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Using datasets to ascertain the Generalisability of clinical cohorts: the example of European QUALity Study on the treatment of advanced chronic kidney disease (EQUAL)

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Abstract

Background: Cohort studies are among the most robust of observational studies but have issues with external validity. This study assesses threats to external validity (generalisability) in the European QUALity (EQUAL) study, a cohort study of people over 65 years with stage 4/5 chronic kidney disease.

Methods: Patients meeting the EQUAL inclusion criteria were identified in The Health Improvement Network database and stratified into those attending renal units (secondary care cohort-SCC) and not (primary care cohort-PCC). Survival, progression to renal replacement therapy (RRT), and hospitalisation were compared.

Results: The analysis included 250, 633, and 2,464 patients in EQUAL, PCC, and SCC. EQUAL had a higher proportion of men in comparison to PCC and SCC (60.0% vs. 34.8% vs. 51.4%). Increasing age (≥85 years odds ratio (OR) 0.25 (95% confidence interval (CI) 0.15-0.40)) and comorbidity (Charlson Comorbidity Index ≥ 4 OR 0.69 (CI 0.52-0.91)) were associated with non-participation in EQUAL. EQUAL had a higher proportion of patients starting RRT at 1 year compared to SCC (8.1% vs. 2.1%%, p <0.001). Patients in the PCC and SCC had increased risk of Hospitalisation (incidence rate ratio=1.76 (95% CI 1.27-2.47) & 2.13 (95% CI 1.59-2.86)) and mortality at one year (hazard ratio=3.48 (95% CI 2.1-5.7) & 1.7 (95% CI 1.1-2.7)) compared to EQUAL.

Conclusions: This study provides evidence of how participants in a cohort study can differ from the broader population of patients, which is essential when considering external validity and applying to local practice.

Keywords

Generalisability

External Validity

Cohort study

EQUAL

THIN

Primary care cohort

Secondary Care cohort

Introduction

The rigour of study design has tended to be considered of higher importance by funding bodies, researchers and journals than the extent to which the results of a study can be generalised to other situations and other people. [1, 2] This emphasis on internal over external validity could explain the delay or even failure to translate research findings into healthcare improvement [3, 4]. Researchers, therefore, need to pay attention to external validity – also known as generalisability – when designing studies.[5]

Threats to external validity can occur at several steps in study design and conduct. Center selection can influence case-mix and introduce bias [6-8], and within centres, recruitment can threaten generalisability, with frailer patients and those with linguistic barriers less likely to take part in studies.[9, 10] Considering recruitment bias specifically, findings may not apply to the patient population that experiences the most morbidity and mortality, especially with absolute risk reduction and numbers needed to treat.[11]

This study aimed to quantify threats to external validity (Generalisability) in the United Kingdom (UK) arm of the European QUALity (EQUAL) study, a high quality, international, prospective, observational cohort study of treatment in older people with advanced Chronic Kidney Disease (CKD), by looking at baseline characteristics and outcomes of recruited participants and comparing these with non-participating patients meeting the EQUAL age and kidney function criteria in primary and secondary care.[12]

Materials and Methods

This was a prospective cohort study.

The EQUAL cohort

EQUAL is an international prospective cohort study of patients aged 65 years of age or older attending nephrology clinic with an incident estimated glomerular filtration rate (eGFR) < 20 ml/min/1.73m^2.[12] The EQUAL cohort in this analysis included the first 250 patients recruited into the study in the United Kingdom (UK) between 30/05/2013 and 22/10/2014, with 12 months follow-up completed by 22/09/2015, censored for death and losses to follow up.

THIN cohorts

A general practice (GP) dataset called The Health Improvement Network (THIN) was used to identify patients registered in GPs who met the EQUAL inclusion criteria: age of ≥ 65 years and incident (first) eGFR reading ≤ 20mls/min/1.73m^2 after their 65th

birthday. THIN has been demonstrated to be generalisable to the UK regarding demographics and crude prevalence of major conditions and been validated for use in epidemiologic studies of chronic kidney disease.[13-15]. THIN holds longitudinal anonymised patient records for 588 of the 9,458 GP across the UK with over 12 million patients, with 157 of these GPs are linked with Hospital episode statistics (HES).

