Assessing the impact of chronic kidney disease on individuals and populations: use of relative and absolute measures

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Chronic kidney disease (CKD) is now recognized as a global public health problem, contributing substantially to the burden of non-communicable disease (NCD) [1, 2]. CKD is associated with a variety of NCD outcomes, including renal [end-stage renal disease (ESRD)], cardiovascular and non-cardiovascular. It is important to quantify the risks associated with CKD on such disease outcomes in individuals and the impact of CKD on whole populations, and given the high prevalence of CKD and increased risks of most NCDs at older ages, how the impact of CKD varies by age.

The paper by Marks et al. is a population-based study using routinely collected data in the Grampian region of Scotland which aimed to determine the effect of CKD (largely Stage 3b–5) on renal replacement therapy (RRT) and all-cause mortality (ACM). The impact of CKD on RRT and ACM was mainly due to CKD in older age groups, a paradox given that the absolute risk of progression to RRT in the CKD cohort and the relative risks of ACM associated with CKD both fell with age. The findings are firstly an illustration of the contrasting information provided by relative and absolute measures of the effects of risk factors, age and CKD on disease outcomes, and secondly highlight the possible interaction between age and CKD. The authors also developed risk prediction tools to determine the absolute risk of RRT and ACM for patients with CKD.

This article considers these concepts in more detail.

Relative measures

Relative measures define the strength or magnitude of associations between risk factors and disease and the most commonly used is the relative risk (see Table 1) [3, 4]. For a dichotomous exposure, this is the ratio of risk in an exposed group divided by the risk in an unexposed (or normal group) derived from a cohort study. Hazard ratios are used where survival analysis is undertaken. In case–control studies, the other main observational design in aetiological epidemiology, the relative risk, is estimated from the odds ratio, which approximates the relative risk well for the most disease frequencies except when they are common. Observational studies do not prove causation but assuming a well-designed study with minimal bias and adjustment for known key confounders the adjusted relative risk is the key effect measure of the strength of causation of a putative causal exposure.

CKD is a complicated exposure as there are two independent components, filtration and kidney damage, usually assessed by estimated glomerular filtration rate (eGFR) and albumin creatinine ratio (ACR) (or dipstick proteinuria). The CKD Prognosis Consortium has shown the independent effects of these measures in general, high-risk and CKD cohorts, for both renal and mortality outcomes [5–8]. While the causative pathway of CKD to ESRD is not in doubt [the only question being the relative contribution of severe acute kidney injury (AKI) to ESRD], the observational association of CKD with cardiovascular disease (CVD) and other NCDs may be partly due to them being manifestations of shared determinants [9].

The study by Marks found that the relative risk of CKD (Stage 3b–5 measured by eGFR) for ACM declined with age, i.e. there was an age–CKD interaction, or age was an effect modifier. In defining interaction, there are differences between biological interaction, i.e. the pathway to causation for two factors is not independent, and statistical interaction. As most multivariate analyses of outcome use logarithmic systems (logistic, Cox proportional hazards model), the interaction found in such statistical models is on a multiplicative scale, whereas biological interaction is any departure from an additive model [10].

Others have also found an age–CKD interaction with ACM [11, 12]. In another UK population-based study using routine data, the relative risk of ACM fell substantially in unadjusted analyses for all CKD stages from Stage 3 and below; for example from Stage 5 CKD (eGFR <15 mL/min), compared to eGFR >60 mL/min, it fell from 26.1 in the age group 20–44 years to 2.5 in the 85 + years age group [11]. The US Veterans data showed an age-related interaction with ACM at all levels of CKD with declining relative risk at older ages, especially in more moderate CKD [12]. In contrast, in the Hunt II study, the associations of eGFR and ACR with cardiovascular mortality were higher...
in those aged over 70 compared to the age group under 70, with similar findings, though not reported, for ACM [13]. The CKD Prognosis Consortium meta-analysis in both general and high-risk cohorts found a tendency for higher relative risk in those with low eGFR for CVD mortality and ACM in younger populations, though with a similar pattern in all ages and no age interaction for ACR [5, 6].

There is still some uncertainty about the presence or degree of any age–CKD (eGFR) interaction [14]. The biological basis of such an interaction is not known but is likely to be related to the very low risk of mortality in people without CKD. The presence of CKD opens up a strong causal pathway with a substantial (relative) impact on mortality, whereas in older people, there are multiple pathways to mortality from different cumulative morbidities, and CKD per se therefore has less potential relative effect on mortality. Differential age-related patterns of CKD diagnoses may also contribute.

### Absolute measures

Absolute measures of risk estimate the impact of a causative factor on disease occurrence in individuals (exposed person or patient) or within a population and thereby the potential scope for reducing disease occurrence from prevention or treatment to lower the exposure or its effect. The extent to which absolute risks of an exposure differ by key non-modifiable demographic factors, such as age, gender, ethnicity, socio-economic status and location (area, country) is an important consideration for assessing equity and for targeting resources.

