Prenatal Pediatrics: Back to the Future

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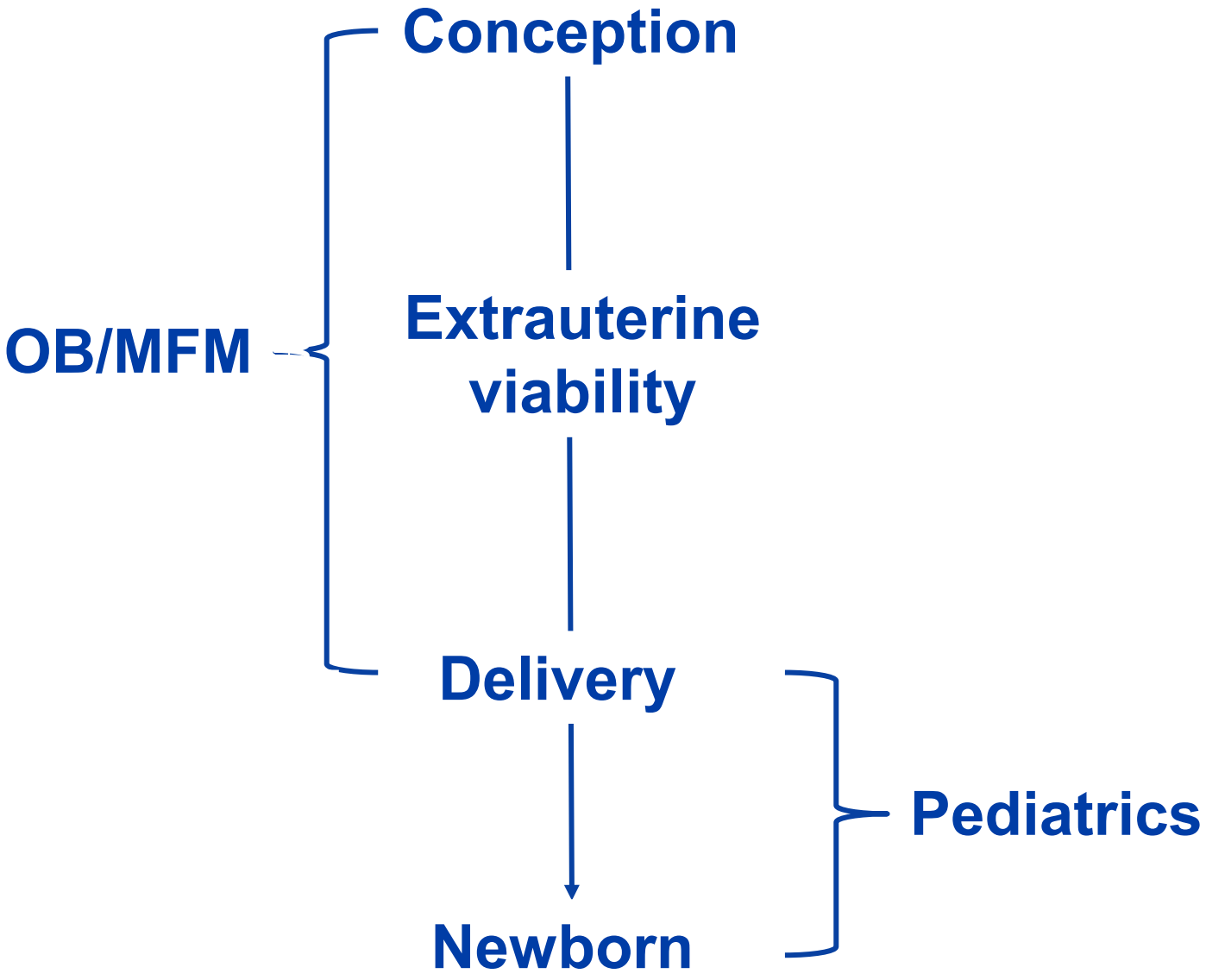
Disclosures

No conflicts to disclose:

- No financial or business interest, arrangement or affiliation that could be perceived as a real or apparent conflict of interest in the subject (content) of their presentation.
- No unapproved or investigational use of any drugs, commercial products or devices.

