Interaction of prenatal psychosocial stress and nutrition: implications for maternal and infant metabolic outcomes

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Introduction

DOHaD theory – exposures/insults occurring at sensitive periods of gestation may adversely impact fetal development with long-term implications for health and disease outcomes

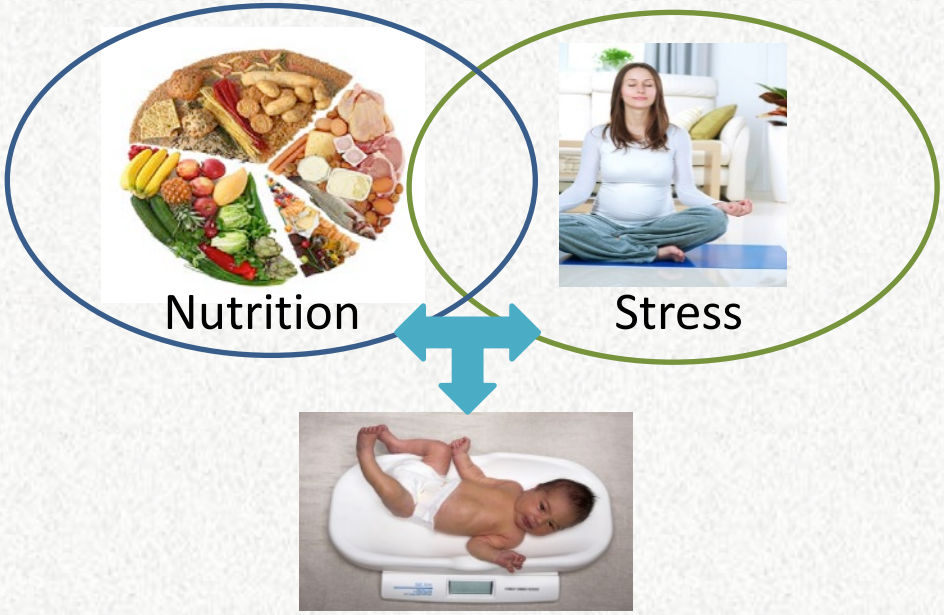
Azad et al., 2016;
Horan et al., 2014, 2016;
Donahue et al., 2011;
Drake & Reynolds, 2010;
Moon et al., 2013;
Okubo et al., 2014;
Reynolds et al., 2011

Offspring obesity risk / metabolic dysfunction

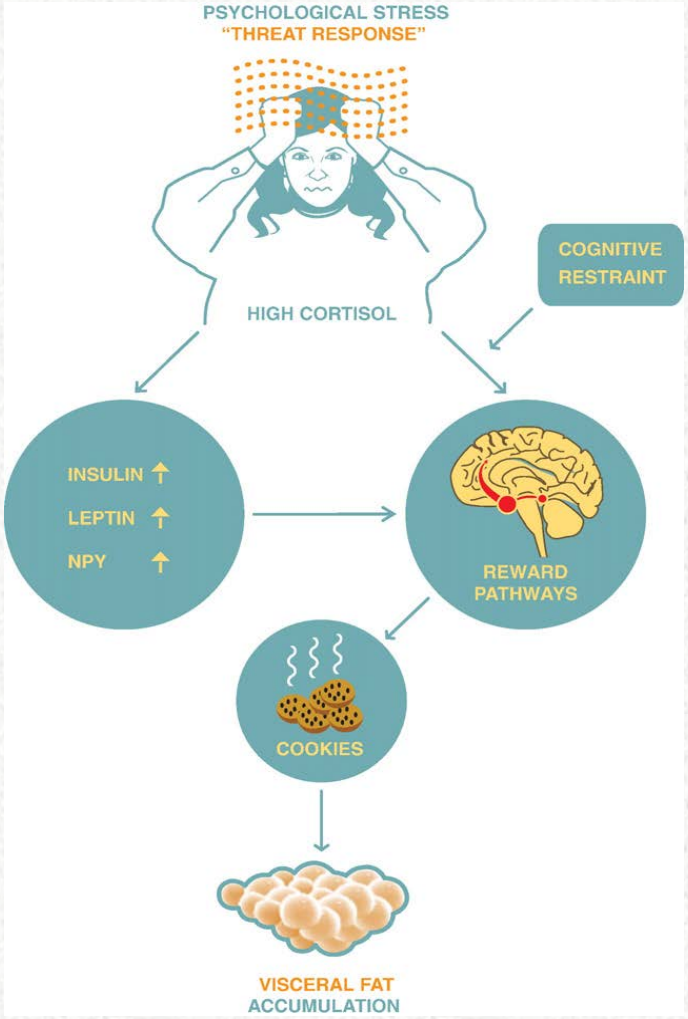
Brunton et al., 2013
Dancause et al., 2015;
Entringer et al., 2008, 2010;
Gillman et al., 2006;
Jasarevic et al., 2015;
Mueller et al., 2006
Tamashiro et al., 2009;

