FRCPath Journal Article Appraisal Questions

Question No	7	**Author**	Hutchesson
Title	Chronic Kidney Disease Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010; 375: 2073-2081		
Origination Date	June 2010	**Review Date**	

	Question	Model Answer
a	What is a meta-analysis? Describe the advantages and problems associated with this type of study, and measures taken by the authors to guard against the latter	A meta-analysis is a statistical method of combining the results of several studies that address a set of similar research hypotheses, to estimate the true "effect size" of an intervention with greater statistical power than that available from a single study. [4] Advantages: • Increased statistical power to determine the true effect size. • Generalisation of results across those recruited to a range of studies, rather than those eligible for a single study. • Comparison of the results of different studies, allowing identification of those with discrepant results to the majority and subsequent exploration of the reasons for this. • Ability to control for between-study variation. • Inclusion of moderators to explain variation between study results. • Derivation and testing of factors/effect size parameters. [1 mark/point; 5 max] Problems: • Inability to control for problems in the underlying studies (a good meta-analysis of bad studies will produce a bad result). • Publication bias ("file drawer problem") – studies with positive outcomes are more likely to be published, those with negative outcomes to be filed away. • Selection of trials for inclusion (objective or subjective?). • Variation between studies in definition and/or measurement of effect size. • Personal or agenda-driven bias.

		[1 mark/point; 5 max] Precautions taken in this study: • Definition of search strategy to identify published studies. • Publicity via personal contacts and website to identify unpublished studies. • Strict definition of inclusion criteria for studies. • Analysis of original data from studies according to an *a priori* analytical plan using standard computer programs. • Use of a funnel plot and the Egger test to test for publication bias. [2 mark/point; 10 max]
b	Describe the relationship between all-cause mortality and estimated GFR, and discuss possible reasons for this	There is a U-shaped (J-shaped) relationship between all-cause mortality and eGFR, with an exponential rise as eGFR falls below 60 ml/min, but also a rise as eGFR increases above this. [2] The authors suggest this may be due to under-estimation of eGFR by the MDRD study equation at eGFR values >60 ml/min/1.73m^2 in healthy individuals, and to over-estimation in individuals with muscle wasting due to poor health. [4] The U-shaped relationship is less noticeable in studies where GFR was estimated from cystatin C, and the authors cite this as evidence for problems with the MDRD equation in those with normal eGFR. The relationship is also less noticeable for cardiovascular mortality, suggesting that muscle loss may lead to a falsely high eGFR in those with systemic illness. [4]
c	The authors state 'These findings suggest that the dipstick test is useful for risk stratification despite being a less precise measure of albuminuria.' Is this conclusion justified? Explain your answer	Table 3 shows that the confidence intervals for hazard ratios using dipstick testing show no overlap between results for "no proteinuria" and "2+ proteinuria" groups; at least for GFR >60 (nb: there are few results for GFR <30). This supports the use of dipstick testing to produce clinically-relevant results. [6 – lose 2 if no evidence cited]

		NB: the wider confidence intervals compared to those for ACR do NOT support dipstick testing being less precise; there were fewer studies using dipstick testing than ACR testing.
d	Discuss whether the results support the current classification of Chronic Kidney Disease	KDOQI proposed stratifying CKD into 5 stages according to GFR; but stages 1 and 2 require additional evidence of renal damage (e.g. proteinuria or haematuria) to be present. This study does not assess the relationship of haematuria with mortality; but it does confirm the relationship with proteinuria. [2] It also demonstrates an exponential increase in mortality as GFR falls below 60 ml/min; but no effect at GFR above this (or a slight increase at higher GFR). [2] These results therefore support: • Use of proteinuria in identifying CKD 1/2. • Use of GFR in identifying CKD 3-5. They also support estimation of proteinuria in addition to GFR to define risk in CKD 3-5. [6]