Continuity of care

What gets lost in transition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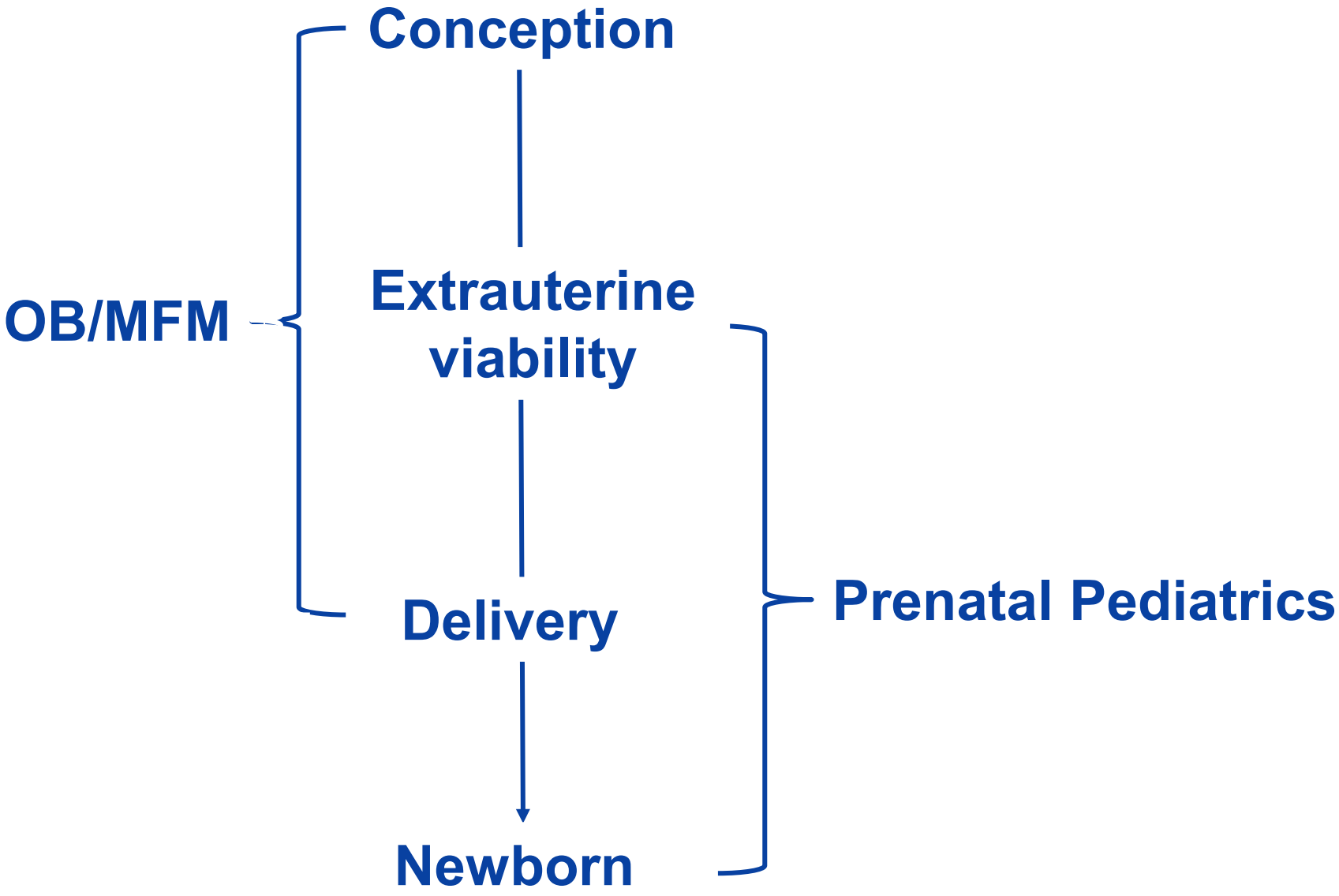
Extrauterine viability
Delivery
Pediatrics
Newborn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The Barker Hypothesis

Dutch Famine (“Winterhonger”) 1944-1945

Maternal malnutrition, birthweight and adverse long-term outcome

The Story of Baby Boy X

- Born at 37 weeks (i.e., not premature) with a BW of 2.5kg (15%^{ile} i.e., not SGA)
- NVD after spontaneous onset of labor and no intrapartum concerns
- Apgar scores were 7^{1} and 9^{5}
- Admitted to the nursery with initial but transient feeding difficulties.
- Rapidly gained weight and regular pediatrician visits were unremarkable with normal developmental gains (Denver Developmental Scales).