Introduction

Combined effects of nutrition and stress on fetal programming are poorly studied



Bi-directional relationship between nutrition & stress



Stress influences nutrition:

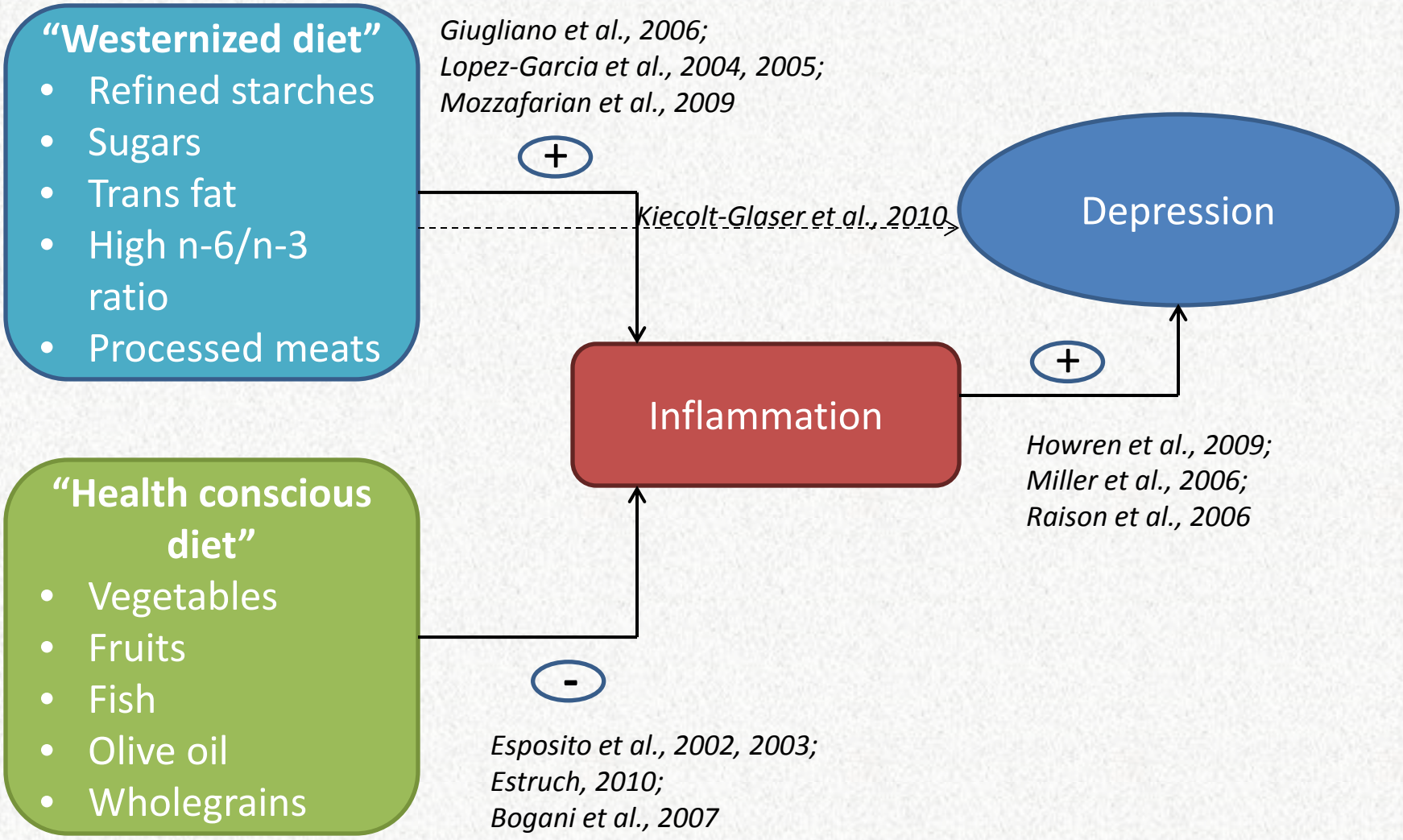
- Quantity & quality of food consumed
- Metabolic response to ingested food
- Metabolic fate in target tissues

