Biliary tract and liver complications in polycystic kidney disease

Running title: ADPKD & biliary/liver disease

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Abstract

Polycystic liver disease is a well-described manifestation of autosomal dominant polycystic kidney disease (ADPKD). Biliary tract complications are less well-recognised. We report a 50-year single-centre experience of 1,007 patients, which raised a hypothesis that ADPKD is associated with biliary tract disease. This was then tested using all-England Hospital Episode Statistics data (1998-2012) within which 23,454 people recorded as having ADPKD and 6,412,754 hospital controls were identified. Hospitalisation rates for biliary tract disease, serious liver complications and a range of other known ADPKD manifestations were adjusted for potential confounders and then compared. Compared to non-ADPKD hospital controls, the rates of admission for biliary tract disease were 2.2-times higher in those with ADPKD (rate ratio [RR] 2.24, 95% confidence interval 2.16-2.33) and 4.7-times higher for serious liver complications (RR 4.67, 4.35-5.02). When analyses were restricted to those on maintenance dialysis or with a kidney transplant, RRs attenuated substantially, but ADPKD remained positively associated with both biliary tract disease (RR 1.19, 1.08-1.31) and with serious liver complications (RR 1.15, 0.98-1.33). The ADPKD versus non-ADPKD hospital control RRs for biliary tract disease were larger for men than women (heterogeneity $p<0.001$), but RRs for serious liver complications appeared higher in women (heterogeneity $p<0.001$). The absolute excess risk of biliary tract disease associated with ADPKD (0.73%/year) was larger than for serious liver disease (0.24%/year), cerebral aneurysms (0.11%/year), or inguinal hernias (0.11%/year), but less than for urinary tract infections (2.20%/year). Biliary tract disease appears to be a distinct and important extra-renal complication of ADPKD.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease.[1,2] It is characterised by progressive enlargement of the kidneys with multiple bilateral cysts and eventual loss of kidney function, often causing end-stage renal disease (ESRD) in middle age.[1,3] Ten percent of renal replacement therapy (RRT) patients in the UK and 5% in the US have a primary renal diagnosis of ADPKD.[4,5] ADPKD is a multi-system disorder with polycystic liver a common extra-renal manifestation.[6-8] The prevalence of liver cysts in people with ADPKD increases with age, with >90% of patients aged >40 years having at least one cyst.[9] Unlike renal cysts (which are unaffected by sex), liver cysts are more common and numerous in pre-menopausal women with ADPKD than in men.[7,9,10] ADPKD is also associated with other abdominal manifestations, including colonic diverticular disease, abdominal wall hernias and pancreatic cysts.[8,10,11] Mild common bile duct dilatation has also been reported,[12] but unlike the much rarer autosomal recessive form of polycystic kidney disease, which is associated with non-obstructive intra-hepatic duct dilation (Caroli's disease) and recurrent cholangitis,[13] clinically significant biliary tract complications are less well recognized in ADPKD.

We made an observation at our tertiary centre that, in addition to the infective and compressive complications caused by polycystic livers, several patients with ADPKD had repeated hospitalisations for biliary tract disease. A systematic literature review of PubMed from its inception through to 22/7/2016 identified a total of 662 potentially relevant abstracts, from which 44 full text articles were read and 10 relevant reports identified (Webfigure 1).[12,14-22] These included six articles reporting obstructive jaundice due to enlarged cysts,[17-22] and four reporting six cases of symptomatic cholecystitis usually with gallstones.[12,14-16] We found no reports which described the range of presentations of biliary tract disease in individuals with ADPKD, nor any which had quantified any excess risk of clinically significant biliary tract disease in ADPKD. In order to explore whether our clinical observations reflect a previously undescribed feature of ADPKD, we aimed, first, to report a single tertiary centre's

~50-year experience of biliary tract disease and serious liver complications in patients with ADPKD. We then tested the hypothesis that biliary tract disease is more common in ADPKD by using routinely collected English hospital inpatient data 1998-2012 to compare hospitalisation rates for biliary tract disease among people with ADPKD versus rates in non-ADPKD control populations.

Results

Oxford Kidney Unit case series 1967-2015

Between 1967 and 2015, 1,011 patients with polycystic kidney disease were cared for at the Oxford Kidney Unit, including 4 patients (0.4%) with autosomal recessive polycystic kidney disease. Of the 1,007 with presumed ADPKD, 35 patients were identified as having developed biliary tract disease and/or a liver complication (Table 1). We noted that biliary tract disease was mostly cholecystitis or other gallstone-related complications, and that this was the prominent presentation in 24 patients. Serious liver complications were the prominent presentation in 11 patients, mostly representing liver cyst infections (Table 1). Nine patients developed both biliary tract disease and a serious liver complication.

