Maternal adipo-enteric-pancreatic-brain crosstalk in pregnancy and fetal growth

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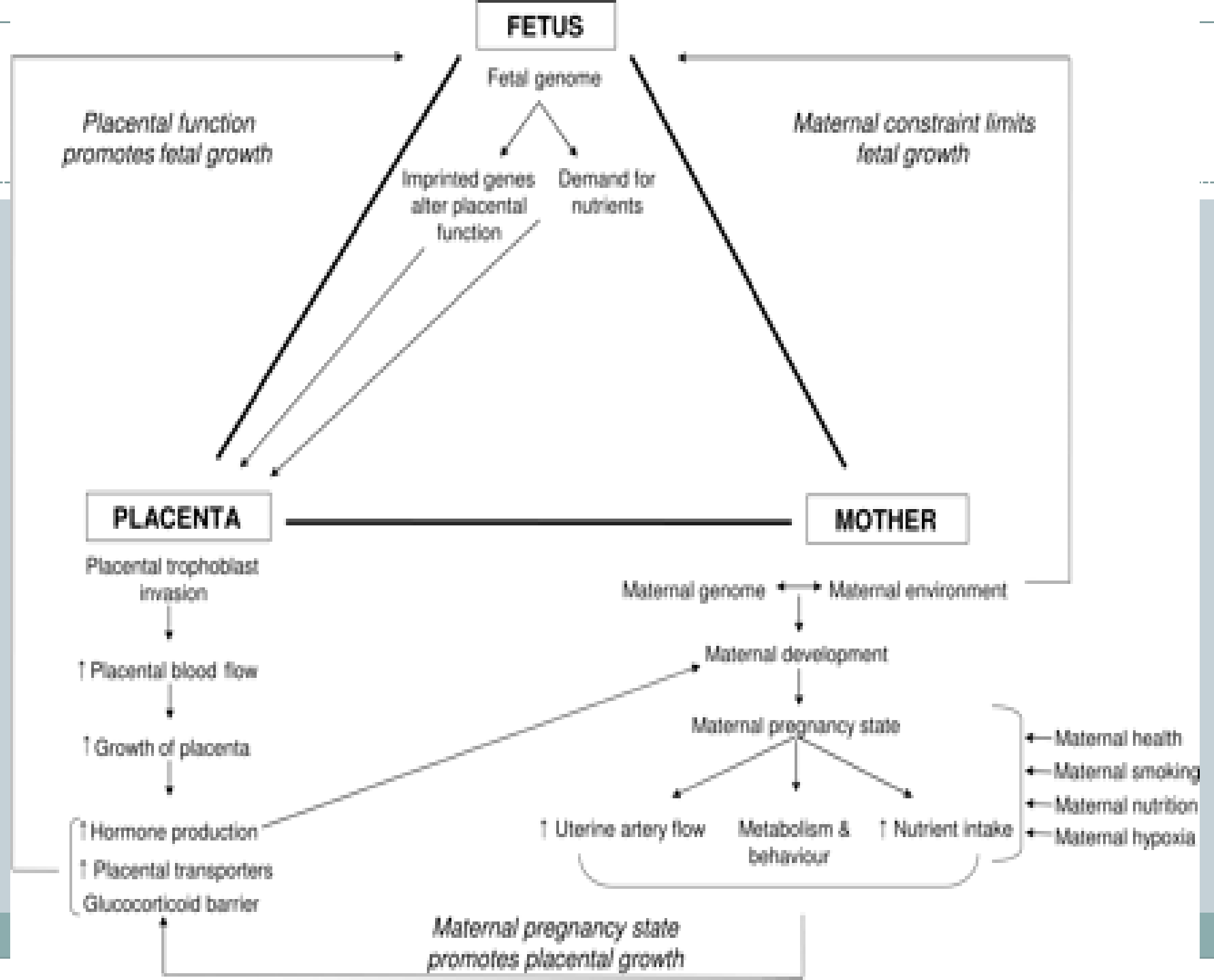
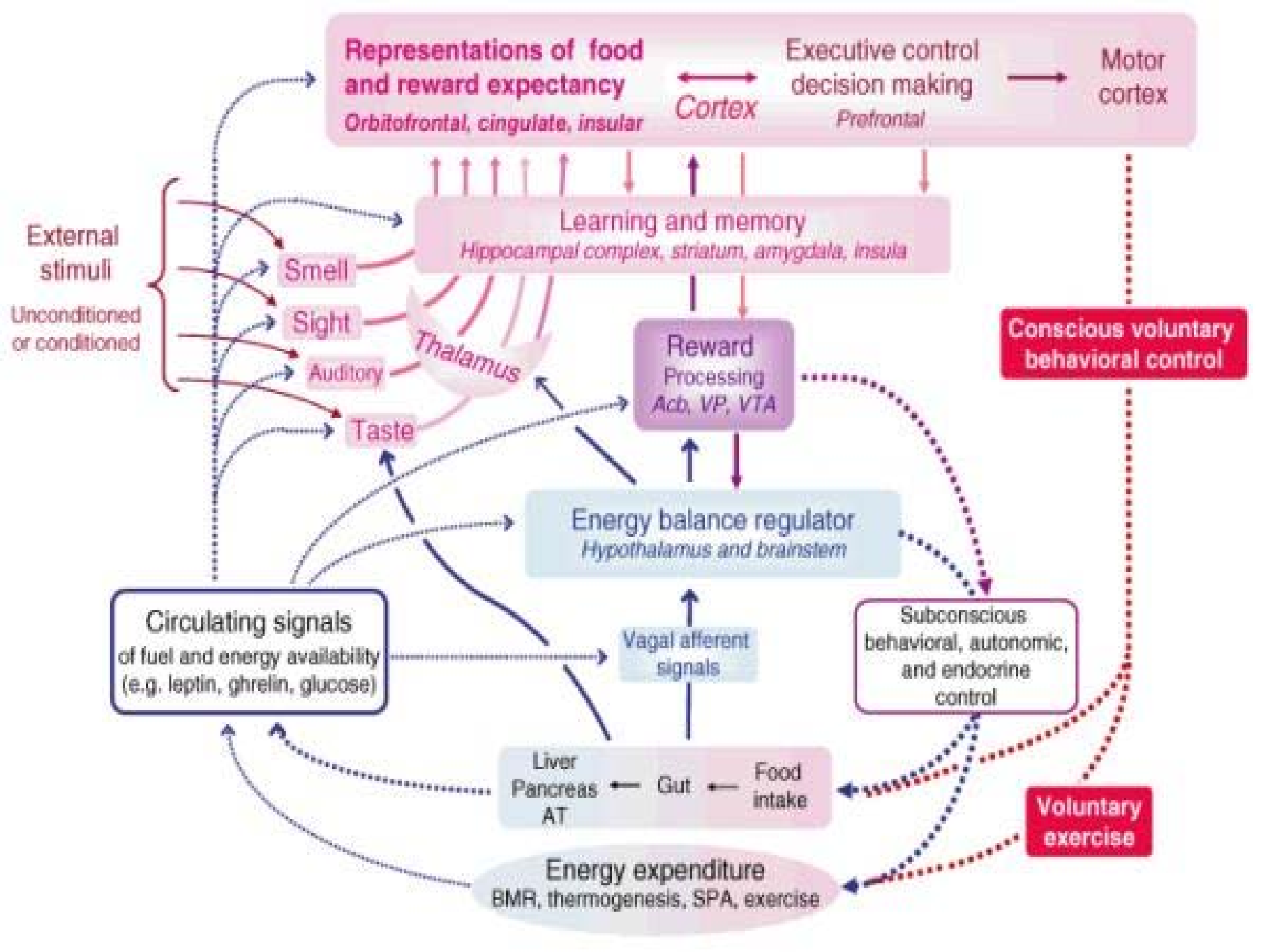
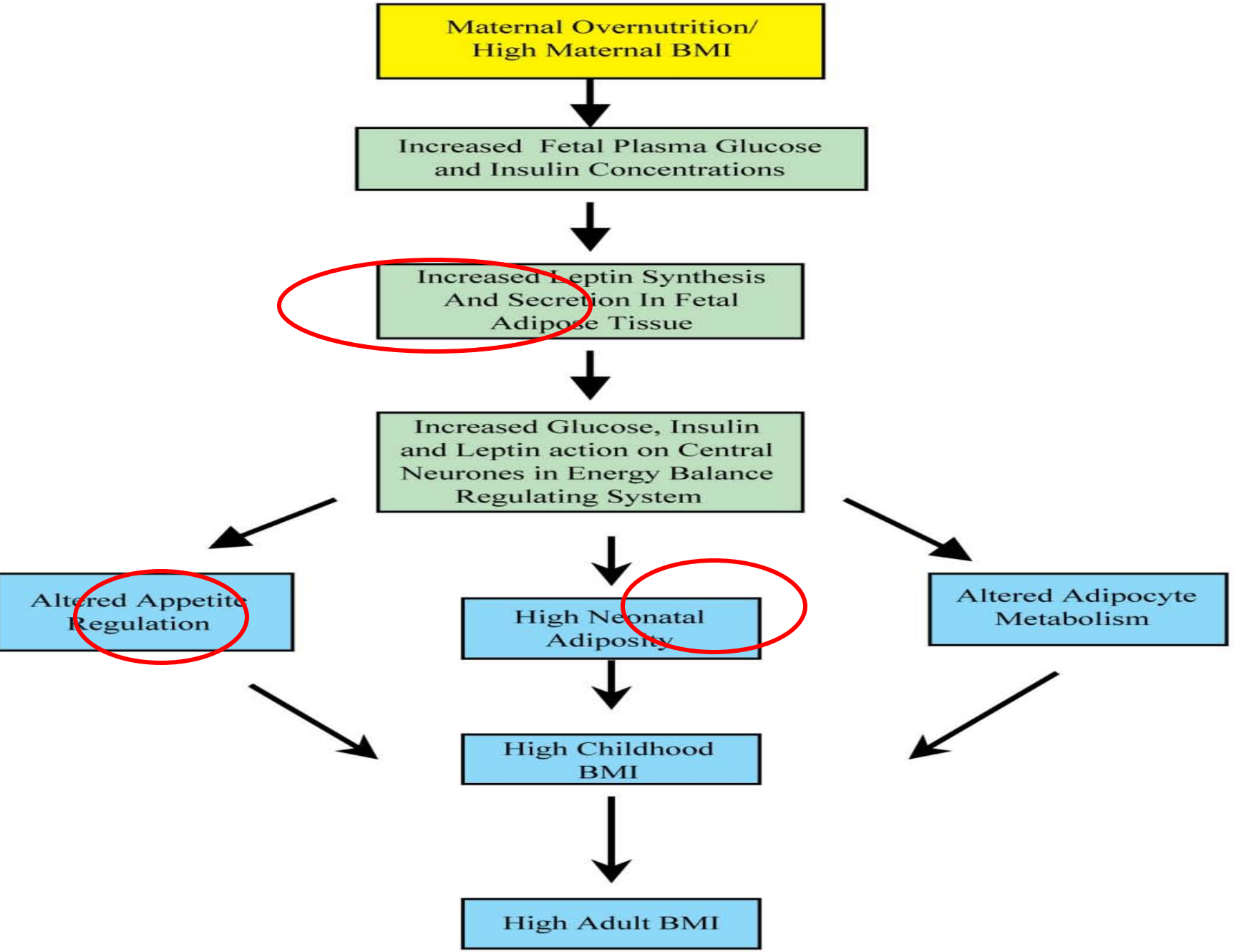
- **Endometrial environment in pregnancy**
- **Insulin resistance in pregnancy**
  - **Role of maternal obesity**
  - **Role of glucose**
  - **Role of the Adipo-Enteric-Insular axis**
- **Fetal anthropometry parameters**
- **Gut hormones in pregnancy**
  - **GLP-1, Ghrelin**
- **Insular hormones in pregnancy**
  - **Insulin, Glucagon, Amylin**
- Perspectives-Conclusions