Nutrition influences stress:

- Perception of stress, mood
- Glucocorticoid response
- Inflammatory response

T.C. Adam, E.S. Epel / Physiology & Behavior 91 (2007) 449–458

Mediating role of inflammation



Evidence for prenatal nutrition x stress interactions

Ref & study design	Population	Diet assessment	Results
Hurley et al., 2005; prospective observational	134 low-risk pregnant women, USA	FFQ at 28 weeks	Stress & anxiety associated with ↑ intake of breads, fats, oils, snacks, total energy, Fe, Zn
Golding et al., 2009; Santos-Vaz et al., 2013; retrospective cross-sectional	>9000 women ALSPAC cohort, UK	FFQ at 32 weeks to assess n-3 intake from seafood and dietary patterns	Low or no n-3 intake ↑ risk of depressive symptoms & anxiety; health conscious & traditional diet patterns ↓ risk anxiety
Chatzi et al., 2011; Retrospective observational	529 healthy pregnant women, Greece	FFQ mid-pregnancy, dietary pattern analysis	Olive oil >40g/day ↓ risk postpartum depression; sugar >29g/day ↑ risk
Vilela et al., 2014; Prospective observational	207 healthy pregnant women, Brazil	FFQ in trimester 1 to assess preconception diet	Healthy and traditional diet patterns –vely associated with anxiety from prenatal to postpartum period
Chang et al., 2015; cross-sectional qualitative	96 low-income overweight & obese women, USA	Focus groups to explore health knowledge & attitudes towards healthy eating and exercise	Barriers to healthy eating: poor self-control, lack of social support, financial constraints. Facilitators: behavioral capacity, autonomous motivation (e.g. concerns re GDM)

Evidence for prenatal stress effects on offspring metabolic states

Experimental animal studies:

- ↑ body weight/postnatal growth *(Amugongo et al., 2014; Mueller et al., 2006)*
- ↓ glucose tolerance/insulin sensitivity *(Balasubramian et al., 2015; Lasage et al., 2004)*
- Dyslipidemia *(Brunton et al., 2013)*

