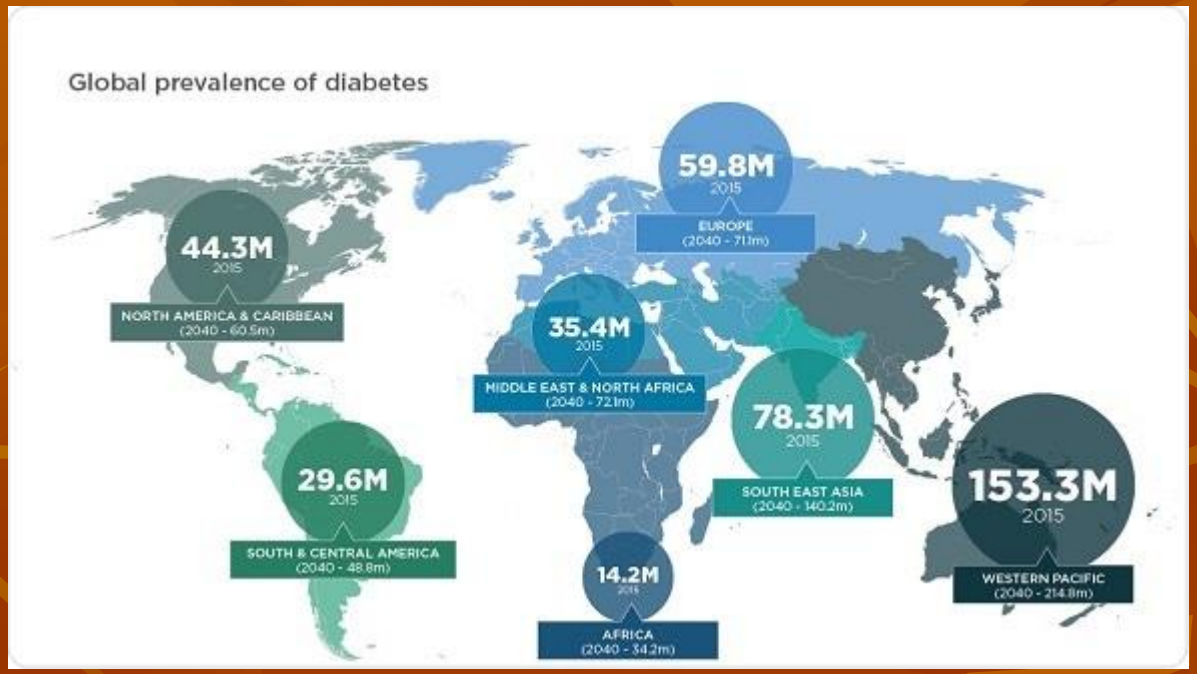
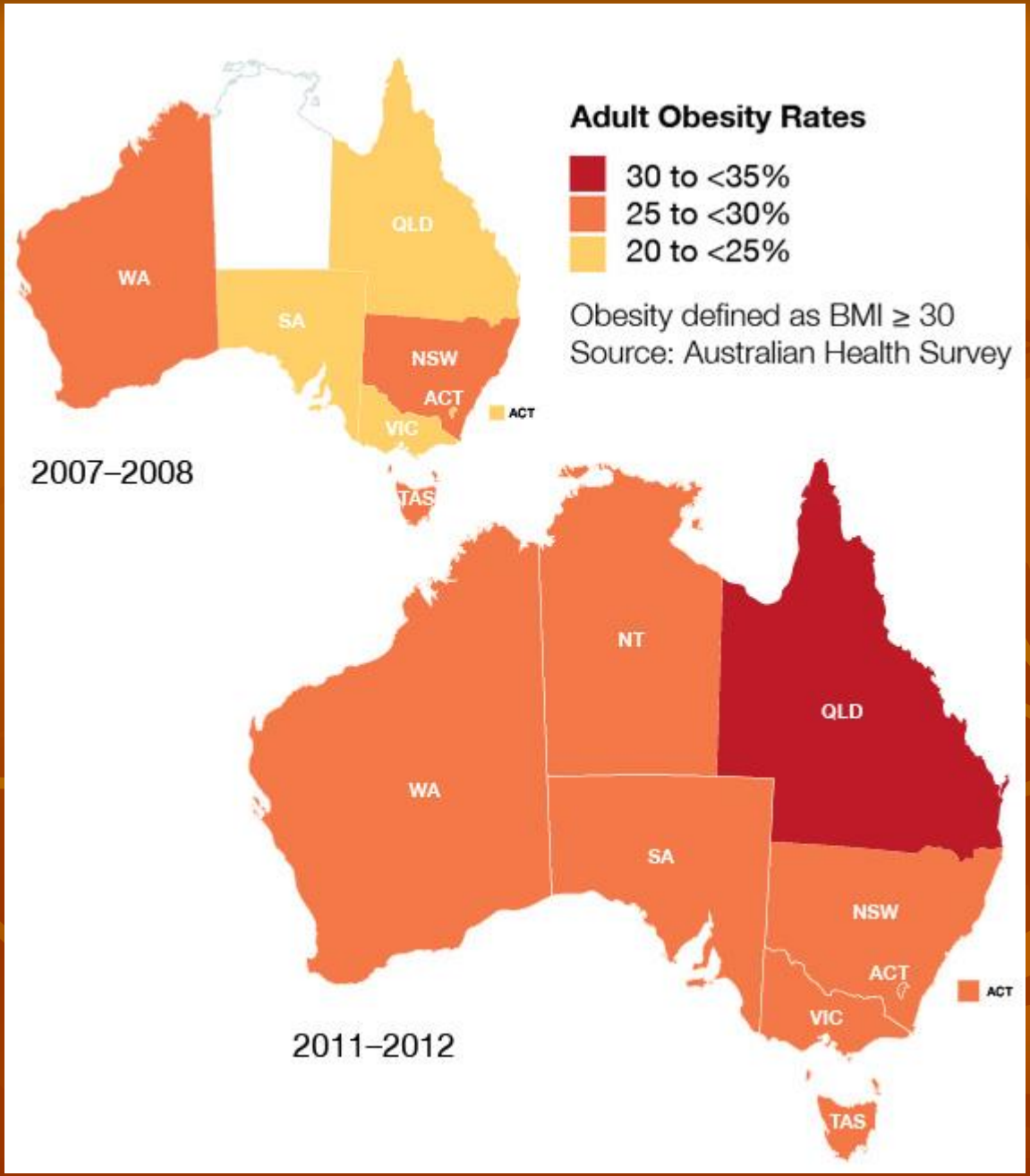
The Long term impacts of Diabetes in Pregnancy

