We read the paper by El Marroun and colleagues on prenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and autistic symptoms in young children with raised concern. Autism is a severe condition that has a significant impact on children and their families. Diagnosis and identification of autism has been on the rise in the past decades. A number of exposures have been sought to explain this increase, with the measles, mumps and rubella (MMR) vaccine probably the most debated. However, it is now generally accepted that there is no causal link between the MMR vaccine and autism. Yet, a consequence of the well-publicised debate on the MMR vaccine and autism is that observational studies have sought to identify whether there may be associations between autism in children of mothers who were depressed in pregnancy against children of women with no exposure to SSRIs and a low score of maternal depressive symptoms. They also compare the latter group against women who were depressed, but not on antidepressants. The question is whether these are meaningful and unbiased comparisons. Table 1 in El Marroun et al reveals that not only do these groups differ in terms of exposure to antidepressants, but also on a range of measured covariates. For example, a quarter of the women on SSRIs were also prescribed benzodiazepines and over 50% were smoking in pregnancy. In contrast, less than 1% of the women in the non-exposure group were prescribed benzodiazepines and less than 25% were smoking. A multivariable regression analysis may appear to account for some of these differences, but only for those variables that were measured and included in the analyses. We cannot ignore the fact that those who continue antidepressants in pregnancy against children of women with no exposure to SSRIs may appear to account for some of these differences, but only for those variables that were measured and included in the analyses. We cannot ignore the fact that those who continue antidepressants in pregnancy for women who were depressed, but not on antidepressants. The question is whether these are meaningful and unbiased comparisons. Table 1 in El Marroun et al reveals that not only do these groups differ in terms of exposure to antidepressants, but also on a range of measured covariates. For example, a quarter of the women on SSRIs were also prescribed benzodiazepines and over 50% were smoking in pregnancy. In contrast, less than 1% of the women in the non-exposure group were prescribed benzodiazepines and less than 25% were smoking. A multivariable regression analysis may appear to account for some of these differences, but only for those variables that were measured and included in the analyses. We cannot ignore the fact that those who continue antidepressants in pregnancy against children of women with no exposure to SSRIs may appear to account for some of these differences, but only for those variables that were measured and included in the analyses. We cannot ignore the fact that those who continue antidepressants in pregnancy for pregnant women may also be women with a history of more severe depression.

Although the paper goes to some lengths in evaluating parental reports on the outcomes there remains the possibility that the outcomes in this study are subject to reporting bias. Moreover, the absence of figures of absolute risks of autism makes it difficult for the reader to assess the numbers of children who actually experienced pervasive developmental problems. Further, if these numbers are small, the results of multivariable regression analysis can be very sensitive to misclassifications of the outcome. El Marroun et al suggest that their results demonstrated an effect of SSRIs on autistic symptoms in young children. They support this statement with evidence from animal models. However, there is an alternative interpretation of the results of this study.
A different interpretation of the results

El Marroun et al showed that compared with children of women without depressive symptoms, in children of women with elevated depressive symptoms the odds ratio of pervasive developmental problems was 2.02 (95% CI 1.53–2.66) and the odds ratio for those prescribed SSRIs in pregnancy was 2.58 (95% CI 1.46–4.54). Indirectly, this suggests that children of women with elevated depressive symptoms and women treated with SSRIs in pregnancy were equally likely to have pervasive developmental problems (Model I, Table 2). A head-to-head comparison of the effect estimates for autistic traits of the SSRI cohort against the cohort of women with depression suggested that children of the SSRI cohort rated slightly higher on all three domains. This, however, does not prove a causal relationship between SSRI exposure in pregnancy and autistic symptoms. Rather the results may suggest that there is an association between maternal depression and childhood autistic symptoms. Hence, some animal studies have established an association between maternal stress and autism.¹⁰

References

Prenatal exposure to selective serotonin reuptake inhibitors and autistic symptoms in young children: another red herring?
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