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Kidney Health Inequalities in the United Kingdom: Reflecting on the past, reducing in the future

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Kidney health inequalities

in the United Kingdom

Reflecting on the past, reducing in the future

Kidney Research UK
Funding research to save lives

Foreword

Twenty years ago evidence was emerging in the UK that kidney disease was a particular problem in our Black and Ethnic Minority (BAME) populations. People from BAME backgrounds are more likely to develop kidney failure, because kidney disease worsens more rapidly in these populations, and are less likely to receive a kidney transplant when compared to those of White European ethnicity. Kidney Research UK drew attention to these wide-ranging issues by commissioning a position paper published in 2001: 'Preventing kidney disease: the ethnic challenge' by Professor Liz Lightstone.

Now in 2018, Kidney Research UK has commissioned this further report: 'Kidney health inequalities in the United Kingdom: reflecting on the past, reducing in the future'

Ethnicity continues to be a major factor influencing susceptibility and outcomes in kidney disease, but in 2018 we have wider concerns about the many individual and societal factors which underlie kidney health inequalities. Extremes of age, deprivation, health literacy, recent migration, homelessness are just some of the elements which will impact inequality in kidney health; and most remain less well studied than ethnicity.

The impact of health inequalities is felt in variations in susceptibility to disease, in severity of disease, in access to care, and in kidney health outcomes. The factors which generate and perpetuate such inequalities are biological, social and economic. The research challenges are not only to understand better the biological mechanisms at work, but to test interventions which reduce inequality in all its forms.

Kidney Research UK is grateful for the energetic and thoughtful commitment of the report's two authors, Dr Fergus Caskey and Dr Gavin Dreyer. We also appreciate the time and energy given by the authors of the expert scoping reviews within the report, and thank many others who contributed to the production of the final document.

The report reflects on the impact of the 2001 paper on ethnicity, describes our current and growing knowledge of the many processes influencing kidney health inequalities, and lays down substantial challenges for Kidney Research UK and for the whole renal community to address the evidence gaps through research.

Kidney Research UK is committed to rising to those challenges. We will encourage the research community to address these questions and require those applying to us for funding to demonstrate, where appropriate, how their work will impact health inequalities. We aim to expand the funds available to facilitate future research grant calls focused on health inequalities, and we will seek partnerships to help us address the many challenges this report lays before us.

John Feehally

Chair of Trustees, Kidney Research UK 2015 - 2018.

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- The clinicians, researchers and people affected by kidney disease who participated in the research prioritisation exercise
- The nine experts in kidney health inequalities who were interviewed for Chapter 2
- Professor Alison Brettle who led the scoping review workshops
- The four scoping review authors
- The teams of expert clinicians who wrote chapters five to eight.

Executive summary

1. Kidney disease is common in the UK:
    - Chronic kidney disease affects one in 10 of the general population (1)
    - Acute kidney injury affects one in 20 hospital admissions (2)
    - One person in 1000 is on dialysis or has a kidney transplant for end-stage kidney disease (3).
2. Acute kidney injury and chronic kidney disease (including end-stage kidney disease) are associated with significant morbidity and mortality and account for 2% of NHS funding (4, 5).
3. Despite healthcare being free at the point of use in the UK, inequalities in kidney health exist. For example:
    - People from South Asian and Black backgrounds are three to five times more likely to start dialysis than people from White backgrounds (6)
    - More women have kidney disease, yet more men start dialysis (1, 3)
    - People from socially disadvantaged backgrounds have a higher burden of kidney disease and are more likely to start dialysis (3, 7)
    - Dialysis patients from South Asian, Black and socially disadvantaged backgrounds are less likely to receive a kidney transplant (8, 9).
4. Given the burden associated with kidney disease and its treatment, other groups at risk of disadvantage must not be forgotten. For example, those at extremes of age, those with mental health issues or cognitive impairment, those living in rural areas, prisoners, those without a home or those who have recently migrated into the UK.
5. The drivers of health inequalities are social, cultural or environmental, though some of the effect may be mediated through biological factors.
6. Based on a consensus exercise, scoping reviews and expert chapter authors, this report makes 27 recommendations:
    - 10 broad research recommendations
    - 17 topic specific research recommendations.
7. To reduce kidney health inequalities at the population level, a range of research methods along the translational pathway will need to be funded, from primary qualitative and quantitative research, to systematic reviews and synthesis of the literature, to interventional studies.
8. Changing behaviour – clinician and patient – requires an understanding of why kidney health inequalities happen and expertise to develop and evaluate complex interventions.
9. Future efforts to address kidney health inequalities must be:
    - Focused on a small number of priorities set by key stakeholders
    - Undertaken as part of a national coordinated strategy
    - Competitively awarded with methods and design optimised through peer review
    - Actively project managed
    - Formally evaluated for impact.
10. Minimising unwarranted kidney health inequalities must become everyone's responsibility, with 'impact assessments' performed for any service redesign, quality improvement or research project.
11. To achieve impact on kidney health inequalities, kidney services, funders and the wider renal community in the UK need to think disruptively and create their own opportunities to change the system and influence policy.

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Chapter 1 Introduction

Dr Fergus Caskey

Dr Gavin Dreyer

Although almost everyone in the UK now lives longer than they did 100 years ago, the difference in premature mortality between the rich and poor, that was falling from the 1920s to the 1970s, has returned over the last 40 years to 1920s levels (1). Addressing this for the UK Government in his 2010 report, 'Fair Society, Healthy Lives', Sir Michael Marmot stated:

> *'Health inequalities result from social inequalities. Action on health inequalities requires action across all the social determinants of health.'* (1)

His six policy objectives to reduce health inequalities cover the life course, from opportunities for children to fair employment, healthy and sustainable communities and stronger health prevention (1). While social factors will often act through biological pathways, the root causes at the population level are largely societal and environmental.

Inequalities also exist in kidney health (see Appendix 1 for an explanation of kidney disease). One of the first to be identified in the 1990s was that people from South Asian and Black ethnic backgrounds were three to five times more likely to start dialysis than those from a White background (2, 3). This was consistent with evidence from the United States (US) in the early 1980s (4). Since then, however, other inequalities have been recognised (Box 1). It is perhaps the burden of end-stage kidney disease (ESKD) and its treatment that makes these inequalities such a policy and research priority.

- People from South Asian and Black backgrounds are three to five times more likely to start dialysis than people from White backgrounds
- More women have kidney disease, yet more men start dialysis
- People from socially disadvantaged backgrounds have a higher burden of kidney disease
- Dialysis patients from South Asian, Black and socially disadvantaged backgrounds are less likely to receive a kidney transplant.

Box 1 Examples of kidney health inequalities in the UK

The initial evidence from the UK was so striking that in the late 1990s key clinicians, researchers and the National Kidney Research Fund (since renamed Kidney Research UK) commissioned a review of ethnicity related health inequalities in kidney disease in the UK (5). Published in 2001, this report highlighted the greater burden of risk factors for kidney disease – diabetes and hypertension – in Black, Asian and minority ethnic (BAME) populations, but also flagged the possible role of genetic, environmental and socioeconomic factors (5).

Following a renewed interest in health inequalities in kidney disease, Kidney Research UK recently commissioned the current updated report. This report reviews the impact of the 2001 report, takes a broader perspective of health inequalities in kidney health beyond BAME populations and provides some recommendations for future research directions.

When considering risk factors for kidney disease, it is important to remember that there are many determinants of kidney health (Figure 1.1). Some determinants may be thought of as 'predisposing' individuals to kidney disease across the life course. For example, certain antenatal and genetic factors may make it more likely that an individual develops chronic kidney disease (CKD) as an adult.

There is a complex interplay between risk factors, for example, acute kidney injury (AKI) is a risk factor for CKD and CKD is a risk factor for AKI (6, 7). Some risk factors are shared, whereas some precipitating factors for AKI are more specific. Some potentially modifiable

determinants of risk, such as obesity and diabetes, are common, but also complex to deal with in their own right. It can be hard to disentangle socioeconomic position and life course influence (8). As an acute condition, AKI may best be considered in terms of factors that increase the chance of an episode occurring, as well as the background risk created by these predisposing and clinical risk factors. Certain conditions, however, may be thought of as risk factors for both AKI and CKD.

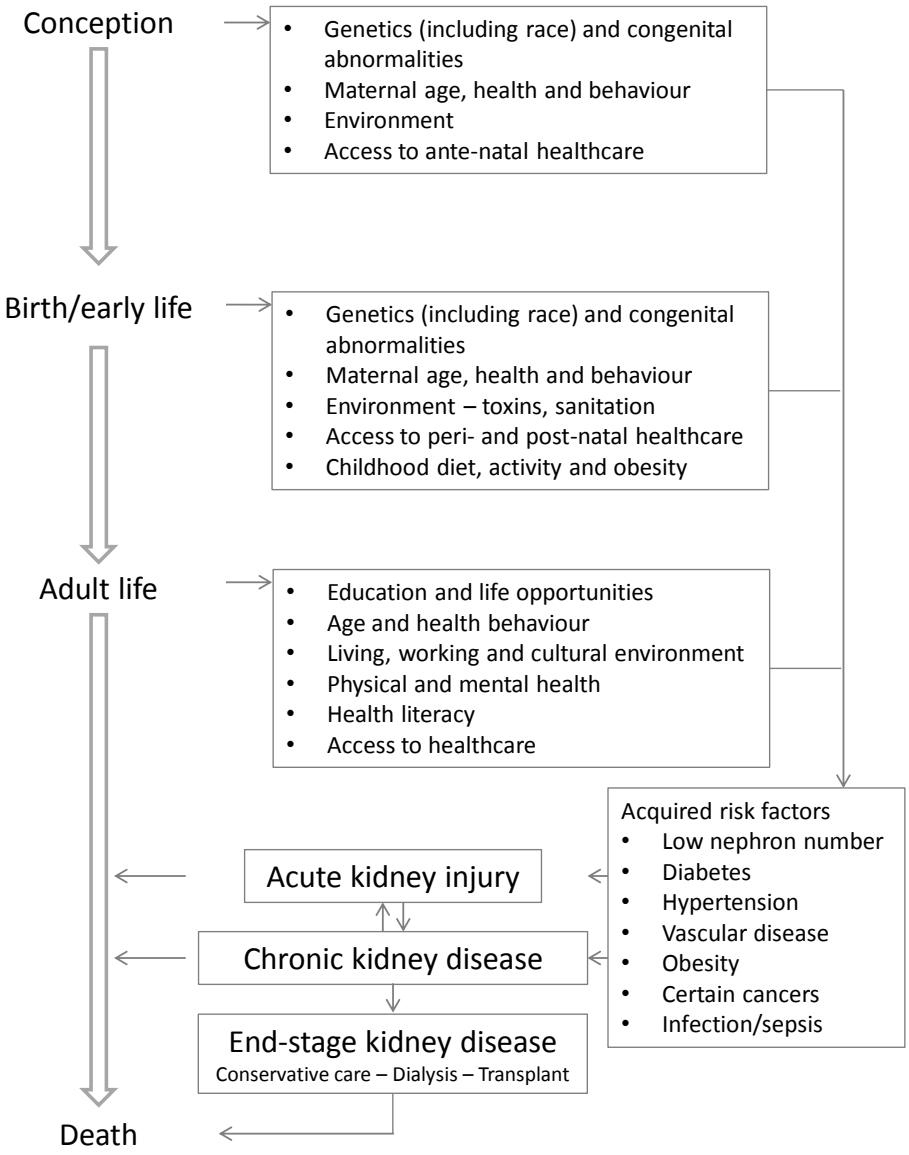

Figure 1.1 Kidney health inequalities: a life course approach

Among each of these predisposing, risk and precipitating factors, some are distributed unequally in populations ('inequality') and some are not. For example, smoking, obesity and lower health literacy (predisposing factors) are more prevalent in populations of lower socioeconomic position. This is also the case for type 2 diabetes, cardiovascular disease (CVD) and heart failure (risk factors) and hospitalisation (a precipitating factor for AKI) (9).

By contrast, the prevalence of primary renal diseases may be largely unrelated to socioeconomic or ethnic factors.

Other important considerations are:

- Modifiability: some of these factors are amenable to intervention (potentially modifiable), such as smoking, and others are not, such as age
- Inequality vs. inequity: 'inequality' (unequal distribution) does not necessarily mean 'inequity' (unfair distribution). Socioeconomic variation is inequitable, for example, the greater prevalence of type 2 diabetes among lower socioeconomic groups. By contrast, there may be unequal distribution of diabetes by age, but it may not be considered inequitable
- Potential for impact: those factors that are common or that operate across the whole life course may have greater potential to influence kidney disease in the population in the long term. Examples might include poverty or limited health literacy
- Awareness: awareness and understanding of kidney function and disease is largely poor in the UK general population, with some differences according to age and education (10).

Risk factors that are common, potentially modifiable *and* inequitable should arguably receive research priority, particularly where intervention has potential for a large impact (11).

This report begins with a chapter reviewing the impact and lessons learned from the 2001 report (5), based on interviews with nine key opinion leaders involved in kidney health inequality work at that time and subsequently.

Recognising the well documented role of factors that are environmental, cultural or related to accessing and utilising the health care system, the report then proceeds to chapters that consider risk at three stages of developing kidney disease: (i) the risk of developing AKI or CKD; (ii) the risk of progressing to an advanced stage of AKI or CKD; and (iii) the risk of reduced access to treatment and adverse outcomes with ESKD. These chapters have been written by small teams of experts in these areas, who were asked to draw on their existing knowledge of the literature. Timelines and resources did not permit wider systematic reviews of the literature for topic areas, but one scoping review was commissioned and funded per chapter to systematically scope out the extent of the available evidence and guide recommendations as to next steps: (i) more primary research is required; (ii) a systematic review/meta-analysis is needed to pull together the existing literature; or (iii) an intervention study is required (Figure 1.2). A prioritisation exercise was circulated to members of the UK renal community to determine the focus of these scoping reviews.

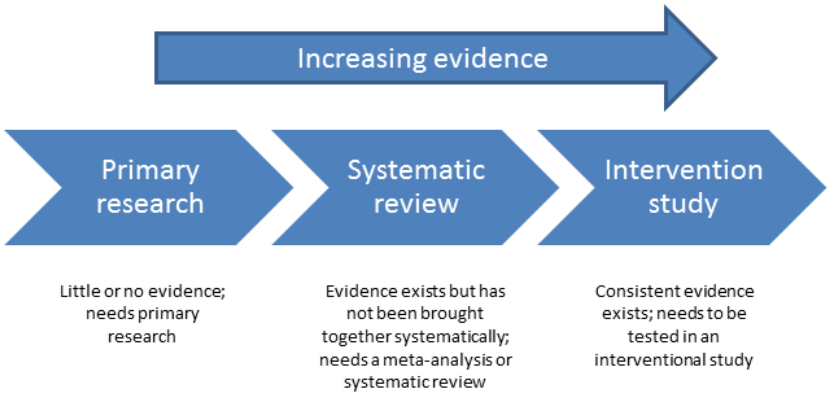

Figure 1.2 The extent of the knowledge gap reported in a scoping review informs future research activity

The report also considers the evidence for biological factors being the determinants of inequalities and asks what work is required to explore promising results and, if possible, convert those into interventions to reduce inequalities. This chapter has been written by expert clinician scientists, with a parallel basic science scoping review.

The report concludes with a chapter of recommendations relevant to Kidney Research UK and other organisations involved in kidney research or quality improvement. These recommendations are based on the reflections and advice from the key opinion leader interviews, the prioritisation exercise, the scoping reviews and the topic expert-led chapters.

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Chapter 2 Review of the impact arising from the 2001 Lightstone report

Dr Gavin Dreyer

Dr Fergus Caskey

2.1 Introduction

In 2001, Professor Liz Lightstone produced a position paper on behalf of the National Kidney Research Fund (now Kidney Research UK) entitled 'Preventing kidney disease: the ethnic challenge' (1). The report brought together much of the existing evidence of health inequalities in kidney disease in the UK, highlighted knowledge gaps in this field and identified strategies designed to reduce the incidence and improve the outcomes of kidney disease in BAME populations.

2.2 Evaluating the 2001 report

This chapter reviews the activities and impacts that arose after the 2001 report and makes recommendations for future research activity in the field of health inequalities in kidney disease in the UK. To achieve this, the senior report authors (FC and GD) interviewed nine key experts involved with kidney health inequality research and/or policy since the 2001 report. The first of these were suggested by Kidney Research UK, with other experts identified as important to speak to based on their activities in the field during the early interviews.

The interviews were designed to identify and review the activities and impacts arising from the 2001 report and learn lessons from the challenges that had been experienced. They also sought strategic recommendations aimed at maximising the impact of the present report to reduce kidney health inequalities in the UK going forwards. Although a topic guide was used to provide a framework for questions, the interviews were not conducted as research. Quotations below are based on the authors' notes from the interviews and are not verbatim quotes.

2.2.1 Activities and impacts arising from the 2001 report

Research into health inequalities in kidney disease

Major research projects arising from the 2001 report and funded by Kidney Research UK

The 'A Better Life through Education and Empowerment' (ABLE) project (2) was a series of projects initially funded by Kidney Research UK in 2003, but later funded by a range of charities and foundations, industry partners and governmental departments. Different projects ran in different parts of the UK, but with a common theme of assessing and raising awareness and knowledge of kidney disease and access to transplant in the South Asian and Black communities, predominantly using a peer educator model (3).

The 'London Life Sciences Prospective Population' (LOLIPOP) study (http://www.lolipopstudy.org/) was designed as a prospective cohort study of CVD with a focus on the South Asian population in West London. The study was subsequently modified to include an evaluation of risk factors for, and biomarkers of, kidney disease. The renal component of this study was funded by Kidney Research UK and publication of the renal

data is due shortly following a recent injection of additional funding from Kidney Research UK.

The 'Kidney Early Evaluation Programme' (KEEP) was devised to assess the prevalence of CKD and associated comorbidities in three community settings in the UK with a high proportion of BAME patients. The study evaluated whether BAME compared to White populations had a higher prevalence of CKD and associated comorbidities.

In addition to these major research projects, which quite clearly arose from the 2001 report, there have been many other studies relating to kidney health inequalities in BAME populations undertaken in the UK since its publication. While it was beyond the scope of this report to comprehensively summarise all such work, we mention areas that we considered sufficiently closely related to the original report:

- A National Institute for Health Research (NIHR) funded study led by Professor Morgan at King's College, London, entitled 'Increasing the acceptability and rates of organ donation among minority ethnic groups: a programme of observational and evaluative research on Donation, Transplantation and Ethnicity' (DonaTE) (4)
- A series of papers exploring attitudes to organ donation, live kidney donation and kidney transplantation, led by Professor Warrens at the Hammersmith Hospital, London and Professor Randhawa at the University of Bedfordshire (5-20)
- An NIHR funded study led by Professor Bradley at the University of Cambridge, entitled 'Access to Transplantation and Transplant Outcome Measures' (ATTOM) (21)
- A paper highlighting the importance of communication at the end of life for people from BAME populations with advanced CKD (22).

Other publications relating to kidney health inequalities were included in the scoping reviews if they fell into the areas prioritised.

