8th September, 2012
Hong Kong

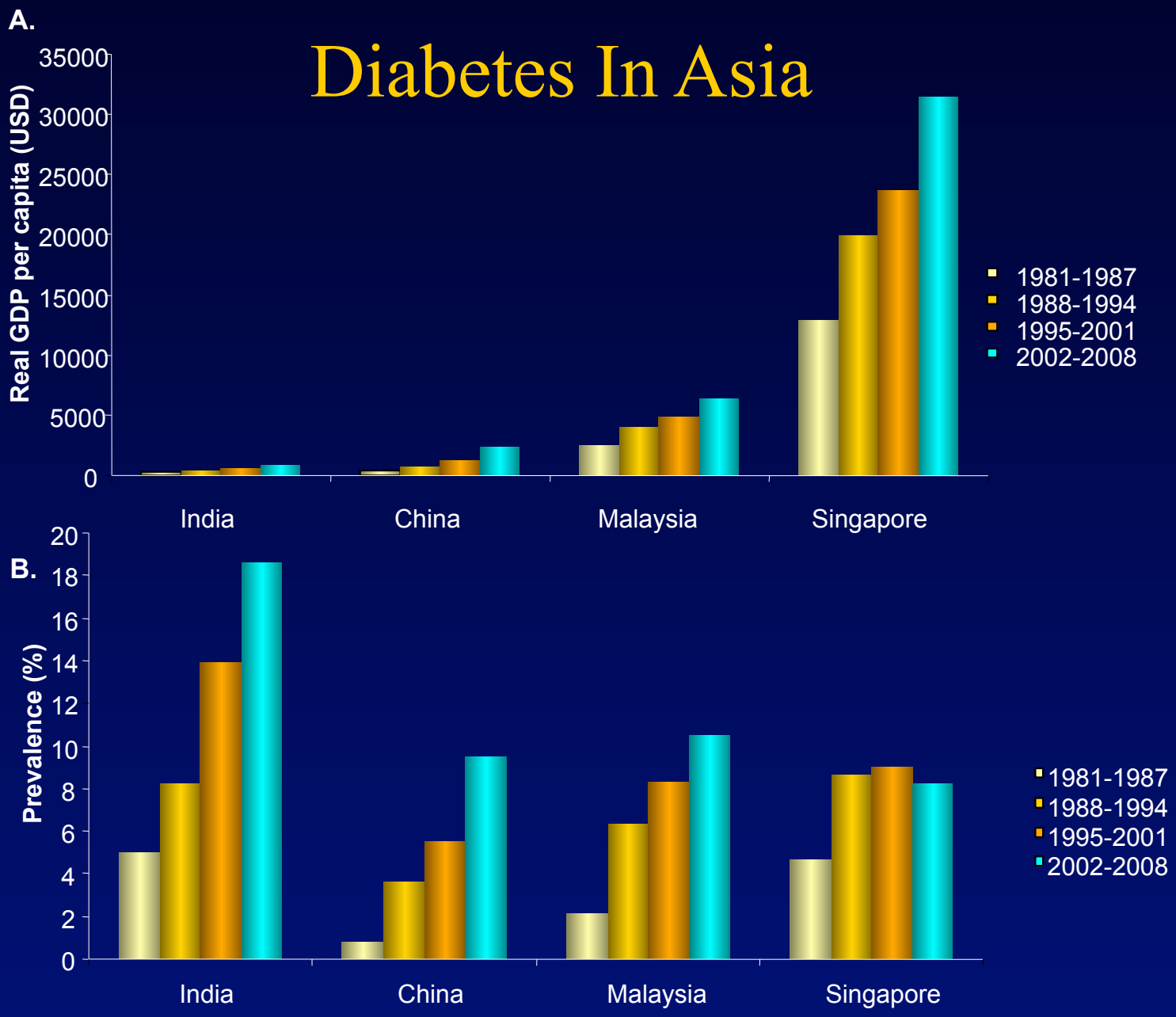
Developmental origins of Type 2 diabetes and obesity - Maternal obesity, GDM and the NCD Epidemic

Ronald Ma
Professor
Dept of Medicine & Therapeutics
Chinese University of Hong Kong

Outline

- Epidemiology of Diabetes and Obesity in Asia
- Risk factors for Diabetes
- Role of the intra-uterine environment
- Gestational Diabetes and long-term risks
- Implications for strategies to prevent diabetes and obesity

Diabetes In Asia

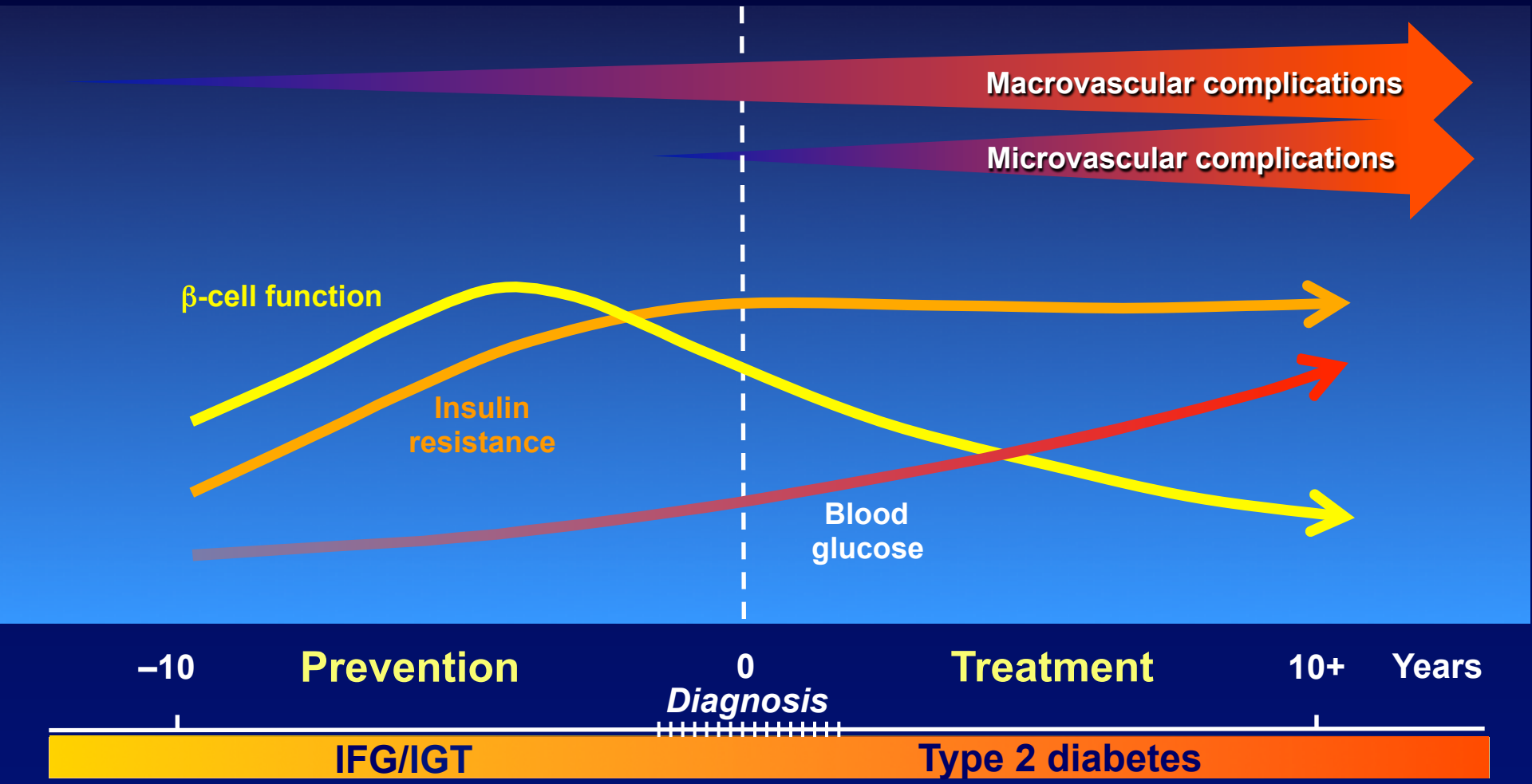


Ramachandran A, Ma RC and Snehalatha DC, Lancet 2010; *Jan 30; 375: 408-18*

Epidemiology of Diabetes in Hong Kong

- **T2 DM affecting 10% of population (in 1990s)**
- **10-30% have MetS**
- **97% type 2 DM**
- **Affects 1 in 4 aged > 65**
- **Among aged 25-34, 2% have DM**
- **Around 20% of DM patients are aged < 40**
  - Risk of CHD ↑14x
  - Risk of CVA ↑30x
  - Nephropathy

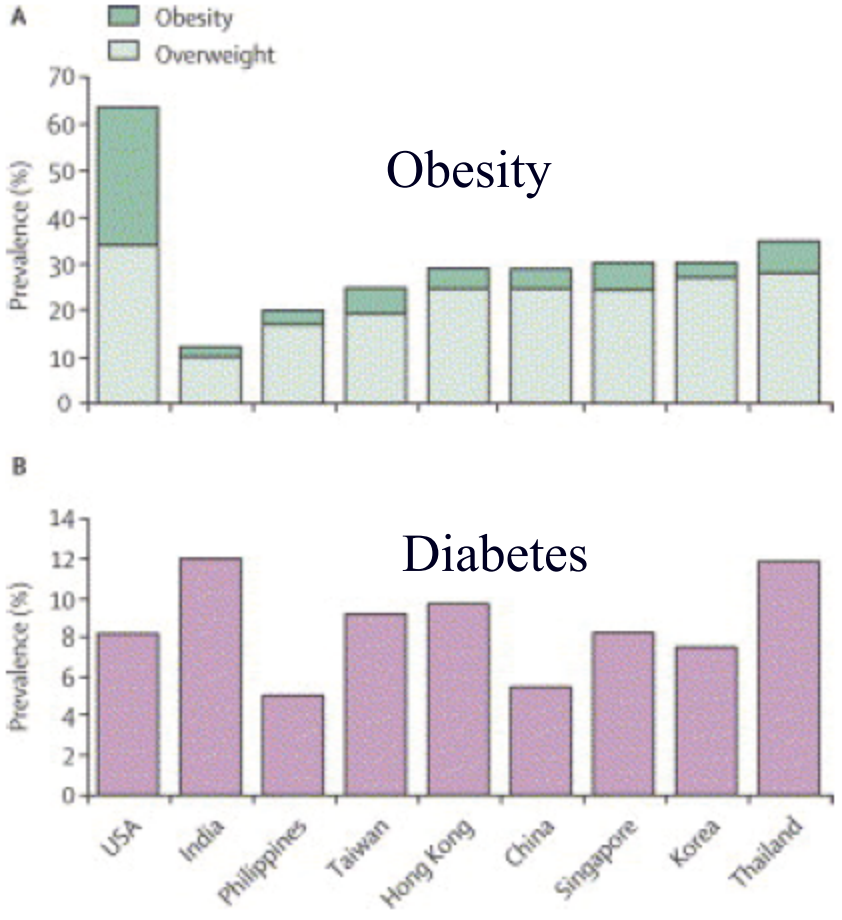
Type 2 diabetes as a Progressive Disease

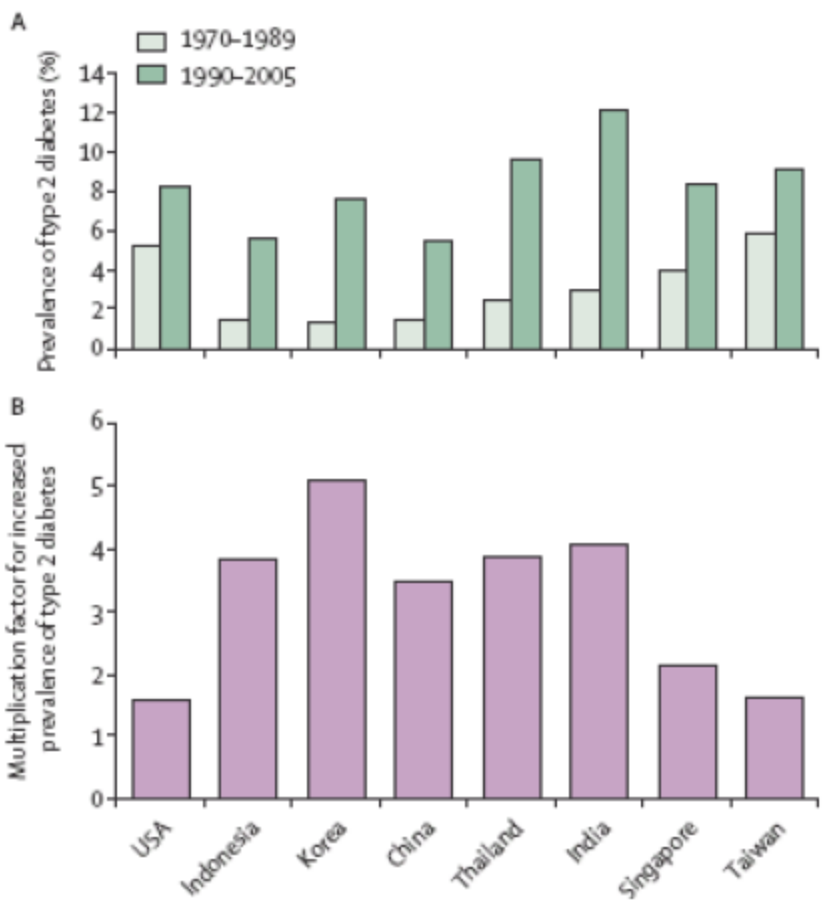


IFG: impaired fasting glucose
IGT: impaired glucose tolerance

Adapted from DeFronzo RA. *Med Clin N Am* 2004;88:787–835.