A “primary care” cohort (PCC) was defined as a representative sample of eligible cases from the THIN database, not attending nephrology services. A “secondary care” cohort (SCC) was defined as a representative sample of eligible cases from the THIN database attending nephrology clinic. These two cohorts are mutually exclusive and together should provide a representative sample of all patients in primary and secondary care meeting the EQUAL age and eGFR eligibility criteria.

The start and end date for identifying patients on THIN meeting EQUAL inclusion criteria in the PCC and SCC were 1/4/2007 (1 year after the introduction of mandatory eGFR reporting in the UK) and 31/12/2012, respectively. Between the two dates, patients would have had an incident eGFR reading ≤ 20mls/min/1.73m^2 and had the outcome of interest (progression to end-stage kidney disease (ESKD), hospitalisation or death). All patients had the opportunity for 12 months follow up from the date they entered the study, censoring for death and losses to follow up.

Further details relating to inclusion and exclusion criteria to identify suitable PCC and SCC patients in THIN are shown in supplementary materials (Figure S1).

Index date and Laboratory data in each cohort

Laboratory data included eGFR. Index eGFR in EQUAL was defined as the first drop in eGFR to 20 ml/min/1.73m^2, or below, within the six months before the baseline visit (30/05/2013-22/10/2014), regardless of subsequent eGFRs. Other laboratory data included creatinine, albumin-creatinine ratio, haemoglobin, calcium, phosphate, parathyroid hormone, albumin, and blood pressure. In EQUAL, they were captured in the case record forms (CRFs) at their baseline visit up to 6 months+6 weeks (222 days) after the index eGFR.

In the THIN database (additional health data codes), the index eGFR was defined as the first drop in eGFR to ≤20mls/min/1.73m^2 after 1/4/2007. Other laboratory data for the PCC and SCC were recorded in a similar window to the blood tests recorded at baseline for patients within EQUAL. Units of measurement for the laboratory data were harmonised to those that were used in the EQUAL study.

Comorbidities and other study measurements

The Charlson Comorbidity Index (CCI) was used to quantify comorbidity. [16, 17] CCI was captured in EQUAL in CRFs. In THIN the comorbidity accrued up until the index date was used to calculate the CCI using the read code to Charlson weight mapping previously validated by Khan et al. [18] CCI was used to provide a summary of

comorbidity for each patient and to adjust for comorbidity burden in the regression models. Given the skewed distribution of CCI in the study population, for adjustment in the Cox-regression models, CCI was grouped into three categories (2–3, 4-5, ≥6) in keeping with other publications. [19, 20]

Other study measurements included Townsend socioeconomic deprivation score and patient medication (antihypertensives, lipid-lowering, and anticoagulants/antiplatelet). Townsend score and urban classification for the PCC and SCC were included in the THIN dataset, and for the EQUAL cohort, this was mapped to the patient's postcode using the subset of postcodes in the THIN dataset. Medication history in EQUAL was captured in the CRFs at baseline visit. In the THIN database, this was determined using the relevant British National Formulary codes (bnfcode) with prescriptions issued in 28 days before the index date were included.

Outcomes

Outcomes included patient survival at one-year post-index date, hospitalisation, progression to ESKD, and renal replacement therapy (RRT). By shifting the start of survival time as below for patients in SCC, the risk of immortal time bias and survival bias was mitigated. [21] Figure S2 illustrates the fix used to negate the risk of immortal time bias. i. The start of survival time for patients in the PCC was the index date. ii. For patients in the SCC under the care of a nephrologist at the time that they became eligible (eGFR ≤ 20mls/min/1.73m2), the average time spent by EQUAL patients from the index date to the 1st study visit (116 days) was added to the index date. iii For patients in the SCC that were referred to a nephrologist after they became eligible, six weeks was added to the referral date (the date referred to a nephrologist) in addition to the average time spent by EQUAL patients from the index date to the 1st study visit (116 days).