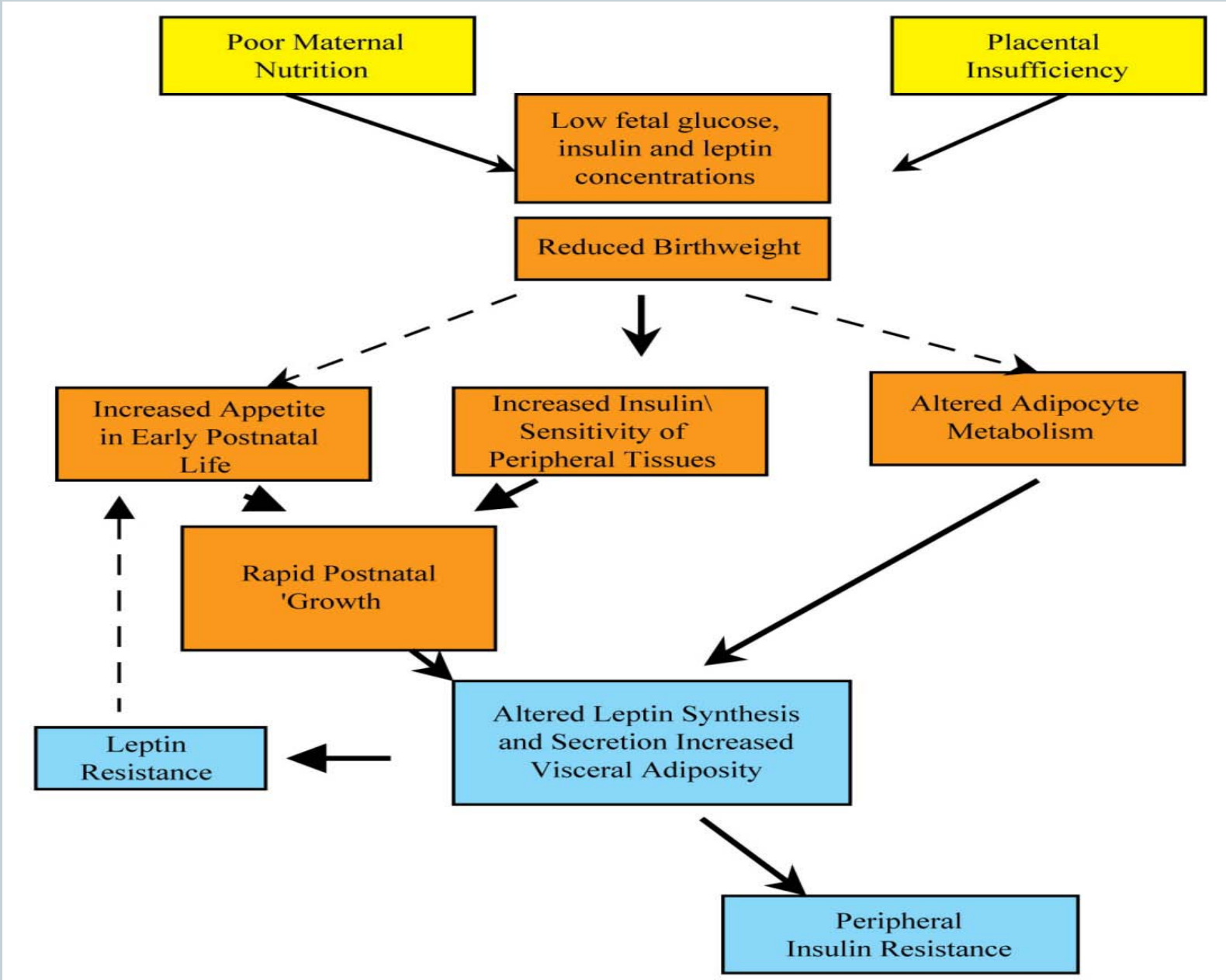

FETUS
Fetal genome
Placental function promotes fetal growth
Maternal constraint limits fetal growth
Imprinted genes alter placental function
Demand for nutrients
PLACENTA
MOTHER
Placental trophoblast invasion
↑ Placental blood flow
↑ Growth of placenta
↑ Hormone production
↑ Placental transporters
Glucocorticoid barrier
Maternal genome
Maternal environment
Maternal development
Maternal pregnancy state
↑ Uterine artery flow
Metabolism & behaviour
↑ Nutrient intake
Maternal health
Maternal smoking
Maternal nutrition
Maternal hypoxia
Maternal pregnancy state promotes placental growth

Factors affecting the endometrial environment

1. Changes in maternal metabolism,
2. dietary habits,
3. anthropometrics,
4. psychological behavioral and personality factors.
5. Placental growth and function.
6. External enviromental factors.
7. The interaction of the triad: mother-placenta-fetus

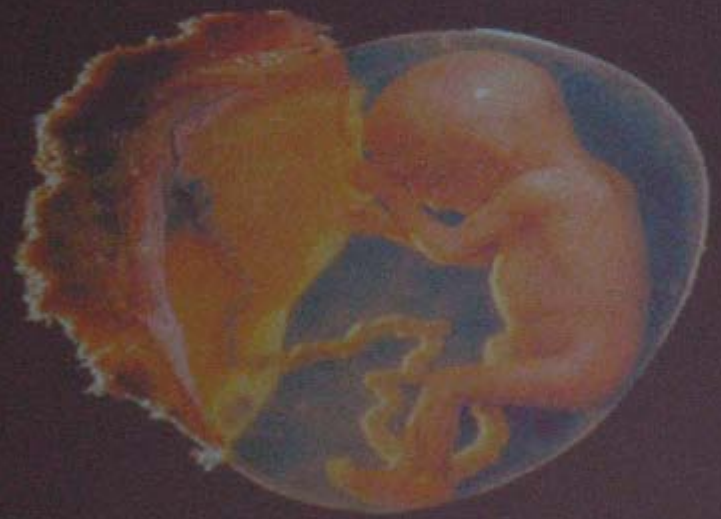

Representations of food and reward expectancy
Orbitofrontal, cingulate, insular
Cortex
Executive control decision making
Prefrontal
Motor cortex
External stimuli
Unconditioned or conditioned
Smell
Sight
Auditory
Taste
Thalamus
Learning and memory
Hippocampal complex, striatum, amygdala, insula
Reward Processing
Acb, VP, VTA
Conscious voluntary behavioral control
Energy balance regulator
Hypothalamus and brainstem
Circulating signals
of fuel and energy availability
(e.g. leptin, ghrelin, glucose)
Vagal afferent signals
Subconscious behavioral, autonomic, and endocrine control
Liver
Pancreas
AT
Gut
Food intake
Voluntary exercise
Energy expenditure
BMR, thermogenesis, SPA, exercise


Maternal Overnutrition/
High Maternal BMI
Increased Fetal Plasma Glucose
and Insulin Concentrations
Increased Leptin Synthesis
And Secretion In Fetal
Adipose Tissue
Increased Glucose, Insulin
and Leptin action on Central
Neurones in Energy Balance
Regulating System
Altered Appetite
Regulation
High Neonatal
Adiposity
Altered Adipocyte
Metabolism
High Childhood
BMI
High Adult BMI


Poor Maternal Nutrition
Placental Insufficiency
Low fetal glucose, insulin and leptin concentrations
Reduced Birthweight
Increased Appetite in Early Postnatal Life
Increased Insulin\ Sensitivity of Peripheral Tissues
Altered Adipocyte Metabolism
Rapid Postnatal 'Growth
Altered Leptin Synthesis and Secretion Increased Visceral Adiposity
Leptin Resistance
Peripheral Insulin Resistance

Fetal Programming

Process whereby a stimulus applied *in utero* establishes a permanent response in the fetus leading to enhanced susceptibility to later disease.



Lucas A. Arch.Dis.Chilhood 19

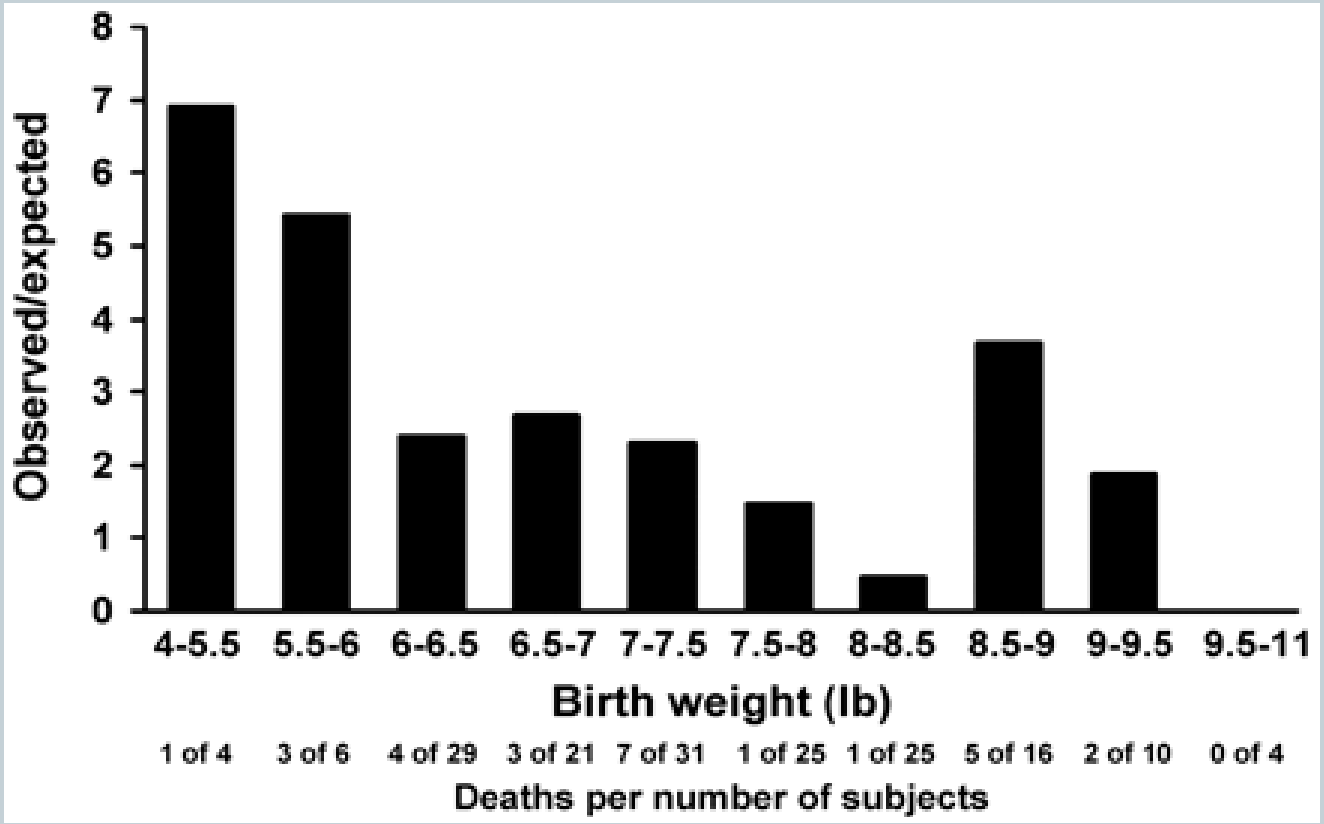
Fetal metabolic adaptations… so far

Hyperinsulinaemia

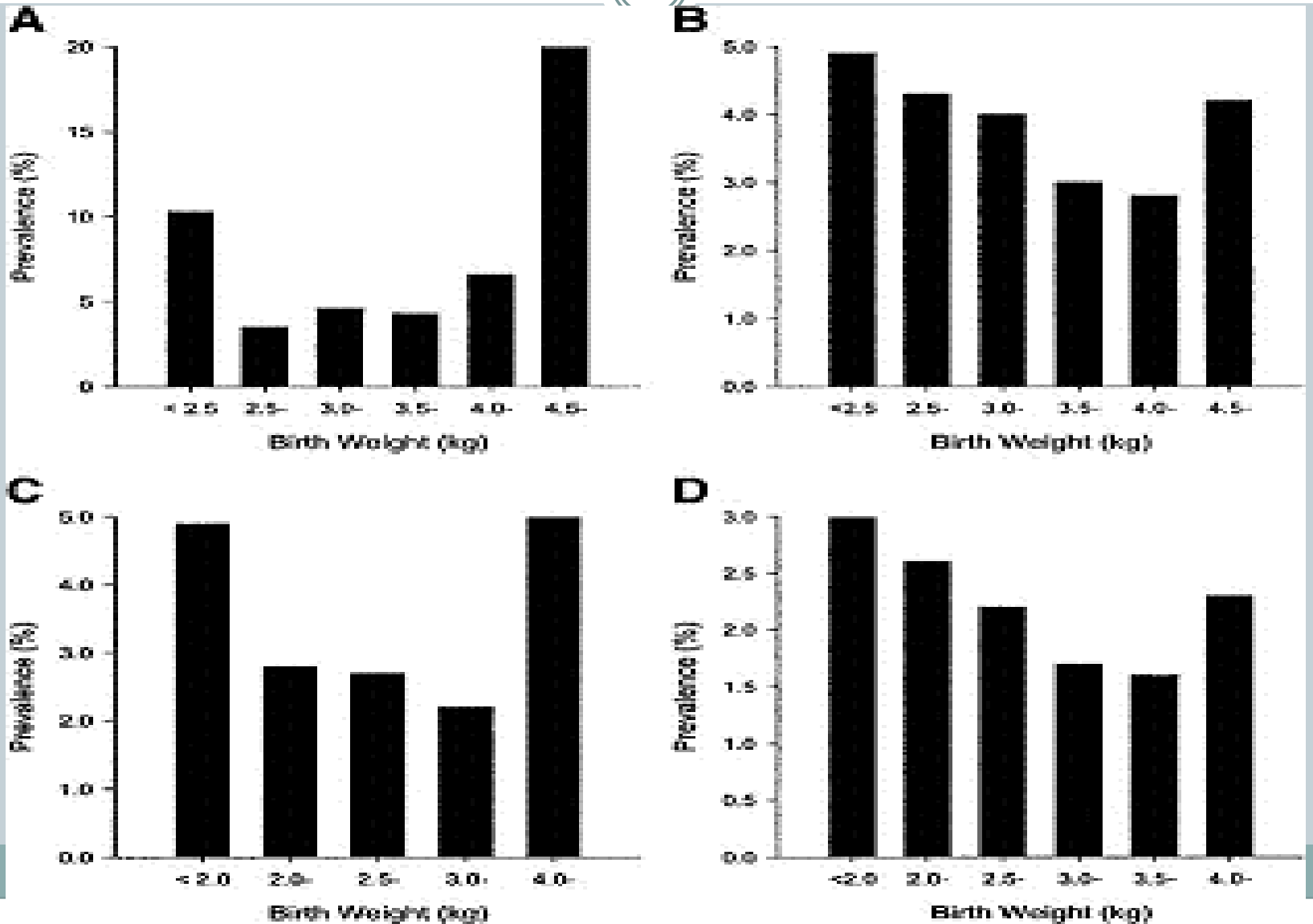
Hyperleptinaemia

Hypercortisolism

Birth weight and overall postpartum mortality



Birth weight and GDM prevalence



Neonatal abdominal circumference

a measure of liver volume and adiposity

reflects the adipose-energy deposits of the neonate

a vital index for the beginning of the neonatal life and predictive of its future growth and metabolic health

Fetal outcomes and maternal pre-pregnancy weight (BMI)

- Large for gestational age
- Birth weight >4000gr
- Neonatal hypoglycemia
- Respiratory distress syndrome
- Jaundice
- Perinatal mortality
- Congenital malformations