The median ages at presentation with biliary tract disease and liver complications were 31 years (interquartile range 26-49) and 38 (31-46) years respectively (Table 1). These complications tended to manifest in people with stage 5 chronic kidney disease (CKD), many of whom had started maintenance renal replacement therapy (RRT) by the time of their first such presentation. A similar proportion of women and men were affected by biliary tract disease (13/522 women versus 11/485 men; p=0.82), but women appeared more likely to develop a serious liver complication (10/522 women versus 1/485 men; p=0.009).

Biliary tract infections accounted for 74% (90/121) of biliary tract presentations and often recurred (there were 90 occurrences among the 21 patients with a biliary tract infection). *Escherichia coli* and *Enterococcus* species were the commonest causes of biliary tract

infection. Liver cyst infections occurred in 67% (12/18) of those with a serious liver complication, accounting for 38% (22/58) of all admissions for serious liver complications. Unlike biliary tract infections, the majority of liver infections were culture-negative (Webfigure 2). Management of liver cyst infections was usually with antibiotic therapy alone, whilst management of biliary tract disease frequently involved both antibiotics and a range of radiological and surgical interventions (Webtable 1). Forty-two percent (11/26) of patients with biliary tract disease had gallstones removed at endoscopic retrograde cholangiopancreatography, 5 patients required sphincterotomies and 3 had biliary stents inserted (Webtable 1).

Disease-association study using all-England Hospital Episode Statistics 1998-2012

We designed a disease-association study using all-England Hospital Episode Statistics (HES) to test the subsequent hypothesis that biliary tract disease might be more common in ADPKD than would be expected compared to the general population.

Using data on 43.2 million people aged over 20 years with at least one hospital admission recorded in linked and anonymised all-England HES between 1998 and 2012, we identified 23,454 people admitted with a diagnostic code for ADPKD and who were unlikely to have autosomal recessive polycystic kidney disease (see Concise methods). Median age at the start of follow-up was 58 years (44-70), 10,789 (46%) were female and 20,011 (85%) were white (Table 2). A history of prior diabetes or vascular disease was recorded in 906 (4%) and 1,747 (7%) respectively. In comparison, 6,412,754 hospital controls were identified from an admission for one of a variety of minor conditions (with no mention of polycystic kidney disease in any admission). Hospital controls were on average younger (median age 48 [34-67] years) and less likely to have diabetes (189,858, 3.0%) or vascular disease (181,832, 2.8%; Table 2).

After adjustment for age, sex, ethnicity, social deprivation, region, prior diabetes, prior vascular disease or cancer, and year of first admission, the rates of admission for a series of disease outcomes were compared among people with ADPKD versus without ADPKD (referred to as 'ADPKD versus non-ADPKD rate ratios', RRs). Compared to hospital controls, adjusted rates of ESRD were 112-times higher in people with ADPKD (2.82% versus 0.03%/year; rate ratio [RR] 112, 95% CI 109-116; Figure 1A). Figure 1A provides adjusted rates and ADPKD versus non-ADPKD RRs for a range of other known manifestations of ADPKD. These include cerebral aneurysms, inguinal and other abdominal wall hernias, urinary tract infections, cardiac valve disease, and diverticular disease (Webtable 2 provides outcome definitions), all of which were positively associated with ADPKD.

Compared to hospital controls, the rates of admission for biliary tract disease were 2.2-times higher in people with ADPKD (1.31% versus 0.59%/year; RR 2.24, 95% CI 2.16-2.33) and 4.7-times higher for serious liver complications (0.31% versus 0.07%/year; RR 4.67, 4.35-5.02; Figure 1A). These equate to an absolute excess risk of biliary tract disease associated with ADPKD of 0.73%/year (95% CI 0.68-0.78%/year), which was larger than the absolute excess risk for serious liver disease (0.24%/year, 0.21-0.28%/year), cerebral aneurysms (0.11%/year, 0.09-0.14%/year), inguinal hernias (0.11%/year, 0.08-0.14%/year), or abdominal wall hernias (0.35%, 0.32-0.38%/year); similar to the excess risk for colonic diverticular disease (0.73%/year, 0.67-0.79%/year); but much less than for urinary tract infections (2.20%/year, 2.10-2.31%/year).

On average, hospital controls are likely to have better kidney function than people with ADPKD, which is important to consider in secondary analyses, as CKD might mediate some of the positive associations between ADPKD and outcomes. We therefore repeated analyses just among the 68,332 people who had started maintenance RRT which effectively adjusts for any effect of advanced CKD.

Within the treated ESRD population, 9% (5,813/68,332) were recorded as having ADPKD. People with ESRD due to ADPKD were on average younger (57 versus 62 years), more likely to be female (46% versus 38%), and less likely to have a history of prior diabetes (8% versus 32%) or vascular disease (13% versus 27%) than those with ESRD due to other causes (Table 2).