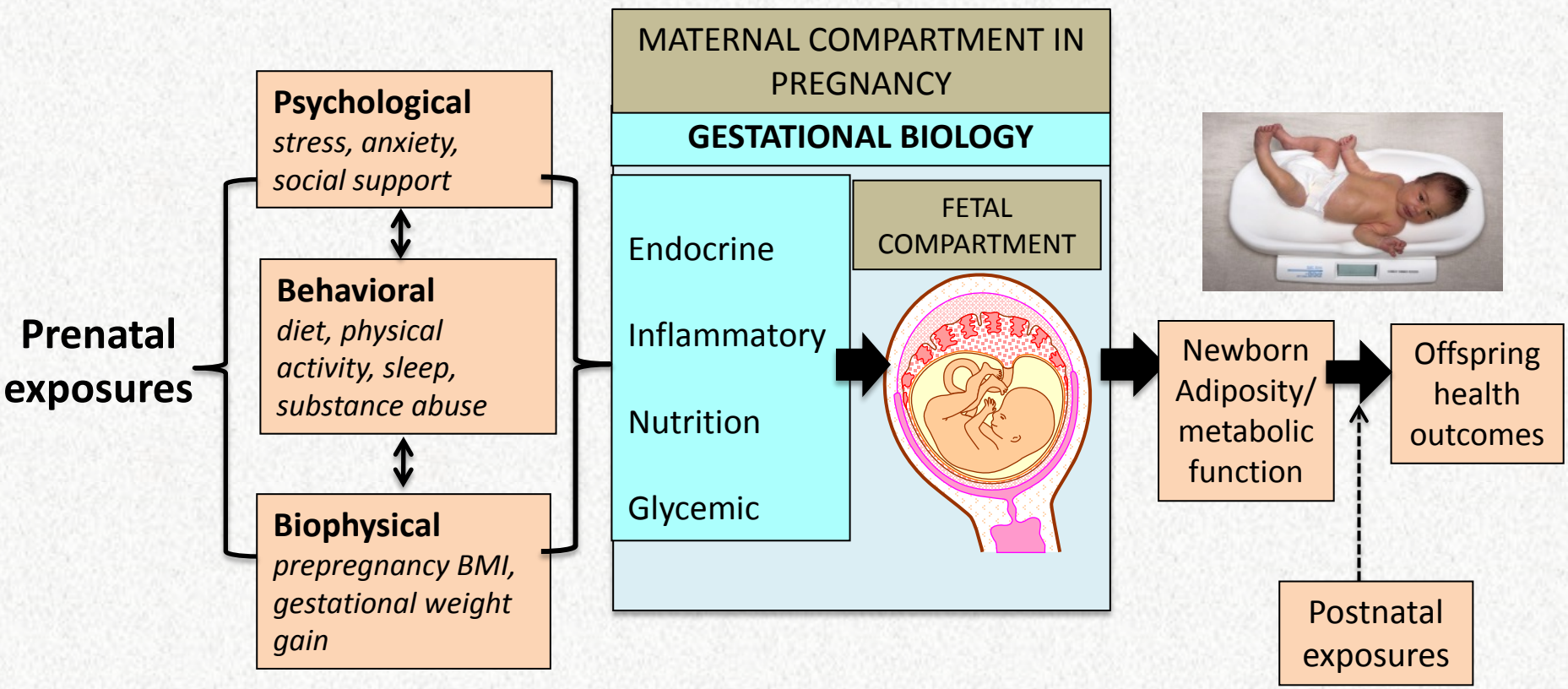
Animal study of prenatal stress +/- high fat diet:

- ↑ leptin and impaired glucose tolerance *(Tamashiro et al., 2009)*

Observational human studies:

- ↓ birthweight – combined maternal depression & anxiety *(Loomans et al., 2012)*
- ↑ adiposity & BMI at age 2.5y *(Dancause et al., 2015)*
- ↑ BMI, insulin insensitivity & VLDL in early adulthood *(Entringer et al., 2008)*

Conceptual Framework: Fetal programming by prenatal nutrition & stress



Characterization of prenatal nutrition & stress

Prenatal Nutrition

- Dietary intake – quantity & quality
- Biophysical status – BMI, fat mass, lean mass
- Nutritional metabolites – fatty acids, amino acids etc. available to the fetus

Prenatal Stress

- Psychosocial – stress, anxiety, social support, depression
- Corticotrophin releasing hormone (CRH)
- Glucocorticoids - cortisol
- Inflammatory cytokines

Overview of EMA Study

Ecological Momentary Assessment (EMA) study at UCI (N=250 mothers)

- Baseline Blood/ Hair Sample
- Fasting Blood sample
- Psychosocial Stress Assessment
- Neuropsychological Battery
- Fetal Ultrasound
- Cervicovaginal Swabs
- Anthropometric Measures
- 4 Day Ambulatory Period:
  - Diurnal Salivary Cortisol (7 per day)
  - Actiheart Device (beat to beat heart rate)
  - Electronic Diary (Smart Phone)
  - 3 x 24-hr Dietary Recall Assessments
  - 24 hr Urine

- Delivery: Placenta, cord blood and cord tissue (telomere biology)

2-4 weeks

- Newborn Body
- Blood/ Saliva Samples
- Anthropometrics
- Neonatal MRI (brain:
- Neonatal Motor

- Infant Body Composition (DXA)
- Total Energy Expenditure
- Blood, Saliva, Hair
- Cognitive, Motor & Emotional Behavior (Bayley's)
- Infant Environment (HOME)
- Maternal sensitivity (stand. Play situation)

- Infant Body Composition (DXA)
- Total Energy Expenditure
- Anthropometrics
- Blood, Saliva, Hair Samples
- Infant MRI (brain: structural MRI, DTI, resting state fMRI; body: whole body scans, brown fat scans)
- Infant Cognitive, Motor & Emotional Behavior (Bayley's)
- Mother/Infant Attachment (Strange Situation