The Story of Baby Boy X

- At 2 years - language and social development “somewhat delayed” - close follow-up
- At 3 years - further language delay – speech therapy started
- At 4 years - social withdrawal and repetitive behavioral stereotypies emerged; neuro-psychologist diagnoses autism spectrum disorder - ABA therapy started.

- At 2 years his weight > 97%ile
- At 3 years he is diagnosed with ‘obesity’
- At 12 years he is obese and has been diagnosed with diabetes

Fetal development in an adverse intra-uterine environment

Placental failure and fetal growth restriction

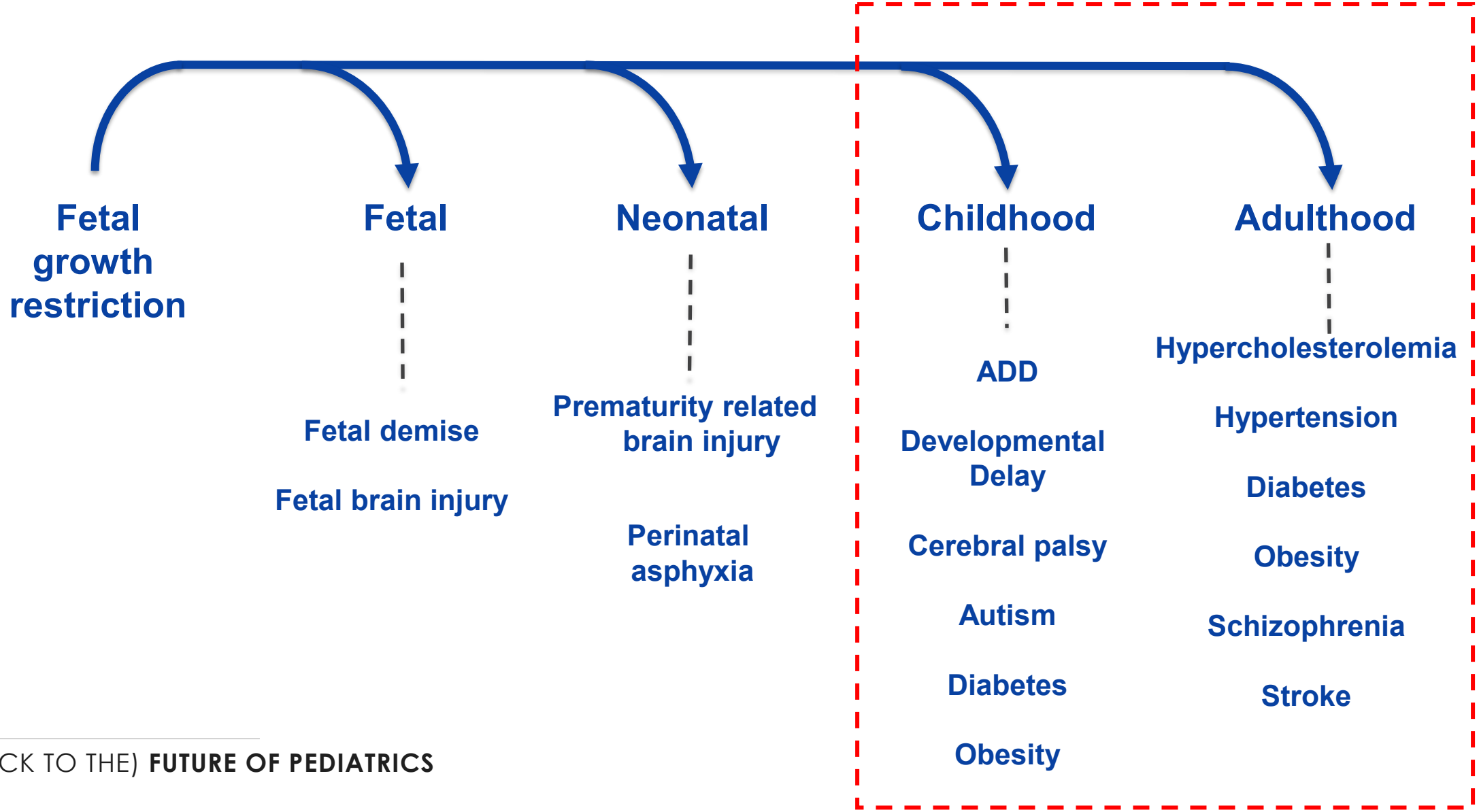
- Affects up to 450,000 pregnancies each year in the USA

Fetal Growth Restriction: Definition and diagnosis

- Defined as the inability of the fetus to achieve it's genetic growth potential due to restricting environmental factors.

