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Age and the eGFR-dependent risk for adverse clinical outcomes

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ABSTRACT

Although the relative risk of kidney failure increases with more severe chronic kidney disease (CKD) independent of age, with older age the absolute risk of kidney failure at a given time horizon becomes smaller. In this article, we first review some epidemiological measures of outcome occurrence (absolute rate or risk) and association (relative measures: difference or ratio of rates or risks). We emphasize that relative measures need to be presented along with absolute measures to be understood and absolute risk is more helpful than absolute rate when making treatment decisions. We then apply these principles to the discussion of the absolute and relative rates or risks of kidney failure and death across categories of estimated glomerular filtration rate and age. Lastly, we discuss the implications of existing studies on whether the definition of CKD should account for age.

Keywords: age, chronic kidney disease, kidney failure, mortality, risk

The prevalence of chronic kidney disease (CKD) in the general population increases with age, from 4% at age <40 years to 47% at age 70 years and older [1], as do more severe CKD stages, characterized by lower estimated glomerular filtration rate (eGFR) and worse outcomes [2]. Understanding how age may modify the association between eGFR and adverse outcomes in people with CKD is not straightforward. In a large meta-analysis of over 2 million participants from the CKD Prognosis Consortium (CKD-PC) [3], with older age the curve of the hazard ratios for mortality associated with a progressively lower eGFR versus a reference of 80 mL/min/1.73 m^2 increased less steeply, while the curve of the absolute mortality rates associated with lower eGFR was steeper. In the same study, the association between eGFR and end-stage kidney disease (ESKD, defined as initiation of kidney replacement treatment or death coded as due to kidney disease other than acute kidney injury) did not vary with age on the hazard ratio or absolute rate scales. How do we interpret these findings? Does age modify the association between eGFR and mortality? Does this study provide evidence that considerations about age are irrelevant with respect to the association between rates of ESKD and levels of eGFR? The role of age in defining CKD and assessing its prognosis has been a matter of longstanding debate [4]. Some members of the kidney community have raised concerns that the current CKD definition based on a single eGFR threshold artificially inflates the size of the population with CKD by labeling many older adults who have an age-related decline in kidney function with a disease that they do not have [5]. Existing studies on how age may modify the association between eGFR and adverse outcomes have been interpreted to support opposite views of how eGFR should be used to define CKD [6], especially in the majority of adults who are 65 years old or older and have an eGFR between 45 and 59 mL/min/1.73 m^2 with normal or mild albuminuria [7]. In this article, we first review epidemiological measures of outcome occurrence and association.

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We then apply these principles to the discussion of the absolute and relative rates or risks of kidney failure (with or without kidney replacement treatment) and death across categories of eGFR and age.

EPIDEMIOLOGICAL MEASURES OF FREQUENCY AND ASSOCIATION

Frequency measures

The first step in estimating the association between exposure and outcome consists of measuring how often the outcome occurs across levels of exposure. Incidence rate and incidence proportion are the most common outcome measures in clinical epidemiological studies. Incidence rate measures the occurrence of new cases of an outcome per unit of person-time. This rate has also been called the person-time rate, incidence density, force of morbidity, hazard rate and disease intensity. The latter three terms are more commonly used to refer to the limit the incidence rate approaches as the unit of time approaches zero [8]. Of note, time is included in the denominator of the incidence rate, which makes the incidence rate a measure of the "speed" of the disease process.

$$\text{Incidence rate} = \frac{\text{Number of event onsets}}{\text{Total person} - \text{times spent in population}}$$

Incidence proportion (or cumulative incidence) measures the proportion of a population at risk that develops the outcome of interest over a specified time period and is a direct estimate of risk [8]. Incidence proportion is unitless and time is not included in the denominator of the fraction. As a result, risk is a measure of the total distance that the outcome process has travelled over a specified time interval. Since the incidence proportion increases monotonically over time, a specific time reference needs to be attached to the estimate of the incidence proportion.

For uncensored binary outcome,

$$\text{incidence proportion} = \frac{\text{Number of people at risk who develop the event of interest during the observation period}}{\text{Total number of people at risk at the beginning of the observation period}}$$

For censored event-history (survival) data, common nonparametric methods to estimate the cumulative incidence function include the Kaplan–Meier (when there are no competing events) and Aalen–Johansen (when there are competing events) estimators.

The term risk is widely used in the medical literature, although the actual outcome measure in a study may be an incidence rate (speed), which is often confused with risk (distance travelled in a time interval). The concept of risk applies to individuals and groups in a population. An individual risk refers to the relative frequency of an event in a group of individuals (the study sample) with similar characteristics to the target population [8]. For example, if a patient is told that he or she has an 80% risk of an event at the 5-year prediction horizon (risk over 5 years), it means that if there were 100 patients like them, 80 would experience the event by 5 years.

In the clinical setting, risk is a more appealing outcome occurrence measure than rate. A patient wants to know their risks of experiencing an event by a certain time in the future (the disease accumulated or distance covered at that time) rather than the speed of the disease process. For example, it is easier for a patient to understand the meaning of a 10% risk of a cardiovascular event in 5 years than a rate of 2 cardiovascular events per 100 person-years, which will result in the same risk at 5 years if this rate remains constant. Instead, a rate, like a speed, often varies over time and thus may provide only indirect information about the distance travelled in a time interval. In addition, in a competing risks setting, each risk depends not only on one hazard rate and one linear predictor (the combination of the individual characteristics and the model coefficients) but on all estimated hazards and linear predictors. Risks calculated assuming other competing risks do not exist are overestimated [9, 10].

