In patients with Chronic Kidney Disease are there differences in prescribing practices (polypharmacy) between specific demographics? A Scoping Literature Review

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IMPERIAL

Chapter 1: Introduction

1.1 What Are Health Inequalities?

The NHS defines health inequalities as "unfair and avoidable differences in health across the population and between different groups within society."(1) Whilst many authors use health inequalities to assess differences in the status of people's health, it also refers to differences in the care that people receive and the opportunities they have to lead healthy lives. Socioeconomic factors, geography, specific characteristics such as sex, ethnicity or disability and socially excluded groups can be compared and assessed to learn about these demographics' differences. (2,3)

Since the COVID-19 pandemic, there has been a fundamental shift in healthcare policy by Governments to reduce existing health inequalities. In the U.K., the NHS adopted a national approach, Core20Plus5, whereby the NHS targets the most deprived 20% of the national population as identified by the national Index of Multiple Deprivation and identifies '5' focus clinical areas requiring accelerated improvement. (4) Whilst subsequent studies conducted by thinktanks, such as the Health Foundation, have commented on the association between health inequalities and individuals' socioeconomic status, ethnicity and living region, recently published papers have shone a light on disparities existing within specific disease cohorts such as individuals living with Chronic Kidney Disease (CKD).

1.2 What is Chronic Kidney Disease?

CKD is a long-term condition defined based on either kidney damage or decreased kidney function for three or more months, irrespective of cause. (5) Those who develop CKD are at a higher risk of premature mortality and cardiovascular disease (CVD), increased health needs, and a lower quality of life (QoL).

Globally, there are six recognised stages of CKD (1, 2, 3a, 3b, 4, 5), which are based on the estimated glomerular filtration rate (eGFR) calculation to quantify the extent of kidney damage and urinary albumin: creatinine ratio (ACR). (6)Normal healthy kidneys should be able to filter more than 90ml/min, with sustained reduced eGFR readings below the 90ml/min threshold suggesting a degree of kidney damage. Damage to the kidneys can be a result of various factors but is most commonly noted in the presence of metabolic and cardiovascular risk factors such as diabetes and hypertension. Whilst individuals with early CKD may not experience any noticeable symptoms, as the disease progresses, symptoms such as fatigue, swollen ankles, changes in urination, and high blood pressure often develop. In severe disease (stage 5), it can lead to end-stage kidney failure, requiring dialysis or a kidney transplant. Management of CKD typically involves controlling underlying conditions, dietary changes, and medications to slow the progression of the disease.

Chapter 2: Literature Review

2.1 Introduction

A rapid scoping literature review was undertaken to review the existing evidence and learn about the inequalities in renal disease. Two databases were searched using OVID, namely Embase and Medline. Keywords and MESH terms were found using Cochrane. Following that, approval was sought from the librarian at Imperial College London. The keywords included were health inequities, renal disease, polypharmacy, and their synonyms. Abstract and title screening was conducted to assess relevance before total text reviews were conducted. The inclusion criteria for this was a systematic review (SR) or meta-analysis (MA), studies conducted on the general population (not specific groups, e.g., Indigenous), those specific to CKD and being published since 2008. Given the project's scope to assess the unique health inequalities seen in the NWL, S.R. and M.A. must have been based on studies conducted in the United Kingdom.

While S.R. and M.A. help us learn about the research landscape, we used the information on NICE as a reference to optimal treatment, given that the information contained within S.R. and M.A. might be outdated.

2.2: What Is The Distribution Of The Inequity Of CKD Seen In The United Kingdom?

Recent evidence shows that there are existing disparities in patient diagnosis, treatment and outcomes of patients with CKD. A recent 2024 meta-analysis conducted by Duff et al.'s team attempted to estimate the global CKD prevalence. (7) Through reviewing 119 studies, the study demonstrated a significant global CKD burden with an estimated global prevalence of 13.0% and 6.6% for those with advanced disease (stages 3–5). Furthermore, the paper highlighted significant disparities in CKD prevalence related to age, sex, and socioeconomic status. In regards to studies which investigated age specifically, Duff et al., the team found that those aged >60 and older consistently had a higher prevalence of CKD than levels present in the general population much higher CKD prevalence (19.3% for stages 1–5 and 15.0% for stages 3–5), compared to studies of the general population. Then, when comparing the prevalence of CKD across all stages, it remained similar in both genders. However, in advantaged disease, the Duff et al. team noted a higher prevalence of stages 3-5 (7.5% vs 6.4%) reported. Finally, in their study, Duff et al.'s team saw that CKD prevalence varied by socioeconomic status (SES): 10.8% in high-income countries, 15.0% in middle-income countries, and 11.4% in low-income countries for stages 1-5. However, whilst recognising the potential role SES plays, the paper did not review the Impact of SES within a country.