Quality improvement, education and awareness projects arising from the 2001 report

Alongside the research activity, a number of quality improvement projects initiated by Kidney Research UK have been designed to increase awareness of kidney disease in BAME populations and improve the care of CKD in primary care. These include 'Quality Improvement in CKD' (QI-CKD), 'Enabling a Better Life through Education' (ENABLE) and 'Identifying and monitoring people at greatest risk of progressive CKD' (ASSIST–CKD). The peer educator model, supported by the development of educational materials including DVDs, has been the predominant model for raising awareness of CKD, its risk factors and organ donation in high risk population groups. A detailed evaluation of all these activities is beyond the scope of this report.

Other kidney health inequality research funded by Kidney Research UK

In addition to the key research and quality improvement projects listed above, a review of Kidney Research UK funding since 2001, undertaken by two of the current report authors (GD and KE), identified a further 21 projects that could be considered to address health

inequalities in kidney disease. These projects represent approximately 3.8% of Kidney Research UK funded studies and approximately 4.7% (£2.4 million) of Kidney Research UK funding since 2001 (see Appendix 2 for details of the methodological approach).

Increased awareness and education for health inequalities in kidney disease

The 2001 report was generally considered by the experts to have raised awareness of kidney health inequalities in the UK. This occurred more notably in BAME populations in specific UK communities that benefitted from the ABLE peer educator programme, but also more broadly within the UK renal community and to a certain extent within the Department of Health. The peer educator programme was considered the predominant model for effecting increased awareness of these issues.

Other impacts

Changes in the way Kidney Research UK worked

The 2001 report was associated with more focused activity at Kidney Research UK within the field of health inequalities. For a time, a health inequalities advisory group reported to the Kidney Research UK trustees on matters including raising awareness, education and research activity for health inequalities. The 2001 report and this advisory group were said by interviewees to have leveraged funding for health inequalities research from non-traditional sources such as the Department of Health and the Big Lottery fund.

Changes in the way clinical services worked

One expert reported that the work arising from the 2001 report led to a clinical service change in their region. The principal nature of the change was a decentralisation of renal services into the communities and closer links with primary care to better detect and manage CKD in an area with a high BAME population.

Other experts felt that initiatives such as the renal National Service Framework, the introduction of estimated glomerular filtration rate (eGFR) reporting and the collection and reporting of ethnicity data by the UK Renal Registry (UKRR) occurred independently of (before or after) the production of the report.

2.2.2 Lessons learned and recommendations for future research arising from the 2001 report

The report

Several of the interviewed experts reported that they did not remember seeing or being aware of the 2001 report. While this may reflect the 16 years experts were being asked to think back over, if correct it is worthy of consideration. At that time, peer reviewed publications were the traditional way to influence clinical practice and it took a fairly standard two years for the synopsis of the report to be published (23). There was, of course, no social media in 2001 and so the landscape for making impact has completely changed. It may therefore be more fruitful to learn lessons on maximising impact from more contemporaneous renal and non-renal reports.

Implementation of the report

In different ways, several experts stated that the 2001 report was not followed by the development of a formal strategic plan to address kidney health inequalities at Kidney Research UK. For example, we believe it was not until 2017 that Kidney Research UK had its first formal call for research into health inequalities in kidney disease. During this time, it was felt that Kidney Research UK's funding was weighted towards laboratory and clinical research, rather than applied health sciences research to evaluate health inequalities. A number of experts reflected on the lack of a formal process for monitoring and evaluating the impact on kidney health inequalities of research studies supported by Kidney Research UK arising from the 2001 report.

In addition, according to one of the interviewees, the KEEP found no increased rate of early stage CKD in BAME populations in the UK. The authors assumed there must have been a flaw in the sampling strategy or study design; later work from the US has since confirmed this counter-intuitive finding and explained the higher rate of ESKD through more rapid progression (24, 25). If the UK authors had had funding for a follow up phase, this study, which remains unpublished, could have been at the cutting edge of the global race to understand this major kidney health inequity. Such missed opportunities are of course not uncommon in the world of research, but we felt there may be a lesson from this anecdote.

The changing nature of the UK population

The interviewees recognised the need to consider the changing demographics of the UK population. The nature of health inequalities is such that issues beyond ethnicity must now be considered. These include, but are not limited to, sociodemographic, biological, genetic and cultural factors.

However, inequalities in BAME populations remain a significant issue (26, 27) and opportunities to study the effect of this through 'natural population experiments' and richly phenotyped cohort studies with biosamples (designed and powered to answer health inequality questions), should be actively considered. BAME groups are often excluded or under-represented from studies due to challenges obtaining informed consent and collecting quality of life data in non-English languages. Efficient ways must be found to make exclusion of these populations an unacceptable default position.

Changing the way we work to address health inequalities

Another expert felt that there were opportunities for '*doing it differently*' – being the first to use new technologies and innovations such as connectivity, learning systems and repurposing of the workforce. The creation of the 'Kidney Quality Improvement Partnership' (KQuIP) was given as one example of the community coming together in response to central decisions to de-prioritise in kidney services, but another example was the National Confidential Enquiry into Patient Outcome and Death's (NCEPOD) refusal to agree to an enquiry into mortality on dialysis – '*we should just get on and do it ourselves'*.

Collaboration and funding

Several experts felt that Kidney Research UK should ring-fence funding priorities to support future research in health inequalities, as occurred in 2017. Kidney Research UK and the renal community should further build links with the funding bodies such as the NIHR, Medical Research Council (MRC), Wellcome Trust and Department of Health to put inequalities in kidney health on their priority agenda. It was felt by several experts that more could be done to fund kidney health inequality research collaboratively with charities such as Diabetes UK, Cancer Research UK and the British Heart Foundation.

There were also felt to be opportunities to conduct research and quality improvement projects to reduce kidney health inequalities through working more collaboratively with the professional organisations (the Renal Association, the British Renal Society and the British Transplant Society), the UKRR and the kidney patient charities, as is now happening through the KQuIP. A similar collaboration in Canada has raised $40 million for patient-centred kidney research (www.cansolveckd.ca).

Establishing goals for health inequalities in kidney disease

Kidney Research UK, together with the wider UK renal community and allied organisations, need to set new, clear national goals and priorities in the field of health inequalities in kidney disease that reflect the changes in the field since the 2001 report. These will need to be determined with patient involvement and full consideration of the human and financial resources required both within and outside Kidney Research UK. As previously undertaken by Kidney Research UK, BAME communities and other disadvantaged groups should be involved in setting those priorities and the solutions. An important first question, it was suggested, should be '*where do you want to make the impact?*', working backwards from that to determine the research, quality improvement or service redesign required to achieve that.

The UK Renal Research Strategy (28) and UK Kidney Research Consortium (www.kidneyresearchuk.org/research/ukkrc) were not mentioned by any of the experts, but would be among the obvious existing mechanisms to use to implement this.

Sustainability

The expert interviewees reflected that Kidney Research UK has made notable achievements in the field of health inequalities. While value for money is important, it may be preferable to fund a smaller number of carefully developed, adequately funded projects that are then actively project managed with internal pilots and progression gateways. This is certainly what other funders are doing and Kidney Research UK is, we believe, increasingly doing this.

A number of experts felt that Kidney Research UK needed to have a system that continuously evaluated the impact of its investment per £ spent, whether in research, quality improvement or education. It should then compare itself against other (non-renal) charities and learn lessons/evolve its strategy.

One expert felt that the culture needed to change in the renal community – '*we must not accept unwarranted variation*'; reducing health inequalities must be made '*part of the day job*'. Routine use of tools such as equality impact assessments made this happen at the Department of Health and could be introduced into everyday clinical and research planning and evaluation.

The importance of increasing and sustaining awareness of kidney health inequalities was raised. Lessons included having a planned 'pipeline' of (smaller) reports and outputs that keep kidney health inequalities on the agenda, rather than putting all efforts into a single big report.

2.3 Summary

The interviews identified some areas of positive change in the field of kidney health inequalities, supported by activities delivered by Kidney Research UK arising from the 2001 report. However, it was recognised that the lack of a coordinated research strategy with targeted funding for health inequalities from the core Kidney Research UK budget had likely reduced its potential impact. None of the experts interviewed felt there had been a measurable reduction in kidney health inequalities since the 2001 report. This may, however, simply reflect the lack of formal evaluation of this work. As pressure on funds for research and clinical care delivery becomes inevitably tighter, the challenge going forwards is to work innovatively, collaboratively and perhaps disruptively towards agreed goals that deliver measurable and sustainable reductions in health inequalities in kidney disease.

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Chapter 3 Identifying research priorities in health inequalities in kidney disease

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3.1 Introduction

To obtain a broad range of perspectives on which health inequalities in kidney disease should be prioritised for research, we undertook a prioritisation exercise involving people affected by kidney disease, researchers and clinicians. This made it possible to:

i. Consider a greater breadth of potentially disadvantaged populations than the 2001 report, which focused solely on BAME populations
ii. Recognise the different stages on the kidney disease pathway, from the risk of developing AKI or CKD to the risk of adverse outcomes with ESKD
iii. Obtain a representative range of opinions of future research priorities from a broad subset of the UK renal community
iv. Use the results of the research prioritisation exercise to determine the focus of the Kidney Research UK commissioned scoping reviews to provide formal evaluation of the evidence base in key areas of kidney health inequalities in the UK.

3.1.1 Scoping reviews

A scoping review is a rapid gathering of available literature for a defined topic, which can help guide future research activity by determining the extent of the current evidence base (Figure 1.2). For example, if it is clear from a scoping review that there is a significant knowledge gap, the most appropriate next step would be to conduct new primary research in the area. The scoping reviews have been used to inform chapters five to eight.

Kidney Research UK requested that one scoping review focus on the role of pathophysiology (basic science) in explaining health inequalities. The other three scoping reviews focus on a population that may be ‘at risk’ at each of the following stages in the life course epidemiology of kidney disease: (i) development of CKD or AKI; (ii) progression to an advanced stage of CKD or AKI; and (iii) poor outcomes with ESKD. The focus populations for the three scoping reviews were chosen by members of the UK renal community using a formal research prioritisation exercise.

3.2 Methods

A modified Delphi method was used (1). This formal and structured technique gives all participants an equal voice and avoids situations where discussions are dominated by the views of a few. The generally accepted minimum number of participants is 20.

Our Delphi approach comprised two rounds of an electronic survey emailed with explanatory cover letters to 59 members of the UK renal community on 17 May 2017 and 5 June 2017, respectively (see Appendix 3 for surveys). We were particularly keen to hear the views of people affected by kidney disease and so contacted 38 members of this group compared to 21 clinicians and researchers. Included were 12 members of the UKRR Patient Council and 23 members of the Kidney Research UK Lay Advisory Committee. Recipients were given 10 days to submit their surveys.

The survey was designed by the report authors following presentation and discussion of (i) the life course approach to kidney disease and (ii) range of groups at risk of kidney health inequalities at a workshop in October 2016 involving health professionals, researchers and patients. An initial draft was then modified following feedback from the UKRR Patient Council and Kidney Research UK. The survey asked about six research areas on the pathway from risk of developing kidney disease to adverse outcomes with ESKD. Within each of these research areas featured the same 10 populations who may be at an increased risk of kidney disease, such as people living in socially deprived areas. In total, there were therefore 60 combinations of research area and population that could be considered by participants.

In round one, each participant was asked to select their top 10 research priorities by awarding 10 hypothetical grants of £100,000 to researchers seeking to tackle inequalities in kidney disease in the UK. They could choose multiple populations within the same research area, or the same population in multiple research areas, or a combination thereof. In a free text box respondents could suggest additional at risk populations to be included in round two. All responses were anonymised and participants were only contacted if they had filled out the free text section or if they had selected more than 10 choices. Round one votes were counted and the results added to the survey, which was then circulated a second time.

In round two, voting was conducted as described above except this time the participants were asked to consider the overall view of the group when providing their 10 choices. Those who had not voted in round one could vote in round two. The results of round two were counted and the three research area/at risk population combinations that received the greatest number of votes were the topics for the three scoping reviews.

3.3 Results

3.3.1 Round one

In round one 248 votes were cast by 25 participants (42.4% response rate). Surveys were submitted by 15 people affected by kidney disease (39.5% response rate) and 10 clinicians or researchers (47.6% response rate). Two participants only cast nine votes. People affected by kidney disease cast 60.0% of the votes. Comments made by five respondents were discussed and feedback provided, but no further at risk populations were added to round two of the survey. Round one results are shown in Table 3.1.

The two CKD research areas received almost three times more votes collectively than the two corresponding AKI research areas (48.4% vs. 18.6%, respectively; Table 3.2). The dialysis research area received a marginally higher proportion of the votes than the transplant research area (17.7% vs. 15.3%, respectively).

Populations prioritised for further research were those that were socially deprived or of a BAME group (23.0% and 26.7% of all votes cast, respectively). The next three most voted for populations were mental health or cognition disorders (9.7%), extremes of age (8.5%) and the obese (8.1%; Table 3.3).

The voting preferences of people affected by kidney disease were more diverse than those of clinicians and researchers. For example, the percentage of votes cast by those affected by kidney disease for socially deprived and BAME populations were 19.4% and 18.1%, respectively; the corresponding percentages for clinicians and researchers were 28.1% and 33.4%. In addition, those affected by kidney disease cast proportionally more votes for the two AKI research areas than clinicians and researchers (20.8% vs. 15.0%, respectively). In contrast, percentages of votes cast for the dialysis research topic were similar for both those affected by kidney disease and clinicians and researchers (18.1% and 17.2%, respectively).

3.3.2 Round two

In round two 306 votes were cast by 31 participants (52.5% response rate). Surveys were submitted by 16 people affected by kidney disease (42.1% response rate) and 15 clinicians or researchers (71.4% response rate). One respondent only selected six choices and three respondents initially selected more than 10 choices. People affected by kidney disease cast 51.0% of the votes in round two. Round two results were very similar to round one (Table 3.1).

As before, the two CKD research areas collectively received many more votes than the two corresponding AKI research areas (42.8% vs. 21.9%, respectively) and the dialysis research area received marginally more votes than the transplant research area (18.0% vs. 17.3%, respectively; Table 3.2).

Similarly, populations prioritised for further research were those that were socially deprived or of a BAME group (34.0% and 33.0% of all votes cast, respectively). As before, the next two most voted for populations were mental health or cognition disorders (9.5%) and extremes of age (7.2%), followed by homelessness (4.9%) which replaced obesity (3.6%) in round one (Table 3.3).

In round two, the voting preferences of the two groups converged somewhat. The percentage of votes cast by those affected by kidney disease for socially deprived and BAME populations increased to 30.2% and 31.5%, respectively; the corresponding percentages for clinicians and researchers were 37.9% and 34.8%. However, those affected by kidney disease still cast proportionally more votes for the two AKI research areas than clinicians and researchers (24.9% vs. 18.8%, respectively).

3.3.3 Scoping review topics

The three research area/at risk population combinations that received the greatest number of votes and were therefore selected as the topics for three of the four scoping reviews were:

i. Risk of developing CKD for people living in socially deprived areas (25 votes)
ii. Risk of poor outcomes/progression of CKD for people from BAME populations (22 votes)
iii. Risk of poor outcomes whilst receiving dialysis for people from BAME populations (23 votes).

Table 3.1 Voting in rounds one and two of the research prioritisation exercise

Research area	Population	No. round 1 votes (N=25)	No. round 2 votes (N=31)
Risk of people developing AKI	In people living in socially deprived areas	10	18
	In people from ethnic minority populations	6	11
	In people who are homeless	1	2
	In people who use intravenous drugs	2	3
	In people from refugee and migrant communities	0	0
	In people who are obese	1	1
	In people with mental health or cognition disorders	4	4
	In people living in rural locations	0	0
	In people according to their gender	1	1
	In people at extremes of age – the very young and very old	3	2
Risk of people developing CKD	In people living in socially deprived areas	14	25
	In people from ethnic minority populations	17	23
	In people who are homeless	3	0
	In people who use intravenous drugs	2	0
	In people from refugee and migrant communities	4	2
	In people who are obese	5	3
	In people with mental health or cognition disorders	4	5
	In people living in rural locations	1	0
	In people according to their gender	2	2
	In people at extremes of age – the very young and very old	5	5
Risk of poor outcomes/progression for people with AKI	In people living in socially deprived areas	4	9
	In people from ethnic minority populations	4	5
	In people who are homeless	1	2
	In people who use intravenous drugs	2	1
	In people from refugee and migrant communities	0	0
	In people who are obese	2	1
	In people with mental health or cognition disorders	2	3
	In people living in rural locations	2	1
	In people according to their gender	0	1
	In people at extremes of age – the very young and very old	1	2
Risk of poor outcomes/progression for people with CKD	In people living in socially deprived areas	13	21
	In people from ethnic minority populations	15	22
	In people who are homeless	4	3
	In people who use intravenous drugs	3	1
	In people from refugee and migrant communities	5	2
	In people who are obese	5	2
	In people with mental health or cognition disorders	5	6
	In people living in rural locations	2	0
	In people according to their gender	4	2
	In people at extremes of age – the very young and very old	7	7
Risk of poor outcomes for people on dialysis	In people living in socially deprived areas	7	15
	In people from ethnic minority populations	12	23
	In people who are homeless	5	5
	In people who use intravenous drugs	3	1
	In people from refugee and migrant communities	2	1

Research area	Population	No. round 1 votes (N=25)	No. round 2 votes (N=31)
	In people who are obese	5	2
	In people with mental health or cognition disorders	4	4
	In people living in rural locations	2	1
	In people according to their gender	2	1
	In people at extremes of age – the very young and very old	2	2
Risk of poor outcomes for people with a kidney transplant	In people living in socially deprived areas	9	16
	In people from ethnic minority populations	12	17
	In people who are homeless	3	3
	In people who use intravenous drugs	1	1
	In people from refugee and migrant communities	1	1
	In people who are obese	2	2
	In people with mental health or cognition disorders	5	7
	In people living in rural locations	0	0
	In people according to their gender	2	2
	In people at extremes of age – the very young and very old	3	4
Total votes cast		**248**	**306**

Table 3.2 Votes cast in rounds one and two by research area

Research area	No. votes (%)	
	Round 1 (N=25)	Round 2 (N=31)
Risk of people developing AKI	28 (11.3%)	42 (13.7%)
Risk of people developing CKD	57 (23.0%)	65 (21.2%)
Risk of poor outcomes/progression for people with AKI	18 (7.3%)	25 (8.2%)
Risk of poor outcomes/progression for people with CKD	63 (25.4%)	66 (21.6%)
Risk of poor outcomes for people on dialysis	44 (17.7%)	55 (18.0%)
Risk of poor outcomes for people with a kidney transplant	38 (15.3%)	53 (17.3%)
Total votes cast	**248**	**306**

Table 3.3 Votes cast in rounds one and two by at risk population

Population	No. votes (%)	
	Round 1 (N=25)	Round 2 (N=31)
In people living in socially deprived areas	57 (23.0%)	104 (34.0%)
In people from ethnic minority populations	66 (26.6%)	101 (33.0%)
In people who are homeless	17 (6.9%)	15 (4.9%)
In people who use intravenous drugs	13 (5.2%)	7 (2.3%)
In people from refugee and migrant communities	12 (4.8%)	6 (2.0%)
In people who are obese	20 (8.1%)	11 (3.6%)
In people with mental health or cognition disorders	24 (9.7%)	29 (9.5%)
In people living in rural locations	7 (2.8%)	2 (0.7%)
In people according to their gender	11 (4.4%)	9 (2.9%)
In people at extremes of age – the very young and very old	21 (8.5%)	22 (7.2%)
Total votes cast	**248**	**306**

3.4 Discussion

Fifty-nine members of the UK renal community were invited to take part in the research prioritisation exercise, including 38 people affected by kidney disease. Response rates were good and increased from 42.4% in round one to 52.5% in round two, easily surpassing the recommended minimum of 20 participants. Despite a marked increase in the response rate of clinicians and researchers from 47.6% in round one to 71.4% in round two, votes from those affected by kidney disease still comprised 51.0% of the total votes cast in round two (down from 60.0% in round one). The choice of the three scoping review topics therefore reflected equally the priorities of those affected by kidney disease and those who work as clinicians or researchers.