Table 1: Common epidemiological measures of outcome occurrence and measures of association.

Outcome occurrence measures	Measures of association
Incidence rate	Incidence rate difference; incidence rate ratio
Hazard rate	Hazard ratio
Risk	Risk difference; risk ratio

Measures of association

The association (or effect, in the absence of bias and confounding) of a factor or exposure on an outcome is the change in the outcome measure (rate or risk) as the level of the factor or exposure changes. Measures of association can be incidence rate difference, incidence rate ratio, hazard ratio, risk difference or risk ratio (Table 1). Providing only relative rates (or risks) may result in misleading information, as the ratio of two rates (risks) may not be clinically meaningful if the reference rate (risk) is low. For example, one cyclist may bike two times as fast as another cyclist, but they will both have travelled a very short distance if the two speeds are 0.5 and 1 km per hour and the total journey is 100 km. If a meaningful distance to cover in 1 h is 10 out of the total 100 km (e.g. a 1-year meaningful risk threshold of 10%), both cyclists will have completed only 0.5–1/100 of the distance in 1 h (their risk of 0.5%–1% at 1 year is far below the threshold of meaningful risk). While a relative speed of 2 is impressive, when the speed ratio is presented with the fraction of the distance travelled per unit time by each cyclist relative to the total journey our interpretation changes. The cyclists travel at different speeds yet the difference in their speeds is irrelevant relative to the entire distance to cover (Fig. 1).

Clinical epidemiologists have proposed measures of clinical relevance such as the number needed to treat (which is the inverse of the difference in absolute risks) [11] to highlight the importance of providing an absolute measure of disease occurrence with the relative effect when presenting results of a clinical trial [12]. Yet, in most observational epidemiological studies, where the same principles apply, too often only measures of associations are presented (relative risks or rates) [13]. When absolute measures are presented, risks are seldom included.

AGE AND ASSOCIATIONS BETWEEN eGFR AND ADVERSE CLINICAL OUTCOMES

The occurrence of adverse clinical outcomes generally increases with advancing age. It is well-known that GFR declines with older age [14]. Most epidemiological studies of the associations between kidney function and adverse outcomes rely on estimated GFR rather than measured GFR. It is important to keep in mind that age is one of the input variables used to estimate GFR and is also included along with eGFR in outcome modeling. The impact of such practice is unclear [15].

Although consideration of a wide range of clinical outcomes is important, existing studies examining the associations

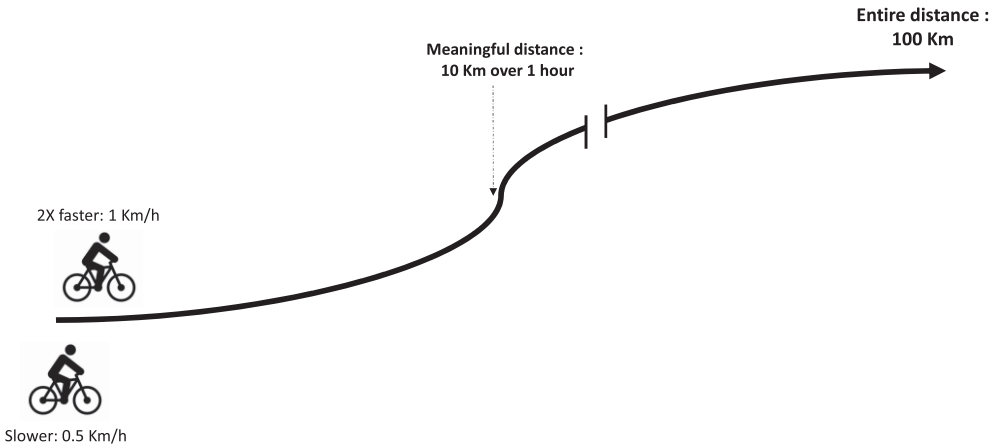

Figure 1: An illustration of relative rate and absolute risk. The cyclists travel at different speed (speed ratio of 2), but the distance they have traveled over 1 h (1 and 0.5 km) is irrelevant for both relative to the entire distance of 100 km.

between eGFR and adverse clinical outcomes according to age have focused on the definitive outcome of all-cause mortality and the most severe kidney outcome of kidney failure, usually defined as initiation of kidney replacement therapy [3, 7, 16, 17]. This definition of kidney failure will misclassify a large fraction of elderly people who chose not to treat kidney failure with kidney replacement therapy [18].

Age and the association between eGFR and all-cause mortality

Relative association (hazard ratio)

In the CKD-PC study, the curve of the adjusted hazard ratio associated with progressively lower eGFR versus a constant reference value became less steep (i.e. increased to a lesser extent) with older age [3]. Relative mortality rate ratio (eGFR 45 versus 80 mL/min/1.73 m^2) decreased as age increased (Fig. 2, top right panel). Using a common reference eGFR of 80 mL/min/1.73 m^2 for every age category, the adjusted hazard ratio for mortality began to increase significantly when the eGFR was approximately <60 mL/min/1.73m^2 across all age groups. This finding of relative change in "speed" was adopted to support the use of single eGFR threshold for defining CKD [19]. However, change in speed does not inform about the distance the disease has travelled by level of exposure and modifier (eGFR and age, respectively), and thus cannot stand alone in the assessment of these associations. In other words, we cannot understand the distance travelled (risk at certain time horizons of interest) from the change in speed.