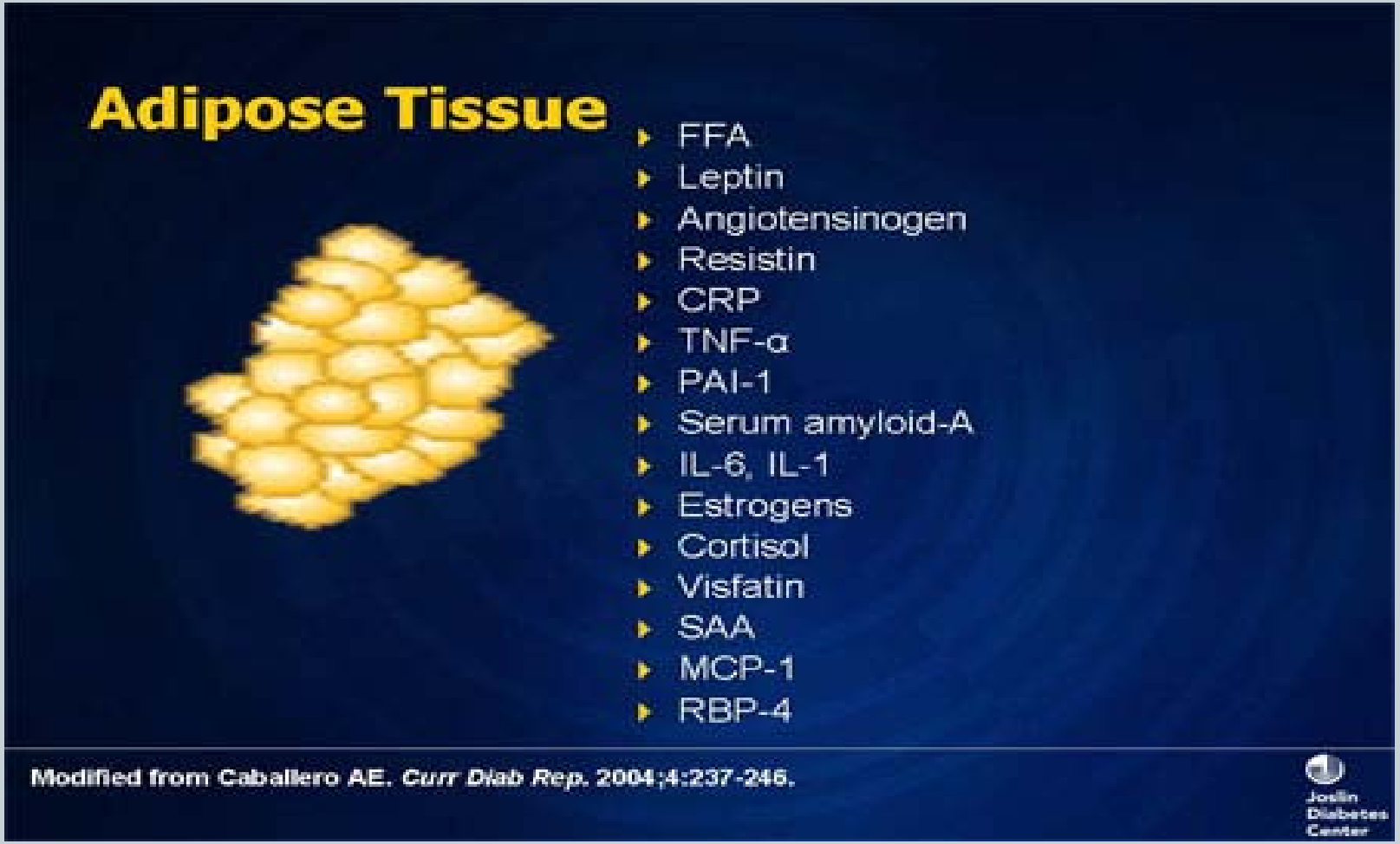
Pregravid maternal BMI and neonatal body composition (Sewell et al.)

Pregravid BMI	BMI>25	BMI<25	P-value
Birth weight (gr)	3436 ± 567	3284 ± 534	0.051
LBM (gr)	3023 ± 410	2951 ± 406	0.22
Fat mass (gr)	416 ± 221	334 ±179	0.008
Body fat (%)	11.6 ± 4.7	9.7 ± 4.3	0.006
Maternal weight gain	6.3 ± 3.4	6.9 ± 2.4	0.001

Prevalence of obesity (BMI>95% age and gender) in offspring of obese women

Prevalence of obesity	age
9.5%	2
12.5%	3
14.8% (Whitaker et al. Pediatrics)	4

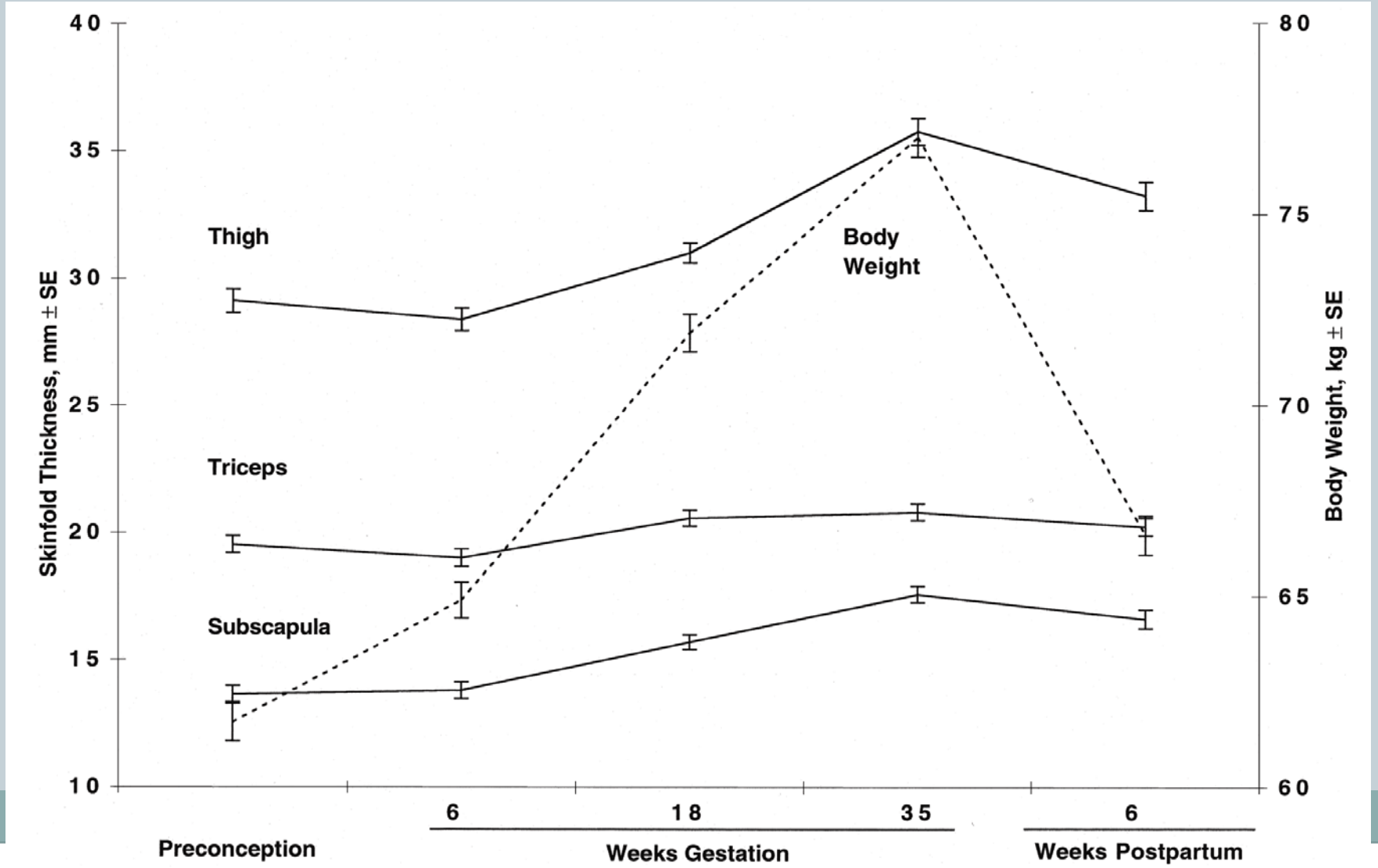
Adipose tissue as an endocrine organ



Adipocytokines in pregnancy

	Adipocyte	SVF	Placenta
TNF-α	+	+ + +	+
IL-6	+	+	+
IL-1b		+ +	
IL-8	+	+ +	+
IL-1Ra	+	+ +	+
IL-10	+	+ +	+
Leptin	+ +	0	+
Adiponectin	+ +	0	–
Resistin	0	+ +	+
MCP-1	+	+ +	+
MIF	+ +	+	+
VEGF	+	+ +	+
PAI-1	+	+ +	+
Cathepsin S	+	+ +	+

Adipose tissue deposition during pregnancy



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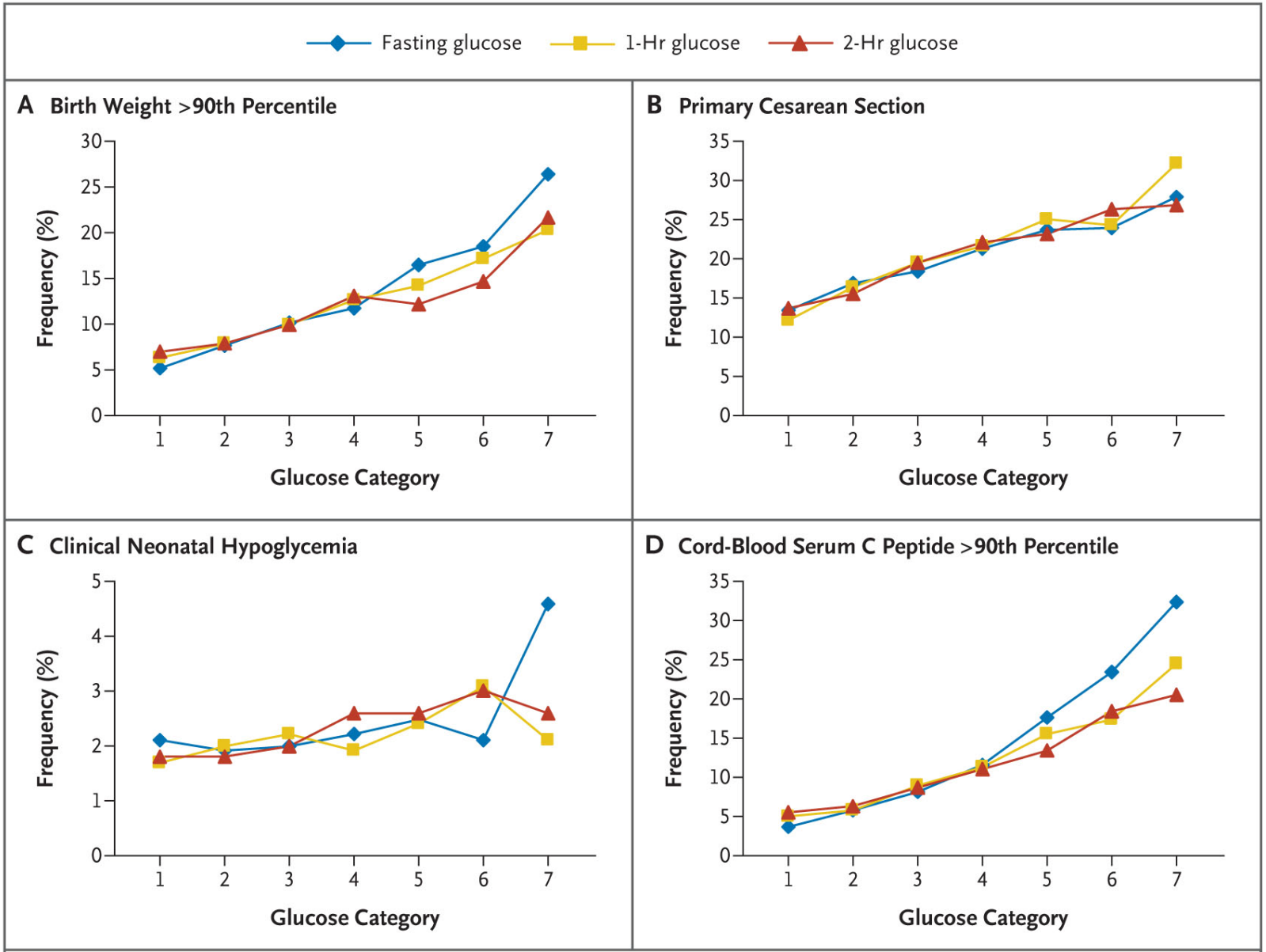
Hyperglycemia and Adverse Pregnancy Outcomes

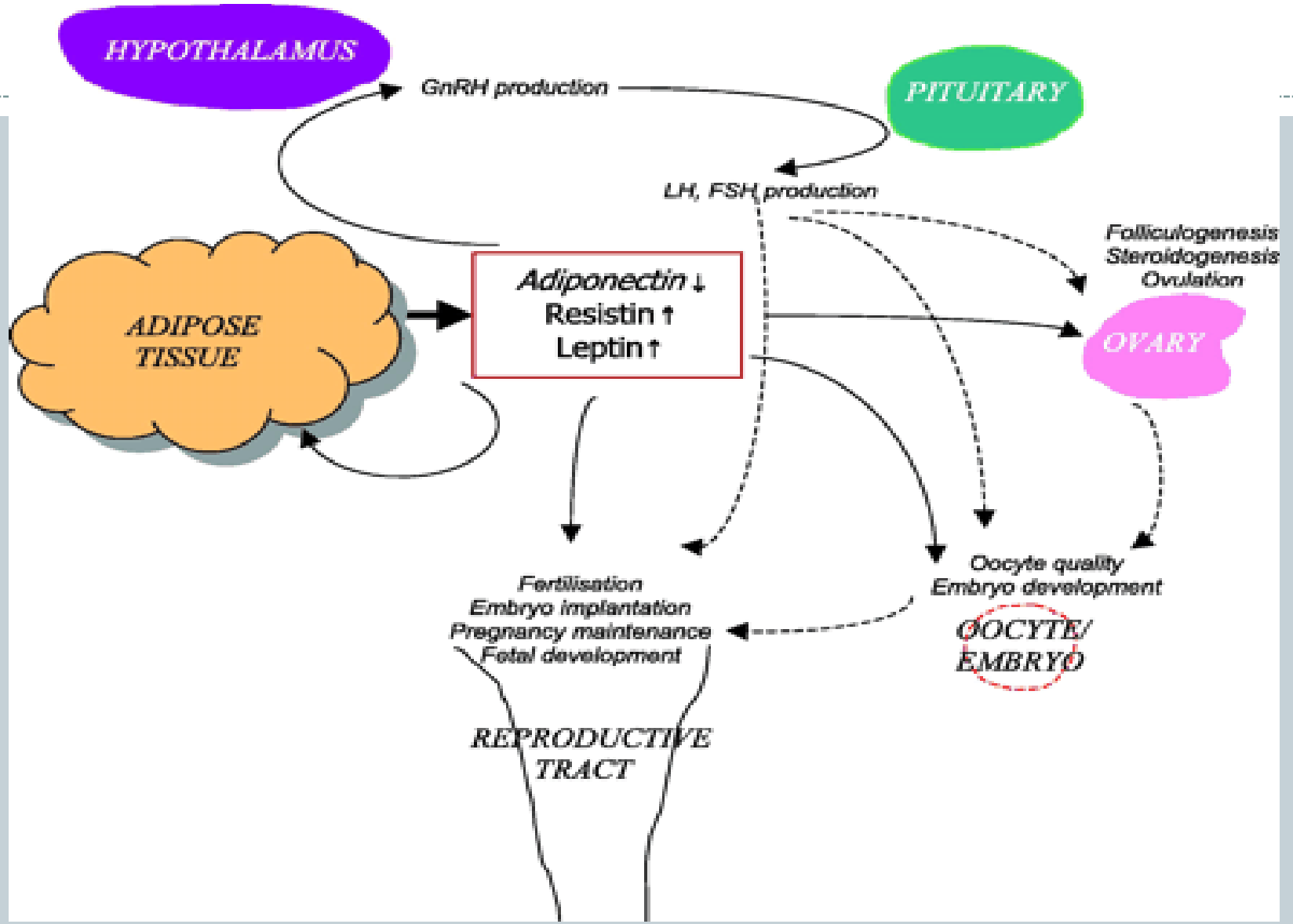
The HAPO Study Cooperative Research Group*

