Fetal exposure to alcohol and cognitive development: results from a Mendelian randomization study

Sarah Lewis
Is moderate drinking during pregnancy really harmful?

**Alcohol and pregnancy - conflict and confusion**

Shouldn't pregnant women be afforded the right to exercise personal choice when deciding whether to drink alcohol?

- GUARDIAN NOVEMBER 12, 2009

Drinking alcohol occasionally when pregnant 'does no harm

- Times 30 October, 2008
Problems of observational studies of alcohol intake and cancer

- Measurement error
- Reporting/interviewer bias
- Disease affects drinking habits
- CONFOUNDING
Aim of the project

- To investigate associations between polymorphisms of the main alcohol metabolizing genes in mother and child and growth and neurodevelopmental outcomes in infants and children.
Metabolism of alcohol

Ethanol $\xrightarrow{\text{ADH, CYP2E1}}$ Acetaldehyde $\xrightarrow{\text{ALDH}}$ Acetic acid

* Mainly occurs in the liver, but some activity is also present in the oral cavity and digestive tract
### ADH genes and SNPs investigated

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH4</td>
<td>rs4699714</td>
</tr>
<tr>
<td>ADH4</td>
<td>rs3762894</td>
</tr>
<tr>
<td>ADH4</td>
<td>rs4148884</td>
</tr>
<tr>
<td>ADH1A</td>
<td>rs2866151</td>
</tr>
<tr>
<td>ADH1A</td>
<td>rs975833</td>
</tr>
<tr>
<td>ADH1A</td>
<td>rs1229966</td>
</tr>
<tr>
<td>ADH1B</td>
<td>rs2066701</td>
</tr>
<tr>
<td>ADH1B</td>
<td>rs4147536</td>
</tr>
<tr>
<td>ADH1B</td>
<td>rs1229984</td>
</tr>
<tr>
<td>ADH7</td>
<td>rs284779</td>
</tr>
</tbody>
</table>
Main Outcomes

- IQ at age 8 years: WISC-III (Wechsler, Golombok and Rust, 1992), age-adjusted
- SATS test results at age 11
OR 0.69 (0.56-0.86)

OR 0.57 (0.45-0.72)

OR 0.54 (0.39-0.74)

Binging during pregnancy

Binging after pregnancy

Weekly intake in 3 categories before pregnancy
Association between ADH1B genotype and alcohol intake

<table>
<thead>
<tr>
<th>Time period</th>
<th>Absolute number</th>
<th>Proportion carrying rare allele - %</th>
<th>Chi-square test for trend</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal alcohol consumption levels</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>never</td>
<td>511</td>
<td>6.5</td>
<td>13.15/1df</td>
<td>0.0003</td>
</tr>
<tr>
<td>&lt;1 drink/wk</td>
<td>2,693</td>
<td>5.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-6 drinks/wk</td>
<td>3,084</td>
<td>4.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7+ drinks/wk</td>
<td>837</td>
<td>3.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First trimester</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>never</td>
<td>3,242</td>
<td>5.8</td>
<td>14.81/1df</td>
<td>0.0001</td>
</tr>
<tr>
<td>&lt;1 drink/wk</td>
<td>2,833</td>
<td>4.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-6 drinks/wk</td>
<td>1,030</td>
<td>3.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7+ drinks/wk</td>
<td>138</td>
<td>2.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Association of confounding variables with maternal ADH1B genotype and maternal alcohol intake

