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Change in the estimated glomerular filtration rate over time and risk of all-cause mortality

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Using a community-based cohort we studied the association between changes in the estimated glomerular filtration rate (eGFR) over time and the risk of all-cause mortality. We identified 529,312 adults who had at least three outpatient eGFR measurements over a 4-year period from a provincial laboratory repository in Alberta, Canada. Two indices of change in eGFR were evaluated: the absolute annual rate of change (in ml/min per 1.73 m^2 per year) and the annual percentage change (percent/year). The adjusted mortality risk associated with each category of change in eGFR was assessed, using stable eGFR (no change) as the reference. Over a median follow-up of 2.5 years there were 32,372 deaths. Compared to the reference participants, those with the greatest absolute annual decline less than or equal to 5 ml/min per 1.73 m^2 per year had significantly increased mortality (hazard ratio of 1.52) adjusted for covariates and kidney function at baseline (last eGFR measurement). Participants with the greatest increase in eGFR of 5 ml/min per 1.73 m^2 per year or more also had significantly increased mortality (adjusted hazard ratio of 2.20). A similar pattern was found when change in eGFR was quantified as an annual percentage change. Thus, both declining and increasing eGFR were independently associated with mortality and underscore the importance of identifying change in eGFR over time to improve mortality risk prediction.

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Studies have consistently demonstrated that more advanced chronic kidney disease (CKD) is associated with an increased risk of mortality across both general and high-risk populations.[1–5] However, these reports have predominantly considered kidney function at baseline, without consideration of how the change in kidney function over time influences the risk of such outcomes. There has been a growing interest in the association between change in kidney function and risk of adverse outcomes. Although population-based studies have reported an association between declining kidney function specifically and adverse clinical outcomes,[6–11] kidney function can be highly variable and improve over time in some patients.[10,12] Although recent studies have reported an association between improvements in kidney function (increasing estimated glomerular filtration rate (eGFR)) and risk of mortality,[7,8] these studies were limited by their select study population (CKD patients only[7]) and small study size.[7,8]

Using a population-based cohort of individuals receiving routine clinical care in a single Canadian province, we investigated the association between changes in kidney function over time and risk of all-cause mortality. We explored change in kidney function using two indices: absolute annual rate of change and the annual percentage change. We hypothesized that both increasing and declining eGFR would be associated with higher mortality risk, as compared with stable kidney function.

RESULTS

Among the participants, 54.8% had an eGFR $\geqslant$90, 37.9% had an eGFR in the range of 60–89, 4.9% had an eGFR in the range of 45–59, 1.7% had an eGFR in the range of 30–44, and 0.7% had an eGFR in the range of 15–29 (all eGFR in ml/min per 1.73 m^2). The median number of measurements available for the study participants was 3. The distribution of annual rate of change appeared normal and centered near the origin (Figure 1). The mean annual rate of change was -1.04 ml/min per 1.73 m^2 per year (s.d.: 3.83), with a median of -0.91 ml/min per 1.73 m^2 per year (interquartile

range (IQR): −2.98 to 1.07). The distribution of the annual percentage change in eGFR, which also appeared normal, is shown in Figure 1. The mean annual percent change in eGFR was −1.52 percent/year (s.d.: 6.05), with a median of −1.07 percent/year (IQR: −3.77 to 1.34).

Compared with study participants, individuals excluded because of an inadequate number of serum creatinine measurements (less than three outpatient serum creatinine measurements spanning a time period of four calendar years—Figure 2) were younger, with fewer comorbidities and a higher level of eGFR at baseline (Supplementary Appendix Table S1 online).