Dr Dorothy Graham

Global diabetes epidemic




Adult Obesity Rates
30 to <35%
25 to <30%
20 to <25%
Obesity defined as BMI ≥ 30
Source: Australian Health Survey
WA
QLD
SA
NSW
ACT
VIC
TAS
ACT
2007–2008
NT
QLD
WA
SA
NSW
ACT
VIC
TAS
ACT
2011–2012

Maternal Diabetes

- Age of onset of type 2 diabetes has decreased significantly- approx 18% age of onset <40

- Global prevalence of hyperglycemia in pregnancy 16.9%, affecting 21 million births in 2013 (Guariguata, 2014)- GDM 87%

HAPO findings

- Progressive increase in adverse fetal outcomes with rising maternal glucose levels
- Maternal obesity combined with elevated glucose further increased risks
- New cutoffs recently adopted in most Australian centers

Consequences of GDM/ Diabetes

MOTHER (Medium-Long term)

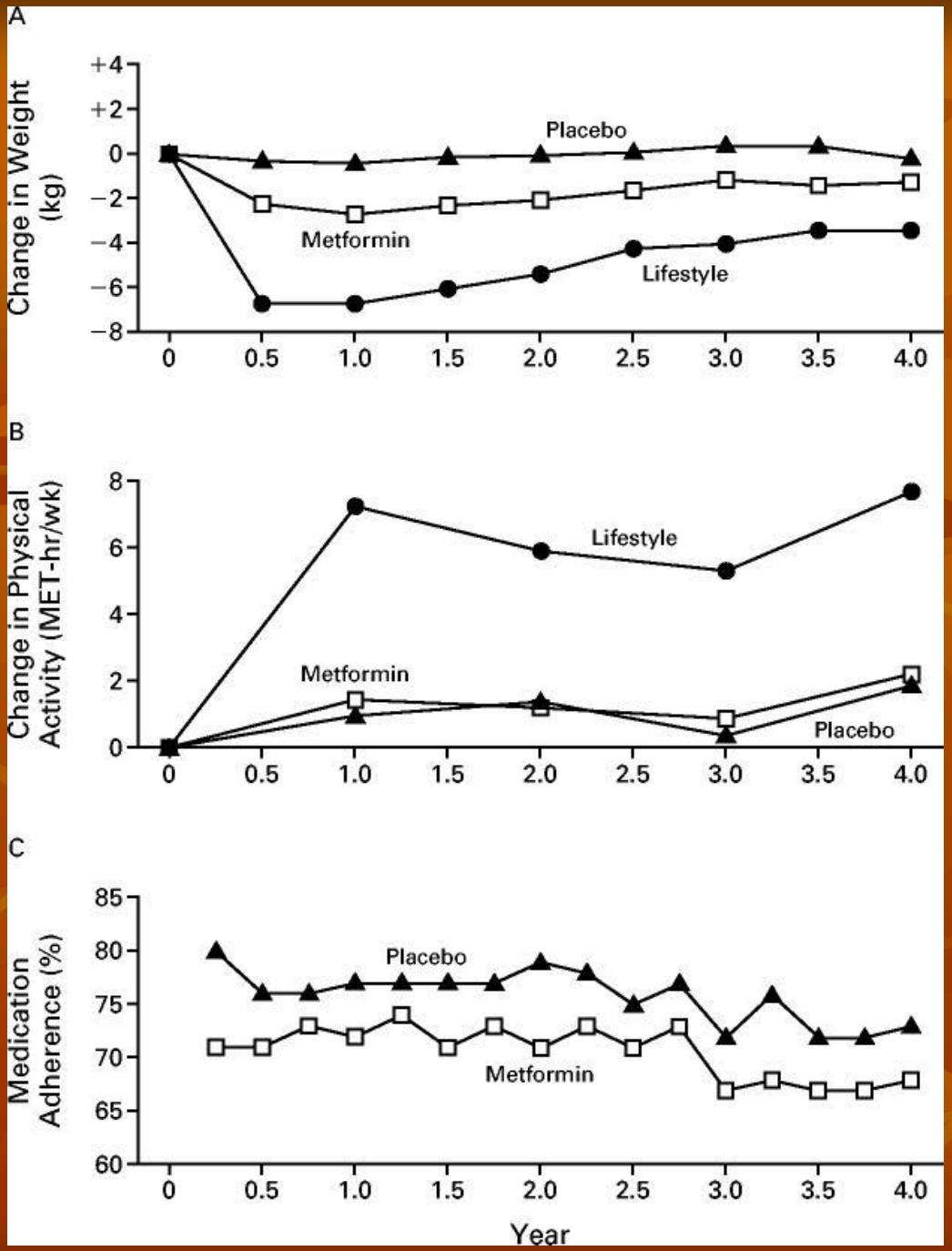
- Recurrent GDM
- Type 2 diabetes
- Hypertension/cardiac disease/vascular disease

OFFSPRING (short term and long term)

- Neonatal- macrosomia, hypoglycemia, prematurity
- Childhood Obesity
- Childhood/early adult type 2 diabetes
- Lower cognition, educational attainment, ADHD