The at risk populations of overwhelming interest to the participants in both rounds one and two were people living in socially deprived areas and people from BAME populations. In round one the socially deprived and BAME populations collectively comprised 49.7% of the vote and in round two this increased to 67.0% of the vote. The other at risk groups at most scored 9.7% in round one (range 2.8–9.7%) and 9.5% in round two (range 0.7–9.5%).

Of the six research areas, the three of greatest interest to the participants were risk of developing CKD, risk of poor outcomes/progression with CKD and risk of poor outcomes on dialysis. The CKD research areas received many more votes collectively than the corresponding AKI research areas (48.4% CKD vs. 18.6% AKI in round one and 42.8% CKD vs. 21.9% AKI in round two), while the gap between the two renal replacement therapy (RRT) research areas was less marked (17.7% dialysis vs. 15.3% transplant in round one and 18.0% dialysis vs. 17.3% transplant in round two).

In addition to the three scoping reviews listed in section 3.3.3, we included a basic science scoping review at the request of Kidney Research UK.

It is worth noting that there was some disparity in the voting preferences of the two groups of participants, particularly in round one. Of the votes cast in round one by those affected by kidney disease, 37.5% were for socially deprived and BAME populations, compared to 61.5% of the clinician and researcher vote. However, the gap narrowed in round two to 61.6% of the affected by kidney disease vote and 72.7% of the clinician and researcher vote. In contrast, the stronger vote for the two AKI research areas by those affected by kidney disease in round one persisted into round two (20.8% vs. 15.0%, respectively, in round one and 24.9% vs. 18.8%, respectively, in round two).

There are limitations to the approach taken. Given the resources and time available, the research prioritisation exercise was not undertaken as research. Although invited participants were purposively sampled for their expertise or patient experience in this area, this did not result in all potentially disadvantaged patient groups being represented in the responses. Further, the process was driven by the report authors, the majority of whom are clinicians, and this may have influenced the structure and content of the survey. Responses to the survey may reflect the age, sex and ethnic origin of respondents, which were not

formally recorded. Finally, the priority that respondents gave to at risk groups may have reflected current awareness of kidney health inequalities.

3.5 Summary

In conclusion, this exercise reached a clear consensus that BAME groups and those living in socially deprived areas should be priorities for efforts to reduce kidney health inequalities. Additionally, the participants placed more emphasis on CKD than AKI and almost equal emphasis on dialysis and transplantation. These priorities informed the work of the subsequent chapters.

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Chapter 4 Methods and short summaries of the four scoping reviews

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Dr Shona Methven

4.1 Introduction

To provide a systematic overview of the extent of evidence available for chapters five to eight, four scoping reviews were funded by Kidney Research UK. While a scoping review systematically identifies the available literature, its remit does not include a critical evaluation or synthesis of the evidence identified (1).

This chapter outlines the methodology used by the invited authors to conduct the four scoping reviews. It then provides short summaries of the findings, focusing where possible on the strength of the available UK evidence and the knowledge gaps identified. The full scoping reviews are available in appendices four to seven.

4.2 Methods

The scoping review authors undertook a series of four workshops held in June and July 2017 at the University of Salford led by Professor Alison Brettle, an information specialist with expertise in evidence-based practice. During the workshops, the authors followed Arksey and O'Malley's (1) framework of scoping review methodology, which breaks the process down into five distinct stages.

4.2.1 Stage one – identifying the research questions

The four research questions were refined following discussions:

i. How may biological factors explain ethnic differences in the incidence and progression of kidney disease? (Dr Jemima Scott)
ii. Why are people who are socially deprived more likely to develop CKD than those who are not? (Dr Michael Rees)
iii. Are people with CKD from ethnic minority groups more likely to experience faster progression and poorer outcomes than people with CKD from non-ethnic minority groups? (Dr Hilda Hounkpatin)
iv. Why do people with ESKD from ethnic minority groups experience poorer outcomes than people with ESKD from non-ethnic minority groups? (Emma Wilkinson)

4.2.2 Stage two – searching for relevant studies

Comprehensive and iterative searches of the literature were undertaken in July and August 2017. Health, sociology and psychology databases were searched as appropriate for each scoping review. There was insufficient time to hand search journals and grey literature. Search terms were wide and sensitive and encompassed a range of relevant thesaurus and free text terms. Search strategies were recorded, together with details of the dates the searches were conducted and the numbers of results obtained. Results of the searches were stored on EndNote reference management software.

4.2.3 Stage three – screening studies for inclusion

Using pre-established inclusion and exclusion criteria, each record was screened independently on the basis of title and abstract. A 10% sample of studies was screened by a second author and the level of agreement was checked. Articles believed to be relevant were then read in full and included or excluded as appropriate. Broadly, but not exclusively, inclusion criteria were post-1992 studies in English referring to an adult population from any country that compared at least two different populations. There was insufficient time to screen reference lists within the included studies.

4.2.4 Stage four – charting the data

Pertinent column headings for evidence tables were agreed within the group by consensus. Headings included study design, sample size, study aims, outcomes of interest, results and author conclusions. Studies that fitted the inclusion criteria were grouped into themes and data were extracted and sorted into the evidence tables.

4.2.5 Stage five – collating, summarising and reporting the results

The findings in each theme were summarised and knowledge gaps identified, with a specific focus on relevance to the UK.

4.3 Results

4.3.1 Short summary of scoping review one: How may biological factors explain ethnic differences in the incidence and progression of kidney disease?

Dr Jemima Scott, Dr Shona Methven and Professor Alison Brettle

This scoping review provides an overview of the literature relating to ethnic differences in biological risk factors for CKD and ESKD. Searches yielded 2,585 potentially relevant studies; applying the inclusion and exclusion criteria reduced this to 95 (published between 1988 and 2017 by authors from 17 countries). In total, 16 renal diagnoses and 52 biological factors were investigated. The 95 studies were grouped into 12 kidney disease themes.

Genetic polymorphism was the focus of most studies (93%), in particular variation in apolipoprotein L1 (APOL1), angiotensin converting enzyme (ACE), human leucocyte antigen (HLA), transforming growth factor-beta (TGFβ) and tumour necrosis factor-alpha (TNFα). Overall, there is good evidence for differences in biological factors underpinning some of the ethnic variation in incidence and progression of kidney disease. Many genes are likely to explain these differences and some genes are implicated in more than one kidney disease.

The diabetic nephropathy studies comprised 19 meta-analyses, nine case controls and one clinical trial. The primary outcome of 24 studies was the risk of developing diabetic nephropathy and 28 distinct biological factors were explored. Particularly strong evidence was reported for an association between the development of diabetic nephropathy and

polymorphisms in the renin-angiotensin-aldosterone system; lipid metabolism pathways; methylenetetrahydrofolate reductase; transcription factor 7-like 2; C-C chemokine receptor type 5; TNFα; engulfment and cell motility protein 1; and vascular endothelial growth factor.

The CKD and ESKD theme studies comprised 13 cohort studies, four case controls and three meta-analyses. The primary outcomes were risk of developing CKD, progression of CKD and risk of ESKD. Ethnic differences in APOL1 polymorphisms were the most frequently studied (six studies); other biological factors were those implicated in the renin-angiotensin-aldosterone system; lipid metabolism pathways; cell signalling; nephron number; myosin heavy chain 9; tumour protein p53; and HLA. Particularly strong evidence was reported for an association between variation in APOL1 and ACE in overall CKD risk and ethnic variation.

Across all 12 kidney disease themes, the most robust evidence was the association between APOL G1/2 alleles and kidney disease. As well as diabetic nephropathy and CKD/ESKD, APOL1 has been linked to lupus nephritis, outcomes in renal transplantation, idiopathic focal segmental glomerulosclerosis and human immunodeficiency virus (HIV) associated nephropathy. Further research should focus on the mechanisms of these interactions to identify potential targets for therapeutic intervention. The role of screening for recognised risk factors such as the APOL G1/2 alleles is not yet clear.

Further studies are required that directly compare populations of different ancestry rather than relying heavily on meta-analyses. In addition, there should be more research focusing on populations within less developed nations.

For further details and references see the full scoping review in Appendix 4.

4.3.2 Short summary of scoping review two: Why are people who are socially deprived more likely to develop CKD than those who are not?

Dr Michael Rees and Professor Alison Brettle

This scoping review examines the literature investigating links between social deprivation and the development of CKD. Searches yielded 6,208 potentially relevant studies; applying the inclusion and exclusion criteria reduced this to 34 (published between 2001 and 2017). The studies were grouped into four themes: (i) CKD in developing countries (14 studies); (ii) CKD globally (13 studies); (iii) CKD in the US (14 studies); and (iv) CKD in the UK (four studies). Some studies were included in more than one category.

Using various social deprivation markers, the four UK studies all identified an increased incidence of CKD among those who were socially deprived. Bello et al. (2008) also examined the link between socioeconomic status (SES) and late presentation. In their retrospective, cross-sectional analysis of 1,657 patients, they found that living in the lowest SES quintile area, compared with the highest, was associated with a greater risk for late presentation, after adjustment for sociodemographic, lifestyle and clinical variables.

Al-Qaoud et al. (2011) in a cross-sectional analysis of 5,533 participants from the Whitehall II cohort investigated the association between SES and decreased eGFR. They explored the role of obesity and metabolic syndrome, taking into consideration the potential confounding effect of lean muscle mass. They showed that individuals of lower SES were 31% more likely to have decreased eGFR and that SES disparity in lean muscle mass was evident in women, but not men. They concluded that body mass index (BMI) and components of metabolic syndrome may explain up to a quarter of the association between low SES and decreased eGFR.

Fraser et al. (2013) combined data from the Health Survey for England 2009 and 2010 to examine the relationships between SES and CKD and albuminuria in England. Prevalence of CKD 3–5 was 5.2% and albuminuria 8.0%. Age-sex adjusted CKD 3–5 prevalence was associated with lack of qualifications, low income and renting tenure. Only renting tenure remained significant in fully adjusted models suggesting that co-variables including ethnicity and lifestyle were on the causal pathway (i.e. that some of the effect of social deprivation is related to ethnicity and lifestyle). Higher albuminuria prevalence remained associated with low income, no vehicle, renting and most deprived area-level quintile after full adjustment, which could be suggestive of an independent mechanism for these key factors.

So et al. (2015) conducted an analysis of 54 primary care practices covering 313,639 adult patients in Scotland to examine the degree to which variation in CKD prevalence rates were explained by practice-level factors (SES, rurality and patients to GP ratio) and patient-level factors (age and sex). In total, 18,285 (5.8%) patients had CKD stages 3–5. Collectively, SES, rurality and patients to GP ratio predicted 39% of the variation; singly, SES exerted the most influence (25%).

There is clear evidence that those who are socially deprived – regardless of the measures used to ascertain social disadvantage – have higher rates of CKD. More research is needed to understand the underlying reasons and, more importantly, to propose interventions to attempt to reduce this disadvantage. While evidence from other migrant and indigenous populations in developed countries such as the US and Australia provides useful data, research that focuses on the issues faced by socially disadvantaged UK citizens is a priority.

For further details and references see the full scoping review in Appendix 5.

4.3.3 Short summary of scoping review three: Are people with CKD from ethnic minority groups more likely to experience faster progression and poorer outcomes than people with CKD from non-ethnic minority groups?

Dr Hilda Hounkpatin and Professor Alison Brettle

This scoping review provides an overview of the literature examining ethnic disparities in progression and outcomes of CKD. Searches yielded 8,059 potentially relevant studies; applying the inclusion and exclusion criteria reduced this to 75 (published between 1997 and 2017, the majority focused on a US population). The studies were split into four groups of outcomes: (i) CKD progression (42 studies); (ii) mortality (31 studies); (iii) non-mortality (15 studies); and (iv) experiences in treatment and care (eight studies). Some studies assessed more than one outcome.

The UK was the focus of just nine studies and comparisons were predominantly between Whites and Blacks, and Whites and South Asians. No UK study compared Whites to East Asians and most studies did not distinguish between ethnic subgroups, for example, African and Caribbean Blacks. Furthermore, most UK studies focused on CKD progression.

Seven of the 42 studies that examined ethnic disparities in CKD progression were of a UK population; findings were mixed. For example, a cross-sectional study of 49,209 adults reported that among people with hypertension and an eGFR <60ml/min/1.73m^2, South Asians had significantly greater risk of severe CKD compared to Whites. In contrast, a prospective cohort study of 329 diabetic CKD patients found no significant differences between South Asians, Whites and Blacks in annual decline in eGFR or progression to ESKD.

Two of the 31 studies that assessed ethnic differences in mortality for CKD patients were of a UK population. Again, findings were mixed. A prospective cohort study of 329 diabetic CKD patients found no significant differences in total mortality between South Asians, Whites and Blacks. In contrast, a prospective cohort study of 848 kidney patients reported that South Asians had a lower risk of mortality than Whites.

There were no UK studies that examined ethnic differences in outcomes other than CKD progression and mortality.

Two of the eight studies that investigated ethnic disparities in experiences in treatment and care for CKD patients used a UK population. A cross-sectional study of 49,209 adults reported a higher proportion of Blacks with an eGFR <60ml/min/1.73m^2 than Whites or South Asians were prescribed calcium channel blockers, thiazide diuretics, alpha and beta blockers and a lower proportion of Blacks than Whites were prescribed an ACE inhibitor or angiotensin receptor blocker. This is likely to reflect, at least in part, BAME-stratified guidance on management of hypertension (2).

This scoping review identified significant gaps in the UK evidence base. A systematic review (and meta-analysis where possible) that collates and critically analyses the nine studies may improve our understanding of ethnic differences in CKD progression and outcomes in the UK. Future studies should recruit people from the major ethnic groups and be adequately powered to detect significant differences across ethnic groups and should control for confounding variables.

For further details and references see the full scoping review in Appendix 6.

4.3.4 Short summary of scoping review four: Why do people with ESKD from ethnic minority groups experience poorer outcomes than people with ESKD from non-ethnic minority groups?

Emma Wilkinson and Professor Alison Brettle

This scoping review provides an overview of the literature examining ethnic disparities in outcomes of ESKD. Searches yielded 2,135 potentially relevant studies; applying the inclusion and exclusion criteria reduced this to 112 (published between 1993 and 2017). The studies were split into five themes: (i) reviews of the topic area (26 studies); (ii) disparities in access and treatment modalities (19 studies); (iii) disparities in care delivery and intermediate outcomes (35 studies); (iv) disparities in outcomes (29 studies); and (v) disparities in end of life care (three studies).

Although the UK leads the way in Europe in having a national registry which records and analyses outcomes by ethnic group, the majority of the evidence came from elsewhere, in particular the US and Australasia. The UK requires concerted evidence-based interventions or people from BAME groups will continue to experience inequalities in access to, and outcomes of, care for ESKD.

UK evidence across the five themes was patchy. Despite a study sample where acceptance rate to RRT for South Asian patients was nearly four times that of White patients, 31% of the former group compared to 19% of the latter group presented late to specialist kidney services. Furthermore, although South Asians gained access to the transplant waiting list at the same rate as Whites, 72% of the White patients received a transplant within three years compared to 55% of the South Asian patients.

In one UK study, quality of life on RRT was worse for South Asian patients compared to White patients; the difference was not improved by transplant. Another study found that non-White patients had a 45% lower chance of activation to the transplant waiting list compared with the White population, even after adjusting for comorbidity.

There is a reported paradox of greater survival of BAME groups on dialysis, which requires further investigation. While this could represent White patients being disadvantaged in some way on dialysis, it is likely to be at least in part explained by differences in CKD progression and access to transplant.

The following evidence gaps were identified:

i. Lack of theory in the literature and lack of UK related evidence
ii. Lack of UK evidence at all stages in the ESKD pathway. There is a heavy reliance on national routine datasets which does not include indicators for all elements of care, nor at an individual level
iii. Lack of studies investigating disparities at the end of the pathway, access to end of life care and experiences of dying with ESKD
iv. Although there were a number of reviews which discussed the different aspects of ethnic disparities, as for gap two, these relied heavily on primary studies that used national routine datasets, which provided limited information about how the different elements interacted
v. A lack of qualitative studies precludes a full understanding of the factors influencing disparities in outcomes
vi. Lack of comparative cross-cultural intervention studies specific to ESKD.

For further details and references see the full scoping review in Appendix 7.

4.4 Discussion

The scoping reviews in this report, and the prioritisation exercise that informed the choice of topics for the reviews, reflect the desire of the report's editorial board to take a systematic approach to tackling kidney health inequalities. In a similar way, the NIHR now requires all research grant applications to provide evidence of a systematic review demonstrating the current evidence base and need for the proposed research. It was not feasible to undertake full systematic reviews for this report, but it was considered essential to explore the current extent of the evidence base when deciding between further primary research or evidence synthesis or interventional studies for the research recommendations.

The four topics for the scoping reviews were based on the results of the prioritisation exercise (three of the topics), and the request from Kidney Research UK to include a review of the basic science literature in the area. Given the social, cultural and environmental basis for most health inequalities, it was initially envisaged that the scoping reviews would focus on the UK evidence base. The research questions were therefore kept fairly broad. The basic science review was the one exception to this, as it was felt likely that the basic science evidence was more likely to transfer across national borders. In the end, however, most of the reviews considered evidence from a wide range of low-middle and high-income countries, partly reflecting the paucity of UK evidence in some key areas. The UK evidence has been summarised above, but there is considerable detail in the full scoping reviews in the online appendices, for interested parties to read in full.

The scoping reviews were undertaken by health services researchers from a range of backgrounds, supervised by an experienced professor of health informatics. The researchers were recommended by experts in the field at the initial kidney health inequalities workshop and attended formal training in scoping review methodology which focused on the

reviews for this report. However, the scoping reviews have some limitations. There was insufficient time to screen reference lists within the included studies, hand search journals or search grey literature.

4.5 Summary

Considerable evidence has been identified by the scoping reviews to describe and begin to explain the inequalities that are observed in kidney health. The results of these reviews provided an up to date and objective resource for the experts who wrote the basic science (Chapter 5) and life course chapters (chapters 6–8) that follow. The guidance from the scoping reviewers has also informed the main recommendations of the report (Chapter 9). Finally, the scoping reviews should act as an invaluable resource for kidney health researchers considering next steps in tackling kidney health inequalities.

4.6 References

1. Arksey H, O'Malley L. Scoping studies: Towards a Methodological Framework. Int J Soc Res Methodol. 2005;8:19–32.

2. National Institute for Health and Clinical Excellence. Clinical guideline [CG127] Hypertension in adults: diagnosis and management. 2016.