Another issue to consider when reporting relative measures is that relative associations depend on the choice of the reference category. If we agree that eGFR declines with older age, we should use an age-adapted eGFR reference category. Instead of using a common reference eGFR for all ages [3], a re-analysis of the data that changed the reference category within each age group reached apparently different results: hazard ratios for mortality increased in a similar way when the threshold of CKD was increased from 60 to 75 mL/min/1.73 m^2 in individuals aged 18–54 years, maintained equal to 60 mL/min/1.73 m^2 in those aged 55–64, and lowered to 45 mL/min/1.73 m^2 in those aged ≥65 years [14]. When using relative measures of association, the choice of the reference category matters.

Absolute rate

In the CKD-PC study [3], the curve of the absolute mortality rates associated with lower eGFR was steeper with older age, suggesting that differences in mortality rates associated with progressively lower eGFR were larger in older than in younger age categories. For example, the difference in mortality rates between an eGFR of 45 versus 80 mL/min/1.73 m^2 was 27.2 deaths per 1000 person-years for age ≥75 years and 9.0 deaths per 1000 person-years for age 18–54 years (Fig. 2, top panels). Comparing differences in mortality rates (speeds instead of distances) across age groups is problematic [14], because mortality increases with age, resulting in different baseline mortality risks across age groups. In addition, the implication of a young person (say a 40-year-old) dying in the next 10 years is very different from an old person (80-year-old) dying in the next 10 years. Finally, mortality rates are seldom constant [20].

Absolute risk

Absolute risk data overcome the limitations of relative associations (which are reference-sensitive) or rates (interpretation- and time-variability). Absolute risk data can be obtained after controlling for confounding by regression (adjusted cumulative incidence functions from cause-specific or sub-hazard regression models [9, 10]) or stratification. A Canadian population-based cohort study reported data on the underlying mortality risks in people 65 years or older with normal or mild albuminuria. In this study including 127 132 people who had CKD according to current eGFR criteria (a fixed threshold of 60 mL/min/1.73 m^2), as many as 54 342 (43%) were 65 years or older and had a baseline eGFR of 45–59 mL/min/1.73 m^2 with normal or mild albuminuria. The difference in the 5-year absolute risk of death between people with an eGFR of 45–59 mL/min/1.73 m^2 and those with an eGFR of 60–89 mL/min/1.73 m^2 (non-CKD controls) was minimal in age groups 65–74 and ≥75 years (Fig. 3, top panels). While 5-year mortality risk was higher for eGFR of 15–44 mL/min/1.73 m^2 within each age subgroup (65–69, 70–74, 75–79 and ≥ 80 years), the difference between eGFR 45–59 and 60–89 mL/min/1.73 m^2 was small in all age categories >65 years (Fig. 4, top panel). Figure 5 shows the distribution of 5-year risk by event type (death and kidney failure) over age treated as a continuous variable. The relationship between age and 5-year risk was only

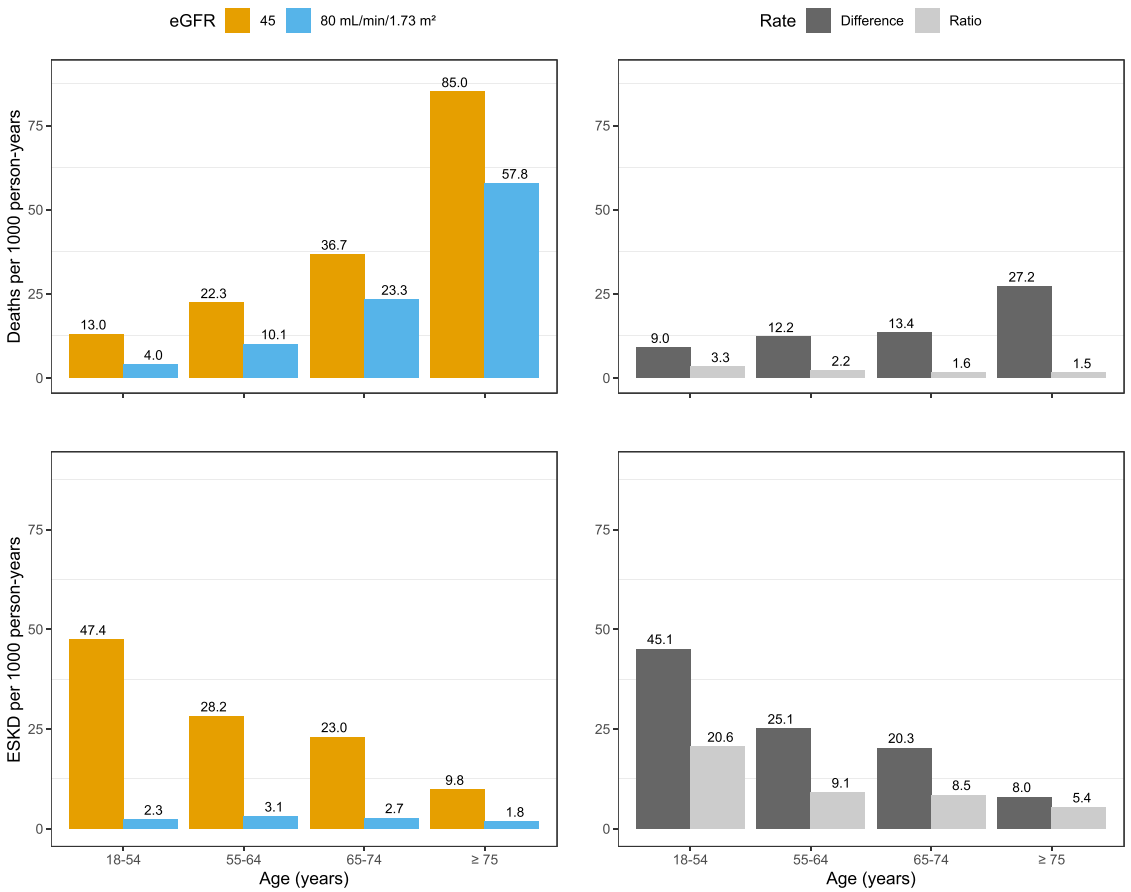

Figure 2: Relative and absolute rates of death and ESKD associated with eGFR according to age categories (CKD-PC study). ESKD was defined as initiation of dialysis, kidney transplantation or death coded as due to kidney disease other than acute kidney injury. Data were from the CKD-PC study [3]. Left panels: absolute mortality (top) and ESKD rates (bottom) associated with an eGFR of 45 versus 80 mL/min/1.73 m^2 across age categories. Right panels: differences and ratios of mortality rates (top) and ESKD rates (bottom) associated with the change in eGFR from 45 to 80 mL/min/1.73 m^2.

slightly altered by eGFR levels of 45–59 and 60–89 mL/min/1.73 m^2 in elderly people with normal or mild albuminuria (the majority of elderly people with CKD according to current eGFR criteria; Fig. 4, bottom panel) [7].

Age and the association between eGFR and kidney failure

Relative association (hazard ratio)

Data from the CKD-PC study show that the relative hazards of ESKD with lower eGFR were comparable across age categories, with the exception of slightly stronger association in the youngest age group with eGFR of 41–51 mL/min/1.73 m^2 [3]. What is the meaning of this apparent lack of evidence of interaction? As compared with a reference eGFR of 80 mL/min/1.73 m^2, an eGFR level of <60 mL/min/1.73 m^2 was associated with an increased hazard of ESKD in both younger and older adults [3]. Does the increased relative hazard of ESKD at eGFR <60 mL/min/1.73m^2 across all age groups support the use of single eGFR threshold for defining CKD?

Absolute rate

In the same study, the authors reported mean incidence rates for ESKD according to eGFR within each age category [3]. Rates of ESKD were close to 0 for eGFR ≥60 mL/min/1.73 m^2 and can be appreciated only when eGFR was below 45 mL/min/1.73 m^2, particularly for older individuals: 23.0 and 9.8 cases per 1000 person-years for age 65–74 and ≥75 years, respectively [3]. The ESKD rate difference associated with an eGFR of 45 versus 80 mL/min/1.73 m^2 appeared to be smaller with increasing age (for example, 45.1 versus 8.0 cases per 1000 person-years for age ≥75 versus 18–54 years; Fig. 2, bottom panels), although "the differences in absolute risk were not significant except for a limited GFR range in which the adjusted average ESKD incidence rate was higher in the youngest age group" [3]. While proper interpretation of relative hazards requires information on absolute measures of disease occurrence, we should remember that the authors reported rates, not risks. A rate is a "speed" and thus provides only indirect information about the absolute risks over a time interval. Estimates of the absolute risk of kidney failure will help us better understand the impact of decreased eGFR on the outcome of kidney failure across age groups.

Absolute risk

Although the relative hazard of ESKD dramatically increases with lower eGFR regardless of age, the absolute risk of kidney failure becomes smaller with older age. Considering elderly

