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Association of chronic kidney disease with adverse outcomes - Authors' reply

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We share Viet Anh-Thu Hentschel and colleagues' concern about the use of baseline blood pressure measures for long-term follow-up and the definition of hypertension in chronic kidney disease (CKD) cohorts in which use of antihypertensive drugs was not incorporated. The use of single measures of estimated glomerular filtration rate (eGFR), albuminuria, and blood pressure is a limitation of our meta-analyses, which could result in some misclassification of participants during long-term follow-up. Despite this limitation, we found strong associations between each of these measures and outcomes. Updating these exposure measures would most likely result in even stronger observed associations, particularly in long-term follow-up.¹ However, we noted largely consistent results across our cohorts despite substantial variation in the length of follow-up. Also, the interpretation of results is different when repeated measures are treated as time-varying covariates and when only baseline measures are taken into account. The former approach tracks traits whereas the latter focuses on individuals.¹ Thus, our approach provides useful information on clinical implications to individual patients at a given timepoint.

We also agree that not having detailed information on anti hypertensive drugs used by participants in the included studies is a limitation of our analyses. However, we did a sensitivity analysis in a subset of studies that included sufficient numbers of individuals not using antihypertensive drugs and noted similar results (see figure 19 in the appendix).²

We appreciate the suggestion by Yuichiro Izumi and colleagues that the Kaplan-Meier method would be more appropriate because the adjusted risks might not portray the higher mortality risk in individuals with hypertension compared with those without hypertension. We wish to emphasise that our aim was not to assess whether hypertensive individuals have

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a higher mortality risk than non-hypertensive individuals. We were interested in how eGFR and albuminuria predispose to adverse outcomes in hypertensive versus non-hypertensive individuals. Cardiovascular risk factors are known to cluster, so univariate risk associations could not be solely ascribed to the presence of one cardiovascular risk factor (ie, hypertension). In fact, even after adjustment for other cardiovascular risk factors, hypertensive individuals did have higher risks of all-cause mortality in the preserved eGFR range (figure 1a).² Owing to interaction between the kidney measures and hypertension, the higher relative risk of all-cause mortality conferred by hypertension disappeared at lower eGFR and higher albuminuria. Indeed, as we discussed,² this phenomenon has been reported in several studies^{3,4} and warrants further investigation.

We agree with Xin Du and colleagues that translation of values across albumin/creatinine ratio (ACR), protein/creatinine ratio (PCR), and dipstick is a simplification where the exact relation is not simple. The approximation of PCR 50 mg/g to ACR 30 mg/g is consistent with clinical guidelines.⁵ Linking dipstick proteinuria to ACR (or PCR) is much more complicated, since dipstick proteinuria from spot urine (a typical scenario for dips tick evaluation) does not account for urine concentration. Although our selection for ACR and dipstick categories was somewhat arbitrary, we were aware of the limitations and thus also showed results for ACR and dipstick separately in the appendix (figures 7 and 8).² These results were generally consistent with each other, supporting the use of summarising across measures of albuminuria and proteinuria.

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