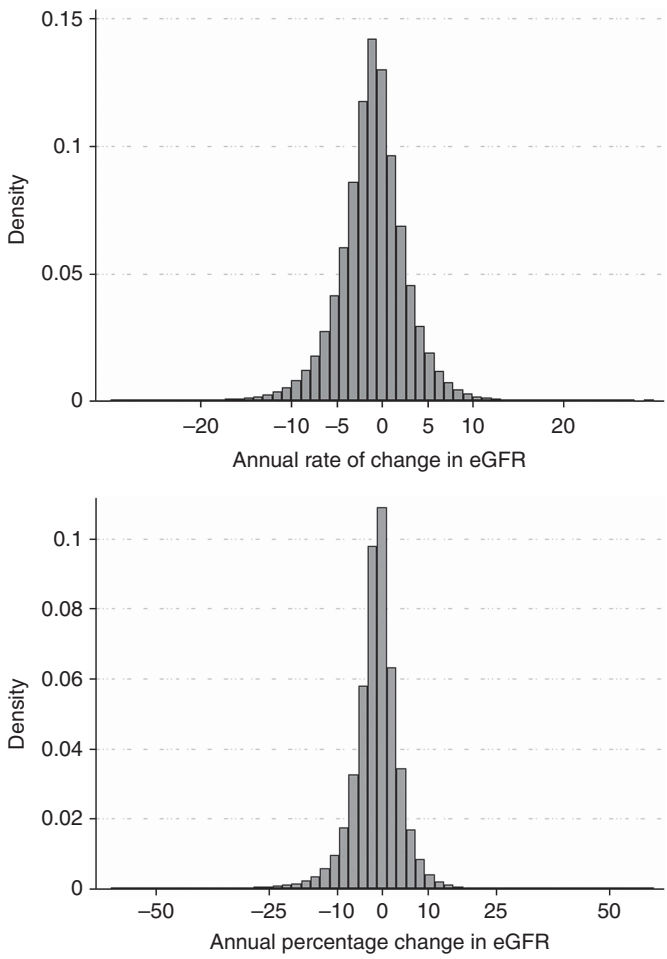

Figure 1 | Distribution of annual rate of change and annual percentage change in estimated glomerular filtration rate (eGFR).

Among the study cohort, 135,804 (25.7%) had stable kidney function (no change in kidney function over the accrual period), 133,723 (25.6%) had a positive slope (improved kidney function), and 257,785 (48.7%) had a negative slope (declining kidney function). Participants experiencing a greater annual decline or increase in eGFR were more likely to be female and had a higher prevalence of comorbidities, in comparison with those with stable kidney function (Table 1).

Over a median follow-up of 2.5 years, there were 32,372 (6.1%) deaths. Adjusted mortality rates were higher, with both declining and increasing eGFR (Table 2), as compared with those with stable kidney function: the greater the change in eGFR, the higher the mortality risk. Mortality rates (per 1000 person-years) were highest for participants with an increase in eGFR of 5 ml/min per 1.73 m^2 per year or more (rate 16.52; 95% confidence interval (CI): 15.78–17.25) and participants with a decline in eGFR of 5 ml/min per 1.73 m^2 per year or more (rate 11.27; 95% CI: 10.90–11.65). Similarly, higher mortality rates were observed for increasing as well as declining percentage change in eGFR (Table 3). The mortality rate was highest (rate 15.15; 95% CI: 14.52–15.78) for participants with an increase in eGFR of $\geqslant$7 percent/year or more, followed by participants with a decline in eGFR of $\geqslant$7 percent/year (rate 11.60; 95% CI: 11.20–11.99).

Compared with those with stable eGFR, the adjusted risk of death was almost two-fold higher in participants with an increase in eGFR of $\geqslant$5 ml/min per 1.73 m^2 per year (hazard ratio (HR) 2.20; 95% CI 2.10–2.31), whereas those with a decline in eGFR of $\geqslant$5 ml/min per 1.73 m^2 per year also had 2-fold increased risk (HR 1.52; 95% CI: 1.46–1.57) (Figure 3). Similarly, we observed a U-shaped relation between percentage change in eGFR per year and all-cause mortality (Figure 4). The risk of mortality was 2.02 times higher (95% CI: 1.92–2.11) for the participants with an increase in eGFR of $\geqslant$7 percent/year or more, and the mortality risk was 1.56 times higher (95% CI: 1.49–1.62) for the participants with a decrease in eGFR of 7 percent/year or more.

Sensitivity analyses

When stratified by category of baseline kidney function (eGFR $\geqslant$90, 60–89, 45–59, 30–44, and 15–29 ml/min/1.73 m^2), increasing as well as declining eGFR was associated

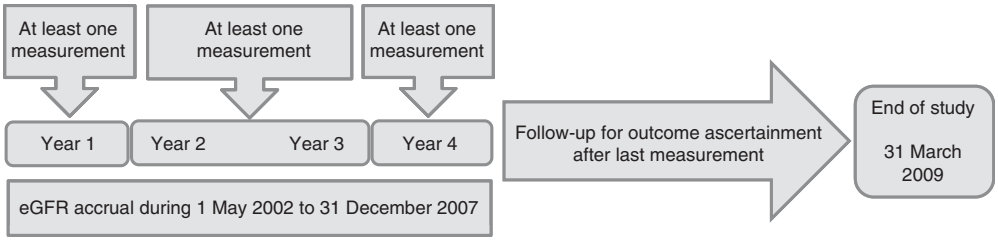

Figure 2 | Overview of cohort creation. eGFR, estimated glomerular filtration rate.