Within EQUAL, hospitalisations between one study visit and the next were recorded retrospectively within the CRFs. To calculate the burden of hospitalisations in the PCC and SCC, the dataset was restricted to patients attending GPs in THIN linked to HES.

Patients that commenced RRT (dialysis or transplantation) in the 12 months after reaching index eGFR ≤ 20mls/min/1.73m^2 were identified using the appropriate codes within THIN (HES). In EQUAL, the RRT modality and date of the first dialysis were captured in the CRFs.

Statistical analyses

Summary statistics were produced using frequencies and proportions for categorical variables and means, standard deviations, medians, and ranges for numeric variables. The three cohorts were compared using the chi-square test for categorical data, one-way analysis of variance for normally distributed numeric data, and the Mann-Whitney test for skewed numeric data.

A logistic regression model was used to identify variables that were associated with being in the EQUAL cohort and to determine if the patients in EQUAL differed from a broader population of eligible patients (SCC). We considered in the models the code 1=Participating in EQUAL and 0=Not participating in EQUAL (SCC). Univariable logistic regression models were run for each of the following explanatory variables of known clinical importance: age, gender, deprivation, urban classification, individual comorbidity, CCI, haemoglobin, albumin, blood pressure, and drug count.[22]

A Cox proportional hazards regression model was used to compare all-cause mortality at the one-year post-index date for patients in the PCC, SCC, and EQUAL cohort. [23] Confounders were chosen based on a priori knowledge of etiological importance [18, 22, 24], and included: sociodemographics (index age as 5-year age bands, sex, Townsend score and rurality, laboratory variables (haemoglobin, albumin, systolic blood pressure, diastolic blood pressure) and CCI. The variables were sequentially added into the model, sociodemographics followed by laboratory variables and comorbidity so we could examine the effect of adjustment for our main exposure. As the THIN database had a higher proportion of patients living in the most affluent areas, Townsend was retained in all the multivariable models. The final models were checked for the assumption of proportionality. Confounders that were not proportional were included as a time-varying covariate (tvc).

Given the over-dispersed count of hospitalisations in the three cohorts, a negative binomial regression model was used to model the number of hospitalisations with adjustment of variables as in the other regression models. [25] A hospital-free risk period was calculated for the patients in each of the three cohorts, based on the number of days during follow up that a patient was out of hospital (and therefore at risk of hospital admission) and the number of admissions to the hospital that were recorded during follow up. All the models were also adjusted for the hospital-free period at risk. The output of the model was reported as an incidence rate ratio (IRR) (risk of hospitalisation in exposed divided by risk of hospitalisation in the unexposed).

All regression analyses were restricted to patients, with 100% completeness for all variables.

All analyses were performed using Stata v13.1 (College Station, TX, USA)

Results

There were 633 patients in the PCC, 2,464 patients in the SCC, and 250 in the EQUAL cohort. The baseline characteristics of the patients in the three cohorts are shown in Table 1. Patients in PCC and SCC were, on average, ten years, and three years older than patients in the EQUAL study, respectively. There was a higher proportion of male participants in the EQUAL study (60.0%) when compared to patients in PCC (34.8%) and SCC (51.4%).

There was a higher proportion of patients in the EQUAL study in the most deprived Townsend quintile (28.4%) compared to those in PCC and SCC (11.2% & 13.6%). EQUAL participants were also more likely to be living in an urban postcode (86.4%) than patients in PCC and SCC (72.4% and 80.3%, respectively). The range of CCI in the SCC was higher when compared to the PCC and the EQUAL cohort.

