

Supplementary Online Content

Kioumourtzoglou M-A, Coull BA, O'Reilly EJ, Ascherio A, Weisskopf MG. Association of exposure to diethylstilbestrol during pregnancy with multigenerational neurodevelopmental deficits. *JAMA Pediatr*. Published online May 21, 2018. doi:10.1001/jamapediatrics.2018.0727

eMethods. Impact of Unmeasured Confounding

eFigure. Estimated E Value for OR = 1.36 and Outcome Prevalence Less Than 15%

This supplementary material has been provided by the authors to give readers additional information about their work.

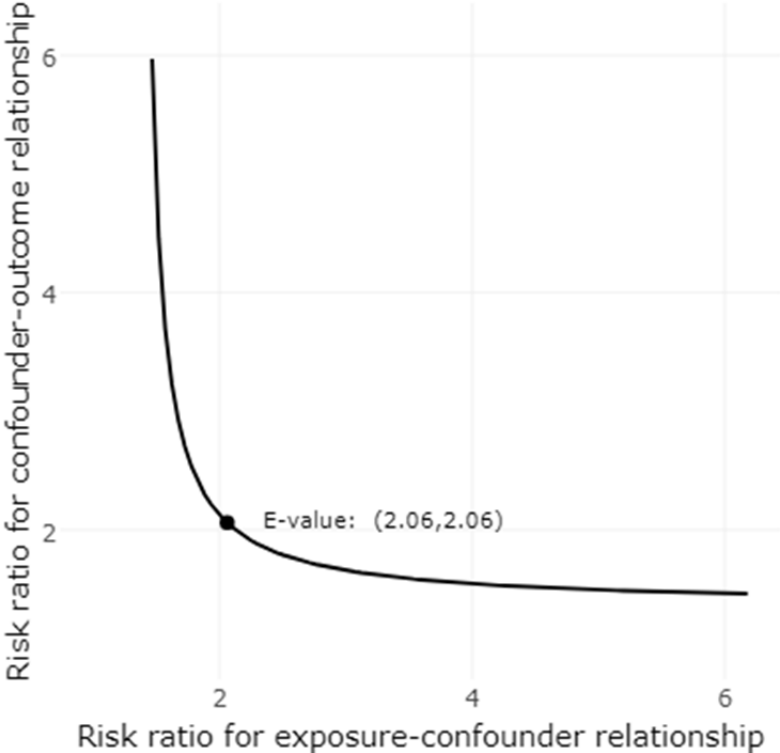
eMethods. Impact of Unmeasured Confounding

We have conducted further sensitivity analyses to assess the sensitivity of our results to residual and unmeasured confounding. First, we estimated the E-value, i.e. how strongly (the minimal strength) a confounder would need to be related both to the exposure and outcome of interest to fully explain the observed association. We used the method as described in VanderWeele and Ding¹ and the online calculator provided by the authors (<https://www.hsph.harvard.edu/tyler-vanderweele/tools-and-tutorials/>). For an odds ratio (OR) of 1.36 of a rare event (outcome prevalence <15%), the E-value estimated was 2.06 (see the eFigure). However, since there are no other existing studies assessing multigenerational neurodevelopmental effects of DES, we cannot assess if it is reasonable to expect that such a confounder exists that we have not considered.

When looking at the results from our main models, the strongest positive association observed with ADHD was with F1 year of birth ($\beta = 0.84$; OR = 2.32) and the strongest negative associations were with race (Asian $\beta = -0.98$; OR = 0.38, and African American $\beta = -0.62$; OR = 0.54). The next strongest association in absolute magnitude in our model was with DES ($\beta = 0.31$; OR = 1.36). We subsequently proceeded to remove each of the potential confounders from the model, one at a time, to assess the impact each of these variables has on the estimated coefficient for DES. The range of the resulting ORs was very tight, i.e. the estimated ORs ranged between 1.35 and 1.38. Removing the two strongest predictors for ADHD (F1 birth year and race) resulted in ORs of 1.36 and 1.37, respectively, indicating that they are not strong confounders. The highest difference (OR = 1.38, i.e. a 4.2% increase in the β coefficient compared to the main analysis) was when we removed F0 smoking during pregnancy from the model.

Although we cannot exclude the possibility of some residual or unmeasured confounding, we included information about several SES-related factors, including smoking during pregnancy. This, combined with the sensitivity analyses described above, indicates that it is not likely that our findings could be completely attributable to residual or unmeasured confounding.

eFigure. Estimated E Value for OR = 1.36 and Outcome Prevalence Less Than 15%



eReference

1. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med.* 2017;167:268-274.