After restricting analyses to those with treated ESRD, ADPKD versus non-ADPKD RRs for the positive control diseases were attenuated (Figure 1B). Nevertheless, compared to those with other causes of ESRD, rates of hospitalisation among people with ADPKD were 2.2-times higher for cerebral aneurysms (0.13% versus 0.06%/year, RR 2.23, 1.53-3.26), 2.5 times higher for other abdominal wall hernias (1.23% versus 0.50%/year, RR 2.47, 2.19-2.80), and about 60 to 70% higher for both inguinal hernias (1.00% versus 0.59%/year, RR 1.70, 1.49-1.95), and colonic diverticular disease (2.70% versus 1.64%/year, RR 1.65, 1.52-1.79; Figure 1B). Rates for serious cardiac valve disease, however, were similar among people with ESRD due to ADPKD and people with other causes of ESRD (1.47% versus 1.63%/year, RR 0.90, 0.81-1.00).

The RRs for biliary tract disease and serious liver complications were also substantially attenuated when analyses were restricted to those with treated ESRD, but ADPKD remained positively associated with both conditions. Compared to those with other causes of ESRD, rates of biliary tract disease were 19% higher among people with ADPKD (1.92% versus 1.61%/year, RR 1.19, 1.08-1.31) and 15% higher for serious liver complications (0.70% versus 0.62%/year; RR 1.15, 0.98-1.33; Figure 1B).

Among people on maintenance RRT, the absolute excess risk of biliary tract complications (0.31%/year, 0.13-0.49%/year) in people with ADPKD remained larger than for serious liver complications (0.09%/year, -0.02-0.2%/year) and for cerebral aneurysms (0.07%/year, 0.03-

196 0.12%/year); became similar to the absolute excess risk for inguinal hernias (0.41%/year,
197 0.29-0.54%/year); but was somewhat smaller than for other abdominal wall hernias
198 (0.73%/year, 0.59-0.87%/year), colonic diverticular disease (1.06%/year, 0.85-1.27%/year)
199 and urinary tract infections (1.36%/year, 1.01-1.72%/year).
200
201 In analyses performed separately for different age groups and by sex, compared with
202 hospital controls, ADPKD versus non-ADPKD RRs for serious liver complications were
203 higher in women than in men (heterogeneity p<0.001), confirming the observation from our
204 case series. However, the reverse was observed for biliary tract disease (heterogeneity
205 p<0.001; Figure 2A). RRs for serious liver disease were larger among younger people with
206 ADPKD (trend p<0.001), but the reverse was also true for biliary tract disease (trend
207 p<0.001; Figure 2A). In analyses restricted to people with treated ESRD, ADPKD versus
208 non-ADPKD RRs for biliary tract disease became similar in both sexes (heterogeneity
209 p=0.22), but RRs for serious liver complications remained higher in women than in men
210 (heterogeneity p<0.001; Figure 2B). There was no difference in RRs for either complication
211 by age in people with treated ESRD (Figure 2B).
212
213 In sensitivity analyses, results were similar when repeated with the exclusion of secondary
214 diagnoses to define disease outcomes (Webfigures 3&4), or with exclusion of people with a
215 serious liver complication (which reduces any over-ascertainment of biliary tract disease
216 identified incidentally during any liver investigations, data not shown).
217
218 *Cause-specific mortality among people with ADPKD*
219 Biliary tract or liver disease are an uncommon underlying cause of death among people with
220 ADPKD, except among those that were hospitalised in the cohort for either biliary tract
221 disease or serious liver complications, in whom it accounted for 8% of deaths (Webfigure 5).
222 This proportion was similar in women and men (9% versus 6%; p=0.06, Webfigure 6).
223

Discussion

We have reported a case series and a large disease-association study including over 23,000 patients with ADPKD. Our case series findings suggested biliary tract disease is as frequent in people with ADPKD as serious liver complications, and has a distinct clinical presentation and sex distribution. Our disease association study confirmed that hospitalisation for biliary tract disease is more common among people with ADPKD than people without, and that the absolute excess risk was larger than for serious liver complications and a range of other better described extra-renal manifestations of ADPKD.

The Halt Progression of Polycystic Kidney Disease Study A (HALT-PKD-A) has characterised the biliary tract and liver imaging features of ADPKD.[23] Common bile duct dilatation was present in 17% of the cohort, but was the only biliary tract abnormality described. These data corroborate earlier observations from a Japanese study of 55 people with ADPKD, where the prevalence of common bile duct dilatation was 40%, compared to 7% in controls.[12] A higher prevalence of common bile duct dilatation in the Japanese study may be accounted for by more advanced ADPKD, as one-half of the Japanese ADPKD patients had started haemodialysis, whilst all HALT-PKD-A participants had an estimated glomerular filtration rate >60mL/min/1.73m^2. In addition to these studies, our systematic literature review identified a few case reports of biliary tract complications in ADPKD (Webfigure 1),[12,14-16] but no study which had assessed if there was an excess risk of clinically significant biliary tract disease associated with ADPKD. The presented results therefore represent the first quantification of the association between ADPKD and serious biliary tract disease.