Table 1: Distribution of socio-demographic characteristics in the three cohorts

Patient Characteristics		Primary care cohort N=633	Secondary care cohort N=2,464	EQUAL N=250	P-value for comparison between the three cohorts
Age (years) at index date: mean (95% CI)		86.3 (85.8-86.8)	79.7 (79.4-79.9)	76.6 (75.8-77.4)	<0.001
Gender=Male: N (%)		220 (34.8)	1,266 (51.4)	150 (60.0)	<0.001
Townsend* quintile N (%)	1	106 (23.6)	469 (25.5)	44 (17.6)	<0.001
	2	98 (21.6)	427 (23.2)	44 (17.6)	
	3	102 (22.5)	377 (20.5)	43 (17.2)	
	4	97 (21.4)	317 (17.2)	48 (19.2)	
	5	51 (11.2)	251 (13.6)	71 (28.4)	
Rurality N (%)	Urban	330 (72.4)	1482 (80.3)	216 (86.4)	<0.001
	Town & Fringe	91 (20.0)	227 (12.3)	18 (7.2)	
	Village & Hamlet	35 (7.7)	136 (7.4)	16 (6.4)	
Charlson Comorbidity Index Median (IQR) range		4 (3-5) 2-10	4 (3-5) 2-11	4 (2-5) 2-10	0.0002

* 1=least deprived, 5=most deprived

Although the overall medication burden was similar between the three cohorts, the EQUAL cohort had a higher proportion of patients on antihypertensive, lipid-lowering drugs, and thromboembolic/antiplatelet drugs when compared to the SCC and PCC. (Table S1).

The absolute mean values of laboratory variables and blood pressure readings were clinically similar between the three cohorts. However, there was a clinically relevant difference in albumin creatinine ratio (ACR) with the patients in the EQUAL cohort having ACR two and eight times the value compared to the SCC and PCC, respectively (Table S2). The more considerable difference between the EQUAL and PCC compared to the difference between the EQUAL and SCC could potentially reflect referral to secondary care and ESKD progression.

Variables associated with participation/non-participation in EQUAL

Patients participating in EQUAL were compared with the SCC of presumed non-participants in EQUAL to explore variables that are associated with being in one cohort versus the other (Table 2). Increasing age was associated with non-participation in EQUAL with patients ≥85 years of age, having a 75% reduced odds of participating. Women had a 29% reduced odds of participating, and patients in the Townsend quintile 4 and 5 had a 1.6 and 3.0 fold increased odds of participating when compared to the

least deprived patients (Townsend quintile 1). An increasing comorbidity burden was also associated with non-participation in EQUAL: Patients with a CCI 4-5 and ≥6 were 30% less likely to participate compared to those with a CCI of <4. Patients who were less likely to take part in EQUAL included those with heart disease (47% reduced odds), peripheral vascular disease (42% reduced odds), and rheumatological disease (69% reduced odds). Patients with a current or history of cancer were 40% increased odds of participating.

Table 2: Univariable model showing variables associated with participation in EQUAL, odds ratio (OR), 95% confidence intervals (CI) and p-values

Secondary care cohort (1,436) * =0 EQUAL cohort (242) * =1		**Univariable model**	
		OR (95% CI)	**P-value**
Age (years)	**≥65 - <70**	1.0	-
	≥70 - <75	0.65 (0.43-0.97)	0.04
	≥75 - <80	0.48 (0.32-0.72)	<0.001
	≥80 - <85	0.39 (0.25-0.59)	<0.001
	≥ 85	0.25 (0.15-0.40)	<0.001
Gender	**male (ref)**	0.71 (0.54-0.92)	0.009
Townsend Quintile 1=least 5=Most deprived	**1**	1.0	-
	2	1.10 (0.71-1.70)	0.68
	3	1.21 (0.78-1.89)	0.39
	4	1.61 (1.05-2.49)	0.03
	5	3.02 (2.01-4.53)	<0.001
Rurality	**Urban**	1.0	-
	Town/Village	0.64 (0.44-0.94)	0.02
Haemoglobin (g/dl)	**(≥ 10 (ref), <10)**	0.72 (0.51-1.03)	0.06
Albumin (g/l)	**(≥ 35 (ref), <35)**	1.04 (0.76-1.42)	0.82
Systolic BP (mm Hg)	**<120**	0.73 (0.47-1.41)	0.17
	≥120 - ≤140	1.0	-
	>140	1.77 (1.33-2.35)	<0.001
Diastolic BP (mm Hg)	**<70**	0.97 (0.72-1.30)	0.84
	≥70 - ≤80	1.0	-
	>80	1.18 (0.82-1.70)	0.38
Charlson Comorbidity Index (CCI)	**2-3**	1.0	-
	4-5	0.69 (0.52-0.91)	0.009
	≥6	0.68 (0.46-1.0)	0.05
	Cardiac (ref=absent)	0.53 (0.38-0.73)	<0.001