- Diagnosed by population-based fetal and neonatal growth charts that are usually not adapted for geography, ethnicity, race, etc.

Consequences of fetal growth restriction and their timing



Neurodevelopmental Consequences of Fetal Growth Restriction

Motor consequences

- Impaired gross and fine motor skills
- Impaired visuo-motor skills

Cognitive and learning consequences

- Decreased IQ
- Impaired executive function
- Impaired memory and learning

Behavioral consequences

- Attentional deficits
- Hyperactivity
- Mood disturbances
- Anxiety
- Autism spectrum disorders

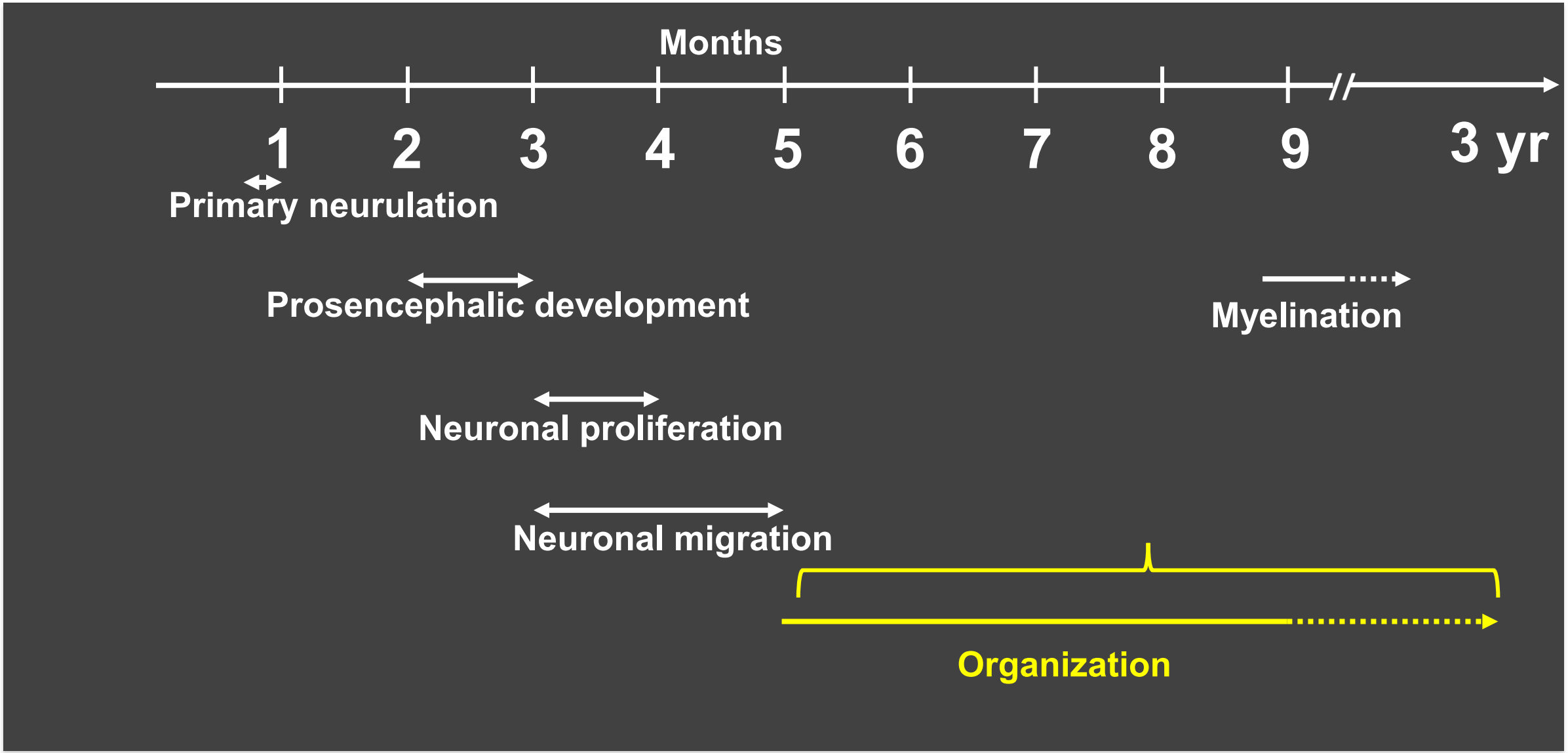
Miller S et al, 2016

- Fetal growth restriction, especially when associated with prematurity, accounts for 25% of special education needs in the USA. (Mackay DF, BJOG, 2013)

