Diet, Nutrition and Attention Deficit Hyperactivity Disorders

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OSU Moore Nutrition Center’s
Food, Nutrition and Health Update

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What is ADHD?

- Behavioral components
  - “inattentive-disorganized”
  - “Hyperactive-impulsive”
- Mechanistic Theories widely varying
- Complicating problems (MBD)
  - Motor control (developmental coordination dis)
  - Language development (learning disorders)
  - Aggression and defiance
  - Cognitive problems (IQ, Executive function)
  - Accidents, injuries, health problems
Low birth weight; maternal nutrition; routine pesticide exposures; maternal stress; extreme family conflict

Genotype; gene expression; temperament; social supports

Child ADHD, gateway

School failure; underachievement

Un- or under-Employment

Drug use, delinquency

Depression, suicide attempts

Serious accidents; injuries; bad driving

Marital problems, conflicts, divorce

Obesity, poor fitness

Genotype; gene expression; temperament; social supports
ADHD HIGHLY HERITABLE: TWIN STUDIES

Heritability (% of variance attributed to genetic factors)
Qualifications: parent vs teacher, ratings vs diagnosis
FOOD IS ONE OF THE MAJOR ENVIRONMENTS OF INTEREST FOR CHILD MENTAL AND PHYSICAL HEALTH

- Major changes in dietary content in recent centuries
- Positive and negative health effects apparent
- Brain = 2% of body mass, 20% of calorie use, 40% of glucose use.
- **Gut-brain axis** increasingly salient
ADHD AND DIET: MULTIPLE ANGLES

- Maternal BMI pre-pregnancy
- Maternal weight gain during pregnancy
- Dietary intake during pregnancy (fat, omega 3, etc)
- Breastfeeding in first 6 months
- Child intake of food additives and allergenic foods
- Child intake of particular micronutrients, e.g., omega-3
- Therapeutic efforts with dietary restriction, nutrient supplementation, and poly-nutrient supplementation with ADHD

• TODAY: a portion of this to give a flavor (pun intended) of the data
INTEGRATIVE THEORETICAL PERSPECTIVE

• Particular foods may work early in development via programming effects; later via other mechanisms; in both cases via epigenetic change

• Interactions with other social and biological stressors

• Possible final common pathways is glucocorticoid-inflammatory complex; so our interest in pro- and anti-inflammatory inputs
  • Breastfeeding
  • Fats and L-PUFA
  • Dietary additives and allergens
  • Omega-3 supplementation

AGREEMENT ON 20-30% INCREASED RISK OF OBESITY IN ADHD (CORTESE SAW SLIGHTLY LARGER EFFECT). TWO KEY AREAS OF DISAGREEMENT

**AGE**
- Cortese et al: Age does not moderate, effect is meaningful in children, 20% increased risk
- Nigg et al: Age does moderate, child effect (17%) is tiny, effect significantly larger in adults than in youth

**GENDER**
- Cortese et al: Gender did not moderate
- Nigg et al: True but barely, and pooled across age the association without covariates was reliable in females (OR=1.19 [1.01-1.41]) but not males (OR=1.10 [0.95-1.23]) when both sexes studied in same sample
- Effect appears earlier in girls, likely accounting for this, and in turn partially due to normal female weight gain and female vulnerability to depression which adds to obesity risk

Odds ratios for the association between ADHD and obesity stratified by three age groups. Y axis = odds ratio. 1.0 = no association; values > 1.0 indicate ADHD associated with more obesity or higher body mass index.