Characteristics of women developing T 2 diabetes by 2 years postpartum

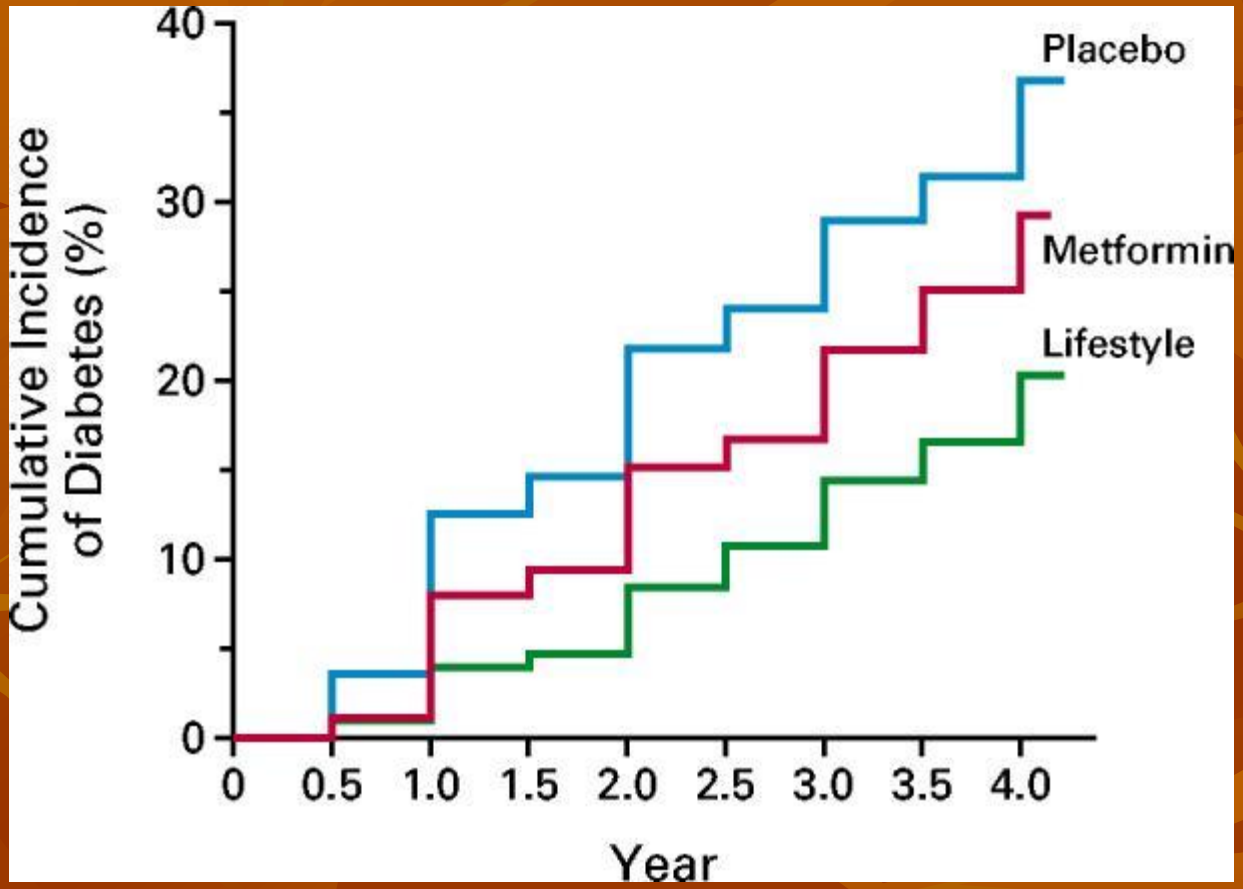
- IGT postpartum, Damm et al., 2004
- Req for insulin or oral meds for GDM (17.28 RR, Greenberg et al., 1995), LGA neonate
- Gest age at diagnosis of GDM, preterm delivery
- Higher BMI/ weight gain (2x risk for each 4.5kg)
- 2 or + abnormal levels on OGTT (Bian, 2000)
- High fasting glucose
- Higher animal fat consumption/ lower activity



Diabetes Prevention Program Group

NEJM, 2002

Risk of progression to diabetes



Effect of further pregnancy following GDM on risk of T2 diabetes

- 16,817 GDM pregnancies followed 4.5 years
- GDM recurred in 41.5%
- Subsequent GDM preg increased risk of diabetes by 1.16
- Subsequent nonGDM preg assoc HR of 0.34

Retnakaran, 2011

- 2 other studies with longer followup showed RR of 2.3 and 3.3 for subsequent GDM pregs

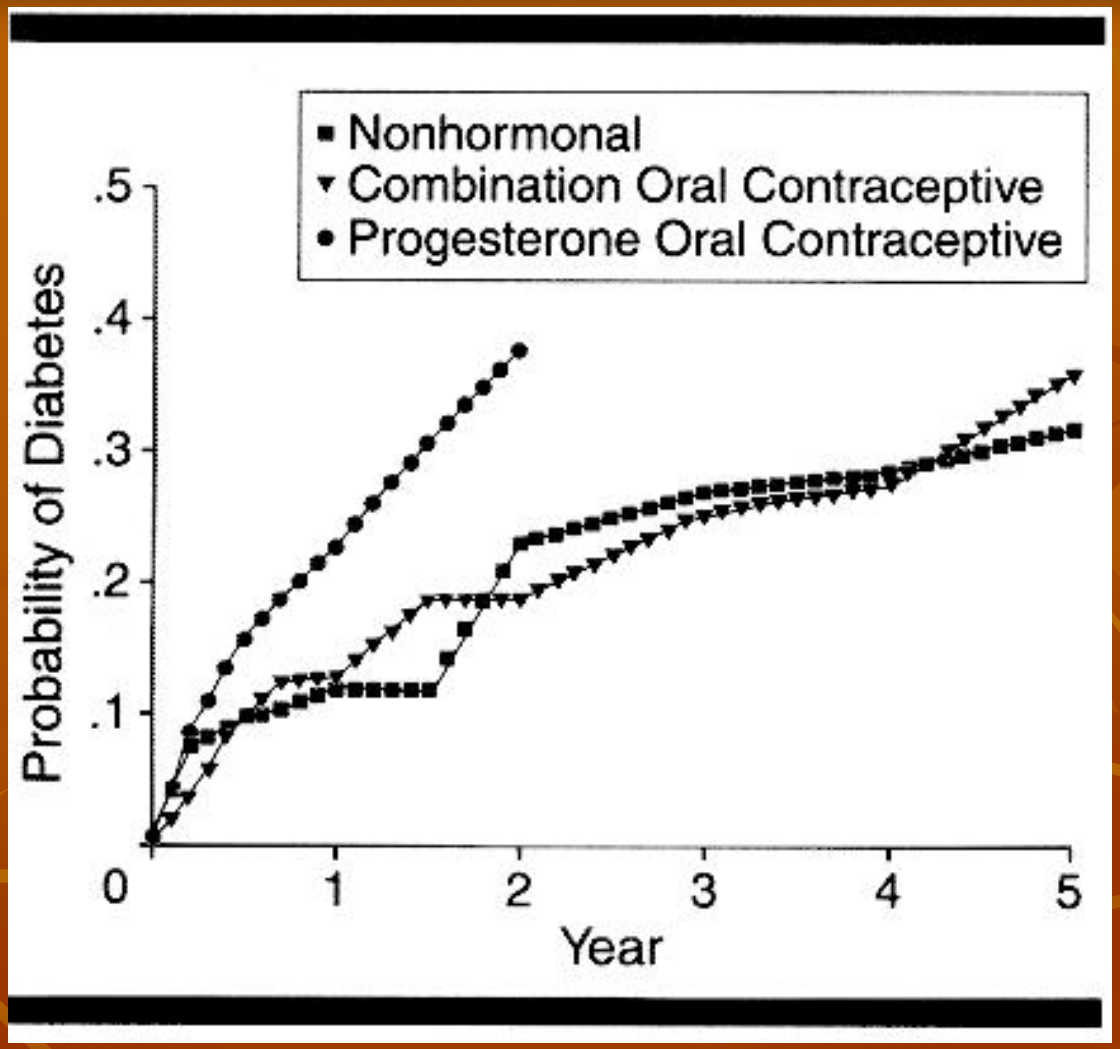
Physical activity and sedentary behaviour and type 2 diabetes risk following GDM