Disparity between prevalance of diabetes and obesity in Asia



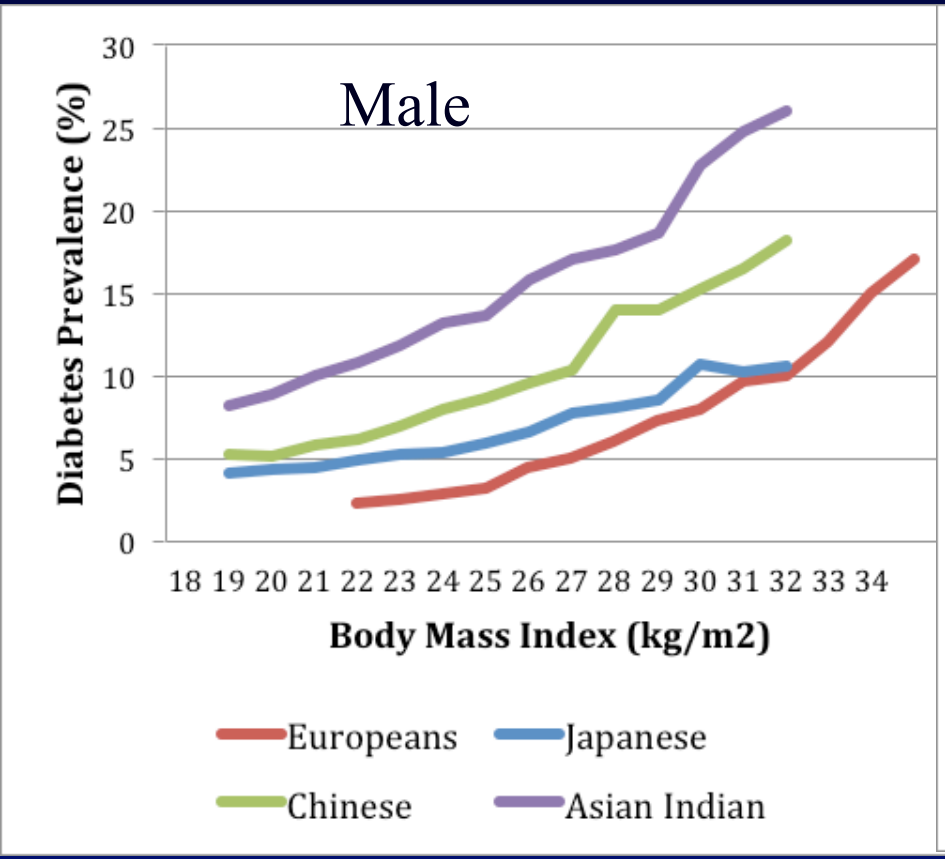


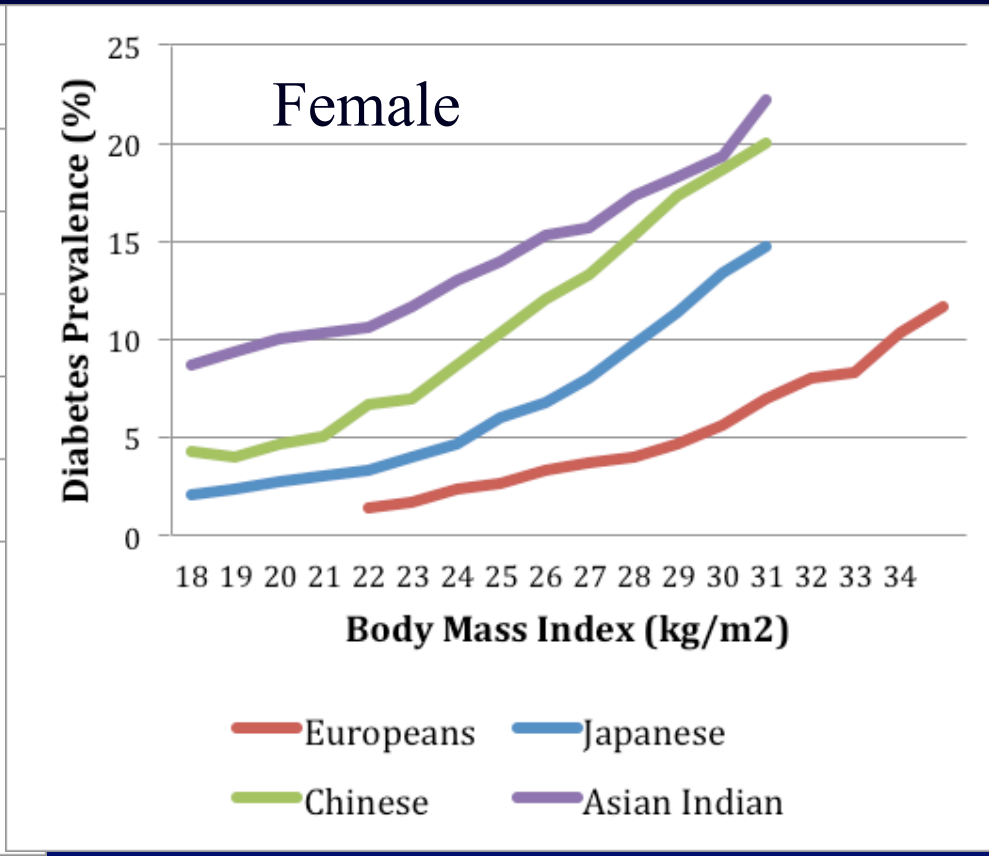
Young onset, strong FH, central obesity

Yoon et al, Lancet 2006

Ramachandran, Ma et al. Lancet 2010

Relationship between BMI and DM prevalence





DECODA Study Group

Adapted from Nyamdorj et al, Int J Obes 2010

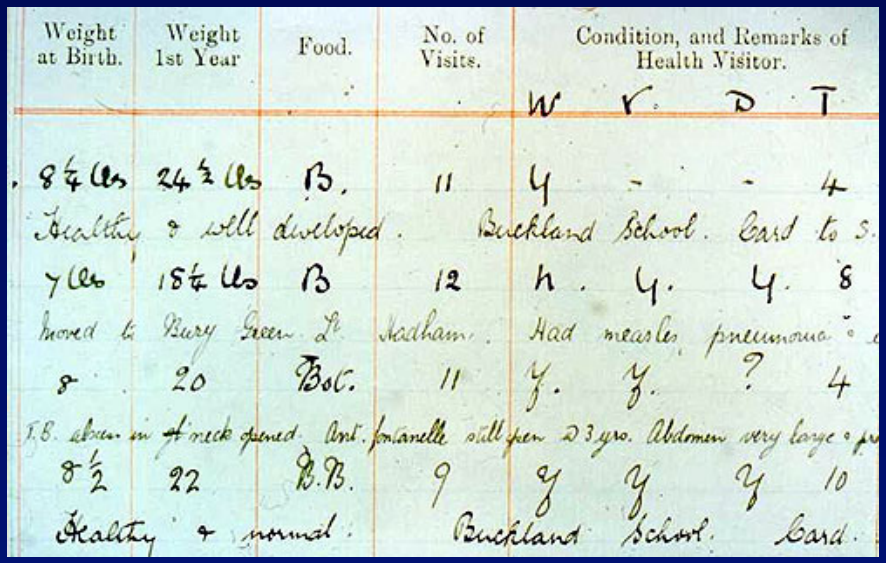
Evidence supporting role of intra-uterine environment in DM

- 1) Link between birthweight and DM
- 2) Maternal nutrition and risk of DM
- 3) Transgenerational effects
- 4) Increased maternal transmission of DM
- 5) Animal models of in-utero malnutrition or overnutrition

Early Epidemiological links: The Hertfordshire Cohort

15726 people born
1911-1930

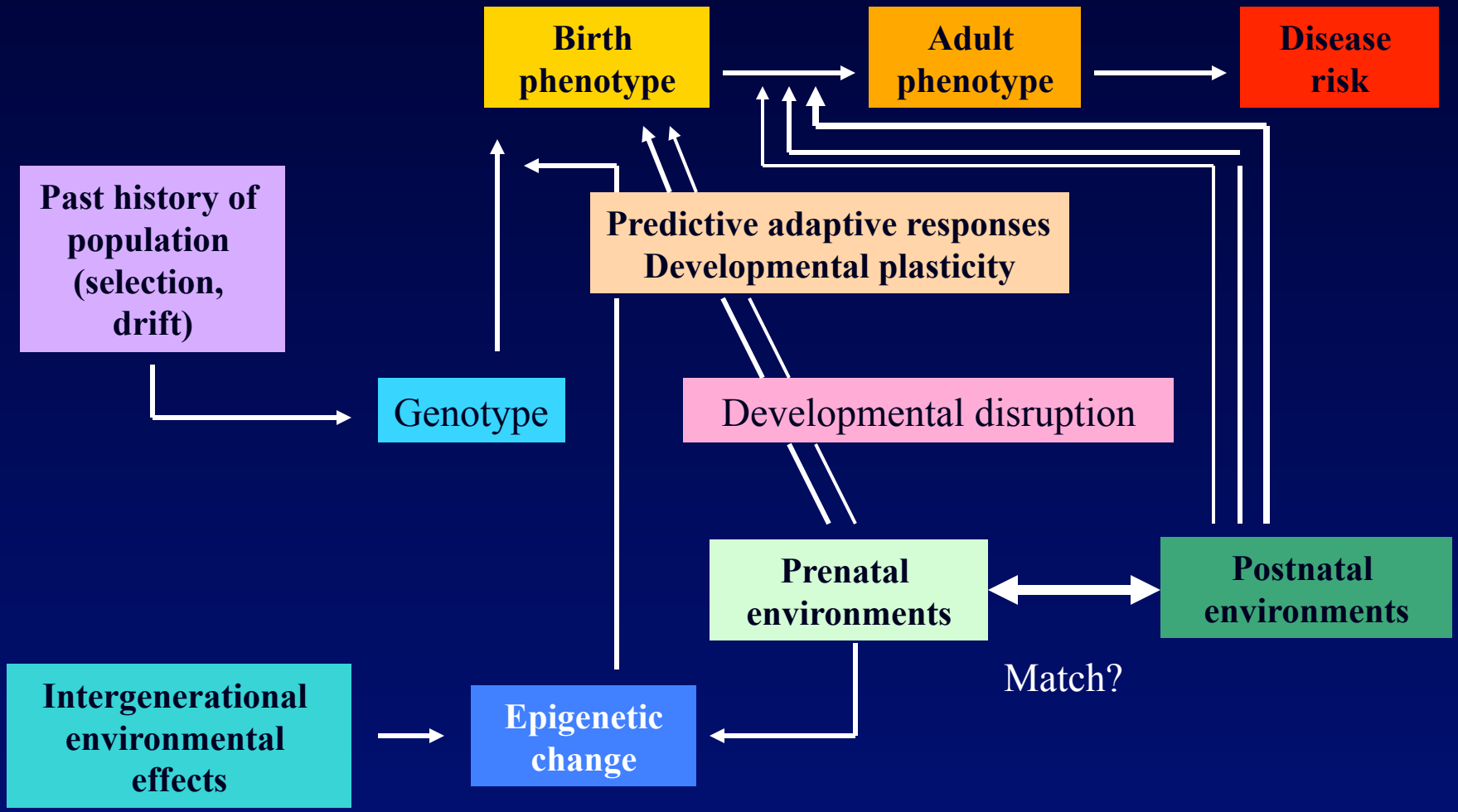
Low birthweight asso. with:
Increased mortality from CHD
Increased risk of T2 DM, IGT



Weight at Birth.	Weight 1st Year	Food.	No. of Visits.	Condition, and Remarks of Health Visitor. W	V	D	T
8¼ lbs	24½ lbs	B.	11	4	-	-	4
Healthy & well developed.				Buckland School. Card to S.			
7 lbs	18¼ lbs	B	12	h.	4.	4.	8
Moved to Bury Green Ld.			Hadham.	Had measles, pneumonia &			
8	20	Bot.	11	Y.	Y.	?	4
T.B. about in 4th week opened. Ant. fontanelle still open @ 3 yrs. Abdomen very large & pr							
8½	22	B.B.	9	Y	Y	Y	10
Healthy & normal.				Buckland School. Card.			