Pre-pregnancy BMI

"real time" assessment of maternal psychosocial states

Nutrient & food group intakes
Overall diet quality

EMA Study:
Assessing diet & psychosocial states

Alternative Healthy Eating Index adapted for Pregnancy (AHEI-P)

- Validated index of diet quality in prenatal populations (*Rifas-Shiman et al., 2009; Rodriguez-Bernal et al., 2010*)
- 10 components:
  - Vegetables
  - Fruit
  - cereal fiber
  - vegetable prot
  - white/red mea
  - PUFA/SFA
  - trans fat
  - folate
  - iron
  - calcium

Ecological Momentary Assessment (EMA) of psychosocial states

- Immediate reports of current state or activity
- Collected in naturalistic settings
- Maternal perceived stress, positive/negative mood, social support
- Multiple times/day over 4 days in each trimester

Association of diet quality with maternal psychosocial states

Trimester 1 AHEI-P

	Variable	N	B	95% CI		P unadjusted	P adjusted*
Trimester 1	Perceived stress	207	-0.010	-0.017	-0.003	**0.007**	**0.003**
	Positive mood	207	0.012	0.003	0.020	**0.006**	**0.004**
	Negative mood	207	0.000	-0.004	0.005	0.922	0.907
	Social support	202	0.009	0.001	0.018	**0.034**	**0.030**
Trimester 2	Perceived stress	200	-0.008	-0.016	-0.001	**0.032**	**0.005**
	Positive mood	200	0.009	0.000	0.018	0.057	**0.020**
	Negative mood	200	-0.001	-0.007	0.004	0.683	0.487
	Social support	195	0.013	0.004	0.022	**0.007**	**0.003**

Trimester 2 AHEI-P

	Variable	N	B	95% CI		P unadjusted	P adjusted*
Trimester 2	Perceived stress	210	-0.006	-0.014	0.001	0.110	**0.048**
	Positive mood	210	0.007	-0.002	0.016	0.141	0.083
	Negative mood	210	-0.004	-0.009	0.002	0.192	0.101
	Social support	206	0.003	-0.006	0.013	0.483	0.455
Trimester 3	Perceived stress	204	-0.008	-0.016	-0.001	**0.033**	**0.011**
	Positive mood	204	0.008	0.000	0.017	0.061	**0.032**
	Negative mood	204	-0.003	-0.009	0.002	0.259	0.143
	Social support	201	0.007	-0.002	0.016	0.120	0.118

* Adjusted for maternal pre-pregnancy BMI and age

Overview of EMA Study

Ecological Momentary Assessment (EMA) study at UCI (N=250 mothers)

10-12 Weeks Gestation | **20-22 Weeks Gestation** | **30-32 Weeks Gestation** | **Birth** | **6 Months** | **12 Months**






Metabolomics
Glycemic parameters
Inflammatory cytokines

Pre-pregnancy BMI

- Baseline Blood/ Hair Sample
- Fasting Blood sample
- Psychosocial Stress Assessment
- Neuropsychological Battery
- Fetal Ultrasound
- Cervicovaginal Swabs
- Anthropometric Measures
- 4 Day Ambulatory Period:
  - Diurnal Salivary Cortisol (7 per day)
  - Actiheart Device (beat to beat heart rate)
  - Electronic Diary (Smart Phone)
  - 3 x 24-hr Dietary Recall Assessments
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2-4 weeks
- Newborn Body Composition (DXA)
- Total Energy Expenditure
- Neonatal MRI (brain: structural MRI, DTI, resting state fMRI; body: whole body scans, brown fat scans)
- Neonatal Motor Performance (TIMP)

- Body
- position (DXA)
- Energy Expenditure
- Blood, Saliva, Hair Samples
- Infant Cognitive, Motor & Emotional Behavior
- nment (HOME)
- Infant stress reactivity (Still face, saliva and heart rate)
- Maternal sensitivity (stand. Play situation)

- Infant Body Composition (DXA)
- Total Energy Expenditure
- Anthropometrics
- Blood, Saliva, Hair Samples
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Role of cytokines in pregnancy

