British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) **81** 1191–1193 1191

LETTER TO THE EDITOR

Meta-analysis requires independent observations and freedom from bias

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Received 20 January 2016; **accepted** 31 January 2016

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The recent meta-analysis by Berard *et al*. [1] associating exposure to paroxetine during pregnancy and risk of cardiac malformations suffers from two major problems: 1) duplication of data in the meta-analyses and 2) difficulty disentangling the effect of paroxetine from confounding by indication (i.e. effects owed to depression, anxiety and correlated risk factors).

It is imperative that subjects included in meta-analyses be only reported once. Duplication will bias risk estimates by overweighting studies that double (or triple) count the same subjects, exaggerate the accuracy of risk estimates and give a false impression of the harm or safety of the drugs [[2] page 59]. Avoiding duplication demands careful review of the original sources of data for each study in the meta-analysis [[3] page 234]. Data from Scandinavian and Nordic countries have made important contributions to our understanding of a possible association between SSRIs and several perinatal outcomes, including congenital malformations. These large studies are population-based, use linked data which avoid reliance on interviews and make use of national medical and congenital malformation registries. Furu *et al*. [4] recently published data for the entire populations of Denmark, Finland, Iceland, Norway and Sweden from 1996 to 2010, a total of 2.3 million singleton births of whom 36 772 were exposed *in utero* to an SSRI. Table 1 shows how Furu *et al*.'s data [4] included, with minor exceptions, all births in eight previous studies. Even among these eight studies there is overlap. Jimenez-Solem *et al*. [5] include all the Danish data reported from three smaller Danish studies and there is duplicative data from four Swedish reports. Two other studies, Louik *et al*. [6] and Alwan *et al*. [8], analyzed by Berard *et al*. [1] in one meta-analysis, are also likely to include some duplicative subjects [[3] page 237].

The meta-analyses by Berard *et al*. [1] contain numerous examples where duplicate subjects are included [9–14]. To give two examples, Figure 2C in Berard *et al*. [1], which examines paroxetine and major malformations, has five of the studies listed in Table 1 including Furu *et al*. [4], providing a typical effect of OR = 1.19, 95% CI 1.05, 1.35. When recalculated with Furu *et al*. [4] alone this is OR = 1.16, 95% CI 1.00, 1.35. Figure 2F in Berend *et al*. [1] reports the cardiac malformation estimate (OR = 1.23, 95% CI 1.06, 1.43) which is less precise if the duplicate data are removed (OR = 1.22, 95% CI 1.02, 1.47).

Other problems with Berard *et al*.'s meta-analysis [1] include data utilized from Sweden [15] which was superseded by Källén *et al*. [16] but both are largely included in Furu *et al*. [4]. Data from Kulin *et al*. [17] and Simon *et al*. [18] are reported as being for paroxetine from a prior meta-analysis but neither study provides separate paroxetine associations (the latter paper reports 28 paroxetine exposures, not the 38 listed by Berard *et al*. [1]).

Confounding by indication is recognized as a major problem by all authors contributing to this literature and Berard *et al*. [1] contend their analysis is 'adjusting for the indication per design'. The most successful studies to control indication did so by comparing risk in women who had used an SSRI before pregnancy but 'paused' during the pregnancy or by restricting analyses to depressed women [4, 5, 19, 20]. In all four papers the authors concluded that indication bias was the likely explanation for any observed associations. Berard *et al*. [1] use the corrected Huybrecht *et al*.'s data, but did not conduct an analysis of 'paused' exposure like Jimenez-Solem *et al*. [5], and excluded the corrected estimates from Ban *et al*. [19] and Furu *et al*. [4]. Deleting duplicate data (above), using Furu *et al*.'s [4] best estimate for SSRI exposure and the corrected Ban *et al*. [19] data, the typical estimates attenuate for all malformations and paroxetine: OR =1.10, 95% CI 0.94, 1.28 and for cardiac malformations OR = 1.09, 95% CI 0.91, 1.30.

To their credit, Berard *et al*. [1] make no claim that paroxetine *causes* congenital malformations, but the fact that their reported associations are small and vulnerable to the challenges of duplicate data and confounding by indication, casts doubt on the validity of their reported associations.

DOI:10.1111/bcp.12898

Table 1

Study subjects in reports from the Nordic countries and duplication with Furu *et al.* [4]

Authors	Jimenez *et al.* [5]	Kornum *et al.* [9]	Pedersen *et al.* [10]	Källén* *et al.* [16]	Nordeng *et al.* [11]	Malm *et al.* [12]	Reis *et al.* [13]	Knudsen *et al.* [14]	Furu *et al.* [4]
Publication year	2012	2010	2009	2013	2012	2011	2013	2014	**2015**
Population	All Denmark	4 Danish counties	All Denmark	All Sweden	All Norway (38% particip)	All Finland	All Sweden	1 Danish county	**All Nordic countries****
Time covered	1997–2009	1991–2007 1996–2007 1998–2007	1996–2003	1996–2011	2000–2006	1996–2006	1995–2008	1995–2008	**1996–2010**
Number exposed SSRI***	4183	2 062	1 370	18 933	462	6881	12 050	845	**36 772**
Sources for all	National Medical Birth Registries Nordic Prescription Registers ICD10 WHO ATC classification (except Malm)				ICD9			EUROCAT	

*Källén [7] and Reis & Källén [13] are included; **Denmark, Finland, Iceland, Norway, Sweden; ***Typically 1st trimester exposure and month before conception.

Competing Interests

Professor Bracken is a consultant and expert witness for Glaxo-Smith-Kline Pharmaceuticals and Forest Research Laboratories, both manufacturers of SSRIs.

Full meta-analyses are available on request.

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