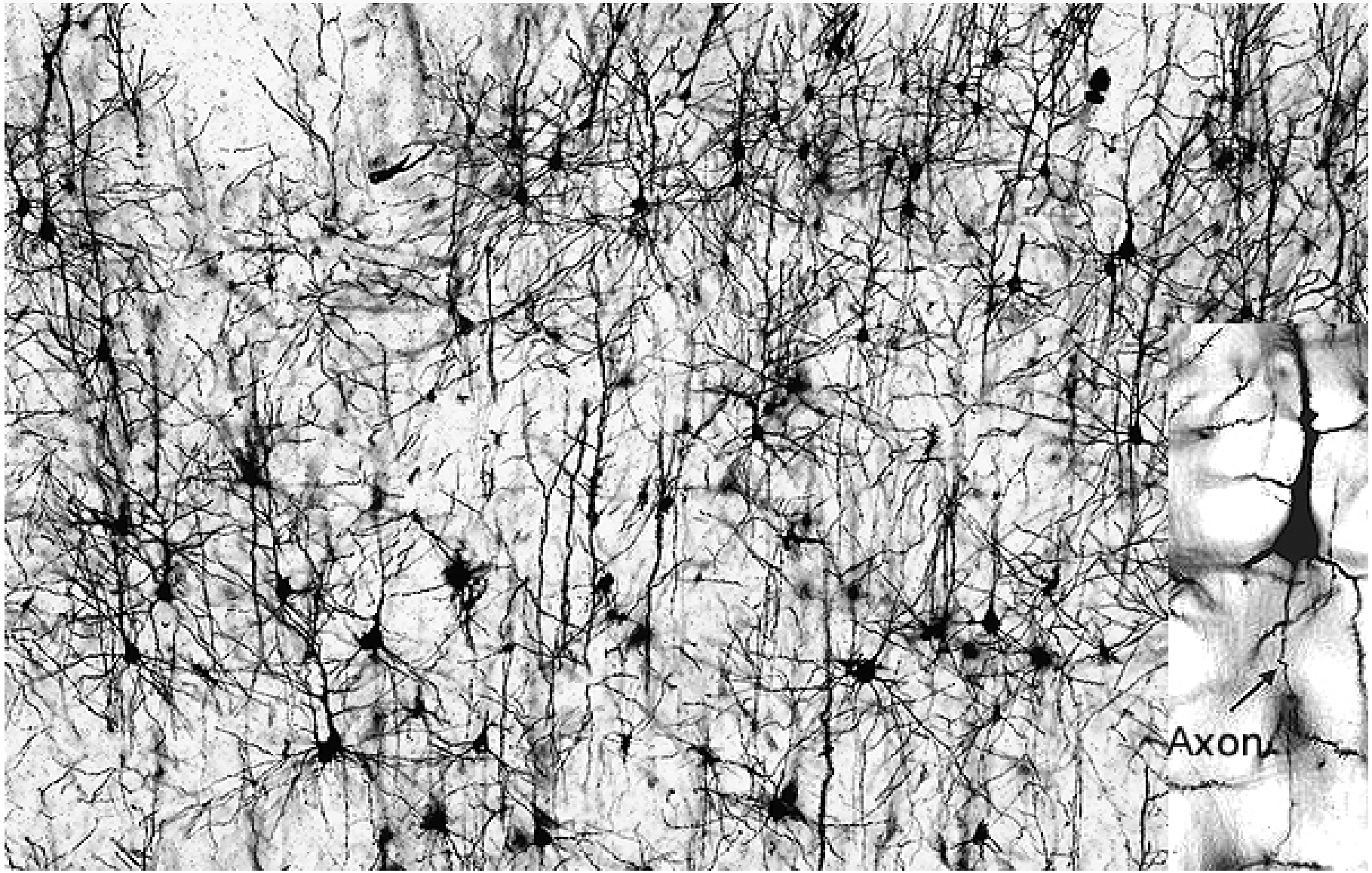
Developmental plasticity

A double-edged sword

Critical periods of brain development and plasticity



The brain at birth is markedly over-endowed



Developmental Plasticity: A Two-Edged Sword

• A *single genome* can result in a *range of phenotypes* when environmentally triggered epigenetic mechanisms modulate gene expression.