Another important finding in both our case series and disease association study is that the relative size of the ADPKD versus non-ADPKD RRs for serious liver complications was higher among women than men, but the reverse was true for biliary tract disease associations. Other ADPKD studies, including the HALT-PKD-A study, have also found the

prevalence of liver cysts is higher in women with ADPKD compared to men.[9,23] Estrogen receptors are expressed in the epithelium of liver cysts,[1,8,24,25] and female sex, exogenous estrogen use and pregnancy all appear to increase cyst cell proliferation and liver cyst size.[1,8,24,25] However, liver enlargement in ADPKD results from both cystic change and increased liver parenchymal volume, and men with ADPKD have been found to have increased height-adjusted liver parenchymal volume.[23] The differing patterns of associations in our subgroup analyses by age and sex suggest that cystic change in the liver - which has been reported to cause obstructive jaundice[17-22] - is not the key cause of biliary tract complications in ADPKD. Polycystin complexes localize to primary cilia in the kidney and biliary tract. In the biliary tract, cilia may act as mechanosensors maintaining the differentiated state of cholangiocyte epithelia and detecting changes in bile flow and composition.[26,27] Mutations in polycystin-encoding genes in ADPKD may therefore affect cholangiocyte cilia resulting in abnormal bile tract function (with biliary stasis and duct dilatation) and/or bile duct gland cyst formation.[15,28] A shared biliary phenotype between mutations which cause autosomal recessive and ADPKD has also been suggested.[29-31]

Biliary tract disease has featured in the results of recent randomized trials of treatments aimed at inhibiting renal cyst cell proliferation and fluid secretion. In a trial of a somatostatin analogue, ocreotide, the rate of kidney volume increase was slowed compared to placebo,[32] and post-hoc analyses suggested octreotide may also reduce liver parenchyme and cyst expansion.[33] However, it also led to increased numbers of non-serious reports of gallstones (octreotide 10/40 [25%] versus placebo 0/39 [0%]) and ‘biliary sand’ (7/40 [18%] versus 1/39 [3%]). The 2 reported serious cases of acute cholecystitis in this study were both among those allocated octreotide.[32] These results are consistent with previous reports of octreotide associated-gallstones, which is attributed to reduced post-prandial gallbladder contractility and biliary stasis (indicated by increased fasting gallbladder volumes).[34] Octreotide exerts its beneficial effects on cysts through inhibition of the secondary messenger cyclic adenosine monophosphate in biliary epithelial cells. However, inhibiting this pathway with the

vasopressin V2-receptor blocker, tolvaptan, significantly reduces the rate of increase in total kidney volume compared to placebo without any reported excess of upper abdominal pain, gallstones or biliary tract adverse events.[35]

Although not our primary aim, these data represent the largest confirmatory study of the size of associations between ADPKD and a range of previously described extra-renal manifestations.[8,36] Interestingly, we also found that despite a known increased prevalence of incompetent mitral and aortic valves in ADPKD,[37] after taking account of renal function, serious cardiac valve disease was no more common in people with ADPKD and ESRD than in those with other causes of ESRD. These findings may influence how nephrologists counsel ADPKD patients. Testing other hypotheses, we also found no evidence that ADPKD was associated with increased risk of hospitalisation with gastro-esophageal reflux disease, renal stones or aortic aneurysms among those with treated ESRD (Figure 1 footnote).

This study uses 'big data' to test bedside observations made over ~50-years, but there are certain limitations. First, pre-dialysis CKD stages are not well recorded in HES and there is no information on laboratory data, so it was not possible to assess comprehensively how much reduced renal function may explain associations with ADPKD. However, HES can be used to identify treated ESRD and analyses focused on maintenance RRT effectively adjust for advanced CKD, partially overcoming this limitation. Secondly, no information on body-mass index - which has been positively associated with cholelithiasis - was available for adjustment. A third limitation is that distinguishing sources of infection in admissions for sepsis is often difficult so rates of infection from particular sources may be underestimates. Lastly, ADPKD definitions were not directly confirmed. Nevertheless, excellent agreement between nurse-recorded primary renal diagnosis and ADPKD recorded in HES data has been shown previously, so any misclassification is unlikely to have led to much underestimation in the size of RRs.[38,39]

In summary, we raised and tested the hypothesis that ADPKD is associated with clinically significant biliary tract disease as well as serious liver complications. We found that women with ADPKD are at higher relative risk of a liver complication than men, but the reverse was observed for the positive association between ADPKD and biliary tract disease, suggesting liver and biliary complications of ADPKD have distinct disease mechanisms. The absolute excess risks of biliary tract complications in people with ADPKD are similar to the absolute excess risks of some of the better established complications, and so biliary tract disease should be a key differential diagnosis in patients with ADPKD presenting with abdominal pain or sepsis.