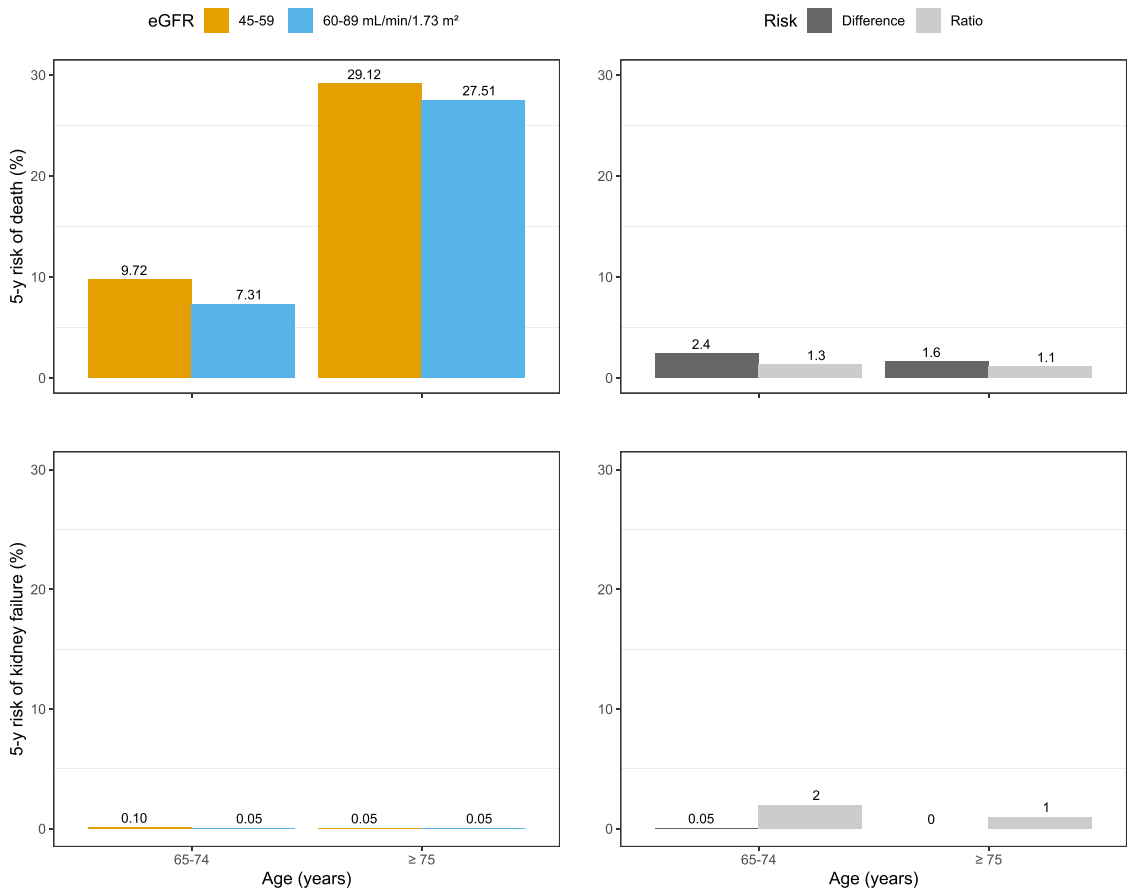

Figure 3: Relative and absolute risks of death and kidney failure at 5 years, by baseline eGFR and age categories (65–74, ≥75 years) in people with normal/mild albuminuria. Kidney failure was defined as the earlier of the initiation of chronic dialysis or kidney transplantation or a sustained eGFR of <15 mL/min/1.73 m^2 for >90 days. Data were from the Canadian population-based cohort study [7]. Left panels: absolute mortality (top) and kidney failure (bottom) risks at 5 years associated with an eGFR of 45 versus 80 mL/min/1.73 m^2. Right panels: differences and ratios of mortality risks (top) and kidney failure risks (bottom).

people with normal or mild albuminuria, even if the relative hazard of ESKD is higher for eGFR of 45–59 versus 60–89 mL/min/1.73 m^2, the absolute risks of kidney failure at 5 years are very low (as low as 0.1%) and thus of questionable clinical relevance (Fig. 3, bottom panel). Conversely, the 5-year absolute risk of death is very high (9.7% and 7.3% among people 65–74 years, respectively; Fig. 3, top panel) [7]. Focusing on relative measures, we may be distracted by noticing that the 5-year risk of kidney failure is about one to two times higher in people with eGFR 45–59 versus 60–89 mL/min/1.73 m^2 up to the age of 80 years and then it may be lower after the age of 80 years (Fig. 5, right panel). However, looking at the risk range of the two events (*y*-axis tick labels) we see what really matters: in elderly people with normal or mild albuminuria with older age the 5-year risk of death increases from 5% to 100%, while the 5-year risk of kidney failure ranges between 0.01% and 0.1%, regardless of whether eGFR is above or below 45 mL/min/1.73 m^2.

To illustrate, let us revisit the bike example. Let us assume there are two pairs of bikers, one aged 65 years and one aged 85 years. For each pair of bikers, one person has an eGFR of 45–59 mL/min/1.73 m^2 and one 60–89 mL/min/1.73 m^2. The person with lower eGFR travels faster toward either event. However, the location of each pair of bikers in the disease trajectory depends on age. At any given time horizon from a time origin when eGFR and age are assessed, older pairs will have travelled a longer journey in the mortality trajectory (will be more likely to die) and a minimal distance on the trajectory toward kidney failure (will have travelled a small fraction of journey toward kidney failure). The opposite will happen to the younger pair (Fig. 6).