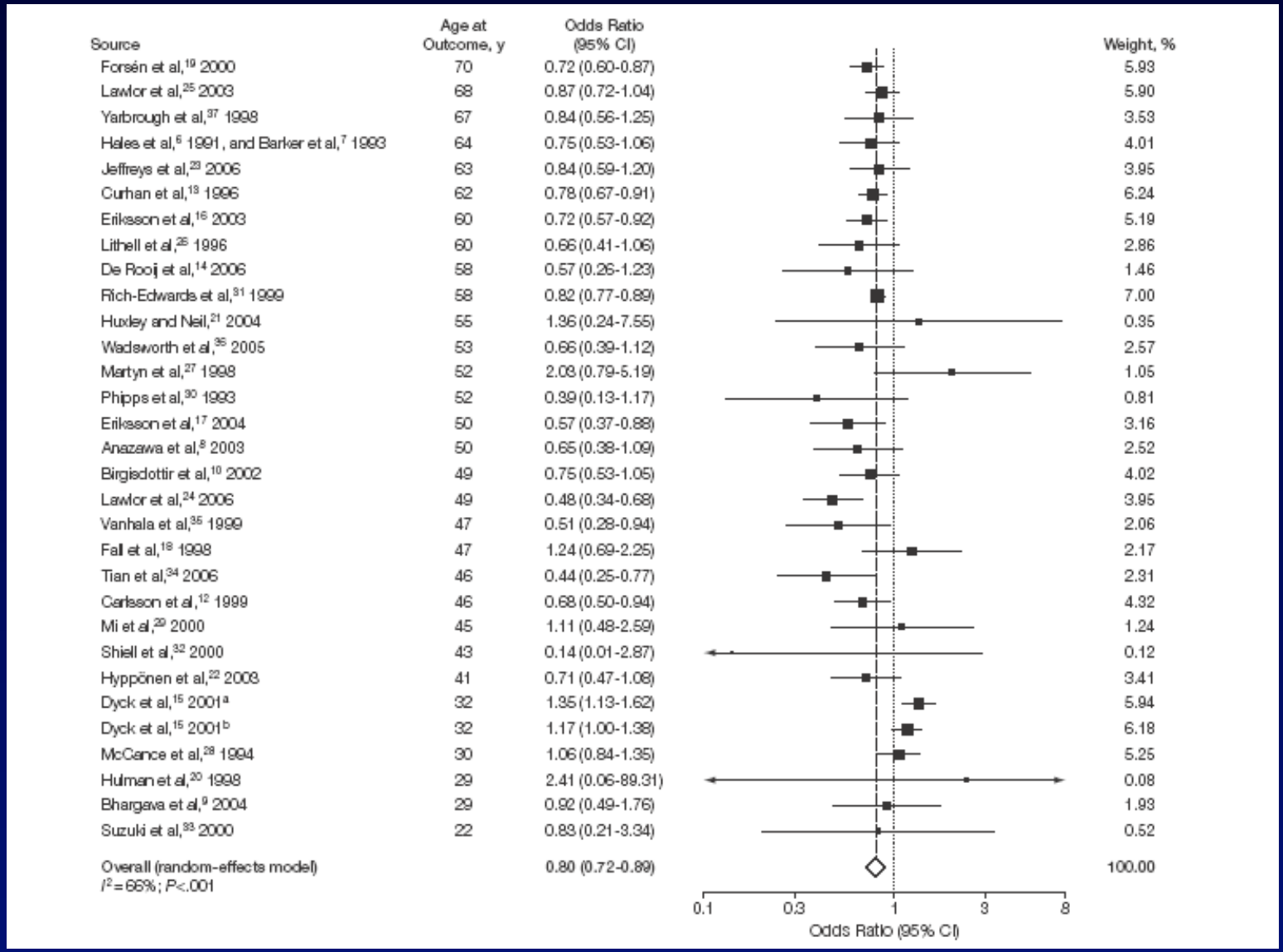
Osmond C, et al. BMJ 1993, 307: 1519-24
Hales CN, et al. BMJ 1991; 303: 1019-22

Developmental Origins of Health and Disease (DOHaD)



Adapted from Gluckman PJ and Hanson MA, Science 2004; 305: 1773-6

Birthweight and Type 2 DM risk



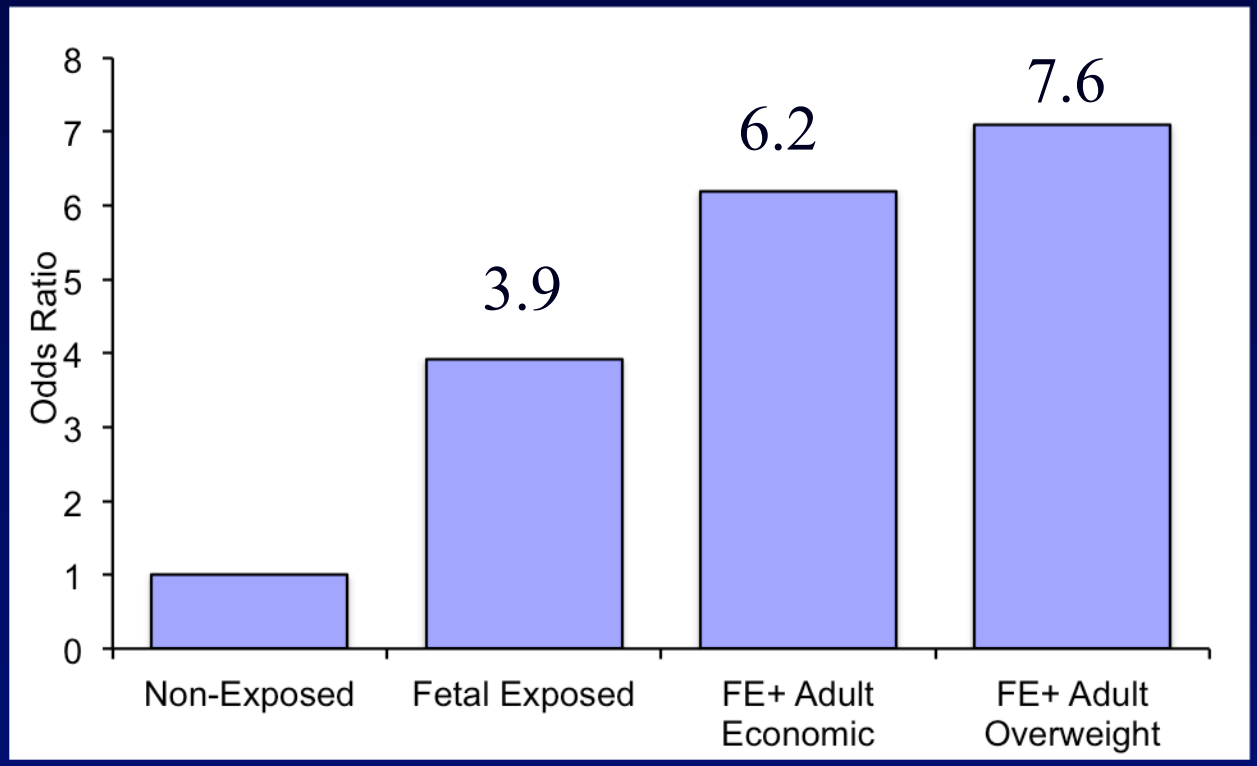
OR 0.75 (0.70-0.81) for T2 DM per 1kg increase in Bwt

Whincup P et al, JAMA 2008

Exposure to Chinese famine and hyperglycaemia in adults

7,874 rural adults
From China
National
Nutrition and Health
survey
Examined exposure
to Chinese famine
1959-61