However, where Duff et al.'s systematic review found that females tended to have a higher prevalence of stages 3-5, Morton et al. systematic review titled The Impact of Social Disadvantage in moderate-to-severe Chronic Kidney Disease concluded a contrasting view.(8) Instead, they found multiple suggests that being female was protective for CKD progression. One study had an odd ratio for eGFR decline/year as a proxy measure for CKD progression as 0.47 (0.26–0.84) for women compared to men. In contrast, another study showed an odd ratio of 1.38 for males versus females, indicating a higher risk of progression for men. The difference in results could be because the Morton et al. review was published in 2013, and Duff et al. exclusion criteria included publications before 2014, which results in both papers having different cohorts. Moreover, the studies by Morton et al. that suggested that being female was protective were based on studies conducted in the USA, which was acknowledged in the S.R. as a limitation regarding generalisability.

Unlike Duff and Al's SR, Morton et al. examined the relationship between prevalence and race. (7,8) In progression to end-stage kidney disease, the S.R. saw that Black individuals had a relative risk of 4.6, suggesting that black individuals are 4.6 times more likely to progress from CKD stages 3 or 4 to ESKD compared to White individuals. Another paper measured annual eGFR decline, which varies across ethnic groups compared to White individuals. While the results were not statistically significant, the Black Odd Ratio was 1.47 (0.73–2.95) compared to white individuals and the Hispanics OR 1.85 (0.90–3.82). This evidence suggests that being black and/or Hispanic leads to faster CKD progression.

Whilst the above studies attempt to show the impact of age, gender and race on CKD progression, Vart et al., S.R. attempts to explore further the relationship between CKD progression measured through low estimated glomerular filtration rate (eGFR), high albuminuria, and renal failure and low SES, using measurements such as education, income, occupation, composite or and area-level. Vart et al concluded that compared with those in high SES, people with low SES have a strong association with the prevalence of: low eGFR (OR=1.41, 95% CI=1.21, 1.62); high albuminuria (OR=1.52, 95% CI=1.22, 1.82); low eGFR/high albuminuria (OR=1.38, 95% CI=1.03, 1.74); and incidence of renal failure (OR=1.55, 95% CI=1.40, 1.71). However, the authors acknowledged that the strength of this association varied depending on how much the researchers in each study adjusted for covariates, especially for low eGFR and high albuminuria, suggesting that some of the observed association between low SES and CKD could be explained by other factors that are correlated with both SES and CKD such as diabetes, hypertension, and obesity. Vart et al.'s study adds to the growing evidence that lower SES, no matter how it is measured, can be considered a risk factor for CKD and its progression; whilst an association exist, the exact causal pathway remains unknown.

The above studies all contribute to our understanding of the health inequalities seen in renal disease and its care. Individuals who are age 60 or older, female, non-Caucasian and living in deprived wards often see greater prevalence and progression of severe renal disease compared to their counterparts.

2.3: What is the current management for CKD?

From a clinical perspective, CKD patients are often a cohort of heavily pharmacologically managed patients due to the kidneys' unique nature in maintaining haemostasis. (9) Pharmacological management is instrumental in slowing the progression of CKD and albuminuria, reducing complications of decreased GFR, reducing the risk of cardiovascular disease and improving survival and quality of life. Failure to manage CKD can lead to end-stage renal failure, where the only treatment is long-term dialysis or transplant. (5)

The National Institute for Health and Care Excellence (NICE) guidelines for CKD suggest that individuals' blood pressure, blood glucose, blood cholesterol and platelet function should be optimised to prevent kidney decline. If individuals have declining kidney function with a history of hypertension or proteinuria, an angiotensin-receptor blocker (ARB) or angiotensin-converting enzyme (ACE) should be an option. Those with diabetes should be offered an ARB or ACE inhibitor as well as an SGLT-2 inhibitor such as Dapagliflozin or Empagliflozin. For individuals with CKD that require primary or secondary prevention of CVD, a statin is indicated, usually atorvastatin, with those requiring secondary statins also requiring an antiplatelet. If ESKD develops, some of the above medications are required to be stopped or reduced to harmful side effects. Instead, in late-stage renal failure, iron supplements, cholecalciferol, bisphosphonates, and phosphate binders should be considered. At the CKD point of diagnosis, doctors should advise on healthy lifestyle measures encompassing healthy diet, exercise, alcohol and smoking cessation. Immunisation should be offered for influenza and pneumococcal disease to reduce infection risk. (9)

