (88.8%) were excellent. Urine volume was 558 ml less than the intake reported in the diet record, likely due to insensible losses during the summer months. The mean urine osmolality at baseline was skewed with 8 of 11 greater than plasma (285 mosm/kg H2O).

**Table 2.4**  
**Urine constituents in 11 individuals with ADPKD by study visit**

<table>
<thead>
<tr>
<th>Urinary Solute Excretion</th>
<th>Baseline</th>
<th>2 weeks</th>
<th>4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium, mEq/d</td>
<td>149.4 ± 36.3</td>
<td>118.7 ± 42.9*</td>
<td>120.3 ± 35.5*</td>
</tr>
<tr>
<td>Potassium, mEq/d</td>
<td>65.9 ± 12.7</td>
<td>101.9 ± 31.4***</td>
<td>102.5 ± 23.9***</td>
</tr>
<tr>
<td>Calcium, mEq/d</td>
<td>8 ± 3</td>
<td>6 ± 3</td>
<td>6 ± 2**</td>
</tr>
<tr>
<td>Magnesium, mEq/d</td>
<td>8 ± 2</td>
<td>8 ± 2</td>
<td>8 ± 3</td>
</tr>
<tr>
<td>Chloride, mEq/d</td>
<td>147 ± 31</td>
<td>128 ± 42</td>
<td>130 ± 32</td>
</tr>
<tr>
<td>Phosphorus, mEq/d</td>
<td>50 ± 13</td>
<td>43 ± 11*</td>
<td>47 ± 8</td>
</tr>
<tr>
<td>Sulfur, mEq/d</td>
<td>41 ± 8</td>
<td>31 ± 8***</td>
<td>32 ± 8***</td>
</tr>
<tr>
<td>Urea Nitrogen, g/d</td>
<td>11.17 ± 2.39</td>
<td>7.83 ± 2.47***</td>
<td>8.14 ± 2.30***</td>
</tr>
<tr>
<td>Uric Acid, mg/dL</td>
<td>573 ± 99</td>
<td>527 ± 120</td>
<td>559 ± 87</td>
</tr>
<tr>
<td>Creatinine, mg/d</td>
<td>1600 ± 294</td>
<td>1491 ± 254*</td>
<td>1495 ± 213*</td>
</tr>
<tr>
<td>Urine osmoles, mosm/d</td>
<td>843 ± 121</td>
<td>718 ± 153**</td>
<td>726 ± 118*</td>
</tr>
<tr>
<td>Urine osmolality, mosm/kg</td>
<td>335 ± 84</td>
<td>205 ± 55***</td>
<td>216 ± 70***</td>
</tr>
</tbody>
</table>

**Fluids**

| Urine volume, mL         | 2671 ± 740 | 3642 ± 849*** | 3598 ± 1005* |

**Urinary acid-base excretion**

| Urine pH, units          | 5.90/6.06 | 6.26/6.90 | 6.21/6.78 |
| Bicarbonate, mEq/d       | 1.50 ± 1.20 | 3.45 ± 2.51** | 3.91 ± 2.85** |
| Net Acid Excretion, mEq/d| 37.8 ± 14.3 | 18.1 ± 17.0*** | 16.6 ± 22.5*** |

---

1. Values are means ± SDs. ADPKD, autosomal dominant polycystic kidney disease.
2. Urinary sulfur was estimated based on an average content of methionine (2.4%) and cysteine (2.0%) from protein intake based on Remer’s equation (40). Protein intake was calculated from the urea excretion (49).
3. mean/median.
4. *p ≤ 0.05 compared to baseline.
5. **p ≤ 0.01 compared to baseline.
6. ***p ≤ 0.001 compared to baseline.
Treatment Outcomes

Subjects eating the test diet had an insignificant decrease in calorie intake, a reduction in dietary fat and protein related to the lower animal protein intake, and an increase in carbohydrates, related to the higher intake of fruits and starchy vegetables (Table 2.3). All macronutrients remained within acceptable ranges.

Subjects also reached the goals for sodium (≤ 1.5 mmol/kg), protein (≤ 1 g/kg), and fluid intake (urine osmolality ≤ 285 mosm/kg) tailored for each patient; changes that were sustained throughout the experimental period (Figure 2.2). Potassium intake increased 150% from baseline, while there was no change in calcium or magnesium. With the increase in potassium and the reduction in protein, NEAP decreased from baseline by ~58 mEq/d at the two week and four week visits.

Sodium excretion decreased (-20%) and potassium excretion increased (+155%) reflecting the changes in the dietary prescription (Figure 2.2). Urea excretion and urinary calcium decreased 28% and 29%, respectively, in response to the decrease in dietary protein intake (50). Urine magnesium excretion remained stable throughout the study. NAE decreased 46% below baseline and was accompanied by a sustained rise in urine pH of 0.33/0.78 (mean/median) units (Figure 2.2, Table 2.4). Urine volume increased 35% above baseline consistent with a 43% increase in fluid consumption and mean osmolality declined reaching the 285 mosm/kg H₂O target in 10/11 subjects (Tables 2.3, 2.4, Figure 2.3).

Body weight and BMI did not change whereas systolic blood pressure tended to decrease during treatment possibly responding to the decrease in sodium intake and increases in potassium intake (Table 2.5). BUN was significantly reduced reflecting the decreased animal-sourced protein intake and serum potassium levels increased significantly secondary to the increased intake of fruits and vegetables.
Table 2.5
Serum components, anthropometrics, and blood pressures in 11 individuals with ADPKD by study visit

<table>
<thead>
<tr>
<th>Serum</th>
<th>Baseline</th>
<th>2 weeks</th>
<th>4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium, mEq/L</td>
<td>137 ± 2</td>
<td>138 ± 2</td>
<td>136 ± 1</td>
</tr>
<tr>
<td>Potassium, mEq/L</td>
<td>3.8 ± 0.3</td>
<td>4.0 ± 0.3</td>
<td>4.1 ± 0.3**</td>
</tr>
<tr>
<td>Chloride, mEq/L</td>
<td>104 ± 2</td>
<td>103 ± 2</td>
<td>103 ± 2</td>
</tr>
<tr>
<td>CO₂, mmol/L</td>
<td>27 ± 2</td>
<td>27 ± 2</td>
<td>28 ± 2</td>
</tr>
<tr>
<td>Anion Gap, mEq/L</td>
<td>7 ± 2</td>
<td>7 ± 3</td>
<td>6 ± 2</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>83 ± 9</td>
<td>86 ± 10</td>
<td>87 ± 13</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>20 ± 8</td>
<td>15 ± 8***</td>
<td>15 ± 9**</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.97 ± 0.24</td>
<td>0.98 ± 0.32</td>
<td>0.98 ± 0.28</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m²</td>
<td>84 ± 25</td>
<td>85 ± 27</td>
<td>83 ± 26</td>
</tr>
<tr>
<td>Uric Acid, mg/dL</td>
<td>4.8 ± 1.6</td>
<td>4.7 ± 1.5</td>
<td>4.8 ± 1.5</td>
</tr>
<tr>
<td>Calcium, mg/dL</td>
<td>9.7 ± 0.3</td>
<td>9.7 ± 0.5</td>
<td>9.7 ± 0.3</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic, mmHg</td>
<td>129 ± 11</td>
<td>120 ± 12*</td>
<td>123 ± 11</td>
</tr>
<tr>
<td>Diastolic, mmHg</td>
<td>77 ± 7</td>
<td>77 ± 8</td>
<td>78 ± 8</td>
</tr>
<tr>
<td>Anthropometrics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>71.3 ± 12.4</td>
<td>71.1 ± 12.1</td>
<td>71.3 ± 12.3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.9 ± 5.1</td>
<td>24.8 ± 5.0</td>
<td>24.9 ± 5.1</td>
</tr>
</tbody>
</table>

Values are means ± SDs. ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

*\(p \leq 0.05\) compared to baseline.

**\(p \leq 0.01\) compared to baseline.

***\(p \leq 0.001\) compared to baseline.

Nutrition Hassles Questionnaire Outcomes

Overall, only one participant reported any of the hassles as “moderately severe” and no hassles were reported as “extremely severe” (Table 2.6). “Somewhat severe” hassles that are noteworthy include planning meals, tracking fruits and vegetables, tracking protein points, tracking fluid intake, and cooking differently. Interestingly, 9 out of 11 (82%) of participants reported that preparing meals was “not a hassle” while only 3 individuals (36%) thought that planning meals was “not a hassle” indicating that planning ahead was more of a hassle than actually preparing the meals.
### Table 2.6
Hassles questionnaire responses in 11 individuals with ADPKD

<table>
<thead>
<tr>
<th>Hassles</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not a hassle</td>
</tr>
<tr>
<td>Planning meals</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Not enough money for food</td>
<td>10 (91)</td>
</tr>
<tr>
<td>Preparing meals</td>
<td>9 (82)</td>
</tr>
<tr>
<td>Tracking fruits and vegetable points</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Tracking protein points</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Tracking fluids for the day</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Limiting sodium in the diet</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Other individuals in your house won’t eat what is prepared</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Planning meals</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Not enough money for food</td>
<td>10 (91)</td>
</tr>
<tr>
<td>Preparing meals</td>
<td>9 (82)</td>
</tr>
<tr>
<td>Tracking fruits and vegetable points</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Tracking protein points</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Tracking fluids for the day</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Limiting sodium in the diet</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Other individuals in your house won’t eat what is prepared</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Cooking differently</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Not enough time to plan meals</td>
<td>9 (82)</td>
</tr>
<tr>
<td>Not enough time to prepare meals</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Concerns about other’s perceptions of your diet</td>
<td>10 (91)</td>
</tr>
<tr>
<td>Not fully understanding what to do</td>
<td>10 (91)</td>
</tr>
<tr>
<td>Grocery shopping</td>
<td>9 (82)</td>
</tr>
<tr>
<td>Using handouts that were given to follow diet</td>
<td>9 (82)</td>
</tr>
<tr>
<td>Meeting family responsibilities</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Meeting your responsibilities</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Eating out</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Cooking for someone else</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Being well-prepared</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Helping to improve someone else’s health</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Identify appropriate food for meals and snacks</td>
<td>0</td>
</tr>
<tr>
<td>Choose appropriate foods to satisfy hunger</td>
<td>0</td>
</tr>
<tr>
<td>Prepare variety of fruits and vegetables</td>
<td>0</td>
</tr>
<tr>
<td>Provide meat as a side dish instead of an entree</td>
<td>0</td>
</tr>
<tr>
<td>Ask for help from family and friends when needed</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Limit protein foods in the diet/follow restriction</td>
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</tr>
<tr>
<td>Limit sodium in meals</td>
<td>0</td>
</tr>
<tr>
<td>Prepare high fruit/vegetable point meals</td>
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<td>Prepare recipes that incorporated fruits/vegetables</td>
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<tr>
<td>Educate others about high fruit/vegetable point foods</td>
<td>0</td>
</tr>
<tr>
<td>Drink prescribed fluids</td>
<td>0</td>
</tr>
<tr>
<td>Eat prescribed fruits/vegetables points</td>
<td>0</td>
</tr>
</tbody>
</table>

1 n(%) (all such values). ADPKD, autosomal dominant polycystic kidney disease.

Of the 11 participants, five experienced uplifts such as cooking for someone else, and meeting family and one’s own responsibilities whereas six did not (Table 2.6).
Ten out of 11 individuals were “somewhat confident” or “very confident” that they could manage the new diet (Table 2.6).

Discussion

The relatively complex diet prescription used in this trial was designed to mitigate risk factors that have recently been shown to associate with the development of large cystic kidneys that progress at accelerated rates to renal failure. None of the individual components in the diet is unique; however, the limitation of sodium and animal-sourced protein intake together with the increased consumption of fruits, vegetables and water has not been evaluated previously in patients with ADPKD. Poor compliance with single component dietary regimens, e.g. sodium, is relatively high in the population at large, so it would be reasonable to suppose that adding more elements to the prescription would further undermine meaningful acceptance. In this respect, ADPKD patients differ from the usual. Many watched a parent or a sibling proceed along the path to kidney failure, dialysis and renal transplantation and appear to be primed to follow medical regimens that may slow the course of the disease. We were pleased to see, with the exception of one person, how well the participants in this study mastered the complexities of diet preparation and record keeping with only modest stress based on their responses to the hassles questionnaire. Although the majority of participants reported planning meals and tracking points as hassles, self-efficacy for managing the prescribed diet was high.

Dietary sodium intake has been extensively evaluated in hypertensive disorders and limitations in the diet to a varying degree have been shown to have an important role in bringing blood pressure into the normal range (51, 52). The hypertension commonly found in ADPKD has an extracellular fluid volume-dependent component involving sodium retention as well as increased renin release secondary to the effects of cysts on renal arterioles. In the current study, the reduction in sodium intake was associated with a tendency for systolic blood pressure to decrease, although remaining in the normal range. For reasons that are just now being unraveled, high sodium intake is associated with larger kidneys and a
faster decline in renal function in ADPKD making sodium a lifestyle factor worthy of strict control (9, 53).

The intake of animal-sourced protein has also been shown to affect cyst growth (18). In the Consortium for Radiologic Imaging of PKD (CRISP) study, ADPKD patients who excreted the largest amounts of urea, a surrogate for protein intake, had larger kidneys that progressed more rapidly to renal failure (9, 18). The mechanisms that render increased animal-sourced protein intake harmful to polycystic kidneys are unknown. In the current study, animal-sourced protein intake was reduced but not to extreme levels. To do otherwise would likely defeat overall compliance and put patients at risk of protein-energy wasting.

Normal kidneys buffer proton excretion with ammonium and phosphate, keeping the concentration of hydrogen ions in plasma and urine relatively low and less likely to injure nephrons. Increased acid excretion accelerated the progression of ADPKD in an animal model of the disorder and the administration of alkali reversed the downward trend (12, 23). Recent studies of chronic progressive renal insufficiency in patients with hypertensive nephropathy approaching the end-stage of the disease have exposed the harmful effects of hydrogen ion excretion in patients eating regular diets containing abundant acid precursors (13, 14). These findings were recently validated in a nationally representative cohort of individuals with chronic kidney disease showing that individuals with higher dietary acid intake progress to kidney failure more rapidly than their low dietary acid consuming peers (16). The mechanisms by which hydrogen ions stimulate renal cyst growth are unknown; however, in light of these studies it seems rational to reduce the amount of dietary acids precursors. In the current study, we show that patients with ADPKD will modify the intake of fruits, vegetables, and animal-sourced proteins sufficient to decrease the excretion of protons in the urine for at least four weeks. NEAP was significantly reduced in the diet and NAE was significantly reduced in the urine, corresponding metrics confirming that the diet prescription met the goal of reducing the excretion of protons (Tables 2.3, 2.4). In view of the excellent recovery of other dietary components, we cannot account for finding the change
in NAE (-20.5 mEq) only 36% as great as NEAP (-57.5 mEq/d). Interestingly, similar discrepancies between NEAP and NAE have previously been found in clinical trials even when urine collections were performed in a clinical trials unit (13, 33). The discrepancy between NEAP and NAE may reside in the estimate of endogenous organic acid (OA) contributions to NEAP. As proposed by Remer, et al., a greater percentage error may occur in diets with a considerable intake of fruit since they contain certain acids that are incompletely metabolized which are not taken into account in the estimation of OA (40).

AVP is a major extrinsic factor that influences cyst growth in PKD (47, 54). An inhibitor targeting the AVP-V2 receptor slowed disease progression in patients with ADPKD (55). Studies in an animal model of PKD lead us to think that reducing plasma AVP levels by increasing the intake of water might have a similar effect on cyst growth (25). Urine osmolality levels exceeding plasma values (~285 mosm/kg H₂O) indicate that circulating levels of AVP are high enough to increase water reabsorption in collecting ducts. In the current study, baseline mean 24-hour urine osmolality in ADPKD patients ranged from 170 to 480 mosm/kg H₂O; values determined throughout the day or night could be higher or lower than the 24-hour mean value, but in general they run above plasma levels in the vast majority of patients (Figure 3)(9, 56). All of the subjects reduced urine osmolality below their individual baseline values and in 91% osmolality was reduced below that of plasma, changes that would certainly be associated with lowered levels of plasma AVP perfusing renal tubules and cysts. Achieving an average 24-hour osmolality goal of 285 mosm/kg H₂O seems reasonable in the short term until formal clinical trials produce results indicating that lower levels of urine osmolality are more protective and can be achieved without harm.

The current study illustrates that in most patients with ADPKD good to excellent compliance can be expected when modest limitations of salt and protein are combined with an increased intake of fruits, vegetables, and fluids. Low sodium, low protein, and weight loss diets are notoriously difficult to maintain over the long term and the increased water drinking prescription to reduce urinary stone formation and shedding is commonly ignored (57-60). To counter these tendencies, in the current study
we offered a palatable diet, relatively simple to prepare, coupled with intense counselling at the outset. One of the 12 enrollees attended all of the sessions but was unable to record dietary information or collect urine samples and we excluded the subject from the final analysis. Of the remaining 11 subjects, >90% reported that none of the dietary hassles were worse than “somewhat severe”, the lowest form of severity on the questionnaire, and the majority of patients were “somewhat confident” or “very confident” in their knowledge and abilities to follow the diet. A treatment plan that frequently reinforces the importance of the prescribed diet as long-term protection from kidney harm would likely gain acceptance by most patients with ADPKD given the seriousness of the condition at the end stage.