CONCLUSIONS

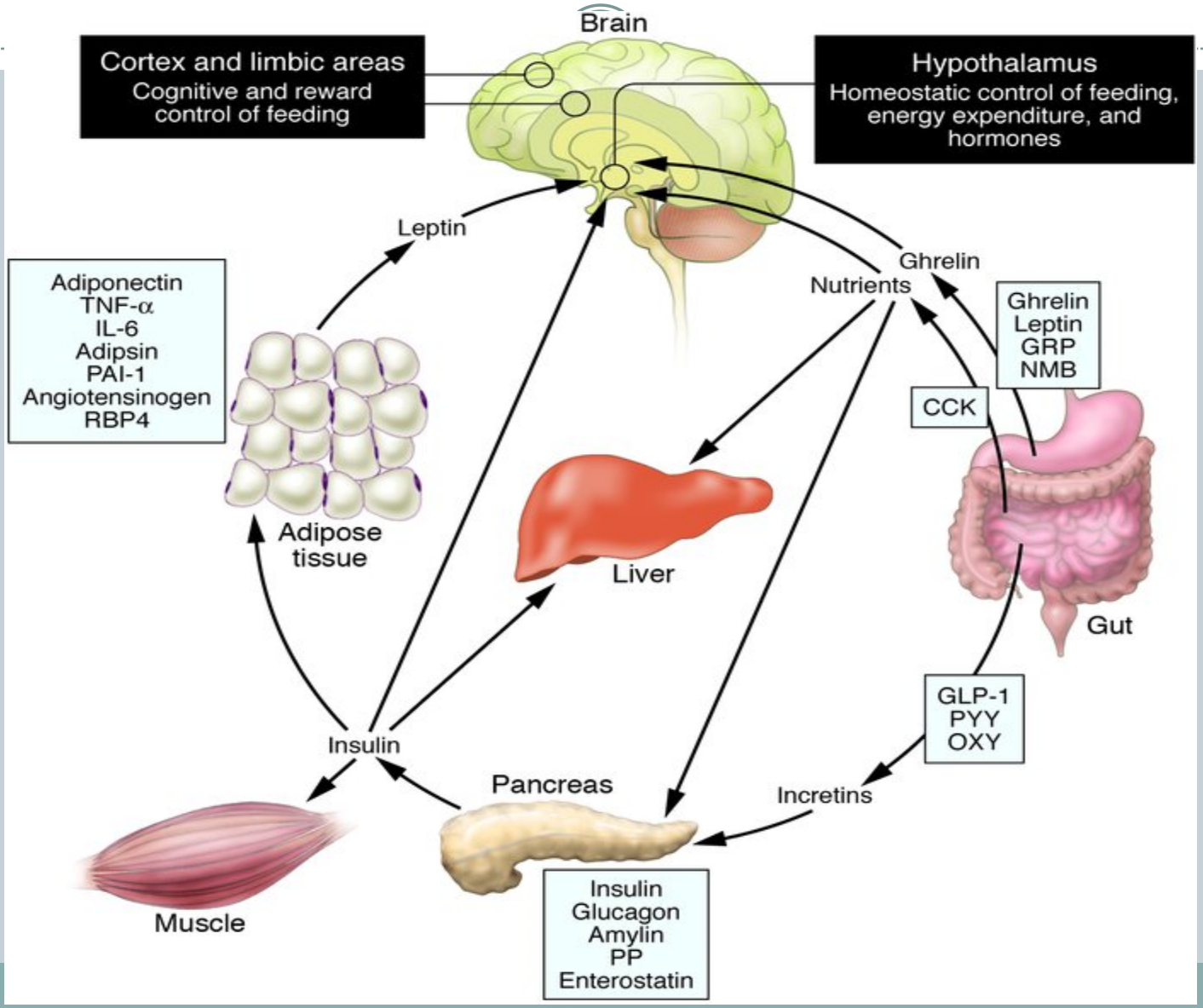
Our results indicate strong, continuous associations of maternal glucose levels below those diagnostic of diabetes with increased birth weight and increased cord-blood serum C-peptide levels.

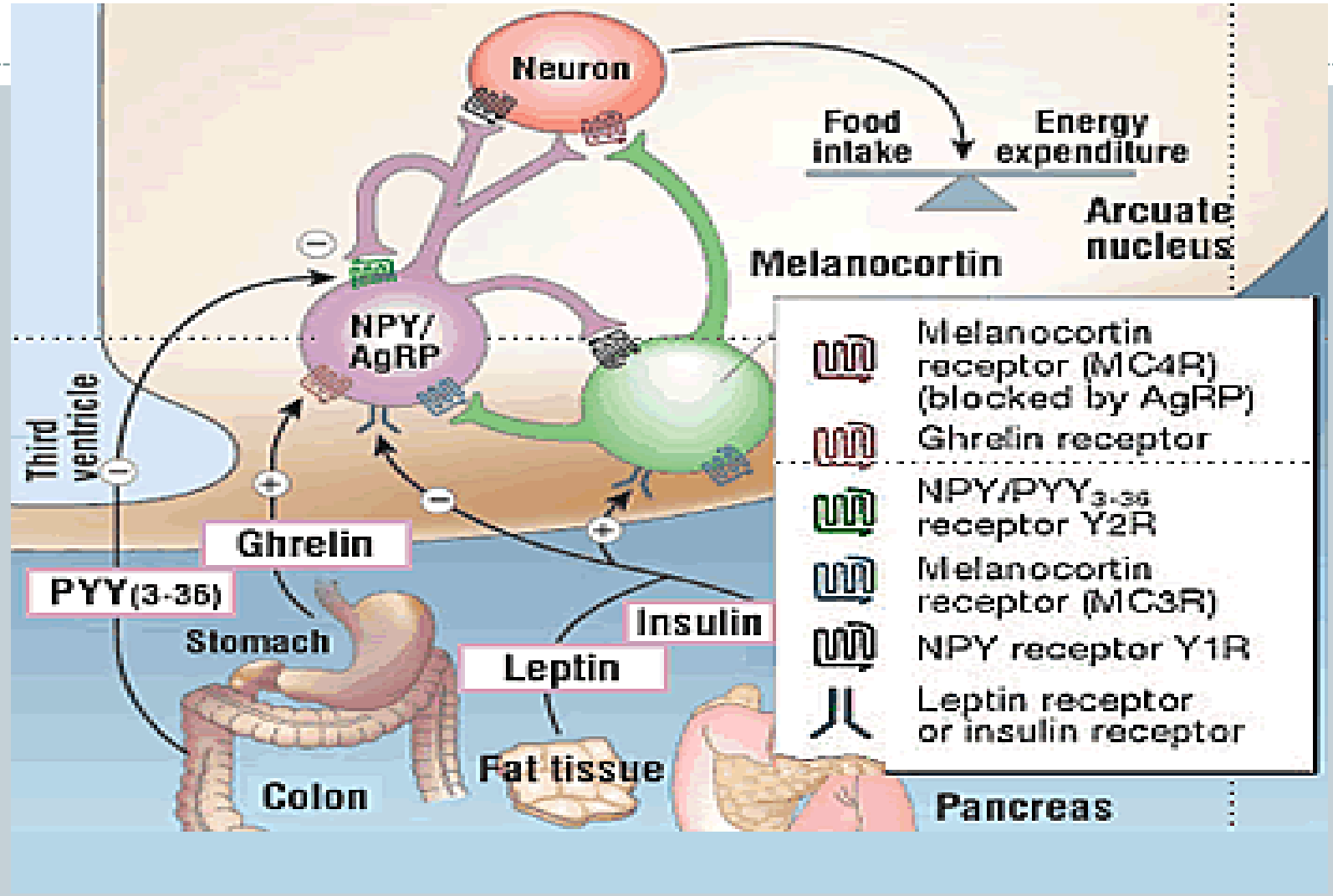
HAPO study

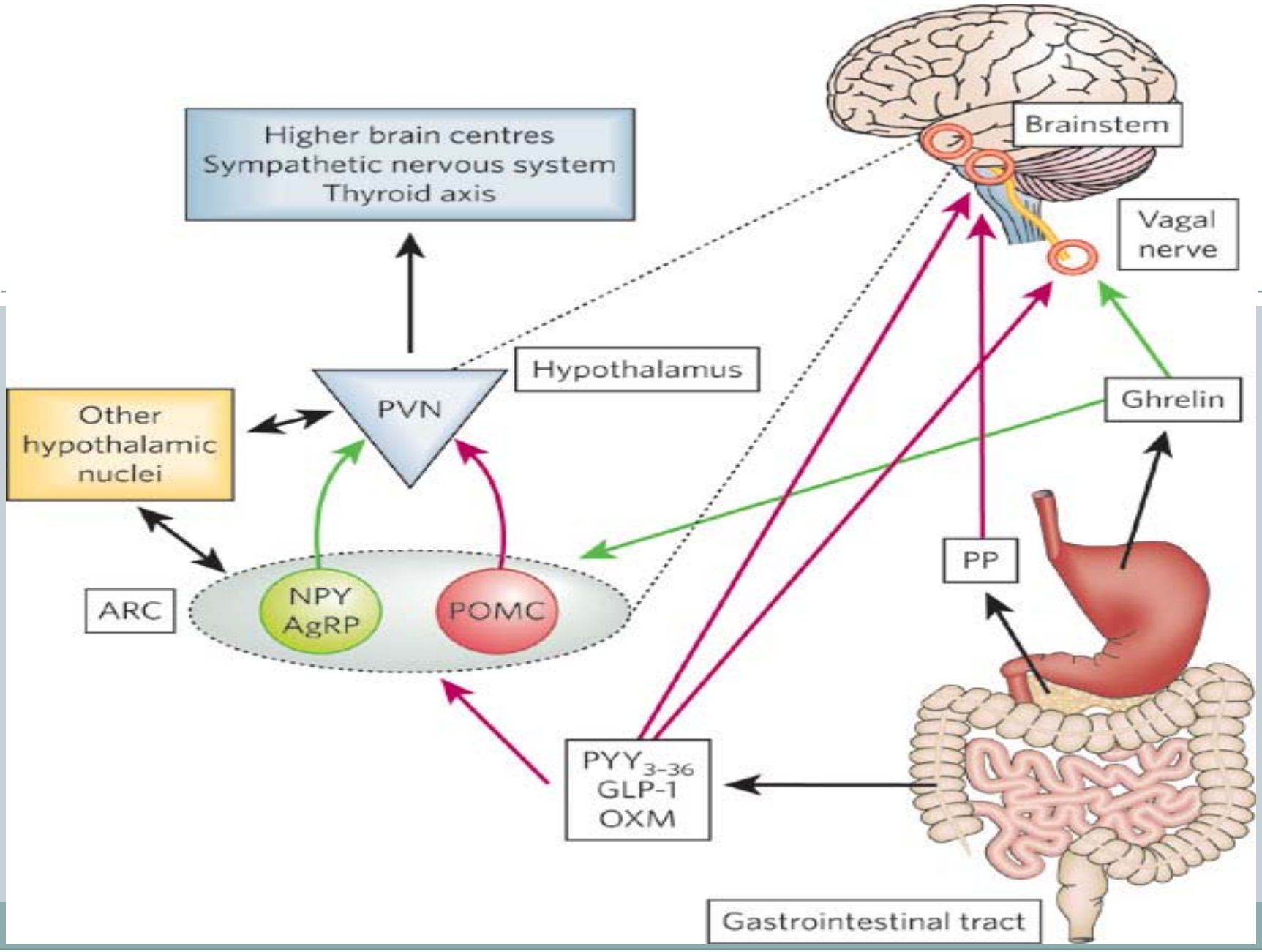

Fasting glucose
1-Hr glucose
2-Hr glucose
A Birth Weight >90th Percentile
Frequency (%)
Glucose Category
B Primary Cesarean Section
Frequency (%)
Glucose Category
C Clinical Neonatal Hypoglycemia
Frequency (%)
Glucose Category
D Cord-Blood Serum C Peptide >90th Percentile
Frequency (%)
Glucose Category


HYPOTHALAMUS
GnRH production
PITUITARY
LH, FSH production
Folliculogenesis
Steroidogenesis
Ovulation
ADIPOSE TISSUE
Adiponectin ↓
Resistin ↑
Leptin ↑
OVARY
Oocyte quality
Embryo development
Fertilisation
Embryo implantation
Pregnancy maintenance
Fetal development
OOCYTE/ EMBRYO
REPRODUCTIVE TRACT