Individual CCI components	**Peripheral vascular disease (PVD) (ref= absent)**	0.58 (0.38-0.88)	0.007
	Pulmonary (ref= absent)	0.80 (0.57-1.13)	0.22
	Diabetes (ref= absent)	0.94 (0.72-1.22)	0.65
	CVA (ref= absent)	0.75 (0.51-1.13)	0.16
	Cancer (ref= absent)	1.41 (1.03-1.93)	0.04
	Rheumatology (ref= absent)	0.31 (0.15-0.65)	0.0002
	Other (ref= absent)	0.34 (0.18-0.66)	0.0002
Drug count (quintile)	**Q1**	-	-
	Q2	1.36 (0.95-1.96)	0.1
	Q3	0.94 (0.66-1.33)	0.72
	Q4	0.99 (0.70-1.41)	0.94

Outcomes

Figure 1 shows the unadjusted mortality at one year for the three cohorts. The EQUAL cohort had a higher proportion of patients alive at one year (90.7%) when compared to SCC (85.0%) and PCC (69.6%) (Log-rank <0.001).

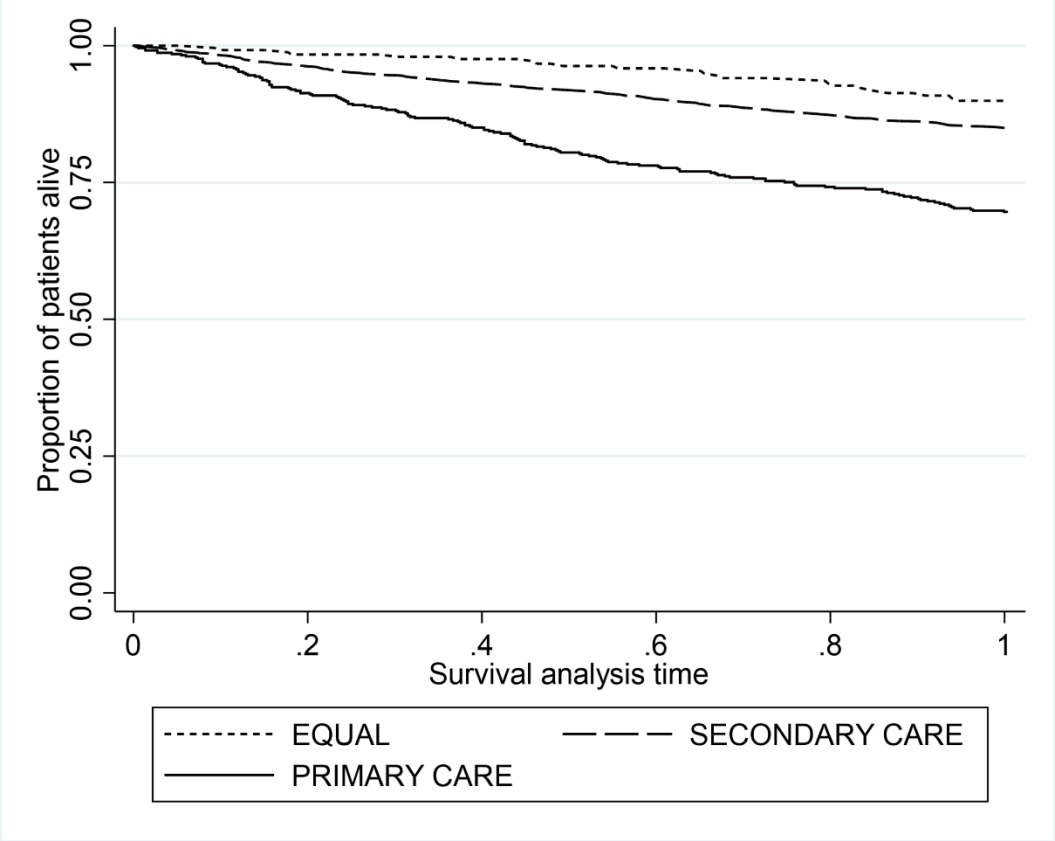

Figure 1: Kaplan Meier survival estimates of EQUAL, Secondary Care and Primary Care cohorts