Limitations in this study include the small sample size and short duration dictated by funding constraints, and a lack of kidney function markers that could monitor renal damage and changes in function over such a short interval of time. Despite these concerns, a pilot study of a relatively complex prescription was needed to determine if it was reasonable to proceed to a more expansive and expensive clinical trial of sufficient length to establish efficacy in respect to disease progression. The results support the design and execution of a larger scale controlled clinical trial to determine if modifying dietary components will slow the progression of ADPKD. Strengths in this study include being the first to address the utility of attacking multiple dietary targets in ADPKD in conjunction with multiple 24-hour urine collections to verify diet records in an outpatient setting.

In conclusion, the experimental diet tested successfully in this study targets factors known to accelerate the progression of ADPKD. Based on the urinary verification of dietary limits and the good acceptance by the participants, this new PKD diet will help to justify a controlled clinical trial to determine the extent to which dietary modifications may ameliorate hypertension, renal pain, hematuria and the progression of biomarkers of renal dysfunction in children and adults.
CHAPTER THREE

Dietary behavior changes and adherence to a low osmolar, low acid diet in individuals with polycystic kidney disease
Abstract

**Background:** Salt, protein, acid precursors, and fluid intake have been identified as factors that influence cyst growth in ADPKD. The purpose of this study is to understand better the experiences of patients following a relatively complex dietary prescription targeting these factors.

**Study Design:** Qualitative study with semi-structured interviews.

**Setting & Participants:** Twelve adults with ADPKD and kidney function >30ml/min/1.73m² were recruited from the University of Kansas Medical Center Polycystic Kidney Disease clinic.

**Methodology:** Semi-structured interviews of participants were conducted following a four week dietary intervention either face-to-face or by telephone.

**Analytical Approach:** Transcripts were analyzed thematically.

**Results:** Participants reported that eating less meat and more fruits and vegetables were the easiest components of the diet, whereas reaching the daily goal amount of fruits and vegetables and tracking the diet constantly were the most difficult components. Participants had little difficulty with fluid intake and reported the prescribed fluid goal as achievable. The tracking system for fruits and vegetables and protein was reported to be both helpful and intuitive, but tracking their intake on paper was tedious. Eating out was the most significant barrier to following the diet with some individuals avoiding restaurants in order to comply with the dietary prescription. Participants reported that an app to reduce the burden of pen and paper tracking of individual dietary components is needed.

**Limitations:** Interviews were conducted on a small sample among a group of predominately middle-aged individuals with moderately reduced kidney function. These findings might not be representative of those under 18 years of age or near the end-stage of disease progression.
**Conclusions:** Participants became more aware of what they were consuming and thought that long-term dietary adherence was feasible by most patients. The development of a user-friendly app or device to track the diet would help maintain long-term adherence.
Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disorder characterized by the growth of cysts in the kidney and is the fourth leading cause of renal failure world-wide (6). Dietary constituents including salt, protein, acid precursors, and fluid intake have all been identified as factors that influence cyst growth and progression to kidney failure in ADPKD (9, 12, 13, 15, 16, 23, 25, 29-32). Unfortunately, adherence to single component dietary prescriptions such as low sodium, low protein, or high fluid intake is relatively poor in the population as a whole, so adding more elements to the prescription would likely reduce long-term acceptance (57-60). Moreover, given that damage occurs to cystic kidneys for a lifetime, adherence to a dietary intervention must begin early and be a life-long commitment. Only recently has a composite dietary pattern reducing sodium, protein, acid precursors, and increasing fluid intake been prescribed, prepared, and followed by patients with ADPKD successfully; however, long-term adherence to this diet remains unstudied (61).

To improve treatment adherence and inform clinical practice, we performed a qualitative research study that expresses the views of individuals with ADPKD while following a diet designed to ameliorate disease progression. Understanding these views and experiences may help identify issues that would lead to long-term nonadherence, a behavior that would render the therapy ineffectual. To understand better the patient’s perspectives on following a relatively complex dietary prescription targeting dietary salt, protein, acid precursors, and fluid intake designed to slow disease progression, we interviewed individuals with ADPKD who had just completed a four week evaluation of a complex dietary prescription.

Methods

Design and Setting

A qualitative study was designed to follow a four week dietary intervention trial to lower the intake of sodium, protein, and acid-precursors and augment the intake of fruits, vegetables, and fluid (61). Briefly, a comprehensive dietary history and two complementary 24-hour urine collections were analyzed.
to determine the intake and excretion of fluid, electrolytes, and protein on the subjects’ usual diet. At baseline, subjects received instructions on how to modify their diet for the next four weeks. Each subject served as their own control in this pre-post feasibility study. The experimental diet was tailored for individual subjects based on their pre-study dietary intake of sodium, protein, fluid and net endogenous acid production (NEAP)(derived from three-day diet records) and measurements of urine osmolality and urine volume (26, 35, 39). The test diet was followed for the next four weeks which included limiting sodium to 1 – 1.5 mEq/kg, protein to 0.8 – 1.0 g/kg body weight/day (prescribed as points with 1 point equivalent to 7 grams of protein), consuming enough fruits and vegetables to reduce NEAP by 50% from baseline (prescribed as points with 1 point reducing NEAP 1 mEq), and drinking enough fluid to reduce mean urine osmolality to ≤ 285 mosm/kg H2O/day. The aims of the current study were to determine (1) what aspects of the diet were the easiest to follow, (2) what aspects of the diet were most difficult to follow, (3) barriers to following the diet, and (4) what can be done to improve the dietary regimen to promote long-term adherence. This study was approved by the Human Subject Committee at the University of Kansas Medical Center. Informed consent was obtained prior to the start of the dietary intervention trial. This trial was registered at clinicaltrials.gov (NCT01810614).

Data Collection

Face-to-face semi-structured interviews were conducted at the clinical and translational science unit, and, if not possible, phone interviews were conducted after the last study visit by an experienced, qualitative researcher (LP) with whom they had no previous contact. The semi-structured interviews allowed participants to describe their experiences of following the prescribed diet in depth and detail. This process was intended to enrich the findings from the trial that examined the effectiveness of the intervention. All interviews were conducted using an interview guide developed by the study team (Supplementary Table 3.1, Appendix I). Participants were asked semi-structured, open-ended questions about the diet and their overall perceptions about the dietary intervention. All interviews were recorded digitally and transcribed verbatim.
Data Analysis

A thematic analysis was conducted from the transcripts of the semi-structured interviews to explore what components of the diet were the easiest to follow, what barriers made adherence to certain components difficult, and participants’ perspectives on areas for improvement that may improve long-term dietary adherence (62). Interviews were reviewed by 3 researchers independently (JMT, LP, CAG), and the interview guide was used as a coding framework for analysis (63). Summaries were organized for each theme to facilitate discussion and analysis by team members (64). Reliability and trustworthiness were established through discussion of any discrepancies among team members and re-examination of the transcripts was undertaken until consensus was achieved (65). Specific quotes were chosen to represent themes that emerged from the transcripts. Participants did not contribute to data analysis or interpretation.

Results

Participant Characteristics

Twelve participants were enrolled in the dietary intervention trial and all participated in the interviews. Interviews ranged from 12 to 59 minutes (median, 28 min). The age range of participants was 22 to 65 years (mean, 48 years). The majority of participants were female (n=7; 58%) and Caucasian (n=10; 83%). Participants had a mean BMI of 25.03 kg/m², mean blood pressure of 129/78, and had an estimated glomerular filtration rate of 83 +/- 22 ml/min/1.73m² (mean +/- SD). Table 3.1 includes basic characteristics of each participant.
Table 3.1
Demographic characteristics of individuals with ADPKD

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<th>ID code</th>
<th>Age, y</th>
<th>Gender</th>
<th>Race</th>
<th>Marital Status</th>
<th>Family history of PKD</th>
<th>Dx date</th>
<th>Stage of CKD</th>
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ADPKD, autosomal dominant polycystic kidney disease; y, year; PKD, polycystic kidney disease; CKD, chronic kidney disease

Qualitative Findings

The six themes and quotes presented below represent the most salient features identified by the subjects.

Theme 1: Easiest components of the diet to follow

Participants (4 men, 4 women) reported that reducing their meat intake was much easier than they anticipated and for some was the easiest component of the diet to follow.

“The easiest I guess probably cutting back on the protein was a pretty simple process. Just don’t eat meat, so that was...that was really easy.” (P7, Female, CKD Stage 1)

Participants also reported that eating more fruits and vegetables, especially those higher in points, was enjoyable and easy to follow.

“I actually really enjoy a lot of the higher point foods. So I think, shockingly, the vegetables were the easiest part for me once I realized...once I realized what I needed in order to get my points for the day.” (P10, Female, CKD Stage 1)
One participant stated that reducing protein in the diet was easy, because the focus was on eating more fruits and vegetables, which essentially replaced meat at meals.

“The focus was on [eating more] fruits and vegetables so...um...I did find it easy to...uh...reduce the protein. I’m not as big a meat eater as I thought. I didn’t miss it like I thought I would.” (P2, Female, CKD Stage 3A)

Theme 2: Most difficult components of the diet to follow

While participants reported eating more fruits and vegetables as one of the easiest components of the diet, reaching the amounts prescribed on the diet was one of the most difficult.

“Just getting enough fruits and vegetables [was difficult] because I have such a high point amount that I usually just ended up picking the highest amount points of fruits and vegetables that I could find and I ended up eating a lot of like...dried fruits and such.” (P5, Female, CKD Stage 1)

Theme 3: Ability to track the diet

With regards to the fruits and vegetables point system, participants reported that it was intuitive and easy to understand. Participants did report some uncertainty when it came to tracking the number of points from particular fruits and vegetables since they were all standardized to half cup portions.

“I thought it was...very...very easy. Especially since we have a scale at home so it was pretty easy to measure out. The fruits and vegetable point system I thought was very, very easy and intuitive.” (P8, Male, CKD Stage 1)

“Um...trying to figure out exactly how to measure things. The hardest thing for me to measure was a banana.” (P2, Female, CKD Stage 3A)
Participants also stated that the protein point system was easy to follow with some reporting it as the easiest part of the diet. A few participants reported difficulty tracking the amount of protein using the point system. They preferred to measure protein in grams as an alternative.

“I think that part was probably the most simplest thing of all.” (P6, Female, CKD Stage 2)

“It would have been easier to me to measure how many grams of protein that I’m supposed to eat instead of how many points.” (P2, Female, CKD Stage 3A)

Participants thought that reducing sodium was easy, but many did not track the exact amount consumed. Participants reported avoiding high sodium foods by reading food labels, not adding salt to foods or replacing with sodium free seasonings while cooking and at the dinner table, and eating at home more frequently to reduce sodium from processed foods and fast food restaurants.

“Well I actually didn’t try to track the sodium much because the difference in the foods I was eating...fresh fruits, fresh vegetables, with no sodium. There were very few things I was putting salt on or having sodium in it.” (P2, Female, CKD Stage 3A)

‘Um...I did my best to reduce sodium, but it wasn’t something that I actively thought about too much. Um...I think part of the reason that my sodium level went down was we were just eating more food at home and less uh...take-out or whatever and that naturally just kind of reduces the sodium level.” (P8, Male, CKD Stage 1)

Most participants reported that while they had to drink more fluid on the diet, it was an attainable amount. Participants primarily reported tracking fluids using a specific size water bottle and tracking the number of bottles consumed each day to account for fluids consumed. Participants stated that when they struggled to reach their goal intake it was because they didn’t have their water bottle with them.

“Uh, I was already drinking quite a bit. Um...I’ve made that a goal more recently to drink more because I know it’s better for me. Um...so I didn’t really add much more for this diet to what I was
drinking before. But yeah, the only time I really do struggle is if I don’t have my water bottle on me or access to any fluids.” (P5, Female, CKD Stage 1)

“Um...I had a couple of water bottles that I kept in the fridge that were, you know, a specific amount. And then I just tracked...the water bottles were 20 ounce each so...I just kept trying to make sure that I always had one going and, you know, where I could see it and then I would just make the effort to drink from it.” (P7, Female, CKD Stage 1)

Participants reported that certain aspects of tracking were difficult to do, primarily in relation to keeping a tally of everything they were eating day in and day out. While participants were able to track their dietary intake over the course of the study (4 weeks), most participants reported that they would not be able to track it using paper documents over the course of their lifetime due to the hassle of writing everything down and tallying their intake manually. Participants reported that they would continue to make dietary changes after completion of the study, but did not feel confident in their ability to continue to track it on a daily basis.

“Most difficult [was] probably having to track every day, every single day. So for me, [it was] documenting it all.” (P1, Female, CKD Stage 2)

“I’m not so much going to track it by points, but just make a conscious effort to eat less protein and more fruits and vegetables just all the time.” (P9, Male, CKD Stage 1)

“Well, I’m trying to kind of follow it somewhat. Well, just eat more fruits and vegetables and not eating so much meat and drinking lots of water because I know I need lots of fluids. No, I’m not really tracking it.” (P3, Male, CKD Stage 3A)
Theme 4: How diet affected other aspects of life

Participants reported a change in the way that they went grocery shopping with an emphasis on reading food labels more closely and selecting more fruits and vegetables, particularly those that were higher in points.

“I definitely spent a lot more time in like the fresh produce area of the grocery store than the rest of it. That was mostly what my diet was made up of.” (P5, Female, CKD Stage 1)

“If you take the list with you of the points it definitely made it a lot easier. I was like, oh hey, this is worth a lot of points, I’ll pick this up. It just made it a lot easier to carry that with me.” (P9, Male, CKD Stage 1)

Some participants avoided eating out due to the uncertainty of what they could eat whereas others reported spending more time looking at online nutrition facts prior to going out, so that they could make the most appropriate selections.

“We didn’t. I mean we did a couple times when I had the events planned but there were several times when we said oh, I guess we can’t do that. [When we did go out], I would look at Sheridan’s versus McDonalds ice cream/custard to see which one was better and we’d go to that one.” (P1, Female, CKD Stage 2)

A few participants even reported taking food with them to social events, so that they could ensure there would be appropriate foods available.

“You know, sometimes at a restaurant or at somebody else’s home when their serving food or whatever, they may not have what I should be eating. A lot of times I brought my own stuff.” (P7, Female, CKD Stage 1)
**Theme 5: Barriers to following the diet**

Attending social events, traveling, and dealing with family medical issues made it particularly difficult for participants to adhere to the prescribed diet. Most participants had to attend at least one social event during the four weeks on the diet or had to travel for personal or business reasons. Participants reported that social events and travel were the most likely times when the diet was not followed because of limited availability of food or having to eat out more frequently where no ideal options were available.

“I went out of town one day and I couldn’t really concentrate on the diet that day because I was out of town and I was busy. That day was hard. Going out of town made it really, really hard.” (P12, Female, CKD Stage 2)

Two individuals reported having to deal with family medical issues where taking care of others took precedent over following the diet at those times.

**Theme 6: Suggestions for improving diet**

Overall, eleven of the twelve participants were able to adhere to the diet over the course of the dietary intervention with eight participants reporting being able to adhere to the diet over a much longer period of time. However, participants reported that the use of an app for a phone was necessary to mitigate the challenges of tracking and tallying what was consumed over the course of the day.

“[Use of] a possible phone app. I mean that would probably work. I think I could do it that way just cause I’m always around my phone.” (P5, Female, CKD Stage 1)

“Most people have phones that you can take notes on or I would think. There might already be a food tracking app where you just like plug in as you go throughout your day. I think that would’ve been helpful.” (P10, Female, CKD Stage 1)
Participants also reported that additional recipes or meal/snack ideas that fit the diet would have been nice to make the initial transition to the diet easier. One participant stated that a gradual progression into each component of the diet might have helped make the initial transition a little easier.

“Like I don’t really know what’s out there that I could make, so maybe more like recipes ideas or something like that or what I can make and, you know, how to best get the higher points and stuff. I think that would help.” (P5, Female, CKD Stage 1)

“I think it would be better, if I were having to do this to start with one item. Like let’s start this week with protein. We want you to cut back your protein to this. Now you can eat as many fruits and vegetables as you want, but cut back your protein and learn to eat less protein. So get that down and then start looking at your sodium. And then start...you know what I mean? I think I would do it gradually because to just do it all at once was a complete diet change for me and I am a pretty healthy eater. I mean I really am, so for me it was still a transition so I can’t imagine what it’s like for someone who is a real meat and potatoes, eat outer…it would be hard.” (P1, Female, CKD Stage 2)

Discussion

In this study, there was general consensus that reducing portion sizes of meat and increasing intake of fruits and vegetables were the easiest components of the diet while keeping track of what they ate and reaching the prescribed goal amount for fruits and vegetables each day were the most difficult components. Participants thought the tracking system (points) for fruits and vegetables and protein was intuitive and easy to use. Although a few participants commented that some fruits and vegetables were difficult to measure since they were all measured in ½ cup portions (i.e. banana), and some participants would have liked the option to measure protein in grams. Participants did not track sodium intake, but instead avoided high sodium foods, salt-based seasonings, and limited eating at restaurants. Water intake was tracked by counting water bottles of a specific size to account for fluid consumed throughout the day and was reported as an attainable amount. Participants reported a change in how they shopped at the
grocery store and that the biggest barrier to following the diet involved being away from home (attending social events and traveling). Overwhelmingly, participants reported that to improve the diet, an app allowing them to track the diet more easily via their cell phones is necessary.