Risk of
hyperglycaemia
OR 3.92



Li Y et al, Diabetes 2010

Transgenerational diabetes

- Early epidemiological studies in the Pima Indian population revealed increased risk of diabetes in offspring of mothers with diabetes (Pettit et al, Diabetes 1988)
- Excess in maternal transmission has been observed in all races and both sexes in a multiethnic cohort (Karter et al, Diabetes Care 1999)
- Risk of DM higher among sibs exposed to intrauterine hyperglycaemia. Sibs exposed to in-utero DM had higher BMI (Dabelea et al, Diabetes 2000), and younger onset of DM (Pettit et al, Diabetes Care 2008)
- Increased risk of DM also seen in offspring of T1 DM (Sobnogwi et al, Lancet 2003)

Pathophysiology/Complications
ORIGINAL ARTICLE

Diabetes in Hong Kong Chinese

Evidence for familial clustering and parental effects

- Among 2310 Chinese patients with late-onset diabetes (onset >35yrs)
  - 25% of subjects with DM have at least 1 diabetic parent, and irrespective of sex, were more likely to have a diabetic mother than a diabetic father
    - 17% vs 13% of male ($p<0.01$)
    - 18% vs 9% of female ($p<0.01$)
- Maternal influence and sex-specific parental effects

Lee SC et al, Diabetes Care 2000; 23: 1365-1368

Increased cardiometabolic risk in offspring exposed to GDM at 8yrs

	NGT (N=101)	GDM (N=63)	*p*
Maternal Characteristics at Pregnancy			
Maternal age at delivery (years)	28.0	28.5	0.064
% Caesarean delivery	**9.9**	**33.3**	<0.001
% male infants	54.5	41.2	0.10
Birth weight of infant (gram)	3245	3292	0.50
Children's Characteristics at Follow-Up			
Mean age (years)	**8.4**	**7.7**	<0.001
Body weight (kg)*	28.2	28.1	0.92
Systolic BP (mmHg)*	**88**	**94**	<0.001
Diastolic BP (mmHg)*	**57**	**62**	<0.001
HDL-C (mmol/L)*	**1.71**	**1.58**	0.019
Mother with DM at FU	**2**	**6**	0.002

Tam WH, Ma RC et al, Paediatrics 2008

Children's long term risk after exposure to GDM- 15 year follow-up

	Hyperinsulinaemia		Odds ratio
At 15 year FU	C peptide > 90th percentile	C peptide < 90th percentile	
Metabolic syndrome	22.2%	2.7%	17.6
Overweight (BMI ≥ 90 percentile)	44.4%	13.7%	10.8

Metabolic syndrome of children (≥ any 3)
WC ≥ age-sex specific 90th percentile
2. FPG ≥5.6 mmol/L
3. BP ≥ age-sex specific 90th percentile 4.
Fasting plasma triglyceride ≥1.7 mmol/L
5. HDL-C <1.03 mmol/L

Tam WH, Ma RC et al. *Diabetes Care 2010*

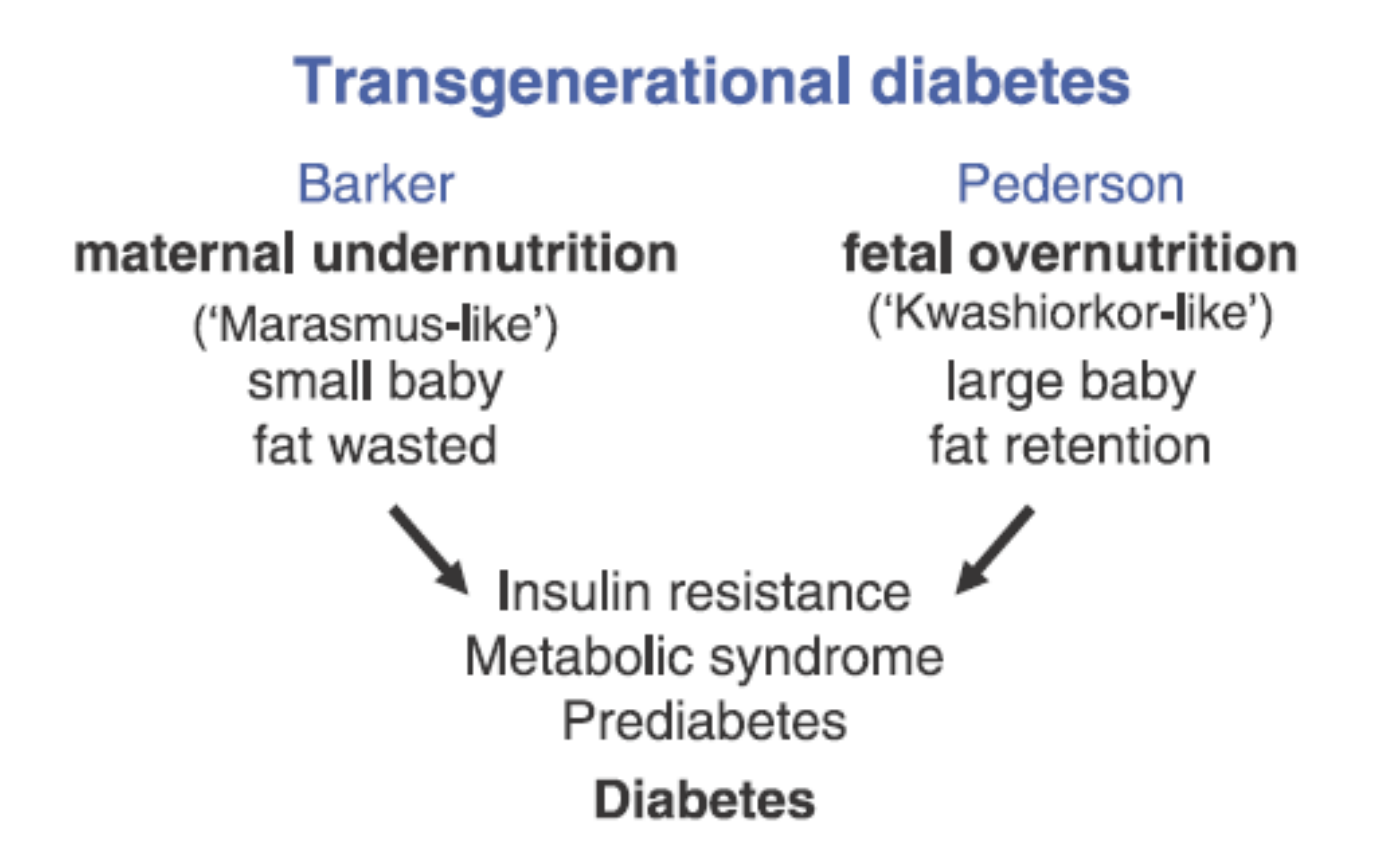
Gradient between maternal glucose and adiposity

	n	>90th percentile†	Model I	Model II
FPG (mmol/l)				
<4.2	3,340	177 (5.3)	1.00	1.00
4.2–4.4	6,270	480 (7.7)	1.48 (1.24–1.77)	1.39 (1.16–1.66)
4.5–4.7	5,186	504 (9.7)	1.92 (1.61–2.30)	1.66 (1.38–1.99)
4.8–4.9	2,287	278 (12.2)	2.47 (2.03–3.01)	2.00 (1.64–2.45)
5.0–5.2	1,556	259 (16.6)	3.57 (2.92–4.37)	2.72 (2.20–3.36)
5.3–5.5	576	119 (20.7)	4.65 (3.62–5.99)	3.37 (2.59–4.38)
≥5.6	174	46 (26.4)	6.42 (4.44–9.29)	4.71 (3.22–6.89)
Continuous‡	19,389	1,863 (9.6)	1.52 (1.45–1.59)	1.39 (1.33–1.47)
1-h Plasma glucose (mmol/l)				
≤5.8	3,482	212 (6.1)	1.00	1.00
5.9–7.3	6,258	483 (7.7)	1.29 (1.09–1.52)	1.22 (1.03–1.45)
7.4–8.6	5,007	468 (9.3)	1.59 (1.34–1.88)	1.50 (1.26–1.78)
8.7–9.5	2,324	310 (13.3)	2.37 (1.98–2.85)	2.22 (1.84–2.69)
9.6–10.7	1,570	245 (15.6)	2.85 (2.35–3.46)	2.63 (2.14–3.22)
10.8–11.7	536	103 (19.2)	3.67 (2.84–4.74)	3.38 (2.59–4.41)
≥11.8	212	42 (19.8)	3.81 (2.64–5.49)	3.57 (2.46–5.20)
Continuous‡	19,389	1,863 (9.6)	1.44 (1.37–1.51)	1.42 (1.35–1.49)
2-h Plasma glucose (mmol/l)				
≤5.0	3,537	209 (5.9)	1.00	1.00
5.1–6.0	6,135	496 (8.1)	1.40 (1.18–1.66)	1.32 (1.11–1.56)
6.1–6.9	4,948	481 (9.7)	1.71 (1.45–2.03)	1.60 (1.35–1.90)
7.0–7.7	2,556	352 (13.8)	2.54 (2.13–3.04)	2.38 (1.98–2.86)
7.8–8.7	1,444	198 (13.7)	2.53 (2.06–3.11)	2.39 (1.93–2.95)
8.8–9.8	576	90 (15.6)	2.95 (2.26–3.84)	2.80 (2.13–3.69)
≥9.9	193	37 (19.2)	3.78 (2.57–5.55)	3.59 (2.42–5.33)
Continuous‡	19,389	1,863 (9.6)	1.37 (1.31–1.44)	1.36 (1.30–1.43)