#### Individual

At the individual level, the question is how much more risk is there from having the exposure, assuming that there will be a baseline risk from other factors and causal pathways. This can be expressed as the absolute risk difference (ARD) or excess risk difference, formulated as the incidence (risk) in exposed minus incidence (risk) in not exposed (see Table 1). An extension is to consider the excess risk as a percentage (or proportion or fraction) of total risk in the exposed. The ARD indicates the potential scope for reducing disease occurrence in those exposed.

The ARD is dependent on two variables: the relative risk or rates and baseline risk in the control or non-exposed group. Even if the relative risk is very high, the ARD is low if the underlying non-exposed group risk is low (multiplying a small number still leaves a relatively small number). Conversely, when the underlying risk in the non-exposed is high even a small relative multiplier can lead to a big absolute difference.

This is the situation found by Mark’s et al. for age, CKD and mortality. For example in the age groups 15–54 and 85+ years, there were 19-fold and 2-fold increases in the relative risk of ACM in those with CKD compared to those without CKD, respectively. However, because of the large age differences in the risk of ACM, this equated to only 2 excess deaths per 100 patient-years among those aged 15–45 years but 17 excess deaths per 100 patient-years among those aged ≥85 years. Similarly, in the Hunt II study, the ARD (cardiovascular deaths per 1000 patient-years) was only 4.1 for those aged under 70 with an eGFR <45 mL/min and microalbuminuria compared to reference (eGFR >75 mL/min, optimal ACR), whereas it was 63.6 in those aged over 70 despite similar relative risks. This was due to a large, 9-fold, difference in underlying CVD risk in the reference group in older compared to younger age groups. Higher absolute risks of ACM and CVD mortality with age were also shown in CKD Prognosis Consortium cohorts [6, 8].

For patients and clinicians, absolute risks of outcomes and the relative balance of competing outcomes are more important than relative risk measures for guiding shared decision making about individual care. This is most developed in the field of cardiovascular disease risk

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**Table 1. Measures of effect**

<table>
<thead>
<tr>
<th>Type of measure</th>
<th>Level</th>
<th>Measure</th>
<th>Derive</th>
<th>Notes and other terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative</td>
<td>Relative risk (RR)</td>
<td>Ratio of incidence in exposed (Ie)/incidence in not exposed (Ine), Ie/Ine</td>
<td>Null = 1. Also derived from hazard ratios from time to event survival analysis. Incidence can be based on risk or rates</td>
<td></td>
</tr>
<tr>
<td>Odds ratio (OR)</td>
<td>Derived from case–control study. Ratio of odds in exposed to non-exposed Ie – Ine</td>
<td>Null = 0. Also called: attributableb risk difference, attributable risk, excess risk, excess risk difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute</td>
<td>Person/patient</td>
<td>Absolute risk difference (ARD)</td>
<td>All derive: absolute risk proportion/fraction, attributable risk proportion/fraction, excess risk fraction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Ie − Ine)/Ie × 100 or (RR − 1/RR) × 100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>Absolute risk percent (AR%)</td>
<td>All called: population absolute risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>It − Ine, It = whole population risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>Population attributable risk (PAR)</td>
<td>All called: population absolute risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Ie − Ine)/It × 100; (RR − 1) p/(RR − 1) p + 1, p = prevalence</td>
<td></td>
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</table>

bThere has been confusion in the epidemiological literature about the use of the term ‘attributable’ risk. Rothman et al. prefer use of the term excess risk.

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Null = 1. Also derive: hazard ratios from time to event survival analysis. Incidence can be based on risk or rates.
assessment where there are desktop tools to generate absolute risk, with preventive strategies tailored to the degree of risk. Marks et al. developed information tools to show the absolute risks of RRT initiation and survival free of RRT (both as percentage at 5 years) in the Gram- pian population by age, gender, albuminuria and CKD stage. Age effects the balance of RRT and mortality with much higher risks of death than RRT, as shown by others [14–16]. Competing risks are a potential issue in such analyses, as the effect of CKD on mortality will alter ESRD and RRT risks [17]. While these prediction tools maybe useful in the source population, generalizability of the information to populations with differing underlying mortality risks and differing policies for RRT provision in the elderly is an issue [18]. For example the Hunt II and ARIC cohorts, which had a similar duration of follow-up, mean age and mean eGFR, had a nearly 2-fold difference in ACM risk as quoted in CKD Prognosis Consortium data [5]. Another example is the 12-fold variation in age-standardized coronary heart disease mortality rates for men in countries in the European region in 2007 [19].

eGFR and ACR have been incorporated into multivariate risk prediction models where their relative effects contribute to predicting individual absolute risk for important NCDs. There is no assumption of causality in such prediction models, though they should allow for interactions. In the Hunt II cohort, eGFR and ACR improved the classification of CVD mortality risk when added to traditional CVD risk factors, and particularly in those aged 70 + years in whom traditional factors perform less well [13, 20]. Tangri et al. developed and validated a predictive model for CKD 3–5 patients referred to nephrologists, of progression to start RRT. A model based on age, sex, eGFR and ACR, similar variables as in Mark’s study, had good discrimination in the development cohort [21]. Increasing age reduced the rate of progression to RRT as in Mark’s study. However, a model including routinely available biochemical variables improved the discrimination and, in the external validation set, had higher net re-classification, though this model requires further external validation.