Concise methods

Oxford Kidney Unit case series (1967-2015)

All patients with presumed ADPKD cared for by Oxford Kidney Unit between 1967 and August 2015 were included. Biliary tract disease and serious liver complications were ascertained by physician review of diagnoses, procedures and investigation reports on the unit's electronic patient record system and local radiology, microbiology and histopathology systems. Once identified, detailed information on each biliary tract disease or serious liver complication was extracted by medical notes review, which included demographics, age and renal status at the time of the complication, details of the clinical presentation, including microbiological findings and clinical management.

Disease-association study using routine hospital admission data (1998-2012)

Ethical approval for analysis of the record linkage study data was obtained from the Central and South Bristol Multi-Centre Research Ethics Committee (04/Q2006/176). We used anonymised linked all-England Hospital Episode Statistics (HES) inpatient records with additional linkage to national mortality records.[40] Since 1998, HES has recorded information on all hospital inpatient activity in England, including: dates of admission and discharge; demographics (including age, sex, ethnicity); measures of social deprivation; the primary

diagnostic reason for admission with relevant secondary diagnoses, coded using the International Statistical Classification of Diseases and Related Health Problems Revision 10 (ICD-10);[41] and all procedures, coded using the Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) version 4.

Identification of autosomal dominant polycystic kidney disease cases

A patient with any mention of ICD-10 codes Q61.2 or Q61.3 in HES was presumed to have a diagnosis of ADPKD. The validity of using these codes has been directly demonstrated previously as part of a clinical trial among kidney transplant patients, in which there was an excellent level of agreement (kappa statistic >0.9) between nurse-reported primary renal diagnosis of cystic kidney disease and ADPKD coded in HES.[38,39] To reduce the chances of including autosomal recessive polycystic kidney disease in analyses, people hospitalised or starting RRT before 20 years of age were excluded.

Identification of control populations

Two control populations with no mention of ADPKD codes in any admission were derived from HES records. The first was a large group of patients admitted for minor diagnoses or procedures (see Table 2 footnote for complete list). The second was any patient who was treated with maintenance RRT (ie, long-term dialysis or kidney transplant) for ESRD and survived for at least 90 days from the start of RRT.

Outcomes

Outcomes for relevant diseases were identified using both information encoded in any diagnostic position (primary or secondary) or any recorded procedure. These included: (i) treated ESRD; (ii) a group of other positive control diseases which have previously been reported to be extra-renal manifestations of ADPKD[8,36] (including complications or treatment of cerebral aneurysms, abdominal wall hernias [separated into inguinal and other], urinary tract infections, serious cardiac valve disease, and diverticular disease); (iii) a group of liver

diagnoses and procedures associated with ADPKD, including liver abscess and liver de-roofing, resection and transplantation; (iv) and biliary tract diagnoses and procedures, including cholecystitis, biliary tract stones, and cholecystectomy (see Webtable 2 for full list of ICD and OPCS codes used to define outcomes); and (v) a negative control disease (breast cancer) which has previously been reported as not associated with ADPKD.[42] In addition, sensitivity analyses were performed excluding diagnostic information recorded as secondary diagnoses, and after excluding people who ever had a serious liver complication.

Covariates

The following patient characteristics were extracted from HES: age; sex; ethnicity (white, non-white, and not recorded); region of residence; English Index of Multiple Deprivation Score (IMD);[43] and comorbidity (diabetes, vascular or cancer considered separately). For hospital control analyses, comorbidity was derived from diagnoses and procedures recorded on the first admission. For the ESRD cohort, comorbidity was derived from the date of the start of RRT and any admission in the preceding two years.

Statistical methods

Baseline characteristics for each derived cohort were expressed as numbers (%) or median (interquartile range) and compared by standard chi-square or Kruskal-Wallis tests respectively. The follow-up time for each outcome began from the index date (defined as the date of the first admission) and ended at the earliest of date of a relevant outcome, death or end of the cohort follow-up (31/03/2012). Rates for each outcome were then calculated using Poisson regression adjusted for age as a continuous variable (using both linear and quadratic terms), sex, ethnicity (3 groups as above), quintiles of IMD score, region of residence (9 groups), prior reported diabetes, vascular disease (excluding subarachnoid haemorrhage) or cancer (excluding breast cancer). Changes in coding practice over time were controlled for by adjustment for calendar year of first admission (or, where relevant, year of start of maintenance RRT).

Primary analyses compared ADPKD to general hospital controls to quantify the 'full effect' of ADPKD on risk of outcomes. Secondarily, we assessed how much advanced CKD may impact on ADPKD versus non-ADPKD RRs by repeating analyses only among those who had already started RRT for ESRD (with the index date increased to the date of start of maintenance RRT).