Median MET-hr/wk	1.5	6.6	15.2	37.2
T2 cases	221	179	127	108
Adjusted RR	1	0.88	0.79	0.72

TV watching	0-5	6-10	11-20	20+
RR	1	1.28	1.41	1.77

Contraceptive choices for women with GDM

- Progestins decrease glucose tolerance, increase insulin resistance and increase low-density lipoprotein levels.
- Breast-feeding women with prior GDM using oral progestin-only contraceptive had almost 3-fold ↑ diabetes progression
- Low dose combination oral contraceptives do not increase progression to type 2 diabetes in women with previous GDM



Cumulative incidence rates of type 2 diabetes as determined by interval-censored survival analysis in 904 Latinas

Kjos,1998

Contraception (cont)

- No studies of implanon in women with prior GDM however no effect on CHO metabolism in healthy women.

- Levonorgestrel-releasing

IUD also considered suitable

Breastfeeding and risk of diabetes

- Nurses study found 15% ↓ risk of T2 diabetes for each year of lifetime lactation after adjusting for family history of diabetes, diet, exercise and body mass index

  JAMA, 2005, 294, 2601-2610

- Breastfeeding women more likely to have normal followup GTT

  O'Reilly et al., 2012

Breastfeeding and risk of type 2 diabetes following gestational diabetes

- SWIFT study (study of women, infant feeding and type 2 diabetes after GDM pregnancy)
- Prospective observational study of 1035 women with GDM 2008-2011
- Followup 6-9 weeks then annually for 2 years with GTT, anthropometry, interviews
- 11.8% developed type 2 diabetes

Adjusted HR of DM within 2 years of GDM by time-dependent lactation duration

	0-2 months n=189	**>2-5 months n=190**	**>5-10 months n=208**	**>10 months n=372**	**P value**
Age-adjusted	1	0.64	0.44	0.38	0.001
Mat-perinatal risk factors, newborn outcomes, pp lifestyle behaviours	1	0.54	0.55	0.43	0.01
Add weight change from delivery to 1 year pp	1	0.48	0.65	0.47	0.037

Breastfeeding and lipids 6-9 weeks postpartum

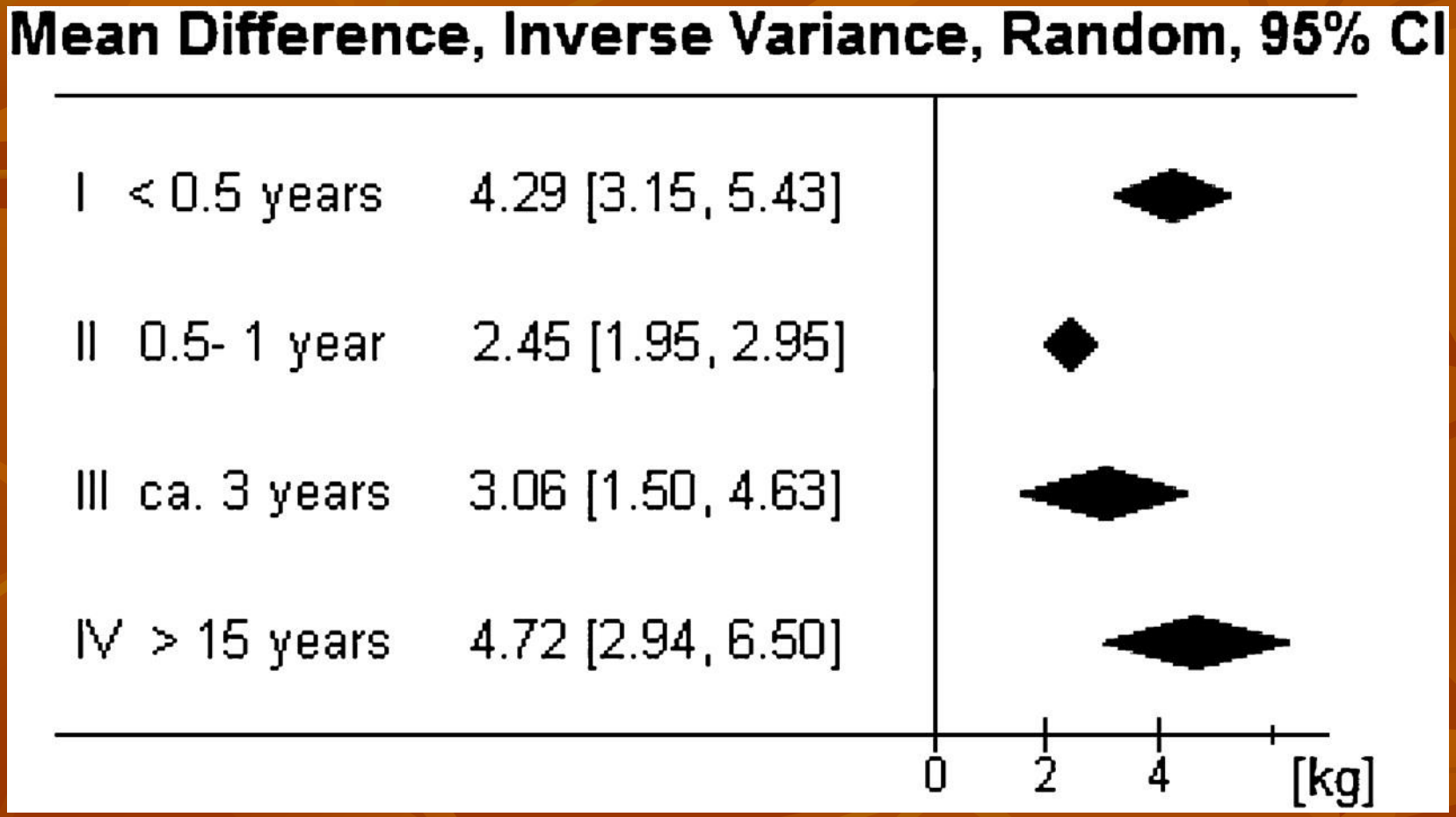
	Exclusive BF n=437	Mostly BF n=183	Mixed n=127	Exclusive FF N=257	P value
HDL	54.2	53.1	51.8	50.4	<0.01
LDL	126.9	126.5	118.3	122.8	0.08
TG	99.1	110.4	125.8	138.8	<0.001