Reduction of salt is essential for patients with ADPKD due to the effects sodium has on raising blood pressure and stimulating the production of vasopressin, factors that likely accelerate the development of cysts in the kidneys (9, 51-53). Previous studies in patients with chronic kidney disease have shown that avoiding use of salt in cooking or at the table and eating fast food less frequently are more frequent behaviors in patients who report self-adherence to a low sodium diet (66). In our study, participants were able to reduce sodium citing these same behaviors are the primary ways they achieved reducing sodium in their diet. While, in general, adherence to a low sodium diet is poor, the employment of general sodium reduction guidelines (reducing salt and sodium-based seasonings and limiting eating at restaurants) seems to be effective at lower sodium consumption in individuals with ADPKD (60, 61).

Consumption of animal-sourced protein also plays a role in the growth of cysts in patients with ADPKD, making protein restriction a viable therapy for ADPKD (9, 18). In the MDRD study, people who were able to adhere to a low-protein diet were more likely to self-monitor intake more frequently and had better adherence when they had non-protein options to replace energy intake (67). Our dietary intervention used similar strategies, which included self-monitoring protein intake daily and replacing some of their meat intake with fruits and vegetables. Participants not only were able to reduce their consumption of protein, but also reported it as one of the easiest components of the diet to follow. Focusing on increasing consumption of fruits and vegetables as a way to take the focus away from meat as the primary entrée seems an effective and easy strategy to reduce protein intake even with typical Midwestern meat-laden diets.

Higher levels of acid excretion have shown to accelerate disease progression in an animal model of ADPKD, while the administration of alkali was able to reverse the damage (12, 23). Recent studies of
chronic progressive renal insufficiency in patients with hypertensive nephropathy approaching the end-stage of the disease have exposed the harmful effects of hydrogen ion excretion in patients eating regular diets containing abundant acid precursors (13, 14). Potassium aids in the renal excretion of dietary acids, and may be kidney protective, giving fruits and vegetables an important place in a variety of kidney diseases, including ADPKD. Patients in our study were able to increase consumption of fruits and vegetables for four weeks and stated that it was one of the easiest components to follow. However, participants did report issues with consuming the prescribed number of points from fruits and vegetables. Some participants made fruit smoothies in the mornings to secure a large portion of their points for the day to avoid consuming large quantities of fruits and vegetables in the evening to reach their prescribed points. The extent to which dietary acids need to be reduced is not known; however, lowering urinary acid excretion in ADPKD to any extent below the subject’s usual level might be beneficial over the long run.

Vasopressin stimulates cyst growth in ADPKD and an inhibitor targeting the vasopressin receptor (AVP-2) has been shown to slow disease progression (47, 54, 55). Increasing the intake of water might also have a similar effect on cyst growth (25). Participants reported that the amount of fluid prescribed on this diet was attainable and that the only barrier to achieving their intake was making sure they had their water bottle with them throughout the day. Patients with ADPKD are often instructed to treat fluid like a prescribed medication given its potential to slow cyst growth and in our dietary intervention the dose likely to lower vasopressin secretion to minimal amounts proved achievable by patients. Physicians should be discussing fluid intake with both adults and children diagnosed or presumed to have ADPKD, since patients even early in the course of the disease appear to be adherent to drinking fluids above the usual amount they would consume.

While participants were able to adhere to the diet for four weeks, most participants reported that while they would continue to try to follow the diet, they would not continue to track or maintain the prescribed dietary goals. Although participants indicated a greater awareness of their food and beverage
consumption, they remarked that substantial changes required by the prescribed diet were not sustainable. The use of apps for dietary changes has shown promise in getting patients to adhere to dietary changes, but most notably it has the ability to improve the willingness to stay on the diet long-term (68). Given that ADPKD is a slow progressing chronic disease, dietary changes would need to be prescribed at a very young age and be followed over the course of their lifetime. The development of an app specifically designed to track sodium, protein, dietary acid load, and fluids would go a long way in improving lifelong adherence to this diet. Given the importance of diet in progressive renal disorders, we think that positive reinforcement of the tested diet by renal dietitians might help patients maintain compliance.

Limitations in this study include the small sample size and enrollment of primarily middle-aged, Caucasian men and women with well-preserved kidney function. Due to the limited demographic of the dietary intervention trial, our qualitative results may not be representative of those individuals under 18 years of age or further along in the course of the disease. Despite these limitations, a qualitative study examining the perceptions following a relatively complex prescription was needed to determine if individuals with ADPKD thought they could follow this diet long-term or if modifications to the diet were needed. The primary strength of this study is that it is the first qualitative study conducted in individuals with ADPKD following a diet specifically designed to ameliorate ADPKD progression. Additionally, the implementation of our newly developed fruits and vegetables points system and protein point system for tracking NEAP and protein was found to be intuitive and easy to follow by most study participants which indicates that further use in dietary trials aimed at reducing dietary acids and protein seems reasonable.

This is the first qualitative study conducted in individuals with ADPKD following a composite dietary intervention that aims to address the dietary components that may accelerate disease progression. Exploring the views of patients on the prescribed diet provided valuable information for clinical practice and insight on how they managed their diets to slow the progression of ADPKD. Overall, participants in this study felt positive about making dietary changes, including a willingness to continue to increase the
consumption of fruits and vegetables, increase the intake of fluids, decrease the amount of protein, and reported a greater awareness of their dietary behaviors. Participants reported being able to reduce sodium, restrict protein intake, increase fruit and vegetable intake, and consume the appropriate amount of fluids with ease. The primary barriers to following the diet were attending social events and traveling. The primary factor participants reported as necessary for staying on the diet long-term was the development of an app to help track their dietary intake on a day-to-day basis. This study demonstrates that while patients are able to adhere to a low-sodium, low-protein diet augmented with fruits, vegetables, and fluids in the short-term, another way of monitoring dietary intake (e.g., an app) is necessary if planning to adhere to the diet over one’s lifetime.
CHAPTER FOUR

The Use of an Electronic Health Record Database to Determine if Body Mass Index and High-Density Lipoprotein are Risk Factors for ADPKD Progression
Abstract

**Background:** Electronic health records (EHRs) are an abundant source of untapped data that can be used to quickly identify and answer pertinent questions in the clinical setting.

**Objective:** To determine if body mass index (BMI) and high-density lipoprotein (HDL) are associated with the progression of autosomal dominant polycystic kidney disease (ADPKD) through the use of data collected from EHRs.

**Methods:** The clinical database (HERON) of the University of Kansas Medical Center identified 858 individuals with polycystic kidney disease. Three hundred sixty-three did not fit inclusion criteria leaving 495 in the final model. Height, weight, BMI, race, gender, serum creatinine, and HDL were obtained from HERON and the time to event (estimated glomerular filtration rate (eGFR) ≤ 15 ml/min/1.73m^2) or time to censoring (did not reach eGFR ≤ 15 ml/min/1.73m^2) was the patients age at the event or censoring.

**Results:** Data collected from the EHR did not show an association of BMI with age at kidney failure (p=0.69, HR=1.096, 95% CI 0.697-1.724) after controlling for the effect of HDL. By contrast, individuals with desirable HDL levels (Men & Women: ≥60 mg/dL) were associated with a significantly slower disease progression when compared to individuals with low (Men: <40 mg/dL; Women <50 mg/dL) (p=0.0147, HR=0.271, 95% CI 0.095-0.774) and acceptable (Men: 40-59 mg/dL; Women 50-59 mg/dL) HDL levels (p=0.0436, HR=0.319, 95% CI 0.105-0.968).

**Conclusion:** With the use of EHR data, we were able to demonstrate that patients with desirable HDL levels were associated with slower progression of ADPKD whereas BMI was not associated with disease progression. This study demonstrates that the EHR may prove useful in identifying modifiable risk factors for ADPKD progression through the use of routine clinical assessments.
Introduction

Electronic health records (EHRs) are an abundant source of untapped data that can be used to quickly identify and answer pertinent questions in the clinical setting. The use of EHR data ranges from determining the effectiveness of new and existing treatments to understanding the drug prescription patterns of physicians (69). EHRs can also be utilized by health care professionals to identify risks factors associated with progression of chronic diseases that would otherwise require large scale observational or randomized clinical trials to be conducted; both of which would require sizable amounts of time and money. Identifying these risk factors by using existing data obtained from patients in the clinical setting would allow physicians and researchers an expedited way to gather evidence of associations and to employ new interventions aimed at controlling these risk factors sooner and at lower costs than would otherwise be possible.

The Consortium for Radiologic Imaging of Polycystic Kidney Disease (CRISP) is an ongoing (2001-2015), observational, multicenter study of 241 people that is being conducted to identify markers of disease progression in patients with autosomal dominant polycystic kidney disease (ADPKD) (9). Subjects were examined at baseline and annually over the course of the study. Patients with higher a body mass index (BMI) and lower high-density lipoprotein (HDL) levels at baseline had a more significant increase in kidney volume and decrease in estimated glomerular filtration rate (eGFR) at 3 years and 6 years. Since EHRs regularly collect this type of data at patient visits, the use of EHRs to identify modifiable risk factors for ADPKD could be used on existing clinical data. Therefore, the goal of the present study was to determine if BMI and HDL were associated with ADPKD progression through data collected from EHRs.
Methods

Study Population

This study cohort was derived from the clinical database (HERON) of the University of Kansas Medical Center (KUMC). The cohort consisted of patients seen at KUMC between June 8, 2000 and March 4, 2014 who had been diagnosed with autosomal dominant polycystic kidney disease (ICD9: 753.13) or polycystic kidney disease, unspecified (ICD9: 753.12). Patients were included in the dataset if they had an eGFR of >15 ml/min/1.73m² at baseline (calculated using MDRD equation which also requires gender, race, age, and serum creatinine), at least one height and weight observation, and were ≥ 18 years of age. Patients were excluded if they had a diagnosis of autosomal recessive polycystic kidney disease (ICD9: 753.14) or did not meet all of the inclusion criteria (Figure 1). Data obtained from HERON was de-identified, so actual dates of observations including date of birth may have been offset by up to 365 days.
Figure 4.1 Consort diagram of patients meeting exclusion criteria and final analysis totals. PKD, polycystic kidney disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein

Data Handling

Laboratory, anthropometric, and demographic data was initially requested from the HERON database on any patients with a diagnosis of polycystic kidney disease (autosomal dominant, autosomal recessive, or unspecified). There were a total of 786,390 observations amongst 858 patient records. Data were reduced to single observations for BMI, HDL, and age at event or censoring, and all other observations and variables included in the initial dataset were removed.
For height and weight, the median value was taken for each day where multiple observations were obtained. To correct for erroneous heights, the median height for each patient in the cohort was measured against each individual height observation and if > ±2% was excluded. The first valid height and weight observations were used to calculate the BMI at baseline. Race and gender only occurred once for each patient in the database and were used in the calculation of eGFR. For serum creatinine, the median value was taken for each day where multiple observations were obtained and was used in the calculation of eGFR using the MDRD equation (70). For patients with an HDL observation, the first HDL obtained was used in the final model. The time to event (eGFR \leq 15 \text{ ml/min/1.73m}^2) or time to censoring (did not reach eGFR \leq 15 \text{ ml/min/1.73m}^2) was the patient’s age at event or censoring.

**Statistical Analysis**

**Survival Analysis**

A Cox proportional hazard model was used to examine the relationship between BMI and HDL with the risk of developing kidney failure. BMI was categorized into two groups, non-obese (<30.0 kg/m²) and obese (\geq 30.0 kg/m²) and HDL was categorized according to the NCEP ATP-III HDL cholesterol guidelines (Men: <40 mg/dL, 40-59 mg/dL, \geq 60 mg/dL; Women: <50 mg/dL, 50-59 mg/dL, \geq 60 mg/dL) (71, 72). A total of 495 patient records were available from which BMI and renal function data could be obtained and 278 had HDL measurements. Both BMI and HDL were included in the model with age at kidney failure (eGFR of \leq 15 \text{ ml/min/1.73m}^2) being used as the time to event. The ph assumption was checked using log-log survival plot and assumptions were met. There was no interaction between BMI and HDL, so an interaction term was not present in the final model. A level of significance of p \leq 0.05 was considered statistically significant. Data cleaning and statistical analyses were performed in SAS 9.3 (SAS Institute, Cary NC) (73).
Results

Cohort Description

The final model included 495 patients with 85 events. A total of 278 patients had an HDL obtained during the study. Table 1 includes demographic and characteristic data of the study cohort.

Table 4.1
Cohort demographics and characteristics (n=495)$^1$

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline study measurement, years</td>
<td>50.5 ± 15.2</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45%</td>
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<tr>
<td>Female</td>
<td>55%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>83%</td>
</tr>
<tr>
<td>African American</td>
<td>9%</td>
</tr>
<tr>
<td>Other</td>
<td>7.5%</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.5%</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m$^2$</td>
<td>62.7 ± 31.7</td>
</tr>
<tr>
<td>CKD stage at baseline measurement</td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>19.4%</td>
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<tr>
<td>Stage 2</td>
<td>31.3%</td>
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<tr>
<td>Stage 3</td>
<td>31.9%</td>
</tr>
<tr>
<td>Stage 4</td>
<td>17.4%</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>28.56 ± 6.72</td>
</tr>
<tr>
<td>BMI Group</td>
<td></td>
</tr>
<tr>
<td>Non-obese (&lt;30 kg/m$^2$)</td>
<td>63.8%</td>
</tr>
<tr>
<td>Underweight/Healthy weight (&lt;25 kg/m$^2$)</td>
<td>33.9%</td>
</tr>
<tr>
<td>Overweight (25-29.9 kg/m$^2$)</td>
<td>29.9%</td>
</tr>
<tr>
<td>Obese (≥30 kg/m$^2$)</td>
<td>36.1%</td>
</tr>
<tr>
<td>HDL, mg/dL (n=278)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>41 ± 14</td>
</tr>
<tr>
<td>Women</td>
<td>48 ± 17</td>
</tr>
<tr>
<td>HDL Group (n=278)</td>
<td></td>
</tr>
<tr>
<td>Low (Men: &lt;40 mg/dL; Women &lt;50 mg/dL)</td>
<td>28.8%</td>
</tr>
<tr>
<td>Acceptable (Men: 40-59 mg/dL; Women 50-59 mg/dL)</td>
<td>16.9%</td>
</tr>
<tr>
<td>Desirable (Men &amp; Women: ≥60 mg/dL)</td>
<td>54.3%</td>
</tr>
</tbody>
</table>

$^1$eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; BMI, body mass index; HDL, high-density lipoprotein

BMI was not associated with the age at kidney failure (p=0.69, HR=1.096, 95% CI 0.697-1.724) after controlling for the effect of HDL, but was left in the model based on the results from CRISP which identifies BMI as a risk factor for ADPKD progression. With regards to HDL, individuals with a desirable HDL level were associated with a significantly slower disease progression when compared to
individuals with HDL levels in the low (p=0.0147, HR=0.271, 95% CI 0.095-0.774) and acceptable HDL range (p=0.0436, HR=0.319, 95% CI 0.105-0.968).

**Discussion**

In our cohort, BMI was not associated with the progression of ADPKD. However, individuals with desirable HDL levels (≥60 mg/dL) were associated with a slower progression towards kidney failure when compared to individuals in the low or acceptable HDL range, results similar to findings from the CRISP cohort (9).

BMI is often used as a clinical assessment of obesity which is a well-known risk factor for many diseases, including cardiovascular disease, diabetes, hypertension, stroke, and chronic kidney disease (74, 75). In the CRISP cohort, having a higher BMI at baseline resulted in a more significant increase in total kidney volume over time, an early indicator of disease progression (9). Conversely, in the EHR cohort, there was no difference in the time to event between obese and non-obese subjects. Our inability to detect an association may be related to the EHR cohort being older (50.5 years compared to 32.4 years), having higher BMIs (28.56 kg/m² compared to 25.9kg/m²), and having more advance kidney disease (62.7 ml/min/1.73m² compared to 89.1 ml/min/1.73m²) than the individuals in CRISP. The evidence suggests that since BMI was associated with disease progression in the CRISP cohort, obesity may have a more significant impact on disease progression earlier in the course of the disease. Using the EHR to identify patients with ADPKD who have elevated BMIs might allow patients to adopt weight management strategies such as calorie reduction and exercise early in the course of the disease and reduce their risk of developing kidney failure (75).