However, more recent studies in the U.K. have focused on evaluating prescribing practices for individuals with CKD. Forbes et al showed that despite NICE guidelines indicating SGTL2 in CKD management, in cohorts who were eligible being females (OR 0.69, 95% CI 0.67–0.72, p <0.0001), black ethnicity (OR 0.84, 95% CI 0.77–0.91, p <0.0001), older individuals (OR 0.95, 95% CI 0.95–0.95, p <0.0001) and of a lower SES were characteristics associated with those less likely to be prescribed an SGLT2 inhibitor. (10) These differences explain why only 17.0% were prescribed an SGLT2 inhibitor despite meeting at least one guideline. Additionally, Forbes et al. saw that many were not prescribed RAS inhibitors. To improve the equitable distribution of SGLT2 and RAS, the research team suggested implementing greater education for patients and professionals on CKD drugs, using targeted approaches for certain demographics, improving albuminuria testing, and offering greater support with adopting guidelines.

2.3: What is meant by Polypharmacy?

CKD often requires polypharmacy as a result of these guidelines; MacRae et al. study demonstrated that individuals with CKD often have multiple comorbidities. Seven or more conditions were more than 40 times more common in patients with CKD compared

to the general population. These comorbidities often include hypertension, heart failure, diabetes, coronary heart disease and peripheral vascular disease. (11)

In recognition of the unique difficulties in managing CKD, Al-Khulaifi et al. conducted a systematic review answering the research question, “What is Polypharmacy in Patients with Chronic Kidney Disease?". Through screening over 478 papers and reviewing 18 studies, Al-Khulafi observed that the common consensus for the diagnostic threshold for polypharmacy was the regular intake of ≥5 medications for ≥4 months or longer. (12)

Using the exact definition, previous studies have sought to examine the prevalence of polypharmacy in CKD. Tinwala et al., S.R. and M.A. were based on 53 studies with 477,909 patients involved in their analysis. When estimating the pooled prevalence of polypharmacy in this cohort of CKD patients, the pooled prevalence rate was 76.2% (95% CI 73.2%-79.1%) and 37.4% in those with excessive polypharmacy (≥10 medications)—excluding those who required ESRD, i.e. a diagnosis of non-dialysis CKD, the polypharmacy prevalence rate of 72.7%. (13) These rates of polypharmacy in CKD were echoed in Naseralallah et al. smaller systematic review, which involved 14 studies comprising 17 201 participants across 13 countries on four continents. In their study, they saw that the overall pooled prevalence of polypharmacy amongst patients with CKD was 69% (95% CI: 49%–86%), modified to 61% and 67% following completion of the sensitivity analysis. (14) However, the authors advised caution when interpreting these figures given that the stages of CKD among the included studied varied considerably, from those requiring dialysis to those with stage 2-3 CKD. As demonstrated, these rates reported are much higher than those who are elderly, living with chronic liver disease or HIV, but instead more comparable to rates reported from those with heart failure.

Despite Tinwala and Naseralallah commenting on the overall association between CKD and polypharmacy, Oosting et al. went one step further to explore the relationship between subgroups of patients with CKD and polypharmacy, given that later stages require more intensive management. The pooled prevalence of all CKD subgroups was higher at 82% (95% Cl 76%-86%) compared to Tinwala and Naseralallah’s study. Postings et al., S.R. were much larger, with 63 studies and 484,915 patients included. However, for those identified with late-stage CKD (CKD stage 3–5), the prevalence was 68% (95% CI, 54% to 79%), with a significant association of higher prevalence of polypharmacy observed in studies with a higher prevalence of hypertension.

Oostings et al. observed that the pooled mean of prescribed medications for CKD patients staged 3–5 was 7.9 (95% CI, 6.8 to 9.1) lower than in the mixed CKD group. Moreover, in the mixed group, the pooled daily pill burden was 14.1 (95% CI, 11.8 to 16.5; 14 studies, 2143 patients). (15) Despite fixed dose combination use being a recognised method to reduce medication burden, only one study was found to investigate the intervention.