RRs and their 95% CIs were calculated using standard statistical methods. Separate ADPKD versus non-ADPKD RRs for men and women and by age groups were calculated and compared using standard tests for heterogeneity and trend respectively. Analyses used SAS version 9.3 (SAS Institute, Cary, NY) and the R version 3.2.1 (www.r-project.org).

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Figure Legends

Figure 1: Association between polycystic kidney disease and risk of hospitalisation for different diseases in all−England Hospital Episode Statistics 1998−2012

CI = confidence intervals. Outcomes include admissions with relevant diagnostic codes in any diagnostic position or any relevant procedural codes. Adjusted for age at entry as a continuous variable (using both linear and quadratic terms), sex, ethnicity, quintile of patients' Index of Multiple Deprivation score, region of residence, calendar year of first recorded admission (or year of renal replacement therapy start) and comorbidities (grouped into vascular, cancer and diabetes). Rate ratios (95% CI) for aortic or other aneurysms are 3.74 (3.53−3.97) for all patients and 0.96 (0.84−1.11) for treated end−stage renal disease patients. Rate ratios (95% CI) for hiatus hernia and gastroesophageal reflux disease are 1.58 (1.53−1.63) for all patients and 1.03 (0.95−1.12) for treated end−stage renal disease patients. Rate ratios (95% CI) for renal stones are 4.63 (4.39−4.87) for all patients and 0.96 (0.81−1.15) for treated end−stage renal disease patients. Rate ratios (95% CI) for breast cancer (negative control) are 1.00 (0.88−1.12) for all patients and 0.62 (0.45−0.86) for treated end−stage renal disease patients.

Figure 2: Association between polycystic kidney disease and risk of hospitalisation for biliary tract and serious liver complications by age and sex in all−England Hospital Episode Statistics 1998−2012

CI = confidence intervals. Het = heterogeneity. Outcomes include admissions with relevant diagnostic codes in any diagnostic position or any relevant procedural codes. Adjusted for age at entry as a continuous variable (using both linear and quadratic terms), sex, ethnicity, quintile of patients' Index of Multiple Deprivation score, region of residence, calendar year of first recorded admission (or year of renal replacement therapy start) and comorbidities (grouped into vascular, cancer and diabetes).

Table 1: Baseline characteristics of individuals with autosomal dominant polycystic kidney disease and either a biliary tract or serious liver complication: Oxford Kidney Unit case series (1967-2015)