Elevated cholesterol levels are one of the major risk factors leading to the development of cardiovascular disease (CVD), the leading cause of death in individuals with kidney failure (10, 76). However, one subgroup of cholesterol, HDL, has shown to be heart protective, and results from the CRISP cohort suggest that it may also be kidney protective in ADPKD (9, 76). We were able to show an
association between HDL levels and ADPKD progression with the use of clinical data taken from the EHR. In our cohort, patients with desirable HDL levels were associated with a slower progression of kidney disease compared to individuals in the low or acceptable HDL range. HDL is known to have anti-atherogenic and anti-inflammatory properties through its role in reverse cholesterol transport and its effects on reducing oxidation of lipids and its involvement with proteins and lipids that have anti-inflammatory effects (77, 78). While the exact mechanisms by which HDL is kidney protective in ADPKD are not known, loss of kidney function in the general population has been shown to be induced both through atherogenesis and through endothelial damage caused by reactive oxygen species, giving two potential pathways by which HDL may be protective (79). Given the effects HDL has on both ADPKD and CVD, physicians should continue to routinely screen HDL at annual check-ups and monitor changes over time using EHRs.

This study demonstrates the ability to obtain routine measurements from a clinical database that can be used to assess risk factors for ADPKD progression. The use of additional laboratory or clinical measurements can also be easily ascertained to build statistical models to examine disease progression that would otherwise require large scale observational or randomized clinical trials. The use of clinical databases, like HERON, allows for the quick identification of routine, modifiable measurements, including BMI and HDL, which may be associated with disease progression. Using data from these databases poses a worthy avenue to assess potential risk factors for disease progression in a variety of diseases.

Limitations in this study include having a cohort of mostly Caucasian individuals and only 278/495 individuals having an HDL which led to the loss of 31/85 events. The EHR cohort is also older, with higher BMIs, and more advanced kidney disease than patients in the CRISP cohort. Assessing patients with well-preserved renal function through the course of the disease would allow for more reliable results when assessing risk factors associated with the age of reaching kidney failure. Diagnosis of PKD was based on ICD9 codes in the clinical database. This may have led to some false diagnoses of

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PKD in our cohort given that diagnosis was not able to be confirmed by imaging studies. Additionally, data was left censored and creatinine observations may not have occurred at regular intervals. It is possible that individuals in our EHR cohort received care at another institution (e.g., kidney transplant), but remained in the dataset. Even with these concerns, we were able to use clinical data obtained in the HERON database at KUMC to demonstrate similar results to that of a large, multicenter observational trial. The use of additional clinical data sets from other facilities would also help with generalizability and allow for more power due to the larger sample size. The primary strength of this study is the use of archived clinical data to model risk factors for ADPKD progression which reduces costs and time that conducting a large scale observational trial would otherwise require. The identification of additional risk factors from HERON would also be possible using a similar strategy to the one represented here.

With the use of EHR data, we were able to demonstrate that having a higher HDL was associated with a slower progression of kidney disease in ADPKD whereas BMI was not associated with disease progression. Monitoring and improving HDL levels through dietary and lifestyle behaviors may provide patients with ADPKD an additional way to help stave off dialysis and transplantation. This study demonstrates that the EHR may prove useful in identifying modifiable risk factors for ADPKD progression using routine clinical assessments.
CHAPTER FIVE

DISCUSSION AND CONCLUSION
Summary of Findings

This series of studies aimed to (1) determine whether patients could adhere to a low sodium, low protein, low acid precursor diet with increased fluid intake; (2) understand participants’ experiences and perspectives as they attempted to follow the diet; (3) reveal potential barriers that may reduce the likelihood of long-term adherence; (4) determine if data obtained from the electronic health record (EHR) can be used to identify risk factors associated with ADPKD progression (BMI and HDL).

The results show that in most patients with ADPKD, good to excellent compliance can be expected when modest limitations of salt and protein are combined with an increased intake of fruits, vegetables, and fluids which can be confirmed through evaluation of diet records and examination of urine collections. During the dietary intervention, participants became more aware of what they were consuming and thought that long-term dietary adherence was feasible by most patients. However, to maintain long-term adherence, the development of a user-friendly app or device to track the diet would help. Finally, with the use of EHR data, we found that while BMI was not associated with ADPKD progression, higher HDL levels were associated with a slower progression of the disease. These findings collectively demonstrate that a long-term dietary trial needs to be examined to determine how restriction of sodium, protein, and acid precursors, along with sufficient fluid intake, directly affects structural and functional changes in the kidneys of patients with ADPKD. Additionally, the EHRs from multiple institutions should be examined to determine other modifiable factors that may play a role in ADPKD progression. Upon identification, these modifiable factors could be included in a more comprehensive lifestyle intervention.

An Innovative Diet Controlling for the Factors Known to Accelerate ADPKD Progression

To our knowledge, this is the first composite diet to be rigorously tested to control for the dietary factors known to accelerate ADPKD progression. We found that while following the test diet, subjects reached the goals for sodium (≤ 1.5 mmol/kg), protein (≤ 1 g/kg), and fluid intake (urine osmolality ≤ 285 mosm/kg) tailored for each patient which were sustained throughout the experimental period.
Additionally, with the increase in fruits and vegetables, there was a 150% increase in potassium intake and excretion. Coupled with the reduction in protein intake, NEAP decreased from baseline by 58 mEq/d at the two week and four week visits. These findings were also reflected in the urine collections taken at the 2 week and 4 week visits. Finally, according to the Nutrition Hassles Questionnaire, only one participant reported any of the hassles as “moderately severe” while following the experimental diet and 10 out of 11 individuals were “somewhat confident” or “very confident” that they could manage the new diet. These findings suggest that not only can individuals follow the newly developed diet, but also that the hassles imposed are minimal and that individuals were confident in their knowledge and abilities to follow the diet.

**Perspectives and Experiences Following the PKD Diet**

We also explored the perspectives of individuals following the experimental diet by conducting semi-structured interviews following the dietary intervention. Overall, we found that reducing portion sizes of meat and increasing intake of fruits and vegetables were the easiest components of the diet while keeping track of what they ate and reaching the prescribed goal amount for fruits and vegetables each day were the most difficult components. Participants thought the tracking system (points) for fruits and vegetables and protein was intuitive and easy to use, although a few participants thought some fruits and vegetables were difficult to measure, and some participants would have liked the option to measure protein in grams. Participants did not track sodium intake, but instead avoided high sodium foods, salt-based seasonings, and limited eating at restaurants. Water intake was tracked by counting water bottles of a specific size and was reported as an attainable amount. While following the experimental diet, participants changed how they shopped at the grocery store and stated that the biggest barrier to following the diet involved being away from home (attending social events and traveling). Overwhelmingly, participants reported that to improve the diet, an app allowing them to track the diet more easily via their cell phones is necessary.
Assessing the Association of BMI and HDL on the Risk of ADPKD Progression using EHRs

Finally, we assessed risk factors for ADPKD progression using data from the EHR. Overall, we found that while BMI was not associated with ADPKD progression, desirable HDL levels were associated with a slower progression of the disease. Findings from our study demonstrate that the EHR can identify modifiable risk factors for ADPKD progression with routine clinical assessments.

Clinical Significance

Previous studies have identified several modifiable factors that may reduce the growth of cysts in polycystic kidney disease (9, 12, 13, 15, 16, 23, 25, 29-32). The results of our studies suggest that not only is it possible to control these factors (sodium, protein, dietary acids, and fluid), but that most participants were able to adhere to it for four weeks and eight participants reported they could follow it over a much longer period of time. Furthermore, we were able to demonstrate that EHR data could be used to identify a risk factor for ADPKD progression which was previously shown in a large observational trial (9). The mining of additional EHR data would allow for other laboratory and clinical measurements to be assessed to determine if additional factors should be routinely monitored in patients with ADPKD.

The results of these studies also suggest that to move forward to long-term dietary trials, the development of an app to help monitor and track dietary intake in individuals with ADPKD is necessary to help maintain long-term adherence. While tracking sodium, protein, and fluid are standard amongst most dietary tracking apps, the ability to measure NEAP is not currently available. The development of a user-friendly app that incorporates this is needed. Additionally, the routine monitoring of HDL levels may provide additional benefits when included as part of the standard of care in patients with ADPKD.
Limitations

The studies in this series were pilot studies and thus were small in sample size. The dietary intervention was the first of its kind so was only trialed over a four week period to determine if patients could adhere to the diet and changes could be observed in dietary records and confirmed in urine collections. Finally, our HERON cohort included mostly Caucasian individuals, had a moderate percentage of our subjects already at CKD stage 4 at baseline, and only about 56% of the individuals included in the model had an HDL measurement. Regardless, the results from these studies seem promising to direct future clinical trials.

Future Directions

Our studies identified a new diet that could be used to potentially ameliorate cysts growth in patients with ADPKD; however, long-term, adequately powered studies that includes the evaluation of structural and functional changes in the kidneys needs to be examined to determine if the diet could preserve kidney function in individuals with ADPKD. Conducting a multicenter trial using similar techniques to that of CRISP to measure kidney structure and function while employing our experimental diet would be ideal. If successful in adults, testing the experimental diet in children may yield more significant effects on preserving kidney function since kidney damage occurs throughout life. Ultimately, since cyst growth occurs exponentially faster in utero than at any other time in one’s life, modifying a mother’s diet during pregnancy may prove highly effective at slowing cysts growth even before a child’s life begins (80).

The development of an app that allows for individuals to track their intake of sodium, protein, dietary acids, and fluids with ease is necessary to increase the likelihood of long-term adherence, especially one that permits patients to monitor their intake easily while eating at restaurants.

Collaborative efforts that would allow for the mining of EHR data from multiple centers would allow for large scale laboratory and clinical measurements to be assessed to determine if additional risk
factors are associated with disease progression and should be routinely monitored in patients with ADPKD. Identification of risk factors associated with ADPKD progression is the first step toward targeting these risk factors in clinical trials in an effort to halt disease progression through dietary, lifestyle, or behavioral modifications.

Finally, studies examining the effectiveness of strategies aimed at improving HDL levels, such as exercise, may also prove beneficial.

Conclusion

The results of the present set of studies suggest that not only is it possible to reduce sodium, protein, and dietary acids, and increase fluid intake, but that most patients (11/12) were able to adhere to it for four weeks and eight participants reported they could follow it over a much longer period of time. It is reasonable to suppose that our experimental diet could be used to potentially ameliorate cysts growth in patients with ADPKD; however, long-term, adequately powered studies that evaluate structural and functional changes in kidney function needs to be examined. However, based on participant reporting, to move forward to long-term dietary trials, the development of an app to help monitor and track dietary intake in individuals with ADPKD is necessary to help maintain long-term adherence, a crucial factor when examining the long-term effects of dietary changes. Additionally, routine monitoring of HDL levels may provide additional benefits when included as part of the standard of care in patients with ADPKD. Lastly, we were also able to demonstrate that EHR data could be used to identify risk a factor for ADPKD progression which was previously shown in a large observational trial. Collaborative efforts that would permit the mining of EHR data from multiple centers would allow for assessment of large-scale laboratory and clinical measurements to determine if additional risk factors for ADPKD progression should be routinely monitored in patients. After risk factors have been identified, developing clinical trials targeting these risk factors is needed to determine the effectiveness of various dietary, lifestyle, or behavioral modifications.


APPENDIX I

SUPPLEMENTARY TABLE
<table>
<thead>
<tr>
<th>Topics</th>
<th>Main Question</th>
<th>Follow-up Question</th>
<th>Probes</th>
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</thead>
<tbody>
<tr>
<td>Kansas PKD Diet</td>
<td>Tell me about your overall experience with the Kansas PKD Diet</td>
<td>What did you feel like were the biggest changes from your usual diet that you had to make to follow the Kansas PKD diet?</td>
<td>When you were not able to follow the diet, what were the barriers?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>What aspects of the diet were the most enjoyable?</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>What components of the diet were easiest to follow?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>What components of the diet were most difficult to follow?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tell me about times when you were not able to follow the Kansas PKD Diet (see probing question)</td>
<td></td>
</tr>
<tr>
<td>Point System (Fruits/Vegetables)</td>
<td>Tell me how easy/difficult it was to use the fruits/vegetables point system handouts to track your points (see probing question)</td>
<td>How well did you understand the fruits/vegetables point system?</td>
<td>What made it difficult to follow?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>What aspects of the point system would you change?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>What aspects of the point system would you absolutely NOT change?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Did you feel like getting the required amount of points each day was a challenge? And was it a realistic goal?</td>
<td></td>
</tr>
<tr>
<td>Point System (Protein)</td>
<td>Tell me how easy/difficult it was to use the protein points system (see probing question)</td>
<td>How well did you understand the protein point system?</td>
<td>What made it difficult to follow?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>What aspects of the point system would you change?</td>
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<td></td>
<td></td>
<td>What aspects of the point system would you absolutely NOT change?</td>
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<tr>
<td></td>
<td></td>
<td>Did you feel like staying below the point restriction each day was a challenge? And was it a realistic goal?</td>
<td></td>
</tr>
<tr>
<td>Topics</td>
<td>Main Question</td>
<td>Follow-up Question</td>
<td>Probes</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Sodium</td>
<td>Tell me how easy/difficult it was to reduced sodium in the diet</td>
<td>How did you go about reducing your sodium intake?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Did you feel like doing these things each day was a challenge? And was it a realistic goal?</td>
<td></td>
</tr>
<tr>
<td>Fluids</td>
<td>Tell me how easy/difficult it was to meet your fluid needs</td>
<td>How did you go about tracking your fluid intake?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Did you feel like meeting your fluid goal was a challenge? And was it a realistic goal?</td>
<td></td>
</tr>
<tr>
<td>Lifestyle</td>
<td>How did following this diet affect other aspects of your life?</td>
<td>Describe your experience grocery shopping while on this diet?</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Describe your experiences eating out while on this diet?</td>
<td></td>
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<td></td>
<td></td>
<td>Were there any difficulties financially while following this diet (assume there was no stipend)?</td>
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<tr>
<td></td>
<td></td>
<td>Did you feel you had the necessary food preparation skills and knowledge to follow this diet?</td>
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<td></td>
<td></td>
<td>Did you feel following the Kansas PKD diet required any additional time commitments?</td>
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<tr>
<td></td>
<td></td>
<td>Did following the Kansas PKD diet affect any other obligations in your life?</td>
<td></td>
</tr>
<tr>
<td>Future</td>
<td>Now that you have completed the study, how would you use this information in the future?</td>
<td>When you think about the Kansas PKD diet, what is the probability you would follow this diet in the future?</td>
<td>If you are not likely to continue following this diet, are there certain...</td>
</tr>
<tr>
<td></td>
<td></td>
<td>How would you feel about continuing to track your Fruits/vegetable points and eating the prescribed points?</td>
<td></td>
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<tr>
<td>Topics</td>
<td>Main Question</td>
<td>Follow-up Question</td>
<td>Probes</td>
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<td>-------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Future</td>
<td>How would you feel about continuing to restrict your sodium intake?</td>
<td>How would you feel about continuing to drink the prescribed amount of water?</td>
<td>components of the diet you may continue to follow?</td>
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<tr>
<td></td>
<td></td>
<td>How would you feel about following this diet over the course of your life?</td>
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<td></td>
<td>What might prevent you from eating in this manner?</td>
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<td></td>
<td>What help/support would be needed to help you follow:</td>
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<td></td>
<td>Fluid requirements?</td>
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<td></td>
<td></td>
<td>Reducing sodium intake?</td>
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<td></td>
<td></td>
<td>Eating more fruits and vegetables?</td>
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<td>Eating less protein (meat, dairy, etc)?</td>
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<td>What aspects of the diet would you change to make it easier to follow?</td>
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<td>What aspects of the diet would you keep?</td>
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<tr>
<td>Suggestions</td>
<td>What do you feel we can improve?</td>
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Abbreviations: PKD, polycystic kidney disease.
APPENDIX II

HSC APPROVAL AND CONSENT FORM
RESEARCH CONSENT FORM
A new diet for patients with autosomal dominant polycystic disease

Sponsor: University of Kansas Medical Center, Department of Nephrology

You are being asked to join a research study. You are being asked to take part in this study because you have been diagnosed with autosomal dominant polycystic disease (ADPKD). You do not have to participate in this research study. The main purpose of research is to create new knowledge for the benefit of future patients and society in general. Research studies may or may not benefit the people who participate.

Research is voluntary, and you may change your mind at any time. There will be no penalty to you if you decide not to participate, or if you start the study and decide to stop early. Either way, you can still get medical care and services at the University of Kansas Medical Center (KUMC).

This consent form explains what you have to do if you are in the study. It also describes the possible risks and benefits. Please read the form carefully and ask as many questions as you need to, before deciding about this research.

You can ask questions now or at any time during the study. The researchers will tell you if they receive any new information that might cause you to change your mind about participating.