Table 3 shows the output of the unadjusted and adjusted multivariable Cox-regression models comparing all-cause mortality at the one-year post-index date for patients in the PCC, SCC, and EQUAL cohort. In the unadjusted model, in comparison to EQUAL, the unadjusted hazard ratio (HR) of all-cause mortality was 1.7 (95% CI 1.1-2.7, p=0.02) and 3.48 (95% CI 2.1-5.7, p=<0.001) in the SCC and PCC, respectively. In multivariable model 3, the HR reduced moderately upon adjustment for socio-demographics, laboratory variables, and comorbidity.

Table 3: Unadjusted and adjusted 1-year all-cause mortality, hazard ratio (HR), 95% confidence interval (CI) and (p-value), for EQUAL, Secondary Care and Primary Care patients

		Unadjusted Model		Multivariable Model 1 (Socio-demographics)		Multivariable Model 2 (Model 1 + Laboratory variables)		Multivariable Model 3 (Model 2 + Comorbidity)	
Cohort		HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
EQUAL (n=236) *		1.0	-	1.0	-	1.0	-	1.0	-
Secondary Care (n=1,203) *		1.71 (1.10-2.65)	0.02	1.61 (1.03-2.52)	0.04	1.52 (0.97-2.38)	0.07	1.47 (0.94-2.31)	0.09
Primary Care (n=183) *		3.48 (2.12-5.71)	<0.001	2.80 (1.65-4.75)	<0.001	2.52 (1.47-4.32)	0.001	2.41 (1.40-4.14)	0.001
Index age (years)	**5-year bands**	-	-	1.19 (1.08-1.30)	<0.001	1.17 (1.07-1.28)	0.001	1.18 (1.08-1.29)	0.001
Gender	**(male (ref)))**	-	-	0.74 (0.58-0.94)	0.02	0.75 (0.59-0.96)	0.02	0.79 (0.62-1.01)	0.06
Townsend Quintile 1=least 5=Most	**1**	-	-	1.0	-	1.0	-	1.0	
	2	-	-	0.91 (0.64-1.29)	0.60	0.87 (0.61-1.24)	0.45	0.88 (0.62-1.25)	0.48
	3	-	-	0.97 (0.68-1.38)	0.85	0.95 (0.66-1.35)	0.76	0.95 (0.66-1.36)	0.77
	4	-	-	0.93 (0.64-1.35)	0.70	0.91 (0.63-1.33)	0.63	0.90 (0.62-1.31)	0.58
	5	-	-	1.07 (0.73-1.56)	0.74	1.07 (0.73-1.56)	0.75	1.04 (0.71-1.53)	0.83
Haemoglobin (g/dl)	**(≥ 10 (ref), <10)**	-	-	-	-	1.32 (1.00-1.75)	0.05	1.31 (0.99-1.74)	0.06
Albumin (g/l)	**(≥ 35 (ref), <35)**	-	-	-	-	1.38 (1.06-1.81)	0.69	1.37 (1.04-1.79)	0.02
Systolic BP (mm Hg)	**10 mmHg bands**	-	-	-	-	0.98 (0.90-1.07)	0.69	0.99 (0.91-1.08)	0.77
Time varying covariate **		-	-	-	-	1.06 (1.00-1.13)	0.05	1.06 (1.00-1.13)	0.05
Charlson Comorbidity Index	**2-3**	-	-	-	-	-	-	1.0	-
	4-5	-	-	-	-	-	-	1.16 (0.88-1.53)	0.28
	≥6	-	-	-	-	-	-	1.58 (1.13-2.19)	0.007

Multivariable model 1 included adjustments for age, sex, and Townsend deprivation quintile; model 2 included an adjustment for haemoglobin, albumin, and systolic blood pressure in addition to the predictor variables included in model 1 and model 3 included adjustments for all predictors included in model 2 and CCI.