Gunderson et al., 2014

Weight Gain

Pre-pregnant BMI	IOM Recommendation	Cedergren Obstet & Gynecol 2007
Underweight (<19.8)	12.5 – 18kg	4-10 kg
Normal weight (19.8- 26.0)	11.5 – 16kg	2- 10 kg
Overweight (26.0 – 29.0)	7 -15 kg	< 9 kg
Obese (>29.0)	min 6.8 kg	< 6 kg

Gestational weight gain and postpartum weight retention



Nehring et al., 2011

Interpregnancy weight change and GDM risk

- 7897 women with 2 births between 2009-2011 in Flanders
- Mean prepreg bmi ↑ from 23.3-23.9
- ↑ prevalence overweight/obesity 25.4-31.4%
- 8.6% of normal weight women shifted to overweight category
- If normal or underweight and gained 2+ bmi units had 2.2 x increased risk of GDM and increased risk of hypertension next preg

Bogaerts et al., 2013

Childbearing & permanent weight gain

- Excess weight gain 10 yrs after 1st pregnancy:
  for normal weight women (BMI<25)=1kg
  for overweight women (BMI≥25)=5-6kg

- Excess waist circumference gains:
  normal weight women=2-3cm
  overweight women=3-6cm
  excess gains also with subsequent births

Gunderson et al., Int J Obesity, 2004, 28, 525-535

Risk of hypertension after gestational diabetes

- Nurses Health Study II
- Risk of hypertension 1.8 times more common if history of GDM
- Adjusted risk (age, bmi, fhx hypertension) 1.26
- Mechanism unclear

CVS risk factors in Chinese women with hx GDM- Hong Kong study

	Control	Previous GDM	P value
Systolic blood pressure	106.7	111.1	<0.001
Diastolic blood pressure	68.2	72.2	<0.001
BMI	22.5	24.8	<0.001
HbA1c	4.44	5.5	<0.001
Triglyceride	0.67	1.08	<0.001
HDL	1.55	1.39	<0.001
LDL	2.91	3.44	<0.001

Ko et al, 1999

Long term maternal cardiovascular morbidity

	GDM (n=4928) %	No GDM (n=42,981) %	Adjusted OR	P value
Cardiovascular hospitalisations	8.9	3.1	2.3	0.001
Invasive cardiac diagnostic procedures	0.8	0.4	1.4	0.051
Simple cardiovascular events	7.4	2.1	2.7	0.001

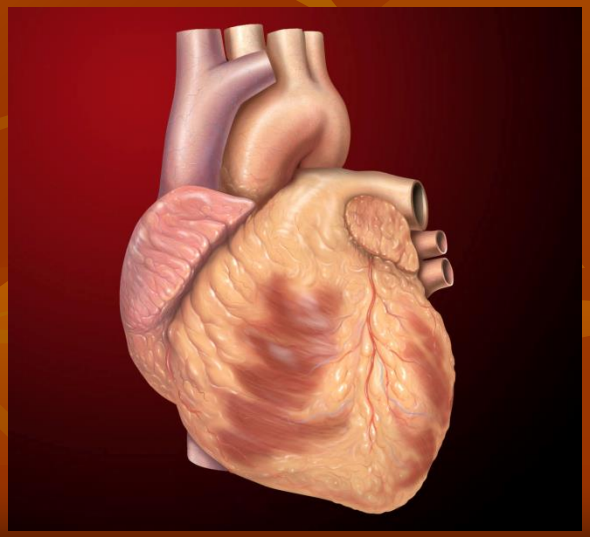
GDM and the Left Ventricle

- CARDIA study
- 64 women with GDM/609 births
- Echocardiography 20 years after initial echo 5 years post enrolment:

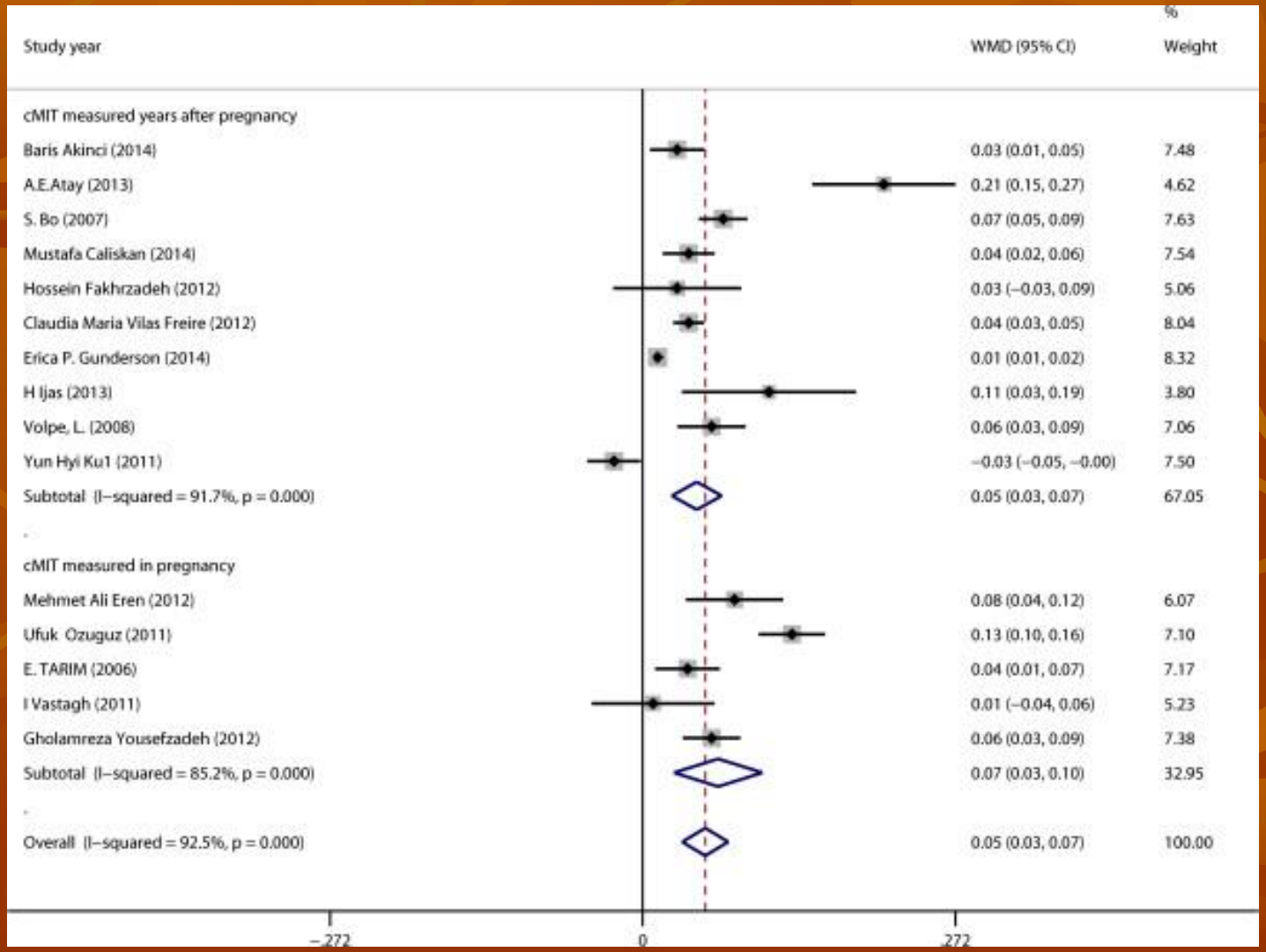
GDM : greater LV mass (14.3 vs 6 g/m^2)

: impaired LV relaxation

: lower LV function



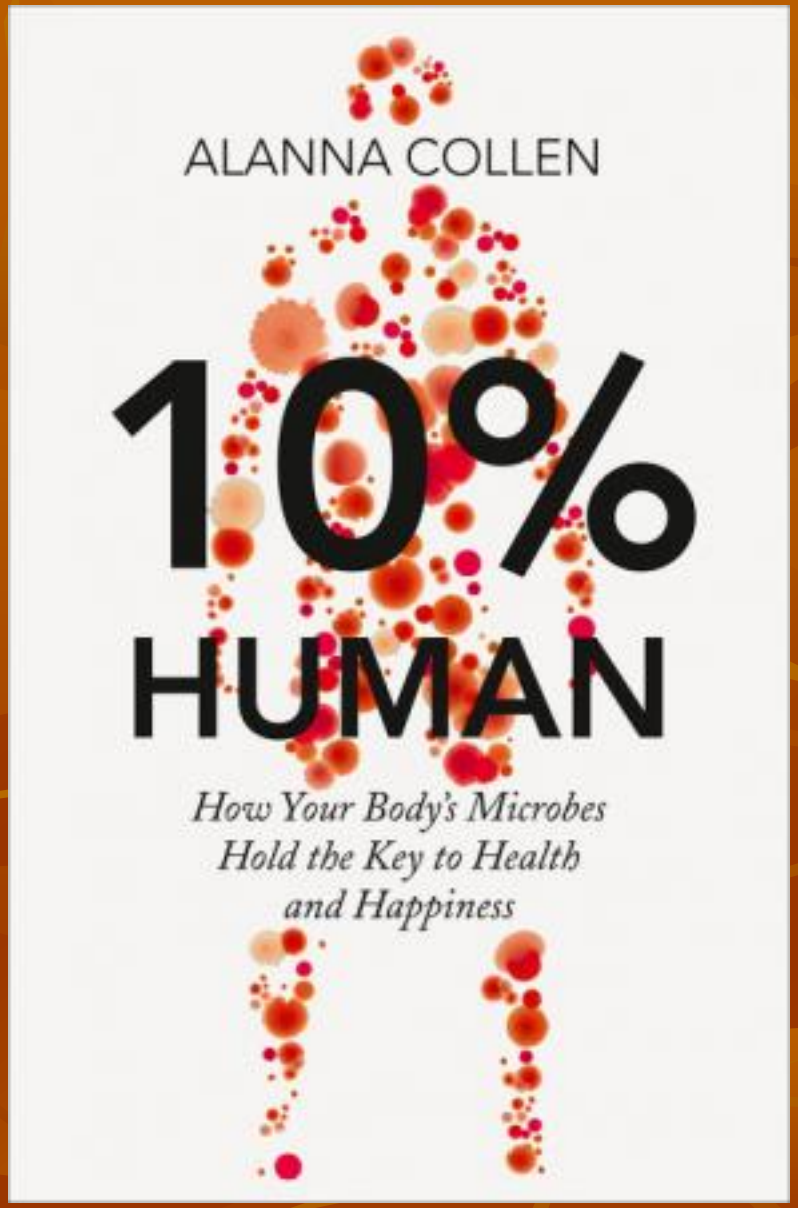
Carotid intimal thickness and GDM- metaanalysis



Li, 2014

Insulin resistance

- Women with previous GDM have relatively decreased insulin secretion (lean and obese) despite normal glucose tolerance- impaired beta cell function and insulin resistance
- Diet extremely important- approx 50% ↓ risk
- Metformin, thiazolidinediones, GLP-1 receptor agonists


ALANNA COLLEN
10%
HUMAN
How Your Body's Microbes
Hold the Key to Health
and Happiness

Probiotics and GDM risk

Non-obese women (average bmi =23.6)
GDM criteria: 4.8/10/8.7

	Diet/probiotics N=85	Diet/placebo N=86	Control N=85	
GDM	10/76 (13%)	27/76 (36%)	25/73 (34%)	p=0.003
Birthweight	3467g	3579g	3611g	p=0.035

Luoto et al., 2010

SPRING- RCT of probiotics in overweight/obese women starting in Brisbane

Probiotics in women with GDM

- **Lindsay et al., 2015**, Am J Obs & Gynae

  100 women with GDM or impaired glucose tolerance randomised to probiotics or placebo until delivery

No difference in glucose levels or outcomes- attenuated rise in LDL cholesterol in probiotic group

Macrosomia

- Diabetic control, maternal bmi, genetic factors, duration of diabetes/vasculopathy, smoking status

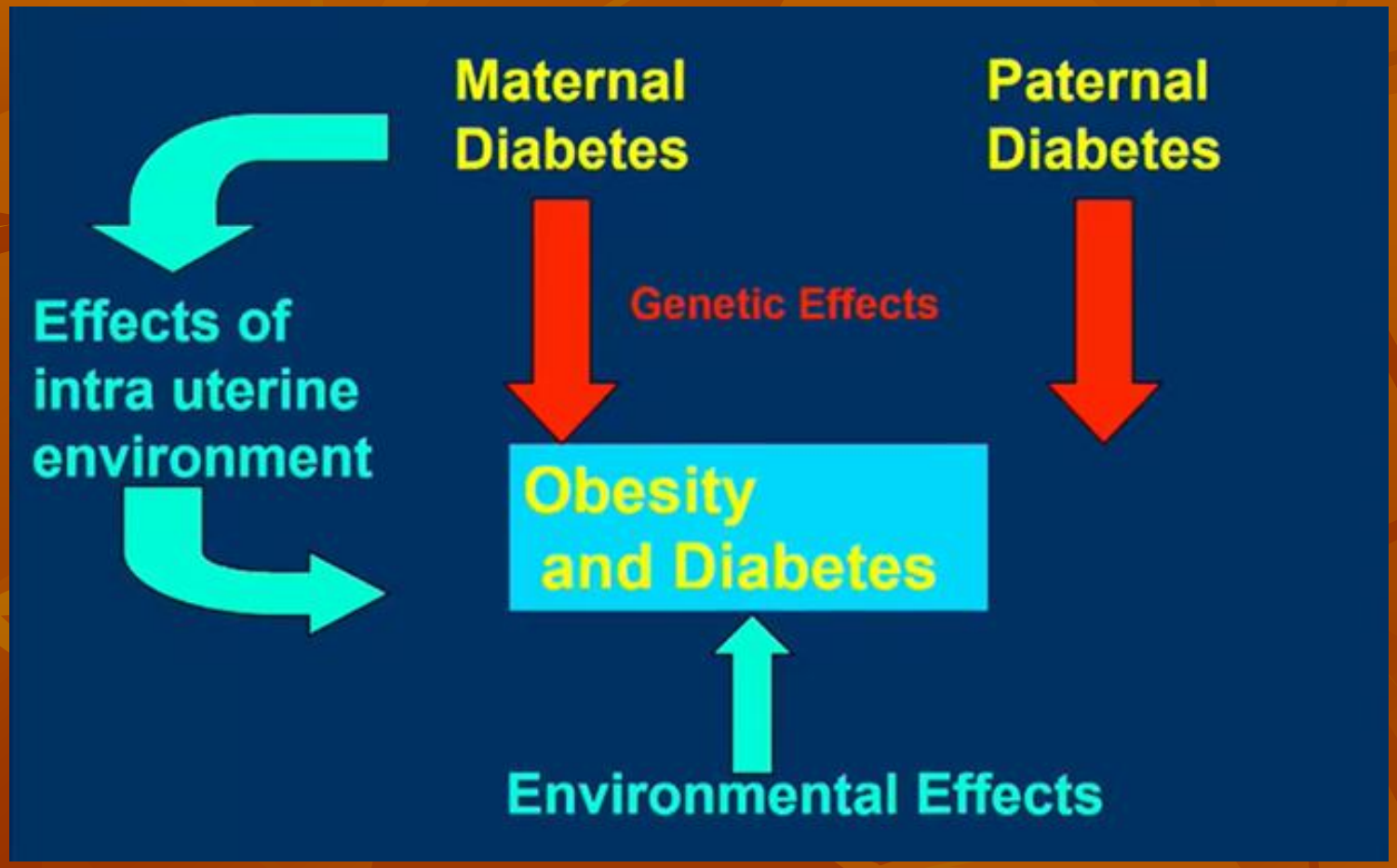
Preeclampsia risk and treatment of gestational diabetes