DOES PRENATAL OMEGA-3 supplementation (DHA) improve attention development: Infants and toddlers: YES

Task 1: Infants: Habituation

- Until 6 mos of age faster habituation=better attention/cognition, seen here in high omega 3 group

Task 2: Toddlers: Free play with single object look duration: Concentration

- During second year of life longer concentration on single object play predicts later IQ and executive function development, seen here again in high omega 3 supplementation group

Source: Columbo et al 2004, Child Development 75, 1254
DOES BREASTFEEDING PROTECT AGAINST ADHD? Breast feeding reduced in mothers of children with ADHD (R. side) vs. mothers of typically developing children (L. side) (p = .002)

DOES Omega 3 supplementation during childhood improve ADHD symptoms? YES

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>g</th>
<th>z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belanger et al 2009</td>
<td>BEST</td>
<td>0.091</td>
<td>0.230</td>
<td>0.818</td>
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<tr>
<td>Gustafsson et al 2010</td>
<td>BEST</td>
<td>0.124</td>
<td>0.593</td>
<td>0.553</td>
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<tr>
<td>Itomura et. al. 2005</td>
<td>BEST</td>
<td>0.296</td>
<td>2.639</td>
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<tr>
<td>Johnson et al 2009</td>
<td>BEST</td>
<td>0.347</td>
<td>1.378</td>
<td>0.168</td>
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<tr>
<td>Kirby et al 2010</td>
<td>BEST</td>
<td>0.047</td>
<td>0.333</td>
<td>0.739</td>
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<tr>
<td>Manor et al 2012</td>
<td>BEST</td>
<td>0.562</td>
<td>2.216</td>
<td>0.027</td>
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<tr>
<td>Milte et al 2012</td>
<td>BEST</td>
<td>0.092</td>
<td>0.856</td>
<td>0.392</td>
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<tr>
<td>Perera et al 2012</td>
<td>BEST</td>
<td>0.696</td>
<td>3.183</td>
<td>0.001</td>
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<tr>
<td>Raz et al 2009</td>
<td>BEST</td>
<td>0.060</td>
<td>0.237</td>
<td>0.813</td>
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<tr>
<td>Richardson &amp; Montgomery 2005</td>
<td>BEST</td>
<td>0.532</td>
<td>2.663</td>
<td>0.008</td>
</tr>
<tr>
<td>Richardson &amp; Puri 2002</td>
<td>BEST</td>
<td>0.850</td>
<td>2.284</td>
<td>0.022</td>
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<tr>
<td>Richardson et al 2012</td>
<td>BEST</td>
<td>0.174</td>
<td>1.371</td>
<td>0.170</td>
</tr>
<tr>
<td>Sinn &amp; Bryan 2007</td>
<td>BEST</td>
<td>0.669</td>
<td>2.963</td>
<td>0.003</td>
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<tr>
<td>Stevens et al 2003</td>
<td>BEST</td>
<td>0.111</td>
<td>0.636</td>
<td>0.525</td>
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<tr>
<td>Vaisman et al 2008 Fish oil</td>
<td>BEST</td>
<td>0.167</td>
<td>0.539</td>
<td>0.590</td>
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<tr>
<td>Vaisman et al 2008 PL omega-3</td>
<td>BEST</td>
<td>0.402</td>
<td>1.238</td>
<td>0.216</td>
</tr>
<tr>
<td>Voigt et al 2001</td>
<td>BEST</td>
<td>0.040</td>
<td>0.157</td>
<td>0.875</td>
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</tbody>
</table>

Pooled effect

Lower omega-3 blood level in ADHD than non-ADHD youth (g = 0.423). The size of the square indicates the study weight, and the width of the diamond is the 95% confidence interval (CI). Source: Hawkey & Nigg, 2014
Synthetic Food Colors associated with slight increase in ADHD symptoms by parent, teacher (not quite), & objective attention tests.
A narrow study selection:
1) Only in children formally diagnosed with ADHD
2) Only looking at ‘probably blinded raters’

(Sonuga Barke et al., 2013)
Summary of two major recent reviews and meta-analyses