This research study will take place at the University of Kansas Medical Center (KUMC) with Jared Grantham, MD as the researcher. About 10 people will be in the study at KUMC.

BACKGROUND

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a genetic disease that affects a great number of people worldwide and can lead to kidney failure which can lead to death. ADPKD is a disease that causes the development of kidney cysts (fluid-filled balloons), which cause worsening kidney function. It is common for people with ADPKD to also have blood in the urine, kidney pain, high blood pressure, kidney stones, kidney infections, and cysts in the brain or other parts of the body. There is currently no treatment known to slow cyst growth or a cure for the disease.

Diet can affect kidney function. Doctors commonly recommend certain diets as part of their treatment plans for end-stage ADPKD. However, there is currently no specific diet prescription account for ADPKD patients in the earliest stages of the disease.

In this pilot study, the researchers will prescribe a certain diet which is thought to benefit kidney function. The ADPKD diet will include eating more fruits and vegetables and less meat and salt.

PURPOSE

By doing this study, researchers hope to learn more about how diet can impact kidney function in ADPKD patients during the earliest stages of the disease.
PROCEDURES

If you are eligible and decide to participate in this study, your participation will last approximately 1 month. You will be asked to visit the clinic 4 times. Some of your study visits may occur at the Clinical and Translational Science Unit (CTSU) at the KU – Clinical Research Center located at 4350 Shawnee Mission Parkway, Fairway, KS 66205. You will be asked to read and sign this consent form before any tests or procedures can be completed. You will be given a copy of this consent form.

A schedule of events is located at the end of this consent form.

Visit 1 / Enrollment Visit (Day 0)
The following procedures will occur at these visits:
- You will be asked questions about your health and medical history.
- You will have a limited physical exam, including measuring your blood pressure, height, and weight.
- You will be asked to continue to eat your usual diet.
- You will be given a food diary to complete on Days 5, 6, and 7.
- You will be given urine sample containers to collect 24 hour urine samples on Days 6 and 7. The study team will provide you with instructions on how to take the samples.
- This visit will take approximately 1 hour.

For the following 7 days, you will continue to eat your usual diet.

Visit 2 / Baseline Visit (Day 8)
The following procedures will occur at these visits:
- Your blood pressure, height, and weight will be measured.
- Approximately 2 teaspoons of blood will be collected from a vein in your arm for blood chemistry tests.
- Your 24 hour urine samples and food diary will be collected.
- A fresh urine sample (10 cc) will be collected to determine biomarkers of ADPKD. Based on the results of your urine samples and food intake diary, the study team will design your ADPKD diet. The study team will give you detailed instructions about how to follow your new diet.
- You will be given a food intake diary to complete on Days 12, 13, and 14.
- You will be given urine sample containers to collect 24 hour urine samples on Days 13 and 14.
- This visit will take approximately 2 hours.

You will be asked to follow the ADPKD diet for the next 4 weeks.

Visit 3/ Interim Visit (Day 15)
The following procedures will occur at these visits:
- Your blood pressure, height, and weight will be measured.
- Approximately 2 teaspoons of blood will be collected for laboratory tests.
- A fresh urine sample (10 cc) will be collected to determine biomarkers of ADPKD.
- Your 24 hour urine samples and food diary will be collected.
- The study team will discuss your food diary with you and review your ADPKD diet recommendations.
- You will be given a food diary to complete on Days 26, 27, and 28.
- You will be given urine sample containers to collect 24 hour urine samples on Days 27 and 28.
- This visit will take approximately 1 hour.
You will continue to follow the ADPKD diet.

Visit 4 / Final Visit (Day 29)
The following procedures will occur at these visits:

- Your blood pressure, height, and weight will be measured.
- Approximately 2 teaspoons of blood will be collected for laboratory tests.
- A fresh urine sample (10 cc) will be collected to determine biomarkers of ADPKD.
- Your 24 hour urine samples and food diary will be collected.
- You will be asked to complete the Nutritional Hassles Questionnaire.
- The study team will conduct a short interview with you to get your feedback on how the diet worked for you. All interviews will be audio-taped and transcribed verbatim.
- This visit will take approximately 3 hours.

**RISKS**

There are not expected to be any major health risks associated with taking part in this study. However, the following are potential unexpected risks.

**Blood Draws**
During the study you will have blood drawn for laboratory tests. The risks of drawing blood from a vein may include bleeding, infection and a slight bruising at the site that is used for the blood draw. This will be minimized by careful and clean techniques.

**Questionnaires**
There is a risk of feeling uncomfortable while answering some of the questions in the questionnaires. If you feel uncomfortable at any time, you may skip a question or stop answering questions all together.

**Possibility of Unknown Risks**
There may be other risks of the study that are not yet known.

**NEW FINDINGS STATEMENT**
You will be told about anything new that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

**BENEFITS**
You may or may not benefit from this study. We hope that the information learned from this study will benefit other patients with ADPKD.

**ALTERNATIVES**
Participation in this study is voluntary. Deciding not to participate will have no effect on the care or services you receive at the University of Kansas Medical Center.
COSTS
The study will pay for all study-related medical services provided during this study. These services include the study visits, and study-related tests and procedures such as the laboratory tests as listed in this consent form.

Any other medical visits and procedures you have outside of the study due to other standard of care treatments or other health issues are billable to you or your insurance through normal hospital billing practices. Standard of care means necessary for the care of a medical issue as determined by your doctor and not necessary for this study.

Your insurance may not cover some or all of the standard care services if you are part of a research study. You may want to talk to your insurance company and review your specific benefits and coverage before deciding to participate. You will be responsible for normal co-pays, deductibles and non-covered services that are not the responsibility of the study. Some procedures require Pre-Certification from your insurance company. Pre-Certification is not a guarantee of payment.

You can still be in the study even if your insurance denies coverage for your standard of care treatment or if you are uninsured. The hospital has a financial assistance program which it makes available to all patients who qualify. If your insurance denies coverage and you do not qualify for the financial assistance, you will be charged for all bills that are not the responsibility of the study. The study staff will be able to provide more information to you.

PAYMENT TO SUBJECTS
You will receive $100.00 for the Enrollment Visit and $100.00 for the Final Visit. If you complete all study visits, you will receive up to $200.00. If your participation in this study ends early, you will be paid only for the visits you have completed.

You will be given a ClinCard, which works like a debit card. After a study visit, payment will be added onto your card by computer. The money will be available within 1 business day. You can use the ClinCard at an ATM or at a store. No one will know where you spent the money.

You will be given one card during the study. If your card is lost or stolen, please call (866) 952-3795.

The KUMC Research Institute will be given your name, address, social security number, and the title of this study to allow them to set you up in the ClinCard system. Study payments are taxable income. A Form 1099 will be sent to you and the Internal Revenue Service if your payments are $600 or more in a calendar year.

Your personal information will be kept on a secure computer. It will be removed from the computer after the study is over and the money on the card has been used. Your information will not be shared with other businesses. It will be kept completely confidential.
**IN THE EVENT OF INJURY**

If you have any problem during this study, you should immediately contact Jared Grantham, MD at 913-588-9252.

**INSTITUTIONAL DISCLAIMER STATEMENT**

If you think you have been harmed as a result of participating in research at the University of Kansas Medical Center (KUMC), you should contact the Director, Human Research Protection Program, Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160. Under certain conditions, Kansas state law or the Kansas Tort Claims Act may allow for payment to persons who are injured in research at KUMC.

**CONFIDENTIALITY AND PRIVACY AUTHORIZATION**

The researchers will protect your information, as required by law. Absolute confidentiality cannot be guaranteed because persons outside the study team may need to look at your study records. The researchers may publish the results of the study. If they do, they will only discuss group results. Your name will not be used in any publication or presentation about the study.

Your health information is protected by a federal privacy law called HIPAA. By signing this consent form, you are giving permission for KUMC to use and share your health information. If you decide not to sign the form, you cannot be in the study.

The researchers will only use and share information that is needed for the study. To do the study, they will collect health information from the study activities and from your medical record. You may be identified by information such as name, address, phone, date of birth, social security number, or other identifiers. Your health information will be used at KU Medical Center by Dr. Jared Grantham, members of the research team, the University of Kansas Hospital Medical Record Department, the KUMC Research Institute, the KUMC Human Subjects Committee and other committees and offices that review and monitor research studies. Study records might be reviewed by government officials who oversee research, if a regulatory review takes place.

All study information that is sent outside KU Medical Center will have your name and other identifying characteristics removed, so that your identity will not be known. Because identifiers will be removed, your health information will not be re-disclosed by outside persons or groups and will not lose its federal privacy protection.

Your permission to use and share your health information remains in effect until the study is complete and the results are analyzed. After that time, researchers will remove personal information from study records.

**QUESTIONS**

Before you sign this form, Jared Grantham, MD or other members of the study team should answer all your questions. You can talk to the researchers if you have any more questions, suggestions, concerns or complaints after signing this form. If you have any questions about your rights as a research subject, or if
you want to talk with someone who is not involved in the study, you may call the Human Subjects Committee at (913) 588-1240. You may also write the Human Subjects Committee at Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160.

SUBJECT RIGHTS AND WITHDRAWAL FROM THE STUDY
You may stop being in the study at any time. Your decision to stop will not prevent you from getting treatment or services at KUMC. The entire study may be discontinued for any reason without your consent by the investigator conducting the study.

You have the right to cancel your permission for researchers to use your health information. If you want to cancel your permission, please write to Dr. Grantham. The mailing address is Jared Grantham, MD, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160. If you cancel permission to use your health information, you will be withdrawn from the study. The research team will stop collecting any additional information about you. The research team may use and share information that was gathered before they received your cancellation.

CONSENT
Dr. Grantham or the research team has given you information about this research study. They have explained what will be done and how long it will take. They explained any inconvenience, discomfort or risks that may be experienced during this study.

By signing this form, you say that you freely and voluntarily consent to participate in this research study. You have read the information and had your questions answered.

You will be given a signed copy of the consent form to keep for your records.

____________________________________
Print Participant’s Name

____________________________________
Signature of Participant

Time Date

____________________________________
Print Name of Person Obtaining Consent

____________________________________
Signature of Person Obtaining Consent

Date
OPTIONAL EMAIL OR TEXT MESSAGES

You can choose to sign up for emails or text messages about this study. The messages will remind you about your study appointments and give you other information that might be helpful during the study. You will pay your standard texting rate. This message service is optional. You are not required to give your cell phone or email address in order to be in the study. If you decide to receive messages when the study starts, you can still change your mind later.

I want to receive visit reminders by (check one):

☑ Email ________________________________ (your email address)

☑ Text message __________________________ (your cell phone number)

☑ Not at all

______________________________________________

(Date / Time) (Printed Name of Individual Obtaining Consent)

______________________________________________

(Signature of Individual Obtaining Consent)

Schedule of Events

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<th>7</th>
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<td>Diet</td>
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<td>Collect 24hr urine sample</td>
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<td>Complete Nutritional Hassles Questionnaire</td>
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APPENDIX III

SAS CODE FOR HERON ANALYSIS
ods html close;
ods listing;

options ls=150 ps=49;

title "Data Cleaning for Descriptive/Lab data";

footnote "First Program: 'X:\Shared\SHP\EDGE laboratory\Jacob Taylor\HERON data files-PKD\Working PKD data files\jacobPoly\jacobPoly-data' &sysdate."

libname data 'X:\Shared\SHP\EDGE laboratory\Jacob Taylor\HERON data files-PKD\Working PKD data files\jacobPoly';

*Create SAS data table;
/**************************************************************************/
* PRODUCT: SAS
* VERSION: 9.3
* CREATOR: External File Interface
* DATE: 19JUL13
* DESC: Generated SAS Datastep Code
* TEMPLATE SOURCE: (None Specified.)
**************************************************************************/
*Reading HERON data set into SAS manually;
data data.jacobPoly;
%let _EFIERR_ = 0; /* set the ERROR detection macro variable */
infile 'X:\Shared\SHP\EDGE laboratory\Jacob Taylor\HERON data files-PKD\Working PKD data files\jacobPoly\jacobPoly-data.csv' delimiter = ',';
MISSOVER DSD lrecl=32767 firstobs=2 ;
informat patient_num best32. ;
informat encounter_num best32. ;
informat variable $55. ;
informat valtype $6. ;
informat tval $99. ;
informat nval best10. ;
informat units $11. ;
informat code $55. ;
informat code_label $99. ;
informat modifier $50. ;
informat modifier_label $50. ;
informat instance best25. ;
informat start_date anydtdtm38. ;
informat end_date anydtdtm38. ;
informat variable_index best5. ;
format patient_num best32. ;
format encounter_num best32. ;
format variable $55. ;
format valtype $6. ;
format tval $99. ;
format nval best10. ;
format units $11. ;
format code $55. ;
format code_label $99. ;
format modifier $50. ;
format modifier_label $50. ;
format instance best25. ;
format start_date datetime38. ;
format end_date datetime38. ;
format variable_index best5. ;
input patient_num encounter_num variable $ valtype $ tval $ nval units $ code $ code_label $ modifier $
    modifier_label $ instance start_date end_date variable_index;
if _ERROR_ then call symputx('_EFIERR_',1); /* set ERROR detection macro variable */
run;
*read in 786390 records and outputed 786390 observations and 15 variables;

/*check number of patients in original data. 858 patients were in the data file;
proc freq data=data.jacobpoly noprint;
  table patient_num/out=junk;
run;
*/

*Clean SAS data set, break data into multiple tables to clean and put back together;
data  data.zCPT data.zICD data.zages data.zlabs data.zdemo data.zBMI data.zBP data.zdx data.zsmoke data.zmisc;
  set  data.jacobPoly;
    if  index(code,'CPT')>0 then output data.zCPT;
    else if index(variable_index,'74')>0 then output data.zICD;
    else if index(variable,'Age')>0 then output data.zages;
    else if index(variable,'(#')>0 then output data.zlabs;
    else if index(variable,'Ethnicity')>0 or index(variable,'Language')>0 or index(variable,'Gender')>0
      or index(variable,'Marital Status')>0 or index(variable,'Race')>0 or index(variable,'Religion')>0 then output data.zdemo;
    else if index(variable,'Ht / Wt')>0 then output data.zBMI;
    else if index(variable,'#5 BP')>0 then output data.zBP;
    else if index(variable,'Polycystic kidney')>0 then output data.zdx;
    else if index(variable,'Smok')>0 then output data.zsmoke;
    else
      output data.zmisc;
  run;

/*check contents of each new data table to make sure data is split up correctly
proc freq data=data.zCPT;
  table variable*patient_num/list;
run;

proc freq data=data.zICD;
  table variable*patient_num/list;
run;

proc freq data=data.zlabs;
  table variable/list;
run;

proc freq data=data.zdemo;
  table variable/list;
run;

proc freq data=data.zBMI;
  table variable/list;
run;

proc freq data=data.zBP;
  table variable/list;
run;

proc freq data=data.zdx;

table variable/list;
run;

proc freq data=data.zsmoke;
  table variable/list;
run;

proc freq data=data.zmisc;
  table variable/list;
run;
*/

*Sort data new data tables by patient_num excluding zCPT, zICD, and zmisc;
proc sort data=data.zlabs;
  by patient_num;
run;

proc sort data=data.zdemo;
  by patient_num;
run;

proc sort data=data.zBMI;
  by patient_num;
run;

proc sort data=data.zBP;
  by patient_num;
run;

proc sort data=data.zdx;
  by patient_num;
run;

proc sort data=data.zsmoke;
  by patient_num;
run;

*Read in and clean zbday data;
data data.zbday;
  %let _EFIERR_ = 0; /* set the ERROR detection macro variable */
infile 'X:\Shared\SHP\EDGE laboratory\Jacob Taylor\HERON data files-PKD\Working PKD data files\jacobPoly\jacobPoly-patient-edit.csv' dlm=','
  MISSOVER DSD lrecl=32767 firstobs=2 ;

  informat patient_num best32. ; informat vital_status $4. ; informat birth_date anydtdtm38. ; informat death_date anydtdtm38. ;
  format patient_num best32. ; format vital_status $4. ; format birth_date datetime38. ; format death_date datetime38. ;

  input patient_num $ vital_status $ birth_date death_date;
  if _ERROR_ then call symputx('_EFIERR_','I'); /* set ERROR detection macro variable */
run;
*858 bday read in;
*format date;
data zbday1;
  set data.zbday;
birth_date=datepart(birth_date);
defate_death=datepart(death_date);
format birth_date death_date mmdyy10.;
run;

*sort bday by patient_num;
proc sort data=zbday1;
  by patient_num;
run;

/*Clean zBMI data, check contents;
proc freq data=data.zBMI;
  table code_label/list;
run;

proc freq data=data.zBMI;
  table units/list;
run;
*/

/*check data from zBMI data table for values of BMI when height or weight is
missing.
proc sort data=data.zBMI;
  by patient_num code_label ;
run;

proc univariate data=data.zBMI noprint;
  var nval;
  by patient_num code_label ;
  output out=test median=nval;
run;

proc sort data=test;
  by patient_num ;
run;

proc transpose data=test out=test1;
  var nval;
  id code_label;
  by patient_num ;
run;

proc freq data=test1;
  where _004___301070_BMI__Calculated_>.and _001___11_Height is missing;
run;

proc freq data=test1;
  where _004___301070_BMI__Calculated_>. and _002___14_Weight is missing;
run;
*/

