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Why My Mother's Prenatal Diet and Pre-Pregnancy Weight Matter: Impact of Offspring Growth and Neurodevelopment

June 7th, 2023

Shibani Ghosh | Carmen Monthé-Drèze

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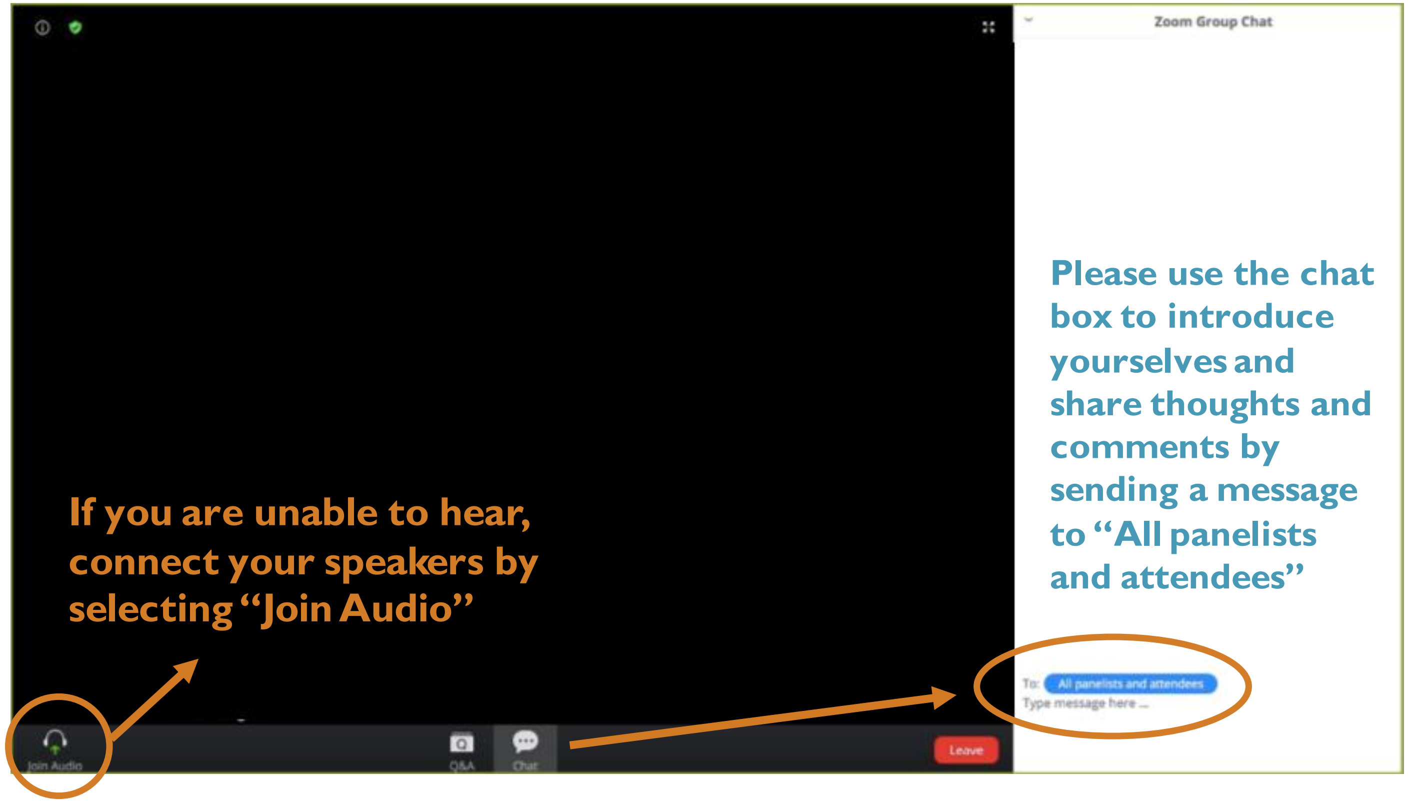

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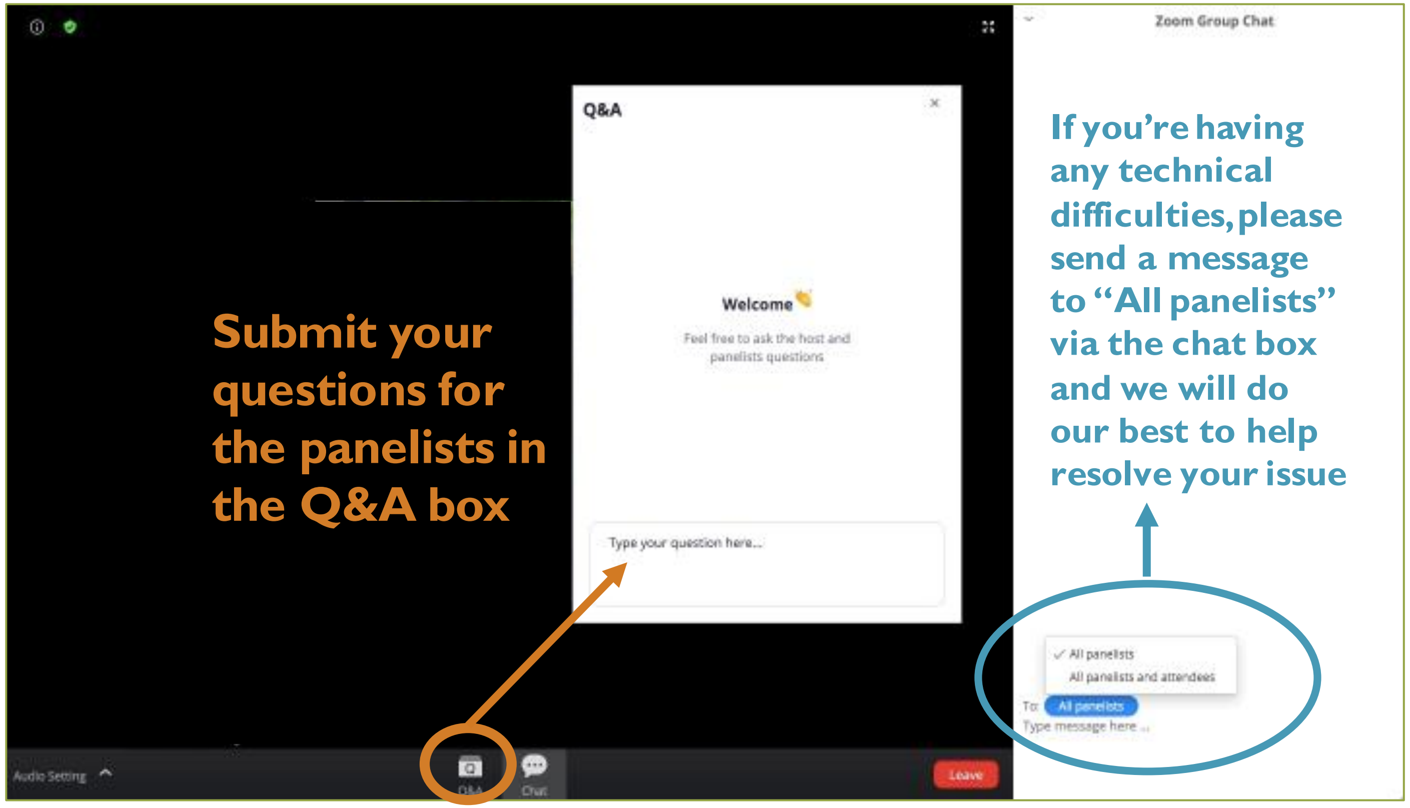

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Jordan Nutrition Innovation Lab Webinar

Why My Mother's Prenatal Diet and Pre-Pregnancy Weight Matter: Impact of Offspring Growth and Neurodevelopment

Wednesday, June 7th, 2023
3:00-4:00 pm Jordan Time | 8:00-9:00 am US Eastern

SHIBANI GHOSH
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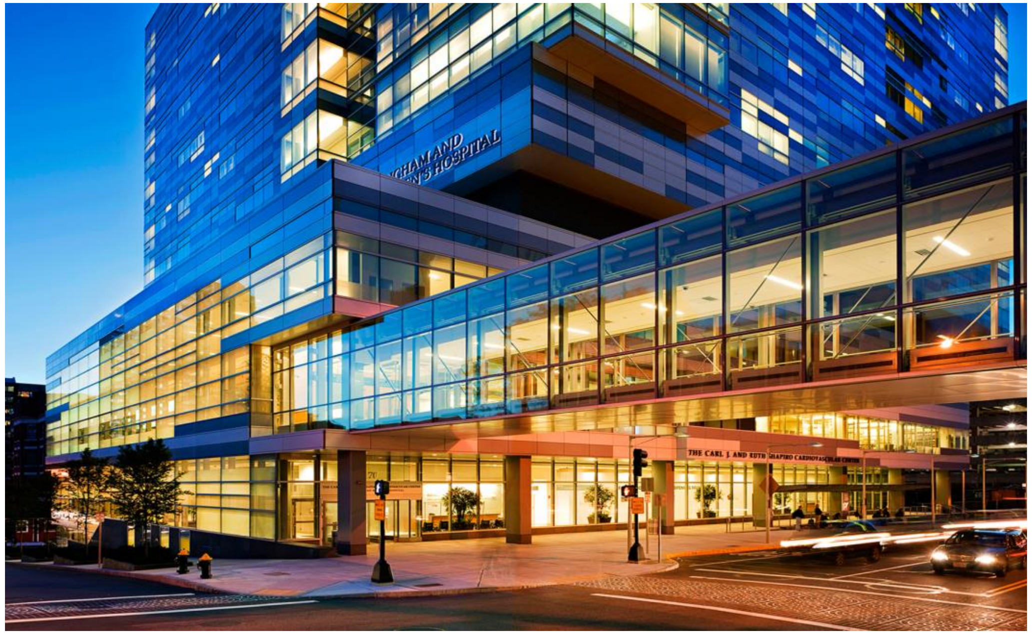
Why My Mother's Prenatal Diet and Pre-Pregnancy Weight Matter: Impact on Offspring Growth and Neurodevelopment



Carmen Monthé-Drèze, MD

Neonatologist and Instructor in Pediatrics
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JNIL Webinar
6/7/2023

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CONFLICT OF INTEREST DISCLOSURE

I have no financial relationships with a commercial entity producing healthcare-related products and/or services.

OVERVIEW

- Review trends obesity and dietary patterns
- Discuss the role of maternal obesity and prenatal diet in child health outcomes
- Describe how maternal obesity and related inutero environment shape developmental adaptations in pregnancy which impact offspring outcomes
- Review the potential role of nutritional interventions in pregnancy
- Discuss current challenges and future directions

EPIDEMIOLOGY OF MATERNAL OBESITY AND DIETARY QUALITY

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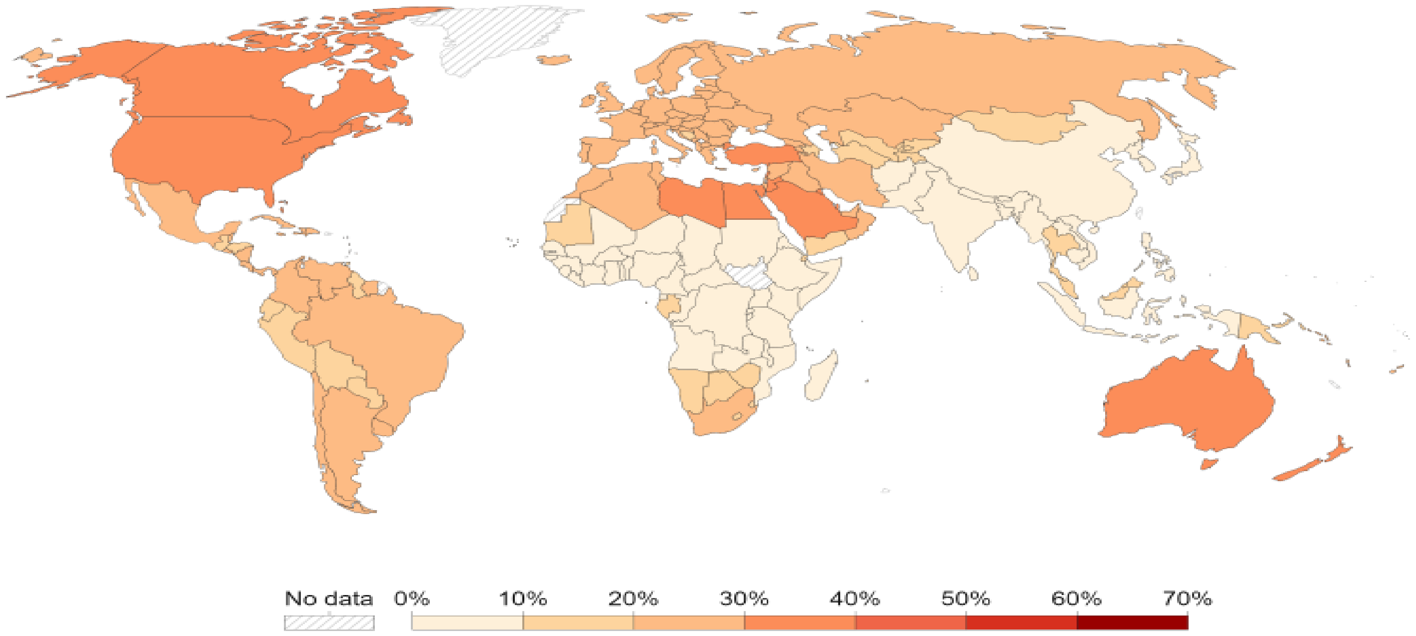
OBESITY IS GLOBAL PUBLIC HEALTH CHALLENGE

Share of adults that are obese, 2016

Our World in Data

Obesity is defined as having a body-mass index (BMI) equal to, or greater than, 30. BMI is a person's weight (in kilograms) divided by their height (in meters) squared.



Source: WHO, Global Health Observatory (2022)

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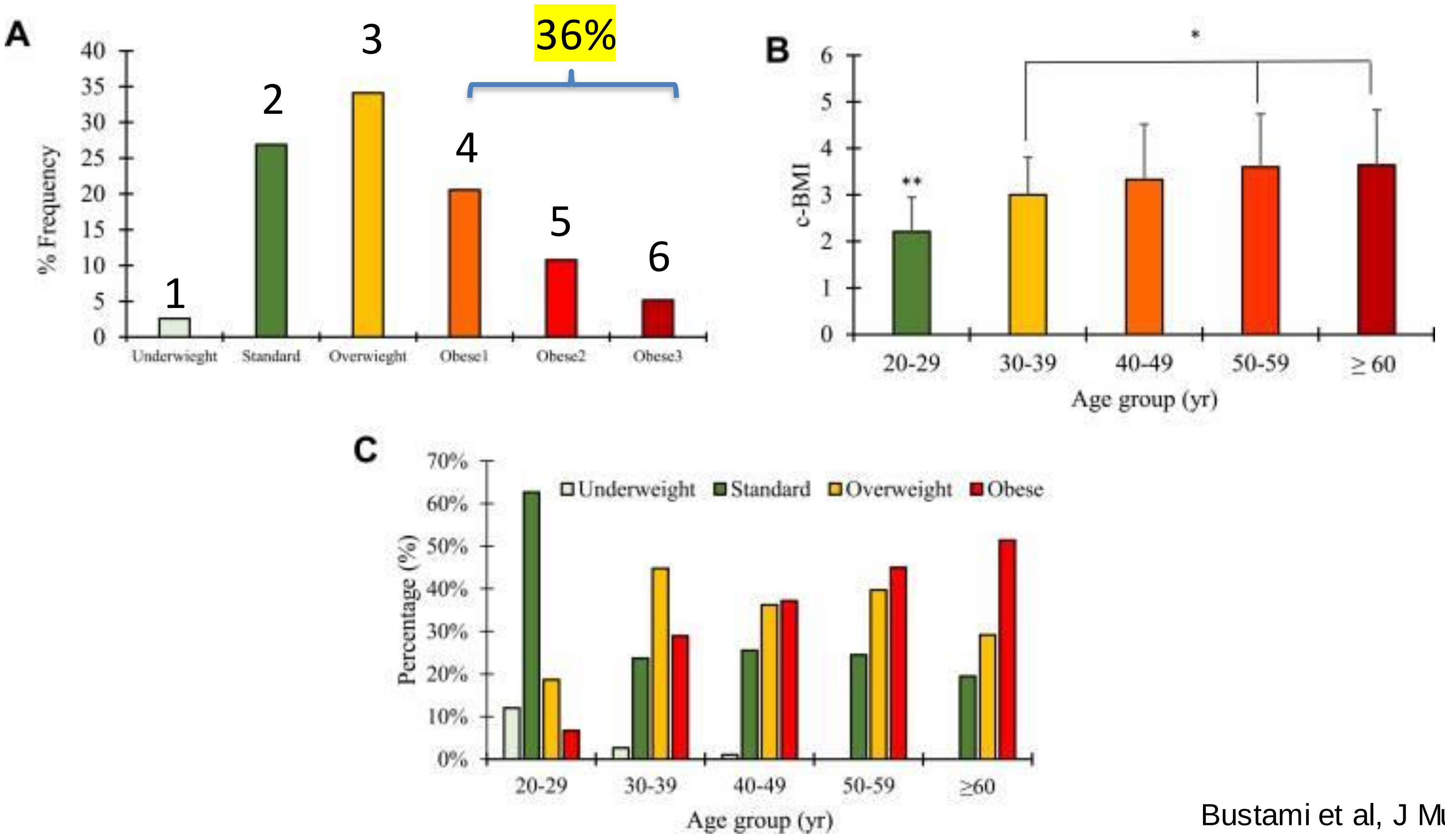
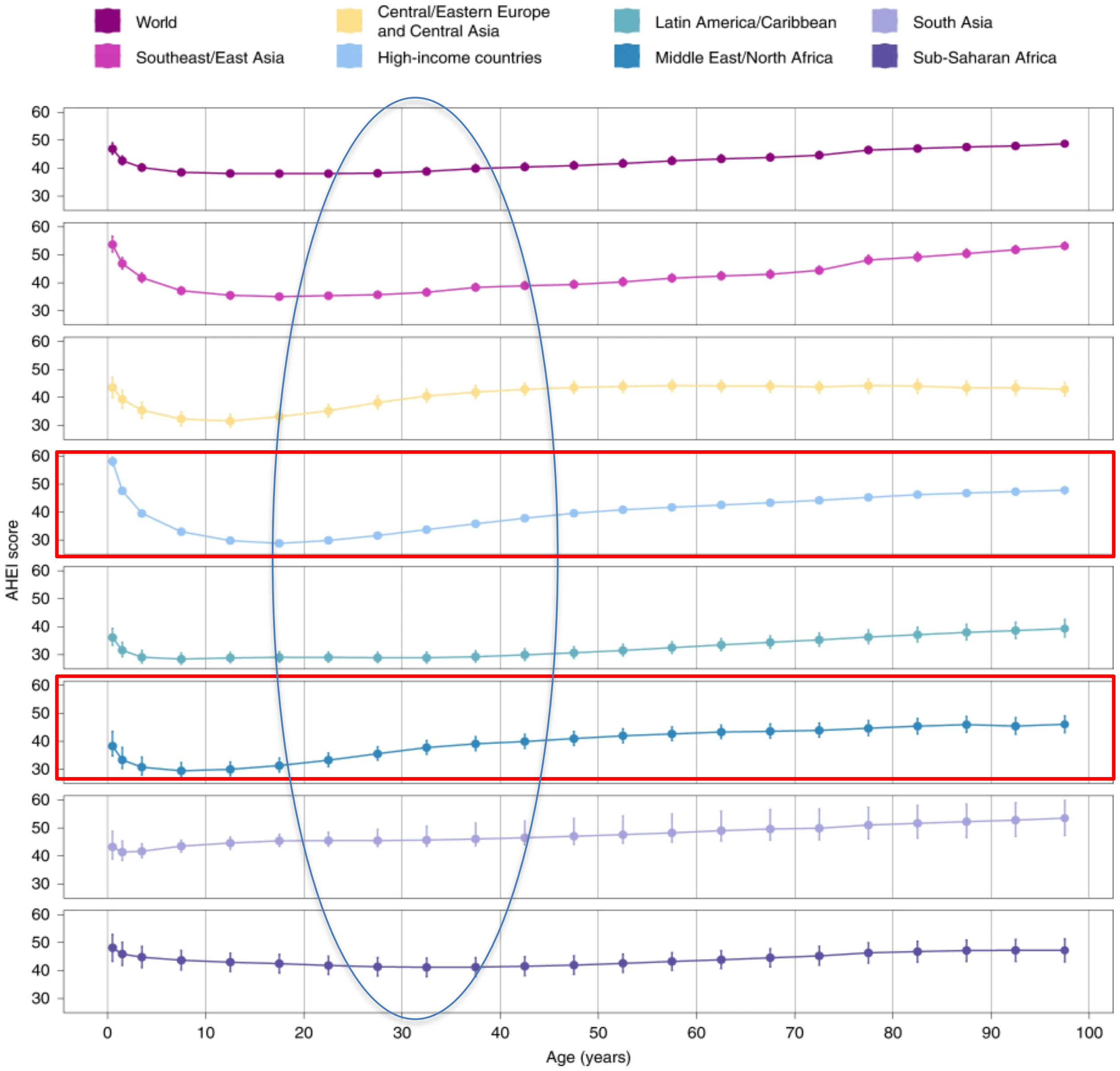
OBESITY AMONG WOMEN IN JORDAN



36% of women in Jordan have a c-BMI of 4 (obese class 1), 5 (obese class 2), or 6 (obese class 3)

Bustami et al, J Multidiscip Healthc, 2021

GLOBAL AND REGIONAL MEAN IN ALTERNATE HEALTHY EATING INDEX BY AGE



By age, most regions had J- or U-shaped relationships, with the highest scores observed among the youngest (≤5 years) and/or oldest age groups (≥75 years)

Miller et al, Nature Food 2022

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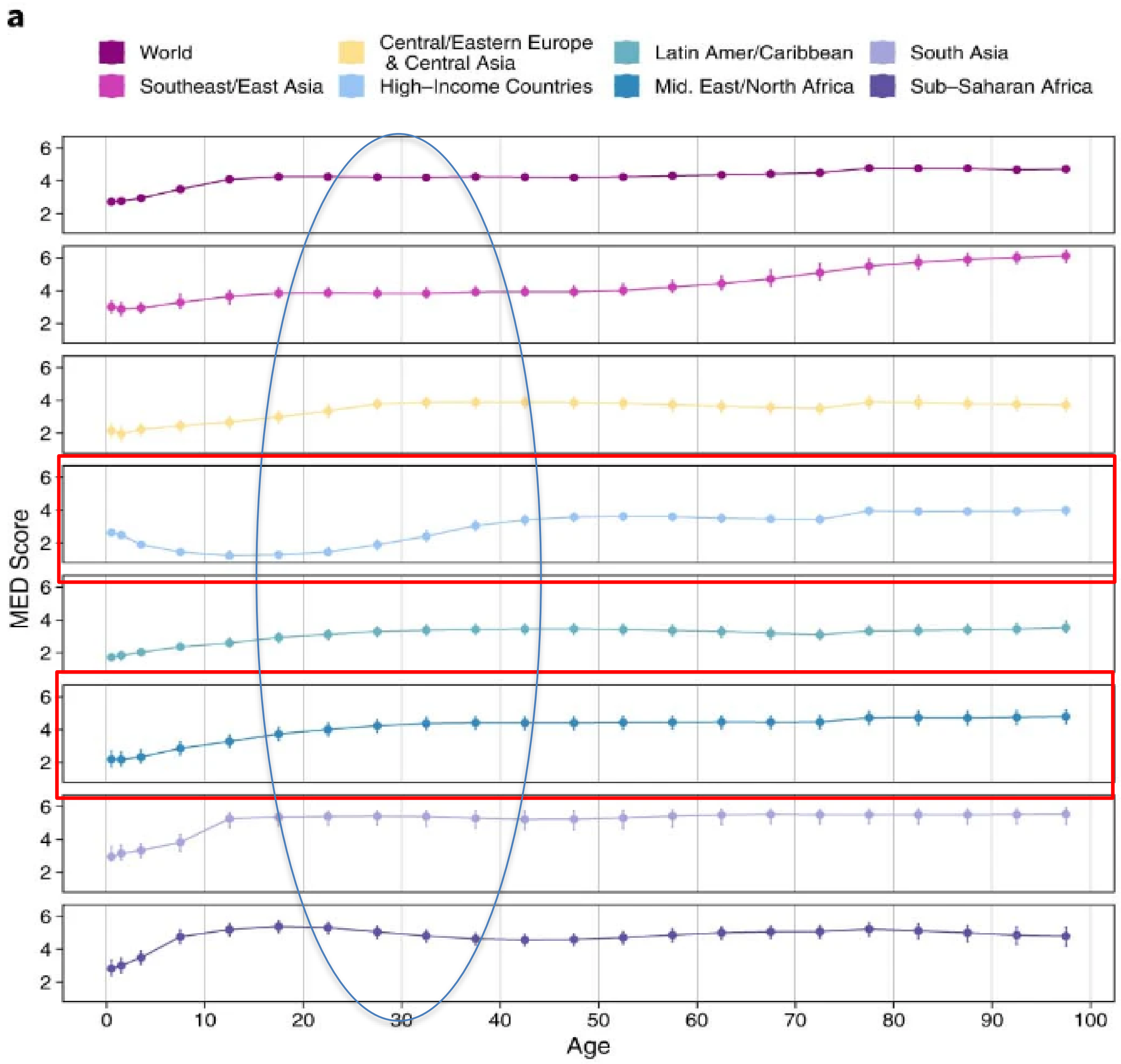
GLOBAL AND REGIONAL MEAN IN MEDITERRANEAN DIET SCORE BY AGE



Miller et al, Nature Food 2022

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PART 1: SUMMARY

- Obesity is a global public health challenge with an estimated 1 in 3 women of reproductive age having obesity in the US and in Jordan

- Dietary quality among women of reproductive age is generally poor

    - What are the implications on the next generation?

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MATERNAL OBESITY, PRENATAL DIET AND NEURODEVELOPMENTAL OUTCOMES

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MATERNAL OBESITY IS ASSOCIATED WITH ADVERSE NEURODEVELOPMENTAL OUTCOMES

Child outcome	Maternal factor	References	Study design
↑ ADHD symptomology/Risk	↑ Pre-pregnancy BMI	Rodriguez et al., 2008 Rodriguez, 2010 Chen et al., 2014 Buss et al., 2012	Cohort Cohort Cohort Cohort
	↑ GWG	Rodriguez et al., 2008	Cohort
	Gestational diabetes & SES	Nomura et al., 2012 Schmitt and Romanos, 2012	Cohort Survey; Cohort
	↓ Dietary intake of omega-3 fatty acids	Field, 2014	Case-control
↑ ASD risk/Severity of symptoms	↑ Pre-pregnancy BMI	Krakowiak et al., 2012 Reynolds et al., 2014 Moss and Chugani, 2014 Dodds et al., 2011 Bilder et al., 2013	Case-control Cohort Cohort Cohort Case-control; Cohort
	↑ GWG	Dodds et al., 2011 Bilder et al., 2013	Cohort Case-control; Cohort
	Diabetes, hypertension, or pre-eclampsia	Krakowiak et al., 2012 Dodds et al., 2011 Lyall et al., 2012 Wallace et al., 2008	Case-control Cohort Cohort Cohort
↑ Anxiety/depression risk	↑ Pre-pregnancy BMI	Rodriguez, 2010 Van Lieshout et al., 2013 Colman et al., 2012	Cohort Cohort Cohort
↑ Schizophrenia risk	↑ Pre-pregnancy BMI	Jones et al., 1998 Schaefer et al., 2000	Cohort Cohort
	↑ GWG	Kawai et al., 2004	Case-control
	Pre-eclampsia/hypertension and diuretic treatment	Dalman et al., 1999 Eide et al., 2013 Sorensen et al., 2003	Cohort Cohort Cohort
↑ Food addiction	↑ BMI 5 months post-delivery	Rising and Lifshitz, 2005	Cohort
	↑ Intake of sweets during pregnancy	Brekke et al., 2007	Cohort
↑ Anorexia nervosa/ Bulimia nervosa risk	↑ BMI 6 months post-delivery Disordered eating	Stice et al., 1999	Cohort
	↑ Intake of sweets during pregnancy	Lamerz et al., 2005	Survey
↑ Risk of cognitive impairments	↑ Pre-pregnancy BMI	Hinkle et al., 2012 Tanda et al., 2013 Neggers et al., 2003 Heikura et al., 2008 Brion et al., 2011 Craig et al., 2013	Cohort Survey; Cohort Survey Cohort Cohort Case-control

Rivera et al. Frontiers in Neuroscience. Review. 2015

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Outcome	BMI category (kg/m²)	Model 0[a]	Model 1[b] β (95% CI)	Model 2[c]
Intelligence measures				
Early childhood				
PPVT-III	18.5–<25.0	0.0 (ref)	0.0 (ref)	0.0 (ref)
	25.0–<30.0	−2.5 (−4.5, −0.5)	−0.4 (−2.2, 1.4)	−0.2 (−2.0, 1.6)
	≥30.0	−2.8 (−5.3, −0.3)	1.9 (−0.4, 4.1)	1.5 (−0.7, 3.8)
Mid-childhood				
KBIT-II verbal	18.5–<25.0	0.0 (ref)	0.0 (ref)	0.0 (ref)
	25.0–<30.0	−3.3 (−5.6, −1.1)	−0.6 (−2.6, 1.3)	−0.4 (−2.3, 1.5)
	≥30.0	−7.2 (−9.8, −4.6)	−1.5 (−3.9, 0.8)	−1.4 (−3.7, 0.9)
KBIT-II non-verbal	18.5–<25.0	0.0 (ref)	0.0 (ref)	0.0 (ref)
	25.0–<30.0	−1.5 (−4.0, 1.1)	0.3 (−2.2, 2.8)	0.5 (−2.0, 2.9)
	≥30.0	−4.1 (−7.1, −1.2)	−0.3 (−3.3, 2.7)	−0.2 (−3.2, 2.7)
Visual-motor measures				
Early childhood				
Total WRAVMA	18.5–<25.0	0.0 (ref)	0.0 (ref)	0.0 (ref)
	25.0–<30.0	−1.4 (−3.0, 0.2)	−0.5 (−1.9, 1.0)	−0.4 (−1.9, 1.1)
	≥30.0	−4.2 (−6.1, −2.3)	−2.0 (−3.9, −0.1)	−2.1 (−3.9, −0.2)
WRAVMA-Fine motor subset (pegboard)	18.5–<25.0	0.0 (ref)	0.0 (ref)	0.0 (ref)
	25.0–<30.0	0.0 (−1.5, 1.4)	0.4 (−1.1, 1.9)	0.4 (−1.1, 1.9)
	≥30.0	−2.8 (−4.6, −1.0)	−1.8 (−3.7, 0.0)	−1.8 (−3.7, 0.0)
WRAVMA-Visual spatial subset (matching)	18.5–<25.0	0.0 (ref)	0.0 (ref)	0.0 (ref)
	25.0–<30.0	−1.7 (−3.5, 0.2)	−0.6 (−2.4, 1.3)	−0.5 (−2.3, 1.3)
	≥30.0	−4.5 (−6.8, −2.2)	−1.8 (−4.1, 0.5)	−1.9 (−4.3, 0.4)
WRAVMA-Visual motor subset (drawing)	18.5–<25.0	0.0 (ref)	0.0 (ref)	0.0 (ref)
	25.0–<30.0	−1.4 (−2.9, 0.2)	−0.7 (−2.3, 0.8)	−0.7 (−2.2, 0.8)
	≥30.0	−2.1 (−4.0, −0.2)	−0.8 (−2.7, 1.2)	−0.8 (−2.7, 1.1)
Mid-childhood				
WRAVMA-Visual motor subset (drawing)	18.5–<25.0	0.0 (ref)	0.0 (ref)	0.0 (ref)
	25.0–<30.0	−1.8 (−4.3, 0.8)	−0.9 (−3.4, 1.6)	−0.8 (−3.4, 1.7)
	≥30.0	−3.1 (−6.0, −0.2)	−1.7 (−4.7, 1.3)	−1.7 (−4.7, 1.3)
Memory and learning measures				
WRAML-visual memory	18.5–<25.0	0.0 (ref)	0.0 (ref)	0.0 (ref)
	25.0–<30.0	0.0 (−0.7, 0.6)	0.2 (−0.5, 0.8)	0.2 (−0.5, 0.9)
	≥30.0	−0.4 (−1.1, 0.4)	0.2 (−0.6, 1.0)	0.2 (−0.6, 1.0)