Population level

The population attributable risk (PAR) and percent (PAR %) are measures of how much of a condition/disease in the population can be ascribed to a particular exposure (see Table 1). If the exposure is causal, this gives an indication of the impact of reducing such exposure on population health (e.g. the percentage of disease potentially preventable if the population is never exposed or at least the potential gain from reducing the exposure). Such measures can help prioritize public health policy by identifying the importance of different exposures overall or within different population groups (e.g. age, ethnic, socio-economic, area). Both measures depend on the relative risk and the frequency (prevalence) of the exposure, and PAR also depends on the underlying risk in the non-exposed as for ARD. Most commonly this approach has been used for identifying the impact of key adverse behaviours or consequences such as smoking, obesity or hypertension. For specific diseases the approach is most useful where the impact is significantly underestimated by coding systems, and/or where disease affects multiple organ systems. Diabetes and CKD would be good examples, whereas the population impact of some diseases is captured well by rates using cause specific coding (e.g. lung cancer). The PAR% has been derived for the impact of diabetes on ACM globally and by different regions, and in the UK by geographical area [22, 23].

Mark’s study illustrates the derivation of PAR in a population with diagnosed CKD for risk of RRT with age at the exposure. The explanation for the predominance of older patients starting RRT in this population is the very high frequency of diagnosed CKD in older age groups (1418 people with CKD 3b–5 aged 75–84 years compared to only 31 in those aged 25–34 years) despite the lower absolute risk of ESRD/RRT (and presumed relative risk) in older age groups. The CKD Prognosis Consortium also found lower absolute risks of ESRD with increasing age and showed reduced relative risks for eGFR and ACR [7]. Given the high excess risk of ACM due to CKD in the Gramian population in older age groups, the population impact will also be high. From the study by Raymond et al. [11], one can estimate the PAR% for ACM due to CKD in different age groups based on the assumed relative risk and prevalence data presented. The CKD prevalence was only 0.5% in the 20–44 age group but 20% in the 75 + age group, and yet despite the higher relative risks in the younger age groups, the PAR% in the former group was ~7% compared to ~16% in the latter group. These age-related measures of population impact could be derived for other disease outcomes associated with CKD. For example, for AKI, the CKD Prognosis Consortium found independent relative effects of eGFR and ACR, with no clear difference of relative risks with age but higher absolute risks of AKI in the elderly, and hence, given the high CKD prevalence, this would indicate a high PAR% of CKD for AKI in older age groups [7].

Within the large prevalent pool of older CKD patients, the challenge is to improve risk stratification to target intervention most cost effectively and safely and prevent CKD-related mortality and morbidity including progression to RRT, as outlined above [13, 21, 24]. The impact of CKD on the burden of NCDs in different countries and on different socio-demographic groups within countries will depend on the prevalence of CKD (both eGFR and ACR), the underlying population risk of NCDs in those without CKD and the relative risks of CKD for NCDs (though these may vary less between populations).

The changing demography in developed countries and many emerging economies of an increasing prevalence of people of older ages will increase the prevalence and hence population impact of CKD. In England, extrapolation of the prevalence estimates from the representative national survey the Health Survey for England to population estimates indicates over a third of the population prevalence of CKD (eGFR < 60 mL/min) is in people >75 years and over 60% in those aged over 65 years [25]. A double impact in a population occurs when CKD prevalence rises at the same time as baseline NCD risk, as with the global obesity and type 2 diabetes epidemic [2].

Given the importance of prevalence on population impact, the reporting of CKD prevalence and its trend
over time provides important public health information about the likely population impact of CKD. This has variously been reported as CKD Stage 3–5 and all CKD Stage 1–5. However, the CKD Prognosis Consortium findings would suggest that NCD risk could also be captured by reporting eGFR <45 mL/min and ACR >30 or 300 mg/g [26]. Valid comparison between populations and over time would be dependent on eGFR estimation method and assay calibration, robust survey design and by age standardization [27].

Other important measures such as disability adjusted life years (DALYs) and differences in premature events such as premature mortality give more weight to the impact of exposures/diseases in younger people. Health care and other costs of an exposure/disease are important too for prioritising investment in prevention, treatment, and care.

Conclusions

Absolute measures are important in understanding the impact of CKD on individuals and populations. Such measures are more dependent on the population context than relative measures. The population impact of CKD is higher in older ages, despite the potential negative interaction between declining eGFR and increasing age on the relative risks of several NCD outcomes, because of the high prevalence of CKD and high underlying risks of NCDs in older age groups. Measurement of ACR (or dipstick protein) is essential for risk assessment in all age groups including people of older ages.

Preventing the development and progression of CKD across the life course is a key goal to reducing this age-related burden.

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(See related article by Marks et al. Translating chronic kidney disease epidemiology into patient care—the individual/public health risk paradox. Nephrol Dial Transplant 2012; 27: iii65–iii72.)

References


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