



## EDITORIAL COMMENT

# Does wealth make health? Cherchez la renal replacement therapy

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## Abstract

In this issue of CKJ, *McQuarrie et al.* have explored the relationship between socioeconomic status and outcomes among Scottish patients with a renal biopsy diagnosis of primary glomerulonephritis. Patients in the lower socioeconomic category had a two-fold higher risk of death. No significant differences were observed on progression to end-stage renal disease (ESRD) requiring renal replacement therapy (RRT), suggesting that overall medical management was appropriate for all socioeconomic categories. The findings are significant since they come from an ethnically homogeneous population with free access to healthcare; they also relate to a specific aetiology of chronic kidney disease (CKD) expected to be less dependent on unhealthy lifestyles than other more frequent aetiologies that dominate studies of CKD in general, such as diabetic or hypertensive nephropathy. A closer look at the data suggests that living in a high socioeconomic area is associated with lower mortality, rather than the other way round. Furthermore, the differences in mortality were most pronounced during the RRT stage of CKD, providing clues for further research. In this regard, *Wilmink et al.* and *Nee et al.* point to access to pre-ESRD nephrology care and to the best kidney transplantation options as modifiable factors to be studied in the realm of T3 translational research to improve CKD patient outcomes.

**Key words:** chronic kidney disease, disadvantaged, glomerulonephritis, mortality, poverty, renal replacement therapy, transplantation, translational research

Chronic kidney disease (CKD) remains a major global health concern. The current definition of CKD uses thresholds for glomerular filtration rate and albuminuria that have been associated with increased all-cause and cardiovascular mortality [1]. Contrary to the classical view that the only concern in CKD patients is to avoid progression to end-stage renal disease (ESRD), it has become clear in recent years that increased risk of death is a major problem and that premature death before progression to ESRD may be an even more frequent outcome than ESRD itself. Limitations in the clinical translation of advances in kidney disease pathophysiology may have contributed to the observation that, in age-adjusted terms, CKD is the fastest growing cause of death worldwide [2, 3].

Thus, every effort should be made to understand the modifiable factors that increase the mortality of CKD patients. The development of new therapeutic interventions based on T1 translational research (bench-to-bedside and back) would be welcomed [2]. However, there is a more pressing need to potentiate T2 translational research (from clinical development to clinical practice), primarily because it has a more favourable cost-effectiveness ratio than T3 translational research, which studies the widespread implementation of clinical practices known to improve outcomes. A lack of resources may impede the implementation of some well-known life-saving interventions. Thus, sevenfold more ESRD patients die every year because of a lack of access to renal

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replacement therapy (RRT) than initiate RRT worldwide [4]. However, benchmarking efforts within or between developed countries are not expected to be marred by a lack of resources. Research aimed at understanding the factors that underly differences in health outcomes between countries of similar wealth or within wealthy developed countries may provide clues for more efficient implementation of already available medical knowledge and techniques.

Worldwide there is an association between wealth and health outcomes in different countries [5]. The Global Burden of Disease study aims to provide a resource that allows the measurement of differences between and within countries that may aid the implementation of public policy that will improve health at the population level [6]. According to the Global Burden of Disease study, there are surprising deficiencies in healthcare in some of the wealthiest and more technologically advanced countries in the world. For example, the USA is ranked 28th in the performance of the health-related Sustainable Development Goals index, just below Greece [5]. Analysis of the ultimate health outcome (life expectancy) [7] discloses a wide margin for improvement in some wealthier countries (Figure 1). Thus, the life expectancy at birth in the USA is below that of countries with a gross domestic product almost five times lower, such as Costa Rica and Peru, and just above that in Cuba. Within the UK, there are differences in life expectancy between the member countries. Life expectancy in Scotland is well below that in England, and is similar to life expectancy in the USA and Peru (Figure 1). Differences in health outcomes exist even within wealthy countries. An association between socioeconomic status and health has previously been observed in population studies within developed countries. Lower socioeconomic status has been associated with worse health outcomes by a variety of measures, including life expectancy in Scotland, which is 13 years lower in patients in the most deprived decile of the population compared with the least deprived decile [8]. Differences between socioeconomic categories may be dragging down the overall health performance of wealthier countries in a clear failure of T3 translational research; resources or knowledge available within some countries does not permeate all layers of society.