*remove everything except ht and wt;
data zBMI1 (keep=patient_num start_date code_label nval) junk;
  set data.zBMI;
  if index(code_label,'#1')>0 then output zBMI1;
  else output junk;
run;

*format start date;
data zBMI2;
  set zBMI1;
  start_date=datepart(start_date);
  format start_date mmddyy10.;
run;

*Sort data in bmi1 table;
proc sort data=zbmi2;
  by patient_num code_label start_date;
run;

*take only median ht and wt for each day;
proc univariate data=zbmi2 noprint;
  var nval;
  by patient_num code_label start_date;
  output out=zbmi3 median=nval;
run;

*Sort data in bmi1 table;
proc sort data=zbmi3;
  by patient_num start_date;
run;

*transpose table to usable format for calculating new BMI/BSA;
proc transpose data=zbmi3 out=zbmi3t (drop=_LABEL_ _NAME_);
  var nval;
  id code_label;
  by patient_num start_date;
run;

*rename columns;
data zBMI4t;
  rename _001___11_Height=Height _002___14_Weight=Weight;
set zBMI3t;
run;

data zBMI4a;
  set zBMI4t;
  retain height2 0;
  if missing(height) = 1 then height = height2;
  else height2 = height;
run;

data zBMI4b;
  set zBMI4t;
  retain weight2 0;
  if missing(weight) = 1 then weight = weight2;
  else weight2 = weight;
run;

data zBMI4t2 (drop=Height Weight);
  merge zBMI4a zBMI4b;
  by patient_num;
run;
**data**  zbmi4t2;
   set  zbmi4t2 (rename=(height2=height) rename=(weight2=weight));
   if  patient_num=1245830 then height=180.34;
**run;**

*calculate BMI and BSA;
**data**  zBMI5;
   set  zbmi4t2;
   DO  BMI=(Weight/((Height/100))**2);
     BSA=(0.007184*Height**0.725*Weight**0.425);
     output;
   end;
**run;**

*remove everything except dates including both ht and wt;
**data**  zBMI6 junk;
   set  zBMI5;
   if  height>. and weight>. then output  zBMI6;
   else output  junk;
**run;**

/*
 proc univariate data=zBMI6 noprint;
   var  BMI;
   by  patient_num;
   output out=testing3  median=medianbmi;
**run;**
*/

*merge BMI and birthdate to get all patients over 18;
**data**  zages;
   merge  zbday1 zbmi6;
   by  patient_num;
**run;**

**proc sort data=zages;**
   by  patient_num start_date;
**run;**

**data**  zages1;
   set  zages;
   Age=(start_date-birth_date)/365;
**run;**

**data**  zages2 junk;
   set  zages1;
   if  Age<18 or Age=. then output  junk;
   else output  zages2;
**run;**

/*check zages2 for those under 18;
**proc freq data=zages2;**
   where  age<18;
**run;**
data testing;
  set zages1;
  by patient_num;
  if last.patient_num and age>=18;
run;

proc freq data=test;
  table patient_num/list;
run;
*/

proc univariate data=zages2 nobin;
  var height;
  by patient_num;
  output out=zages3 median=medianht;
run;

data zages4;
  merge zages2 zages3;
  by patient_num;
run;

data zages5;
  set zages4;
  if patient_num=1238289 then medianht=180.34;
  if patient_num=425121 then medianht=177.8;
  if patient_num=487454 then medianht=160.7;
  if patient_num=494217 then medianht=188;
  if patient_num=923230 then medianht=180.34;
  if patient_num=1236150 then medianht=152.4;
  if patient_num=1344211 then medianht=189.23;
  if patient_num=1642166 then medianht=155.8;
  if patient_num=1662978 then medianht=187.96;
run;

data zages6;
  set zages5;
  htdev=((height-medianht)/height)*100;
  by patient_num;
  if first.patient_num then FirstBMI=first.patient_num;
  else FirstBMI+1;
run;

* categorize all htdev within 2% either direction;

data zages7;
  set zages6;
  if FirstBMI=1 and -2<htdev<2 then x=1;
  if FirstBMI+1 and -2<htdev<2 then x=1;
run;

/*
proc means nolabels data=zages7 Max;
  by patient_num;
  output out=htdev;
run;

data htdev1 junk;
set htdev;
    if _STAT_='MAX' and X=0 then output htdev1;
    else output junk;
run;

proc freq data=zages7;
where
    proc means nolabels data=zages7 Min Max;
    by patient_num;
    output out=htdev;
run;

data htdev1 junk;
    set htdev;
    if _STAT_='MIN' and htdev<-2 then output htdev1;
    if _STAT_='MAX' and htdev>2 then output htdev1;
    else output junk;
run;
    */

data zages8 junk;
    set zages7;
    if x>. then output zages8;
    else output junk;
run;
    /*
data zages8;
    set zages8;
    Y=1;
run;

data testing;
    merge zages7 zages8;
    by patient_num;
run;

data testing1 testing2;
    set testing;
    if Y ne 1 then output testing1;
    else output testing2;
run;

proc univariate data=zages8 noprint;
    var BMI;
    by patient_num;
    output out=testing median=medianbmi;
run;
    */

data zages9 (drop=medianht htdev FirstBMI x) junk;
    set zages8;
    by patient_num;
    if first.patient_num then output zages9;
    else output junk;
run;

   proc freq data=zages9;
        where age<18;
   run;

*Clean zsmoke data, format start date;
   data zsmoke1 (keep=patient_num variable tval start_date);
      set data.zsmoke;
      start_date=datepart(start_date);
      format start_date mmddyy10.;
   run;

   proc sort data=zsmoke1;
        by patient_num start_date variable;
   run;

*split into smoking and smokeless data tables to work with;
   data out1 out2;
      set zsmoke1;
      if index(variable,'Smoking')>0 then output out1;
      else if index(variable,'Smokeless')>0 then output out2;
   run;

   proc sort data=out1;
        by patient_num start_date tval;
   run;

   data out1;
      set out1;
      by patient_num;
      if first.patient_num then visit=1;
      else visit+1;
   run;

   data out1a;
      set out1;
      by patient_num;
      if first.patient_num then do;
         Firstdate=start_date;
      end;
      retain firstdate;
   run;

   data out1aa;
      merge out1 out1a;
      by patient_num;
   run;

   data out1b;
      set out1aa;
      datediff=start_date-Firstdate;
   run;

   data out1c junk;
      set out1b;
      if datediff>90 then output junk;
else output out1c;
run;

proc transpose data=outlc out=outlt prefix=Assessment_;
  var tvl;
  id visit;
  by patient_num;
run;

proc transpose data=outlc out=outlt2 prefix=vdate_;
  var start_date;
  id visit;
  by patient_num;
run;

data out1d out1dd (keep=patient_num i smokestat smokedate);
merge outlt (drop=_NAME_) outlt2 (drop=_NAME_);
  by patient_num;
array assess1(108) assessment_1-assessment_108;
array assess2(108) vdate_1-vdate_108;
DO i=1 to 108;
  if i=1 then do;
    smokestat=assess1(i);
    smokedate=assess2(i);
    output out1dd;
  end;
  else if i<109 then do;
    if assess1(i) ne smokestat and assess1(i) ne " " then do;
      smokestat=assess1(i);
      smokedate=assess2(i);
      output out1dd;
    end;
  end;
else i=108;
end;
output out1d;
run;

proc transpose data=out1dd out=out1ddt;
  var smokestat;
  by patient_num;
run;

*take first smoking status in <90days from baseline and assign smoking status;
data data.zsmoker (keep=patient_num smokestatus);
set out1ddt;
  if COL1='Never Assessed' and COL2=' ' then smokestatus=COL1;
  else if COL1='Never Assessed' and COL2 ne ' ' then smokestatus=COL2;
  else if COL1 ne 'Never Assessed' then smokestatus=COL1;
else smokestatus='X';
run;

/* check smokestatus freqs;
proc freq data=data.zsmoker;
table smokestatus/list;
proc sort data=out2;
   by patient_num start_date tval;
run;

data out2;
   set out2;
   by patient_num;
   if first.patient_num then visit=1;
   else visit+1;
run;

data out2a;
   set out2a;
   by patient_num;
   if first.patient_num then do;
      Firstdate=start_date;
      end;
   retain firstdate;
run;

data out2aa;
   merge out2 out2a;
   by patient_num;
run;

data out2b;
   set out2aa;
   datediff=start_date-firstdate;
run;

data out2c junk;
   set out2b;
   if datediff>90 then output junk;
   else output out2c;
run;

proc transpose data=out2c out=out2t prefix=Assessment_;
   var tval;
   id visit;
   by patient_num;
run;

proc transpose data=out2c out=out2t2 prefix=vdate_;
   var start_date;
   id visit;
   by patient_num;
run;

data out2d out2dd (keep=patient_num i smokelessstat smokelessdate);
   merge out2t (drop=_NAME_) out2t2 (drop=_NAME_);
   by patient_num;
   array assess1(108) assessment_1-assessment_108;
   array assess2(108) vdate_1-vdate_108;
   do i=1 to 108;
if i=1 then do;
    smokelessstat=assess1(i);
    smokelessdate=assess2(i);
    output out2dd;
end;
else if i<109 then do;
    if assess1(i) ne smokelessstat and assess1(i) ne " " then do;
        smokelessstat=assess1(i);
        smokelessdate=assess2(i);
        output out2dd;
    end;
end;
else i=108;
end;
output out2d;
run;

proc transpose data=out2dd out=out2ddt;
    var smokelessstat;
    by patient_num;
run;

*take first smoking status in <90 days from baseline and assign smoking status;
data data.zsmokeless (keep=patient_num smokelessstatus);
    set out2ddt;
    if COL1='Unknown' and COL2=' ' then smokelessstatus=COL1;
    else if COL1='Unknown' and COL2 ne ' ' then smokelessstatus=COL2;
    else if COL1 ne 'Unknown' then smokelessstatus=COL1;
    else smokelessstatus='X';
run;

proc freq data=data.zsmokeless;
    table smokelessstatus/list;
run;

*Clean zdemo data, format date;
data zdemo1 (keep=patient_num start_date variable tval);
    set data.zdemo;
    start_date=datepart(start_date);
    format start_date mmddyy10.;
run;

proc sort data=zdemo1;
    by patient_num start_date;
run;

*transpose table to usable format;
proc transpose data=zdemo1 (drop=start_date) out=zdemolt (drop=_NAME_);
    var tval;
    id variable;
    by patient_num;
run;

*break table into creatinine and all other labs;
data data.zfx zlabs1;
set data.zlabs;
if index(variable,'(#2009)')>0 then output data.zfx;
else output zlabs1;
run;

/*Check contents of new tables;
proc freq data=data.zfx;
  table variable/list;
run;
*/

*clean zfx data;
data zfx1 (keep.patient_num start_date variable nval);
  set data.zfx;
  start_date=datepart(start_date);
  format start_date mmddyy10.;
run;

proc sort data=zfx1;
  by patient_num variable start_date;
run;

*take daily median value for creatinine;
proc univariate data=zfx1 noprint;
  var nval;
  by patient_num variable start_date;
  output out=zfx2 median=nval;
run;

proc sort data=zfx2;
  by patient_num;
run;

*transpose creatinine data;
proc transpose data=zfx2 out=zfx2t (drop=_LABEL_ _NAME_);
  var nval;
  id variable;
  by patient_num start_date;
run;

*clean zlabs data;
data zlabs1 (keep.patient_num start_date variable nval);
  set data.zlabs;
  start_date=datepart(start_date);
  format start_date mmddyy10.;
run;

proc sort data=zlabs1;
  by patient_num start_date variable;
run;

*take daily median value for all non-creatinine labs;
proc univariate data=zlabs1 noprint;
  var nval;
  by patient_num start_date variable;
  output out=zlabs2 median=nval;
run;
proc sort data=zlabs2;
   by patient_num start_date;
run;

*transpose labs data by date;
proc transpose data=zlabs2 out=zlabs2t (drop=_LABEL_ _NAME_);
   var nval;
   id variable;
   by patient_num start_date;
run;

*Clean zBP data, format start date;
data zBP1;
   set data.zBP;
   start_date=datepart(start_date);
   format start_date mmddyy10.;
run;

*Sort data in bp1 table;
proc sort data=zBP1;
   by patient_num code_label start_date;
run;

*format data in data value column to median daily value for BP;
proc univariate data=zBP1 noprint;
   var nval;
   by patient_num code_label start_date;
   output out=zbp2 median=nval;
run;

*sort data in zbp2 table;
proc sort data=zbp2;
   by patient_num start_date;
run;

*transpose table to usable format for merging;
proc transpose data=zbp2 out=zbp2t;
   var nval;
   id code_label;
   by patient_num start_date;
run;

*rename columns;
data zbp3 (drop=_NAME_ _LABEL_);
   rename _5_DIASTOLIC=Diastolic _5_SYSTOLIC=Systolic;
set zbp2t;
run;

proc sort data=data.zdx;
   by patient_num variable;
run;

data zdx1;
   set data.zdx;
   by patient_num;
   if first.patient_num then visit=1;
else visit+1;
run;

proc transpose data=zdx1 out=zdx1t prefix=dx_
var variable;
  id visit;
by patient_num;
run;

data zdx3 zdx3a;
merge zdx1t (drop=_NAME_) by patient_num;
array assess1(448) dx_1-dx_448;
  DO i=1 to 448;
    if i=1 then do;
      dxstat=assess1(i);
      output zdx3a;
    end;
    else if i<449 then do;
      if assess1(i) ne dxstat then do;
        dxstat=assess1(i);
        output zdx3a;
      end;
    else i=448;
  end;
output zdx3;
run;

data zdx3b;
set zdx3a;
if dxstat=' ' then i=i-1;
run;

proc transpose data=zdx3b out=zdx3bt prefix=dx_
var dxstat;
by patient_num;
run;

proc transpose data=zdx3b out=zdx3ct prefix=i_
var i;
by patient_num;
run;

data zdx4;
merge zdx3bt (drop=_NAME_) zdx3ct (drop=_NAME_) by patient_num;
run;

data zdx5;
set zdx4;
  if i_1=i_2 then dxl=dx_1;
  if i_1=i_2 then dxcount1=i_2;
  if i_2>i_1 then dxl=dx_1;
if i_2>i_1 then dx2=dx_2;
if i_2>i_1 then dxcount1=i_2-i_1;
if i_2>i_1 then dxcount2=i_3-i_2;
if i_3>i_2 then dx1=dx_1;
if i_3>i_2 then dx2=dx_2;
if i_3>i_2 then dx3=dx_3;
if i_3>i_2 then dxcount1=i_2-i_1;
if i_3>i_2 then dxcount2=i_3-i_2;
if i_3>i_2 then dxcount3=i_4-i_3;
if i_3=i_2 then dxcount2=1;
run;

data zdx6;
set zdx5;
  if dxcount2=.
     then pkddx=dx1;
   if dxcount1>dxcount2>dxcount3 then pkddx=dx1;
   if dxcount1>dxcount2>dxcount3 then pkddx=dx1;
   if dxcount2>dxcount1>dxcount3 then pkddx=dx2;
   if dxcount2>dxcount1>dxcount3 then pkddx=dx2;
   if dxcount3>dxcount2>dxcount1 then pkddx=dx3;
   if dxcount3>dxcount2>dxcount1 then pkddx=dx3;
   if dxcount1=dxcount2>dxcount3 then pkddx=dx1;
   if dxcount1=dxcount2>dxcount3 then pkddx=dx2;
run;

/*proc freq of those with ARPKD which need to be excluded;
proc freq data=zdx6;
  where pkddx='Polycystic kidney, autosomal recessive';
  by patient_num;
run;
*/

*merge all static variables together;
data static (drop=dx_1 dx_2 dx_3 dx_4 i_1 i_2 i_3 i_4 dx1 dx2 dx3 dxcount1
       dxcount2 dxcount3);
  merge zages9 data.zsmoker data.zsmokeless zdemolt zdx6;
  by patient_num;
if BMI>. and pkddx ne 'Polycystic kidney, autosomal recessive';
run;

*merge all changing variables together;
data change;
  merge zfx2t zlabs2t zbp3;
  by patient_num;
run;

/* check to see if ARPKD or missing BMI included;
proc freq data=static;
  where pkddx='Polycystic kidney, autosomal dominant';
run;

proc freq data=static;
  where BMI=.;
run;
*/
*merge all datasets together;

data data.full;
   merge static change;
   by patient_num;
run;

*get variables to calculate eGFR;
data full1;
   set data.full;
   Gender_Race=cats(Gender,'_',Race);
run;

/*
proc freq data=full1;
   where age<18;
run;
*/

/*Check gender/race categories;
proc freq data=full1;
   table Gender_Race;
run;
*/