Chapter 5 Basic science insights into the development of kidney disease

Professor Jeremy Hughes

Professor Neil Turner

5.1 Introduction

The scoping review of the published literature examined the influence of biological factors upon the incidence and progression of kidney disease in mainly non-UK populations, with diabetic nephropathy being most heavily studied (Appendix 4). The assembled evidence varied in quality and strength with many studies being meta-analyses of studies examining gene polymorphisms and the development or outcome of disease. These will be discussed together with other factors involved in health inequalities such as nephron number, age, sex, socioeconomic deprivation, and important disease comorbidities such as diabetes. Areas of basic science research that may lead to improved outcomes and reduced health inequality in kidney patients in the future are highlighted. Lastly, future generic and specific research priorities are considered.

5.2 Literature review

UK patients from Black and South Asian ethnic backgrounds were three to five times more likely to start dialysis than those from a White background (1, 2) and this is in accord with US data (3). Ethnic disparities in kidney outcomes are seen in many other countries, including Hispanics and First Nation individuals in the US. It is rarely clear how much of this imbalance is genetic versus social, environmental or behavioural in nature (4, 5). Worse outcomes are also associated with lower SES and lower educational attainment and these may compound racial and ethnic differences (6-9). Recent trends suggest that some differences in the US have reduced in recent decades, a rate of change that might suggest that environmental factors are likely to be important (Figure 5.1). For example, in some groups (Hispanic, American Indian/Alaska Native) a marked convergence with the US White rate has occurred in the last 15 years (Figure 5.1). This seems too fast for genetic explanations to be paramount, although this could have been blurred by definition changes – for example, in willingness of individuals to acknowledge ethnic background. However, it is notable that the increased rate of ESKD in Black individuals has not changed across the same period (Figure 5.1). This group has the strongest evidence for a primary genetic explanation. Note that the rate shown for White individuals is almost three times the typical rate for Whites in Northern Europe, including the UK.

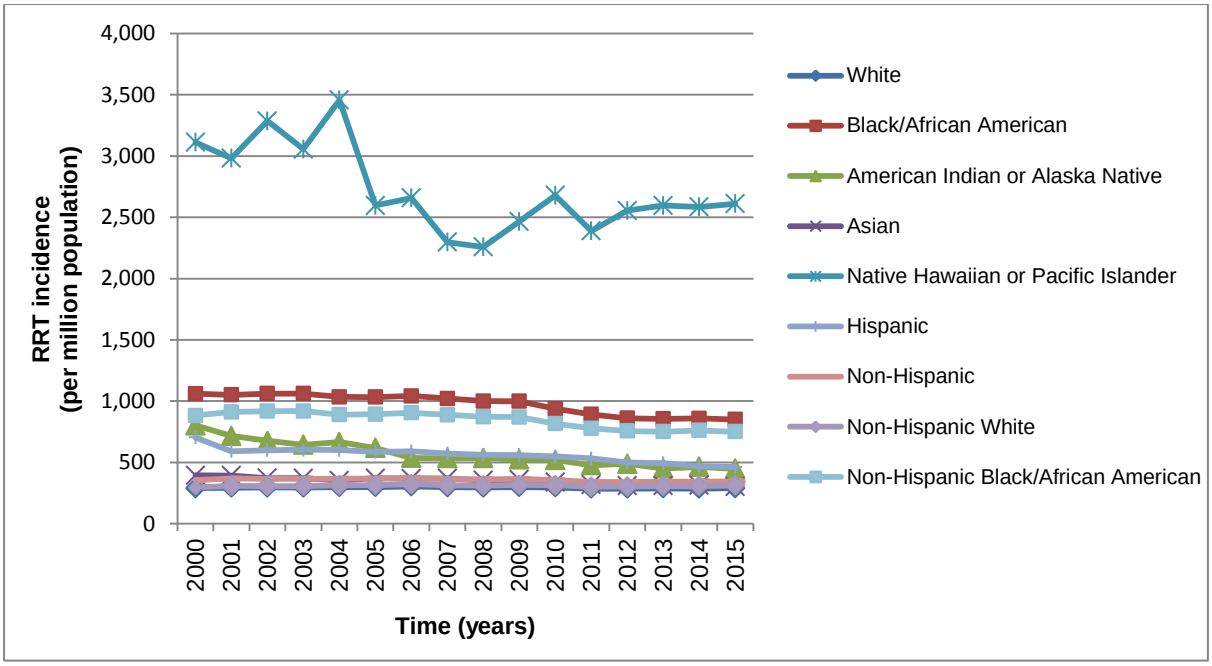

Figure 5.1 Trends in incidence of RRT over time by ethnic group. Data from the US Renal Data System show marked differences in the incidence of ESKD in different racial groups (USRDS 2017 Annual Data Report, https://www.usrds.org/adr.aspx)

5.2.1 Genetic predisposition to kidney disease

Many studies have examined predispositions to kidney diseases. If studies demonstrate associations between the frequency of genetic polymorphisms and disease incidence or severity, then this may provide insights into the underlying biological processes involved, if the function of the gene product is understood. Some studies may shed less light into disease pathogenesis or progression, but have some future utility in patient stratification to identify those at high risk of progression.

Single gene kidney disease

It is striking that most common single-gene diseases, such as polycystic kidney disease, are reasonably evenly distributed (10). Exceptions may be caused by founder effects in small, closed populations leading to locally high incidences of particular conditions (autosomal dominant or recessive); and by cousin marriage in some traditions which leads to increased incidence of autosomal recessive disorders.

Diseases with marked racial disparity with a genetic explanation

Many more common kidney diseases have evidence for a genetic contribution, but there is hard evidence for a role for particular genes in only a few. The strongest is for the gene APOL1 predisposing to disease including HIV nephropathy, primary focal segmental glomerulosclerosis and hypertensive ESKD. APOL1 is the gene encoding apolipoprotein L1 in humans and some primates, and US studies indicate that two common variants in APOL1 (termed G1 and G2) are associated with non-diabetic kidney disease in African Americans (APOL1 nephropathy). An APOL1 polymorphism has been shown to be responsible for

much of the increased susceptibility of Black African-origin individuals to focal segmental glomerulosclerosis, for the unique susceptibility of this racial group to classic HIV nephropathy, and for much of the excess risk of renal disease attributed to 'hypertension', or of unknown origin, in Black Americans (11). Patients with two copies of the APOL1 disease variants have a higher risk of developing proteinuria and a more rapid deterioration in eGFR to ESKD (12-14). The restriction of these mutations to African-origin DNA is explained by positive selection for them, because in endemic areas they give greater resistance to trypanosomiasis.

Recent seminal work adopted a 'bedside-to-bench' approach with the aim of understanding how APOL1 disease variants lead to disease. Beckerman and colleagues generated transgenic mice with podocyte specific expression of the human normal APOL1 gene or APOL1 disease variants (15, 16). Podocyte expression of the APOL1 disease variants resulted in proteinuria, renal impairment, podocyte effacement, glomerulosclerosis and podocyte death indicating direct pathogenic causality. Defects in podocyte endosomal trafficking and autophagy were noted (15) with separate studies demonstrating abnormal podocyte vesicle trafficking (17) suggesting a potential pathogenic mechanism for the cytotoxic effects upon podocytes. This murine model and cultured podocytes expressing APOL1 disease variants represent tools to determine the effect of either novel compounds or known drugs upon podocyte biology, structure and function thereby setting the scene for future clinical trials in affected patients (18).

Important diseases with marked racial disparity without an adequate genetic explanation

The discovery of APOL1 disease variants is unusual. Other diseases with marked racial imbalances have not so far found such straightforward explanations. In the UK, diabetic nephropathy in South Asians is particularly prominent. Much work has examined the potential role of genetic polymorphisms in the development of diabetic nephropathy in different ethnic populations. These include polymorphisms related to the renin angiotensin system, endothelial nitric oxide synthase, lipid metabolism pathways, mediators of inflammation and fibrosis and other potential pathogenic pathways (Appendix 4). The lack of any clear and robust genetic influence on the predisposition to diabetic nephropathy in South Asians and other BAME populations may result from the involvement of multiple genes, or it may reflect that various environmental factors exert a more important impact.

There are other important examples. Interstitial nephritis of unknown cause in South Asians in the UK (19, 20) may not be homogeneous, as interstitial nephritis has many aetiologies besides genetic causes, including infections and toxins. Immunoglobulin A nephropathy is common in White populations, but rare in patients of African origin. Geographically it shows a distribution of increasing occurrence as you travel north or east from Africa (Figure 5.2). Genetics appear to explain only a small part of this variation.

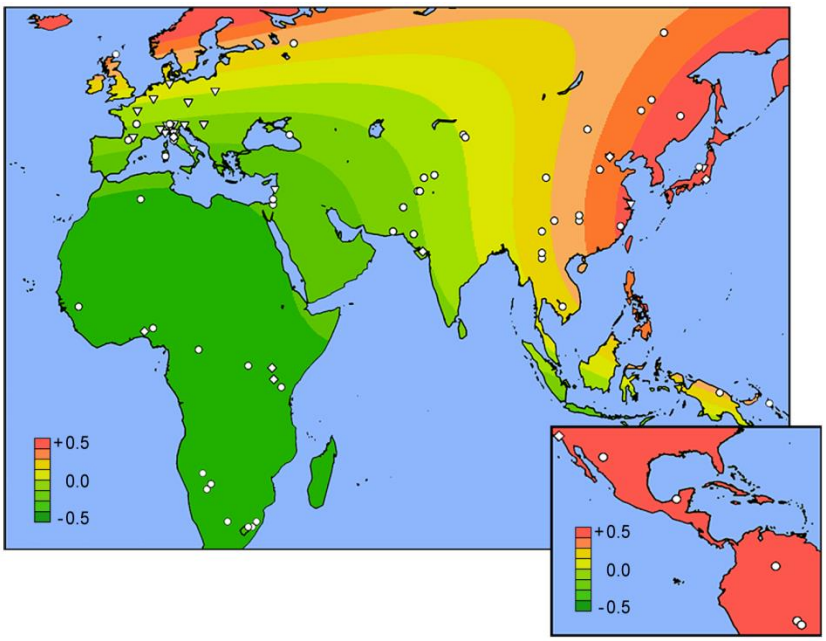

Figure 5.2 Worldwide geospatial risk of immunoglobulin A nephropathy. Surface interpolation of the standardised risk score over Africa and Euroasia (main) and Americas (inset). Symbols represent the locations of sampled populations from the publicly available Human Genome Diversity Panel (circles) and International Haplotype Map-III Project (diamonds) and from healthy controls (triangles) sampled by Kiryluk et al. (21)

Diseases where there is partial understanding of genetic susceptibility

In some autoimmune conditions there is wide racial variation in incidence, with clear evidence of genetic influence. For example, lupus has around 50 genes implicated in susceptibility. However, they explain only 20% or so of susceptibility in individuals and it is not clear how much of the international/racial variation this can account for.

Progression of CKD to ESKD

Although studies have examined the effect of ethnicity upon the rate of progression of CKD (22, 23), the numbers of patients included is often small and there are relatively few studies of UK populations. Apart from the adverse impact of APOL1 polymorphisms upon podocytes, there is relatively weak evidence for a strong role of other specific genetic influences in susceptibility to, or progression of, CKD.

Future directions

An important research question is whether there are further genetic explanations for the ethnic disparities we see in kidney disease. Studies require sufficient numbers of well phenotyped subjects and use of the optimal genetic analysis platform (e.g. whole genome sequencing) appropriate to the BAME population studied to ensure adequate power to definitively detect or refute significant genetic effects upon disease incidence or outcome. An example of the benefits of adopting this approach is the LOLIPOP study based in West London and established in 2002. This population based prospective study of over 30,000 individuals is focused upon cardiac disease, stroke, obesity and diabetes and includes many

South Asians. Participants underwent a detailed baseline assessment with biobanking of blood samples and long term follow up. The LOLIPOP study has provided important insights into genetic loci that influence renal function and CKD (24) and contributed to the study of combined populations by genetic consortia and networks that have examined aspects of ethnicity and CKD (25). These studies typically highlight multiple genes that, unlike APOL1 disease variants, have less utility for the design of novel therapeutics.

It is striking that a large number of genetic studies have now failed to identify factors that account for the variability in ESKD between populations. The unexpected discovery of APOL1 disease variants, using an innovative 'admixture' analysis technique aimed at identifying striking differences between races, proves that we do not necessarily have the final answer. However, the chances of more such transformational discoveries being made look lower as each year goes by.

Epigenetic changes, rather than direct alteration in DNA sequence, may also play an important role in the predisposition and modulation of kidney disease and this less well studied area merits future investigation (26). MicroRNAs also represent an additional layer of post-transcriptional regulation because they are capable of suppressing the translation of multiple messenger RNA species. Emerging evidence suggests involvement of microRNAs in kidney disease such as diabetic nephropathy (26, 27), but it is unclear whether there may be differences in microRNA expression between BAME groups.

5.2.2 Ageing and cell senescence

Although increasing age is often associated with comorbidities such as hypertension, the age of an individual has an impact upon the prevalence of CKD, the risk of developing AKI as well as the extent of subsequent recovery (28, 29). Birth cohort studies indicate that the biological and chronological age of individuals diverge even in young adults. A study using the 10-biomarker US National Health and Nutrition Survey-based measure of 'biological age' found that the biological age of ~1000 individuals aged 38 years ranged from 28 to 61 years (30). SES and educational attainment are associated with leukocyte telomere shortening, a marker of cellular ageing (31, 32). Senescent cells accumulate in various organs including the kidney with age and in CKD and are pro-inflammatory and pro-fibrotic (28, 33). Senescent cell deletion is beneficial in accelerated models of ageing in mice (34) and, although there are no kidney data available, there is significant interest in developing novel strategies including drugs to limit adverse biological ageing by inducing senescent cell death (35). Thus, multiple factors impact upon the biological age of the kidneys including chronological age, CKD, comorbidities as well as socioeconomic factors.

5.2.3 Sex

The increased prevalence of CKD in women, but preponderance of males reaching ESKD and commencing dialysis has been identified in every continent despite women having 12% fewer nephrons on average (36). It has not been explained why men are more severely affected than women and this remains an important question that merits research (37). Male preponderance to kidney disease is also seen in animal models (38) and, although sex

hormones and cytokines such as TGFβ and TNFα have been implicated, further study is required (39, 40).

5.2.4 Environmental factors

Relevant environmental influences that may differ between BAME populations are listed in Table 5.1. Examples that may operate in the UK include tuberculosis, which is more common in first and second generation immigrants from South Asia and has been thought to be responsible for some renal disease. It is unproven that it is a numerically important factor. HIV infection is more common in immigrants from Africa. Exposure to toxins, e.g. herbal products, cosmetics and food toxins could play a role. Nutritional factors may be important. For example, the content of salt, protein and calories relative to energy expenditure is variable and there may be unknown effects of nutrients and vitamins on progression of, or complications from, CKD. Diet and disease may affect the microbiota and there is increasing evidence that changes in the microbiome may be associated with CKD progression and cardiovascular risk (41-43). Suggested mechanisms include the generation of toxins within the gut that may gain access to the circulation secondary to abnormal intestinal permeability thereby predisposing to a pro-inflammatory 'endotoxaemia' (44). Also, dietary phosphate and red meat intake has been linked to accelerated biological ageing (31). Social deprivation and poverty is associated with stress, lower engagement with healthcare and important comorbidities such as obesity and type 2 diabetes (45).

Table 5.1 Environmental factors that may affect kidney function

Environmental factors that may affect kidney function
Intrauterine environment (nephron number)
Consequence of direct infection (e.g. tuberculosis)
Remote infection (e.g. HIV)
Toxins – herbal medicines or in food, other exposure
Nutritional factors
Alteration of the microbiome in CKD, obesity, diabetes, etc.
Extremes of environmental conditions
Availability of or engagement with healthcare

5.2.5 Renal size and nephron endowment

The Barker foetal origins of adult disease hypothesis states that foetal development and subsequent birth weight can have a significant impact on disease in adulthood. Associations have been demonstrated for hypertension, CVD, diabetes and CKD (46, 47). Although the average number of nephrons is ~10^6 per kidney it can vary 10-fold between individuals; from 2×10^5 to 2.5×10^6 nephrons (48). Low birth weight is associated with reduced renal size and lower nephron number, with reduced birth weight being a recognised surrogate for reduced nephron number (36). Reduced birth weight is more common in South Asians and Blacks in the UK with socioeconomic, maternal and infant factors involved (49). Also, reduced birth weight in South Asians in Bradford was associated with a 16% reduction in mean kidney volume even after adjustment for potential confounders (50). It is thus pertinent

that there is a significant association between low birth weight and CKD and ESKD with a higher risk found in South Asians and Black Americans (51-53). Autopsy studies of individuals with a sudden or unexpected death have been informative. For example, Aboriginal Australians, who exhibit reduced average birth weights, had 30% fewer glomeruli compared to non-Aboriginal Australians with compensatory glomerular hypertrophy (51). Furthermore, Aboriginal Australians with a history of hypertension had 30% fewer nephrons than Aboriginal Australians without a history of hypertension. In contrast, similar autopsy studies revealed no differences in mean nephron number or glomerular volume between African American and White individuals, with nephron number being strongly related to birth weight (52). Thus, nephron endowment is complex and may be related to ethnicity, SES, the intrauterine environment, foetal development and birth weight.

Other factors that may affect renal size include maternal age (<16 years and >35 years) and maternal nutrition during pregnancy. Low nephron number associated with glomerular hypertrophy may predispose to glomerular hyperperfusion and hyperfiltration and the development of CKD, though there are other possible mechanisms. A reduced nephron number would be predicted to increase the rate of progression of CKD in the context of any kidney disease and a key research question is whether nephron number at birth can be increased in humans because this may confer long term protection.

Nephron endowment can be manipulated experimentally and maternal protein restriction or glucocorticoid treatment in mice reduces nephron endowment in offspring by ~20% (54, 55), whilst a high fat diet can increase nephron number (56). In contrast, the kidneys of TGF-β2 heterozygote mice exhibit increased ureteric branching, 30–60% more nephrons than control mice and protection from the hypertensive effect of a chronic high salt diet (57, 58).

Magnetic resonance imaging using cationised ferritin can quantify the number and size of glomeruli in rat kidneys in vivo (59) and murine and human kidneys ex vivo (60, 61). Studies in ageing mice with reduced renal function show a reduction in glomerular number and increased glomerular volume (62).

5.2.6 Progression of CKD

The observation that CKD populations resemble ESKD populations poorly is important. The most glaring example of this is the reversed gender balance in CKD and ESKD populations, but a similar picture can be seen for BAME group distribution. The logical explanation for this is that the key differences between more and less susceptible groups is not the incidence of the primary diseases, but the rate of progression to ESKD. There are now many confirmations that rate of progression of CKD is higher in those more represented in ESKD populations. To make a difference to inequalities in ESKD, it therefore becomes paramount to better understand what influences the rate of progression.

Experimental and human data indicate that myriad cellular and molecular factors play a role in the progression of CKD towards ESKD irrespective of the aetiology of the primary disease and these are beyond the scope of this chapter. However, albuminuria and proteinuria remain biologically relevant and clinically useful prognostic markers of progressive CKD. A

recent study of a translationally relevant rat model of diabetic nephropathy highlighted reduced tissue expression and urinary levels of epidermal growth factor (EGF) (63). In humans, reduced urinary EGF was associated with the development of CKD in patients with diabetes (63) and was an independent risk factor of diabetic and non-diabetic CKD progression (64). Indeed, the urinary EGF/creatinine ratio correlated with interstitial fibrosis and tubular atrophy (64). These data suggest that urinary EGF may be a useful indicator of 'renal tubular reserve'.