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rare allele carrier (n=361)</th>
<th>Rare allele non-carrier (n=7265)</th>
<th>P*</th>
<th>Drink &lt; 1 unit per wk (n=5568)</th>
<th>Drink ≥ 1 unit per wk (n=6753)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother’s age (mean, SD)</td>
<td>28.5 (4.7)</td>
<td>28.2 (4.8)</td>
<td>0.248</td>
<td>27.6 (4.9)</td>
<td>28.5 (4.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Parity (1st baby)</td>
<td>157 (45.9%)</td>
<td>3137 (45.6%)</td>
<td>0.945</td>
<td>3538 (64.3%)</td>
<td>3209 (48.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Higher than O-level education</td>
<td>131 (39.2%)</td>
<td>2386 (35.6%)</td>
<td>0.189</td>
<td>1424 (28.0%)</td>
<td>2632 (41.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Manual social class</td>
<td>173 (59.9%)</td>
<td>3435 (62.7%)</td>
<td>0.344</td>
<td>2419 (54.1%)</td>
<td>2336 (39.2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mother smoked during 1st trimester</td>
<td>70  (20.1%)</td>
<td>1678 (24.2%)</td>
<td>0.094</td>
<td>1372 (24.7%)</td>
<td>1734 (25.7%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Calcium mg per week (mean, sd)</td>
<td>6741 (2010)</td>
<td>6555 (1945)</td>
<td>0.106</td>
<td>6432 (1990)</td>
<td>6731 (1945)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vitamin C mg per week (mean, sd)</td>
<td>582 (247)</td>
<td>561 (240)</td>
<td>0.132</td>
<td>533 (237)</td>
<td>585 (241)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Iron mg per week (mean, sd)</td>
<td>74.6 (23.3)</td>
<td>72.6 (22.7)</td>
<td>0.126</td>
<td>71.1 (23.1)</td>
<td>74.7 (22.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Folate mg per week (mean, sd)</td>
<td>1786 (513)</td>
<td>1741 (501)</td>
<td>0.128</td>
<td>1712 (512)</td>
<td>1781 (498)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High EPDS score</td>
<td>57  (17.2%)</td>
<td>1076 (19.9%)</td>
<td>0.841</td>
<td>925 (18.3%)</td>
<td>1046 (16.7%)</td>
<td>0.05</td>
</tr>
</tbody>
</table>
## Association between maternal ADH1B and children’s cognitive outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sample</th>
<th>Number</th>
<th>Average difference in score (SE)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key Stage 2 Score</strong></td>
<td>Original sample</td>
<td>6,637</td>
<td>1.99(0.57)</td>
<td>0.00045</td>
</tr>
<tr>
<td></td>
<td>Original sample adjusted for pre-pregnancy alcohol</td>
<td>6,342</td>
<td>2.25(0.56)</td>
<td>0.00006</td>
</tr>
<tr>
<td></td>
<td>UK born only</td>
<td>5,579</td>
<td>1.92(0.60)</td>
<td>0.0014</td>
</tr>
<tr>
<td></td>
<td>UK born &amp; adjusted for ASPM, MCPH1 &amp; lactase persistence</td>
<td>5,410</td>
<td>2.83(1.31)</td>
<td>0.031</td>
</tr>
<tr>
<td><strong>IQ score</strong></td>
<td>Original sample</td>
<td>4,175</td>
<td>0.72(1.16)</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>Original sample adjusted for pre-pregnancy alcohol</td>
<td>4,103</td>
<td>0.98(1.17)</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>UK born only</td>
<td>3,704</td>
<td>0.41(1.22)</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>UK born &amp; adjusted for ASPM, MCPH1 &amp; lactase persistence</td>
<td>3,588</td>
<td>-1.02(2.77)</td>
<td>0.71</td>
</tr>
</tbody>
</table>
Other genotypes

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Mother (coef, 95% CI, p-value)</th>
<th>Child (coef, 95% CI, p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH4</td>
<td>rs4148884</td>
<td>-2.23 (-4.13 to -0.33) p=0.022</td>
<td>1.86 (-0.11 to 3.82) p=0.064</td>
</tr>
<tr>
<td>ADH1A</td>
<td>rs2866151</td>
<td>1.01 (-0.70 to 2.71) p=0.247</td>
<td>-2.81 (-4.51 to -1.10) p=0.001</td>
</tr>
<tr>
<td>ADH1A</td>
<td>rs975833</td>
<td>1.14 (-0.68 to 2.96) p=0.219</td>
<td>-2.39 (-4.24 to -0.54) p=0.011</td>
</tr>
<tr>
<td>ADH1B</td>
<td>rs414736</td>
<td>0.62 (-1.17 to 2.41) p=0.498</td>
<td>-2.26 (-4.11 to -0.42) p=0.016</td>
</tr>
<tr>
<td>ADH7</td>
<td>rs284779</td>
<td>0.11 (-0.93 to 1.16) p=0.829</td>
<td>-1.20 (-2.22 to -0.175) p=0.022</td>
</tr>
</tbody>
</table>

Per allele effects - Model selected by AIC (Akaike's information criterion) - best model based on data
Conclusions and Future work

- Maternal ADH1B genotype is associated with maternal alcohol intake during pregnancy and offspring school performance at age 11.

- Child’s genotype at the ADH1A, ADH1B, ADH4 and ADH7 locus is associated with IQ score at age 8.

- Results need to be replicated in other cohorts, but suggest that mothers’ alcohol intake affects offspring cognition and school performance.
Prenatal alcohol exposure, childhood development and teenage drinking: a study of trans-generational effects

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Research fellowship awarded to Luisa Zuccolo (Bristol, UK) l.zuccolo@bristol.ac.uk

Cohorts

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C Stoltenberg (Oslo, Norway)
C Relton (Newcastle, UK)

Collaborators

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D Leon (London, UK)
L Palmer (Perth, W Australia)
M Schuckit (San Diego, USA)
Prenatal alcohol exposure, childhood development and teenage drinking: a study of trans-generational effects

Methods

- Life-course modelling
- Maternal/paternal comparisons
- Within-siblings comparisons (MoBa)
- Epigenetic effects – candidate genes DNA methylation
- Mendelian Randomization
- Instrumental variable analyses
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University of Queensland
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