*create variable to estimate GFR based on equation;
data full2;
   set full1;
   if Gender_Race='Female_Black or African American' then
      GR_Code='Female_Black';
   else if Gender_Race='Female_American Indian or Alaskan Native' or
      Gender_Race='Female_Asian' or Gender_Race='Female_Declined' or
      Gender_Race='Female_Not Recorded-@' or Gender_Race='Female.Other' or
      Gender_Race='Female_Two Races' or Gender_Race='Female_White or Caucasian'
      then GR_Code='Female.Other';
   else if Gender_Race='Male_Black or African American' then
      GR_Code='Male_Black';
   else if Gender_Race='Male_American Indian or Alaskan Native' or
      Gender_Race='Male_Asian' or Gender_Race='Male_Declined' or
      Gender_Race='Male_Not Recorded-@' or Gender_Race='Male.Other' or
      Gender_Race='Male_White or Caucasian' then GR_Code='Male.Other';
run;

/*check new GR codes;
proc freq data=full2;
   table GR_Code;
run;
*/

data full3;
   set full2;
   by patient_num;
   Age=(start_date-birth_date)/365.25;
   Age=floor(age);
run;

proc sort data=full3;
by patient_num;
run;

*create column for GFR and CKD stage;
data full4 (drop=GR_Code Gender_Race);
set full3;
if GR_Code='Female_Black' then do;
  GFR=(186*CREATININE___2009**-1.154)*(age**-0.203)*0.742*1.210;
  end;
if GR_Code='Female_Other' then do;
  GFR=(186*CREATININE___2009**-1.154)*(age**-0.203)*0.742;
  end;
if GR_Code='Male_Black' then do;
  GFR=(186*CREATININE___2009**-1.154)*(age**-0.203)*1.210;
  end;
if GR_Code='Male_Other' then do;
  GFR=(186*CREATININE___2009**-1.154)*(age**-0.203);
  end;
GFR=floor(GFR);
run;
data full5;
set full4;
length BMIstatus $30.
if BMI<25 then BMIstatus='Under/Healthy Weight';
if 25<=BMI<30 then BMIstatus='Overweight';
if 30<=BMI then BMIstatus='Obese';
if BMI=. then BMIstatus='Unknown';
run;
data full6 junk;
set full5;
if BMIstatus='Unknown' then output junk;
else output full6;
run;

/*
data testing junk;
set full5;
by patient_num;
if first.patient_num then output testing;
else output junk;
run;
data testing2 junk;
set testing;
if BMIstatus='Unknown' then output junk;
else output testing2;
run;
proc freq data=full5;
  where BMIstatus='Unknown';
run;
proc univariate data=full5 noprint;
  var BMIstatus;
  by patient_num;
output out=testing  median=medianbmi;
run;
*/

*check number in each BMIstatus category;
proc transpose data=full6 out=full6t prefix=BMI_;
   var BMIstatus;
   by patient_num;
run;
/

proc freq data=full6t;
   table BMI_1/list;
run;
proc freq data=full6;
   table GFR/list;
   by patient_num;
run;
*/

data full7 junk;
   set full6;
      if GFR=. then output junk;
      else output full7;
run;
/

proc univariate data=full7 noprint;
   var GFR;
   by patient_num;
   output out=testing  median=GFR;
run;
*/

proc means nolabels data=full7 Min Max;
   by patient_num;
   output out=MinMax;
run;

data MinMax1 MinMax2;
   set MinMax;
      if _STAT_='MIN' and GFR>. then output MinMax2;
      else output MinMax1;
run;

data MinMax2;
   set MinMax2;
   length BMIstatus $30. GFRstat 3.;
   if BMI<25 then BMIstatus='Under/Healthy Weight';
   if 25<=BMI<30 then BMIstatus='Overweight';
   if 30<=BMI then BMIstatus='Obese';
   if BMI= . then BMIstatus='Unknown';
   if GFR<=15 then GFRstat=1;
   if GFR>15 then GFRstat=0;
run;
/** proc freq to check BMI status and GFRstatus; */
proc freq data=MinMax2;
   tables BMIs*GFRstat/list;
run;
proc freq data=MinMax;
   tables _STAT_*GFR/list;
run;
*/
*remove all data after first date with GFR<=15;*

**data** full8;
   **set** full7;
   **by** patient_num;
   retain KidFail;
      **if** first.patient_num then Kidfail=0;
      **if** GFR<=15 then Kidfail=1;
run;
**data** full8a junk;
   **set** full8;
   **if** Kidfail=1 then output full8a;
   else output junk;
run;
**data** full8b junk;
   **set** full8a;
   **by** patient_num;
   **if** first.patient_num then output full8b;
   else output junk;
run;
**data** full8d junk;
   **set** full8;
   **if** kidfail=0 then output full8d;
   else output junk;
run;
**data** full9;
   **merge** full8d full8b;
   **by** patient_num;
run;
**proc sort data=full9;**
   **by** patient_num start_date;
run;
**data** data.comp;
   **set** full9;
run;
*/
**data** testing junk;
   **set** data.comp;
   **by** patient_num;
   **if** first.patient_num then output testing;
else output junk;
run;
*/

data compl1;
  set data.comp;
  by patient_num;
  if last.patient_num then do;
    Lastage=start_date-birth_date;
  end;
run;

/*
data testing junk;
  set compl1;
  by patient_num;
  if first.patient_num then output testing;
  else output junk;
run;
*/

proc sort data=compl1;
  by patient_num Lastage Kidfail;
run;

proc transpose data=compl out=comp2 (keep=patient_num Lastage Kidfail);
  by patient_num Lastage Kidfail;
run;

/*
data testing junk;
  set comp2;
  by patient_num;
  if first.patient_num then output testing;
  else output junk;
run;
*/

data comp3;
  set comp2;
  by patient_num;
  if last.patient_num then last=1;
  else Last=0;
run;

/*
data testing junk;
  set comp3;
  by patient_num;
  if first.patient_num then output testing;
  else output junk;
run;
*/

data comp4 junk;
  set comp3;
  if last=1 then output comp4;
else output junk;
run;

/*
data testing junk;
set comp4;
by patient_num;
if first.patient_num then output testing;
else output junk;
run;
*/
data comp5 (drop=last);
merge compl (drop=lastage kidfail) comp4;
by patient_num;
run;

/*
data testing junk;
set comp5;
by patient_num;
if first.patient_num then output testing;
else output junk;
run;
*/
data comp6;
set comp5;
by patient_num;
if first.patient_num then firstvisit=start_date;
output;
retain;
run;

/*
data testing junk;
set comp6;
by patient_num;
if first.patient_num then output testing;
else output junk;
run;
*/
data comp7;
set comp6;
datediff=start_date-firstvisit;
run;

/*
data testing junk;
set comp7;
by patient_num;
if first.patient_num then output testing;
else output junk;
run;
*/
data comp8 junk;
  set comp7;
  if datediff<=90 then output comp8;
  else output junk;
run;

/*/data testing junk;
  set comp8;
  by patient_num;
  if first.patient_num then output testing;
  else output junk;
run;
*/

proc sort data=comp8;
  by patient_num start_date;
run;

/*take median of all continuous variables to get 1 obs for each participant
to check n counts;
proc univariate data=comp8 noprint;
  var CREATININE__2009 ALBUMIN__2023 ALK_PHOSPHATASE__2071 ALT__2065
  ANION_GAP__2006 AST__2064 BUN__2007 CALCIUM_2017
  CHLORIDE__2004 CO2__2005 GLUCOSE__2010 HEMATOCRIT__3004
  HEMOGLOBIN__3000 POTASSIUM__2002 SODIUM__2000 AMYLASE__2067
  CHOLESTEROL__2318 FERRITIN__3176 HDL__2320 IRON__3172
  LDL__2321 LIPASE__2068 TRIGLYCERIDE__2319 GLUCOSE_UA__7006
  MAGNESIUM__2020 PO4__2033 PROTEIN_UA__7004 URINE_PH__7003
  URINE_SPEC_GRAVITY__7002 URIC_ACID__2022 CREAT_24_HRS__7068
  VOLUME_URENE__7060 SATURATION__3173 IRON_BINDING__3174
  PTH_HORMONE__2195 ALUMINUM__2047 GFR_ESTIMATED__191
  GFR_ESTIMATED_AFRICAN_AMERICAN__ VITAMIN_D_25_OH__TOTAL__2341
  GLUCOSE__2011 IONIZED_CALCIUM__2018 HEMOGLOBIN_A1C__2034
  ZINC__2053 CALCIUM_24_HRS__7112 PHOS_24_HRS__7174
  SODIUM_24_HRS__7061 UR_OSMOLALITY__7067 PREALBUMIN__2058
  COPPER__2052 GLUCOSE_FASTING__2035 TOT_PRO_24_HRS__7083
  ALBUMIN_Urine__7052 POTASSIUM_24_HRS__7063 CITRATE_24_HRS__7119
  URIC_ACID_24_HRS__7190 SP_GRAVITY__7182 UREA_NIT_24_HRS__7188
  ALDOSTERONE__7095 CHLORIDE_24_HRS__7065
  GLUCOSE__2036 MAGNESIUM_24_HRS__7155 BICARBONATE_Urine__7235
  diastolic systolic;
  by patient_num;
  output out=test median=CREATININE__2009 ALBUMIN__2023
  ALK_PHOSPHATASE__2071 ALT__2065 ANION_GAP__2006 AST__2064 BUN__2007
  CALCIUM_2017 CHLORIDE__2004 CO2__2005 GLUCOSE__2010 HEMATOCRIT__3004
  HEMOGLOBIN__3000 POTASSIUM__2002 SODIUM__2000 AMYLASE__2067
  CHOLESTEROL__2318 FERRITIN__3176 HDL__2320 IRON__3172
  LDL__2321 LIPASE__2068 TRIGLYCERIDE__2319 GLUCOSE_UA__7006
  MAGNESIUM__2020 PO4__2033 PROTEIN_UA__7004 URINE_PH__7003
  URINE_SPEC_GRAVITY__7002 URIC_ACID__2022 CREAT_24_HRS__7068
  VOLUME_URENE__7060 SATURATION__3173 IRON_BINDING__3174
  PTH_HORMONE__2195 ALUMINUM__2047 GFR_ESTIMATED__191
  GFR_ESTIMATED_AFRICAN_AMERICAN__ VITAMIN_D_25_OH__TOTAL__2341
  GLUCOSE__2011 IONIZED_CALCIUM__2018 HEMOGLOBIN_A1C__2034
  MAGNESIUM_24_HRS__7112 PHOS_24_HRS__7174
  SODIUM_24_HRS__7061 UR_OSMOLALITY__7067 PREALBUMIN__2058
*/
ZINC_2053  CALCIUM_24_HRS_712  PHOS_24_HRS_7174  
SODIUM_24_HRS_7061  UR_OSMOLALITY_7067  PREALBUMIN_2058  
COPPER_2052  GLUCOSE_FASTING_2035  TOT_PRO_24_HRS_7083  
ALBUMIN_Urine_7052  POTASSIUM_24_HRS_7063  CITRATE_24_HRS_7119  
URIC ACID_24_HRS_7190  SP_GRAVITY_7182  UREA_NIT_24_HRS_7188  
ALDOSTERONE_UR_7095  CHLORIDE_24_HRS_7065  
GLUCOSE_2036  MAGNESIUM_24_HRS_7155  BICARBONATE_Urine_7235  
diastolic systolic;  
run;  
*check n for each continuous variable to determine which may be used as  
covariates based on n;  
proc means data=test;  
var CREATININE_2009  ALBUMIN_2023  ALK_PHOSPHATASE_2071  ALT_2065_ 
ANION_GAP_2006  AST_2064  BUN_2007  CALCIUM_2017  
CHLORIDE_2004  CO2_2005  GLUCOSE_2010  HEMOGLOBIN_3000  
POTASSIUM_2002  SODIUM_2000  AMYLASE_2067  
CHOLESTEROL_2318  FERRITIN_3176  HDL_2320  IRON_3172  
LDL_2321  LIPASE_2068  TRIGLYCERIDE_2319  GLUCOSE-UA_7006  
MAGNESIUM_2020  PO4_2033  PROTEIN-UA_7004  URINE_PH_7003  
URINE_SPEC_GRAVITY_7002  URIC_ACID_2022  CREAT_24_HRS_7068  
VOLUME_Urine_7060  SATURATION_3173  IRON_BINDING_3174  
PTH_HORMONE_2195  ALUMINUM_2047  GFR_ESTIMATED_191  
AFRICAN_AMERICAN  VITAMIN_D_25_OH_TOTAL_2341  
GLUCOSE_2011  IONIZED_CALCIUM_2018  HEMOGLOBIN_A1C_2034  
ZINC_2053  CALCIUM_24_HRS_7112  PHOS_24_HRS_7174  
SODIUM_24_HRS_7061  UR_OSMOLALITY_7067  PREALBUMIN_2058  
COPPER_2052  GLUCOSE_FASTING_2035  TOT_PRO_24_HRS_7083  
ALBUMIN_Urine_7052  POTASSIUM_24_HRS_7063  CITRATE_24_HRS_7119  
URIC ACID_24_HRS_7190  SP_GRAVITY_7182  UREA_NIT_24_HRS_7188  
ALDOSTERONE_UR_7095  CHLORIDE_24_HRS_7065  
GLUCOSE_2036  MAGNESIUM_24_HRS_7155  BICARBONATE_Urine_7235  
diastolic systolic;  
run;  */

data albumin (keep=patient_num ALBUMIN_2023) alkp (keep=patient_num 
ALK_PHOSPHATASE_2071)  
alt (keep=patient_num ALT_2065) anion (keep=patient_num 
ANION_GAP_2006)  
ast (keep=patient_num AST_2064) bun (keep=patient_num BUN_2007)  
calc (keep=patient_num CALCIUM_2017) cholest (keep=patient_num 
CHOLESTEROL_2318)  
c1 (keep=patient_num CHLORIDE_2004) co2 (keep=patient_num 
CO2_2005)  
diastol (keep=patient_num diastolic) gluc (keep=patient_num 
GLUCOSE_2011)  
hct (keep=patient_num HEMATOCRIT_3004) hd1 (keep=patient_num 
HDL_2320)  
hgb (keep=patient_num HEMOGLOBIN_3000) k (keep=patient_num 
POTASSIUM_2002)  
l1d (keep=patient_num LDL_2321) mag (keep=patient_num 
MAGNESIUM_2020)  
na (keep=patient_num SODIUM_2000) ph (keep=patient_num 
URINE_PH_7003)  
phos (keep=patient_num PO4_2033) systol (keep=patient_num systolic)  

data albumin (keep=patient_num ALBUMIN_2023) alkp (keep=patient_num 
ALK_PHOSPHATASE_2071)  
alt (keep=patient_num ALT_2065) anion (keep=patient_num 
ANION_GAP_2006)  
ast (keep=patient_num AST_2064) bun (keep=patient_num BUN_2007)  
calc (keep=patient_num CALCIUM_2017) cholest (keep=patient_num 
CHOLESTEROL_2318)  
c1 (keep=patient_num CHLORIDE_2004) co2 (keep=patient_num 
CO2_2005)  
diastol (keep=patient_num diastolic) gluc (keep=patient_num 
GLUCOSE_2011)  
hct (keep=patient_num HEMATOCRIT_3004) hd1 (keep=patient_num 
HDL_2320)  
hgb (keep=patient_num HEMOGLOBIN_3000) k (keep=patient_num 
POTASSIUM_2002)  
l1d (keep=patient_num LDL_2321) mag (keep=patient_num 
MAGNESIUM_2020)  
na (keep=patient_num SODIUM_2000) ph (keep=patient_num 
URINE_PH_7003)  
phos (keep=patient_num PO4_2033) systol (keep=patient_num systolic)  

data albumin (keep=patient_num ALBUMIN_2023) alkp (keep=patient_num 
ALK_PHOSPHATASE_2071)  
alt (keep=patient_num ALT_2065) anion (keep=patient_num 
ANION_GAP_2006)  
ast (keep=patient_num AST_2064) bun (keep=patient_num BUN_2007)  
calc (keep=patient_num CALCIUM_2017) cholest (keep=patient_num 
CHOLESTEROL_2318)  
c1 (keep=patient_num CHLORIDE_2004) co2 (keep=patient_num 
CO2_2005)  
diastol (keep=patient_num diastolic) gluc (keep=patient_num 
GLUCOSE_2011)  
hct (keep=patient_num HEMATOCRIT_3004) hd1 (keep=patient_num 
HDL_2320)  
hgb (keep=patient_num HEMOGLOBIN_3000) k (keep=patient_num 
POTASSIUM_2002)  
l1d (keep=patient_num LDL_2321) mag (keep=patient_num 
MAGNESIUM_2020)  
na (keep=patient_num SODIUM_2000) ph (keep=patient_num 
URINE_PH_7003)  
phos (keep=patient_num PO4_2033) systol (keep=patient_num systolic)  