- Placental secretion - mediates normal gestational physiological processes
- Raised pre-pregnancy BMI/adiposity - ↑ inflammatory profile
- Potential effects on:
  - Maternal/fetal insulin resistance via fatty acid / BCAA accumulation
  - Placental AA transport to fetus, may promote excess fetal growth *(Jones et al., 2006; Jansson et al. 2013)*
- Maternal IL-6 in late pregnancy has been associated with increased neonatal adiposity *(Radaelli et al., 2007)*

PLOS ONE

RESEARCH ARTICLE

Longitudinal Metabolomic Profiling of Amino Acids and Lipids across Healthy Pregnancy

Karen L. Lindsay[1], Christian Hellmuth[2]*, Olaf Uhl[2], Claudia Buss[1,3], Pathik D. Wadhwa[1], Berthold Koletzko[2], Sonja Entringer[1,3]

- Several AA decrease with advancing gestation, including branched chain amino acids (BCAA) leucine & valine
- May represent fetal uptake and/or use as gluconeogenic or ketogenic substrates in fasted state

International Journal of Obesity (2016), 1–11

www.nature.com/ijo

ORIGINAL ARTICLE

Association of maternal prepregnancy BMI with metabolomic profile across gestation

C Hellmuth[1,5], KL Lindsay[2,5], O Uhl[1], C Buss[2,3], PD Wadhwa[2,4], B Koletzko[1] and S Entringer[2,3]

- Glutamic acid positively associated, asparagine negatively associated with BMI
- Similar associations observed in obese Hispanic children *(Butte et al., 2013)*
- Early pregnancy glutamic acid positively associated with birthweight centile

IL6 significantly associated with pBMI

IL-6 measurement	Total cohort N=214	Normal weight (BMI <25.0) N=112	Overweight (BMI 25.0-29.9) N=53	Obese (BMI >30.0) N=46	p-value[b]
Trimester 1	0.63 (0.68)	0.47 (0.50)	0.70 (0.54)	1.12 (0.74)	<0.001§
Trimester 2	0.67 (0.81)	0.53 (0.61)	0.74 (0.72)	1.13 (0.85)	<0.001§
Trimester 3	0.94 (0.80)	0.80 (0.67)	0.79 (0.88)	1.22 (0.93)	<0.001¥
p-value[a]	<0.001*	<0.001*	0.019**	0.053	

Natural increase in IL6 across gestation

Higher BMI attenuates natural gestational increase

Higher BMI women enter pregnancy with raised IL6

Metabolomic analysis of plasma AA in EMA study

Non-essential AA	Essential AA
Alanine	Methionine
Arginine	Phenylalanine
Asparagine	Threonine
Aspartic acid	Tryptophan
Citrulline	Isoleucine
Glutamine	Leucine
Glutamic acid	Valine
Glycine	
Ornithine	
Cysteine	
Serine	
Tyrosine	
Proline	

Branched chain AA

Association of BMI*IL6 interaction with AA metabolites

- Cross-sectional regression models within each trimester:
  - AA ~ IL-6*BMI + (IL-6 + BMI + age + ethnicity +OB risk score + smoking)
- No significant associations in T1 or T2
- BCAA positively associated in T3