					Biliary tract disease and serious liver complications			
	Gender (male/ female)	Age at presentation with ADPKD (years)	Time from ADPKD diagnosis to first biliary tract disease / serious liver complication (years)	CKD stage at first biliary tract disease / serious liver complication	Number of admissions with gallbladder or bile duct disease	Gallstones ever diagnosed	No. of admissions with liver cyst infection	Relevant biliary tract and liver disease diagnoses or procedures
Biliary tract disease predominant presentation								
1	F	22	22	5D	18	Yes	0	Cholelithiasis with complications (recurrent biliary sepsis)
2*	M	28	32	5D	14	Yes	1	Cholelithiasis requiring 4xERCPs and sphincterotomy. Non-obstructive intrahepatic biliary tract duct dilatation and hepatic fibrosis. Liver cyst infection
3	M	48	10	5T	9	Yes	0	Cholelithiasis with complications requiring ERCP and sphincterotomy
4*	F	15	46	5T	9	No	1	Cholelithiasis with complications and liver abscess
5*	M	34	26	5T	8	Yes	3	Biliary obstruction and sepsis due to enlarged hepatic cysts and gallstones. Cholecystectomy. Cyst de-roofing. Liver cyst infections
6	M	18	44	5T	7	Yes	0	Cholelithiasis with complications, 3xERCPs and sphincterotomy
7	F	51	11	5D	7	Yes	0	Cholelithiasis with complications, 2xERCPs and biliary tract stenting
8	M	29	39	5T	6	Yes	0	Cholecystitis, biliary obstruction and cholecystectomy. Refractory ascites
9	F	18	46	5T	3	Yes	0	Cholelithiasis with complications (recurrent cholecystitis)
10*	M	24	32	5T	3	Yes	0	Cholelithiasis with complications requiring ERCP. Liver cyst de-roofing
11	M	26	35	5T	3	No	0	Non-obstructive intrahepatic biliary tract duct dilatation and hepatic fibrosis. Recurrent biliary sepsis.
12	F	31	43	5D	2	Yes	0	Cholelithiasis with complications. Cholecystectomy
13*	F	26	30	4/5	2	Yes	2	Cholelithiasis with complications. Liver cyst infections & haemorrhage
14	M	58	2	5T	1	Yes	0	Cholelithiasis with complications requiring 3xERCPs, sphincterotomy and biliary tract stent
15	F	57	4	5	1	No	0	Biliary sepsis
16*	F	21	32	5D	1	Yes	0	Cholelithiasis & biliary sepsis requiring cholecystectomy. Subphrenic abscess, liver cyst aspiration, cyst de-roofing, partial hepatectomy
17	M	56	16	5D	1	No	0	Biliary sepsis
18	F	52	25	5T	1	Yes	0	Cholelithiasis with complications. ERCP
19*	F	68	12	3	1	Yes	0	Cholelithiasis with complications. Autoimmune hepatitis
20	F	44	10	5T	1	Yes	0	Cholelithiasis with complications. ERCP & sphincterotomy. Cholecystectomy
21	M	45	12	5T	1	Yes	0	Obstructive jaundice, cholecystitis
22	F	47	4	5	1	Yes	0	Cholelithiasis requiring ERCP complicated by pancreatitis
23	F	31	31	3	1	Yes	0	Cholecystectomy
24	M	28	44	5D	1	Yes	0	Cholecystectomy
Subtotal	**M11:F13**	**Median 31 (IQR 26-49)**	**Median 28 (IQR 12-36)**		**Median 3 (IQR 1-8)**	**83% (20/24)**	**Median 0 (IQR 0-0)**	
Serious liver disease predominant presentation								
25	F	32	13	5D	0	No	3	Liver cyst infections. Massive polycystic liver with cyst drainage
26	F	41	25	5T	0	No	3	Recurrent liver cyst infections and liver abscess
27*	F	24	22	5	1	Yes	2	Liver cyst infections. Cholelithiasis
28*	F	48	6	4/5	1	Yes	2	Liver cyst infections. Cholelithiasis requiring cholecystectomy
29	F	44	5	5	0	No	2	Liver cyst infections. Cyst de-roofing (x2)
30	F	30	33	5D	0	No	1	Liver cyst infection. Cholelithiasis with complications requiring 2xERCP's and biliary tract stent insertion
31	M	20	32	5D	0	No	1	Liver cyst infection
32	F	48	20	5T	0	No	1	Lliver cyst infection
33	F	38	0	1	0	No	0	Massive polycystic liver (transplanted)
34	F	36	8	5T	0	No	0	Cyst aspiration and de-roofing
35	F	49	9	5	0	No	0	Massive polycystic liver (transplanted)
Subtotal	**M1:F10**	**Median 38 (IQR 31-46)**	**Median 13 (IQR 7-24)**		**Median 0 (IQR 0-0)**	**18% (2/11)**	**Median 1 (IQR 0.5-2)**	

ADPKD=autosomal dominant polycystic kidney disease; CKD=chronic kidney disease; ERCP=endoscopic retrograde cholangiopancreatogram; IQR=interquartile range; cholelithiasis with complications=gallstones with biliary sepsis (cholecystitis and/or cholangitis). * Patients with both biliary tract and serious liver presentations. Imaging was available on 46% (85/185) of living maintenance renal replacement therapy patients with ADPKD. 89% (76/85) had evidence of multiple liver cysts, 26% (22/85) had common bile duct dilatation and 16% (14/85) had gallstones.

Table 2: Baseline characteristics of polycystic kidney disease patients versus control populations at date of entry (all-England Hospital Episode Statistics 1998-2012)