In Tinwala et al., the research team found 17 studies reported significant associations between CKD polypharmacy and adverse health outcomes. These complications included potentially inappropriate medication use, drug-drug interactions, drug-related problems, medication-related problems, adverse drug reactions, decreased quality of

life, decreased kidney function, hospitalisation, and mortality. (13)Oostings et al. defined these outcomes as "patient-important" outcomes and sought to categorise the risk that polypharmacy in CKD poses. Reviewing 30 studies showed a pooled hazard ratio of 1.24 (95% CI, 1.06 to 1.45) between CKD polypharmacy and all-cause mortality. Oostings saw that the odds ratio for the decline in eGFR of ≥3 ml/min per 1.73 m2 per year, was significant, at 1.2 (95% CI, 1.06 to 1.34) and subsequent progression to kidney failure was had a hazard ratio of 1.38 (95% CI, 0.99 to 1.91). More notably, polypharmacy was associated with lower QoL, as seen through higher physical and mental component summary scores, lower EuroQoL scores, and general mental health scores, in those patients who were given a higher number of medications, increased medication nonadherence and inappropriate medication.

Laville et al. conducted a 2-year multicentre study observing 3033 outpatients with CKD and eGFR<60 ml/min per 1.73 m^2 in France to demonstrate the impact of the burden of adverse drug reactions in CKD. Over the study period, 536 patients had 751 adverse drug reactions, with 150 classified as serious. Among the severe cohort, 32% were considered preventable or potentially preventable. (16) Renin-angiotensin system inhibitors (15%), antithrombotic agents (14%), and diuretics (10%) were the drugs to which the most adverse drug reactions were imputed. However, antithrombotic agents caused 34% of severe adverse drug reactions, where vitamin K antagonists and heparin were the main culprits. Three inappropriate pharmacodynamic drug interactions were identified: two between vitamin K antagonist and heparins and one between vitamin K antagonist and an antibiotic was observed.

2.4 Is there a link between polypharmacy and deprivation?

While this study does not question the need or use of these medications, it has been established that polypharmacy has been associated with adverse health outcomes. A recent 2023 meta-analysis examined the impact of polypharmacy and deprivation and saw significant correlations between the two variables. Through assessing 18 studies, Iqbal et al. saw a pooled OR of 1.10 (95% CI 0.98–1.23; $I^2 = 46\%$) for receipt of polypharmacy in those of a low compared to high income. A further three studies were used to assess the impact of social class on polypharmacy, and it was found that those of lower social class had a pooled OR of 1.31 compared to higher social class. Whilst the authors thought of potential causal pathways which might explain the higher rates through increased multimorbidity, whereby people of lower socioeconomic status have a higher risk of multimorbidity, or through healthcare access, that higher SES navigating healthcare systems, the authors were unable to specify the exact causal nature for the associations seen.

Chapter 3: Conclusion

To date, very few studies have looked at the disparities between prescribing practices between different population cohorts and demographics in the presence of renal disease. Since North West London is home to over 2.4 million people from more than 200 ethnicities, with 12.3% of the population over 65, its ethnic and social diversity will be extremely valuable in examining the differences in polypharmacy experiences between groups. (17) This will allow us to learn about the role polypharmacy plays in an ethnically diverse population and, in turn, will add to the growing understanding of polypharmacy in renal patients

Proposed Next Steps

Due to time delays in securing ethics and data permission, we were unable to complete the project as expected. To continue the project and learn about differences in nwl, we proposed the following study protocol. Firstly tilter the existing data-set to produce a new data-set containing patients with known diagnosis of CKD (ICD10) and procedures (OPCS4) related to CKD. From there, use descriptive statistics to understand patterns of polypharmacy and use regression analysis to understand relationships between polypharmacy within patients with renal diagnosis and patients' demographics such as gender, age, ethnicity. Through looking for differences in patient cohorts, look to discover the extent to which health inequalities exist in NWL. After looking for any differences based on demographic, employ a similar approach to explore existing demographic differences in polypharmacy based disease progressions (such as CKD stages), and outcomes (dead or alive). If the data allows, also look for variation in polypharmacy across different geographical boundaries within NWL. A statistical analysis should be completed on all relationships deduced to test the significance. Methods such as T-Test and single/multivariate regressions will be used where indicated. Finally, if the data allows, use time-series analysis to identify trends, seasonality, and cyclic patterns in prescription data.

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