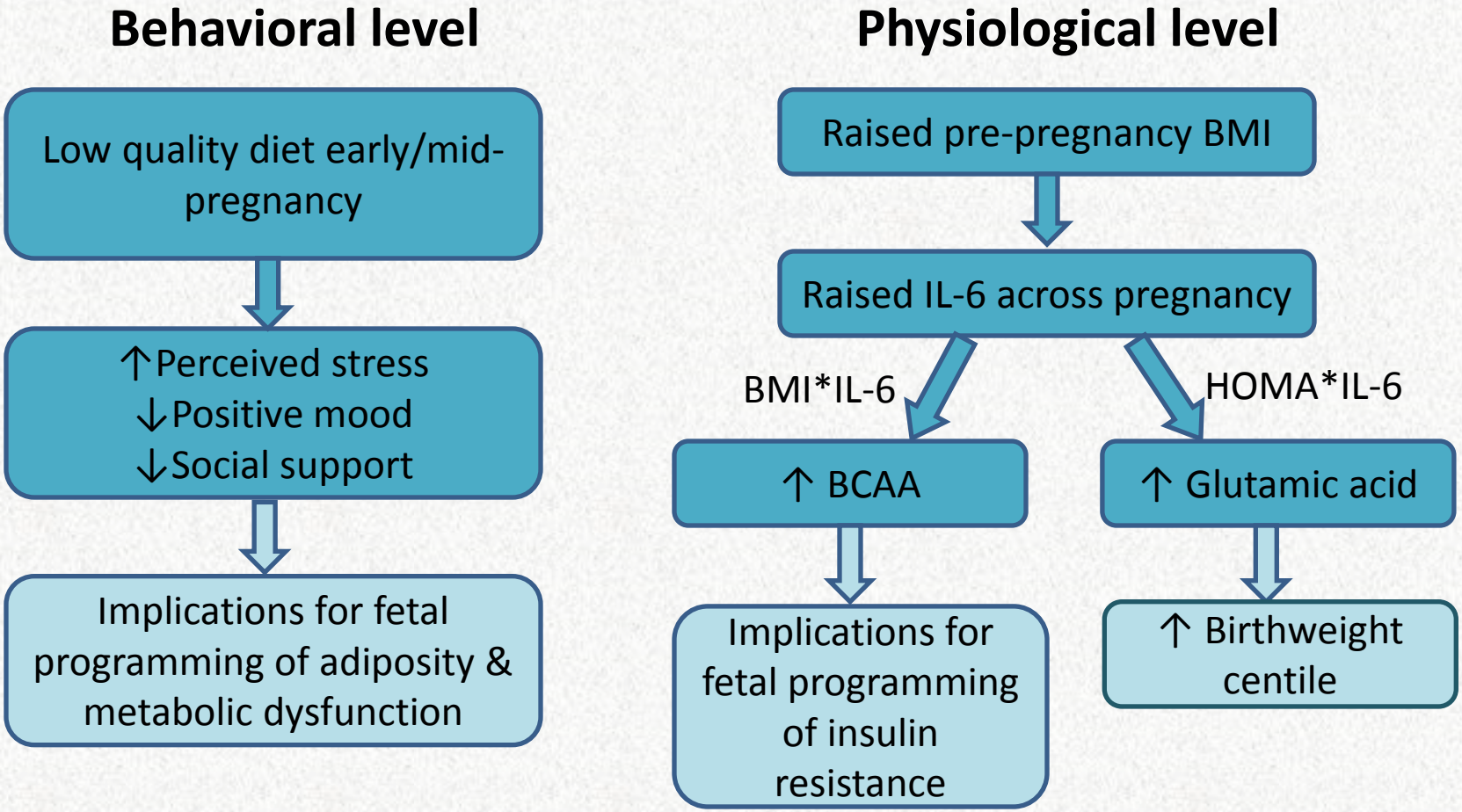
Trimester 3 AA	Beta	p-value	95% CI	
Isoleucine	0.026	**0.037**	0.002	0.051
Leucine	0.033	**0.005**	0.010	0.057
Valine	0.031	**0.012**	0.007	0.055
Asparagine	0.029	**0.006**	0.011	0.033
Aspartic acid	0.035	**0.001**	0.002	0.043

Insulin resistance and IL-6

- IL-6 across pregnancy +ve correlation with HOMA
  - trimester 1 (r=0.25, p=0.002)
  - trimester 2 (r=0.173, p=0.032)

- But HOMA*IL-6 interaction showed few associations with plasma AA
  - Glutamic acid positively associated in trimester 3 (B=0.093, p=0.038)
  - Not actively transported across placenta
  - Positive association with birthweight centile - fetal programming pathway for obesity?

Summary


Behavioral level
Low quality diet early/mid-pregnancy
↑Perceived stress
↓Positive mood
↓Social support
Implications for fetal programming of adiposity & metabolic dysfunction
Physiological level
Raised pre-pregnancy BMI
Raised IL-6 across pregnancy
BMI*IL-6
HOMA*IL-6
↑ BCAA
↑ Glutamic acid
Implications for fetal programming of insulin resistance
↑ Birthweight centile

Future Directions

- Long term impact of biological and psychosocial stress on offspring adiposity and metabolic function
- Moderating/mediating effects of prenatal diet on the fetal programming effects of maternal stress
- Specific nutritional components associated with biological and psychosocial stress

Thank you

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