5.2.7 Acute kidney injury

Individuals with AKI differ across the globe with patients from low income countries being younger and having fewer comorbidities including CKD than patients from higher income countries (65). CKD is a risk factor for AKI, with increased AKI also associated with age, male gender and ethnicity in some studies (66, 67). Black ethnicity is a risk factor for AKI in hospitalised diabetic patients (68), whilst SES may also be an important determinant (69).

Although there is much interest in urinary biomarkers that are elevated in AKI such as kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin, there is no established urinary biomarker for the risk of developing AKI except proteinuria (70). Recent work suggests that a low urinary EGF level is a predictor of AKI in pre-term infants (71).

5.3 Future directions for research

All renal research that allows earlier detection or amelioration of kidney disease caused by diabetes, obesity, hypertension and vascular disease could be used to target and reduce health inequalities in BAME populations. However, although ambitious in scope, we suggest some particular areas of research and development that might impact upon inequalities in the future.

5.3.1 Birth weight, renal size and nephron endowment

Birth weight, renal size and nephron number have a powerful influence on lifetime risk of CKD as well as other cardiovascular outcomes. Environmental, particularly maternal factors (nutrition, age, smoking, etc.) have been strongly associated with reduced nephron number and, since low birth weight is a clinical surrogate for reduced kidney size and nephron number, consideration should be given to adopting some of the recommendations from a recent consensus document for both high risk mothers and affected infants (36). This will require discussions with other specialities including obstetrics and paediatrics. It is likely that interventions to increase nephron number, or mitigate the consequences of low nephron number, have the potential to improve outcomes.

Possible research areas and studies:

i. Imaging: facilitate development of robust in vivo ultrasound or magnetic resonance imaging to determine renal size and volume and estimate glomerular number and volume in high risk individuals

ii. Biomarker: explore utility of biomarkers of ‘renal tubular reserve’ such as the urinary EGF/creatinine ratio in BAME populations and determine relationship of urinary EGF/creatinine to birth weight, renal size/volume and eGFR in cross-sectional and longitudinal cohort studies (e.g. ‘Born in Bradford’ study)
iii. Nephron number: explore experimentally whether nephron number can be increased as this may offer long term protection, e.g. using limited antagonism of TGF-β2 signalling in early kidney development to increase ureteric branching (57). Murine kidney development could be used with quantification of glomerular number whilst renal organoids derived from human induced pluripotent stem cells provide a human system for experimentation (72)
iv. Human studies: based on experimental studies (54, 56), it may be feasible to explore whether nutritional interventions providing increased protein or energy (fat) can increase birth weight and renal size of infants of ‘high risk’ mothers in ethnic BAME populations
v. Renoprotection of low birth weight individuals: explore whether preventive measures (e.g. ACE inhibitor treatment) can reduce the long term risk of individuals with a reduced birth weight and renal size (surrogate for low nephron number) or a reduced urinary EGF/creatinine ratio.

5.3.2 Progression of CKD and risk of AKI

We have clinical markers for risk of progression (most strikingly proteinuria, blood pressure, eGFR), but these are all seen late in the day. Three demographic factors have a major influence on the incidence of ESKD – age, sex and birth weight. Age, in particular, has effects that are similar to those of ethnic predisposition to ESKD. It seems likely that the mechanisms of these may overlap with progression mechanisms in ethnically predisposed groups. Further effort to understand the impact of biological ageing, and perhaps also sex, on progression of renal disease, may cast light on the poor renal outcomes of disadvantaged groups.

Possible research areas and studies:

i. Epidemiological: explore whether age-adjusted ESKD rates of ethnic groups in the UK is changing, as seen in the US Renal Data System (Figure 5.1)
ii. Biological ageing: explore the range of cellular age-related changes in the leukocytes (telomere shortening) and kidneys (cell senescence) of normal/predisposed individuals from different BAME groups
iii. Whole organism ageing: use translationally relevant experimental models of CKD and AKI in aged rodents to define potential therapeutic targets. Assess effects of interventions to limit AKI or CKD progression (e.g. manipulate the burden of senescent cells in normal/injured kidneys). These studies could also assess the utility of biomarkers (e.g. urinary EGF/creatinine ratio) and imaging (e.g. magnetic resonance imaging) as these may translate to human studies

iv. Human studies: explore the utility of using biomarkers such as urinary EGF/creatinine ratio to stratify patients at high risk of progression of CKD or the development of AKI to enable treatment optimisation.

5.3.3 Cohort and biobank studies

While genetic analysis has not been very productive, the same cohorts may be useful to study environmental factors or markers of risk. Beyond genetic testing, setting up such cohorts is costly. Rather than setting up new cohorts, the best places to start may be to study existing collections, suited to different ends. Some biobanks have the potential disadvantage of recruiting patients quite late in life if we think the foundations of risk are set very early in life (e.g. recruitment at age 40–69 years for the 500,000 individuals in the UK Biobank). Bespoke biobanks typically have the potential for extensive sampling and phenotyping information, for example, the 'National Unified Renal Translational Research Enterprise' (NURTuRE) study, which opened in the UK in 2017, aims to collect detailed baseline data as well as blood, urine and renal biopsy tissue in 3,000 people with CKD. Disease in patients of different ethnicities may be explored including studies examining the interaction and associations of genetic profiling, transcriptomic studies of renal tissue (e.g. whole cortex, laser captured glomeruli or tubules), proteomic analyses (e.g. plasma, urine), novel biomarker (e.g. extracellular vesicles, microRNA) and clinical phenotypic data (e.g. nature of disease, rate of progression, etc).

5.4 Summary

The increased level of AKI and CKD in BAME populations is multifactorial (Figure 5.3). There are some biological drivers including genetics (APOL1 gene variants) and nephron endowment at birth, factors that affect non-BAME populations such as ageing and sex and an increased prevalence of important comorbidities such as diabetes. The effect of SES adds an additional layer of complexity which may also have a biological component (e.g. stress, altered gut microbiome). We suggest that current and further in vitro and in vivo research in the areas of developmental kidney biology, kidney imaging, the biology of ageing and biomarkers of kidney tubule health/number in both rodents and humans will suggest novel strategies to reduce health inequalities in the future.

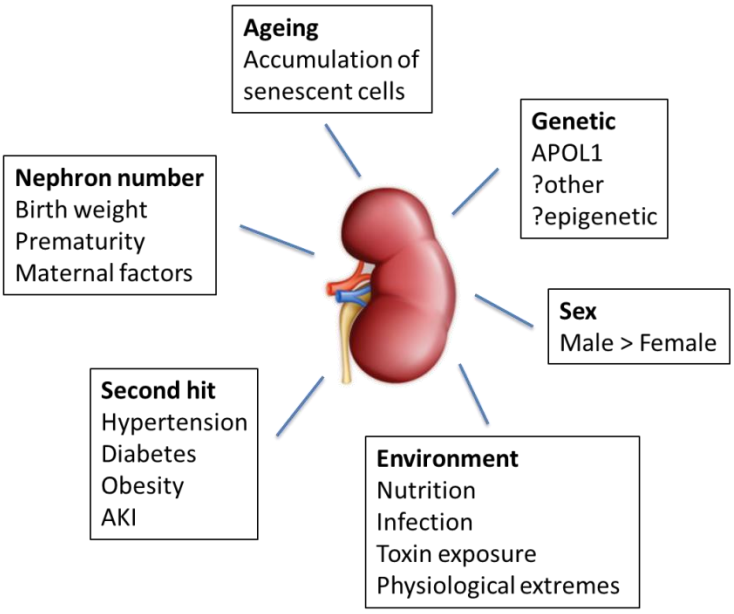

Figure 5.3 Interacting factors contributing to increased risk of CKD

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Chapter 6 Development of AKI and CKD

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6.1 Introduction

Factors that increase the risk of developing CKD and AKI are numerous, prevalent and potentially modifiable. This chapter discusses the most prevalent and modifiable risk factors (high BMI, smoking, hypertension, CVD, diabetes) and the most commonly considered (and measurable) dimensions of inequality (age, sex, SES, ethnicity) (1-7). Other less commonly considered risk factors (ante-natal aspects, low birth weight) and dimensions (such as geographical location and health literacy) will be addressed where possible, though information is limited. We consider CKD and AKI separately, while remembering their inter-relation. Kidney health and disease are not two ends of a single condition. A heterogeneous set of conditions can lead to a measureable reduction in kidney function. A person may have a single cause, multiple causes, or no identifiable cause for reduced kidney function. Each underlying cause of 'disease' may have distinct or overlapping risk factors.

6.2 Literature review

The UK population has a complex, unequal and often inequitable distribution of risk factors across the life course and across CKD disease pathways. This is illustrated, by way of example, for people of differing SES in Figure 6.1. Some risk factors have influence through more than one pathway. For example, obesity may increase CKD risk both directly and indirectly by increasing the risk of diabetes and hypertension (4, 8). Similarly, smoking promotes atherogenesis (and therefore indirectly CKD), but there is also evidence that nicotine causes direct nephrotoxic effects (3, 9-13).

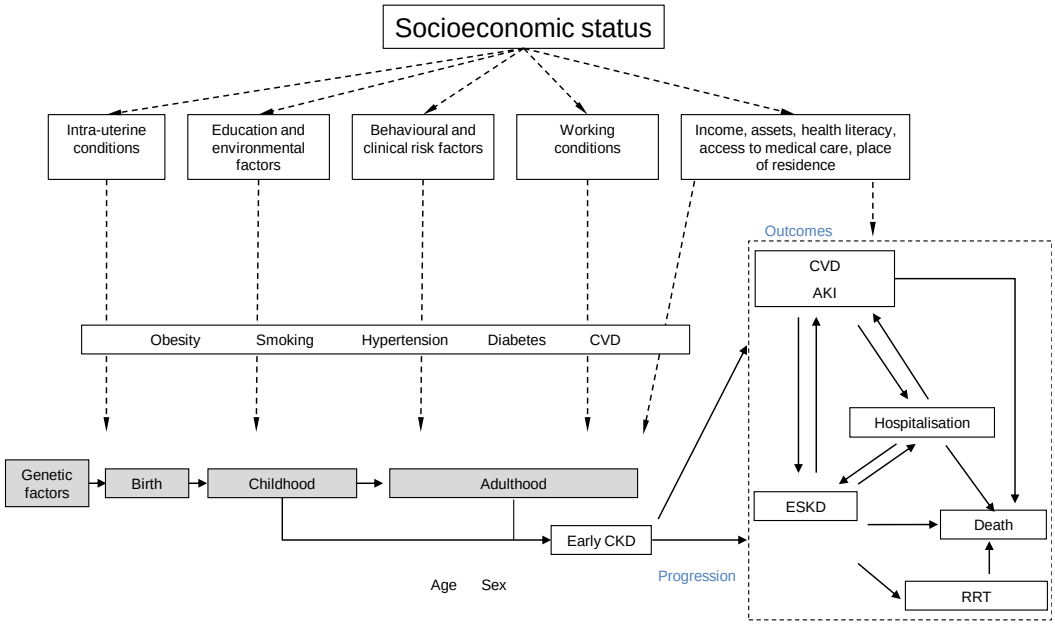

Figure 6.1 Some factors along the CKD pathway influenced by SES

6.2.1 Patient level risk factors

This section focuses mainly on the most common, potentially modifiable risk factors for developing CKD – high BMI, smoking, hypertension, CVD and diabetes.

Early life influences on CKD risk

Genetic and epigenetic factors influence the risk of developing CKD (14). In addition, low birth weight is associated with greater risk of later development of ESKD, possibly linked to lower number of nephrons (increasing the risk of later hypertension) (15, 16). Low birth weight is also closely associated with lower SES in the UK (17, 18) and with very young or older mothers (19). High birth weight and infant adiposity are linked to increased risk of childhood obesity and later type 2 diabetes (20, 21).

Age

Data from the nationally representative Health Survey for England and the National Diabetes Audit show that overweight and obesity, type 2 diabetes, hypertension and CVD all increase in prevalence with age, though the prevalence of diabetes and obesity tail off in people over 65 years (22-26). Mean systolic blood pressure increases into older age in the general population, while mean diastolic has a peak in middle age (24, 25). Type 1 diabetes prevalence is highest in middle age (23).

Sex

Prevalence of being overweight (but not obese) is higher in men, with obesity prevalence similar between the sexes and very high waist circumference more common among women (22). Diabetes (both type 1 and type 2), smoking, CVD and hypertension have higher prevalence in men (23-25, 27-29).

Socioeconomic status

Low birth weight, obesity, type 2 diabetes, hypertension, smoking, lower physical activity, and CVD all have higher prevalence and cluster in lower socioeconomic groups (23-27, 30-33). Very little variation by SES is seen in type 1 diabetes (34). Dietary quality, known to be poorer in lower socioeconomic groups, has been associated with incident CKD and is a key driver of obesity, hypertension and type 2 diabetes (35-37). Exposure to greater environmental toxins, including nephrotoxins, is associated with lower SES (38). Limited health literacy (defined as ‘people’s knowledge, motivation and competences to access, understand, appraise and apply health information’) is prevalent in people with CKD and associated with lower SES, although its role on the pathway from risk factors to CKD outcomes is yet to be mapped in full (39, 40).

Ethnicity

Assessment of CKD risk factor variations by ethnicity is challenging due to varying definitions and lack of current available data. Obesity prevalence is highest in Black and Pakistani women, though calculation of diabetes risk applying alternative BMI thresholds for BAME groups has identified Black and South Asian men and women at greatest risk, despite

South Asian men having the lowest mean BMI (41, 42). Type 2 diabetes prevalence is higher in Blacks and South Asians (42). Smoking prevalence has been observed as highest in Bangladeshi and Irish men, although this has not been recently assessed in population-representative surveys, and lowest in most female groups (43). Prevalence of hypertension has been shown to be higher in Black Caribbean and South Asian than White populations (44, 45). CVD prevalence is higher in South Asian-Bangladeshis, -Indians and -Pakistanis (45). Low birth weight is more prevalent among BAME groups (46). These are summarised in Table 6.1.

Table 6.1 Summary of the distribution of risk factors for CKD

Risk factor	Age	Sex	SES	Ethnicity
Low birth weight	Increased risk for mothers aged <16 or ≥35 years	Slight increased risk if female infant	Higher prevalence among people of lower SES	BAME infants more likely to be low birth weight
Overweight and obesity	Increase with age. Prevalence tails off in older people	Prevalence of overweight (but not obese) higher in men. Obesity prevalence similar between sexes. Very high waist circumference more common in women	Higher prevalence among people of lower SES	Obesity prevalence highest in Black and Pakistani women
Smoking	Higher prevalence of 'current smokers' among people aged 16–34 years	Higher prevalence in men	Higher prevalence among people of lower SES	Smoking prevalence high in Bangladeshi and Irish men
Type 1 diabetes	Highest prevalence in middle age	Higher prevalence in men	Very little variation by SES	Evidence for UK unclear
Type 2 diabetes	Increase with age. Prevalence tails off in older people	Higher prevalence in men	Higher prevalence among people of lower SES and greater risk of late diagnosis and poor control	Black and South Asian men and women at greatest risk
Hypertension	Increase with age. Mean systolic blood pressure increases into older age. Mean diastolic has a peak in middle age	Higher prevalence in men	Higher prevalence among people of lower SES and greater risk of late diagnosis and poor control	Higher prevalence in Black Caribbean and South Asian populations
CVD	Increase with age	Higher prevalence in men	Higher prevalence among people of lower SES and greater risk of late diagnosis and poor control	Prevalence higher in BAME

Other chronic disease

Primary renal disease

There is little evidence relating to socioeconomic or ethnic variation in the incidence of major primary renal diseases in the UK (glomerulonephritis, pyelonephritis, polycystic kidney disease), although evidence exists of disparity globally (47).

Liver disease/alcohol

There is a strong social gradient and evidence of SES as an effect modifier in alcohol-related morbidity and mortality, though there is a complex picture of consumption patterns and outcomes (48, 49). Severe non-alcoholic fatty liver disease is increasing in the UK and shares risk factors with CKD (obesity, diabetes). Its interaction with CKD is not well studied.

Cancer

Full exploration is beyond the remit of this chapter, but well documented inequalities exist in cancers with important issues such as reduced awareness of (or engagement with) cancer symptoms in lower socioeconomic and BAME groups (50, 51). There is also a clear link with inequalities in tobacco consumption (27). Diet and obesity are linked to higher risk of several cancers (52). Important unanswered questions remain about interactions between a variety of cancer types, their therapy, and risk of both CKD and AKI.

Chronic urological tract obstruction

A clear age and sex association exists with benign prostate enlargement and lower urinary tract symptoms (53). Little other information is available on sociodemographic variation in conditions causing chronic urological tract obstruction.

Renal artery stenosis

This is most often caused by atherosclerosis, so the population distribution largely reflects other vascular conditions (particularly peripheral arterial disease) and smoking behaviour.

Myeloma

Myeloma is more common in older people. There is no evidence of gender or socioeconomic inequality in incidence (51). Black males have higher myeloma risk in the UK (54).

Rate of CKD in different at risk populations

The prevalence of CKD depends on how it is defined and measured. In the UK, data from the Health Survey for England has identified a prevalence of CKD stages 3–5 of 5.2% in 2009/10 (based on a single creatinine sample using the CKD-Epidemiology Collaboration serum creatinine formula). For eGFR <45ml/min/1.73m^2 (corresponding with stages 3b–5), prevalence was 1.4% (55). Prevalence of CKD 3–5 (using either Modification of Diet in Renal Disease or CKD-Epidemiology Collaboration serum creatinine equations to define eGFR) increases markedly with age and there is higher prevalence in women (56). There is a paradox of greater CKD prevalence among women, but greater RRT incidence among men (57). Recent evidence suggests that the overall prevalence of CKD may have fallen

between 2003 and 2009/10 despite rising obesity and diabetes in this period, although this trend needs to be confirmed in future Health Surveys for England (55). There is evidence of higher prevalence in lower socioeconomic groups and higher prevalence of advanced (but not stage 3) CKD in South Asians (44, 58-60).

Modelling the geographical distribution of absolute levels of CKD 3–5 in England suggests a close link with the age distribution of the population, with highest prevalence in the north and along southern and eastern coastal regions, whereas age standardised rates show greater association with the distribution of poverty (61). This distribution differs from the distribution of diagnosed CKD in the GP Quality and Outcomes Framework, though there is recognised under-coding of CKD in practice (62). There are also challenges of measuring and interpreting renal function in different ethnic groups. Adjustment of creatinine-based estimating equations for eGFR should be undertaken for Blacks, while cystatin C is less affected by muscle mass (63, 64). There is limited information on the performance of eGFR formulae in South Asian populations (65).

Risk factors for developing AKI

In considering variation in risk factors for AKI, it should be remembered that, as with CKD, not all AKI is the same phenotypically. AKI incidence may be similarly influenced by the distribution of risk factors shared with CKD (and their clustering) such as diabetes, smoking, obesity hypertension, CVD and heart failure (and by CKD itself), though evidence is not as well established.

Age, sex, ethnicity and SES

Direct triggers to AKI may vary by age, sex, SES and ethnicity, such as risk of major trauma, sepsis and major surgery. Older age is associated with greater AKI risk, but is also linked to other contributory factors such as multimorbidity, greater risk of hospitalisation, need for surgery, sepsis and use of nephrotoxins (such as non-steroidal anti-inflammatory drugs and possibly proton pump inhibitors) (66-68).