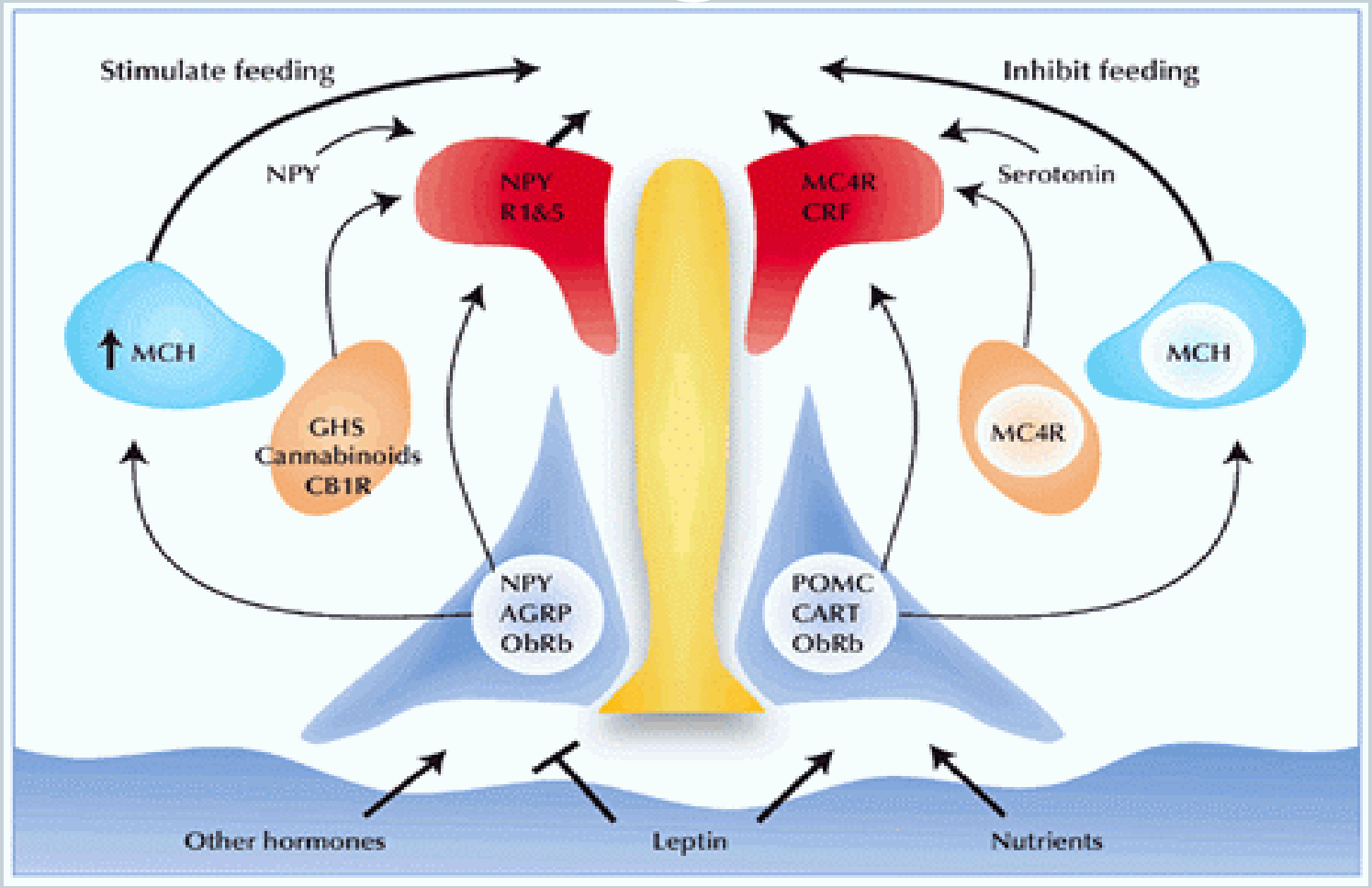
Adipose-**enteric**-insular-brain crosstalk

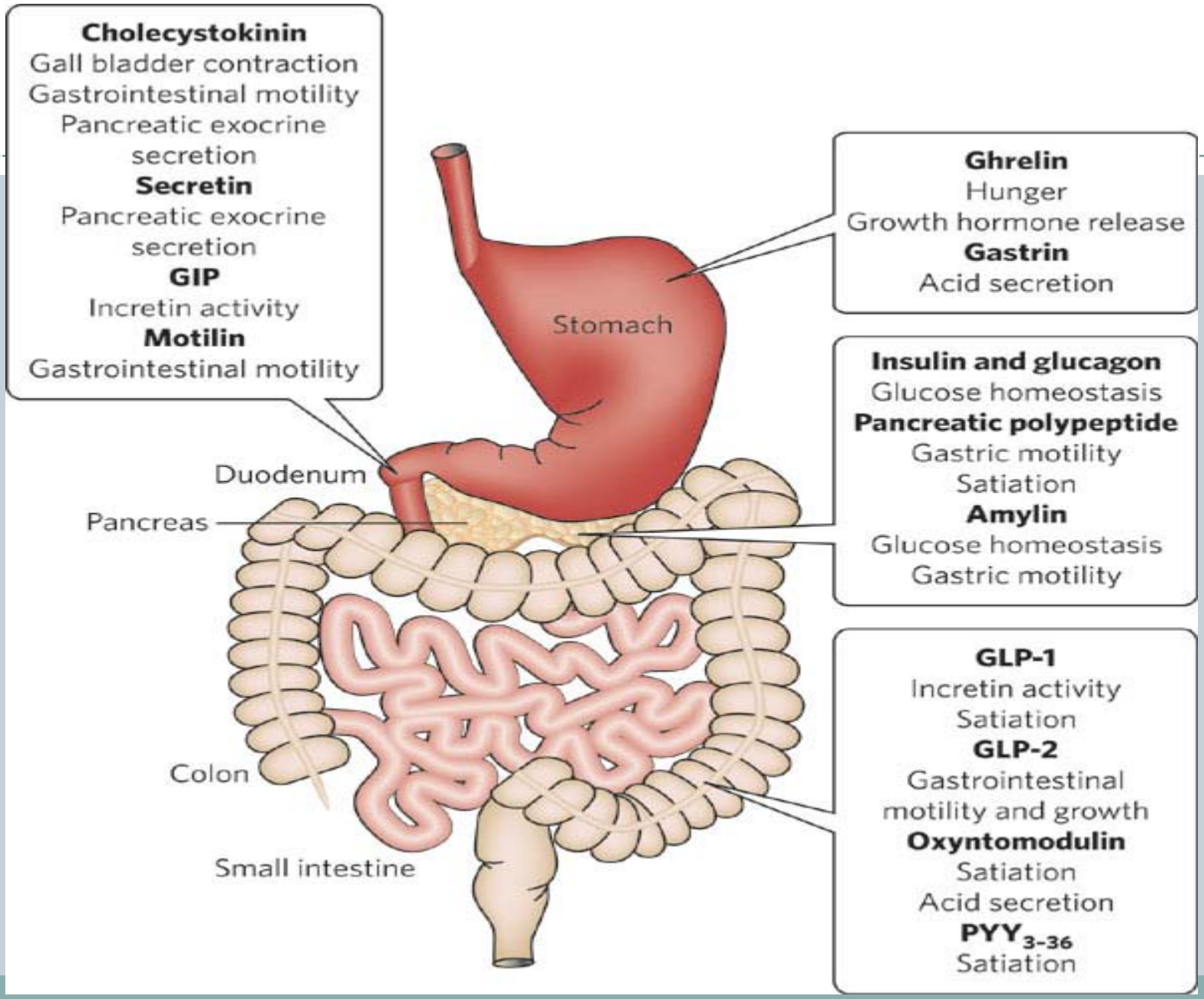



Neuron
Food intake
Energy expenditure
Arcuate nucleus
Melanocortin
NPY/ AgRP
Third ventricle
Ghrelin
PYY(3-36)
Stomach
Insulin
Leptin
Fat tissue
Colon
Pancreas
Melanocortin receptor (MC4R) (blocked by AgRP)
Ghrelin receptor
NPY/PYY3-36 receptor Y2R
Melanocortin receptor (MC3R)
NPY receptor Y1R
Leptin receptor or insulin receptor


Higher brain centres
Sympathetic nervous system
Thyroid axis
Brainstem
Vagal nerve
Hypothalamus
PVN
Other hypothalamic nuclei
Ghrelin
ARC
NPY
AgRP
POMC
PP
PYY3–36
GLP-1
OXM
Gastrointestinal tract

Πυρήνες-ανώτερα κέντρα και ενεργειακή ισορροπία




Cholecystokinin
Gall bladder contraction
Gastrointestinal motility
Pancreatic exocrine secretion
Secretin
Pancreatic exocrine secretion
GIP
Incretin activity
Motilin
Gastrointestinal motility
Stomach
Duodenum
Pancreas
Colon
Small intestine
Ghrelin
Hunger
Growth hormone release
Gastrin
Acid secretion
Insulin and glucagon
Glucose homeostasis
Pancreatic polypeptide
Gastric motility
Satiation
Amylin
Glucose homeostasis
Gastric motility
GLP-1
Incretin activity
Satiation
GLP-2
Gastrointestinal motility and growth
Oxyntomodulin
Satiation
Acid secretion
PYY_{3-36}
Satiation

Aim of our study

is the detection of connections between markers of maternal and fetal metabolism during pregnancy with the subsequent growth and metabolism during neonatal and childhood life.

methodology

1)Maternal anthropometrics-haemodynamics

- weight, height, BMI, waist, hip, skinfolds, BP, pulses

2)OGTT 75 gr

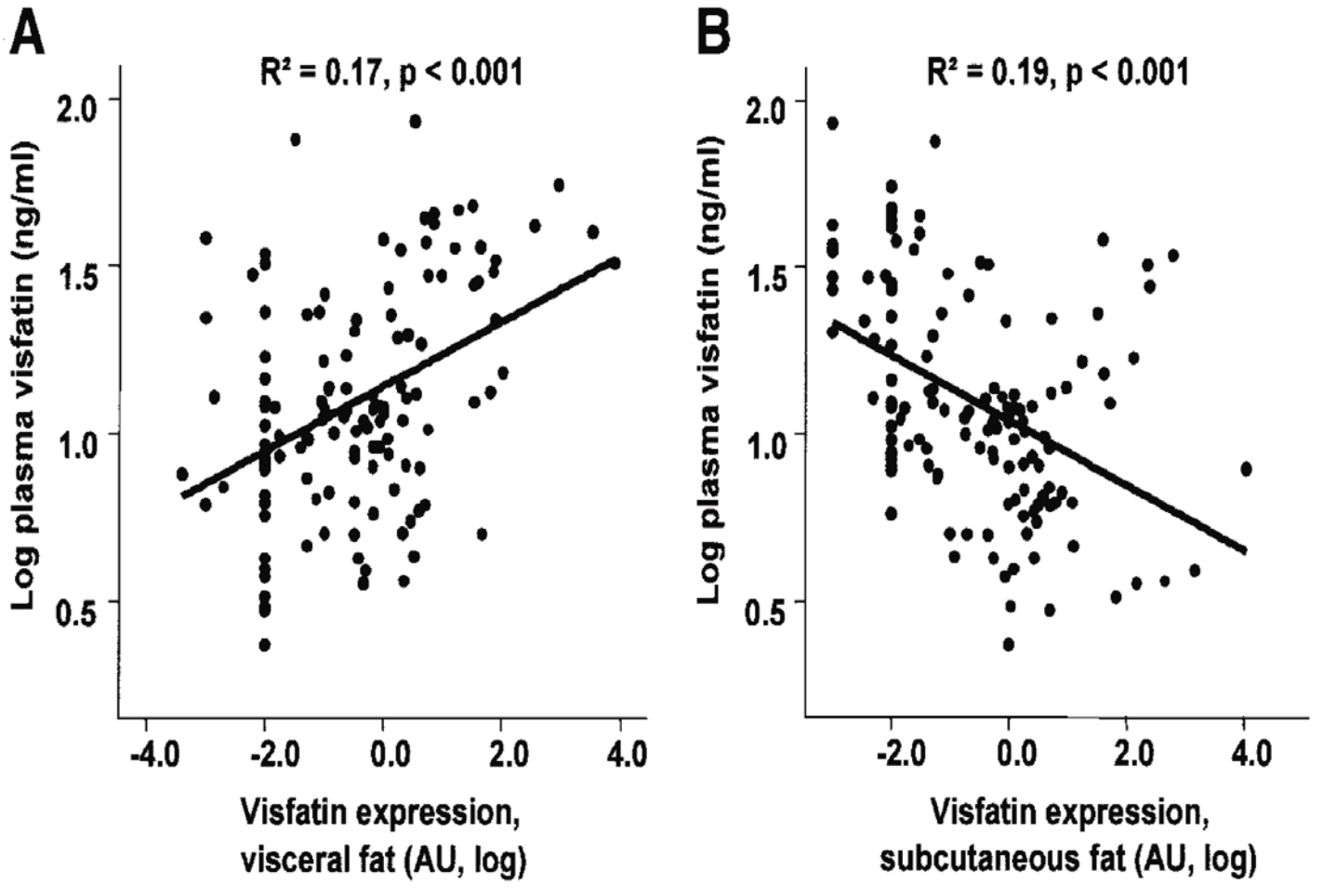
- collection insulin, glucose at 0, 5, 15, 30, 60, 90, 120 min
- peptides-hormones at 0, 30, 60, 120 min

3) Fetal ultrasound

4) Cord blood peptides

4) Birth weight and waist

visfatin


A
R² = 0.17, p < 0.001
Log plasma visfatin (ng/ml)
2.0
1.5
1.0
0.5
-4.0
-2.0
0.0
2.0
4.0
Visfatin expression,
visceral fat (AU, log)
B
R² = 0.19, p < 0.001
Log plasma visfatin (ng/ml)
2.0
1.5
1.0
0.5
-2.0
0.0
2.0
4.0
Visfatin expression,
subcutaneous fat (AU, log)

Adipocytokines and insulin sensitivity

Table 3. Statistically significant correlations among carbohydrate metabolism variables and adipocytokines.[a]

1st trimester								
Variable 1	1st PHIS	1st PHIS	2nd PHIS	2nd PHIS	ΔAUCI	ΔAUCI	ISI	ISI
Variable 2	Leptin	HsCRP	Leptin	hsCRP	Leptin	hsCRP	Leptin	hsCRP
r-Spearman	0.56	0.53	0.53	0.5	0.48	0.68	−0.54	−0.5
2nd trimester								
Variable 1		1st PHIS			2nd PHIS			ΔAUCI
Variable 2		Leptin			Leptin			Leptin
r-Spearman		0.43			0.45			0.48

[a] The r-Spearman correlation is significant at $P < 0.05$.