* All the models included patients with 100% completeness for all variables.

****** Systolic BP was included as a time-varying covariate as the variable was not proportional and as the effect of a systolic BP is likely to change over time

Table S3 shows the output of the unadjusted and adjusted negative binomial regression models comparing the number of hospitalisations at the one-year post-index date for patients in the PCC, SCC, and EQUAL cohort. Patients in PCC and SCC had over twice the rate of hospital admissions compared to patients in EQUAL.

EQUAL had a higher proportion of patients starting RRT in the 1-year follow up period after reaching index eGFR ≤ 20mls/min/1.73m^2, compared to those in the SCC (8.1% vs. 2.1%, p <0.001). There were no patients who started RRT in the PCC in this one year follow up period.

Discussion

This study examined whether patients participating in EQUAL were similar to "real-world" patients with eGFR dropping below 20 mL/min/1.73m^2 regarding baseline characteristics, survival, and hospitalisation. Patients in EQUAL were more likely to be younger, male, and from an urban setting compared to the PCC and SCC patients. EQUAL patients were also less likely to have cardiovascular, peripheral vascular, and rheumatic diseases. EQUAL patients were more likely to start RRT and had a higher probability of being alive at one year compared to PCC and SCC patients. The overall better health of EQUAL patients meant that they were less likely to be admitted to hospital for illnesses.

There were decreasing odds of participation in EQUAL for every 5-year age band increase. It has been recognised that patients recruited into a study may differ from the target population and be younger and healthier than referred and registry patients. [26, 27] This is a common problem in research, with a middle-aged group of patients more likely to be enrolled in studies and patients at the extremes of ages (youngest and the oldest groups) less likely to participate [28]. Hence, the study sample is less likely to include the elderly [29, 30] who have a higher burden of comorbidity and, therefore, higher expected mortality [31]. Such patients may also differ from younger participants regarding treatment effects. The implications of this are that "evidence-based' research findings based on younger patients are applied to elderly patients with comorbidities, through clinical practice guidelines. [32] Health research should therefore, be conducted in the populations most affected by high disease prevalence. [33] Solutions such as liberal inclusion criteria, improved communication, reducing respondent burden, provision of travel support, and data collection at home, may facilitate the participation of older people in research. [34, 35] Unfortunately, despite these measures, as the older patients increase as a proportion of the population, those who agree to participate in RCTs and observational studies may be less representative of the population.

Women were less likely to be represented in EQUAL in the UK, with only 40.0% of participants in EQUAL being women when compared to 48.6% and 65.2% in the SCC and PCC. A probable explanation for a lower proportion of women in the EQUAL cohort could be due to slow progression rates in this gender.[36] The slower progression rates mean that there will be a smaller cohort of women reaching an incident eGFR of ≤ 20mls/min/1.73m^2 or commencing RRT. The variation in gender seen in EQUAL can be explained by the variation in the incidence of CKD amongst men and women, with a

higher incidence of CKD in women but a lower incidence of progression to ESKD requiring RRT.[37] A large European registry study by Antlanger et al. assessed sex-specific differences in RRT incidence and prevalence using data from nine countries, which showed that the incidence and prevalence rates were consistently higher in men than women.[38] The recruitment of women in research studies is an essential issue for researchers. Medical research results cannot be extrapolated between genders as the pathophysiological process varies. For example, cardiovascular disease and some of the cancers are affected by hormones. As a result, much of our understanding of illnesses and its treatments are based on research conducted disproportionately with men. [39] Alternatively, women are no more likely than men to decline to participate in studies but merely underrepresented in target populations. [40]

In the univariable logistic regression model, higher comorbidity was associated with lower odds of participation in EQUAL. The findings of this study are consistent with prior reports in other study designs showing that patients participating in trials have better survival not only on account of being healthier but perhaps also reflecting the better medical oversight.[41-43]

There was a higher proportion of EQUAL participants starting RRT compared to SCC patients. The potential explanation for this finding could be that they represented a cohort of patients who had a quicker rate of progression of their kidney disease and therefore and formed a cohort of patients that were chosen to be studied. This is necessarily not a limitation of EQUAL, but the results cannot be generalised to all patients below eGFR of 20 mL/min/1.73m^2.