	All patients			Treated end-stage renal disease patients		
	Polycystic kidney disease	Hospital controls	P-value	Polycystic kidney disease	Other ESRD causes	P-value
N	23,454	6,412,754		5,813	62,519	
Demographics						
Female	10,789 (46%)	3,349,541 (52%)	<0.0001	2,665 (46%)	23,813 (38%)	<0.0001
Median age, years (IQR)	58 (44-70)	48 (34-67)	<0.0001	57 (48-66)	62 (48-73)	<0.0001
20 - 30	1,679 (7%)	1,140,480 (18%)	<0.0001	95 (2%)	3,177 (5%)	<0.0001
30 - 40	2,822 (12%)	1,253,004 (20%)	<0.0001	382 (7%)	6,078 (10%)	<0.0001
40 - 50	3,753 (16%)	946,595 (15%)	<0.0001	1,291 (22%)	8,368 (13%)	<0.0001
50 - 60	4,558 (19%)	862,344 (13%)	<0.0001	1,689 (29%)	10,527 (17%)	<0.0001
60 - 70	4,646 (20%)	833,212 (13%)	<0.0001	1,365 (23%)	14,002 (22%)	0.06
70 - 80	4,273 (18%)	847,183 (13%)	<0.0001	793 (14%)	14,782 (24%)	<0.0001
≥80	1,723 (7%)	529,936 (8%)	<0.0001	198 (3%)	5,585 (9%)	<0.0001
Ethnicity						
White	20,011 (85%)	5,209,271 (81%)	<0.0001	5,086 (87%)	49,059 (78%)	<0.0001
Non-white	2,133 (9%)	464,484 (7%)	<0.0001	647 (11%)	12,233 (20%)	<0.0001
Unknown	1,310 (6%)	738,999 (12%)	<0.0001	80 (1%)	1,227 (2%)	0.0018
Quintiles of IMD score						
Q1 - lowest	3,714 (16%)	979,301 (15%)	0.02	998 (17%)	8,323 (13%)	<0.0001
Q2	5,253 (22%)	1,401,590 (22%)	0.05	1,348 (23%)	12,181 (19%)	<0.0001
Q3	5,015 (21%)	1,395,153 (22%)	0.17	1,202 (21%)	13,197 (21%)	0.44
Q4	4,931 (21%)	1,357,995 (21%)	0.57	1,227 (21%)	14,041 (22%)	0.02
Q5 - highest	4,541 (19%)	1,278,715 (20%)	0.03	1,038 (18%)	14,777 (24%)	<0.0001
Region of residency						
East Midlands	1,810 (8%)	397,065 (6%)	<0.0001	414 (7%)	3,986 (6%)	0.03
East of England	2,020 (9%)	578,715 (9%)	0.03	587 (10%)	5,222 (8%)	<0.0001
North East	397 (2%)	122,249 (2%)	0.02	92 (2%)	820 (1%)	0.08
North West	1,111 (5%)	325,304 (5%)	0.02	247 (4%)	2,368 (4%)	0.08
South East	2,910 (12%)	703,644 (11%)	<0.0001	703 (12%)	6,563 (10%)	0.0002
South West	1,525 (7%)	447,399 (7%)	0.0044	376 (6%)	3,670 (6%)	0.06
West Midlands	807 (3%)	251,870 (4%)	0.0001	245 (4%)	2,541 (4%)	0.58
Yorkshire and Humber	203 (1%)	81,723 (1%)	<0.0001	59 (1%)	635 (1%)	1.00
Other	12,671 (54%)	3,504,785 (55%)	0.05	3,090 (53%)	36,714 (59%)	<0.0001
Year of entry						
1998	4,979 (21%)	1,032,212 (16%)	<0.0001			
1999	3,661 (16%)	959,561 (15%)	0.01			
2000	2,613 (11%)	740,815 (12%)	0.05	563 (10%)	5,363 (9%)	0.0041
2001	2,039 (9%)	591,746 (9%)	0.0048	473 (8%)	4,855 (8%)	0.31
2002	1,705 (7%)	504,447 (8%)	0.0007	480 (8%)	4,737 (8%)	0.06
2003	1,505 (6%)	447,877 (7%)	0.0007	458 (8%)	4,700 (8%)	0.32
2004	1,246 (5%)	387,909 (6%)	<0.0001	413 (7%)	4,679 (7%)	0.29
2005	1,070 (5%)	335,854 (5%)	<0.0001	426 (7%)	4,721 (8%)	0.54
2006	964 (4%)	295,583 (5%)	0.0003	447 (8%)	5,222 (8%)	0.08
2007	868 (4%)	267,603 (4%)	0.0003	526 (9%)	5,484 (9%)	0.48
2008	823 (4%)	246,447 (4%)	0.01	512 (9%)	5,421 (9%)	0.72
2009	726 (3%)	219,299 (3%)	0.01	453 (8%)	5,626 (9%)	0.0020
2010	619 (3%)	192,632 (3%)	0.0011	487 (8%)	5,509 (9%)	0.26
2011	503 (2%)	155,615 (2%)	0.01	486 (8%)	5,102 (8%)	0.59
2012	133 (1%)	35,154 (1%)	0.70	89 (2%)	1,100 (2%)	0.20
Comorbidities						
Diabetes	906 (4%)	189,858 (3%)	<0.0001	470 (8%)	20,119 (32%)	<0.0001
Vascular	1,747 (7%)	181,832 (3%)	<0.0001	765 (13%)	16,820 (27%)	<0.0001
Cancer	681 (3%)	77,098 (1%)	<0.0001	245 (4%)	5,321 (9%)	<0.0001

Data are n or n (%) or median (IQR=interquartile range). IMD = index of multiple deprivation. ESRD=end-stage renal disease. The 'hospital controls' were individuals who had been admitted to hospital for any one of a wide range of minor medical or surgical conditions across the 12 years (excluding any patient with a polycystic kidney disease). These included admissions with diagnoses of squint, cataracts, otitis externa/media, varicose veins, hemorrhoids, upper respiratory tract infections, nasal polyps, teeth disorders, nail diseases, sebaceous cyst, soft tissue knee complaints, bunions, contraceptive advice, limb fractures, dislocations sprains and strains, minor head injury and superficial injuries or contusions, and operations included appendiectomy, dilation and curettage, primary lower limb arthroplasties, tonsillectomy and adenoidectomy.