Of note, absolute measures are dependent on many factors, which need to be considered carefully when interpreting study findings [3, 7]. For example, the CKD-PC study estimated absolute rates for a given value of eGFR within an age category using regression models. Rate estimation (i.e. speed assessment) does not need to account for competing events. However, risks cannot be derived from rates directly in the presence of competing risks. The Canadian study reported absolute risks, including competing risks, stratified by eGFR and age. In addition, the population under study, and thus baseline risks, are different in the two studies. The Canadian study used population-based data and included people with CKD defined as sustained eGFR below a threshold for more than 3 months (following guideline's recommendation [21]), and its main analyses focused on elderly people with normal or mild albuminuria, for whom CKD definition is debated. The CKD-PC study included general and high cardiovascular risk cohorts as well as CKD cohorts (whether

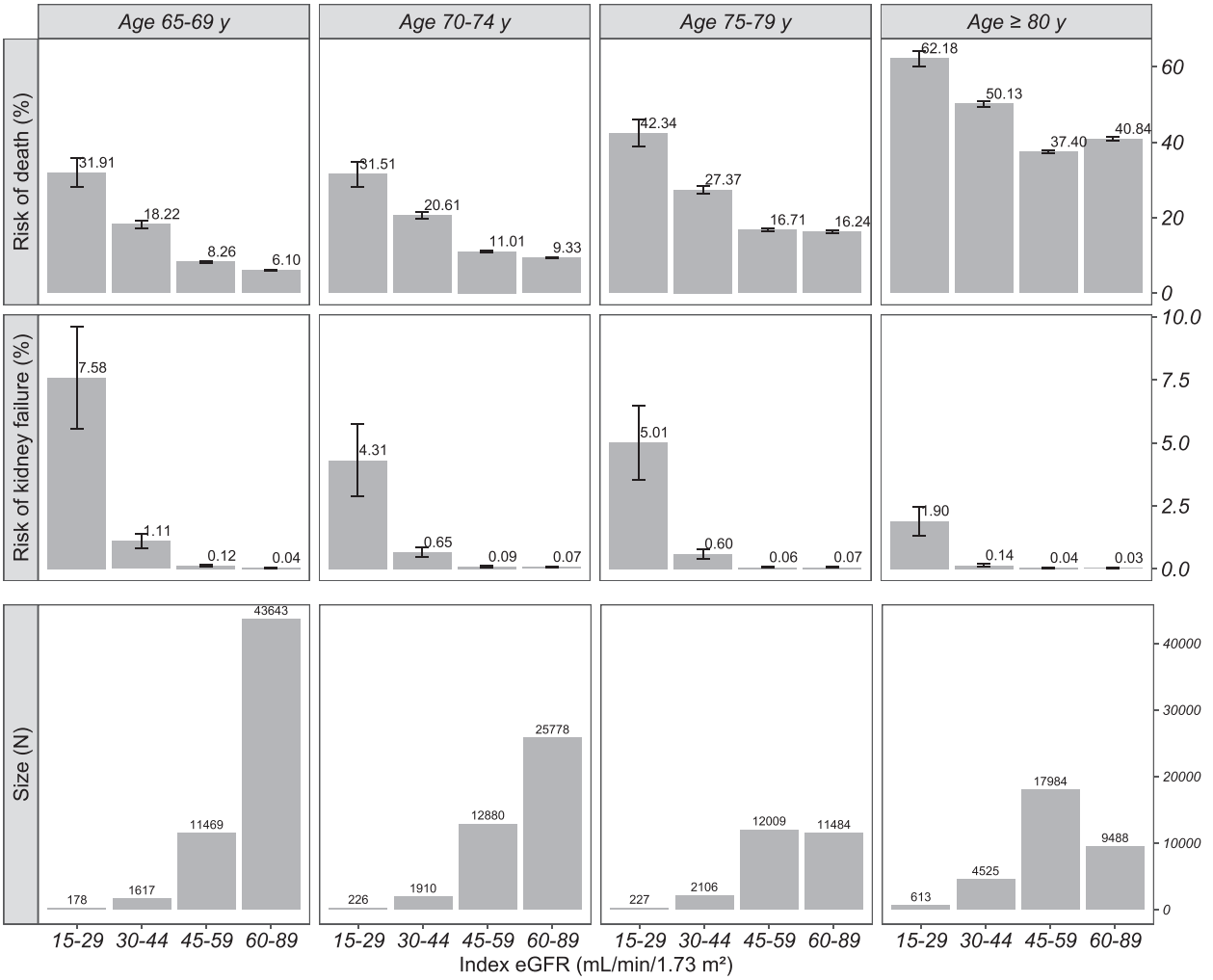

Figure 4: Relative and absolute risks of death and kidney failure at 5 years, by baseline eGFR and age categories (65–69, 70–74, 75–79, ≥80 years) in people with normal/mild albuminuria. This figure is from Liu *et al.*, Accounting for age in the definition of chronic kidney disease (2021), by permission of *JAMA Intern Med* [7]. Risks of kidney failure (KF) and death at 5 years by index eGFR (baseline eGFR) and age in elderly people with normal/mild albuminuria.

CKD was defined as sustained reduction of eGFR below a threshold for a period of time is unclear), and only 7.3% of the CKD-PC participants were 75 years or older. Finally, in the CKD-PC study, ESKD was not a comprehensive definition of kidney failure. The choice of avoiding kidney replacement and opt for conservative care of kidney failure is more common with older age [18].