Around 20000 offspring

HAPO investigators, Diabetes 2009; 58: 453-459

Extending the Pederson Hypothesis to milder degrees of in-utero hyperglycaemia



Hadden DR. Diabet Med 2008; 25: 1-10

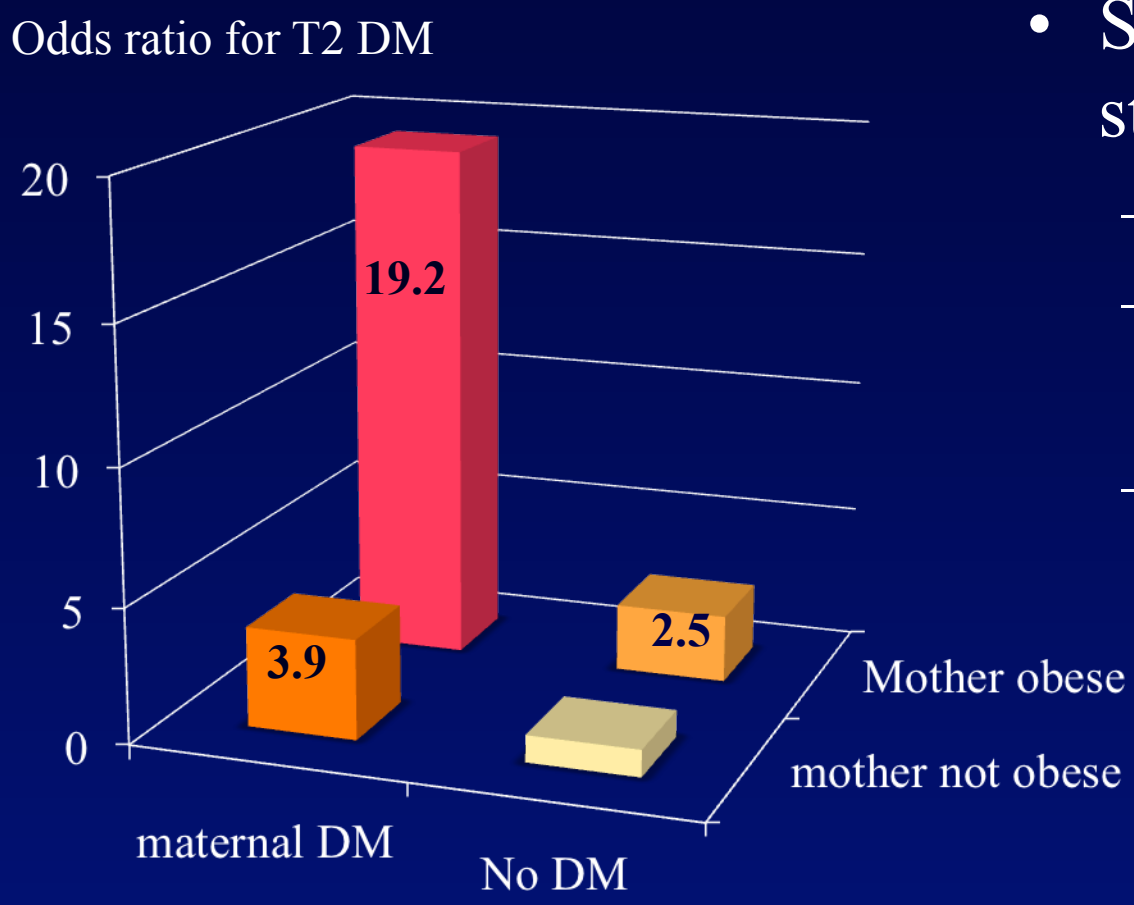
Maternal Obesity and Hyperglycaemia interact to increase risk

BMI	Glucose		
	Normal	Intermediate	GDM
ORs for birth weight >90th percentile: plasma glucose and BMI combined			
Normal, underweight	1.00	1.77	2.58
Overweight	1.75	3.09	4.52
Obese	2.07	3.66	5.35
Mean difference in birth weight: plasma glucose and BMI combined (g)			
Normal, underweight	0	90	164
Overweight	124	214	288
Obese	174	264	339

*Adjusted for gestational age at delivery, ethnicity, baby's sex, parity, maternal age, height and gestational age at the OGTT, smoking, alcohol use, hospitalization before delivery, family history of diabetes, and mean arterial pressure. All ORs and differences in birth weight compared with the referent group were significant ($P < 0.001$).

Catalano PM et al, Diabetes Care 2012 April; 35: 780

Contribution of maternal hyperglycaemia and obesity



- SEARCH case-control study
  - 79 youths with T2 DM
  - 190 normal youths
  - Overall, 47.2% of T2 DM in youth attributable to maternal DM or maternal obesity