Patients in the PCC and SCC had over twice the rate of hospital admissions compared to patients in EQUAL. EQUAL Hospitalisation data came from the nurse collected CRFs, whereas the THIN data came from the HES linkage. It could be that the HES linkage identified more hospital admissions. An alternate explanation for this finding could be attributed to the source of the Hospitalisation data.

In observational studies, the classification errors, selection bias, and uncontrolled confounders and the uncertainty introduced by these types of biases are seldom quantified. When designing a study, incorporating a comparison between experimental and the eligible study population at the same time would enhance understanding of the Generalisability of future studies. This was done in the North American Atherosclerosis Risk in Communities (ARIC) study were Generalisability was examined by nesting study patients in communities covered by broad surveillance.[44] Alternatively, embedding trials/studies within chronic disease registries will allow Generalisability to be ascertained. The International Society of Nephrology iNET-CKD (International Network of Chronic Kidney Disease cohort studies) initiative, which includes twelve prospective cohort studies and two registries covering 21 countries, will play a significant role in understanding the Generalisability of current, and future CKD research.[45] Accrual to Clinical Trials (ACT) is an initiative created to improve the efficiency of clinical trials by effectively identifying eligible participants in the recruitment stage of a study and, therefore, might have a crucial role to play in improving the Generalisability at recruitment stage of future studies.[46] Finally, using statistical techniques such as probabilistic sensitivity analysis (Episens model (st0138), Orsini et al.) in the analysis

stage may help to quantify the effect of bias and researchers can report results that take into account the systematic errors and hence avoid overstating their certainty about the effect under study. [47, 48]

The strengths of this study are the usage routinely collected generalisable general practice data (THIN) to understand the generalisability of an observational cohort study.[14] This has, therefore, not necessitated the recruiting of patients who have declined to participate in a study and overcome the complex ethical issues of re-approaching patients who have already refused to take part in a study. In the era of ‘big data,’ research using routinely collected data offers more significant potential and has underpinned research in recent years. [49] The strengths of general practice data are that they are population-based and are derived from a representative subset of the population. [14, 50]

There were several limitations to this study. Identification of the appropriate comparison control group was crucial to an inference of the study as any observational design will always be limited by unmeasured confounding. [51] Although this study did not directly assess the generalisability of EQUAL data by understanding the differences between EQUAL agreed and EQUAL declined patients, routinely collected data has shown the differences in EQUAL patients and patients in secondary care meeting the same eligibility criteria. There is also the potential for multiple biases as a result of differences in data capture methods between THIN and EQUAL and resultant misclassification of the THIN subjects.

This paper provides empirical evidence concerning how participants in a carefully conducted observational cohort study differ from the broader population of patients that they are intended to represent. Older and sicker patients were less likely to be recruited into EQUAL in the UK, and this was supported by follow up data on health outcomes with patients in EQUAL more likely to be hospitalised and alive at twelve months. This selection pattern is likely to be found in most observational studies of chronic diseases. These issues can be overcome by designing observational studies to be embedded within disease registries or by using novel statistical techniques in the analysis.

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Conflict of Interest

Dr. Wanner reports grants from Sanofi, personal fees from Sanofi, personal fees from Takeda, personal fees from Chiesi, personal fees from Amicus, personal fees from Idorsia, grants from Idorsia, grants from Boehringer-Ingelheim, personal fees from Lilly, personal fees from MSD, personal fees from Mundipharma, personal fees from GSK, personal fees from Boehringer-Ingelheim, personal fees from Boehringer-Ingelhim, personal fees from AstraZeneca, personal fees from Bayer, personal fees from Reata, personal fees from GSK, personal fees from Akebia, personal fees from Triceda, outside the present work.

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Rest of the authors have no conflict of interest to report.

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