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Recalling Biases: The Authors Respond

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We thank *Henriksen et al*. for their interest in our article and would like to address the potential biases they raise, starting with recall bias. There is little empirical evidence of recall bias in case-control studies of birth defects in assessments that use a control group consisting of subjects with malformations,[1,2] ask about nonexistent medications,[3] or use medical records to validate maternal reports.[4,5] In our study, we found no evidence of recall bias in evaluating SSRI use outside the etiologically relevant window and use of non-SSRI medications for depression in the exposure window (assuming recall bias would not affect reporting of exposure timing or would be restricted to a specific class of medication).[6] Furthermore, recall bias is unlikely to be defect-specific and reproducible associations of SSRIs have been reported for only a small number of specific defects.[7-9] *Henriksen et al*. cite a case–control study where maternal questionnaires were compared with prenatal care logbooks as evidence of recall bias. Unfortunately, *Henriksen et al*. failed to acknowledge a major limitation (which the authors themselves discuss): the log books only included medications prescribed by obstetricians.[10] Many medications unrelated to pregnancy would not be prescribed by an obstetrician and would be missed in the logbooks. Indeed, they found 25% of drugs reported by maternal interview were not recorded in the logbooks.[11]

Henriksen et al. state that the prevalence of SSRI use in our study was too low relative to other reports. However, the cited studies reported prevalences for any anti-depressant medications. Our observed SSRI prevalence (3% in controls) is similar to those reported among controls in two similarly- designed case–control studies (2.7%-3.8%)[7,9] and two prescription databases (1.9%-3.8%)[12,13]

Our participation rates were different for case and controls which *Henriksen et al*. proposed could explain our observed increased odds ratios (ORs) if exposed controls did not participate at the same rate as cases. We conducted a bias analysis and determined that the exposure prevalence among nonparticipating controls would have to be at least three times as high to attenuate the OR to 1.0, which seems unlikely.

Henriksen et al.'s OR of 1.3 for SSRIs in relation to clubfoot in the Danish population was subject to limitations. First, ICD9 codes do not identify true cases. Direct examination is

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necessary to distinguish positional from structural clubfoot; in our study, structural clubfoot was ruled out in 22% of initial cases based on orthopedic specialist review.[14] In addition, structural clubfoot cases that occur secondary to neural tube or renal defects should be excluded. Also, prescription records do not necessarily translate to exposure, as shown in a Swedish study in which, based on exposure information from both the drug register and interviews, early pregnancy antidepressant use was lower in the prescription drug register (55% of exposures were identified) than in prospectively collected interview data (75% of exposures were identified).[15] Further, pregnant women are more likely to reduce their use of antidepressants, after they recognize they are pregnant,[6,15] leading to misclassification of exposure if one relied solely on prescription data.

While our study has limitations, we believe it also has strengths that improve on previous analyses, including review of orthopedic medical records and treatment information, standardized detailed questionnaires which prompted for depression and specific SSRIs, and multiple exposure categories, all of which reduce concerns regarding the potential biases discussed above. *Henriksen et al*. suggest that the result of our studies should not be used to inform clinical decisions and we agree that results of one study alone should not lead to treatment recommendations or be disseminated to patients. Instead, all the epidemiologic evidence should be used to weigh the risks and benefits, allowing women and their healthcare providers to make informed decisions about their care.

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