Dabelea D et al, Diabetes Care 2008

Maternal factors

Obesity

Family History

Genetics

PCOS

Low-grade infections

↑ Risk of GDM

↑ Risk of DM in offspring

Offspring factors

Physical inactivity

Obesity

Family History

Genetics epigenetics

Education

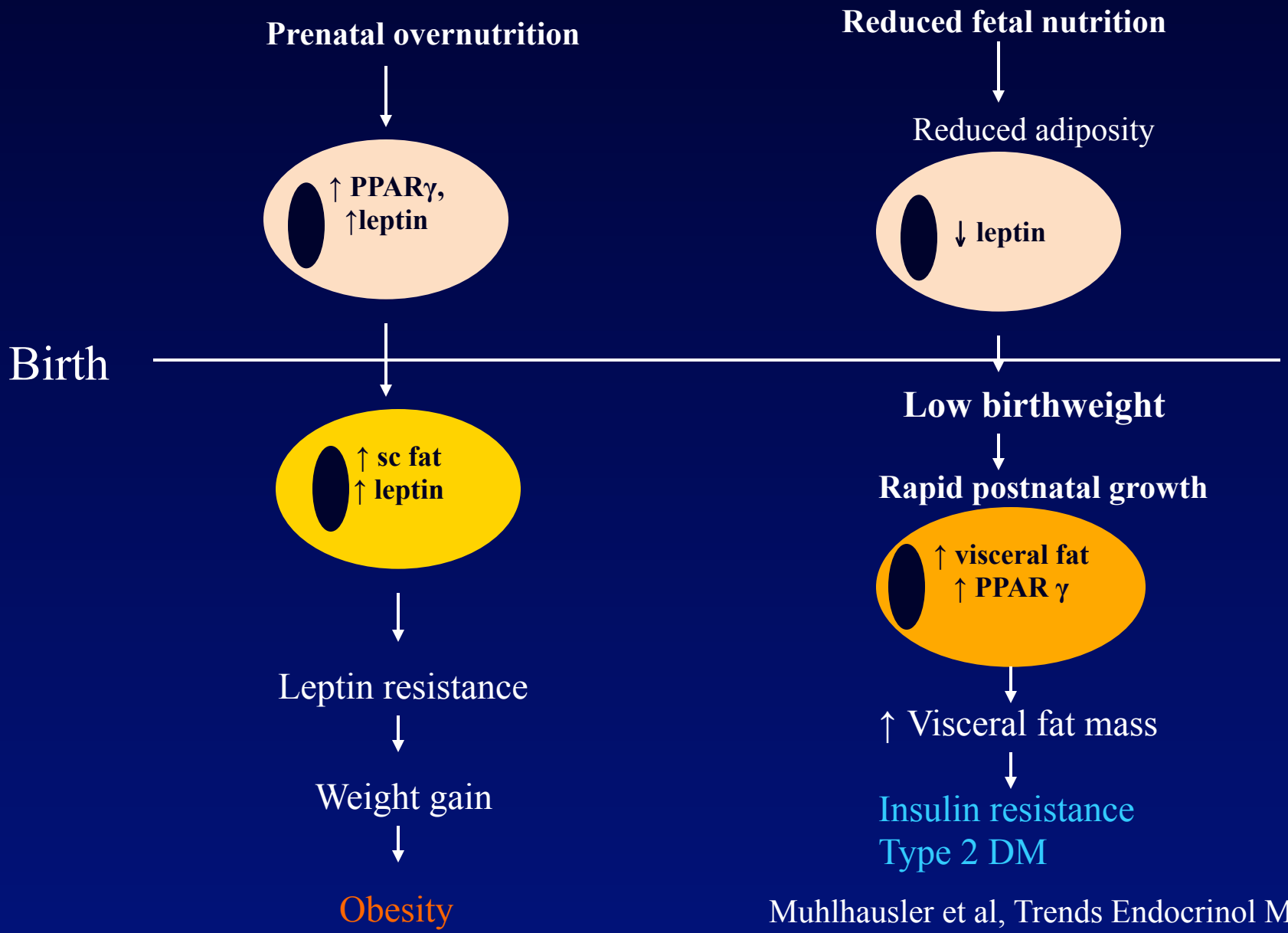
Sleep deprivation

Ma RC and Chan JC. Int J Gynae Obst 2009

Animal models of fetal programming of DM

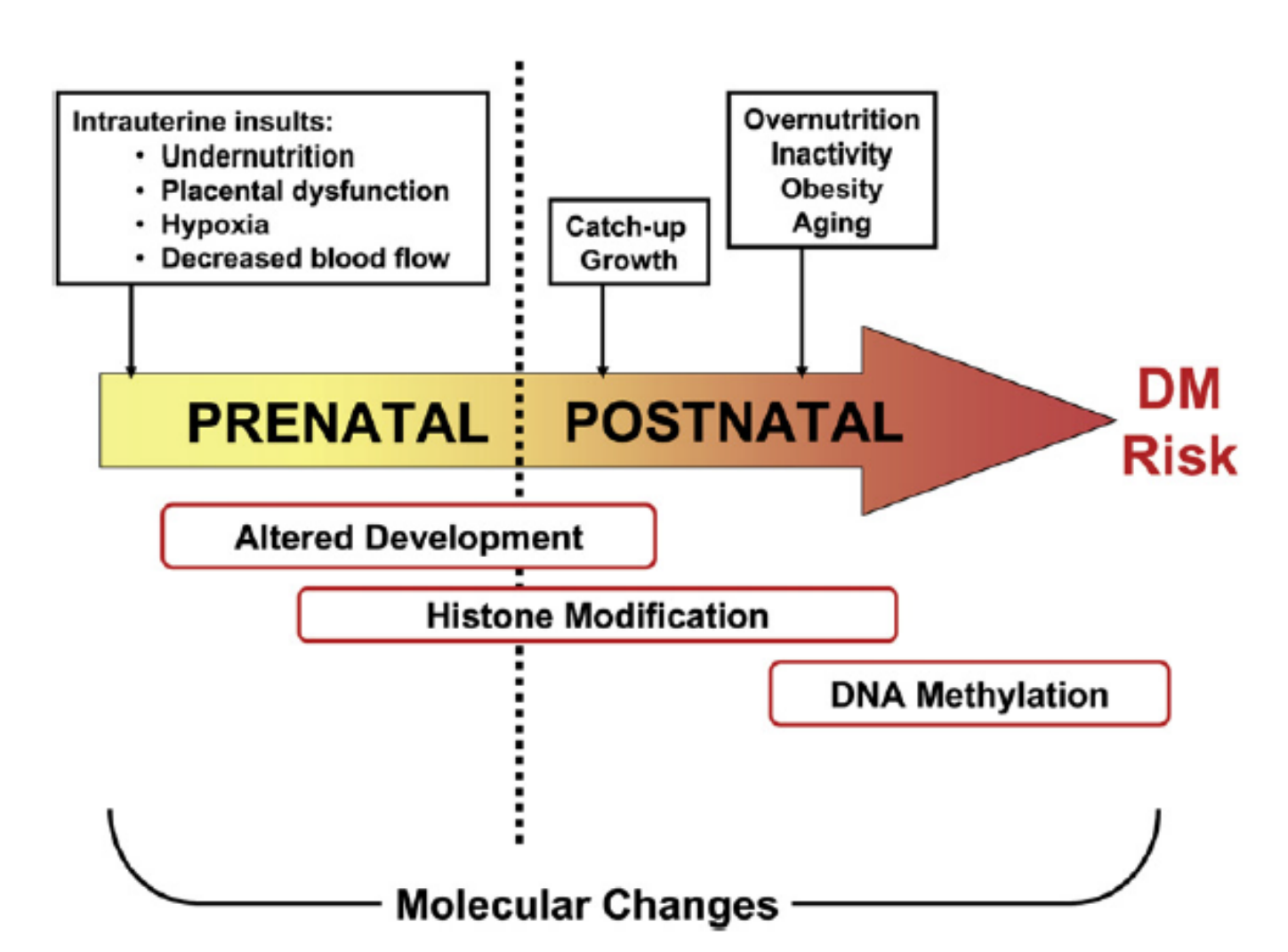
- Rats, guinea pigs, mice, sheep, pigs etc.
- Maternal undernutrition
  - Protein undernutrition
  - Low calorie diet
  - Uterine artery ligation
  - IUGR
- Maternal overnutrition
  - High fat feeding
  - Maternal obesity
  - Maternal diabetes

Intra-uterine nutrition and adipocyte



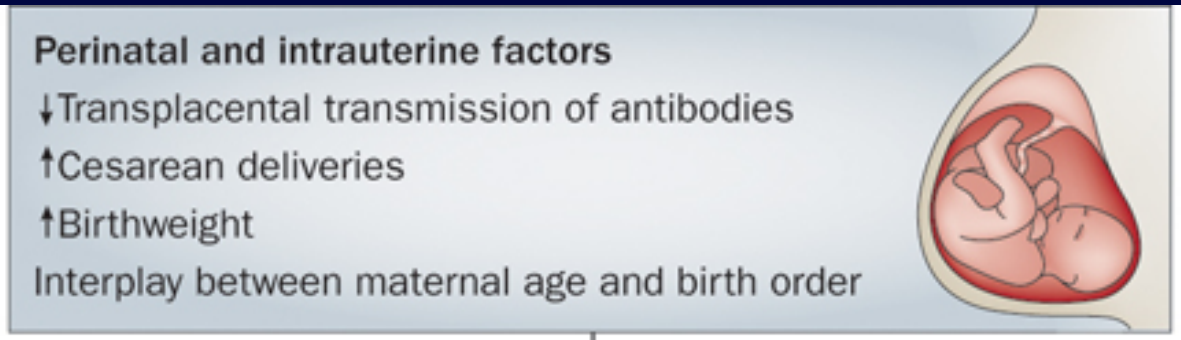
Muhlhausler et al, Trends Endocrinol Metab 2008