Table 5. Backwards multiple regression analysis for dependent variable ISI 2nd trimester.[a]

	Coefficient	SE of coefficient	*P* value
Visfatin 1st trimester	1.018	0.024	0.015
HsCRP 1st trimester	0.157	0.024	0.099

[a] The term "coefficient" is the generally used term for the effect of each predictor (independent variable) on the respective dependent variable in a linear regression analysis.

Mastorakos et al. Clin. Chemistry 2007

Maternal Serum Visfatin at 11–13 Weeks of Gestation in Gestational Diabetes Mellitus

Table 2. Median (IQR) of maternal serum concentration of adiponectin and visfatin in the outcome groups.

	Nondiabetic controls	GDM
n	300	100
Adiponectin		
μg/L	12 035 (8595–7 085)	7591 (4552–11 059)
MoM	1.02 (0.70–1.29)	0.66 (0.50–0.92)[a]
Visfatin		
μg/L	0.89 (0.47–1.71)	1.20 (0.63–2.55)
MoM	1.00 (0.53–1.92)	1.34 (0.70–2.87)[a]

[a] $P < 0.05$. Comparisons between groups by Mann–Whitney *U*-test.

Table 3. Performance of screening for GDM by maternal factors, maternal serum adiponectin MoM, visfatin MoM, and their combinations.

Screening test	AUROC[a] (95% CI)	Detection rate for false-positive rate of 10% (95% CI)
Maternal factors	0.828 (0.777–0.878)	58.0 (48.2–67.2)
Maternal factors plus		
Adiponectin	0.854 (0.807–0.900)	66.0 (56.3–74.5)
Visfatin	0.825 (0.774–0.876)	64.0 (54.2–72.7)
Adiponectin and visfatin	0.855 (0.808–0.901)	68.0 (58.3–76.3)

[a] AUROC, area under the ROC curve.

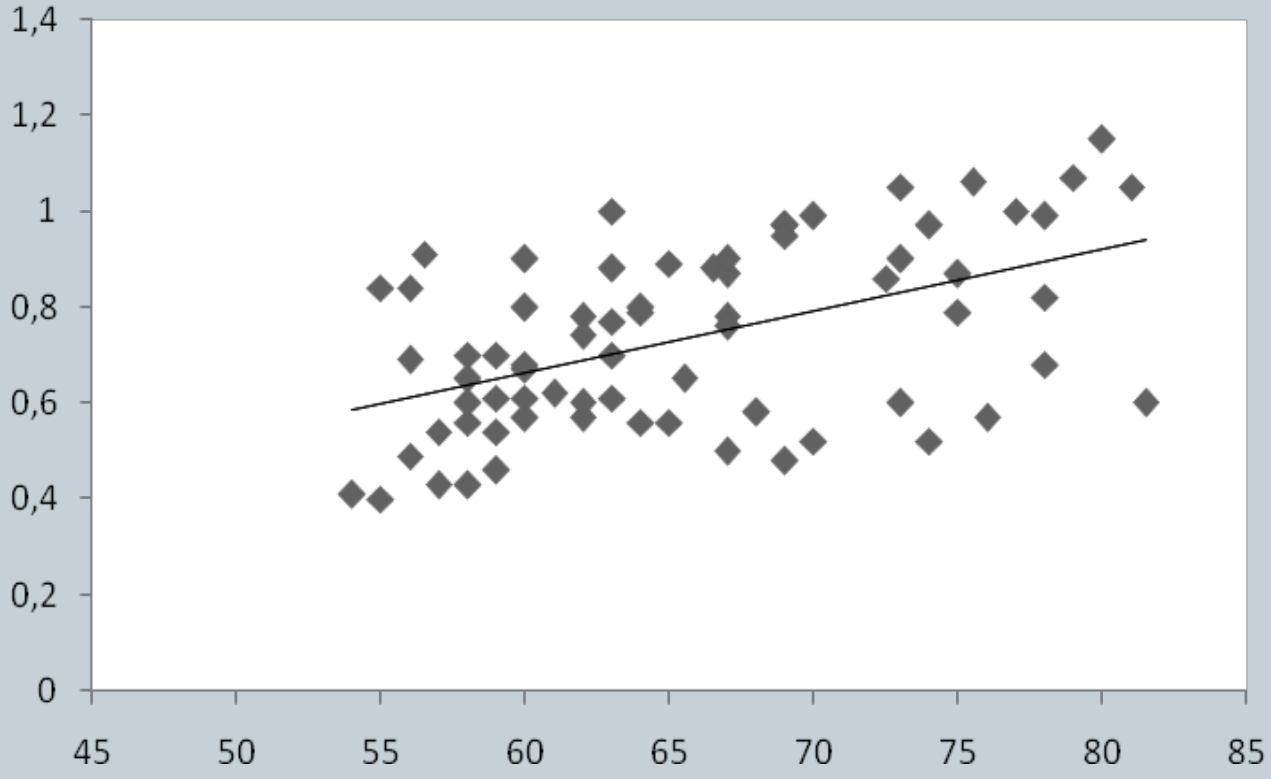
Ferreira AFA et al., Clinical Chemistry 2011

Associations of maternal adipocytokines

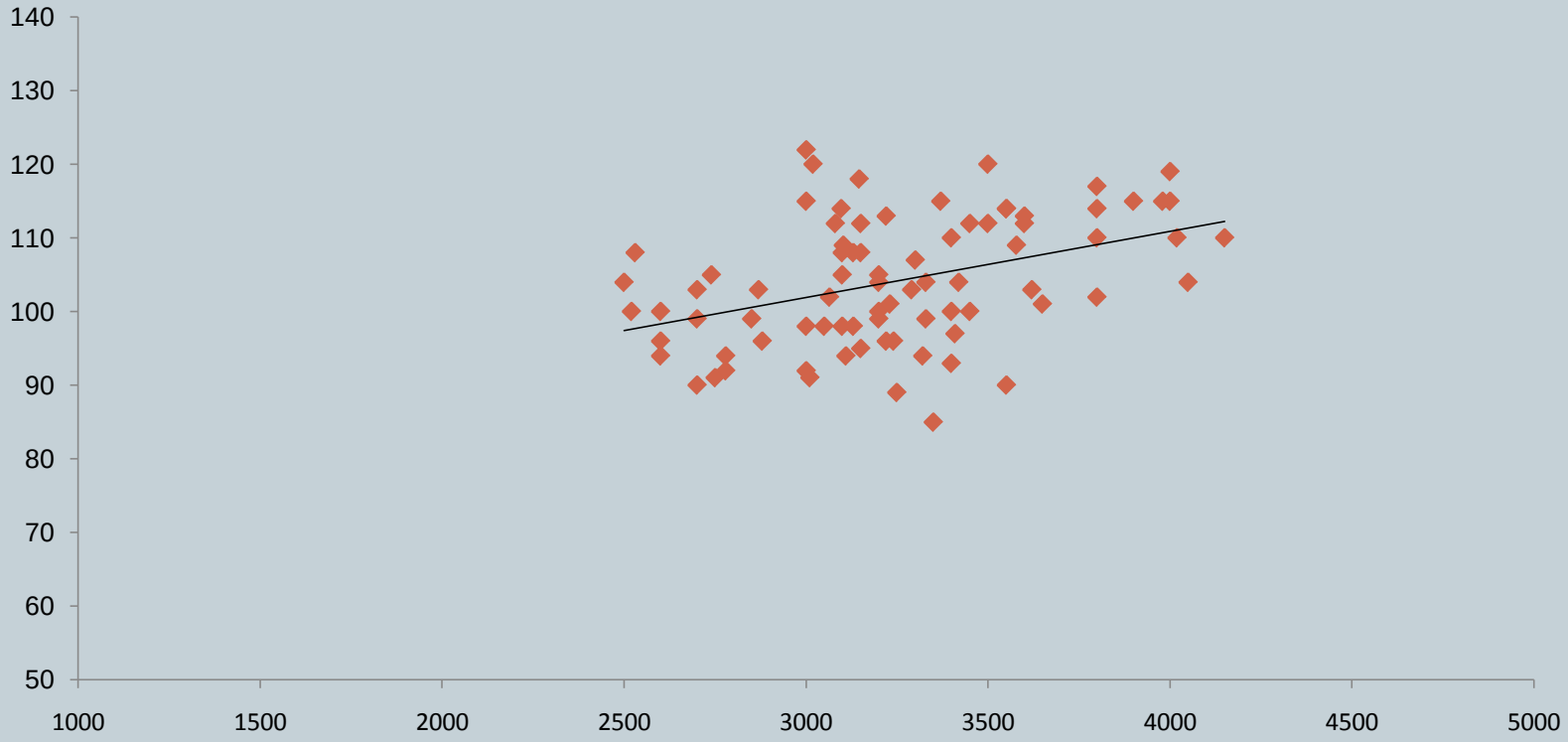
1st trimester					**2nd trimester**	**3rd trimester**
Variable 1	Maternal visfatin	Materna visfatin	materna leptin	Maternal hip	Maternal ghrelin active	Maternal visfatin
Variable 2	Maternal %fat	Maternal hip	maternal weight	birth weight	birth waist	birth weight
r-Spearman	-0.75	-0.61	0.85	0.52	0.75	-0.72

ΠΟΙΟΙ ΑΝΘΡΩΠΟΜΕΤΡΙΚΟΙ ΚΑΙ ΒΙΟΧΗΜΙΚΟΙ ΠΑΡΑΓΟΝΤΕς ΤΗς ΜΗΤΕΡΑς ΣΥΣΧΕΤΙΖΟΝΤΑΙ ΜΕ ΤΗΝ ΑΝΑΠΤΥΞΗ ΚΑΙ ΤΟ ΜΕΤΑΒΟΛΙΣΜΟ ΤΟΥ ΕΜΒΡΥΟΥ

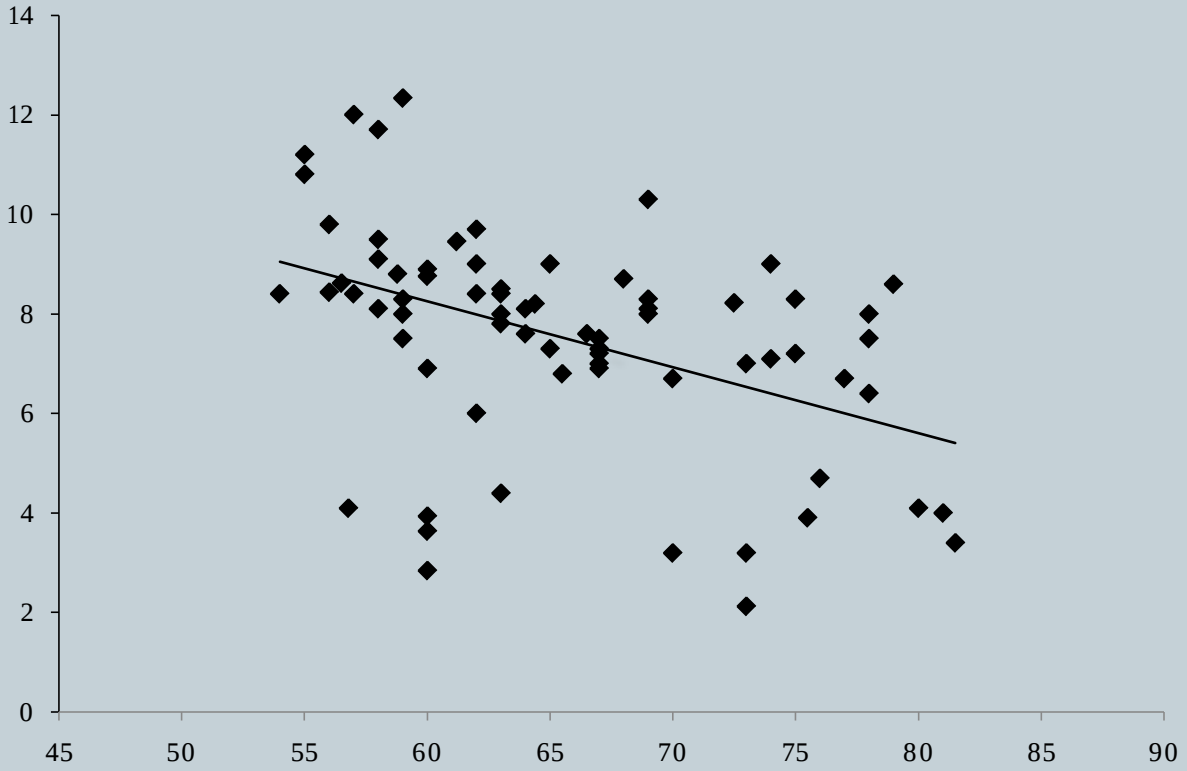
1st trimester maternal weight and cord blood c-peptide (p=0.035, r=0.74).(Valsamakis et al.submitted)

