Reviewer’s report

Title: Endothelial Nitric Oxide Synthase Gene Polymorphism (Glu298Asp) and Development of Pre-eclampsia: a nested case-control study and a meta-analysis.

Version: 1 Date: 29 November 2005

Reviewer: Georgia Salanti

Reviewer’s report:

The methods are well described and the main conclusions sensible. However, I have a few essential comments that need addressing before publication.

-- It is well known that Q is a rather unreliable for addressing heterogeneity. Not significant heterogeneity is detected in figure 1, but this may be due to low paper. The appropriate measure is I² [Higgins]. Moreover, it is not advisable to decide about the meta-analytic model (random effects or fixed effects) on the basis of a p-value. I suggest random effects models to be applied as default, since homogeneity is rather the exception in genetic association studies.

-- You need to address further sources of heterogeneity for the meta-analysis as the genotyping method and the compliance to HWE. The studies are not enough to explore them, but you need to consider them.

-- Please make a proper stratified analysis for the nested case-control study by ethnicity, and report the estimates.

Here are some further comments to improve the presentation

-- In table 1, SD or 95% CI should be reported along with the point estimates for continuous outcomes. The p-value for primiparous and smokers cannot be based on ANOVA, I guess you did a X² analysis?

-- Are the studies in the forest plots in random order? If yes, order them by date of publication or sample size. Next to the polled effect size, print the point estimate and the 95% CI.

-- For the nested case-control study add a 3x2 table for the numbers per genotype in cases and controls.

-- In table 2, add the ORs for the clinical factors included in the model.

-- Statistical analysis methods are mixed with the systematic review methods.

-- The fact that the cases in the nested case-control study are in HWE corroborates the conclusion of no association between Asp and pre-eclampsia.

References: