ADHD & Intrauterine Growth Restriction (IUGR)
The Definition of ADHD

- Not really....
Intrauterine Growth Restriction (IUGR)

Definition

- A significant reduction in fetal growth rate that results in a birth weight in the lowest 10\textsuperscript{TH} percentile for gestational age, OR a relative reduction of the fetal growth curve.
- Fetuses affected by IUGR form a subset of cases of small for gestational age (SGA) infants.
Intrauterine Growth Restriction (IUGR) Definition

• Estimated to occur in 5-7% of all pregnancies
  Data from 2013 in USA reveals an increase with 10% of low birth rate between 1990 and 2006 in singletons.

• Most common cause is *placental insufficiency*
Etiology of IUGR

Maternal factors
- Constitutionally small
- Substance use and abuse (smoking, alcohol)
- Poor nutrition, severe anemia, eating disorder
- High altitude, social deprivation

Maternal medical illnesses *
- Pregestational diabetes mellitus with vasculopathy, hypertension, renal disorders, antiphospholipid antibody syndrome, autoimmune disease, cyanotic heart disease

Placental and cord abnormalities
- Circumvallate placenta, placental tumours, marginal cord insertion
- Single umbilical artery

Fetal malformations
- Congenital diaphragmatic hernia, congenital heart disease, omphalocele

Drugs and teratogens
- Infection: Malaria, TORCH, syphilis
- Multiple gestation
- Chromosomal abnormalities (Trisomy 13, 18, 21)

* Maternal illnesses
- Hypertension, renal disorders, antiphospholipid antibody syndrome, autoimmune disease, cyanotic heart disease
Neonate and Placenta in IUGR

Normal & IUGR
Newborn babies

Normal & IUGR
Placentas
Animal Model of IUGR

Control

IUGR

LA  Ao  RA

LV  RV

300.0um

300.0um
The consequences of IUGR

• **Short term:**
  Higher risk for birth and perinatal complications

• **Long Term:**
  Higher risk for neurodevelopmental disorders

• Growth Failure

• Adult cardiovascular disease, hypertension, Diabetes, obesity, “Metabolic Syndrome”.

  *Barker et al.*

  ”The Thrifty hypothesis”
  ”The fetal origins of disease”
Intrauterine Growth Restriction (IUGR)

- About 30-50% of extremely preterm neonates are also IUGR (Rosenberg 2008)

- It is responsible of almost 50% of perinatal mortality

- It is the second fetal risk factor after premature birth

- Growth-restricted fetuses have an augmented risk of mortality and morbidity:
  - Intraventricular hemorrhage
  - Bronchopulmonary dysplasia
  - Necrotizing enterocolitis
  - Infections
  - Pulmonary hemorrhage
  - Polycythemia
  - Hypothermia and hypoglycemia
Abnormal placenta and altered uterine blood flow

Maternal malnutrition and/or maternal undernutrition

Impaired fetal nutrition

Intrauterine growth restriction (IUGR)
Altered organ growth and maturation

Kidneys
- nephron number

Heart
- cardiomyocyte number

Vasculature
- endothelial function

Pancreas
- insulin secretion

HPA axis
- alterations

Programming of cardiovascular disease
Neurodevelopmental Outcome of Children With Intrauterine Growth Retardation: A Longitudinal, 10-Year Prospective Study

Yael Leitner, MD, Aviva Fattal-Valevski, MD, Ronny Geva, PhD, Rina Estel, PhD, Hagit Tolelano-Albade, MD, Michael Rotstein, MD, Haim Bassan, MD, Bella Rashmon, RN, Ora Bitchkowsky, BA, Ariel J. Jaffa, MD, and Shaul Harel, MD

One hundred twenty children with intrauterine growth retardation were prospectively followed from birth to 9 to 10 years of age in order to characterize their specific neurodevelopmental and cognitive difficulties and to identify clinical predictors of such difficulties. Perinatal biometric data and risk factors were collected. Outcome was evaluated at age 9 to 10 by neurodevelopmental, cognitive, and school achievement (P < .001) was found between the children with intrauterine growth retardation and controls. Children with intrauterine growth retardation demonstrated a specific profile of neurodevelopmental and IQ was the Cephalization index (P < .001). Somatic catch-up growth at age 2 and at age 9 to 10 cor-

Six-Year Follow-Up of Children With Intrauterine Growth Retardation: Long-Term, Prospective Study

Yael Leitner, MD; Aviva Fattal-Valevski, MD; Ronny Geva, PhD; Haim Bassan, MD; Edith Posner, MD; Miriam Kutai, MD; Ariel Many, MD; Ariel J. Jaffa, MD; and Shaul Harel, MD

ABSTRACT

This prospective study was designed to characterize the neurodevelopmental and cognitive difficulties specific to children with intrauterine growth retardation and to detect early clinical predictors of these difficulties. Eighty-one children with intrauterine growth retardation were monitored up to 6 to 7 years of age using biometric parameters, perinatal risk questionnaire, and detailed neurodevelopmental and cognitive assessments. Forty-two children served as age-matched, appropriate for gestational age controls. A significant difference in growth parameters (P < .01), neurodevelopmental score (P < .05), and IQ (P < .05) was found between the children with intrauterine growth retardation and controls. A specific profile of difficulties in coordination, internalization, spatial and graphomotor skills, and abundance of associated movements is typical of the children with intrauterine growth retardation and hints at possible later learning disabilities. The clinical parameters best predicting neurodevelopmental outcome were the neonatal risk score (P < .05) and the weight and height at 6 years of age (P < .05). The children with intrauterine growth retardation with neonatal complications had lower neurodevelopmental scores than the controls but no difference in IQ. Intrauterine growth retardation children diagnosed prenatally had the same neurodevelopmental and IQ scores as those diagnosed at birth, probably due to the careful perinatal and obstetric care provided. Children with intrauterine growth retardation demonstrated a specific profile of neurodevelopmental disabilities at preschool age. Early diagnosis and intervention could probably reduce these difficulties to a minimum. (J Child Neurol 2006;11:731–736)

Original Article

Neuropsychological Outcome of Children With Intrauterine Growth Restriction: A 9-Year Prospective Study

Ronny Geva, Rina Estel, Yael Leitner, Aviva Fattal-Valevski and Shaul Harel

Pediatrics 2006;118:91-100
DOI: 10.1542/peds.2005-2343

This information is current as of July 4, 2006

Original Article

Neurodevelopmental Outcome in Children With Intrauterine Growth Retardation: A 3-Year Follow-Up

Aviva Fattal-Valevski, MD; Yael Leitner, MD; Miriam Kutai, MD; Edith Tal-Posener, MD; Abraham Tumer, MD; Deborah Lieberman, MD; Ariel Jaffa, MD; Ariel Many, MD; Shaul Harel, MD

ABSTRACT

The study was designed to detect early clinical predictors of developmental outcome in children with intrauterine growth retardation. Eighty-five children with intrauterine growth retardation were followed up prospectively to 3 years of age, using biometric parameters, perinatal risk questionnaire, and neurodevelopmental evaluation. Forty-two children served as controls. A significant difference in neurodevelopmental score at 3 years of age was noted between the intrauterine growth retardation and control groups (P < .001). In the intrauterine growth retardation group, the clinical parameters that most significantly correlated with outcome were cephalization index (head circumference/weight ratio), neonatal risk score, and birth weight. The best predictor of 3-year outcome was the cephalization index (P < .05). The children with intrauterine growth retardation with neonatal complications had significantly lower IQ scores (P < .05) and a poorer neurodevelopmental outcome (P < .05) than those without complications. Children with intrauterine growth retardation are at higher risk for developmental disabilities than are controls, especially in the presence of neonatal complications and a high cephalization index. (J Child Neurol 1994;9:724–727)

Intrauterine growth retardation occurs in 3% to 5% of all pregnancies and is often associated with impaired performance in a broad range of cognitive and motor functions. However, different studies have shown a wide variation in neurodevelopmental outcomes. Predictors of neurodevelopmental retardation remain unclear, though the strongest are apparently difficulties in motor development, and IQ scores. This study is part of a long-term, prospective follow-up investigation of infants with intrauterine growth retardation aimed at determining school age developmental and cognitive outcomes. All consecutive infants born at the Latzer Maternity Hospital, Tel Aviv Sourasky Medical Center (Israel) in September 1989 to September 1992 were included for this study. Gestational age was calculated by the last menstrual period. Exclusion criteria were the presence of genetic syndromes, major malformations, or congenital infections. We excluded eight children: four had congenital heart disease, one had non-syndromic microcephaly, one had congenital toxemia, and one had a seizure at 1 year of age. The study continued for 3 years and was followed up prospectively.
IUGR Outcome Research
12 years of prospective follow-up
S. Harel et.al

Table 2. Developmental Outcome in Children With Intrauterine Growth Restriction and Controls

<table>
<thead>
<tr>
<th>Developmental Parameter</th>
<th>Intrauterine Growth Restriction (n = 123)</th>
<th>Control (n = 63)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurodevelopment</td>
<td>85.9 ± 9.6</td>
<td>91.2 ± 5.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IQ</td>
<td>98.39 ± 12.9</td>
<td>107.5 ± 10.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>School achievement</td>
<td>588.6 ± 80.2</td>
<td>636.63 ± 55.7</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

a. Percentage of optimal items.
b. Estimated IQ.
c. Kauffman Assessments

FIGURE 1
Comparison between IUGR and control children: neuropsychological borderline/suboptimal performance at 9 to 10 years. *P < .001; **P < .05; ***P < .01.
Preterm Birth and Poor Fetal Growth as Risk Factors of Attention-Deficit/Hyperactivity Disorder

Minna Sucksdorff et al.  PEDIATRICS 2015

Population based study: 10,321 ADHD (ICD 10), 38,355 CONTROLS.
Birth weight as an independent predictor of ADHD symptoms: A within-twin pair analysis

Erik Pettersson

*J Child Psychology Psychiatry 2015*

The aims of the study were to:

- Examine if birth weight was uniformly related to all forms of DSM-based ADHD symptoms, including continuous total score, inattention, and hyperactivity-impulsivity.
- Examine if these associations held up within twins pairs, that is, after controlling unmeasured genetic and shared environmental confounds.
METHOD

Parents of all Swedish 9- and 12-year-old twins born between 1992 and 2000 were interviewed for DSM-IV inattentive and hyperactive-impulsive ADHD symptoms by the Autism – Tics, AD/HD and other Comorbidities (A-TAC) inventory (N = 21,775 twins).

Birth weight was collected prospectively through the Medical Birth Registry. We used a within-twin pair design to control for genetic and shared environmental factors.

RESULTS

Reduced birth weight was significantly associated with a mean increase in total ADHD (β = −.42; 95% CI: −.53, −.30), inattentive (β = −.26; 95% CI: −.33, −.19), and hyperactive-impulsive (β = −.16; 95% CI: −.22, −.10) symptom severity.

These results imply that a change of one kilogram of birth weight corresponded to parents rating their child nearly one unit higher on the total ADHD scale.

These associations remained within pairs of MZ and DZ twins, and were also present when restricting the analyses to full term births.

CONCLUSIONS

There is an independent association between low birth weight and all forms of ADHD symptoms, even after controlling for all environmental and genetic confounds shared within twin pairs.
Are fetal growth impairment and preterm birth causally related to child attention problems and ADHD? Evidence from a comparison between high-income and middle-income cohorts

*Murray E, et al. J Epidemiol Community Health 2016*

- Cross-cohort comparison is an established method for improving causal inference.
- This study compared 2 cohorts, 1 from a high-income country and another from a middle-income country.
- Aims:
  1. Establish whether birth exposures may play a causal role in the development of childhood attention problems
  2. Identify whether confounding structures play a different role in parent-reported attention difficulties (by SDQ) compared with attention deficit hyperactivity disorder (ADHD)(by DAWBA) diagnoses
Are fetal growth impairment and preterm birth causally related to child attention problems and ADHD? Evidence from a comparison between high-income and middle-income cohorts

*Murray E, et al. J Epidemiol Community Health 2016*

Associations between exposures and outcomes were compared between 7-year-old children from the

**Avon Longitudinal Study** of Parents and Children (ALSPAC) in the UK (N=6849) and the

2004 **Pelotas cohort** in Brazil (N=3509)

**Birth exposures included:**

- Low birth weight (LBW),
- Small-for-gestational age (SGA),
- Small head circumference (HC)
- Preterm birth (PTB).

**Outcomes:**

- Attention difficulties (Strengths and Difficulties Questionnaire, SDQ)
- ADHD (Development and Well-Being Assessment, DAWBA).
Table 4  Unadjusted and adjusted associations between birth anthropometric measures and ADHD/attention difficulties in ALSPAC and Pelotas cohorts

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted*</th>
<th></th>
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<th>Model 1†</th>
<th></th>
<th></th>
<th>Model 2‡</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>p Value</td>
<td>OR</td>
<td>95% CI</td>
<td>p Value</td>
<td>OR</td>
<td>95% CI</td>
<td>p Value</td>
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<tr>
<td><strong>Attention difficulties (SDQ)</strong></td>
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<td><strong>ALSPAC</strong></td>
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<tr>
<td>Low birth weight</td>
<td>1.66</td>
<td>1.16 to 2.36</td>
<td>0.005</td>
<td>1.69</td>
<td>1.17 to 2.42</td>
<td>0.005</td>
<td>1.46</td>
<td>0.98 to 2.17</td>
<td>0.060</td>
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<tr>
<td>Small-for-gestational age</td>
<td>1.71</td>
<td>1.33 to 2.19</td>
<td>&lt;0.001</td>
<td>1.62</td>
<td>1.23 to 2.14</td>
<td>0.001</td>
<td>1.59</td>
<td>1.20 to 2.19</td>
<td>0.001</td>
</tr>
<tr>
<td>Small head circumference</td>
<td>1.92</td>
<td>1.39 to 2.67</td>
<td>&lt;0.001</td>
<td>1.73</td>
<td>1.20 to 2.50</td>
<td>0.003</td>
<td>1.64</td>
<td>1.11 to 2.41</td>
<td>0.012</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.44</td>
<td>1.03 to 2.01</td>
<td>0.031</td>
<td>1.44</td>
<td>1.03 to 2.01</td>
<td>0.031</td>
<td>1.37</td>
<td>0.95 to 1.98</td>
<td>0.094</td>
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<tr>
<td><strong>Pelotas</strong></td>
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<tr>
<td>Low birth weight</td>
<td>1.35</td>
<td>0.97 to 1.88</td>
<td>0.077</td>
<td>1.31</td>
<td>0.94 to 1.83</td>
<td>0.114</td>
<td>1.21</td>
<td>0.86 to 1.71</td>
<td>0.287</td>
</tr>
<tr>
<td>Small-for-gestational age</td>
<td>1.47</td>
<td>1.14 to 1.89</td>
<td>0.003</td>
<td>1.43</td>
<td>1.10 to 1.84</td>
<td>0.007</td>
<td>1.35</td>
<td>1.04 to 1.75</td>
<td>0.023</td>
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<tr>
<td>Small head circumference</td>
<td>1.31</td>
<td>1.00 to 1.71</td>
<td>0.047</td>
<td>1.32</td>
<td>1.01 to 1.72</td>
<td>0.043</td>
<td>1.17</td>
<td>0.89 to 1.54</td>
<td>0.256</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.10</td>
<td>0.83 to 1.46</td>
<td>0.513</td>
<td>1.03</td>
<td>0.77 to 1.37</td>
<td>0.848</td>
<td>0.99</td>
<td>0.74 to 1.32</td>
<td>0.938</td>
</tr>
<tr>
<td><strong>Any ADHD disorder (DAWBA)</strong></td>
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<td><strong>ALSPAC</strong></td>
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<tr>
<td>Low birth weight</td>
<td>2.13</td>
<td>1.11 to 4.11</td>
<td>0.024</td>
<td>2.13</td>
<td>1.11 to 4.12</td>
<td>0.024</td>
<td>2.29</td>
<td>1.09 to 4.80</td>
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<tr>
<td>Small-for-gestational age</td>
<td>0.83</td>
<td>0.42 to 1.63</td>
<td>0.583</td>
<td>0.83</td>
<td>0.42 to 1.63</td>
<td>0.583</td>
<td>0.65</td>
<td>0.30 to 1.41</td>
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<td>Small head circumference</td>
<td>1.05</td>
<td>0.46 to 2.40</td>
<td>0.917</td>
<td>1.05</td>
<td>0.46 to 2.40</td>
<td>0.917</td>
<td>1.06</td>
<td>0.43 to 2.65</td>
<td>0.896</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>2.23</td>
<td>1.24 to 3.99</td>
<td>0.007</td>
<td>2.23</td>
<td>1.24 to 3.99</td>
<td>0.007</td>
<td>2.33</td>
<td>1.23 to 4.42</td>
<td>0.009</td>
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<tr>
<td><strong>Pelotas</strong></td>
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<tr>
<td>Low birth weight</td>
<td>0.83</td>
<td>0.36 to 1.92</td>
<td>0.668</td>
<td>0.81</td>
<td>0.35 to 1.87</td>
<td>0.618</td>
<td>0.78</td>
<td>0.34 to 1.80</td>
<td>0.560</td>
</tr>
<tr>
<td>Small-for-gestational age</td>
<td>1.77</td>
<td>1.07 to 2.94</td>
<td>0.027</td>
<td>1.71</td>
<td>1.03 to 2.84</td>
<td>0.038</td>
<td>1.69</td>
<td>1.02 to 2.82</td>
<td>0.043</td>
</tr>
<tr>
<td>Small head circumference</td>
<td>0.91</td>
<td>0.48 to 1.72</td>
<td>0.764</td>
<td>0.87</td>
<td>0.46 to 1.65</td>
<td>0.671</td>
<td>0.85</td>
<td>0.45 to 1.62</td>
<td>0.630</td>
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<tr>
<td>Preterm birth</td>
<td>0.95</td>
<td>0.50 to 1.79</td>
<td>0.863</td>
<td>0.90</td>
<td>0.48 to 1.71</td>
<td>0.754</td>
<td>0.87</td>
<td>0.46 to 1.65</td>
<td>0.664</td>
</tr>
</tbody>
</table>

*Adjusted for age at time of testing.
†Adjusted for age at time of testing and maternal, family and demographic variables (maternal education, income, maternal age at delivery).
‡Adjusted for model 1 and gestational (smoking, alcohol use, and depression during pregnancy) and perinatal variables (mode of delivery and Apgar score at 5 min).
ADHD, attention deficit hyperactivity disorder; ALSPAC, Avon Longitudinal Study of Parents and Children; DAWBA, Development and Well-Being Assessment; SDQ, Strengths and Difficulties Questionnaire.
Are fetal growth impairment and preterm birth causally related to child attention problems and ADHD? Evidence from a comparison between high-income and middle-income cohorts

*Murray E, et al. J Epidemiol Community Health 2016*

**Conclusions**

The findings suggest that fetal growth impairment may play a causal role in the development of **attention difficulties** in childhood, as similar associations were identified across both cohorts.

Confounding structures, however, appear to play a greater role in determining whether a child meets the full diagnostic criteria for ADHD.
Sex differences in the association between fetal growth and child attention at age four: specific vulnerability of girls.

Murray E. et al

*J Child Psychol Psychiatry. 2015*

**METHODS:**
• A total of 3,749 neonates from the 2004 Pelotas birth cohort (Brazil)

**RESULTS:**
• In girls, attention difficulties were associated with being born SGA (OR = 1.40, CI = 1.08-1.82, p = .012), with a small HC (OR = 1.52, CI = 1.11-2.08, p = .009), or with a low PI (OR = 1.29, CI = 1.08-1.54, p = .005). There were no associations identified between attention difficulties and any fetal growth indices in boys.

**CONCLUSIONS:**
• Our results show that girls with impaired fetal growth may be particularly at risk of attention difficulties in childhood. This is consistent with emerging research that female fetuses may be more vulnerable to certain suboptimal intrauterine environments, inducing epigenetic changes that lead to disturbed growth and long-term developmental impairment.
Cognitive and behavioral Outcomes of IUGR
School-Age Children

Pediatrics 2016

Meta-analysis

• Included: Case – control studies. (15 with cognitive data, 6 with behavioral data)
  A total of 1559 cases and 1630 controls

• The controls had significantly higher IQ than IUGR

• The IQ of the IUGR were not significantly correlated with GA or BW

• The incidence of ADHD was not significantly different between the two groups.

• Number of studies assessing behavioral and ADHD outcome is small

• Conclusion:
  • IUGR is associated with lower cognitive scores, however, larger scale studies are needed to assess the effect of IUGR on behavior and ADHD
Figure 1. Adjusted Group Mean Scores on the Adult Problem Questionnaire in the Term Comparison Group (CONTROL=172) and the Very-Low-Birth-Weight (VLBW,SGA=52,AGA=110) Subjects by Gestational Age Subgroup

*p≤0.05. **p<0.01.
Why is IUGR associated with ADHD?

What do we know?
Decreased blood flow to the frontal lobe

During growth restriction due to placental insufficiency, hemodynamic adaptation occurs with blood flow redistribution preferentially to the brain, i.e. the brain sparing effect.

In early stages, brain sparing is expressed as a reduction in the Doppler cerebro-placental blood flow ratio (<1), which is present in almost all early-growth restricted fetuses with placental insufficiency.

However, as placental insufficiency and hypoxia progress, a further decrease in resistance to blood flow in the middle cerebral artery (MCA) is observed.

Abnormal MCA Doppler findings indicate an advanced stage of brain-sparing, since it is correlated with established hypoxemia, and with a relative decrease in blood flow in the frontal areas in favor of the basal ganglia.

Figuera et al.
MCA flow in IUGR


Figure 1 Proportion of abnormal Neonatal Behavioral Assessment Scale scores according to study group: appropriate-for-gestational age (□); intrauterine growth restricted (IUGR) with normal middle cerebral artery (MCA) (■); and IUGR with abnormal MCA (■). Paired significant differences (adjusted P-value by logistic regression) are indicated.

Middle cerebral artery Doppler waveforms

(A) Normal middle cerebral artery (MCA) at term - normal peak systolic velocity (58 cm/s), high resistance, low end-diastolic velocity.

(B) ‘Brain sparing’ MCA - lower peak, much higher diastolic velocity suggests cerebrovasodilation.

(C) Anemic fetus with retained high resistance, elevated peak systolic velocity (77 cm/s).
Decreased Brain Volumes

Prospective follow-up study at age 20 included 39 adults born small for gestational age at term and 37 adults born appropriate for gestational age at term. Detailed neurocognitive skills were assessed (IQ, attention and memory). Anatomical images were analyzed using Voxel-Based-Morphometry and FreeSurfer.

Suffren et al. Early Human Development. 2017

Table 2

<table>
<thead>
<tr>
<th></th>
<th>SGA (n = 39)</th>
<th>AGA (n = 37)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IQ (WASI-II)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal comprehension</td>
<td>87(2.15)</td>
<td>88(2.72)</td>
<td>0.984</td>
</tr>
<tr>
<td>(composite score)</td>
<td></td>
<td></td>
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<tr>
<td>Perceptual reasoning</td>
<td>84(2.09)</td>
<td>89(2.52)</td>
<td>0.171</td>
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<tr>
<td>(composite score)</td>
<td></td>
<td></td>
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<tr>
<td>Full scale 4</td>
<td>84(1.83)</td>
<td>87(2.61)</td>
<td>0.484</td>
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<tr>
<td>(composite score)</td>
<td></td>
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<tr>
<td><strong>Memory</strong></td>
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<tr>
<td>CVLT-II immediate correct</td>
<td>46(1.67)</td>
<td>49(1.85)</td>
<td>0.307</td>
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<tr>
<td>free recall</td>
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<tr>
<td><strong>Attention/executive functions (T-scores)</strong></td>
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</tbody>
</table>
| TAP alertness            | 49(1.49)    | 53(1.52)    | 0.032*
| TAP divided attention    | 45(1.18)    | 48(1.02)    | 0.139|
| (omissions)              |             |             |     |
| TAP sustained attention  | 39(1.87)    | 46(2.66)    | 0.024*|
| (false alarms)           |             |             |     |
| TAP sustained attention  | 35(1.79)    | 41(2.15)    | 0.049*|
| (omissions)              |             |             |     |
| TAP working memory       | 48(1.59)    | 53(2.06)    | 0.051|
| (omissions)              |             |             |     |
| TAP working memory: RT   | 56(1.63)    | 56(2.31)    | 0.533|
| TAP Go/noGo: false       | 47(1.37)    | 52(0.93)    | 0.005*|
| alarms                   |             |             |     |
| TAP Go/noGo: RT (median) | 49(1.32)    | 44(1.64)    | 0.005*|

Note. IQ, Intellectual Quotient; WASI, Wechsler Abbreviated Scale of Intelligence; CVLT, California Verbal Learning Test; TAP, Test-battery of Attentional Performance; RT, Reaction Time.

* Highest TAP scores indicate better outcome.

* T-test between the two groups, p < 0.05.

Fig. 1. Clusters represented a smaller volume in the participants born small for gestational age, compared to those born appropriate for gestational age, from the VBM analyses, for (a) the frontal lobe; (b) the cerebellum; (c) the temporal lobe; and (d) the parietal lobe. The color bar represents the t scores.
Epigenetics

The molecular link between adverse neurobehavioral outcomes and a suboptimal prenatal environment may involve epigenetic changes (DNA methylation, histone methylation or acetylation (Jirtle and Skinner, 2007; Weaver et al., 2004; Szyf, 2009).
Epigenetics in ADHD

- Shumay, Fowler, and Volkow (2010) revealed pronounced sensitivity of DAT1 gene to epigenetic factors due to some of its features including the abundance of variable number of tandem repeats (VNTRs) (indicating a tendency for open chromatin structure and increased accessibility to chromatin modifiers) and high CpG density throughout the gene.

- Family-based studies and genetic association studies have reported that some alleles at ADHD candidate genes have preferential paternal transmission to the affected offspring (Hawi et al., 2005). This parent-of-origin effects could be explained, among other genetic mechanisms, by genomic imprinting (Zayats, Johansson, & Haavik, 2015).