<table>
<thead>
<tr>
<th></th>
<th>Nigg</th>
<th>Sonuga Barke</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of studies</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>best reporter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>parent (bias corrected)</td>
<td>g=.12*</td>
<td>d=.42*</td>
</tr>
<tr>
<td>Teacher (all studies)</td>
<td>g=.07 (ns)</td>
<td></td>
</tr>
<tr>
<td>Teacher (high quality)</td>
<td>g=.22*</td>
<td></td>
</tr>
<tr>
<td>attention test</td>
<td>g=.27*</td>
<td></td>
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</tbody>
</table>

*Survives correction for publication bias
Suggests a bit larger effect in studies of children diagnosed with ADHD versus community studies.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Hedges's g and 95% CI</th>
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<tbody>
<tr>
<td>Conners et al., 1976(^2)</td>
<td></td>
</tr>
<tr>
<td>Egger et al., 1985(^3)</td>
<td></td>
</tr>
<tr>
<td>Harley et al., 1978(^4)</td>
<td></td>
</tr>
<tr>
<td>Kaplan et al., 1989(^5)</td>
<td></td>
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<tr>
<td>Schmidt et al., 1997(^6)</td>
<td></td>
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<tr>
<td>Summary</td>
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</tr>
</tbody>
</table>

33% response rate

-1.00  -0.50  0.00  0.50  1.00
Restriction diet makes ADHD symptoms: worsen improve

Restriction Diet alternative analysis of effect size (*not* response rate)
Limited to children diagnosed with ADHD

(Sonuga Barke et al., 2013)
### Updated Estimated Response rate to Restriction diet for children with ADHD not preselected for dietary problem or response in adequately blinded and controlled trials (Nigg & Holton 2014)

<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>Δ Criterion</th>
<th>N</th>
<th>Rate (%)</th>
<th>LL (%)</th>
<th>UL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conners et al, 1978</td>
<td>25%</td>
<td>15</td>
<td>26.7</td>
<td>10.4</td>
<td>53.3</td>
</tr>
<tr>
<td>Harley et al, 1978</td>
<td>10%</td>
<td>23</td>
<td>22.8</td>
<td>12.6</td>
<td>37.8</td>
</tr>
<tr>
<td>Kaplan et al, 1989</td>
<td>25%</td>
<td>24</td>
<td>41.7</td>
<td>24.1</td>
<td>61.7</td>
</tr>
<tr>
<td>Schmidt et al, 1997</td>
<td>100%</td>
<td>49</td>
<td>24.5</td>
<td>14.5</td>
<td>38.3</td>
</tr>
<tr>
<td>Williams et al, 1978</td>
<td>33%</td>
<td>24</td>
<td>19.2</td>
<td>8.2</td>
<td>38.7</td>
</tr>
<tr>
<td><strong>Pooled effect</strong></td>
<td></td>
<td>135</td>
<td><strong>26.4</strong></td>
<td>20.0</td>
<td>34.1</td>
</tr>
</tbody>
</table>

**Note:** N, Year of studies
Effect of food additives on hyperactivity in 8 yr olds is moderated by histamine degradation gene (*HNMT* Thr105Ile and *HNMT* T939C). On the left (Thr105Ile), note that when the T allele is present, the food additive challenge has no effect. When the T allele is absent, the food additives cause more hyperactivity than the placebo. Source: Stevenson et al., 2010, Am J Psychiatry, 167, 1108-1115. H3 receptors

New Directions: Personalized or precision medicine. Who should get these interventions?
CONTEXT: Treatment Effect Sizes for Different ADHD Treatments For ADHD Symptom Change

Source: Faraone and Antshel, 2014
Conclusions: is ADHD inflammation mediated on top of genetic liability?

- Omega 3 have real but small effect
- Maternal prenatal and post-natal feeding may influence ADHD or its elements
- Synthetic food dyes effect: very small, old studies
- Average effect: misleading
  - A small number of children may respond markedly
- Study design: should be genetically informed
  - Identify who will benefit dietary intervention
Thank you to collaborators
- Erica Musser, Diane Stadler, Katie Holton, Jeni Johnstone, Jackie Shannon, and many others

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- Abaracadabra Foundation (Dr. Nigg)