IMPLICATIONS ON CKD DEFINITION

According to the 2012 KDIGO guidelines, CKD is defined as abnormalities of kidney structure (such as abnormal albuminuria) or function (i.e. GFR <60 mL/min/1.73 m^2) for more than 3 months, with implications for health [21]. Some members of the kidney community argue that in the absence of significant albuminuria current criteria using a fixed GFR threshold of 60 mL/min/1.73 m^2 for the diagnosis of CKD in adults does not separate kidney disease from kidney aging (physiologic age-related decline in GFR), and therefore does not hold for all ages [22]. Age-adapted thresholds for CKD of 75 mL/min/1.73 m^2 for age below 40 years, 60 mL/min/1.73 m^2 for age between 40 and 65 years, and 45 mL/min/1.73 m^2 for age above 65 years have been proposed. The evidence supporting such proposal is mainly based on hazard ratio data on all-cause mortality. Among younger persons, mortality increases with lower eGFR below the threshold of 75 mL/min/1.73 m^2, whereas in elderly people mortality increases with lower eGFR below the threshold of <45 mL/min/1.73 m^2 [22]. The Canadian population-based cohort study provided absolute risk data from a wide age range (including a large fraction that mirrors the global population ageing) that support this age-adapted definition. People who had CKD according to current eGFR criteria but not according to the age-adapted thresholds were 65 years or older and had an eGFR of 45–59 mL/min/1.73 m^2 with normal or mild albuminuria. These elderly people comprised a substantial proportion (43%) of the patient population who have CKD according to current age-independent eGFR criteria. Importantly, their absolute risk of kidney failure (and also the absolute risk of death) was similar in magnitude to that of non-CKD controls and they were far more likely to die than to develop kidney

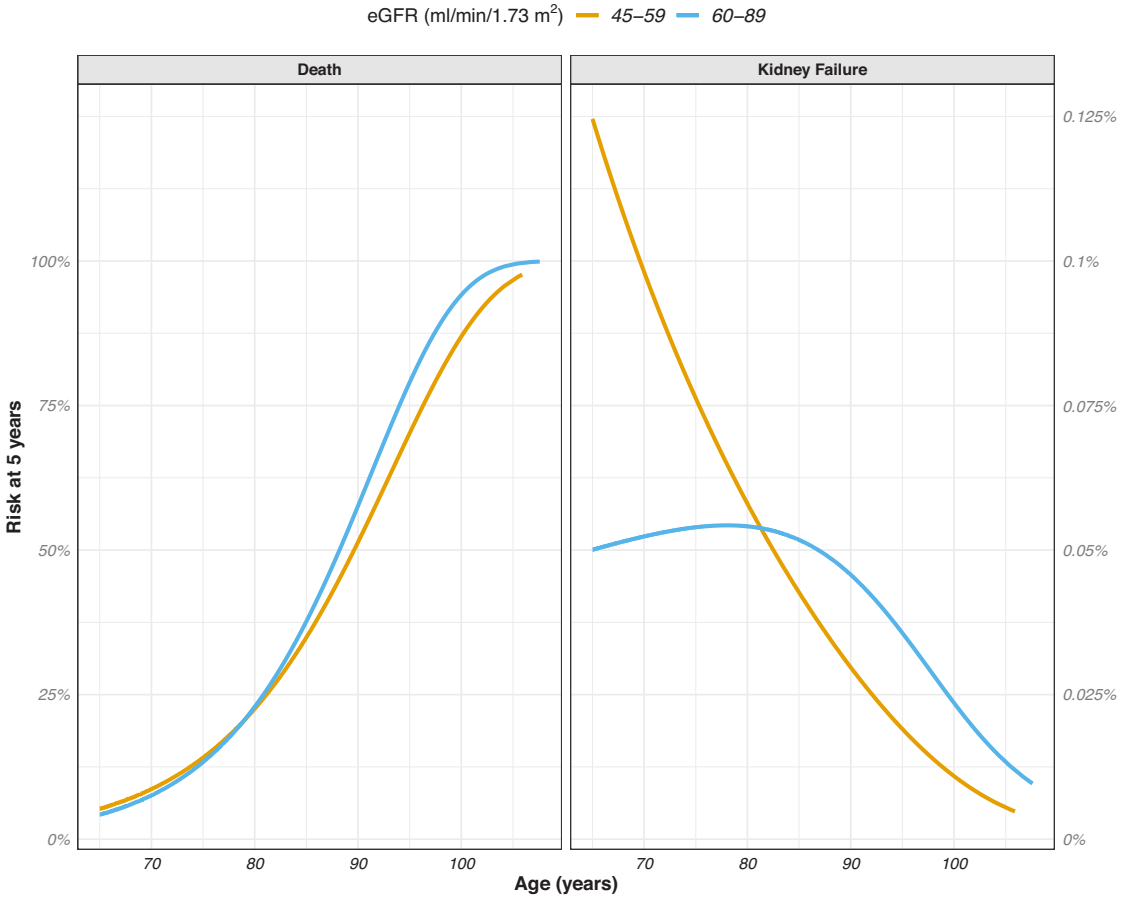

Figure 5: Relative and absolute risks of death and kidney failure at 5 years, by baseline eGFR and continuous age in elderly people with normal/mild albuminuria. Data were from the Canadian population-based cohort study [7]. The relationship between continuous age and 5-year risks of death and kidney failure was only slightly altered by eGFR levels of 45–59 and 60–89 mL/min/1.73 m^2 in people 65 years old or older with normal or mild albuminuria.

failure [7]. Relative or absolute rate data do not provide direct information on risk and thus can be misleading, especially if older age groups are poorly represented in the study sample.