Males and people with hypertension were at greater risk in one UK cohort study among older people, although there was a slight female predominance among people with community-acquired, not-admitted AKI in a large Scottish study (69, 70). There is little evidence of ethnic variation in AKI risk in the UK for hospitalised AKI, although US studies have shown that Black patients may be at greater risk (71, 72). Socioeconomic and ethnic variation in shared risk factors for CKD (hypertension, diabetes, smoking, CVD and obesity) are likely to have a similar impact on inequalities in the distribution of AKI incidence, though specific evidence of the link is currently lacking with regard to AKI.

Nephrotoxicity

Many drugs are known to have nephrotoxic effects and a full exploration of the renal risks of all medications and their interactions is beyond the scope of this chapter. It is important to consider the poorly understood influence of increasing multimorbidity and polypharmacy, which have evidence of variation by SES. Prospective studies investigating nephrotoxicity incidence and associations are sparse. Studies that have attempted to describe the

epidemiology of AKI risk by drug and associated patient/disease characteristics are helpfully summarised by Awdishu et al. (78). They include aminoglycosides (age, diabetes, CKD, sepsis), aciclovir (older children, obesity, CKD), calcineurin inhibitors (genetic variations), cisplatin (age, African Americans, CKD), colistin (age, obesity), ifosfamide (age, CKD, nephrectomy), lithium (CKD), protease inhibitors, proton pump inhibitors (age), trimethoprim (diabetes, hypertension, CKD), tenofovir, vancomycin (age, obesity, sepsis, CKD, active cancer) and vascular endothelial growth factor inhibitors (78). There is, however, little published information on sociodemographic variation in drug prescription, consumption or nephrotoxicity.

Heart failure

Heart failure is a particularly important risk factor for AKI. There is evidence of socioeconomic inequality in heart failure, but also that targeted efforts are reducing inequalities in aspects of care, such as uptake of appropriate therapies (77).

Rate of AKI in different at risk populations

A large prospective cohort study in Wales showed higher incidence in the most deprived percentile using the Welsh Index of Multiple Deprivation (incidence approximately double that in lowest percentile) (73). Further research is needed to clarify the relationship between AKI and SES, for example in variation by community or hospital-acquired AKI.

Many studies have shown increasing AKI incidence with increasing age (66). Acute tubular necrosis, the commonest cause of intrinsic renal AKI is common in severe illness (66). Children at greater risk of AKI include: those with nephro-urological, cardiac or liver disease, malignancy and/or a bone marrow transplant; those dependent on others for access to fluids; and those whose medication may adversely affect renal function (renin-angiotensin-aldosterone system inhibitors, non-steroidal anti-inflammatory drugs, aminoglycosides, calcineurin inhibitors) (74-76). Children are also at risk in the context of sepsis, hypoperfusion/dehydration and major surgery. Neonates are at higher risk (74-76).

In terms of geographical variation, evidence from linked database studies using consistent methodology suggests that AKI incidence is remarkably similar across UK regions, with consistent increased incidence in older people (Sawhney et al. submitted).

6.2.2 Access to care as a risk factor for developing AKI/CKD

Access to care issues apply not only to CKD, but to the detection and management of predisposing and risk factors such as diabetes and hypertension. Full exploration of variation in this for each condition by age, sex, SES and ethnicity is beyond the scope of this chapter but may drive variation and inequity in CKD.

Chronic kidney disease

Diagnosing CKD in clinical practice can be challenging. There are issues of identifying chronicity, detecting proteinuria and timely and appropriate ordering of investigations. There is some evidence of socioeconomic inequity in CKD diagnosis in UK primary care, issues

around disclosure to patients and divided clinician opinion on the appropriateness of making and communicating a CKD diagnosis, particularly for older people (79-82).

There are also varying points of health care access for people with CKD – most are diagnosed in primary care and some in secondary care, with a small but important group presenting late to secondary care (83). In primary care, many people are asymptomatic when diagnosed, some are detected as a result of tests undertaken as part of the NHS Healthcheck programme, but the majority are identified through routine blood testing, particularly among older people with comorbidities such as hypertension, diabetes and CVD. Reduced access to or quality of care may lead to under-identification and treatment of risk factors for CKD and AKI such as diabetes, hypertension and use of nephrotoxic drugs. For the NHS Healthcheck, uptake has been variable across the country and there is some evidence that among those at greater risk, such as the more socially disadvantaged, uptake has been marginally higher than among more affluent groups where specifically targeted (84, 85). CKD detection in routine primary care may be adversely influenced by changing GP Quality and Outcomes Framework targets over recent years (such as reduction in the requirement to record proteinuria testing) (86, 87).

There is some evidence of greater likelihood of increased diagnosis in women (potentially related to greater attendance at health services) and little evidence of age being a barrier to timely identification of CKD (79). A greater likelihood of timely albuminuria testing has been observed in younger people after adjustment for confounders and a lower likelihood of testing in people without diabetes (79). There is little evidence of a socioeconomic barrier to primary care diagnosis of CKD, and evidence that lower socioeconomic groups are less likely to be tested for albuminuria appears to be explained by other factors (79). Low health literacy may influence access to diagnosis, though this has not been established (39).

Aspects of primary care, where most CKD is diagnosed and managed, such as waiting times and continuity of care, have been evaluated more negatively by BAME groups (88). The effect of this on risk of under-diagnosis of CKD is not known. Communication issues relating to language barriers or limited health literacy may lead to increased renal risk in both primary care and hospital settings. Misunderstanding important issues such as medication dose and fluid management advice may lead to increased risk of AKI, for example (89).

Acute kidney injury

A significant proportion of AKI events have some iatrogenic element to the precipitants, with some episodes of AKI potentially preventable (90). A significant proportion of AKI occurs in the community and a high proportion of people with AKI are seen in non-nephrology settings (69, 91). Little is known about direct differential care quality issues across sociodemographic groups in the context of AKI. However, at risk groups, such as people with certain conditions (e.g. diabetes, CKD or heart failure), older people, people with dementia, mental health problems, or those with learning disabilities may experience variation in access to acute care with potential associated increased risk of AKI (92).

The epidemiology of community-acquired AKI has not been fully described but large database studies of routine health data are adding to understanding. They have a potentially important role in being able to monitor the impact of quality improvement interventions and policy changes (93).

A substantial proportion of people with AKI receive either no follow up or no specialist follow up in the subsequent 90 days after leaving hospital, despite this being a period when readmissions with either recurrent AKI or recurrent pulmonary oedema occur in more than one third of people (94, 95).

6.2.3 Interventions to address risk factors for developing AKI/CKD

Interventions to address risk factors for primary prevention of CKD can be considered at both population and individual level (including those considered at 'high risk'). While important individual risk factors need addressing in clinical contexts, the public health response to reduce the risk at population level through targeting wider determinants (such as poverty, tobacco control, diet and physical inactivity) may result in a greater impact on number of incident cases. Rose identified that 'a large number of people at a small risk may give rise to more cases of disease than the small number who are at high risk.' (96). For example, addressing high levels of salt added to food may have a significant impact at population level on hypertension related CKD (97).

For CKD, the population approach includes the public health response to common cardiovascular risk factors. Examples include addressing primary prevention through lifestyle factors such as smoking cessation, physical activity promotion and obesity prevention (98). It also includes proactive case finding for CKD in the context of predisposing conditions such as hypertension, diabetes and previous AKI, as well as efforts to improve the detection and management of these conditions (99).

For AKI it is important to encourage good hospital care standards for all, with particular attention to vulnerable or less well served groups. Good basic hospital care in fluid management, infection control and treatment, medicines management, etc. are all important components. AKI detected through the automatic e-alert system, now standard in most UK hospitals, can be considered as a red flag for people at risk/deficiencies of care. Given the many contexts in which people with AKI present, population level interventions for AKI include all efforts to improve health systems in both community and hospital settings and efforts to improve public awareness of risks to kidney health, which is currently poor in the UK (100). Identifying people at risk of AKI at the earliest possible opportunity (for example, in the community, on arrival in hospital, or around surgery) is important. Some risk tools have been developed/are under development, but are not widely used at present (101).

As with any population level intervention, the challenge is to achieve improvement without *widening* health inequalities. Some healthcare interventions may be at risk of doing this. There is some evidence of national health policy narrowing inequalities in England. The four themes of the English health inequalities strategy included supporting families, engaging communities in tackling deprivation, improving prevention, treatment and care and tackling

underlying social determinants of health (102). For behavioural aspects such as smoking, which has considerably higher prevalence and slower rate of decline among more disadvantaged groups, there is evidence that tailoring smoking cessation delivery may be necessary to successfully support quitting in certain groups (103).

To address inequalities in risk associated with predisposing conditions, identifying unmet need is the first step. This includes both the detection and control aspects of disease. Diabetes UK, for example, has made recommendations on ways of reducing health inequalities that include monitoring access to services, provision of written protocols to address the particular needs of diverse groups, appropriate and targeted funding for people living in poverty and training of staff working in particular settings such as care homes or prisons (104). Efforts to improve health literacy are also worthy of further exploration (105). Each such endeavour may be in need of further evidence from research.

6.3 Future directions for research

i. Evidence really poor/need more primary research:

- Identify the impact of shared risk factors for CKD (hypertension, diabetes, smoking, CVD and obesity) on socioeconomic and ethnic variation in the distribution of AKI incidence and outcomes
- Identify the barriers for people in BAME groups in accessing diagnosis and good quality care of shared risk factors for CKD
- Develop valid eGFR estimating equations for all ethnic groups, particularly South Asians
- Understand better the role and impact of the NHS Healthcheck as a major national public health programme in the detection and prevention of CKD and diabetes
- Develop impact models to demonstrate the effect of changes in risk factors on CKD occurrence.

ii. Existing evidence needs bringing together systematically in a systematic review/meta-analysis:

- Systematically summarise the most promising population-level interventions to address shared risk factors for CKD.

iii. Ready to do some/bigger interventional studies:

i. Test effective and simple interventions in primary and secondary care to reduce AKI incidence and recurrence in those at risk in a way that does not increase inequalities

ii. Test the generalisability of measures to prevent AKI, such as targeted medication suspension prior to surgery.

6.4 Summary

Inequalities exist in AKI and CKD. These are manifest in both the risk factors for the conditions and their incidence and prevalence. Much remains unknown about the existence of inequities in the development of CKD and AKI and ways of reducing them. The biggest impact on AKI and CKD incidence is likely to be gained from efforts to target the common modifiable risk factors that are more prevalent among people of low SES: obesity, hypertension, diabetes and CVD. This will be best achieved through public health and health system approaches.

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Chapter 7 Progression of AKI and CKD

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Dr Clare Castledine

7.1 Introduction

Adverse outcomes for CKD and AKI include progression to ESKD, hypertension, CVD and cerebrovascular disease, and death. There are also several less well studied adverse outcomes of both CKD and AKI such as hospitalisation, missed employment opportunities, unemployment, relationship breakdown, childlessness, poverty and mental illness. We have primarily considered inequality in outcomes following CKD/AKI across age groups, sexes, ethnic/racial groups, by SES and in the presence of mental health problems (Figure 7.1). For some of these population groups, associations may be complex. For example, having kidney disease and mental health problems, which are unrelated to kidney disease, may result in missed employment opportunities, because the affected person may have fewer opportunities and resources to secure employment, leading to social deprivation.

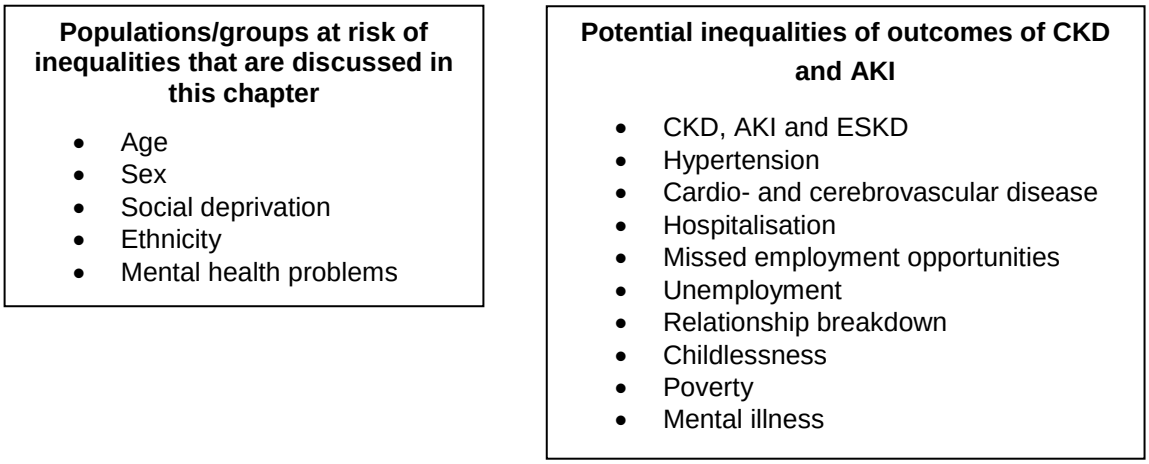

Figure 7.1 Populations/groups that are discussed in this chapter (left box) and potentially unequal outcomes of CKD and AKI (right box)

7.2 Literature review

We draw on the findings of the three scoping reviews supporting this report: scoping review one: basic sciences and CKD (Appendix 4); scoping review two: social deprivation and development of CKD (Appendix 5); and scoping review three: ethnicity and progression of CKD (Appendix 6).

7.2.1 Patient level risk factors

Age

Older people with CKD tend to have a higher absolute risk of poor outcomes. However, the relative risk of having a poor outcome is more pronounced at younger ages – this was a continuous interaction in that the youngest ages (18–54 years) have the worst outcomes with the least pronounced relative risk when compared to those aged 75 years or more (1). Amongst those starting RRT, people with diabetic nephropathy are younger than those without, those with diabetic nephropathy are more likely to come from more deprived

geographical settings, and younger people with diabetic nephropathy die considerably faster when they require RRT, especially for age groups <55 years (2).

Sex

Whilst available data suggest that the prevalence of CKD is roughly equivalent for men and women (3), with potentially more women than men being affected by CKD, the opposite is true for those starting dialysis. Currently 50–70% of the incident dialysis population in the UK is male (4, 5). This observation is consistent across a range of developed health settings (6, 7). An individual participant meta-analysis investigated whether the risk of death or dialysis was different for men and women according to the level of observed kidney function and found that women were overall at slightly higher risk than men to progress to ESKD at the same level of kidney function and when taking into account their cardiovascular risk markers (8). Therefore, the counter-intuitively lower rate of dialysis take-on in women when compared to men needs to be understood in more detail.

Social deprivation

CKD is more prevalent in socially deprived groups (9-12), as has been covered in Chapter 6 in more detail. The different ways of measuring SES crudely describe the individual's relative position within the economic-social-cultural hierarchy for individual measures and the access to resources for neighbourhood measures (e.g. clean air, fresh food, high quality GP practices, meaningful employment). These two clearly interact but regardless of how SES is measured, the strong relationship between CKD outcomes and SES persists. In the scoping review on this question (Appendix 5), differences between studies looking at CKD prevalence were largely explained by the amount of adjustment variables included.

Progression of CKD has been shown to be faster in more deprived socioeconomic groups (13, 14). Faster progression may be due to an increased prevalence of albuminuria in low SES groups (15). This association could be explained by obesity, smoking, hypertension, and diabetes – all variables known to relate to worse outcomes of CKD. Diabetes is strongly associated with SES (16, 17) and cohorts with large numbers of diabetic patients may find a stronger link between SES and CKD and progression. There is some evidence that lower SES groups have disproportionately more immunoglobulin A nephropathy (18) and that even patients with congenital or genetic kidney disease are more likely to progress to RRT if they are from more deprived neighbourhoods (19). Glycaemic control in a diabetic cohort (20) and blood pressure control in patients diagnosed with a primary glomerulonephritis (18) have been shown to be worse in low SES groups. These factors may explain some of the greater incidence of RRT for patients from more deprived backgrounds.

Mortality with CKD has been shown to be higher in low SES groups (21), but whether this is attributable to the kidney disease itself or to the higher risk of death in low SES groups has not been established. The impact of health literacy and its correlate educational attainment on outcomes with CKD have been suggested (22), but not formally investigated as far as we are aware.

There is currently far less certainty about the relationship between SES and AKI (see Chapter 6). CKD is a clear risk factor for AKI and therefore it seems likely that a similar relationship exists. The effects of birth circumstances and biological development along with lifestyle opportunities along the whole life course may affect the risk of CKD and AKI and resulting adverse outcomes. However, the converse relationship may also apply. Individuals affected by CKD or AKI may fall down the socioeconomic scale relative to those around them because of their ill health.

We had difficulties finding studies on adverse outcomes following AKI with respect to SES and a more formal systematic literature review into this would be welcomed. Existing data are limited by a lack of repeated creatinine measurements making the frequency of AKI diagnosis difficult to quantify (23-25).

Ethnicity

There is a complex interaction between SES and ethnicity. To date, it has been challenging to disentangle the association of ethnicity from that of socioeconomic deprivation. There is no doubt that individuals from particular BAME populations progress faster to RRT compared to their White counterparts in the same setting, for example, Aboriginals in Australia (26). Similarly, in the UK, those of South Asian, Black African and Black Caribbean descent are over-represented on dialysis, and are known to have higher rates of hypertension and CVD (27). As outlined in scoping review three (Appendix 6), depending on study design and which factors were adjusted for, study authors were able to confirm or refute an association of kidney disease progression with ethnicity.

Some of this confusion arises because a subset of study authors tend to use the term ‘ethnicity’ without considering which biological association they wish to capture, i.e. adjusting for pathway factors (e.g. behavioural and clinical risk factors), or not. Whilst it is well understood that poorer life circumstances directly relate to low birth weight (not least through maternal smoking), and that poorer life circumstances and education associate with lifestyle choices and subsequent risk of developing hypertension, obesity, diabetes and CVD, the precise role of ethnicity is not well defined. It seems that there is a higher prevalence of proteinuria in BAME populations, but we do not know what explains this higher prevalence, i.e. whether it is a genuine kidney disease that manifests with proteinuria and is more common in a particular ethnicity, for example, as shown for carriers of the APOL1 risk polymorphisms, or whether it is simply a result of ethnically determined low nephron mass. Accurately measuring life course lifestyle choices is difficult and currently observed independent associations for ethnicity, which were adjusted for concurrently measured cardiovascular risk factors, may simply be due to residual confounding by not having quantified lifestyle over the life course appropriately. The use of data from US studies may be less relevant to the UK context with access to healthcare playing a major role in the US and therefore introducing selection bias.

With regards to other outcomes apart from progression of kidney disease, there is to date no convincing evidence that people from BAME populations who have CKD have a higher

mortality than those of White ethnicity when cardiovascular risk factors and deprivation have been taken into account (Appendix 6).

Mental health status

People with severe mental illness, including schizophrenia, bipolar disorder and other non-organic psychosis, are known to have shorter life expectancy, by around 10–20 years, than the general population (28-33). Most cases of premature death in this population group are not attributable to suicide and accident, but instead to physical illnesses (especially CVDs such as coronary heart disease and stroke) (32-37). The high rate of cardiovascular deaths in patients with severe mental illness compared to the general population has been variously attributed to: high prevalence of lifestyle related conditions (e.g. smoking and obesity) (38-41); suboptimal screening/assessment of cardiovascular risks (42, 43); and poor management of underlying diseases (e.g. hypertension and dyslipidemia) in patients with severe mental illness (44-46). In addition, antipsychotic medications may contribute to sudden death and increased CVD risk (47). Evidence is emerging for the UK that people with severe mental illness have more prevalent CKD and higher prevalent numbers on RRT, compared to those without severe mental illness (Iwagami M et al. submitted). More research is needed to investigate progression of CKD amongst those with mental health and cognitive problems.