PPVT-III Peabody Picture Vocabulary Test-3rd edition, KBIT-II Kaufman Brief Intelligence Test-2nd edition, *WRAVMA* Wide Range Assessment of Visual Motor Abilities, *WRAVML* Wide Range Assessment of Memory and Learning
[a]Model 0. Unadjusted
[b]Model 1. Adjusted for maternal age at enrollment, race/ethnicity, education, pre-pregnancy smoking status, and parity; household income and partner education; and child sex and age at outcome
[c]Model 2. Model 1 + maternal IQ

MATERNAL OBESITY IS LINKED TO LOWER VISUAL MOTOR ABILITIES (VMA) IN THE OFFSPRING IN EARLY CHILDHOOD

- VMA CORRELATE WITH EXECUTIVE FUNCTION SKILLS

Monthé-Drèze et al, Peds Research 2019

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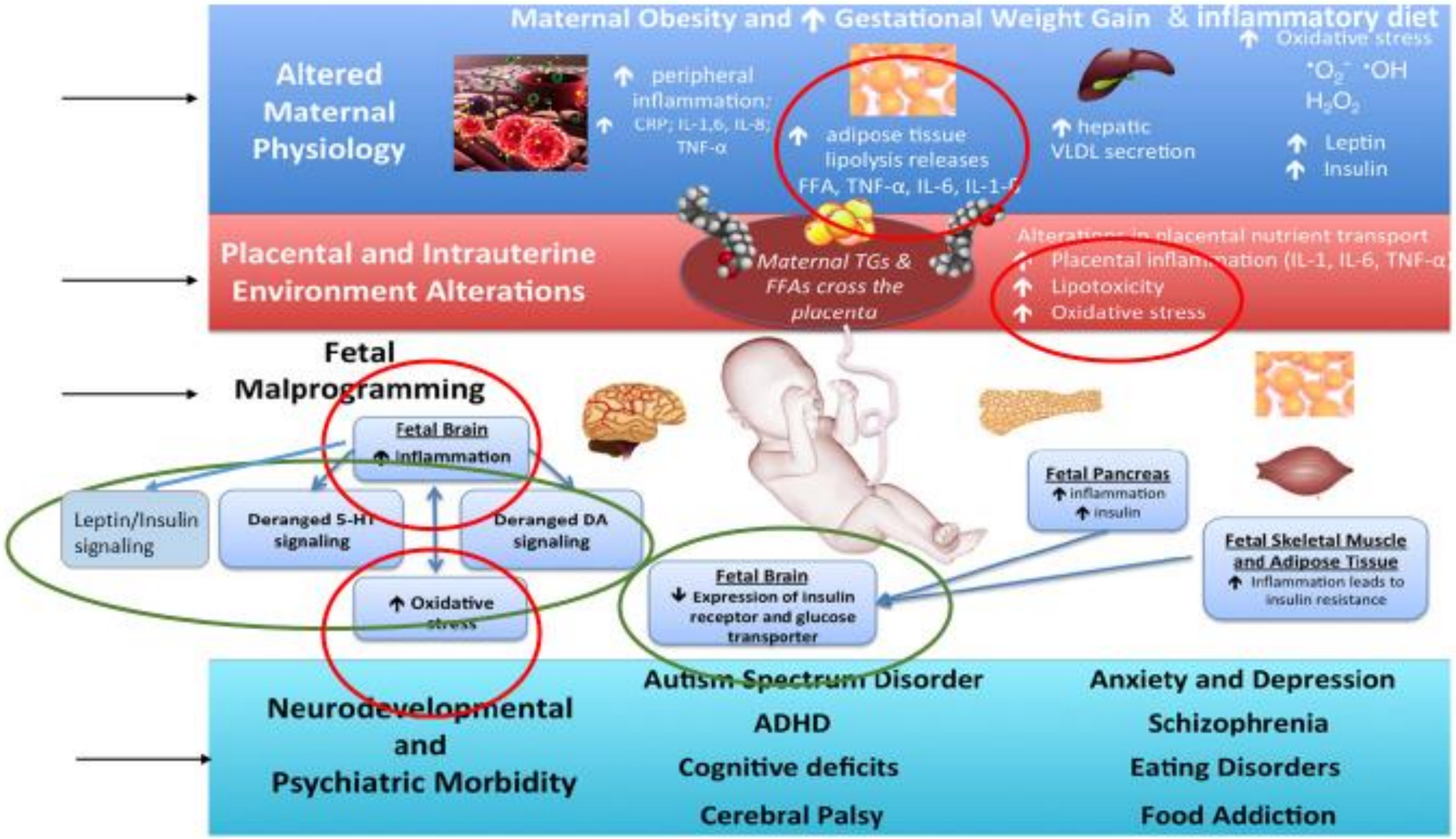
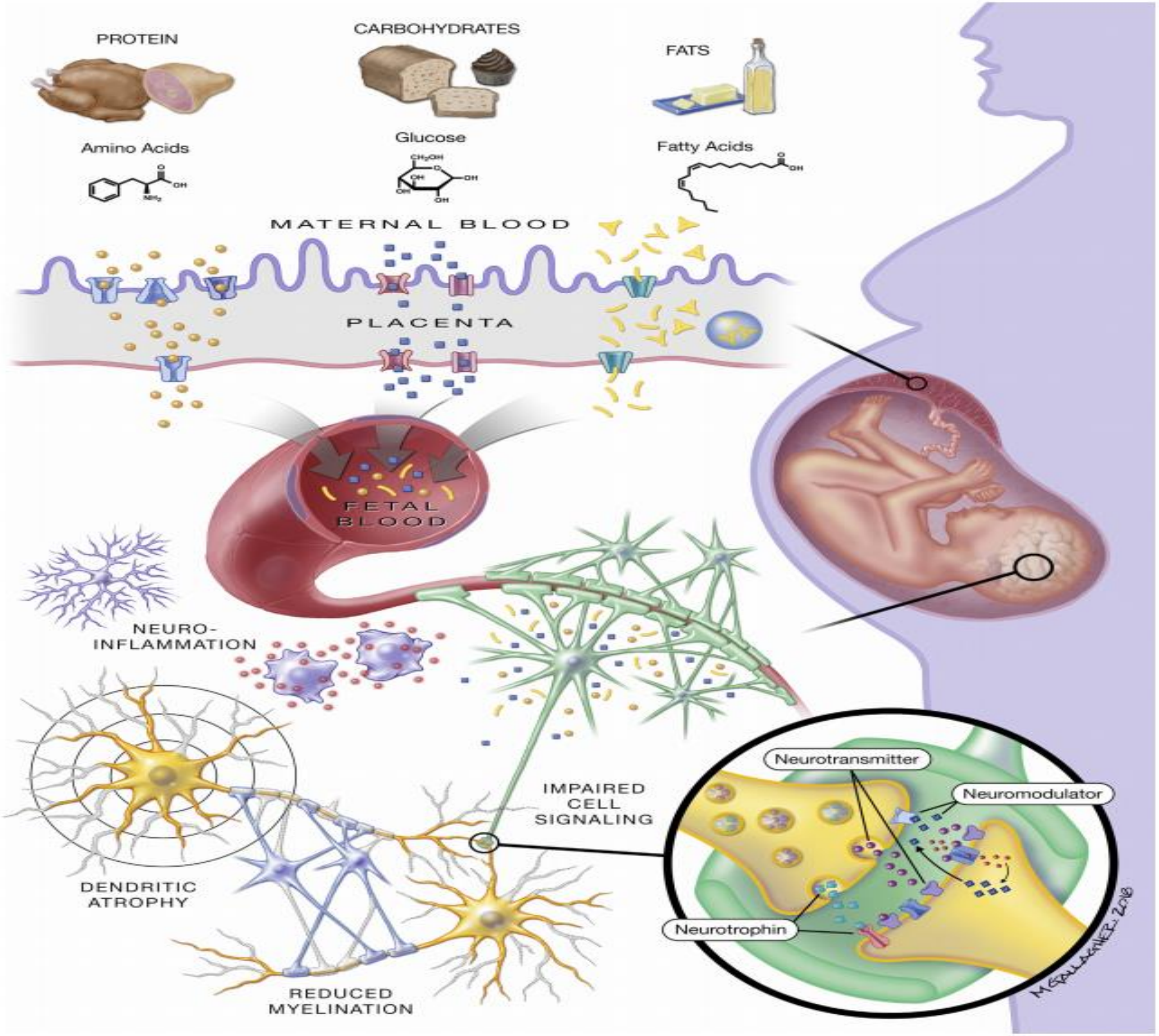
Programming of neurodevelopmental disorders in maternal obesity



Edlow, Prenatal Diagnosis, 2017



RODENT MODELS

Neuro-inflammatory signaling and oxidative stress lead to structural brain changes in fetal brains (e.g, hippocampus, amygdala and hypothalamus) of obese dams:

- Diminished proliferation
  - Decreased neurotrophic factors
- Synaptic remodeling
- Reduced migration and maturation
- Impaired cell signaling

DeCapo et al, J biospych 2019

WHAT EVIDENCE EXIST IN HUMANS THAT OBESITY RELATED INFLAMMATION AND DIETARY QUALITY ARE LINKED TO IMPAIRED NEURODEVELOPMENT IN THE OFFSPRING?

MATERNAL OBESITY IS ASSOCIATED WITH SYSTEMIC AND DIETARY PROINFLAMMATORY PROFILES

Table 3. Associations of maternal pre-pregnancy BMI category with markers of inflammation during pregnancy

Outcome	BMI category (kg/m^2)	Unadjusted β (95% CI)	Adjusted[a] β (95% CI)
2nd trimester CRP, mg/L	18.5–<25.0	0.0 (ref)	0.0 (ref)
	25.0–<30.0	0.5 (0.3, 0.7)	0.5 (0.3, 0.7)
	≥30.0	1.0 (0.7, 1.3)	0.9 (0.6, 1.2)
2nd trimester plasma n-6:n-3	18.5–<25.0	0.0 (ref)	0.0 (ref)
	25.0–<30.0	0.6 (0.0, 1.2)	0.5 (−0.1, 1.1)
	≥30.0	1.7 (0.7, 2.6)	1.4 (0.5, 2.4)
Mean 1st + 2nd trimester DII, units	18.5–<25.0	0.0 (ref)	0.0 (ref)
	25.0–<30.0	0.3 (0.1, 0.4)	0.1 (0.0, 0.3)
	≥30.0	0.5 (0.3, 0.8)	0.2 (0.0, 0.4)

CRP C-reactive protein, *n-6:n-3 omega-6* omega-3, *DII* Dietary Inflammatory Index.
[a]Adjusted for maternal age at enrollment, race/ethnicity, education, pre-pregnancy smoking status, parity, and household income

Maternal obesity is associated with

- **Higher** CRP
- **Higher** systemic omega-6:omega-3 ratio, a marker of inflammation
- **Higher** Dietary inflammation index (DII), a marker of dietary inflammation.
  - Index developed to characterize and quantify the cumulative inflammatory potential of an individual's diet.
  - The DII score positively correlates with interval changes in markers of systemic inflammation in pregnant adults

Monthe-Dreze et al, Peds Research 2019
Monthe-Dreze et al, Nutrients 2018
Sen et al, J Nutrition 2016

Monthe-Dreze et al, Peds Research 2019

THE ROLE OF MATERNAL OBESITY-RELATED INFLAMMATION (VIVA COHORT):

Table 4. Associations of inflammatory markers with early ($n = 1246$) and mid-childhood ($n = 1070$) cognitive outcomes

Exposures	CRP β (95% CI)		n-6:n-3 β (95% CI)		DII β (95% CI)	
Outcomes	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Intelligence measures						
Early childhood						
PPVT-III	−0.8 (−1.6, 0.0)	−0.1 (−0.9, 0.6)	−0.2 (−0.6, 0.1)	0.1 (−0.2, 0.3)	−2.4 (−3.0, −1.7)	−0.6 (−1.2, 0.1)
Mid-childhood						
KBIT-II verbal	−1.3 (−2.3, −0.3)	−0.1 (−1.0, 0.8)	−0.6 (−1.0, −0.3)	−0.3 (−0.6, 0.0)	−3.1 (−3.8, −2.4)	−0.6 (−1.3, 0.0)
KBIT-II non-verbal	−0.5 (−1.5, 0.6)	0.3 (−0.7, 1.3)	0.1 (−0.3, 0.4)	0.2 (−0.2, 0.6)	−1.4 (−2.2, −0.7)	0.0 (−0.9, 0.8)
Visual-motor measures						
Early childhood						
Total WRAVMA	−0.8 (−1.4, −0.1)	−0.3 (−1.0, 0.3)	−0.2 (−0.4, 0.0)	−0.1 (−0.4, 0.1)	−0.8 (−1.3, −0.3)	0.1 (−0.5, 0.6)
WRAVMA-Fine motor (pegboard)	−0.8 (−1.4, −0.2)	−0.6 (−1.3, 0.0)	−0.1 (−0.3, 0.1)	−0.1 (−0.3, 0.1)	−0.2 (−0.7, 0.3)	0.2 (−0.3, 0.7)
WRAVMA-Visual spatial (matching)	−0.5 (−1.3, 0.3)	0.0 (−0.9, 0.8)	−0.1 (−0.3, 0.2)	0.0 (−0.2, 0.3)	−1.2 (−1.8, −0.6)	−0.1 (−0.7, 0.6)
WRAVMA-Visual motor (drawing)	−0.3 (−1.0, 0.3)	−0.1 (−0.7, 0.6)	−0.2 (−0.5, 0.0)	−0.2 (−0.5, 0.0)	−0.4 (−0.9, 0.1)	0.1 (−0.5, 0.6)
Mid-childhood						
WRAVMA (drawing)	−0.2 (−1.3, 0.8)	0.1 (−1.0, 1.2)	−0.2 (−0.5, 0.2)	−0.1 (−0.5, 0.3)	−0.5 (−1.2, 0.3)	0.2 (−0.7, 1.1)
Memory and Learning measures						
WRAML visual memory	0.0 (−0.3, 0.3)	0.1 (−0.2, 0.4)	0.0 (−0.1, 0.1)	0.0 (−0.1, 0.1)	−0.1 (−0.3, 0.1)	0.1 (−0.1, 0.3)

PPVT-III Peabody Picture Vocabulary Test-3rd edition, *KBIT-II* Kaufman Brief Intelligence Test-2nd edition, *WRAVMA* Wide Range Assessment of Visual Motor Abilities, *WRAVML* Wide Range Assessment of Memory and Learning, *CRP* C-reactive protein, *n-6:n-3 omega-6* omega-3, *DII* Dietary Inflammatory Index
[a]Adjusted for maternal age at enrollment, race/ethnicity, education, IQ, pre-pregnancy smoking status, parity, household income and partner education, child sex and age at outcome

- Altered maternal fatty acid balance and dietary inflammation are associated with lower verbal reasoning skills in mid-childhood (MC)
- Higher maternal inflammation and altered maternal fatty acid balance are associated with impaired visual-motor skills in MC
- Mediation analysis showed that CRP explained up to **28%** of the relationship between maternal obesity and offspring visual motor outcomes

Monthé-Drèze et al, Peds Research 2019

Monthe-Dreze et al, Peds Research 2019

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THE ROLE OF MATERNAL OBESITY-RELATED INFLAMMATION (BMI-BASED PRENATAL VITAMINS RCT STUDY, NCT02802566) AND IMPLICATION FOR TIMING OF INTERVENTION

- **First trimester (mean GA 10 wks) CRP (aOR 1.10; 95% CI 1.00-1.12, p = 0.045) was modestly associated with odds of failing in the problem-solving domain on the ASQ**
- CRP in the 2nd and 3rd trimester were not associated with odds of failing any domain in the ASQ. Associations with oxidative stress markers were null.
- Results suggest that inflammation **in early pregnancy** may play a role in the programming of neurodevelopmental disorders in these dyads.
- Any Intervention trials in these dyads should therefore start **before** conception.

Monthé-Drèze et al, unpublished

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Monthe-Dreze et al, Peds Research 2019

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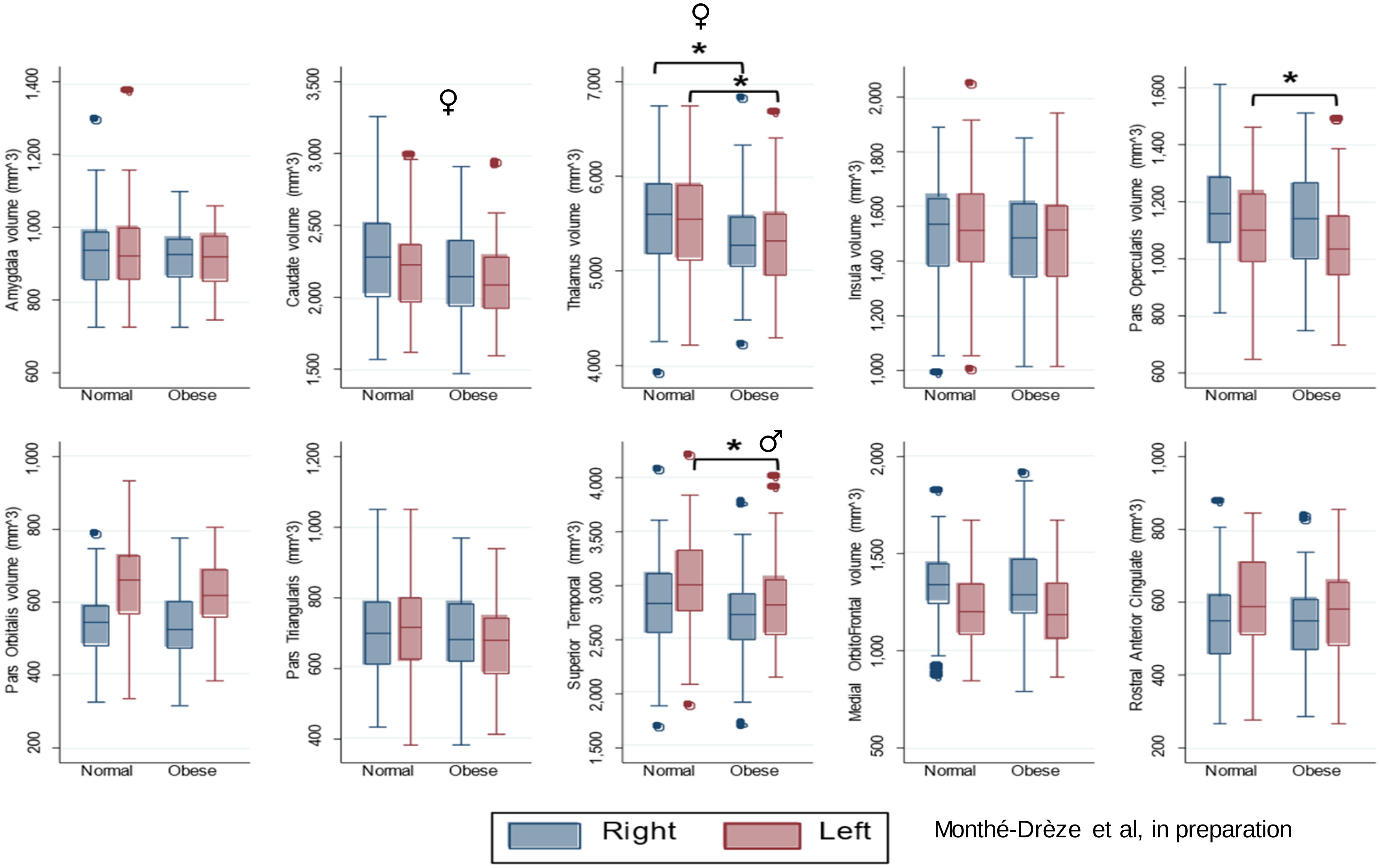
INFANTS EXPOSED TO MATERNAL OBESITY IN UTERO HAVE LOWER REGIONAL BRAIN VOLUMES



Monthé-Drèze et al, in preparation

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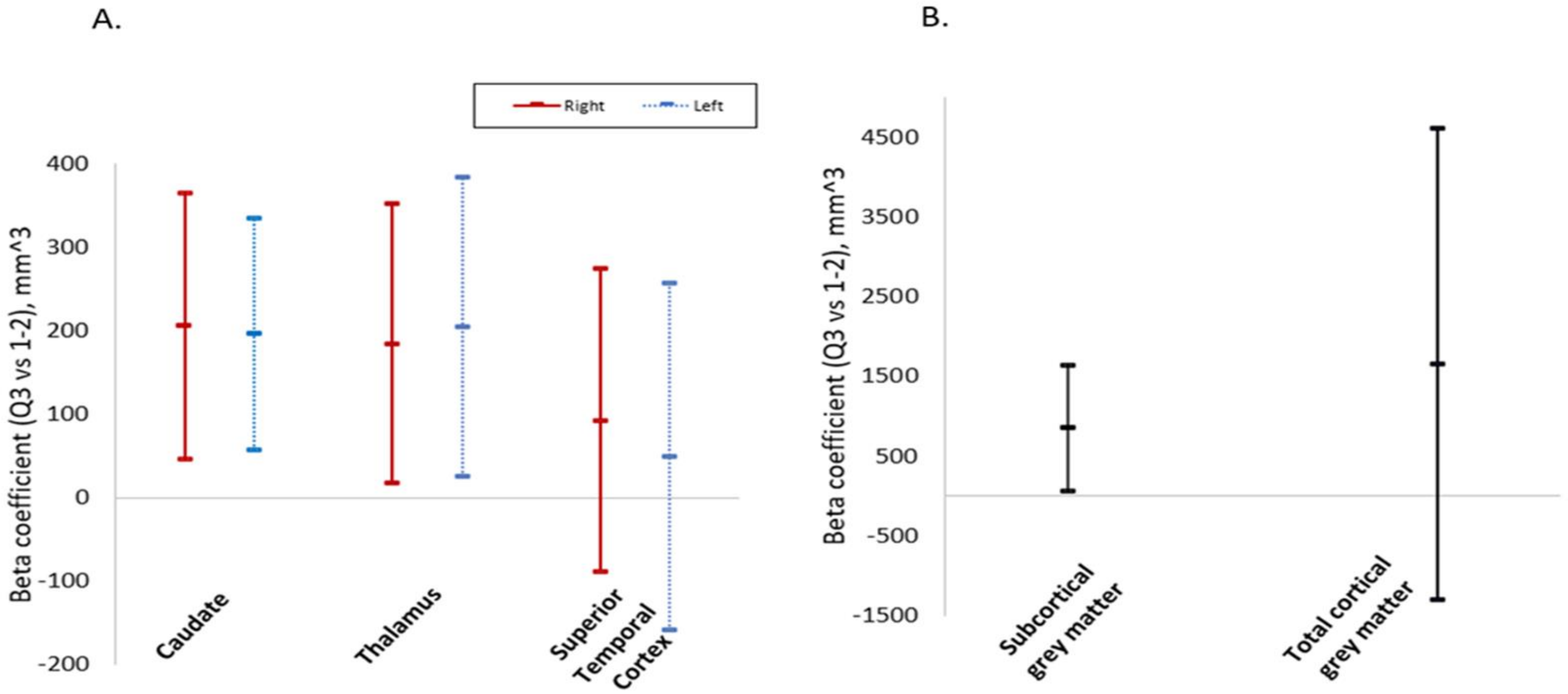
AMONG NEONATES OF MOTHERS WITH PRE-PREGNANCY OBESITY, IN UTERO EXPOSURE TO BETTER DIETARY QUALITY WAS ASSOCIATED WITH GREATER NEONATAL GREY MATTER VOLUMES IN SPECIFIC REGIONS THAT PLAY CRUCIAL ROLE IN ATTENTION AND BEHAVIOR



Monthé-Drèze et al, in preparation

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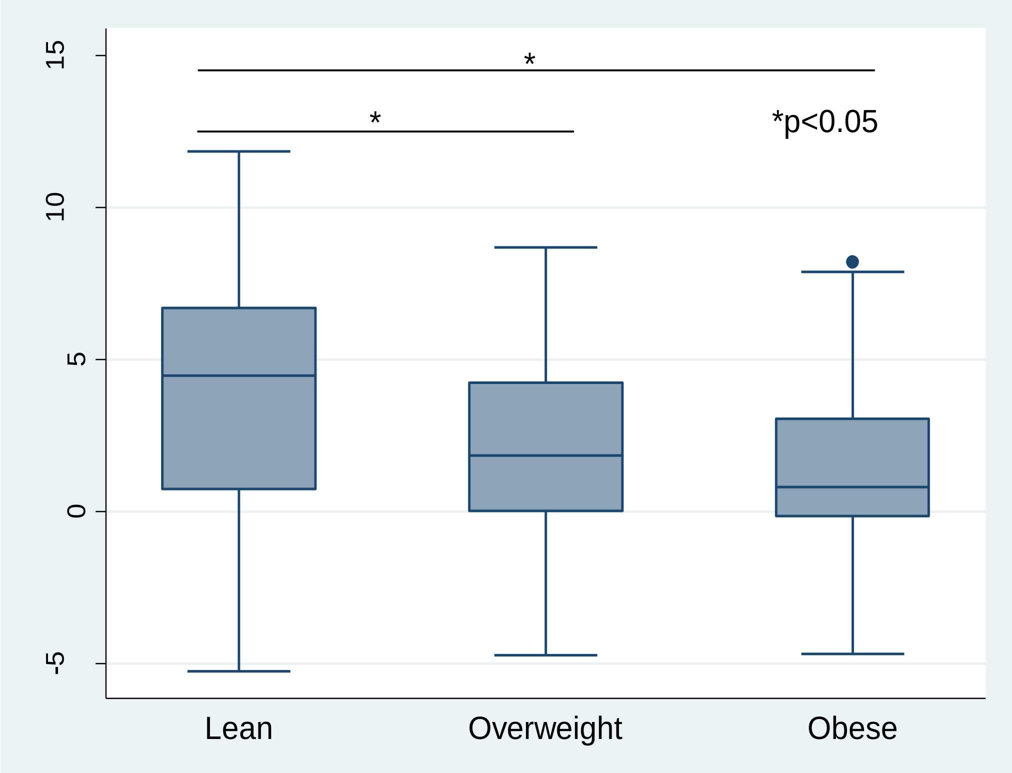
THE ROLE OF NUTRITIONAL INTERVENTIONS FOR OPTIMAL BRAIN AND NEURODEVELOPMENT: CURRENT LIMITATIONS

- Observational studies suggest a link between prenatal n6:n3 ratio, fish intake and neurodevelopmental outcomes in children
- However, **meta-analysis** of all published RCTs looking at the effect of n-3 PUFA supplementation in pregnancy on child development outcomes revealed mixed results, largely due to methodological limitations
- Interventions were started later in pregnancy, missing what may be the most critical periods of brain development and highest susceptibility to in utero metabolic disturbances
- Populations with a lower socioeconomic status and at highest risk were underrepresented and studies lacked racial and ethnic diversity

Makrides et al., JAMA 2010
Gould et al. AJCN 2013
Ramakrishnan et al, AJCN 2016
Nevins et al, J Nutrition 2021

Monthe-Dreze et al, Peds Research 2019

THE ROLE OF NUTRITIONAL INTERVENTIONS (OMEGA-3 FISH OIL) FOR OPTIMAL BRAIN AND NEURODEVELOPMENT: HAVE WE FIGURED THE APPROPRIATE DOSING?



- Significant increase in total DHA+EPA (Δ% median (IQR): 2.3% (0.0, 5.3; $p < 0.05$) following 2g /day of n-3 supplementation in pregnancy
- However, observed effects differed by BMI category (Lean: β = 4.03%; CI: 3.24, 4.82; Overweight: β = 2.14%; CI: 1.17, 3.10; Obese: β = 2.12%; CI: 1.32, 2.92; p for interaction = 0.000)
- Change observed following supplementation in women with obesity was lower by 2.04% total fatty acids (CI: −3.19, −0.90) compared to the change seen in women with normal BMI, equivalent to a 50% difference in the effect size between these two BMI groups.