CKD appears to be particularly sensitive to socioeconomic issues, with regards to both incidence of CKD and access to renal healthcare. CKD in disadvantaged populations is a major

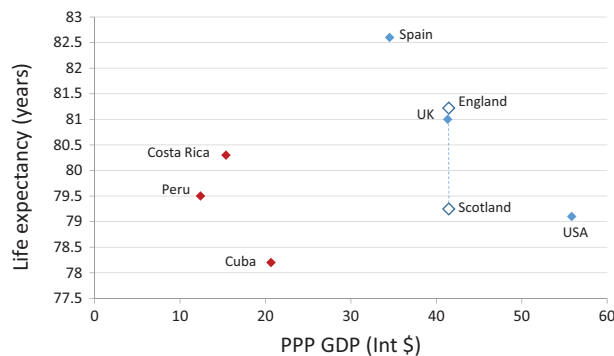


Fig. 1. Wealth and health worldwide: life expectancy at birth according to the Global Burden of Disease (GBD) 2015 study. Life expectancy according to the GBD study [7] versus gross domestic product (at purchasing power parity) per capita (PPP GDP) in international dollars (Int \$) according to the World Bank (<http://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD>). PPP GDP for 2015, except Cuba (2013). Note that despite the huge difference in PPP GDP, life expectancy in the US and Scotland is closer to life expectancy in Peru and Cuba than to life expectancy in England and Spain.

concern and the 2015 World Kidney Day was devoted to this issue [9]. Indeed, some of the CKD hotspots throughout the world are located in developing countries or in disadvantaged populations within developed countries [10, 11]. In this issue of CKJ, three manuscripts address the role of socioeconomic status on healthcare outcomes in CKD [12–14].

McQuarrie et al. [12] report on the impact of multiple socioeconomic deprivation on survival following renal biopsy diagnosis of primary glomerulonephritis in Scotland. Socioeconomic deprivation was categorized in tertiles, calculated by the use of the Scottish Index of Multiple Deprivation datazones, corresponding to the geographic locations where the patients lived. The first piece of information was that the distribution of patients with primary glomerulonephritis did not fit into tertiles. Rather, patients with low socioeconomic status were overrepresented (Figure 2a). The authors previously described a significant association between multiple socioeconomic deprivation and the incidence of immunoglobulin A (IgA) nephropathy, an association not seen in other primary glomerulopathies [15]. Understanding and addressing the causes of this excess occurrence of primary glomerulonephritis may be the most cost-effective way to decrease the deleterious consequences of CKD on health. No significant differences were observed on progression to ESRD requiring RRT, suggesting that overall medical management was appropriate for all socioeconomic categories. However, patients in the most deprived tertile of deprivation were more than twofold more likely to die within a 6-year follow-up than those in the least deprived tertile. The findings are significant because they come from an ethnically homogeneous population with free access to healthcare and relate to a specific aetiology of CKD, primary glomerulonephritis, which is expected to be less dependent on unhealthy lifestyles than other more frequent aetiologies that dominate studies of CKD in general, such as diabetic or hypertensive nephropathy. The authors nicely discuss the potential causes of the observation and the shortcomings of the study, and identify areas for further research.

Despite the emphasis on the most deprived tertile, a closer look at the data suggests that living in a high socioeconomic area is associated with lower mortality than living in the two other tertiles, and that the differences between the two more deprived tertiles were not as marked as between these two lower tertiles and the less deprived tertile (Figure 2b). These are raw, unadjusted data and further definition is required. However, this may not merely be a semantic issue. It suggests that the focus of research should be on how the less deprived tertile differs from the two more deprived tertiles, rather than the differences between the two extreme tertiles. Paradoxically, in order to address the issue of the effects of deprivation on health, the focus should be on the non-deprived population: by understanding the factors that drive their better outcomes, we may be able to define policies that improve the outcomes of the most deprived.

An additional observation, derived from a closer analysis of the data, suggests that the differences in mortality were most pronounced during the RRT stage of CKD, providing clues for further research. A raw, unadjusted calculation of mortality while patients were on RRT disclosed that patients in the two more deprived tertiles were 2.4-fold more likely to die than those in the least deprived tertile (Figure 2b). This difference is higher than the difference in mortality in the pre-RRT stage (60% higher in more deprived tertiles) or those in need of RRT (30% higher in more deprived tertiles). The potential factors underlying the observation of higher mortality while on RRT are

very diverse. During follow-up, patients in the least deprived tertile achieved better blood pressure control in the first 2 years after diagnosis. The cumulative effect of better control of cardiovascular risk factors may have resulted in lower on-RRT mortality. Alternatively, better blood pressure control may be a surrogate for better compliance with medication, either due to cultural issues or access to medications. During RRT, low compliance may be deadly. Pre-ESRD renal care may have differed between the tertiles, as discussed below based on the results of Nee *et al.* [14], although this is unlikely given the small differences in the need for RRT. Access to transplantation or to the best transplantation options may have been an issue, as discussed below based on the findings by Wilmink *et al.* [13]. A future focus on factors centred on the RRT stage is likely to yield answers. In the original analysis, the impact of deprivation on mortality was only observed for focal segmental glomerulosclerosis (FSGS) [hazard ratio (HR) = 7.4 for the lowest versus the highest tertile] and IgA nephropathy (HR = 2.7), and was absent in membranous nephropathy. However, when focusing on on-RRT death, differences appeared to occur in all three diagnoses. Thus, the percentage of RRT patients dying in the two more deprived tertiles versus the least deprived tertile was 50% versus none for FSGS, 33 versus 18% for IgA nephropathy and 30% versus none for membranous nephropathy.