7.2.2 Basic science aspects of risk factors for adverse outcomes from AKI/CKD

There have been some theoretical studies exploring the effects of prematurity or low birth weight, both strongly associated with SES, on subsequent CKD (48). The presence of low nephron numbers may explain the higher prevalence of disease progression in low income groups (49). Other studies looking at the biological mechanisms responsible for faster CKD progression in low SES groups have postulated telomere shortening and increased DNA methylation (50). Dietary phosphate from carbonated drinks has also been investigated and a potential link between phosphate intake, SES and CKD progression suggested (50). Research into anti-fibrotic agents which may be useful to slow disease progression in a low nephron number environment may prove useful, but to our knowledge this is not being investigated with respect to low income groups. The basic science scoping review (Appendix 4) suggested a number of potential candidate genes for CKD progression, but to date, genetic risk factors for renal disease for Blacks or South Asians are not well characterised.

7.2.3 Access to care as a risk factor for adverse outcomes from AKI/CKD

We did not find literature exploring access to care for specific groups of people with AKI who then suffer as a result worse outcomes; the information below refers only to those with CKD.

Age

People at younger age are less often tested for kidney disease but it appears that primary care is successfully detecting people with CKD stages 3–5 at all ages in an equal fashion (3). In the National CKD Audit, there was evidence of inequity with regards to age in terms of

whether a person received a Read code with a CKD diagnosis in the presence of biochemical CKD on testing, with people of younger age (aged ≤65 years) being less likely to be Read coded for CKD than older people (51). Those of younger ages with CKD are less likely to receive cardiovascular prevention, for example, statin treatment (4). When scrutinising incidence data on people starting RRT in the UK, it is noticeable that late referral is proportionally more common in young age, suggesting that quality improvement of the care of the working age population is required (52).

Sex

For young women with CKD, there is limited information from relatively small studies on best fertility and pregnancy care (53-55). At present, the Renal Association is convening a guideline writing group to address this knowledge gap with regards to best care of women of reproductive age with CKD.

Future research needs to investigate whether there are gender imbalances with regards to access to renal care, and whether women of a particular ethnic background are predominantly affected.

Social deprivation and ethnicity

A German diabetic cohort described that those with lower SES had lower renal function independent of smoking, albuminuria and duration of diabetes (56). Such associations may suggest reduced access to care to prevent poor outcomes in socially deprived groups, which explains corresponding data from the UKRR (2). People from more deprived backgrounds suffer often from multiple morbidities, including mental health problems at younger age, with resulting increased complexity of care (57). This complexity of care arises in a population with fewer resources to cope, which may explain poor outcomes (58). Access to complex medical interventions has been shown to be less good in the UK amongst socially deprived neighbourhoods (59, 60), although access to RRT, specifically, has not been studied in this regard. The scoping review on ethnicity and progression of kidney disease (Appendix 6) suggested that there is no evidence for poorer care as such, but there may be issues with health literacy. Low rates of referral to nephrology services (61, 62) and access to RRT (23) post-AKI have been investigated in only a few studies outside the UK.

Mental health problems

There has been no formal investigation into whether people with severe mental illness have appropriate access to renal services in the UK; our cross-sectional analysis suggests that they may have less access to kidney transplantation and peritoneal dialysis (Iwagami M et al. submitted), and at younger age, mental health problems, multimorbidity tend to co-occur in those who are most deprived (57).

There are marginalised groups, for example, those with intravenous drug use, who may benefit from more tailored care to prevent poor renal outcomes.

7.2.4 Interventions to address risk factors for adverse outcomes from AKI/CKD

We are not aware of studies investigating whether targeting low income groups with enhanced health monitoring interventions from early life could result in a reduction in the observed disparities between socioeconomic groups and between different ethnicities.

7.3 Future directions for research

We recommend two main approaches for future research:

i. Routine data analysis of linked electronic health records to investigate inequalities of access to care and outcomes: there should be a more formal systematic literature review on access to care and adverse outcomes post-AKI with respect to age, SES and ethnicity. Depending on the findings of this systematic review, research on investigating outcomes post-AKI could be taken forward. In the meantime, large electronic health record studies linked between primary and secondary care data should be used to investigate dialysis incidence, AKI, referral, and competing mortality for the following groups:

    - Women versus men
    - Those with severe mental illness compared to those without.

ii. Complex intervention of better management of people of working age living with CKD to prevent poor outcomes: despite suggestive evidence of relatively poor outcomes for those aged <65 years with diabetes and CKD in the UK, we are not aware of a study that specifically investigates people of working age living with CKD, especially those of deprived or BAME backgrounds. There are no studies evaluating complex interventions (lifestyle factors, health literacy with regards to CKD, blood pressure control, and better diabetes care for those with diabetes) to prevent such poor outcomes. Following the MRC guidance on designing complex intervention studies, as part of planning such a study, formal systematic reviews of ethnicity and outcomes of those with CKD should be conducted, bearing in mind that scrutiny should be given as to how previous studies were designed and study results were adjusted for. Any designed intervention study should capitalise on previous work on prevention of CKD outcomes in those with hypertension, CVD and diabetes from particular ethnic groups. As part of the suggested complex intervention study, data could be collected on outcomes relevant to a working population such as missed employment opportunities, unemployment, relationship breakdown and poverty.

7.4 Summary

We have highlighted four areas where there is particularly limited evidence on whether there are inequalities of outcomes for those with CKD and AKI:

i. There was very limited information on access to care and outcomes of AKI for population groups typically at risk of inequalities (age, sex, ethnicity, SES and severe mental illness)
ii. To date there is an unexplained gender gap in take-on rates onto dialysis, which should be explored in more detail
iii. Access to care and outcomes of care appear to be worse in those of working age, especially if they are from a deprived background. There are a range of complex issues that need unpacking in this population: at the provider front (age, cultural/ethnic biases in pre-dialysis education programmes), amongst those with kidney disease (complexity of care in a working age, often deprived and multimorbid population with limited resources and ability to cope), and how this affects shared decision making and involvement in care (including the mental health aspects), and ability to continue contributing to society (e.g. impact on disability, employment). Multidisciplinary research should be carried out to determine how best to mitigate the range of possible and devastating consequences of kidney disease in the working age population
iv. There is to date limited information on progression and outcomes of those with mental health problems in the UK.

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Chapter 8 Access to treatment and adverse outcomes with ESKD

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8.1 Introduction

ESKD is becoming increasingly common, with rising incident and prevalent populations on RRT (1). It is well recognised that for patients who are medically suitable and in agreement, the optimal form of RRT is a renal transplant. It is crucial to recognise all risk factors for adverse outcomes of RRT to allow patient management to be optimised and person-specific. Traditional risk factors are well recognised: patients with multiple comorbidities, particularly CVD, are both less likely to receive a renal transplant and more likely to have difficulties with dialysis. However, it is increasingly recognised that there are multiple other non-disease specific risk factors for adverse outcomes. Many of these non-disease specific risk factors relate to determinants of health which may be associated with limitations in access to treatments, specifically modalities of RRT. These non-disease specific determinants of outcomes related to management of ESKD may be grouped as personal, and therefore risk factors specific to an individual or environmental risk factors. These are not completely mutually exclusive, such as more patients living in an urban area may on a personal level be of a certain ethnic group. On an environmental (or population) level, patients resident in Northern Ireland have better access to living donor transplantation (2). Coincidentally, Northern Ireland is less ethnically diverse than Birmingham or London. Therefore, it is unclear if the personal factors associated with access to transplantation, such as ethnicity, map directly to geographical factors associated with poorer outcomes with ESKD. Many of these relationships are difficult to tease out, but when considering interventions to improve differences in outcomes related to inequality, it is important to conceptualise the nature of these personal (or individual specific) factors in the context of associated environmental (or population) factors.

8.2 Literature review

8.2.1 Patient level risk factors

Personal risk factors to consider include age, sex, ethnicity, BMI, cognitive impairment and frailty. Many of these factors are inter-linked. It is well recognised that for patients on RRT, advancing age is associated with increased mortality and older patients are less likely to receive kidney transplants (3). Cognitive impairment has also been shown to develop in the haemodialysis population, with older age a strong risk factor for faster decline in cognition (4). In addition, frailty, a term used to help describe reduced functional capacity, is an adverse prognostic factor for patients with ESKD (5). A recent systematic review found that functional and cognitive impairment, and frailty, were independently associated with adverse outcomes in patients with ESKD (6). It is therefore important to carefully consider these factors when providing information to patients with advanced CKD approaching need for RRT, particularly with the knowledge that the prevalent RRT population is increasing in age. BMI is also a recognised risk factor for cardiovascular mortality in the ESKD population, with waist circumference, an indicator of abdominal obesity, shown to be an independent and strong predictor of both cardiovascular and all-cause mortality in both haemodialysis and peritoneal dialysis populations. It should be acknowledged that like many relationships

between risk factors and outcomes with ESKD, the relationship between BMI and risk of premature death is actually ‘U-shaped’ whereby patients with very low BMI, as well as the obese, are also at greater risk (7, 8).

BAME groups make up just under a quarter (22.7%) of the prevalent RRT population in the UK (1) so it is important to recognise and reduce disparities in this population. There is widespread geographical variation: in some London boroughs, over 60% of the prevalent RRT population are from a BAME background, contrasting with 0.4% in other parts of England (9). It is well recognised that BAME populations are less likely to have renal transplants, particularly living donor transplants (2, 10, 11). It is recognised that some ethnicities have a survival advantage with ESKD in general terms compared to Whites. In terms of outcomes on dialysis, there is some evidence to suggest this advantage persists in some populations (for example, Hispanics and older Blacks), although there are likely to be confounding factors (11). Similar findings have been observed in the UK where patients of South Asian and Black ethnicity have been observed to have better survival on dialysis (12).

It is also important to consider environmental factors when considering health inequalities. These include urban factors, geographical location, social deprivation, education, and lifestyle and diet. Factors such as housing can have a significant impact on the modality of RRT: for peritoneal dialysis, adequate storage of dialysis fluid is required; for home haemodialysis, a room which can be plumbed to a sterile water supply is necessary. Geographical location is also of key importance: for rural populations, haemodialysis may not be a feasible option due to lack of access to satellite units, which may necessitate either peritoneal dialysis or a change in location. Transportation may also be a challenge, particularly if patients are dependent on the Ambulance Service to travel to and from haemodialysis. These issues are routinely considered when patients require RRT and may influence the eventual modality. Access to transplant should be equitable irrespective of geographical location, but a recent study has shown there is a significant increase in the likelihood of both living donor transplantation and pre-emptive transplantation if the patient lives in Northern Ireland (2).

Deprivation is associated with poorer survival on dialysis, although this may simply be due to patients from deprived areas having increased comorbidity, because when statistical adjustment for comorbidity is performed, the association between deprivation and poorer survival is not observed (13). In the UK, deprivation is associated with lower rates of peritoneal dialysis (13). It is also associated with lower rates of renal transplant, including living donor and pre-emptive transplants (2). This pattern is seen across the world irrespective of whether healthcare is free at the point of access. There is some evidence to suggest that patients from more deprived areas have increased rates of kidney transplant rejection (14). However, in terms of survival, results are more conflicting, with one study finding a significant association between socioeconomic deprivation and increased recipient mortality following transplant (15), but two others finding no associations (16, 17). It is recognised that BAME populations have more deprivation than White populations which may confound associations between ethnicity and health (18). Education also influences both

timing of presentation to renal services and access to transplant, with those less educated presenting later and having less access to renal transplantation (2, 3, 10).

A healthy lifestyle with regular physical activity and avoidance of smoking is known to reduce the risk of adverse outcomes in patients with CKD (19). A recent Cochrane review provides supportive evidence that regular exercise (more than 30 minutes three times per week) in patients with all stages of CKD (including dialysis patients and transplant recipients) has beneficial effects on physical fitness, blood pressure, some nutritional parameters and quality of life (20). There may be economic (i.e. cost of gym membership) and cultural barriers to participating in exercise. Overall, it should be recognised that there are multiple personal and environmental risk factors for adverse outcomes in patients with ESKD which must not be neglected in favour of traditional disease related risks.

8.2.2 Basic science aspects of risk factors for adverse outcomes with ESKD

Although it is outwith this chapter to discuss extensively the basic science associated with adverse outcomes in patients with ESKD, there are two salient examples where there are parallels between ESKD and socioeconomic deprivation associated with reduced survival and premature CVD. ESKD has many phenotypic features of premature ageing, characterised by stiffening of large arteries and arterial calcification, very much like that seen in premature ageing (progeria) syndromes (21) such as Hutchinson-Gilford syndrome. Cellular ageing as a marker for biological age has been characterised using telomere biology, whereby shortened telomeres represent an ageing state (22). Telomeres are structures at the ends of chromosomes that erode with genetic damage. Changes are observed consistent with premature ageing with shortened telomeres in the setting of an environment of socioeconomic deprivation (including second hand cigarette smoke) (23). Similar changes in telomeres are seen in dialysis patients, highlighting that accelerated ageing is seen both clinically (with excess CVD), but also at a cellular level in dialysis and renal transplant patients, and is likely to be augmented by socioeconomic deprivation (24).

Chronic inflammation has recently been recognised as a target suitable for therapeutic targeting to reduce risk of CVD (25). In parallel, inflammation is well recognised to be associated with poor outcomes in dialysis patients (26, 27). Furthermore, it appears that in the absence of kidney disease, socioeconomic deprivation co-localises with inflammation, and atherosclerosis (28). Better understanding of the fundamental drivers of inflammatory processes relevant to ESKD when aligned to socioeconomic deprivation may lead to future treatment strategies in ESKD.

8.2.3 Access to care as a risk factor for adverse outcomes with ESKD

Access to in-centre dialysis care

Geographical, ethnic and socioeconomic differences exist in the incidence and prevalence of RRT in the UK. Incidence rates are highest in the most deprived areas and in those with the greatest proportion of Black and South Asian people (29). Those who live in areas with

higher levels of deprivation are more likely to commence on RRT. Similarly, prevalence rates vary greatly by geographical area with as much as 10-fold differences in RRT prevalence rates between a few districts (29). The question arises therefore whether geographical areas with relatively low RRT incidence and prevalence rates have a lower need for RRT. The incidence of RRT in areas with greater deprivation is likely to be influenced by factors that are socioeconomically distributed such as diabetes. There may be other geographical or regional specific effects on RRT incidence and conflicting data exist. Previous reports do not show major differences in requirement for RRT across socioeconomic strata in Scotland (30). This could be explained in a number of ways. It may be that fewer patients from socially deprived areas require RRT because they are more likely to die from other diseases associated with socioeconomic deprivation (e.g. cancer, CVD) before needing RRT. Alternatively, patients from socially deprived areas may have differential access to RRT. Analysis of UKRR data suggests that even after correction for sociodemographic differences, risk of commencing RRT is variable in different geographical areas, suggesting that inequalities exist in access to RRT. Distance of the home from the renal unit in the UK has been shown to be associated with incidence rate of RRT, with adjusted incidence rates for RRT 20% lower in areas with >45 minutes travel time from a renal unit (29). An inverse relationship exists between distance to renal unit and incidence of RRT at least with historical epidemiological data (31). However, there is a paucity of non-epidemiological data exploring access, availability and barriers to in-centre dialysis provision.

Access to home dialysis care

There is great variation in uptake and prevalence of home haemodialysis and peritoneal dialysis across the UK, with the ratio of patients on home therapies to those on in-centre haemodialysis varying from 0.06 (6%) to 0.32 (32%) in the latest UKRR report (32).

Systematic differences in uptake of home therapies by ethnicity are identified by the UKRR, with overall only 13% of patients on home haemodialysis and 22% of those on peritoneal dialysis having non-White background compared to 28% of those on in-centre haemodialysis. This is graphically illustrated in Figure 8.1 (32). However, the extent to which these ethnic differences in uptake and access to home therapies impact outcomes has not been studied.

Social deprivation continues to be a risk factor for reduced uptake of home therapies and latest UKRR data indicate that the magnitude of this effect appears to be greatest in peritoneal dialysis and less pronounced in home haemodialysis (32). It is hard to capture data on whether social deprivation influences clinicians' decision making (intentionally or more likely due to unintentional bias) on offering encouragement to take up home-based therapies (peritoneal dialysis and home haemodialysis) by patients with ESKD.

Geographical distance lived from peritoneal dialysis centre, as a measure of access to peritoneal dialysis care, has not been studied in the UK, but data from Australia and New Zealand suggest that patients who live at greater distance from peritoneal dialysis centres have a greater risk of peritonitis (33). Limited, relatively historic UK data, at least from one region, suggest the prevalence of peritoneal dialysis is greater in those who live at greater

distance from nearest renal unit (29) but the extent to which this impacts on adverse outcomes has not been studied in the UK.

The above described substantial differences in provision of home therapies care with respect to geography, ethnicity and deprivation have not been studied with respect to the impact on outcomes of these inequalities from our review of the literature.

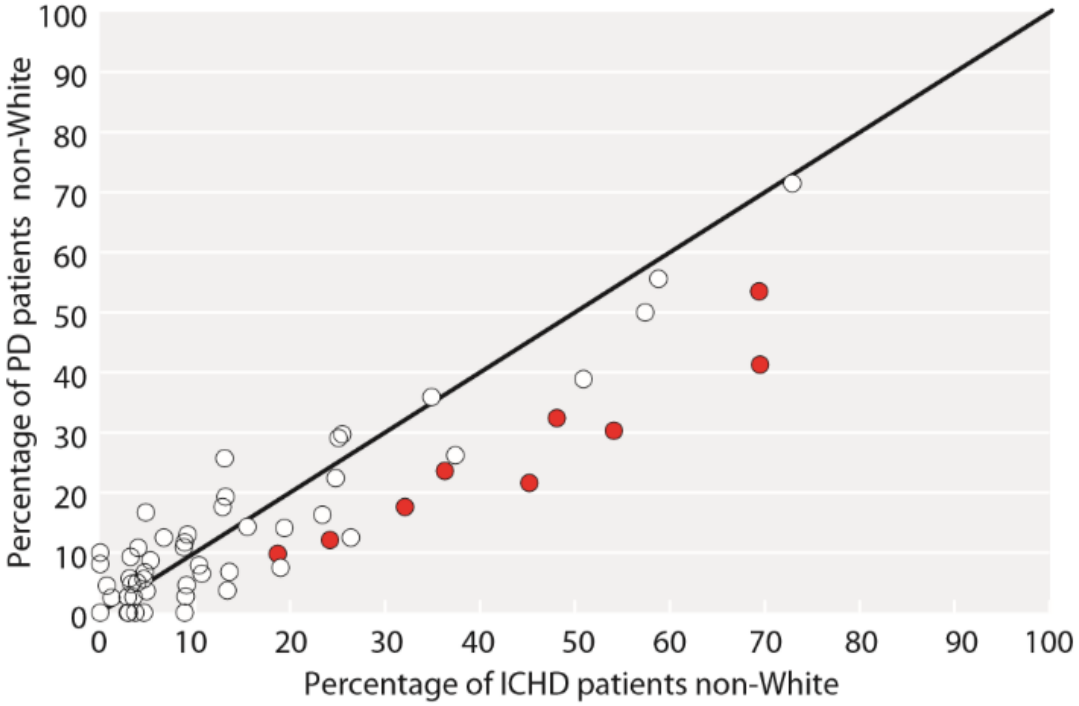

Figure 8.1 Percentage of non-White prevalent peritoneal dialysis patients relative to non-White in centre haemodialysis patients on 31 December 2015 (32). Centres with a lower than expected percentage of ethnic minorities on peritoneal dialysis are highlighted (shown as red/filled dots) only if they had a minimum of five non-White patients on peritoneal dialysis. PD: peritoneal dialysis; ICHD: in-centre haemodialysis

Access to transplantation

Access to the deceased donor transplant list has been studied in the UK extensively and the impact of social deprivation and ethnicity defined. In a previous large study of patients commencing RRT where deceased donor listing and time to listing was explored, the most deprived quintile had a 40% reduced risk of being listed compared to the least deprived quintile. There is significant interaction between SES and ethnicity which makes relationships between ethnicity and transplant listing, independent of socioeconomic status hard to infer (34).

