Dear Sir,

The paper by Tyler et al\textsuperscript{1} provides novel data on the important issue of brain damage and maternal medication on which currently there is little published literature.

The authors report a positive association between maternal aspirin use during pregnancy and quadriparesis and between maternal NSAIDs use during pregnancy and quadriparesis and diparesis in infants delivered very preterm\textsuperscript{1}. Tyler et al\textsuperscript{1}'s discussion highlights the possibilities for confounding by indication and the need for replication in larger cohorts.

Using an already recruited cerebral palsy cohort\textsuperscript{2} we were able to replicate part of these analyses is 145 quadriplegics, 149 diplegics and 191 hemiplegics, a cohort with 3-11 times the number of each cerebral palsy subtype reported by Tyler et al but recruited from deliveries at all gestational ages. Our cohort had insufficient power to independently replicate the associations reported by Tyler et al in very preterm infants (68 cases of cerebral palsy born at <28 weeks) but for all gestational ages no association was apparent with Aspirin and NSAID use and cerebral palsy outcomes.

In contrast, we report negative associations of maternal antibiotic use with diplegia and hemiplegia (see table 1) which was unexpected as perinatal infection is a risk factor for cerebral palsy\textsuperscript{3}.

Retrospective analysis of rare outcomes such as cerebral palsy is required to achieve large sample sizes. Our data was collected using a maternal health questionnaire administered at the time of participation and may be subject to recall bias. Time between birth and study participation may account for the low reported use of Aspirin and NSAIDs compared to the report of Tyler et al. Our analysis adjusts for similar, but not identical confounders. It is possible that NSAID and Aspirin use is higher amongst mothers who deliver very preterm infants when compared to mothers delivering at term. The interesting results of Tyler et al described in infants born before 28 weeks may not generalize to cerebral palsy children born at later gestational ages.

The question of over-the-counter medications and cerebral palsy is difficult to answer as prospective studies with high quality data provide small samples, yet larger cohorts from retrospective studies provide less reliable data.

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(357/400 words)

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Table 1. Maternal medications and association with cerebral palsy subtypes

<table>
<thead>
<tr>
<th>Maternal Medication</th>
<th>Controls (1,154)</th>
<th>Quadriplegia (145)</th>
<th>Diplegia (149)</th>
<th>Hemiplegia (191)</th>
<th>All CP Cases (587)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>OR (95% CI), p value</td>
<td>n (%)</td>
<td>OR (95% CI), p value</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>58 (5)</td>
<td>7 (4.8)</td>
<td>0.3 (0.09-1.01), 0.052</td>
<td>11 (7.4)</td>
<td>0.17 (0.06-0.52), 0.002</td>
</tr>
<tr>
<td>Aspirin</td>
<td>4 (0.3)</td>
<td>0 (0)</td>
<td>-</td>
<td>1 (0.7)</td>
<td>-</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>9 (0.8)</td>
<td>1 (0.7)</td>
<td>1.57 (0.11-22.4), 0.74</td>
<td>1 (0.7)</td>
<td>1.6 (0.11-22.97), 0.73</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>265 (23)</td>
<td>25 (17.2)</td>
<td>1.26 (0.68-2.33), 0.465</td>
<td>29 (19.5)</td>
<td>0.7 (0.4-1.23), 0.215</td>
</tr>
</tbody>
</table>

* Adjusted for gestational age, birth weight centile and evidence of maternal infection in perinatal notes.