Monthe-Dreze et al, Nutrients 2018

THE ROLE OF NUTRITIONAL INTERVENTIONS FOR OPTIMAL BRAIN AND NEURODEVELOPMENT: FUTURE DIRECTIONS

- ***Lack* of evidence of an effect *is not* the *same* as evidence of that there is "no effect"**
- ***Choosing the right population:*** Pregnant women with obesity and their offspring may benefit from prenatal lifestyle modification (vs. women with normal BMI) due to poorer nutritional status and greater dysmetabolism at baseline, and greater susceptibility to adverse outcomes in the offspring
- ***Choosing the right timing*:** early pregnancy/peri-conception is a critical window for brain development
- ***Choosing the right assessment tools*:** Apropriate measures of cognition is key. Global assessment of cognitive functions (e.g., Bayleys) may not be sensitive enough to detect differences in SPECIFIC cognitive processes that may be differentially affected by key nutrients
    - For example, specific cognitive outcomes related to DHA intake include attention, processing speed, problem solving, distractibility, higher-order function (Cheatham et al, AJCN 2006)

PART 2: SUMMARY

- Pre-pregnancy BMI and prenatal diet are associated with adverse offspring brain and neurodevelopmental outcomes

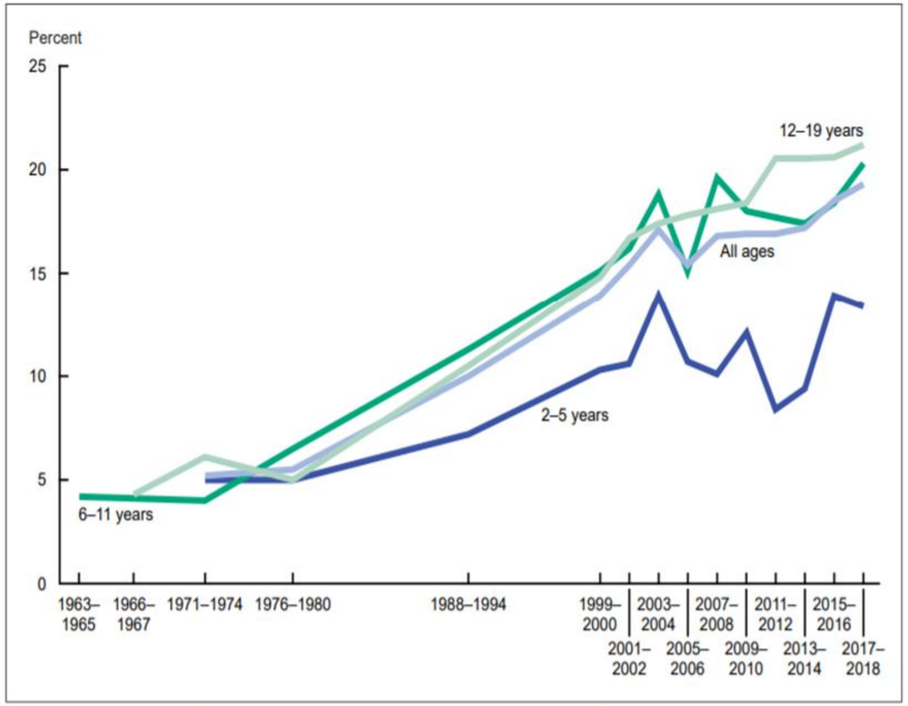
- Obesity and diet- related dysmetabolism (inflammation, lipotoxicity, altered fatty acid profiles, oxidative stress, hyperinsulinemia, hyperleptinemia) may be important mediators in these relationships

- There may be a role for interventions (diet, fish oil?) specifically for higher risk population (e.g maternal obesity) targeting inflammation/dysmetabolism, though more research is needed

MATERNAL OBESITY, PRENATAL DIET, AND CHILD GROWTH OUTCOMES

CHILD OBESITY TRENDS ARE ALARMING

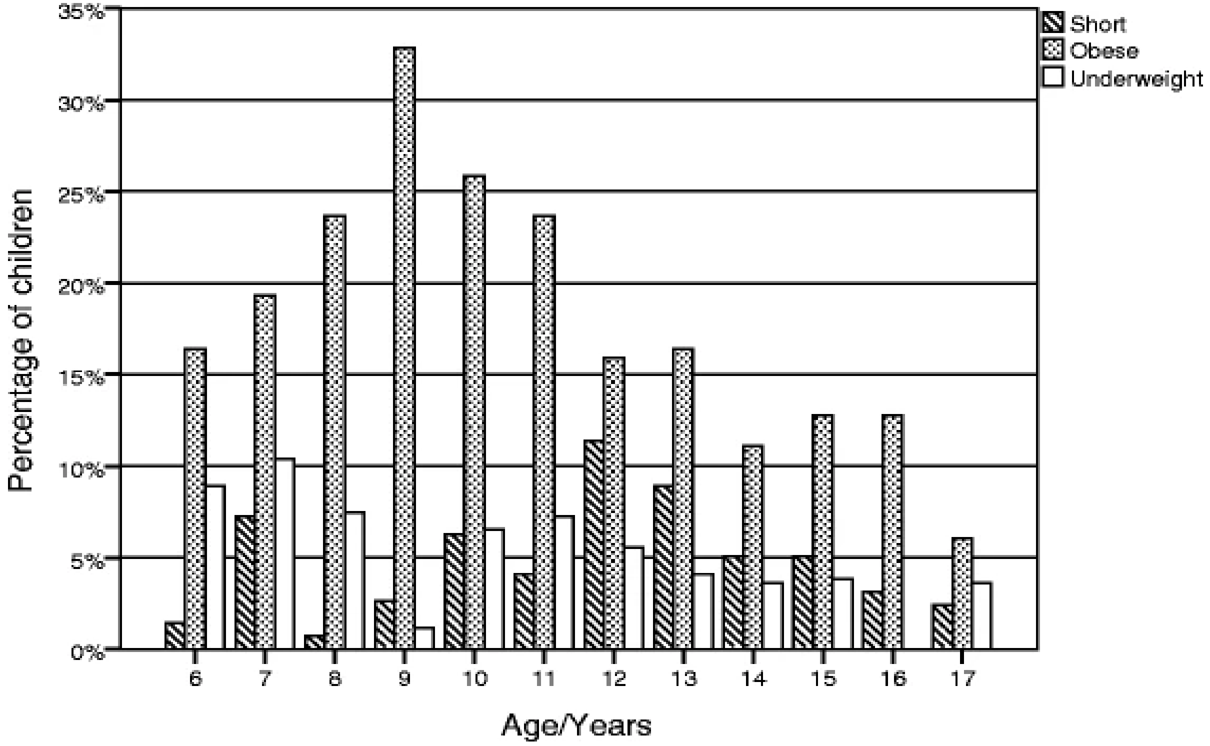
USA



NOTE: Obesity is body mass index (BMI) at or above the 95th percentile from the sex-specific BMI-for-age 2000 CDC Growth Charts.
SOURCES: National Center for Health Statistics, National Health Examination Surveys II (ages 6–11), III (ages 12–17); and National Health and Nutrition Examination Surveys (NHANES) I–III, and NHANES 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, and 2017–2018.

cdc.gov

JORDAN



Zayed et al, BMC Public Health 2016

CHILDHOOD OBESITY IS ASSOCIATED WITH ADULT OBESITY

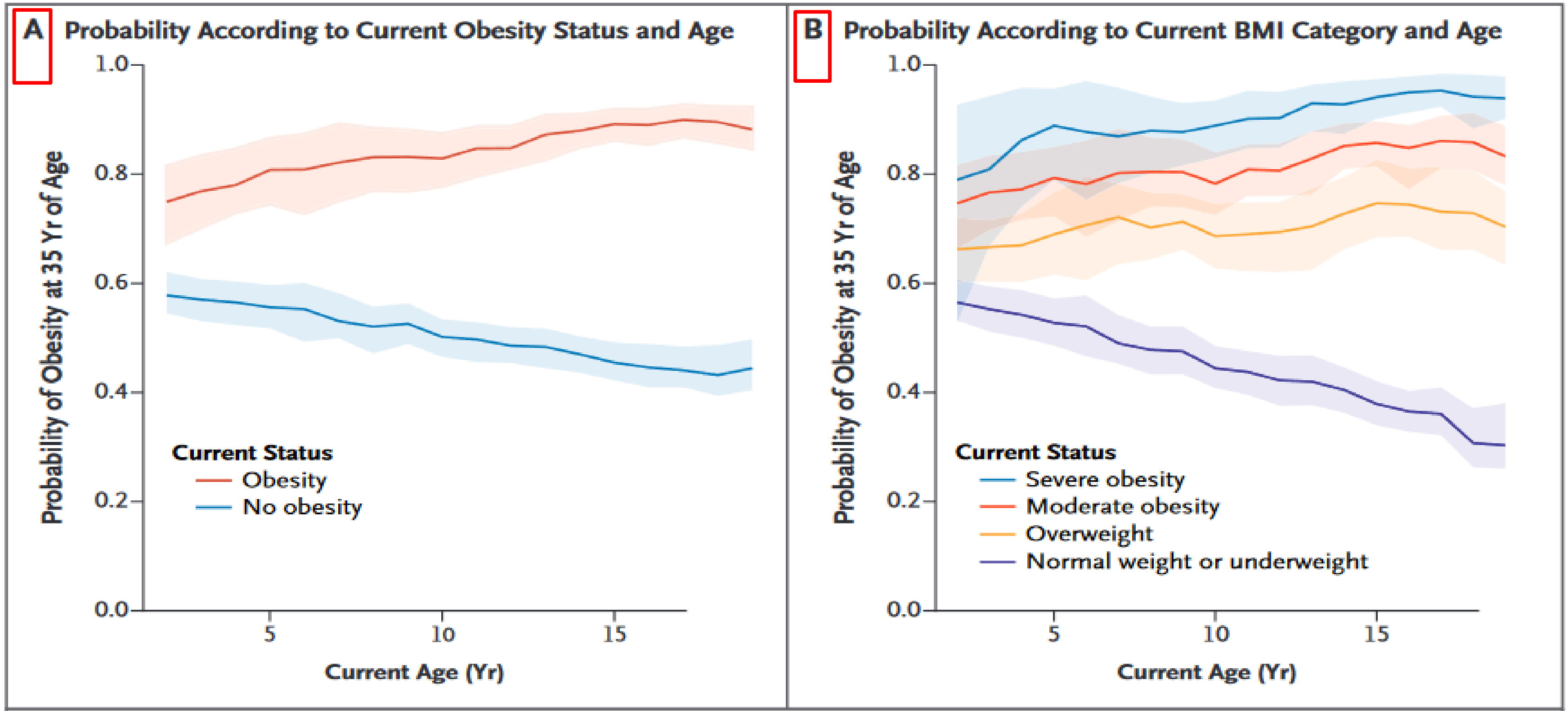
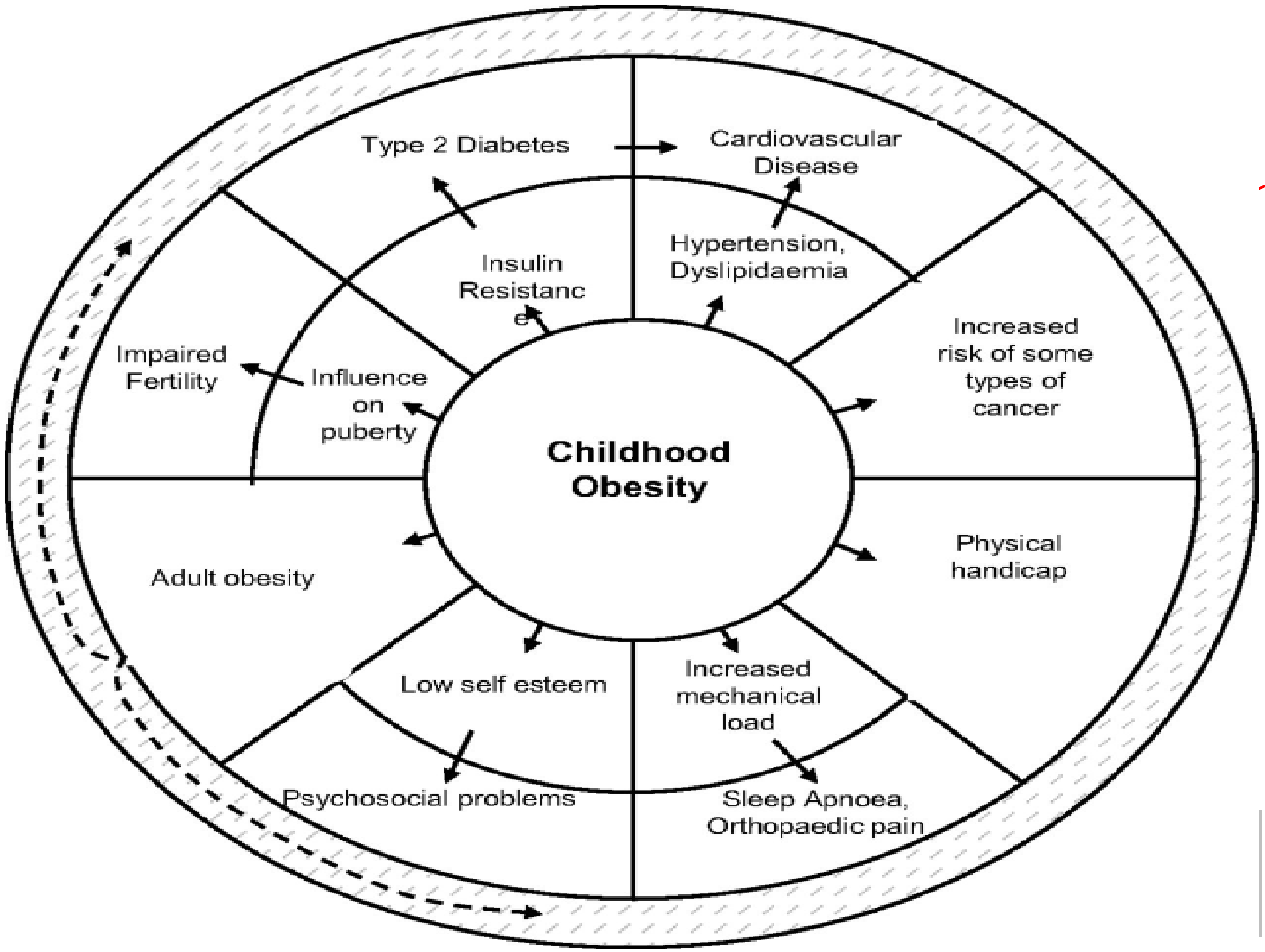


Figure 4. Predicted Probability of Obesity at the Age of 35 Years, According to Current Age, Obesity Status, and BMI Category.

Shown is the probability of obesity at the age of 35 years, according to current age and obesity status (Panel A) and BMI category (Panel B). The shaded areas indicate 95% uncertainty intervals.