The age-adapted definition for CKD, if implemented, will facilitate earlier identification of young people at increased risk of kidney failure and avoid diagnosing CKD in many older individuals who simply have an age-related loss of eGFR. Avoiding mislabeling these older individuals with CKD would reduce the psychological effect of a disease label, the burden and costs of repeated assessment, testing, and potentially wasteful referrals and unnecessary treatment. However, the use of age-specific thresholds to define CKD has limitations. One is the "birthday paradox," according to which healthy people can be classified as having CKD simply by becoming 1 year older. While the same applies to the current single-threshold definition, using an age-adapted approach with three thresholds will increase the number of times this may happen. On the other hand, an age-adapted definition is a step function that uses wide age ranges and then changes abruptly within a year when age crosses a threshold. The age-adapted definition may be improved by using percentiles for each year of age at the cost of adding complexity to CKD definition. Thus age-adapted percentiles of GFR need further considerations, such as establishment of reference percentiles for healthy persons of different ethnicities, implementation in clinical practice and research, and ease of understanding for patients.

In summary, the largest existing study on the association between eGFR and adverse CKD outcomes suggests that age modifies the association between eGFR and mortality, but not ESKD on the hazard ratio and absolute rate scales. These findings have been used to support a common definition of CKD based on eGFR for all age groups in international guidelines. We emphasize the importance of presenting absolute risks along with relative associations for proper interpretation of the clinical impact of these associations. Among people 65 years or older in the absence of significant albuminuria, although a mild reduction in eGFR (45–59 versus 60–89 mL/min/1.73 m^2) is associated with higher relative hazard rates of ESKD and death, the absolute risks for kidney failure and death over 5 years are similar in magnitudes, and the occurrence of kidney failure is far less frequent than that of death. These data challenge current definition of CKD using a GFR threshold of under 60 for all adults independent of age.

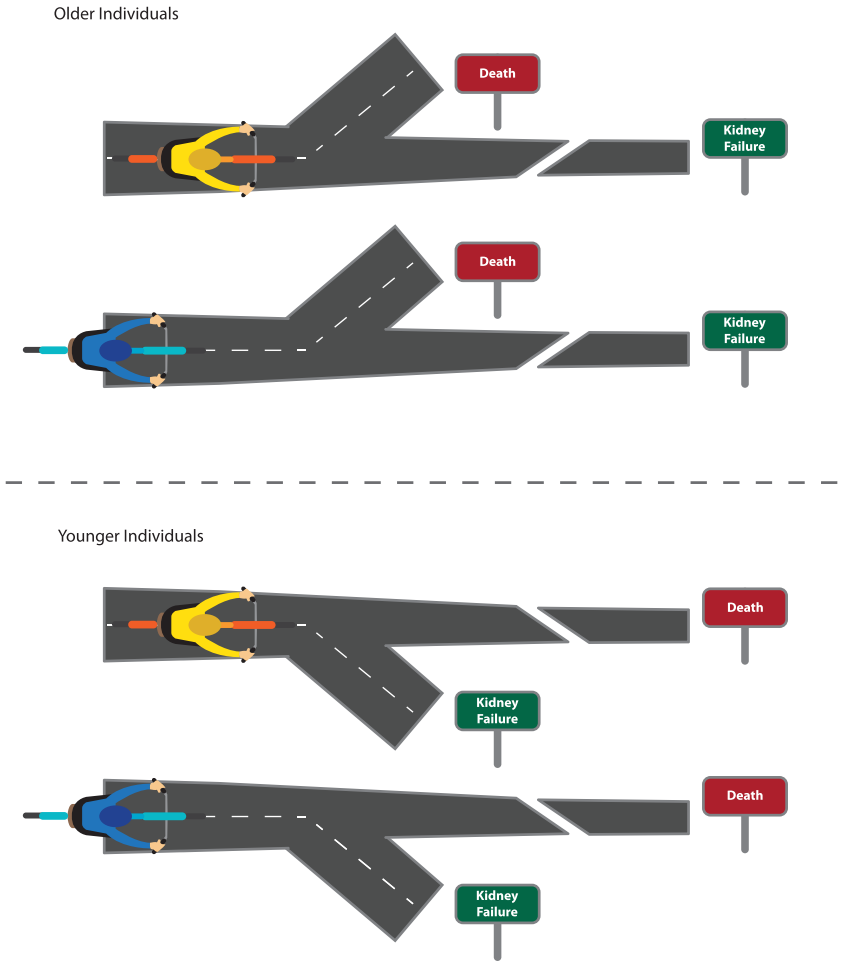

Figure 6: An illustration of relative risks and absolute risks. One pair of cyclists is 60 years old and one 80 years old. For each pair of cyclists, one person has an eGFR of 45–59 mL/min/1.73 m^2 (orange) and one 60–89 mL/min/1.73 m^2 (blue). The person with lower eGFR travels faster toward the event. However, the location in the disease trajectory depends on age. At any given time horizon from a time origin when eGFR and age are assessed, older pairs will have travelled a longer journey in the mortality trajectory (i.e. shorter distance towards the destination of death) and a minimal distance on the trajectory toward kidney failure (i.e. longer distance towards the destination of kidney failure). The opposite will happen to the younger pair.

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DATA AVAILABILITY STATEMENT

No new data were generated or analyzed in support of this research.

CONFLICT OF INTEREST STATEMENT

None declared.

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