However, the latest UKRR data suggest that differences in chance of transplant listing between ethnic groups seem to have been reduced such that in the latest dataset patients who are from BAME populations are not significantly less likely to be listed for transplant compared to White patients (35). Older patients were less likely to be listed for transplantation, an unsurprising finding given their greater burden of comorbidities and the

risk of transplantation associated with age (35). Similarly, odds of transplant listing were lower in those with a prior history of diabetes. Regarding odds of receiving a renal transplant, UKRR data indicate that BAME patients are significantly less likely to receive a transplant from a donor after brainstem death (odds ratio [OR] 0.79, confidence interval [CI] 0.71–0.89) and also from a donor after cardiac death or living kidney donor (OR 0.45, CI 0.39–0.51) within two years of transplant listing (35). Odds of receiving both of these organ types reduces with increasing age which is not unexpected for a number of reasons associated with older patients on the transplant list, chiefly the patient's health or comorbidity status. Female patients appear to also have lower odds of receiving a transplant from a donor after cardiac death or living kidney donor (OR 0.87, CI 0.78–0.98), but a similar OR of receiving a transplant from a donor after brainstem death. It is unclear whether these differences in sex are related to comorbidity factors with respect to transplantation.

The transplantation chapter of the UKRR report highlighted that there are significant differences after adjustment for case mix between renal centres in the rate of transplant wait listing, time to acceptance on the transplant list and differences between rates of live donor and deceased donor transplantation across UK centres. It is unknown whether this relates to differences in practice across UK transplant centres regarding screening tests required for transplant listing specific to age, CVD or comorbidity highlighted previously (36).

The landmark ATTOM study has dissected out many of these factors, providing key insights, metrics and detail into risk factors where there were assumptions made around transplantation (2). In addition to confirming much of the information held in registries, it is apparent that many of the simple attributes clearly associated with social status such as car ownership or educational attainment are linked to better access to kidney transplantation. It is also notable that across the UK, there are variations in clinical practice in transplant listing highlighted in work performed preceding the ATTOM study (36). It highlights that some geographical inequalities in care, irrespective of whether these are clinically justifiable, are outwith patients' control, and may yet impact on access to RRT modalities.

Late presentation and access to care

Late presentation to nephrology services with advanced CKD and symptoms of uraemia often leads to commencement of dialysis using a temporary central venous catheter. Delays may occur in assessment for the kidney transplant list whilst the patient's health is stabilised. All these factors are associated with reduced survival. Late presentation makes informed decisions about RRT modality challenging, including deciding when to access conservative management of advanced CKD, which may be most appropriate for some patients with severe comorbid disease. There are fairly limited data available on the relationship between access to healthcare and/or factors related to healthcare inequalities and late presentation to nephrology services (37). In a recent UK study, late presentation was associated with increased mortality after adjusting for comorbidity, transplantation and permanent vascular access (38). Further work is required to address whether late presentation is avoidable and what factors are associated with avoidable late presentation with advanced CKD. Although, conservative management of ESKD has been covered in less detail in this chapter than dialysis or transplantation, it is important to recognise that for many patients with significant

comorbidity, or the very elderly, conservative management of ESKD may represent the most appropriate approach to avoid excessive medicalisation of a patient's final months of life with dialysis which is inconvenient, poorly tolerated and affords limited management of symptoms which are most important to the individual patient. Advanced planning for the need for RRT in patients with advanced CKD is only achievable with sufficient time to allow patients to digest the information about treatment options for ESKD, including conservative care. Late presentation to nephrology services limits the time to make these important decisions. It may be that there are patient related factors such as healthcare avoidances which may be due to personal reasons, mental health or cultural beliefs or extreme comorbidity preventing interacting with healthcare. Alternatively, there may be healthcare system issues whereby detection and management of CKD could be optimised. The ASSIST-CKD study will give insights into improving management of progressive CKD (39).

8.3 Future directions for research

Prior to initiatives to address inequalities in care which are associated with adverse outcomes in patients requiring RRT, further understanding of the mechanisms by which inequalities lead to adverse outcomes is required. This should lead to optimal targeting of initiatives, allowing greatest benefit in vulnerable groups and ensuing sustainability of interventions. The following areas of research or strategic initiatives are required:

i. A detailed study to identify whether factors associated with adverse outcomes are directly or indirectly associated with adverse outcomes with ESKD. An example might be that diabetes is relatively more prevalent in patients of South Asian origin. South Asians with ESKD have lower rates of undergoing live kidney donation. Is this low rate of live kidney donation independent of the fact that South Asian patients with ESKD have fewer potential live donors due to the higher background prevalence of diabetes in this population precluding donation?
ii. A study is required of the interaction between the environmental factors which drive premature CVD in ESKD (second hand smoking, diesel fumes etc.) and to what degree these are modifiable. Do patients choose to live in these environments, or does SES lead to their 'migration' to these areas as more affluent individuals move to areas with less exposure to these factors? And what consequences would a change to an individual's environment have on management of ESKD?
iii. Better understanding is needed of the complex dynamic between patient related factors associated with health inequality (mental health, sex, age, race, obesity, disease) and environmental factors (geography, housing, air quality, etc.). These factors clearly overlap, but in making decisions about initiatives to improve outcomes, it would be prudent to identify which inequalities associated with these factors might be amenable to intervention
iv. Variations in access to RRT modality, in particular transplantation dictated solely by centre practice are hard to justify. There may be multiple factors involved, such as background patient comorbidity, centre staffing, expertise, resource or facilities to permit higher volume of transplants, variation in acceptance of donor kidneys or

undertaking kidney transplantation in patients requiring specific expertise such as desensitisation. Detailed understanding of these factors and their impact on transplant outcomes is needed to identify optimal steps to take to ensure equitable access to kidney transplantation for appropriate patients across the UK.

8.4 Summary

Health inequalities exist between patients requiring RRT in the UK and are associated with differences in selection of or access to RRT modality. These inequalities include patient age, ethnicity, sex, BMI, SES, as well as comorbidities. There are also inequalities associated with location both regarding where the patient lives (size/type and geography) as well as renal unit centre which impact on RRT modalities. Furthermore, these various inequalities have been associated to some degree with differences in outcomes including patient survival. To date, it is unknown if these associations between inequalities and outcomes are causal. Further research and subsequent initiatives are required to address these factors and ensure equitable outcomes for patients with ESKD in the UK.

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Chapter 9 Recommendations to reduce kidney health inequalities in the UK

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9.1 Introduction

This chapter sets out 27 key recommendations aimed at reducing kidney health inequalities. They are divided into:

i. Broad research recommendations, of which there are 10
ii. Topic specific research recommendations, of which there are 17.

A small number of strategic recommendations have also been provided to Kidney Research UK outside this report.

These recommendations are derived from the interviews with kidney health inequalities experts as well as the learnings from the scoping reviews and the basic science and life course chapters in the report. The recommendations have been reviewed and edited by the senior report authors (GD and FC).

The populations and research areas from the prioritisation exercise are implicitly considered throughout the recommendations, but not necessarily explicitly stated. In line with the prioritisation exercise, there are more recommendations for CKD compared to AKI. There are also more recommendations for dialysis and kidney transplantation than conservative care. Recommendations are not in priority order.

9.2 Broad research recommendations

1. **Align kidney health inequality research with the wider renal community and its research activity** – Kidney Research UK could provide leadership to align the national kidney health inequalities research agenda through, for example:
    - The UK Renal Research Strategy
    - The UK Kidney Research Consortium clinical study groups
    - Other renal research funders, such as the British Renal Society and Kidney Care UK
    - The KQuIP.
2. **Use diverse research techniques to achieve results efficiently** – consideration should be given by Kidney Research UK to the full range of applied health services research methods that could be used to efficiently generate evidence in the field of kidney health inequalities.
3. **Identify and capitalise on existing research infrastructure** – Kidney Research UK should explore opportunities for efficient studies using existing infrastructure and databases, such as existing cohort studies with biorepositories, general practice databases, the renal registries, hospital statistics and mortality statistics.
4. **Evaluate new exposures and outcomes in kidney health inequalities** – research studies in kidney health inequalities should evaluate non-traditional exposure and outcome measures including, but not limited to, the role of religion, poverty and employment loss.
5. **Recognise the changing UK population and its impact on kidney health inequalities** – Kidney Research UK should consider the changing demographics

in the UK when predicting and therefore funding research into kidney health inequalities. This includes the ageing population, first generation migrants, second and subsequent generation migrants, childhood obesity, the 2007–2008 financial crisis and resulting austerity programme, the planned departure from the European Union and the increasing automation of unskilled and skilled jobs.

6. **Translate promising research findings into clinical practice and improvements in population health** – Kidney Research UK should work with research and clinical leaders in primary and secondary care to identify and formally evaluate new effective treatments and treatment pathways to deliver reductions in inequalities in kidney health.
7. **Change research recruitment practice and infrastructure to enhance the inclusion of disadvantaged populations in primary research** – Kidney Research UK must find efficient ways to make the inclusion of disadvantaged populations in primary research studies the default position. This should include:
    - Ensuring research materials such as consent forms, patient information sheets and patient questionnaires are accessible to those for whom English is not their first language and those with low health literacy
    - Ensuring studies are adequately powered to detect important differences in disadvantaged populations, such as BAME populations
    - Using a peer educator approach to increase understanding and participation in kidney health inequalities research.
8. **Embed kidney health inequalities in all proposals for clinical research and service improvement work** – the potential impact of all service improvement and clinical research work should be set out at the proposal stage of any clinical research study or service improvement project, with consideration of enhanced weighting of proposals likely to positively impact on kidney health inequalities in the UK.
9. **Assess the impact of all clinical research and service development on kidney health inequalities** – Kidney Research UK should develop a robust and sustainable process for monitoring and evaluating the impact of kidney health inequalities clinical research and service development. This should be applied at the project level, the programme level and nationally to demonstrate a reduction in kidney health inequalities over a defined period of time.
10. **Take a systematic approach to achieving reductions in kidney health inequalities** – Kidney Research UK should assess the current extent of the evidence base and fund research along the life course pathway to deliver this, evaluating the need for:
    - Primary research including epidemiological studies, qualitative research and basic science (when a new hypothesis needs testing or evidence exists but is insufficient to change practice or take forward in an interventional study)
    - Evidence synthesis through systematic reviews or meta-analyses (when sufficient primary research evidence exists to undertake these)
    - Interventional studies (when a systematic review of the literature has demonstrated sufficient evidence exists to conduct these).

This approach has been adopted in the topic specific research recommendations below.

9.3 Topic specific research recommendations

9.3.1 Basic science insights into the development of kidney disease

Acute kidney injury

Evidence synthesis is recommended

11. **To establish the utility of biomarkers to explain differences in AKI risk and outcomes between different ethnic groups** – given the rapid evolution of the evidence base in this area, a review of published and grey literature is needed before deciding how primary research should proceed.

Chronic kidney disease

Primary research is recommended

12. **To develop techniques that identify individuals at high life-time risk of CKD, early in life** – this could include methods to assess nephron number and early life biomarkers that predict later life risk of developing CKD.
13. **To establish how high risk alleles increase chance of developing CKD –** there is strong evidence for the role of APOL1 across a number of renal diseases in Blacks, but the mechanism of action has not been established and this is needed before interventions can be developed and tested. Primary research has yet to be undertaken to systematically search for such candidate genes in South Asians in the UK.
14. **To improve our understanding of biological and whole organism ageing** – the full range of cellular age-related changes of normal and predisposed individuals from different ethnic groups needs to be better understood in relation to CKD. To define potential therapeutic targets, there will then be a need to develop translationally relevant experimental models of CKD and AKI.

9.3.2 Development of AKI and CKD

Acute kidney injury

Primary research is recommended

15. **To identify the impact of shared risk factors for CKD on socioeconomic and ethnic variation in the distribution of AKI incidence** – this should include hypertension, diabetes, smoking, CVD and obesity.

Chronic kidney disease

Primary research is recommended

16. **To identify the barriers for people in different ethnic groups in accessing diagnosis and good quality care for both CKD and its risk factors** – this could be a two step process, first establishing where the barriers occur and second exploring what can be done to address them.

Evidence synthesis is recommended

17. **To establish whether there is sufficient evidence to take forward an intervention targeting early life risk factors for life-time risk of CKD** – this should look at targeting acquirement of early life risk factors as well as protecting kidney function in those who acquire those early life risk factors.
18. **To summarise the most promising population level interventions to address later life shared risk factors for CKD** – this could inform models of the impact of interventions and hence decisions about where to most effectively and efficiently focus efforts to reduce kidney health inequalities.

9.3.3 Progression of AKI and CKD

Acute kidney injury

Evidence synthesis is recommended

19. **To evaluate access to care and adverse outcomes (e.g. incidence of or progression of CKD) following an episode of AKI with respect to age, socioeconomic deprivation and ethnicity** – this review could lead to either more primary research or an interventional study investigating outcomes after an episode of AKI in groups where inequalities in outcomes may have been identified or predicted.

Chronic kidney disease

Primary research is recommended

20. **To investigate health inequalities in rates of CKD, referral to renal services with CKD, rates of RRT and competing mortality** – this should look at all potentially disadvantaged populations, how they overlap and interact and whether there are signals about mechanism from trends over time.

Evidence synthesis is recommended

21. **To summarise traditional (e.g. mortality, cardiovascular events) and non-traditional outcomes (e.g. employment status and mental health) in different ethnic groups** – this will need to be conducted with due consideration to how previous studies were designed and adjusted for.
22. **To establish whether there is sufficient evidence to take forward an intervention to improve the outcomes of people from disadvantaged groups**

of working age living with CKD – any such intervention is likely to be complex and outcomes would need to be culturally and medically relevant.

9.3.4 Access to treatment and adverse outcomes with ESKD

Dialysis

Primary research is recommended

23. **To study the interaction between environmental, socioeconomic and patient specific factors which drive premature CVD in patients with ESKD treated with dialysis** – this could lead to clinical phenotyping studies of identified high risk groups or studies to understand the fundamental drivers of the inflammatory process.

An interventional study is recommended

24. **To enhance the use of home therapies in groups that are traditionally low users of this service, as identified by pre-existing data** – the intervention is likely to be complex and will need to be developed according to the various stages of the MRC complex intervention development guidance. It will need to take into account ongoing quality improvement work in this area.

Transplantation

Primary research is recommended

25. **To identify if there is variation by transplant centre in the listing of patients from groups where health inequalities are likely to be prevalent, for example, BAME, migrant and elderly populations** – some of this may be addressed by the soon to be published ATTOM papers, but it should not be assumed that this area is covered.
26. **To establish whether there are inequalities in kidney transplant outcomes in the UK** – where these have been demonstrated in other countries, they often reflect health system or indigenous populations that do not apply to the other populations. A comprehensive UK assessment is required.

Conservative care

Primary research is recommended

27. **To understand how the documented variation in provision of conservative care affects disadvantaged populations** – this will need to look beyond the traditional clinical factors to include the communication of risk and benefit and culturally specific issues such as religious beliefs.

9.4 Summary

While some kidney health inequalities may reflect wider social and cultural effects, there is plenty that the renal community can do to improve experiences and outcomes for people living in the UK with all stages of kidney disease. This will require the coordinated and concerted action of all key stakeholders, using existing, traditional and novel, opportunistic mechanisms to leverage funding and influence policy.

An evidence-based, coordinated, strategic and, crucially, sustainable approach is needed to fund research that will reduce kidney health inequalities across the life course pathway, particularly where these inequalities represent inequities. Many issues will be culturally specific to the UK, but some will be more rapidly and efficiently addressed through international collaboration.

The disadvantaged populations prioritised during the consensus methods work for this report were BAME groups and the socially deprived, and this is reflected in the recommendations above. However, other disadvantaged populations must not be forgotten and the priorities for research will need to be re-evaluated when the extent of inequalities in these other populations has been quantified and public awareness raised.

List of appendices

Links to appendicies 1-5 are available below

Appendix 1: Kidney disease described for non-physicians.
This appendix was reproduced from the 2016 UK Renal Registry Annual Report with kind permission of the UK Renal Registry.

Appendix 2: Identification of funding awarded by Kidney Research UK since 2001 that relates to kidney health inequalitites.
Dr Gavin Dreyer and Dr Katharine Evans.

Appendix 3: Surveys circulated in the research prioritisation exercise.
Dr Shona Methven and Dr Katharine Evans.

Appendix 4: Scoping review one: Basic sciences and CKD.
Dr Jemima Scott, Dr Shona Methven and Professor Alison Brettle.

Appendix 5: Scoping review two: Social deprivation and development of CKD. Dr Michael Rees and Professor Alison Brettle.

Appendix 6*: Scoping review three: Ethnicity and progression of CKD. Dr Hilda Hounkpatin and Professor Alison Brettle.

Appendix 7*: Scoping review four: Ethnicity and outcomes of ESKD. Emma Wilkinson and Professor Alison Brettle.

* This appendix is being worked up for peer-reviewed publication and so can not yet be published on this platform. Once it has been accepted for peer reviewed publication a pre-publication draft will be made available here. In the meantime please contact the author for any further information you require.

List of shortened forms

ABLE	A Better Life through Education and Empowerment
ACE	Angiotensin converting enzyme
AKI	Acute kidney injury
APOL1	Apolipoprotein L1
ASSIST-CKD	Identifying and monitoring people at greatest risk of progressive CKD
ATTOM	Access to Transplantation and Transplant Outcome Measures
BAME	Black, Asian and minority ethnic
BMI	Body mass index
CI	Confidence interval
CKD	Chronic kidney disease
CVD	Cardiovascular disease
EGF	Epidermal growth factor
eGFR	Estimated glomerular filtration rate
ESKD	End-stage kidney disease
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
KEEP	Kidney Early Evaluation Programme
KQuIP	Kidney Quality Improvement Partnership
LOLIPOP	London Life Sciences Prospective Population
MRC	Medical Research Council
NIHR	National Institute for Health Research
OR	Odds ratio
RRT	Renal replacement therapy
SES	Socioeconomic status
TGFβ	Transforming growth factor-beta

TNFα	Tumour necrosis factor-alpha
UKRR	UK Renal Registry
US	United States of America

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