Ward et al., NEJM, 2017

CHILDHOOD OBESITY AND CHRONIC HEALTH PROBLEMS THROUGH LIFESPAN



- Annual cost of childhood obesity in the US is ~$14 billion/year
- Annual cost of adult obesity in the US is $170 billion/year in excess costs

Hammond et al., *Diabetes Metab Syndr Obes* 2010
Trasande et al., *Obesity,* 2009
Lakshman et al, *Circulation,* 2012

Risk Factors for Child Obesity

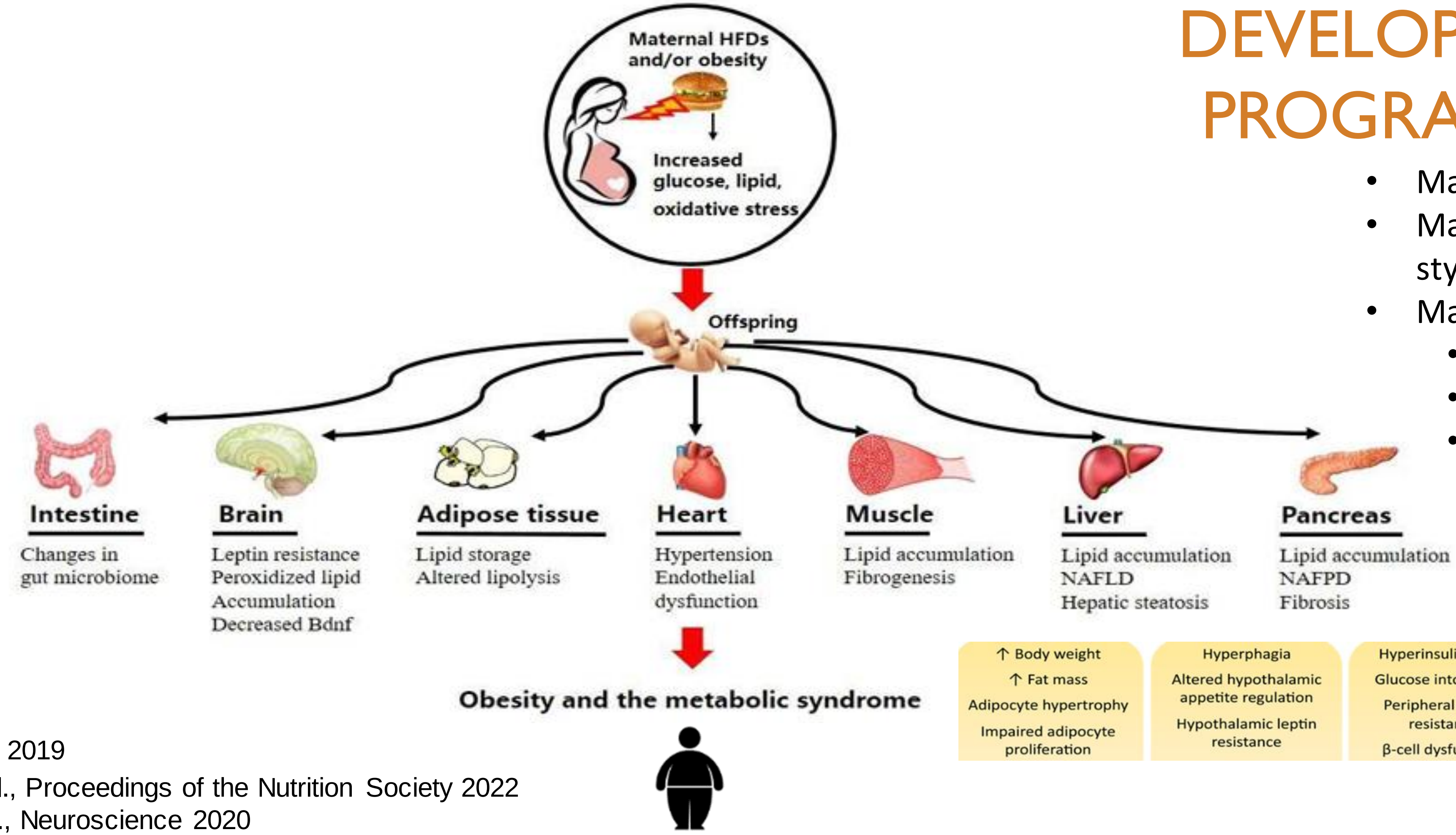
Obesogenic Environment

- **Home & Family Characteristics**
  - Parenting styles
  - Feeding styles and practices
  - Parental dietary patterns and intake → food available in the home
  - Parental eating behaviors and food preferences
  - Parental nutritional knowledge and activity patterns
- **Community and Neighborhood Characteristics:**
  - Quality and affordable food
  - School physical education program
  - School lunch programs
  - School outdoor activity spaces
- **Society**
  - Healthcare inequities
  - Socioeconomic status

- **Child characteristics**
  - Physical activity; Screen time/sedentary behavior
  - Excessive caloric intake/"western diet"
  - Self-regulation
  - Satiety cues

DEVELOPMENTAL PROGRAMMING

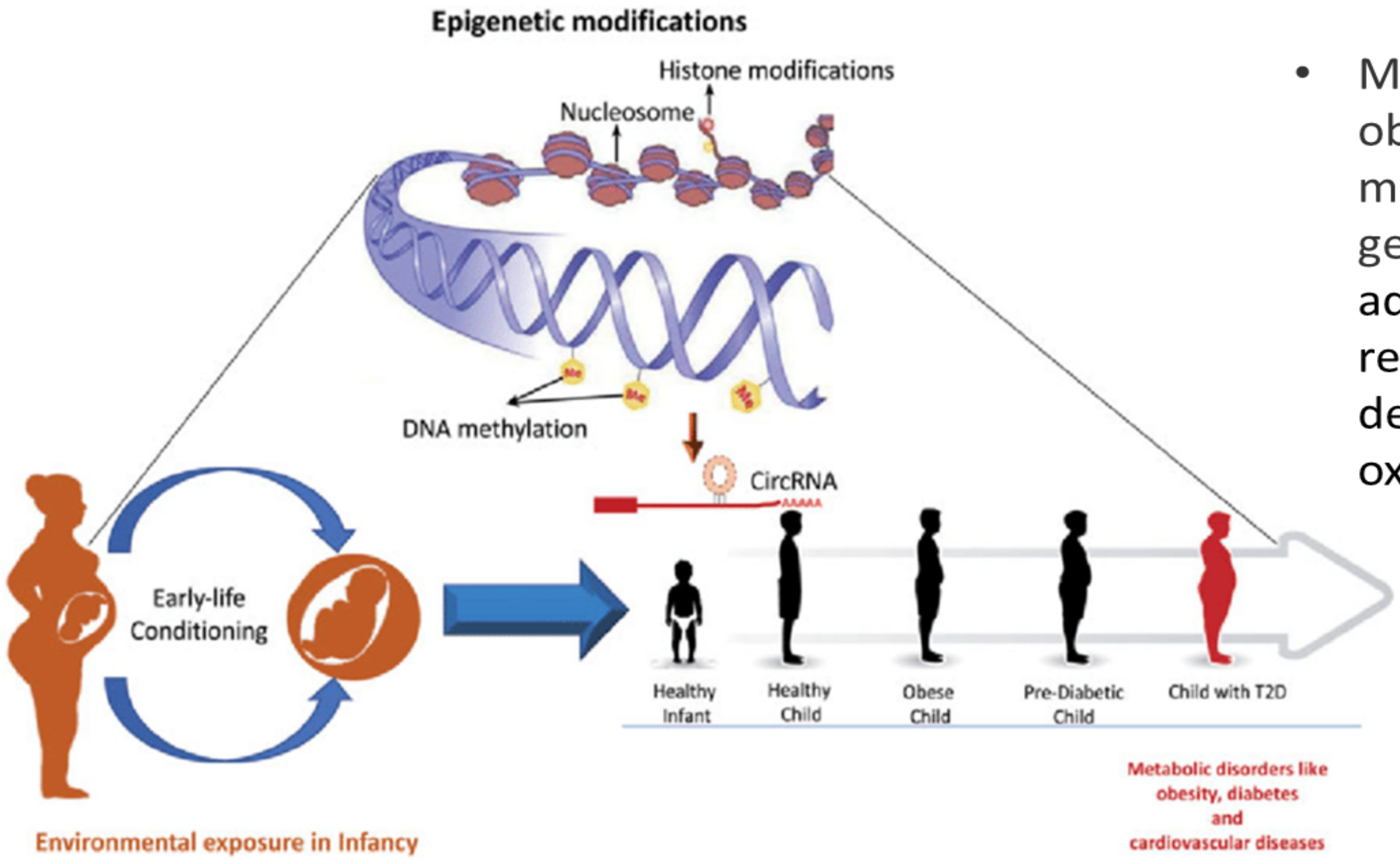
- Maternal undernutrition
- Maternal overnutrition (Western style diet, high-fat/high-fructose)
- Maternal dietary quality
  - High omega 6 vs. 3 fatty acids
  - Low protein diets
  - Low micronutrients (VitD, B12, antioxidants, methyl donors)



↑ Body weight ↑ Fat mass Adipocyte hypertrophy Impaired adipocyte proliferation	Hyperphagia Altered hypothalamic appetite regulation Hypothalamic leptin resistance	Hyperinsulinaemia Glucose intolerance Peripheral insulin resistance β-cell dysfunction	Cardiac dysfunction Cardiac hypertrophy ↑ cardiac inflammation ↑ cardiac oxidative stress	Hypertension Altered vascular structure Altered response to vasoactive signals

Zhen et al, 2019
Inzani et al., Proceedings of the Nutrition Society 2022
Cirulli et al., Neuroscience 2020

EPIGENETICS MAY PLAY A ROLE



- Maternal diet- and maternal obesity-induced changes in the methylation of promoter regions of genes involved in lipid metabolism, adipocyte differentiation, insulin resistance and growth and development, inflammation and oxidative stress.

Bordeleau et al., Front Cell Neurosci. 2021,
Agarwal et al., Critic Rev in Clin Lab Sci. 2018

PRENATAL DIETARY QUALITY IS ASSOCIATED WITH CHILD BMI TRAJECTORIES

- Population: Mother-child dyads in project Viva pre-birth cohort with dietary quality indices available in pregnancy and ≥ 3 body mass index (BMI) measures in the children
  - Dietary Inflammatory Index (DII)
  - Adherence to Mediterranean dietary pattern: Mediterranean diet score (MDS)
  - Alternate Healthy Eating Index for Pregnancy (AHEI-P)

- Exposure: Dietary indices were summarized as quartiles. Exposure group were children with *in utero* exposure to the highest quartile of DII (Q4) or the lowest quartile of MDS or AHEI-P (Q1)

- Comparison: Children with *in utero* exposure to the lowest quartiles of DII (Q1); or the highest quartile of MDS or AHEI-P (Q4)

- Outcome: BMI-z trajectories from birth to adolescence

Monthe-Dreze et al, AJCN 2021

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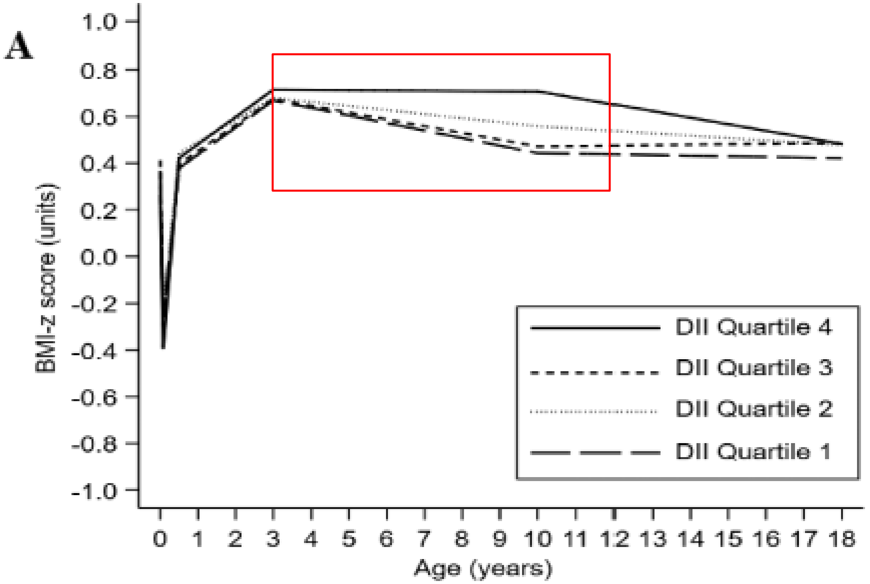
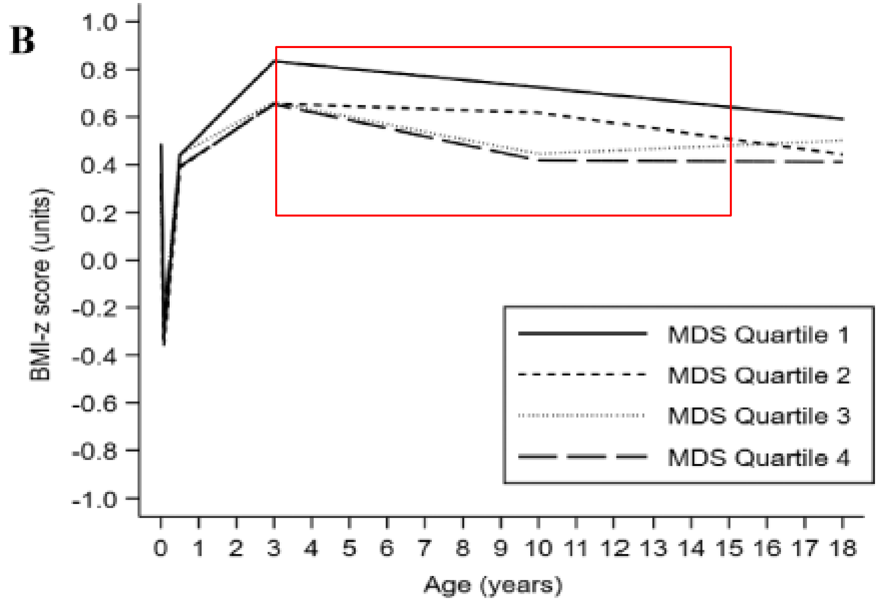
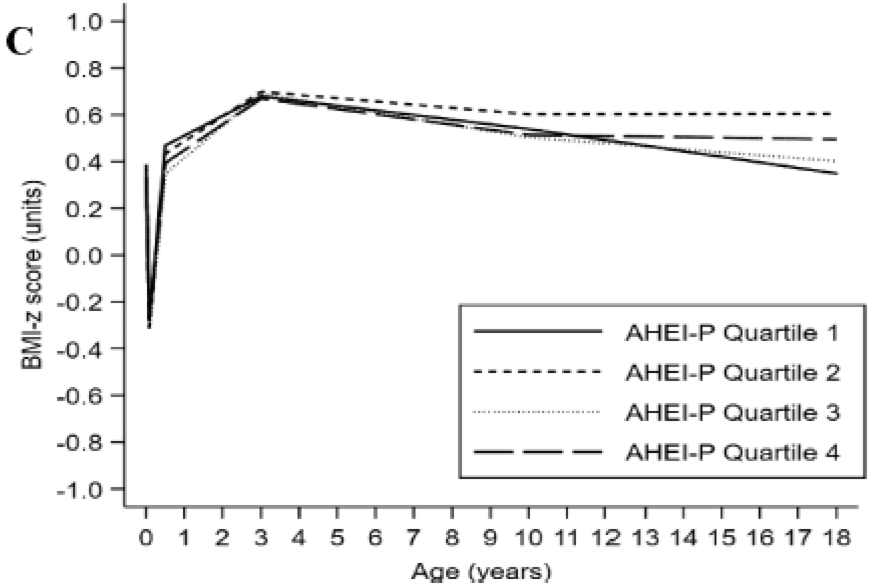