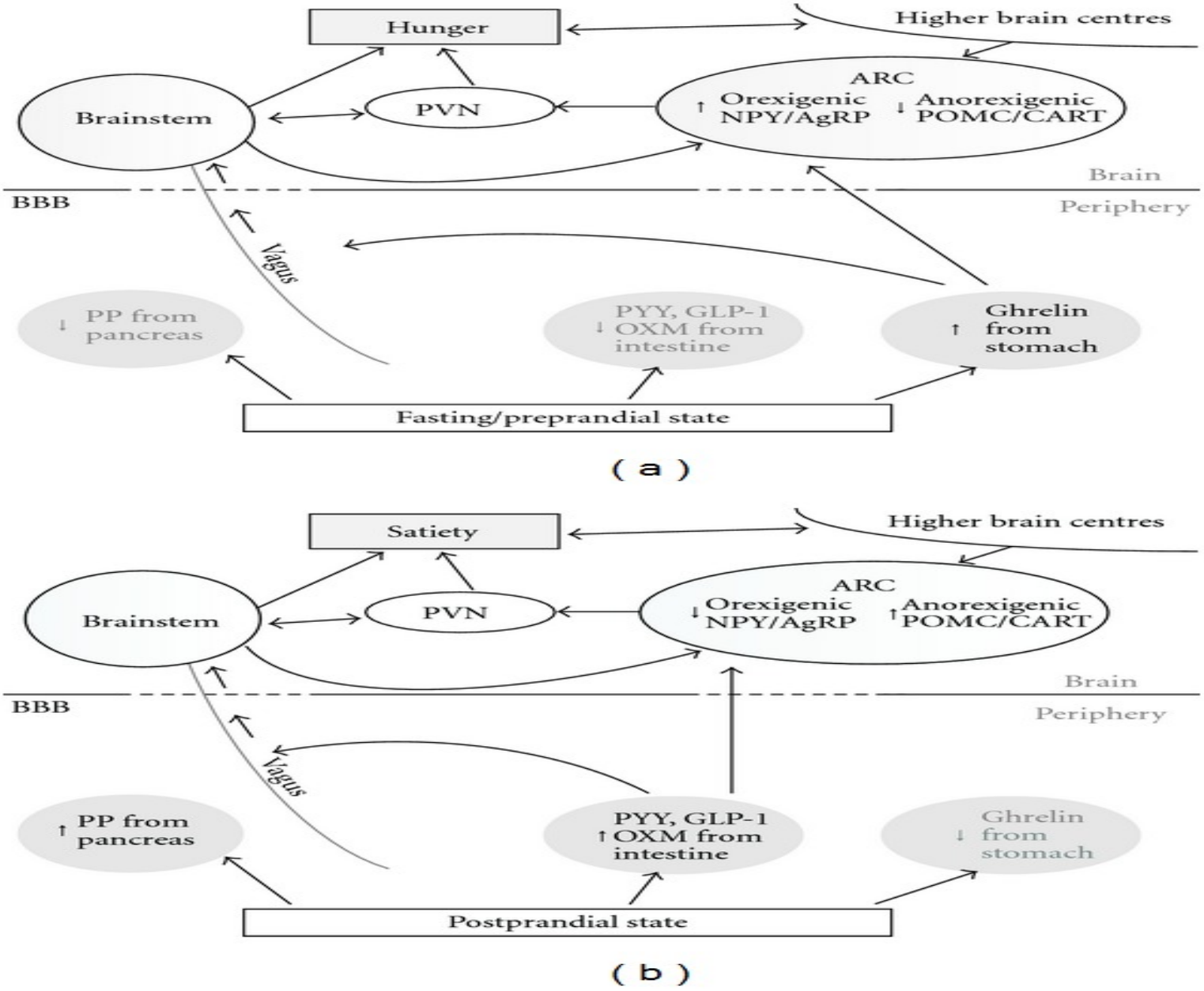


First trimester maternal hip vs birthweight (p=0.026, r=0.52)



1st trimester maternal weight and cord blood visfatin (p=0.049, r=-0.67)




Hunger
Higher brain centres
Brainstem
PVN
ARC
↑ Orexigenic NPY/AgRP
↓ Anorexigenic POMC/CART
Brain
BBB
Periphery
Vagus
↓ PP from pancreas
PYY, GLP-1
↓ OXM from intestine
↑ Ghrelin from stomach
Fasting/preprandial state
(a)
Satiety
Higher brain centres
Brainstem
PVN
ARC
↓ Orexigenic NPY/AgRP
↑ Anorexigenic POMC/CART
Brain
BBB
Periphery
Vagus
↑ PP from pancreas
PYY, GLP-1
↑ OXM from intestine
↓ Ghrelin from stomach
Postprandial state
(b)

Leptin-ghrelin interactions: hypothalamus

- active ghrelin
- adipocytokine leptin at high levels produces satiation, appetite control system.
- both“inform” the corresponding hypothalamic centers about the nutritional status and the level of energy storage

- (Heppner KM et al. Methods in Enzymology 2012)

AMPK

- AMPK is an intracellular energy sensor and energy regulator
- switching off ATP-consuming pathways
- switching on ATP-producing pathways such as glucose uptake and fatty acid oxidation

Leptin-ghrelin AMPK balance: hypothalamus (2)

- 1) Negative energy balance is associated with:
- increase of plasma ghrelin,
- Increase of hypothalamic AMPK
- Increase of food intake

- 2) Incr. leptin leads to suppressed hypothalamic AMPK activity and contributes to restriction of food intake

- (Stark R et al. Mol Cel Endocrinology 2013)

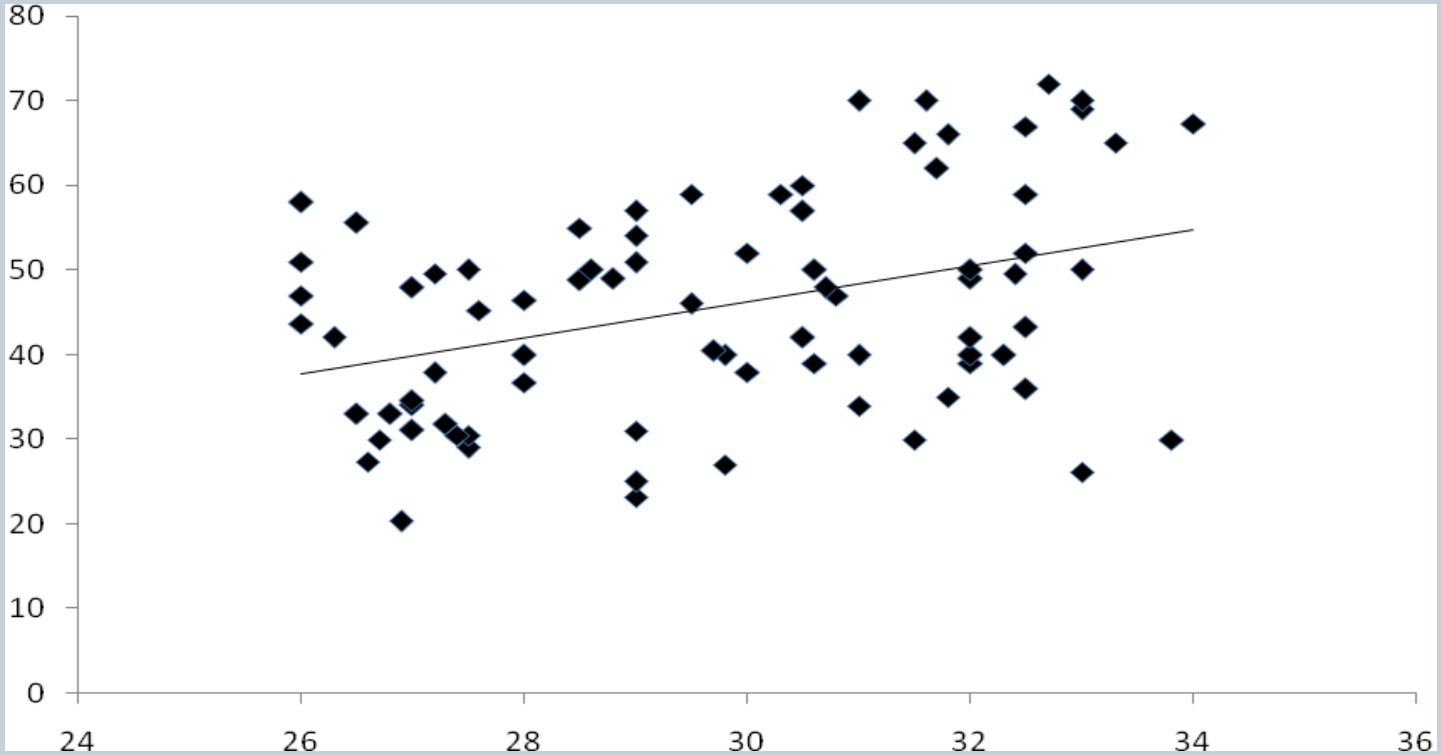
Ghrelin and AMPK: visceral fat

in mice active ghrelin acting through its GHSR receptor :

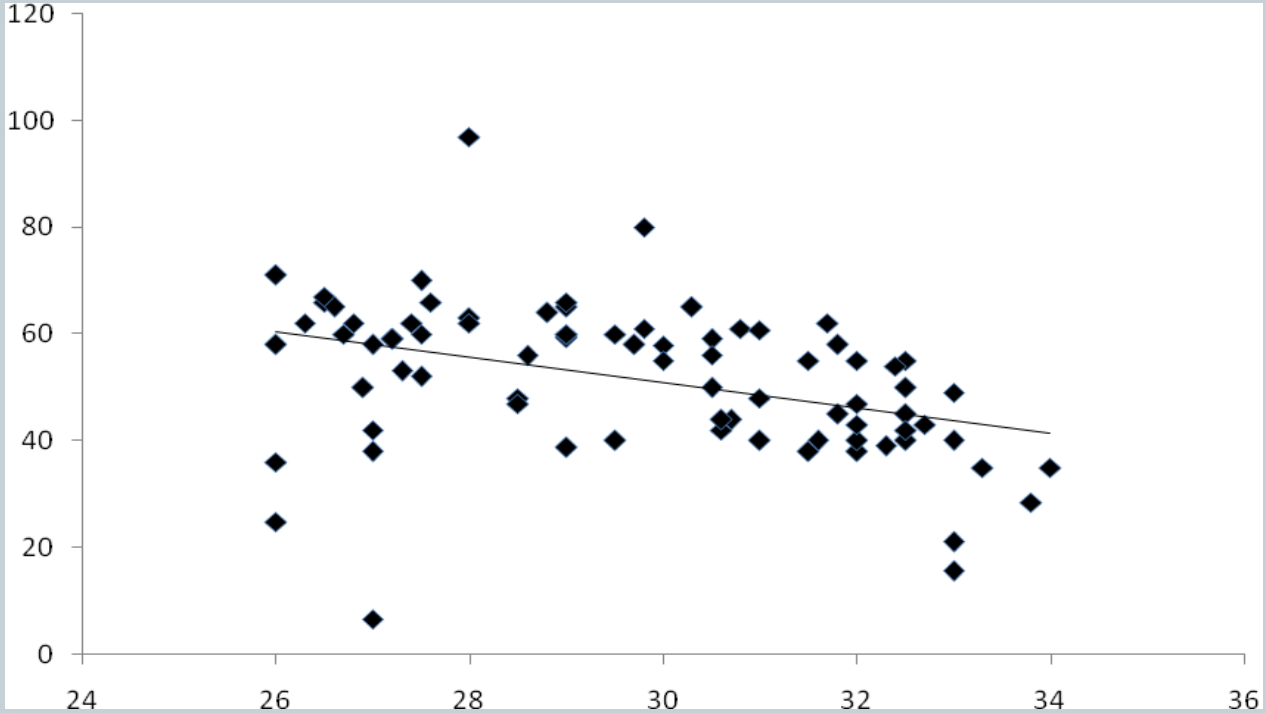
- stimulates the hypothalamic AMP-activated protein kinase (AMPK) activity
- inhibits (AMPK) activity in the liver and visceral fat (mesenteric fat)

- (Lim CT et al. Mol Cel Endocrinology 2013)

second trimester maternal active ghrelin levels with neonatal birth waist circumference (p=0.04, r=0.75) (Valsamakis et al. submitted)



third trimester maternal leptin levels with neonatal birth waist circumference (p=0.027, r=-0.81) (submitted)



Ghrelin and insulin secretion

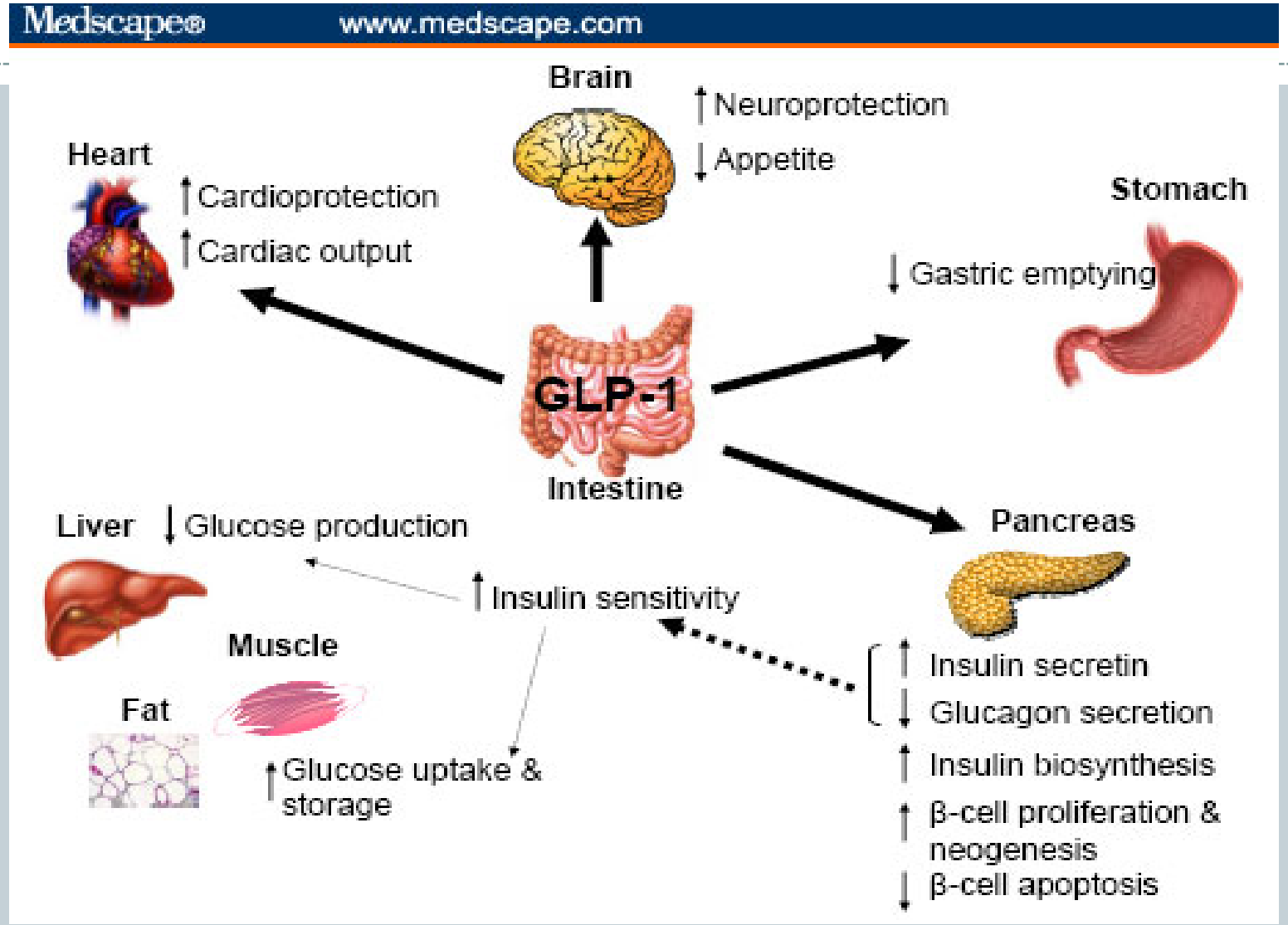
- ghrelin is expressed in pancreatic cells
- inhibits maternal glucose-driven insulin release in humans
- Resulting in increased maternal circulating glucose levels

Third trimester maternal plasma active ghrelin levels (submitted)

- correlated negatively with:

1. percent total neonatal body fat ($p=0.04$, $r=-0.94$),
2. cord blood insulin levels ($p=0.04$, $r=-0.829$)
3. fetal HOMAR ($p=0.021$, $r=-0.829$).