Diabetes Risk Begins In Utero



Woo M and Patti ME. Cell Metab 2008

Prenatal, perinatal and postnatal factors and Type 1 diabetes mellitus



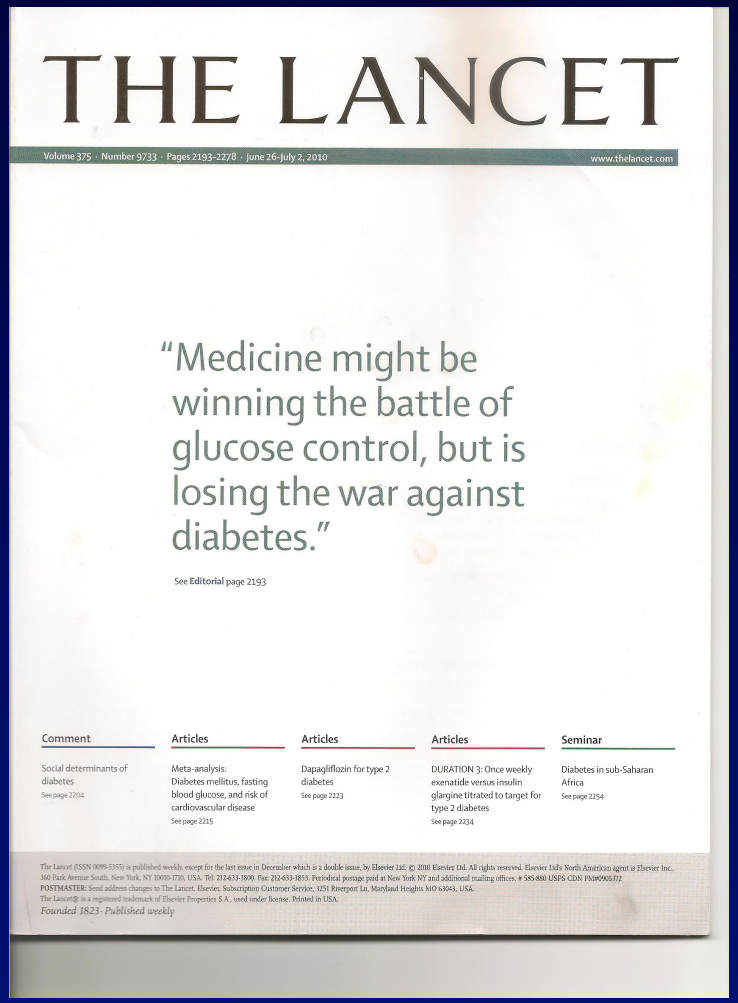
Prenatal factors
Genetic factors
HLA genotype

Islet autoimmunity

Clinical type 1 diabetes mellitus

Postnatal factors
↓Breastfeeding
↑Cow's milk exposure
↓Vitamin D intake
↓Childhood infections
↑Obesity
Viral infections
Other dietary factors

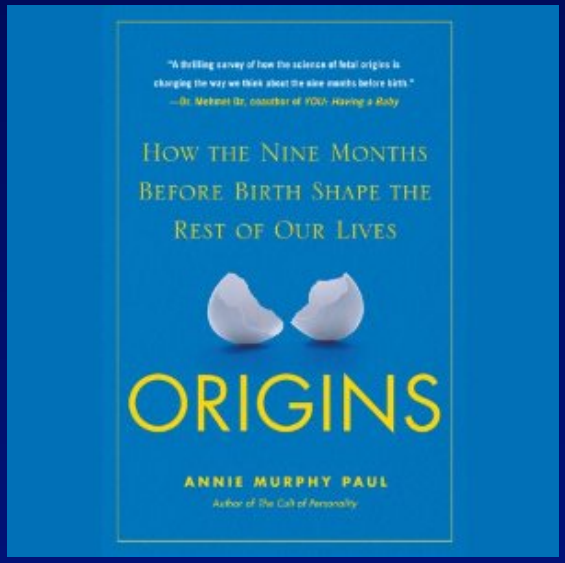
Ma, R. C. W. and Chan, J. C. N. (2009)
***Nat. Rev. Endocrinol.* doi:10.1038/nrendo.2009.180**



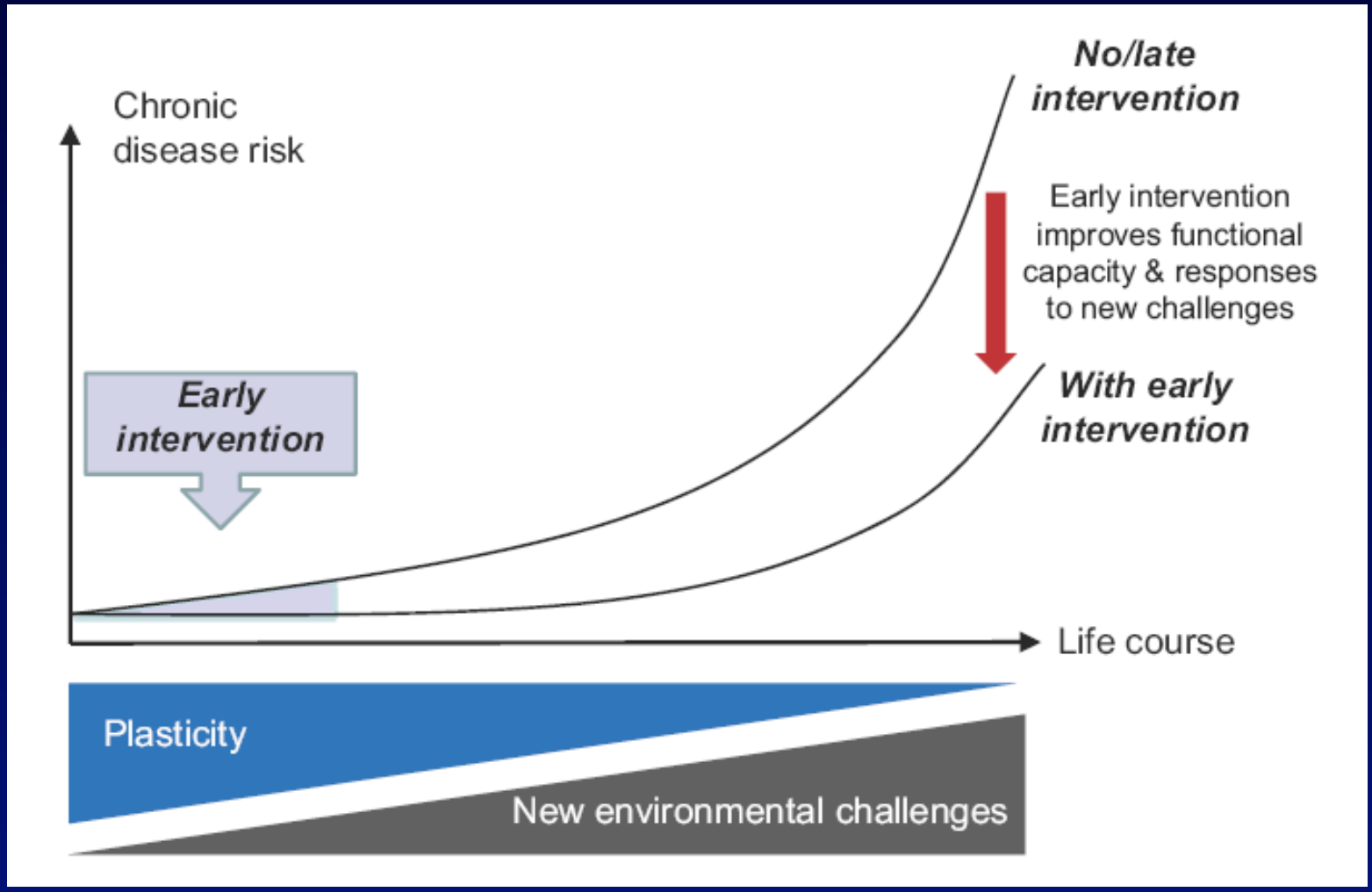
"Medicine might be winning the battle of glucose control, but is losing the war against diabetes"

The Lancet, 26 June 2010

"A Womb with a View"
-New York Times 27.9.10



Window of opportunity for Prevention of NCD



Hanson M et al, Prog Biophy Mol Biol 2011

Pre-pregnancy

- Education on the importance of good glycaemic control to optimize pregnancy outcome
- Screen for diabetes before conception in subjects with risk factors
- Encourage adequate physical activity
- Advocate balanced nutrition

During Pregnancy

- Early screening for pre-existing overt diabetes
- Repeat OGTT screening for GDM at 24-28 weeks if negative during first trimester
- Optimization of blood glucose levels during pregnancy for mothers with GDM or pre-existing diabetes
- Morphology scan at around 20 weeks in case of DM or GDM
- Fetal surveillance for growth parameters for DM or GDM

Peri-partum

- Close monitoring and maintain normoglycaemia
- Consider earlier delivery in cases with poor glycaemic control
- Consider elective Caesarian section for selective cases with macrosomia

After delivery

- For GDM mothers, post-partum oral glucose tolerance test at 6 weeks after delivery to exclude pre-existing DM
- Exclusive breast feeding should be encouraged for at least 6 months (WHO policy)
- Avoid over-nutrition and monitor weight gain for offspring

Long-term prevention

- Active lifestyle modification
- Monitoring of offspring growth

Summary

- Epidemic of diabetes and obesity in Asia
- Emerging importance of intra-uterine environment and epigenetic changes
- Maternal diabetes and obesity are important risk factors for childhood obesity and metabolic disturbances
- Maternal DM, GDM and obesity may perpetuate a vicious cycle of “diabetes begetting diabetes”
- Optimal nutrition during pregnancy and interventions of high-risk women provide opportunity for prevention


Thank you
Contact:
rcwma@cuhk.edu.hk