Dietary Inflammatory Index



Mediterranean Diet Score

Alternate Healthy Eating Index for Pregnancy



Monthe-Dreze et al, AJCN 2021

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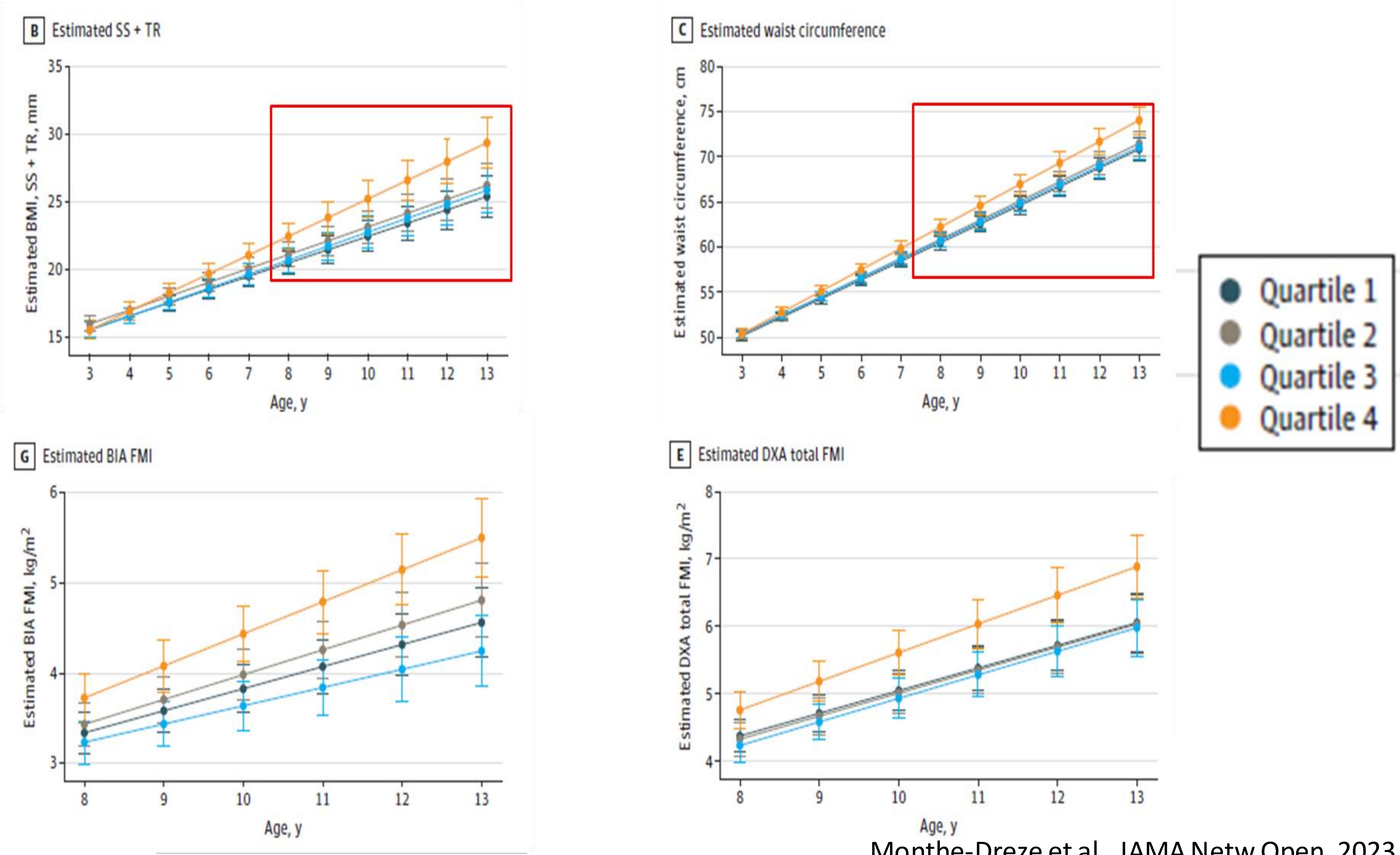
THE MODERATING ROLE OF THE PSYCHOLOGICAL STRESS IN THE PRENATAL DIET-CHILD GROWTH RELATIONSHIP

In Utero Exposure to the Highest Quartile of DII was Associated with Faster Adiposity Gain Over Time



Monthe-Dreze et al., JAMA Netw Open, 2023

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Associations of Prenatal DII with Childhood Adiposity were Stronger Among Offspring of Mothers with Higher EPDS (Edinburgh depression scores) in Pregnancy

Variable, by DII Q	EPDS score category	β (95% CI) DII × EPDS interaction	β (95% CI) DII × age × EPDS interaction
WC, cm (n = 1054)			
Q1	Low	1 [Reference]	1 [Reference]
Q2	High	0.88 (−1.58 to 3.33)	−0.14 (−0.86 to 0.58)
Q3	High	1.54 (−0.84 to 3.91)	−0.22 (−0.91 to 0.46)
Q4	High	3.14 (0.70 to 5.57)	−0.13 (−0.81 to 0.55)
P value for trend[b]	NA	.01	.69
BIA FMI, kg/m^2 (n = 908)			
Q1	Low	1 [Reference]	1 [Reference]
Q2	High	−0.06 (−1.30 to 1.18)	−0.03 (−0.32 to 0.26)
Q3	High	−0.17 (−1.35 to 1.02)	−0.03 (−0.32 to 0.25)
Q4	High	1.40 (0.21 to 2.59)	−0.10 (−0.38 to 0.19)
P value for trend[b]	NA	.05	.59
BIA fat % (n = 908)			
Q1	Low	1 [Reference]	1 [Reference]
Q2	High	−0.17 (−4.60 to 4.26)	−0.24 (−1.19 to 0.72)
Q3	High	−0.33 (−4.58 to 3.93)	−0.23 (−1.18 to 0.72)
Q4	High	3.08 (−1.19 to 7.36)	−0.83 (−1.79 to 0.14)
P value for trend[b]	NA	.22	.14

Variable, by DII Q	EPDS score category	β (95% CI) DII × EPDS interaction	β (95% CI) DII × age × EPDS interaction
DXA FMI, kg/m^2 (n = 704)			
Q1	Low	1 [Reference]	1 [Reference]
Q2	High	−0.14 (−1.49 to 1.21)	0.21 (−0.14 to 0.56)
Q3	High	−0.11 (−1.29 to 1.06)	0.07 (−0.20 to 0.35)
Q4	High	1.73 (0.52 to 2.95)	−0.18 (−0.48 to 0.12)
P value for trend[b]	NA	.03	.44
DXA trunk FMI, kg/m^2 (n = 704)			
Q1	Low	1 [Reference]	1 [Reference]
Q2	High	−0.10 (−0.70 to 0.49)	0.13 (−0.05 to 0.30)
Q3	High	−0.04 (−0.56 to 0.48)	0.03 (−0.11 to 0.17)
Q4	High	0.77 (0.23 to 1.32)	−0.05 (−0.20 to 0.10)
DXA fat % (n = 704)			
Q1	Low	1 [Reference]	1 [Reference]
Q2	High	−0.82 (−5.25 to 3.61)	0.17 (−0.77 to 1.11)
Q3	High	−0.37 (−4.22 to 3.48)	0.25 (−0.48 to 0.97)
Q4	High	3.50 (−0.51 to 7.52)	−0.96 (−1.77 to −0.14)
P value for trend[b]	NA	.20	.12

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Brigham and Women's Hospital
Founding Member, Mass General Brigham

Monthe-Dreze et al., JAMA Netw Open, 2023

The Cycle of Intergenerational Obesity: Mechanisms

Pre-pregnancy Obesity (and diet!)

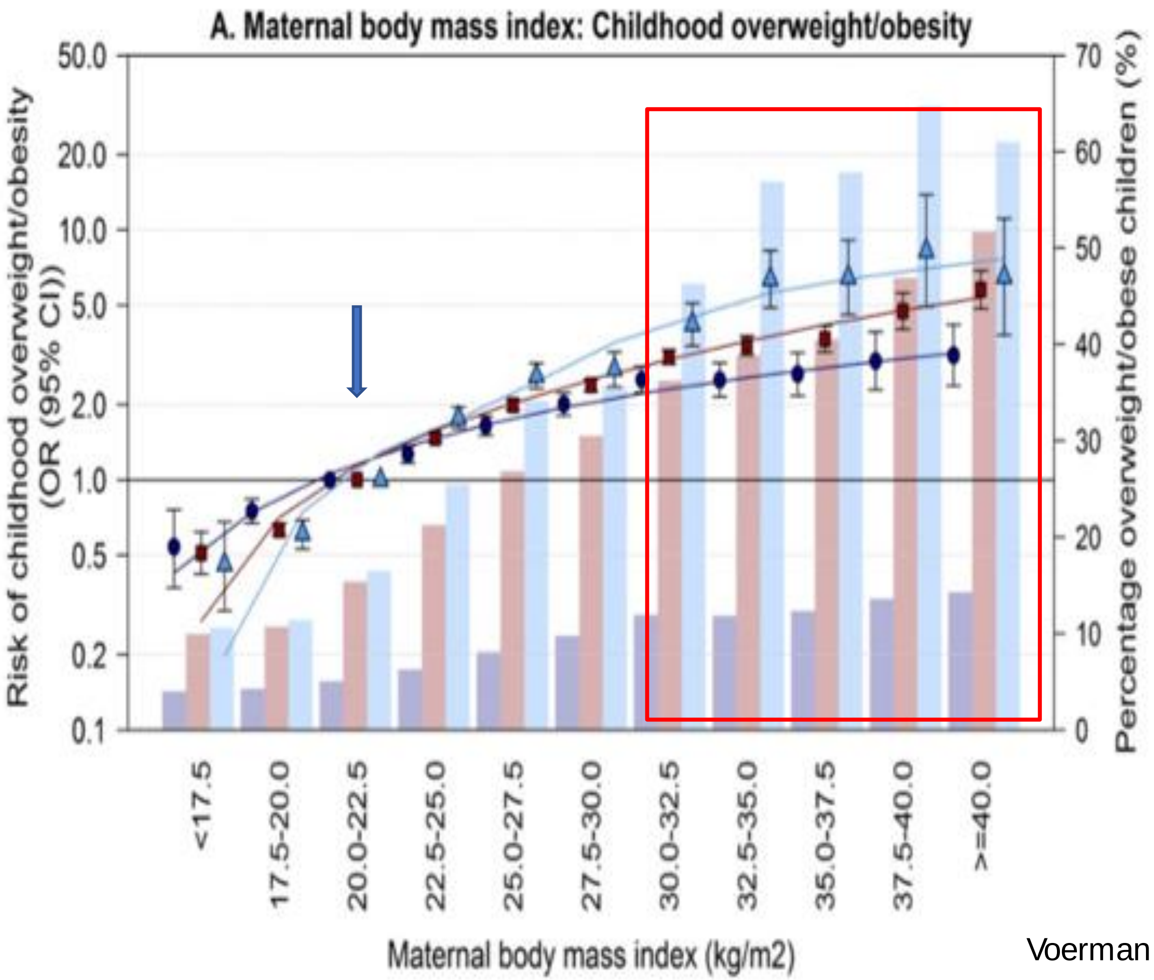
Adult Obesity

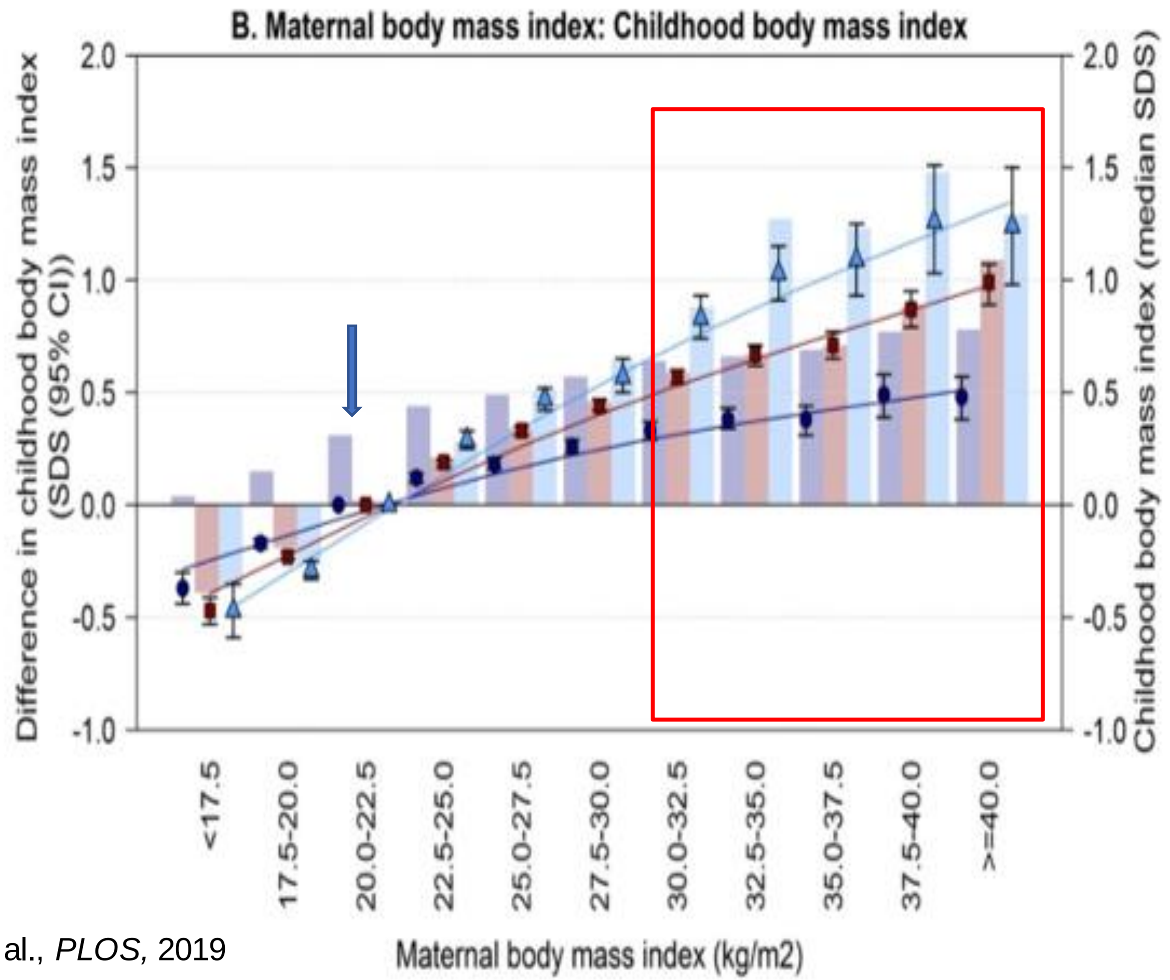
Abnormal *in utero* Pro-Inflammatory Metabolic Environment
- **Epi/genetic dysregulation**
- **Fetal metabolism**
- **Inflammatory/immune dysregulation**
- **Oxidative Stress**