- Methylene tetrahydrofolate reductase (MTHFR) gene polymorphisms (C677T and A1298C) were associated with ADHD (Gokcen, 2011). Thus, decreased MTHFR enzyme activity in case of nucleotide polymorphisms (Weisberg, 1998) alters histone and DNA methylation, disturbing the expression of genes regulated by epigenetic mechanisms.
Epigenetics in ADHD

• The methyl CpG binding protein 2 gene (MeCP2) expression was also found to be altered in ADHD. In frontal cortex samples, significantly reduced MeCP2 levels were described (Nagarajan, Hogart, Gwy, Martin, & LaSalle, 2006). This protein interferes with epigenetic regulation.

• Kandemir et al. (2014) evaluated several miRNA levels in 52 ADHD patients versus a matched control group, and significant dysregulation of circulating miRNA levels were found in the ADHD group (Kandemir et al., 2014). These molecules, as previously seen, are part of epigenetic regulation mechanisms.
Environmental Factors, Epigenetic Marks, and ADHD Risk

- **Nutritional factors**
  Folate, protein deficiency

- **Toxic Factors:**
  Maternal smoking,
  Alcohol consumption (alcohol affects folate absorption metabolism and S-adenosyl methionine bioavailability causing disturbances in DNA methylation) (Tollefsbol, 2010).
  Synthetic glucocorticoids, PCB’s, Lead.

- **Psychosocial Factors:**
  Maternal stress during and after gestation (via hypomethylation of the corticotropin-releasing factor gene)
Early Life Protein Restriction Alters Dopamine Circuitry

Zivjena Vucetic, et al.
Neuroscience 2010

• Mouse dams were fed a protein deficient (8.5% protein) or isocaloric control (18% protein) diet through pregnancy and lactation (a well validated rodent model of IUGR).
• Dopamine-related gene expression, dopamine content and behavior were examined in adult offspring.
• IUGR offspring have 6–8 fold over-expression of dopamine (DA)-related genes (tyrosine hydroxylase (TH) and dopamine transporter) in brain regions related to reward processing (ventral tegmental area (VTA), nucleus accumbens, prefrontal cortex (PFC) and homeostatic control (hypothalamus), as well as increased number of TH-ir neurons in the VTA and increased dopamine in the PFC.
• Cyclin-dependent kinase inhibitor 1C (Cdkn1c) is critical for dopaminergic neuron development. Methylation of the promoter region of Cdkn1c was decreased by half and there was a resultant 2–7 fold increase in Cdkn1c mRNA expression across brain regions.
• IUGR animals demonstrated alterations in dopamine-dependent behaviors, including altered reward-processing, hyperactivity and exaggerated locomotor response to cocaine.
Early Life Protein Restriction Alters Dopamine Circuitry
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- Increased PFC dopamine and TH-ir cells in the VTA
- Top right: Dopamine and dopamine metabolites were measured in the PFC of control (grey) and IUGR animals (black, n=6/group). There was a significant increase in dopamine, and a significant decrease in dopamine turnover (DOPAC:DA ratio). Top left: A significant increase in TH-ir neurons was seen in the VTA (n=4/group). Representative images are shown in the lower panels (control-left, IUGR-right). *p<.05.
The British epidemiologist Dr. David J. Barker introduced the concept that the “the womb may be more important than the home.”

In the intervening years, we have come to appreciate that prenatal programming occurs, in part, through epigenetic mechanisms by which genes are activated or deactivated based on environmental influences during fetal development ...

Though Dr. Barker’s original concept—the womb may be more important than the home—likely underestimates the role of the postnatal environment on the development of disease..

The prenatal period is certainly critical to the evolving “three-hit hypothesis of disease vulnerability and resilience.” With genetic predisposition as “hit 1,” the prenatal environment could be viewed as “hit 2,” altering gene expression and leading to phenotypes with differing susceptibility to later life experiences and exposures (hit 3).
Summary

• IUGR is strongly associated with ADHD. (often with other comorbid difficulties)

• While prenatal influences are critical, epigenetic mechanisms are also involved

• Both the prenatal period, and early postnatal influences are amiable to intervention

• Further research is mandatory (different ADHD phenotype in IUGR? Different response to intervention?)