• Environmental triggers exert maximal developmental influence during *critical periods of developmental 'plasticity'* when organs develop heightened sensitivity to stimuli

• Critical periods of plasticity are *time-limited, i.e., they wax and wane* at different times in different organs and even within the same organ (e.g., brain).

• Once a critical period is over, sensitivity to environmental influences, positive or negative, decreases and the system is *'programmed'* with largely irreversible trajectories thereafter.

•A critical period for neurodevelopmental outcome extends from *mid-gestation through the first three years* after birth.

Back to Baby Boy X ….

What was lost in transition?

- Baby Boy X's fetal weight had decreased from the 80%^{ile} to the 15%^{ile} over the last 6 weeks of pregnancy (although it never dropped below the 10%^{ile})

- Antenatal Doppler studies had shown normal uterine artery resistance and decreased middle cerebral artery resistance ('brain sparing').

Back to Baby Boy X ….

What windows of opportunity were missed?

- UA Dopplers did not suggest ‘placental failure’ and ‘brain sparing’ is not brain sparing but rather an indication of fetal brain hypoxemia.
- The baby never met standard criteria for SGA or prematurity (‘slipped between the criteria’) – going beyond binary health evaluation
- The baby’s perinatal course (Apgars, newborn nursery course) and early infancy course (good {too good?} weight gain) and reassuring early development.

The current situation and challenges for the future

Critical steps going forward

- Greater involvement of pediatric specialties in the development of diagnostic and management protocols for high-risk fetal conditions
- Optimizing communication of data from prenatal to postnatal caretakers
- Targeted monitoring and individualized care plans for children delivered from an adverse fetal environment (protocols embedded into medical records)
- Diagnostic techniques that identify the earliest postnatal signs of future adversity
- Individualized care plans instituted as early as possible in the period of maximal developmental plasticity
- Early life interventions in infants with previous FGR improve neurodevelopmental outcomes.*(Rao MR, 2002, Acta Paediatr; Illa M, 2017; Fetal Diagn Ther)*

The current situation and challenges for the future

The Situation

- Many chronic childhood neurodevelopmental and other health conditions have their origins in the fetal period and are often not clinically evident in infancy
- There is a prolonged latency period between the fetal ‘insult’ and adverse outcome
- During this latency period ‘the clock is running down’ on a critical phase of developmental plasticity, after which the vulnerable phenotype is imprinted and programmed.