- (Valsamakis et al. submitted)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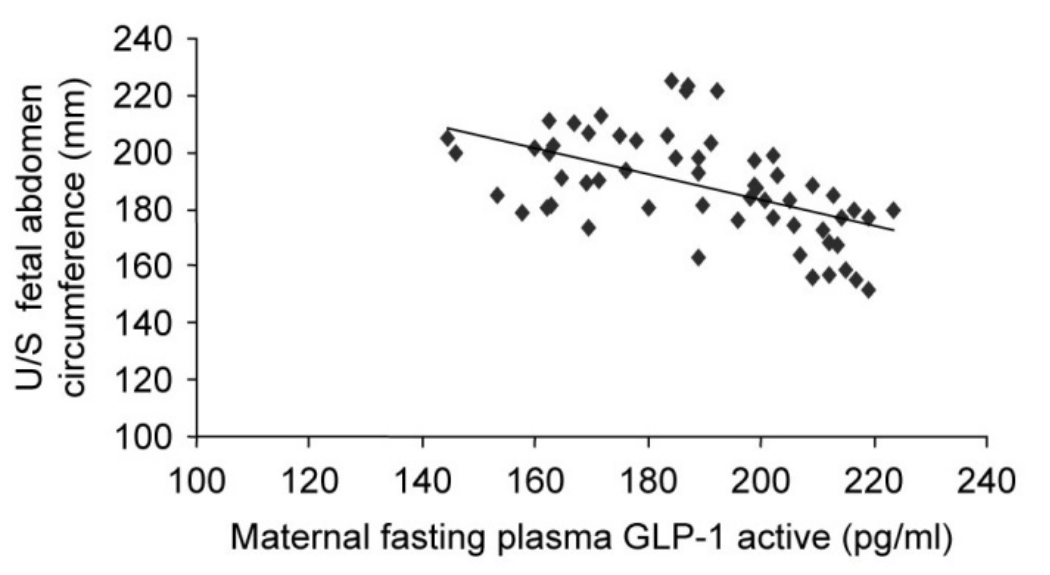
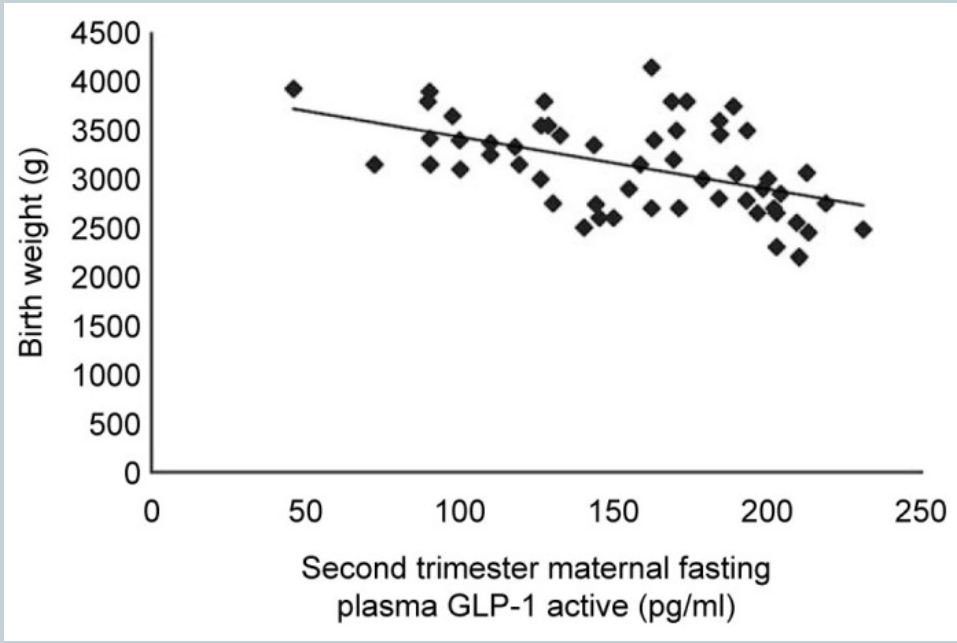
Heart
↑ Cardioprotection
↑ Cardiac output
Stomach
↓ Gastric emptying
GLP-1
Intestine
Liver
↓ Glucose production
Pancreas
↑ Insulin sensitivity
Muscle
Fat
↑ Glucose uptake & storage
↑ Insulin secretin
↓ Glucagon secretion
↑ Insulin biosynthesis
↑ β-cell proliferation & neogenesis
↓ β-cell apoptosis



2nd trimester GLP-1 and U/S fetal abdomen

2nd trimester GLP-1 and neonatal birth weight



Valsamakis G et al., Eur. J. of Endocrinology, 2010

Amylin,

1. is a 37-residue peptide hormone secreted by pancreatic β-cells at the same time as insulin (in a roughly 100:1 ratio).

2. functions as part of the endocrine pancreas and contributes to glycemic control.

3. slows gastric emptying, promote satiety, inhibit secretion of glucagon during hyperglycemia, and therein reduce the total insulin demand.

4. Rodent amylin knockouts are known to fail to achieve the normal anorexia following food consumption. ..

Gut hormones associations

1st trimester							**2nd trimester**		
variable 1	Ghrelin active	PP	Ghrelin active	PP	Ghrelin active	PYY total	leptin	Glucagon	glucagon
Variable 2	GLP-1 active	GLP-1 active	PP	PYY total	GIP	GLP-1	GIP	Amylin active	adiponectin
r-Spearman	0.55	0.45	0.43	0.54	0.5	0.46	-0.75	-0.45	-0.93
3rd trimester									
variable 1	Ghrelin active	Ghrelin active	glucagon						
Variable 2	GLP-1 active	GIP	PYY total						
r-Spearman	0.69	-0.47	-0.76						

Best predictor of insulin resistance change: maternal visfatin change

The longitudinal regression model taking in consideration all three trimesters revealed that visfatin change was the best positive and negative predictor of insulin resistance (HOMAR) ($p=0.0002$, t-value=4.48) and sensitivity (ISI) ($p=0.002$, t-value=-3.65) changes, respectively, during pregnancy among active ghrelin, active GLP-1, GIP, glucagon, PP, total PYY, active amylin, leptin and adiponectin levels

Best predictor of maternal weight change: maternal active amylin change

The longitudinal regression model taking in consideration all three trimesters revealed that active amylin change during pregnancy was the best negative predictor ($p=0.02$, t-value=-2.41) of maternal weight change during pregnancy among active ghrelin, active GLP-1, GIP, glucagon, PP, total PYY, visfatin, leptin and adiponectin levels.

Best birth weight predictor: early adiposity

Stepwise multiple regression analysis revealed that 1st trimester visfatin levels were the best negative predictor (p=0.017, beta=-1.23) together with leptin (p=0.022, beta=-1.09) levels of birth weight among 1st trimester plasma levels of active ghrelin, active GLP-1 total PYY, active amylin, glucagon, PP and adiponectin levels.

Best birth waist circumference predictor: 2nd trimester maternal circulating ghrelin

Stepwise multiple regression analysis revealed that 2nd trimester active ghrelin levels were the best positive predictor ($p=0.03$, beta=0.84) of neonatal waist circumference among 2nd trimester plasma levels of active GLP-1, total PYY, GIP, active amylin, PP, visfatin, leptin and adiponectin

Best cord blood insulin: maternal ghrelin

- Stepwise multiple regression analysis revealed that third trimester maternal circulating active ghrelin levels were the best negative predictor ($p=0.02$, beta=-0.99) of cord blood insulin levels among third trimester maternal weight and fasting plasma leptin, active GLP1 and total PYY levels

Conclusions (1)

- an association among first trimester maternal adipose tissue (as represented by maternal weight and maternal serum visfatin levels of first trimester) with:

1. fetal insulin secretion
2. birth weight

Conclusions (2)

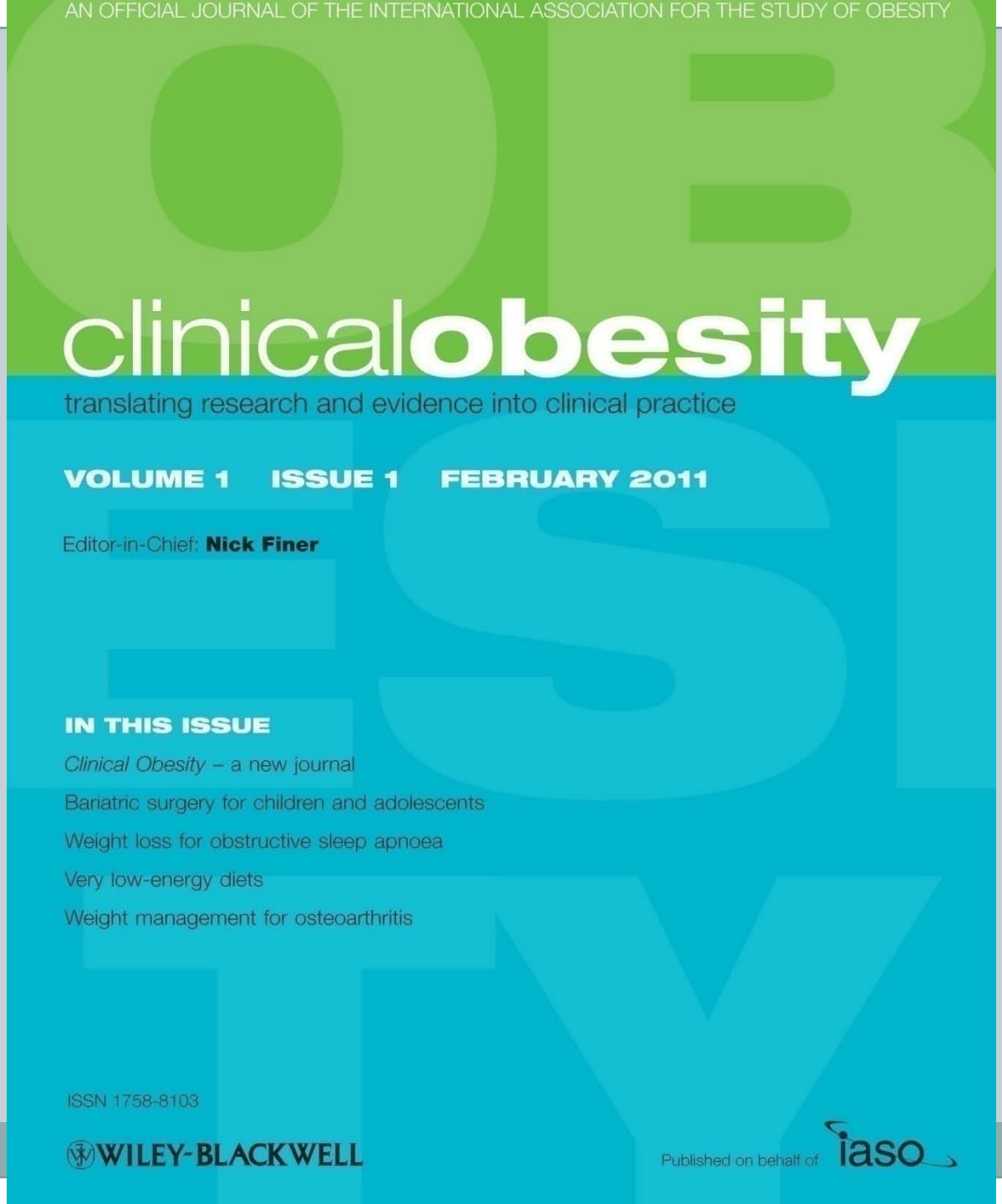
- ghrelin, increases maternal appetite
- might increase nutrient supplies to the fetus resulting to its positive energy balance.
- It might also contribute to the visceral storage of energy supplies *via* the inhibition of the visceral AMPK activity.

Conclusions (3)

- Maternal ghrelin ensures adequate fasting glucose and nutrient supplies to the fetus.
- fetal insulin secretion decreases
- overall fetal adipose tissue deposition is avoided

Conclusions: hypothesis

- it seems that maternal adipo-entero-pancreatic hormones together with the probable placental secretion of certain among them might be involved in an interplay during pregnancy including maternal adipose tissue, appetite and insulin resistance, and fetal adipose tissue, growth and metabolism resulting to the birth of a healthy neonate sufficiently equipped to deal with a possibly hostile environment during the first days of its life.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