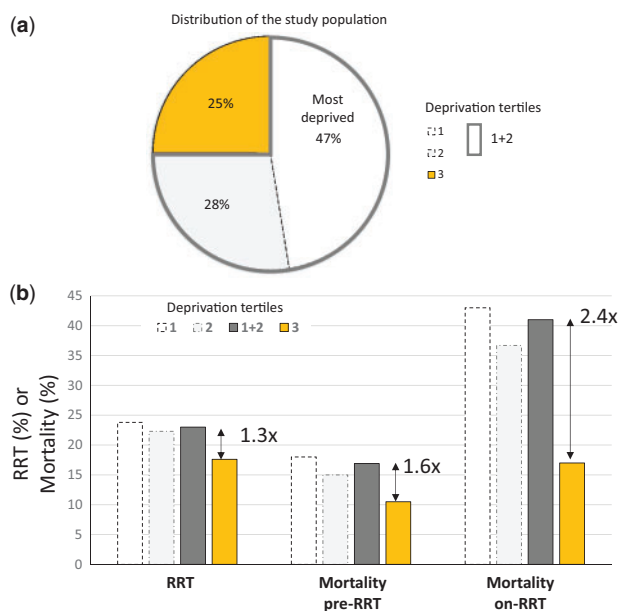


Fig. 2. Impact of socioeconomic status on RRT-associated mortality in patients with a renal biopsy diagnosis of primary glomerulonephritis. (a) Distribution of the population studied by McQuarrie *et al.* [12] according to tertiles of deprivation calculated by the use of the Scottish Index of Multiple Deprivation data-zones. Three-quarters of enrolled patients lived in the two most deprived tertiles (1 and 2). (b) Impact of socioeconomic status on RRT-associated mortality in patients with a renal biopsy diagnosis of primary glomerulonephritis. Deprivation tertiles 1–3 according to McQuarrie *et al.* [12]. Tertiles 1 and 2 represented the two most deprived categories and have been grouped since they were similar regarding occurrence of RRT (expressed as percentage of the whole population in that socioeconomic category that required RRT), pre-RRT mortality (expressed as percentage of the whole population that died pre-RRT among those in each socioeconomic category) and on-RRT mortality (expressed as percentage of patients that died among those requiring RRT in each socioeconomic category). To calculate pre-RRT deaths, patients in the ‘RRT’ category were subtracted from the ‘Death or RRT’ category in Table 3 from reference [12]. On-RRT deaths were obtained by subtracting pre-RRT deaths from total deaths.

Wilmink *et al.* [13] found no effect of ethnicity and socioeconomic group on mode of starting haemodialysis (arteriovenous fistula, graft or catheter), primary arteriovenous fistula failure rate or arteriovenous fistula survival. The study was also performed in the UK, albeit in a different context: an ethnically diverse community in England. Despite the different geographical location, the data argue against roles of haemodialysis initiation or arteriovenous fistula issues in the higher mortality during RRT of the two lower socioeconomic categories in Scotland. However, they do provide insights into factors that may differ according to socioeconomic status. Thus, no differences were found in the distribution of transplantation, but a low socioeconomic status was associated with a lower rate of pre-emptive kidney transplantation, considered the best RRT option [16].

The third study was performed in the USA [14], a country where access to healthcare for disadvantaged populations is a serious problem, and that routinely lags behind the rest of the developed world in RRT outcomes [17–19]. Indeed, even after adjustment for age, gender, race and 25 comorbid conditions, the relative risk of mortality was 3.78 and 1.33 for US haemodialysis patients when compared with patients in Japan and Europe, respectively [17]. Thus, variability in demographic and comorbid conditions fails to account for the higher mortality of US haemodialysis patients [17]. A variety of clinical practice approaches may contribute to the higher mortality of haemodialysis patients in the USA, including shorter duration of haemodialysis, although a higher mortality was also observed in US peritoneal dialysis patients [20–22]. Nee *et al.* [14] now describe that, in a large population (over 700 000 patients initiating maintenance dialysis), individual- and area-level measures of poverty, African American race and Hispanic ethnicity are independently associated with a lower likelihood of pre-ESRD nephrology care. A key observation is that insurance type is associated with the likelihood of pre-ESRD nephrology care, suggesting the contribution of a lack of access to nephrological care. The findings are relevant, since pre-ESRD nephrology care was associated with a significantly lower risk of death in the initial 4 months of dialysis, the period when risk of death is highest [23]. Pre-dialysis care had previously been identified as an important factor determining RRT care [24, 25].

In conclusion, better understanding of the factors driving the worse health outcomes of CKD patients from more deprived neighbourhoods or of lower socioeconomic status is required to provide these populations with the same standard of care that is available to patients of higher socioeconomic status within their own country. The manuscripts published in this issue of CKJ point to RRT as a modifiable factor that should be studied in the realm of T3 translational research to improve CKD patient outcomes, including access to pre-ESRD nephrology care and the best kidney transplantation options. They also point to the benefits of making less deprived proportions of populations the subject of research, in order to benchmark a wide range of potential factors that have driven the results, which are not limited to healthcare itself.

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