Q&A

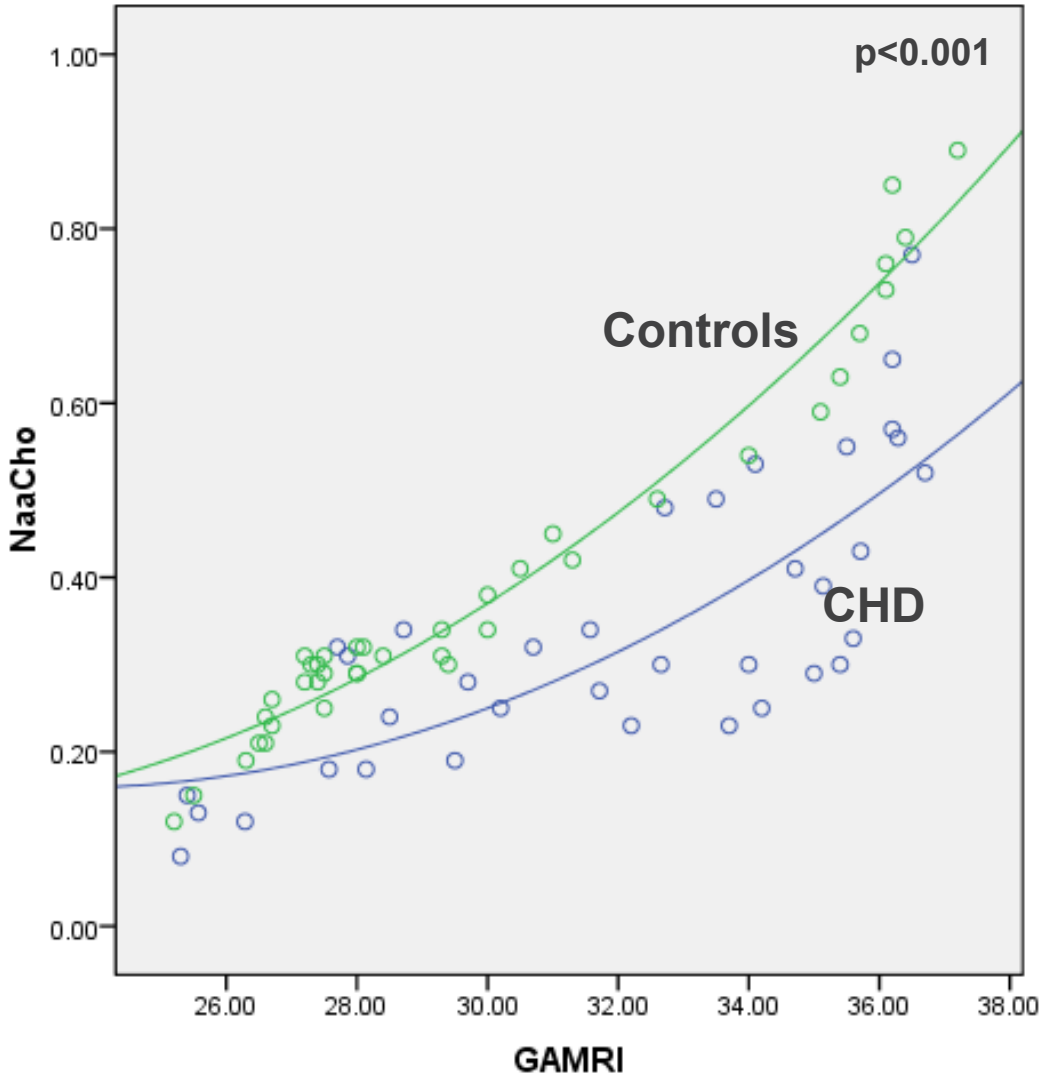
Back to Baby Boy X ….and into the future

- Understanding health status as more than binary (AGA vs SGA; Prematurity)
- Increased pediatric involvement in the development of prenatal management guidelines.
- Improved communication of prenatal data to postnatal caretakers.
- Identifying at-risk children with focused screening.
- Developing specific early intervention protocols targeting the specific postnatal risks of the prenatal environment.
- Early life interventions in infants with previous FGR improve neurodevelopmental outcomes.*(Rao MR, 2002, Acta Paediatr; Illa M, 2017; Fetal Diagn Ther)*
- Development of more sensitive tools for identifying high-risk intrauterine environments and maladaptive prenatal and postnatal development in fetuses and children.