Childhood Obesity

Neonatal Adiposity and/or Altered Metabolic Phenotype

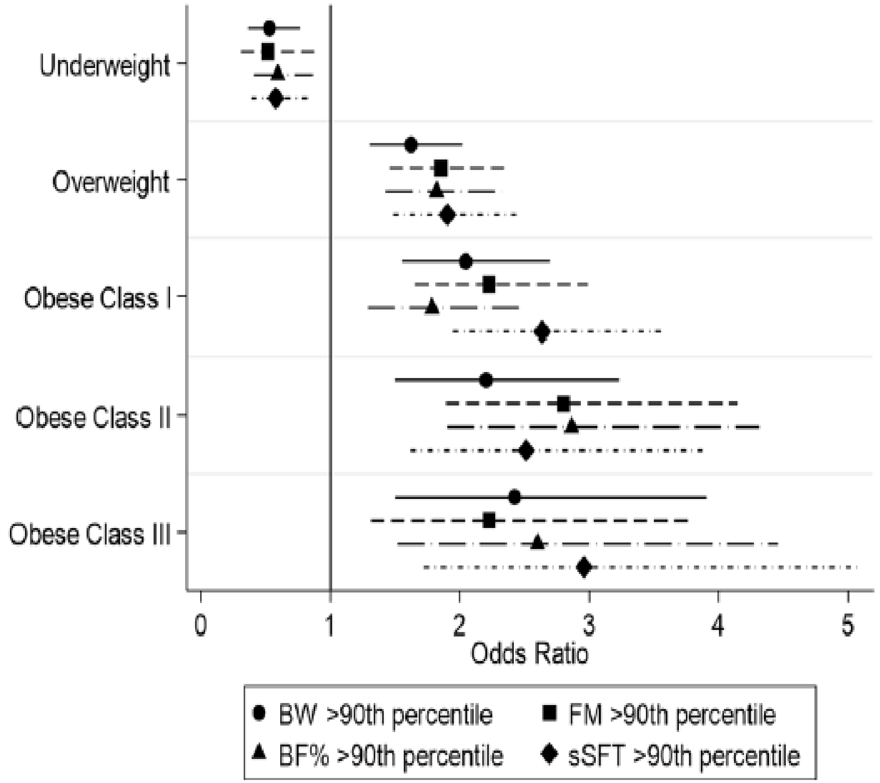
MATERNAL OBESITY IS ASSOCIATED WITH CHILD BMI

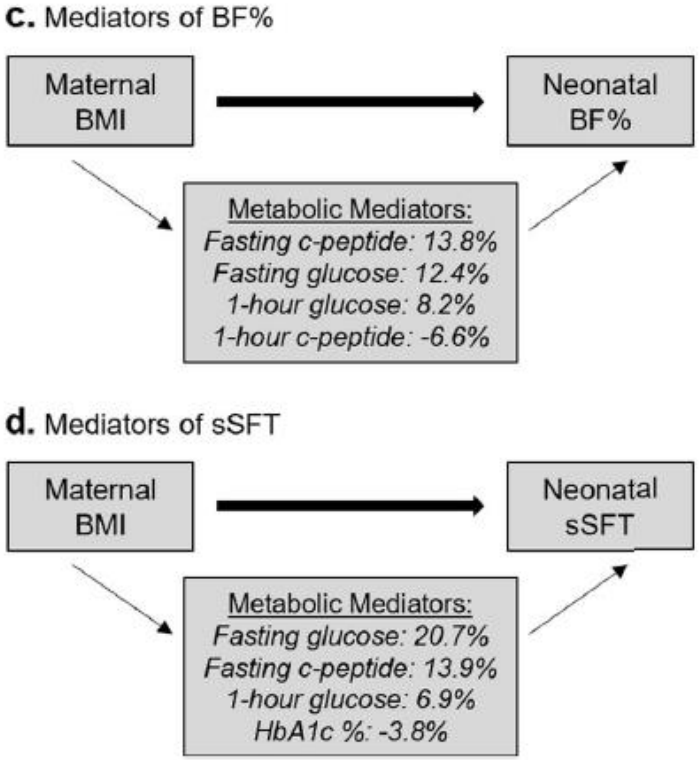




Voerman et al., *PLOS*, 2019

MATERNAL OBESITY IS ASSOCIATED WITH NEONATAL/FETAL ADIPOSITY AND IMPAIRED GLUCOSE METABOLISM MAY PLAY A ROLE





MEDIATORS:

- **Fasting blood Glucose and c-peptide (markers of maternal glucose metabolism control)**

Andrews et al., *IJO 2021*

NEONATAL ADIPOSITY IS ASSOCIATED WITH INCREASED PREVALENCE OF CHILDHOOD OVERWEIGHT/OBESITY

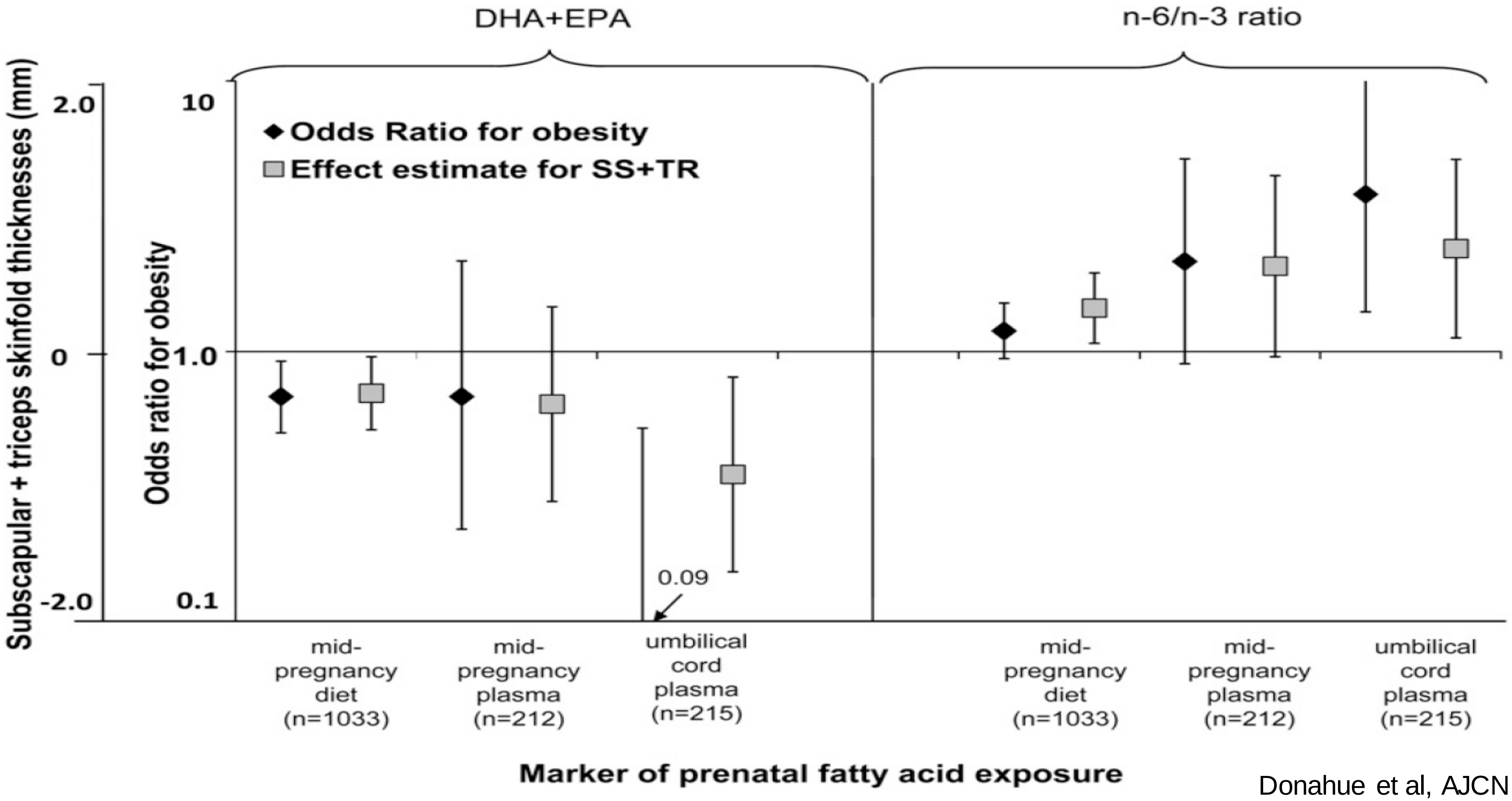
Proportion of Children by Age Who Were Classified as Overweight or Obese According to Neonatal Adiposity

Neonatal Adiposity	2–3 y		3–4 y		4–5 y		5–6 y	
	n	Percent (95% CI)	*n*	Percent (95% CI)	*n*	Percent (95% CI)	*n*	Percent (95% CI)
5.1% (mean – 1 SD)	132	15 (9 to 21)	87	13 (6 to 20)	82	10 (3 to 16)	36	3 (0 to 8)
9.1% (mean)	527	18 (15 to 21)	362	19 (15 to 23)	386	17 (13 to 21)	136	15 (9 to 21)
13.1% (mean + 1 SD)	120	23 (15 to 30)	69	22 (12 to 32)	97	14 (7 to 21)	30	23 (9 to 39)
P for trend	—	*P* = .08	—	*P* = .08	—	*P* = .26	—	*P* = .02

Moore et al, Pediatrics 2020

Fetal Overgrowth and Adiposity May Mediate the Associations of Maternal Pre-Pregnancy Obesity with Childhood Obesity

Higher Pregnancy Dietary and Umbilical Cord n-3 PUFA is Associated with Lower Childhood Obesity Risk



Donahue et al, AJCN 2011

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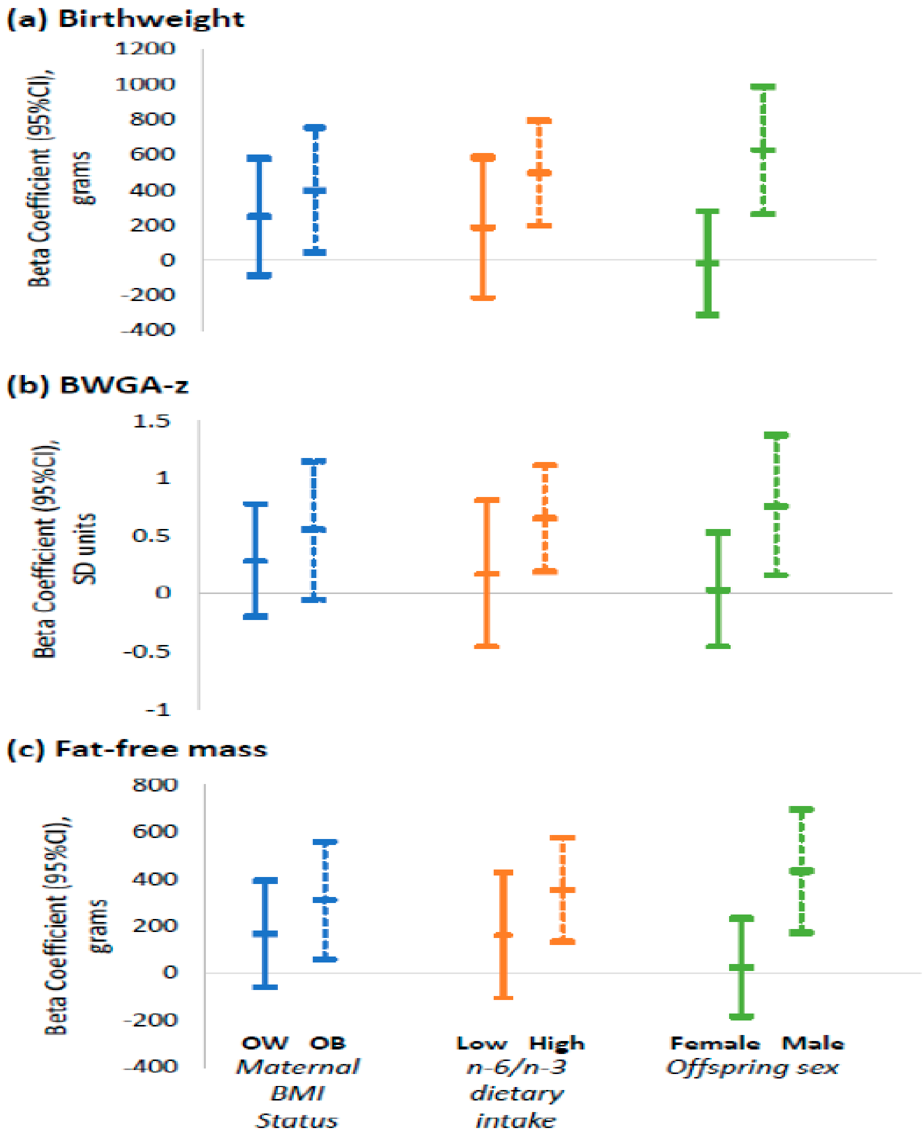
Omega(n)-3 Supplementation in Overweight/Obese Pregnancies is Associated with Increased Fetal Growth AND Increased Neonatal Fat Free Mass



Specific subgroups that might get a greater benefit:

- Women with obesity
- Women with high prenatal dietary n6/n3 PUFA ratio
- Male infants

Monthe-Dreze et al, *Nutrients* 2021

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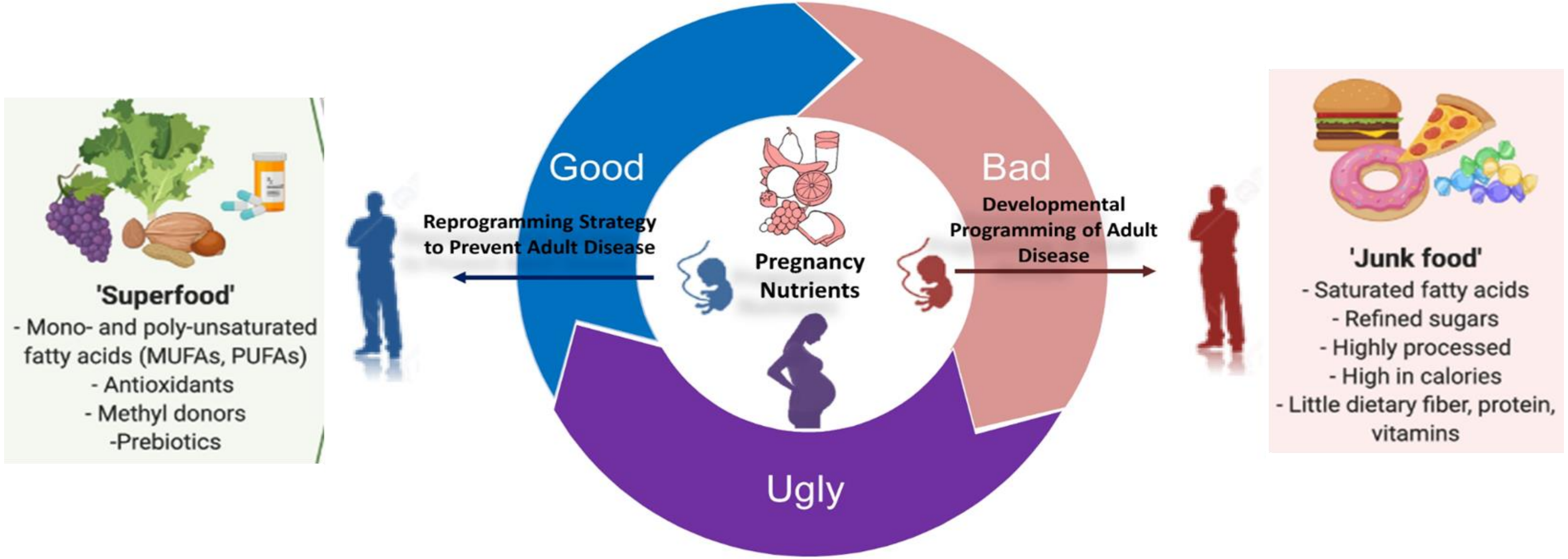
Nutritional Programming: The good, Bad and Ugly



"Right" nutritional intervention for the "right" person (mother or offspring) at the "right" time remains largely unknown.

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Lifestyle Intervention in Preparation for Pregnancy (LIPP):The **Right** Intervention at the **Right** Time?

- **Study**: 200 women with history of pre-pregnancy obesity are recruited after delivery to participate in a RCT of preconception lifestyle intervention geared towards improved nutrition (Mediterranean diet) and physical activity in preparation for their next pregnancy.
- **Outcomes:**
  - Maternal metabolic status before and during subsequent pregnancy
  - Child adiposity

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ClinicalTrials.gov NCT03146156

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PART 3: SUMMARY

- Pre-pregnancy obesity and prenatal dietary quality are linked to higher offspring BMI and adiposity from birth to adolescence. In turn, childhood obesity is linked to later adult obesity and metabolic syndrome.

- Prenatal metabolic dysregulation and epigenetics play important mechanistic roles

- Prenatal psychosocial stress may play an important moderating role

- Trials evaluating the effects of prenatal dietary interventions among women with obesity on offspring adiposity may require initiation during pre/periconception period as well as long-term follow-up at least through mid childhood.

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BRIGHAM AND WOMEN'S HOSPITAL

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- Patrick Catalano, MD

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN

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Boston Children's Hospital
Until every child is well

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- Jack Keller, BA

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- ***Loan Repayment Award***
- ***NRSA T32***

THANK YOU FOR YOUR ATTENTION

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Q&A

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