data albumin (keep=patient_num ALBUMIN_2023) alkp (keep=patient_num 
ALK_PHOSPHATASE_2071)  
alt (keep=patient_num ALT_2065) anion (keep=patient_num 
ANION_GAP_2006)  
ast (keep=patient_num AST_2064) bun (keep=patient_num BUN_2007)  
calc (keep=patient_num CALCIUM_2017) cholest (keep=patient_num 
CHOLESTEROL_2318)  
c1 (keep=patient_num CHLORIDE_2004) co2 (keep=patient_num 
CO2_2005)  
diastol (keep=patient_num diastolic) gluc (keep=patient_num 
GLUCOSE_2011)  
hct (keep=patient_num HEMATOCRIT_3004) hd1 (keep=patient_num 
HDL_2320)  
hgb (keep=patient_num HEMOGLOBIN_3000) k (keep=patient_num 
POTASSIUM_2002)  
l1d (keep=patient_num LDL_2321) mag (keep=patient_num 
MAGNESIUM_2020)  
na (keep=patient_num SODIUM_2000) ph (keep=patient_num 
URINE_PH_7003)  
phos (keep=patient_num PO4_2033) systol (keep=patient_num systolic)
trig (keep=patient_num TRIGLYCERIDE__2319_) uric (keep=patient_num URIC_ACID__2022_)
urinesp (keep=patient_num URINE_SPEC_GRAVITY__7002_);
set comp8;
by patient_num;
if ALBUMIN__2023_ > . then output albumin;
if ALK_PHOSPHATASE__2071_ > . then output alkp;
if ALT__2065_ > . then output alt;
if ANION_GAP__2006_ > . then output anion;
if AST__2064_ > . then output ast;
if BUN__2007_ > . then output bun;
if CALCIUM__2017_ > . then output calc;
if CHLORIDE__2004_ > . then output cl;
if CO2__2005_ > . then output co2;
if HEMATOCRIT__3004_ > . then output hct;
if HEMOGLOBIN__3000_ > . then output hgb;
if POTASSIUM__2002_ > . then output k;
if SODIUM__2000_ > . then output na;
if CHOLESTEROL__2318_ > . then output cholest;
if HDL__2320_ > . then output hdl;
if LDL__2321_ > . then output ldl;
if TRIGLYCERIDE__2319_ > . then output trig;
if MAGNESIUM__2020_ > . then output mag;
if P04__2033_ > . then output phos;
if URINE_PH__7003_ > . then output ph;
if URINE_SPECGRAVITY__7002_ > . then output urinesp;
if URIC_ACID__2022_ > . then output uric;
if GLUCOSE__2011_ > . then output gluc;
if diastolic> . then output diastol;
if systolic> . then output systol;
run;

data labs junk;
merge albumin alkp alt anion ast bun calc cholest cl co2 diastol gluc hct
hdl hgb k ldl mag na ph phos systol trig uric urinesp;
by patient_num;
if first.patient_num then output labs;
else output junk;
run;

data complete;
COPPER__2052__GLUCOSE__FASTING__2035__TOT_PRO_24_HRS__7083_
ALBUMIN__URINE__7052__POTASSIUM_24_HRS__7063__CITRATE_24_HRS__7119_
URIC_ACID__24_HRS__7190__SP_GRAVITY__7182__UREA_NIT_24_HRS__7188_
ALDOSTERONE__UR__7052__CHLORIDE_24_HRS__7065_
GLUCOSE__2036__MAGNESIUM_24_HRS__7155__BICARBONATE__URINE__7235_
diastolic systolic) labs;
by patient_num;
rename ALBUMIN_2023=albumin
ALK_PHOSPHATASE__2071=alkphos
ALT__2065=alt
ANION_GAP__2006=anion
AST__2064=ast
BUN__2007=bun
CALCIUM__2017=calcium
CHLORIDE__2004=cl
CO2__2005=co2
GLUCOSE__2011=gluc
HEMATOCRIT__3004=hct
HEMOGLOBIN__3000=hgb
POTASSIUM__2002=k
SODIUM__2000=na
CHOLESTEROL__2318=cholest
HDL__2320=hd1
LDL__2321=ld1
TRIGLYCERIDE__2319=trig
MAGNESIUM__2020=mag
PO4__2033=phos
URINE_PH__7003=ph
URINE_SPEC_GRAVITY__7002=urinesp
URIC_ACID__2022=uric;
run;
data complete1 junk;
set complete;
by patient_num;
if first.patient_num then output complete1;
else output junk;
run;
data complete2;
set complete1;
if GFR<15 then CKDStage=5;
if 15<=GFR<=29 then CKDStage=4;
if 30<=GFR<=59 then CKDStage=3;
if 60<=GFR<=89 then CKDStage=2;
if 90<=GFR then CKDStage=1;
run;
proc freq data=complete2;
table CKDStage/list;
run;
data complete3 junk;
set complete2;
if CKDStage=5 then output junk;
else output complete3;
run;
**proc rank data=complete3 groups=4 out=complete3;**
  var albumin alkphos alt anion ast bun calcium cl co2 gluc hct hgb k na cholest hd1 ld1 trig mag ph urinesp uric systolic diastolic;
  ranks rank_albumin rank_alkphos rank_alt rank_anion rank_ast rank_bun rank calcium rank_cl rank_co2 rank_gluc rank_hct rank_hgb rank_k rank_na rank_cholest rank_hd1 rank_ld1 rank_trig rank_mag rank_phos rank_hct rank_urinesp rank_uric rank_systolic rank_diastolic;
run;

**proc freq data=complete3;**
  tables rank_albumin rank_alkphos rank_alt rank_anion rank_ast rank_bun rank calcium rank_cl rank_co2 rank_gluc rank_hct rank_hgb rank_k rank_na rank_cholest rank_hd1 rank_ld1 rank_trig rank_mag rank_phos rank_hct rank_urinesp rank_uric rank_systolic rank_diastolic;
run;

**proc freq data=complete3;**
run;

*check all variables to determine if collapsing or dichotamizing is needed;

**proc freq data=complete3;**
  table smokestatus/list;
run;

**proc freq data=complete3;**
  table smokelessstatus/list;
run;

**proc freq data=complete3;**
  table gender/list;
run;

**proc freq data=complete3;**
  table ethnicity/list;
run;

**proc freq data=complete3;**
  table Language/list;
run;

**proc freq data=complete3;**
  table Marital_Status/list;
run;

**proc freq data=complete3;**
  table Race/list;
run;

proc freq data=complete3;
    table pkddx/list;
run;
/
/*
proc plot data=complete1;
    plot albumin*start_date;
run;
*/

*categorize variables according to categories;
data complete3a (drop=ethnicity language religion);
    set complete3;
    if smokestatus='Current Everyday Smoker' then smokestatus='Smoker';
    if smokestatus='Current Some Day Smoker' then smokestatus='Smoker';
    if smokestatus='Former Smoker' then smokestatus='Smoker';
    if smokestatus='Never Assessed' then smokestatus='Unknown';
    if smokestatus='Never Smoker' then smokestatus='Nonsmoker';
    if smokestatus='Passive Smoker' then smokestatus='Nonsmoker';
    if smokestatus='Smoker, Current Status Unknown' then smokestatus='Unknown';
    if smokestatus='Unknown If Ever Smoked' then smokestatus='Unknown';
    if smokestatus='Unknown' then smokestatus='Unknown';
    if smokelessstatus='Current User' then smokelessstatus='User';
    if smokelessstatus='Former User' then smokelessstatus='User';
    if smokelessstatus='Never Used' then smokelessstatus='Nonuser';
    if smokelessstatus='Unknown' then smokelessstatus='Unknown';
    if smokelessstatus=' ' then smokelessstatus='Unknown';
    if marital_status='Single-S' then marital_status='Single';
    if marital_status='Divorced-D' then marital_status='Other';
    if marital_status='Married-M' then marital_status='Married';
    if marital_status='Separated-X' then marital_status='Other';
    if marital_status='Unknown-U' then marital_status='Unknown';
    if marital_status='Widowed-W' then marital_status='Other';
    if race='White or Caucasian' then race='White';

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if race='American Indian or Alaskan Native' then race='Other';
if race='Asian' then race='Other';
if race='Black or African American' then race='Black';
if race='Declined' then race='Unknown';
if race='Other' then race='Other';
if race='Two Races' then race='Other';
run;

*run covariate analysis using categorical variables and first lab obs within 90 days of baseline visit;
filename mprint "C:\Users\Jacob\Desktop\PhD Dissertation\check.sas"
lrecl=2048;
options symbolgen mprint mlogic mfile;

%macro phregcon(var1,refval);
proc phreg data=complete3a;
class &var1. (param=ref ref="&refval.");
model Lastage*Kidfail(0) =&var1. / risklimits alpha=0.05;
   ods output Phreg.Type3=Type3_&var1.;
run;

%if "&var1."="CKDStage" %then %do;
   proc datasets library=work;
      delete one;
      quit;

      data one;
      set Type3_&var1.;
      run;
%end;
%else %do;

      data one;
      set one Type3_&var1.;
      run;
%end;
%mend phregcon;

%phregcon(CKDStage,1);
%phregcon(Smokestatus,Nonsmoker);
%phregcon(Smokelessstatus,Nonuser);
%phregcon(Gender,Male);
%phregcon(Marital_Status,Single);
%phregcon(Race,White);
%phregcon(rank_albumin,0);
%phregcon(rank_alkphos,0);
%phregcon(rank_alt,0);
%phregcon(rank_anion,0);
%phregcon(rank_ast,0);
%phregcon(rank_bun,0);
%phregcon(rank_cl,0);
%phregcon(rank_co2,0);
%phregcon(rank_gluc,0);
%phregcon(rank_hct,0);
%phregcon(rank_hgb,0);
%phregcon(rank_k,0);
%phregcon(rank_na,0);
%phregcon(rank_hdl,0);
%phregcon(rank_ldl,0);
%phregcon(rank_trig,0);
%phregcon(rank_mag,0);
%phregcon(rank_phos,0);
%phregcon(rank_ph,0);
%phregcon(rank_urinesp,0);
%phregcon(rank_uric,0);
%phregcon(rank_systolic,0);
%phregcon(rank_diastolic,0);
%phregcon(BMIstatus,Overweight);

*run chi squared to look for associations among variables;
filename mprint "C:\Users\Jacob\Desktop\PhD Dissertation\check2.sas"
lrecl=2048;
options symbolgen mprint mlogic mfile;

%macro chisqcon(var1);
proc freq data=complete3a;
  table &var1.*CKDStage/chisq cmh;
  ods output  Freq.Table1.ChiSq=ChiSq_&var1.;
proc freq data=complete3a;
  table &var1.*rank_albumin/chisq cmh;
  ods output  Freq.Table1.Chisq=ChiSq2_&var1.;
proc freq data=complete3a;
  table &var1.*rank_ast/chisq cmh;
  ods output  Freq.Table1.Chisq=ChiSq3_&var1.;
proc freq data=complete3a;
  table &var1.*rank_bun/chisq cmh;
  ods output  Freq.Table1.Chisq=ChiSq4_&var1.;
proc freq data=complete3a;
  table &var1.*rank_cl/chisq cmh;
  ods output  Freq.Table1.Chisq=ChiSq5_&var1.;
proc freq data=complete3a;
  table &var1.*rank_co2/chisq cmh;
  ods output  Freq.Table1.Chisq=ChiSq6_&var1.;
proc freq data=complete3a;
  table &var1.*rank_hct/chisq cmh;
  ods output  Freq.Table1.Chisq=ChiSq7_&var1.;
proc freq data=complete3a;
  table &var1.*rank_hgb/chisq cmh;
ods output  Freq.Table1.Chi=ChiSq8_&var1.;

proc freq data=complete3a;
    table &var1.*rank_k/chisq cmh;
    ods output  Freq.Table1.Chi=ChiSq9_&var1.;

proc freq data=complete3a;
    table &var1.*rank_hdl/chisq cmh;
    ods output  Freq.Table1.Chi=ChiSq10_&var1.;

proc freq data=complete3a;
    table &var1.*rank_phos/chisq cmh;
    ods output  Freq.Table1.Chi=ChiSq11_&var1.;

proc freq data=complete3a;
    table &var1.*rank_diastolic/chisq cmh;
    ods output  Freq.Table1.Chi=ChiSq12_&var1.;

proc freq data=complete3a;
    table &var1.*BMIStatus/chisq cmh;
    ods output  Freq.Table1.Chi=ChiSq14_&var1.;
run;

%mend chisqcon;

%chisqcon(CKDStage);
%chisqcon(rank_albumin);
%chisqcon(rank_ast);
%chisqcon(rank_bun);
%chisqcon(rank_cl);
%chisqcon(rank_co2);
%chisqcon(rank_hct);
%chisqcon(rank_hgb);
%chisqcon(rank_k);
%chisqcon(rank_hdl);
%chisqcon(rank_phos);
%chisqcon(rank_uric);
%chisqcon(rank_diastolic);
%chisqcon(BMIStatus);

%macro chisqcon(var1);

%if "&var1."="CKDStage" %then %do;
    proc datasets library=work;
        delete two;
    quit;

data two;
    set ChiSq_&var1.;
run;
%end;
%else %do;
   data two;
      set two ChiSq_&var1. ChiSq2_&var1. ChiSq3_&var1. ChiSq4_&var1.
             ChiSq5_&var1. ChiSq6_&var1. ChiSq7_&var1.
             ChiSq8_&var1. ChiSq9_&var1. ChiSq10_&var1. ChiSq11_&var1.
             ChiSq12_&var1. ChiSq13_&var1. ChiSq14_&var1.;
   run;
%end;
%mend chisqcon;

%chisqcon(CKDStage);
%chisqcon(rank_albumin);
%chisqcon(rank_ast);
%chisqcon(rank_bun);
%chisqcon(rank_c1);
%chisqcon(rank_co2);
%chisqcon(rank_hct);
%chisqcon(rank_hgb);
%chisqcon(rank_k);
%chisqcon(rank_hdl);
%chisqcon(rank_phos);
%chisqcon(rank_uric);
%chisqcon(rank_diastolic);
%chisqcon(BMIstatus);

data three junk;
   set two;
      if index(Statistic, 'Chi-Square') then output junk;
   else
      output three; run;

data threea (drop=statistic df value) junk;
   set three;
      if index(Statistic, 'Chi-Square') then output threea;
   else
      output junk; run;

data complete4;
   set complete3a;
      if BMIstatus='Under/Healthy Weight' then
         BMIstatus2='Under/Healthy/Overweight';
      if BMIstatus='Overweight' then
         BMIstatus2='Under/Healthy/Overweight';
      if BMIstatus='Obese' then
         BMIstatus2='Obese';
      if 0<=rank_hdl<=2 then rank_hdl2=0;
      if rank_hdl=3 then rank_hdl2=1;
   run;

proc phreg data=complete3a;
   class BMIstatus (param=ref ref='Overweight');
   model Lastage*Kidfail(0) =BMIstatus / risklimits alpha=0.05;
run;
PROC PHREG DATA=COMPLETE4;
CLASS BMISStatus2 (param=ref ref='Under/Healthy/Overweight');
MODEL Lastage*Kidfail(0) =BMISstatus2 / risklimits alpha=0.05;
RUN;

PROC PHREG DATA=COMPLETE4;
CLASS BMISStatus2 (param=ref ref='Under/Healthy/Overweight') rank_hdl2 (param=ref ref='0');
MODEL Lastage*Kidfail(0) =BMISstatus2 rank_hdl2 / risklimits alpha=0.05;
RUN;

DATA complete5;
    SET complete4;
    IF rank_hdl= . THEN rank_hdl2=9;
RUN;

*correct 4 ages;
data complete6;
    SET complete5;
    IF patient_num=74247 THEN Age=18;
    IF patient_num=822914 THEN Age=18;
    IF patient_num=854098 THEN Age=18;
    IF patient_num=1674354 THEN Age=18;
RUN;

PROC PHREG DATA=COMPLETE5;
CLASS BMISStatus2 (param=ref ref='Under/Healthy/Overweight') rank_hdl2 (param=ref ref='0');
MODEL Lastage*Kidfail(0) =BMISstatus2 rank_hdl2 / risklimits alpha=0.05;
RUN;

ODS GRAPHICS ON;
PROC LIFETEST DATA=COMPLETE5 PLOTS=(LLS) NOTABLE;
TIME Lastage*Kidfail(0);
STRATA rank_hdl2;
RUN;
ODS GRAPHICS OFF;

*check assumptions;
PROC FREQ DATA=COMPLETE4;
    TABLE BMISstatus*rank_hdl1/chisq cmh;
RUN;

PROC FREQ DATA=COMPLETE4;
    TABLE BMISstatus*Lastage/chisq cmh;
RUN;

PROC FREQ DATA=COMPLETE4;
    TABLE rank_hdl1*Lastage/chisq cmh;
RUN;

*Misc data for results;
PROC SORT DATA=COMPLETE4;
    BY rank_hdl1;
RUN;

PROC MEANS DATA=COMPLETE6;
var Age GFR;
run;

proc means data=complete4;
var HDL;
by rank_hdl;
run;

proc freq data=complete6;
run;