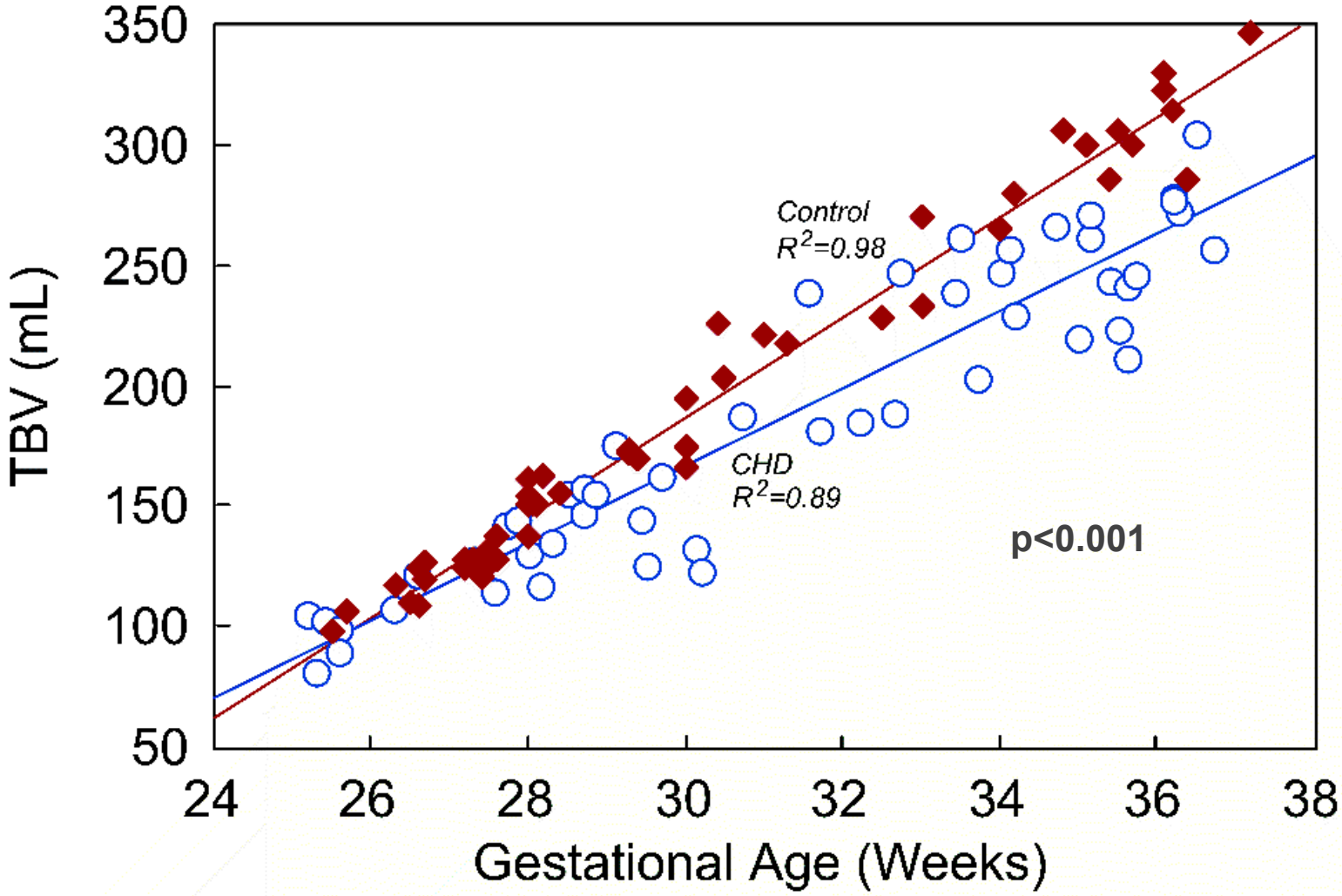
The spectrum of adverse intrauterine environments is broad

- Infections
- Toxins
- Maternal physical conditions (immunologic, endocrine, etc)
- Congenital malformations, e.g., CHD
- Maternal mental health
- Many others

Brain development in fetuses with congenital heart disease: Relationship between cerebral NAA/Cho and GA



Brain development in fetuses with congenital heart disease: Total Brain Volume vs. GA in CHD and Control Fetuses



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Brain development in fetuses with congenital heart disease: Impaired fetal brain growth and 18-month outcomes

Fetal Volumes	Bayley Cognition	Bayley Language	Bayley Motor	BITSEA Problem	BITSEA Competence	BITSEA Internalizing
Cortical Gray Matter	0.313	0.173	0.747	0.112	0.606	**0.029**
White Matter	0.143	0.211	0.917	**0.023**	0.979	0.706
Lateral Ventricles	**0.004**	0.060	**0.0004**	0.441	**0.011**	**0.068**
Cerebellum	**0.001**	**0.0003**	0.250	0.568	0.427	0.569
Brainstem	**0.008**	0.0151	0.459	0.704	**0.027**	0.842
SubCortical Gray Matter	0.042	**0.003**	0.717	0.361	0.660	0.671
Total Brain Volume	**0.002**	**0.0008**	0.396	0.023	0.677	0.420

Bold p-value: significant after adjusting for BI; length of CPB; postop complications and multiple comparison

Neuropsychiatric consequences of an adverse intrauterine environment

- Fetuses conceived during peak famine had increased neural tube defects (spina bifida and anencephaly)
- Autism, attentional, learning and behavioral outcomes
- First trimester maternal stress is associated with schizophrenia in male offspring *(Khashan et al, Arch Gen Psych 2008)*
- Fetuses exposed to famine in the second trimester had an increase in schizophrenia, schizotypal personality, and neurological disorders in later life *(Susser, Arch Gen Psychiat, 1996)*
- Prenatal undernutrition increases risk of schizophrenia two-fold in adult life *(Brown AS, Schizoph Bull 2008; Xu MQ, Schizophr Bull, 2009)*