Maternal Outcomes.*

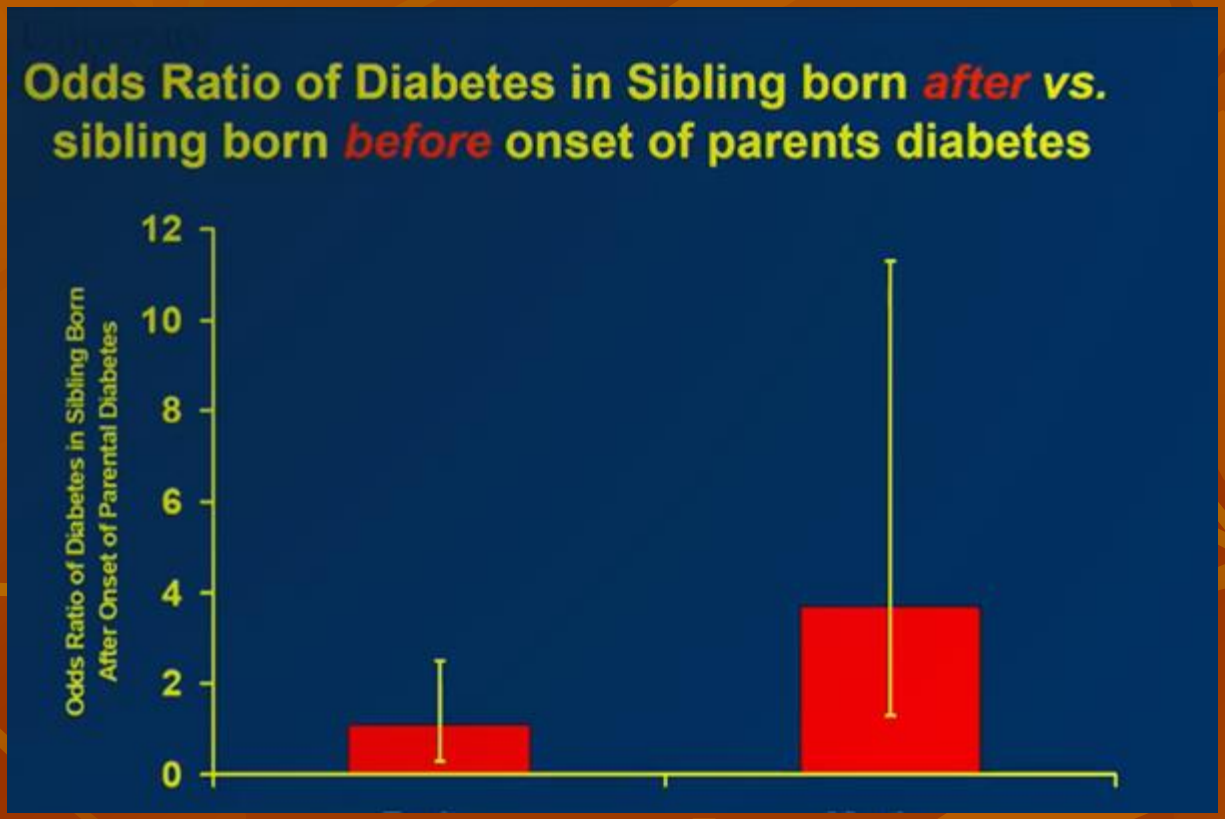
Outcome Variable	Treatment Group (N = 476)	Control Group (N = 455)	Relative Risk (97% CI)	P Value
Induction of labor — no. (%)	130 (27.3)	122 (26.8)	1.02 (0.81–1.29)	0.86
Cesarean delivery — no. (%)	128 (26.9)	154 (33.8)	0.79 (0.64–0.99)	0.02
Shoulder dystocia — no. (%)	7 (1.5)	18 (4.0)	0.37 (0.14–0.97)	0.02
Preeclampsia — no. (%)	12 (2.5)	25 (5.5)	.46 (0.22–0.97)	0.02
Preeclampsia or gestational hypertension — no. (%)	41 (8.6)	62 (13.6)	0.63 (0.42–0.96)	0.01
Body-mass index at delivery†	31.3±5.2	32.3±5.2		<0.001
Weight gain — kg‡	2.8±4.5	5.0±3.3		<0.001

*Plus–minus values are means ± SD. The number in each group refers to the number of women for whom all delivery data were available.
†The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡Weight gain refers to weight gain from enrollment in the trial until delivery.

Landon, 2009


Maternal Diabetes
Paternal Diabetes
Genetic Effects
Effects of intra uterine environment
Obesity and Diabetes
Environmental Effects

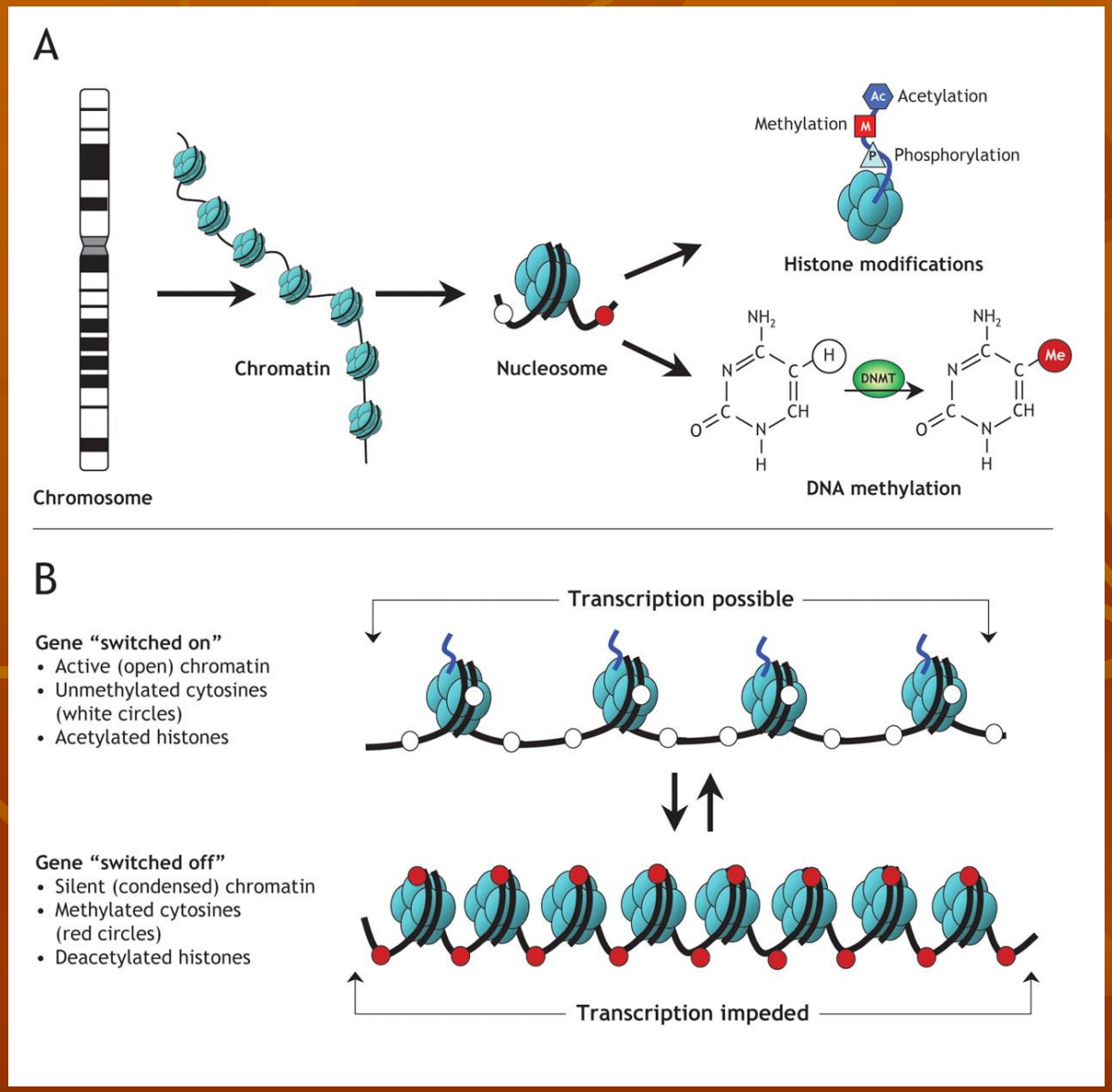
Paternal vs maternal diabetes



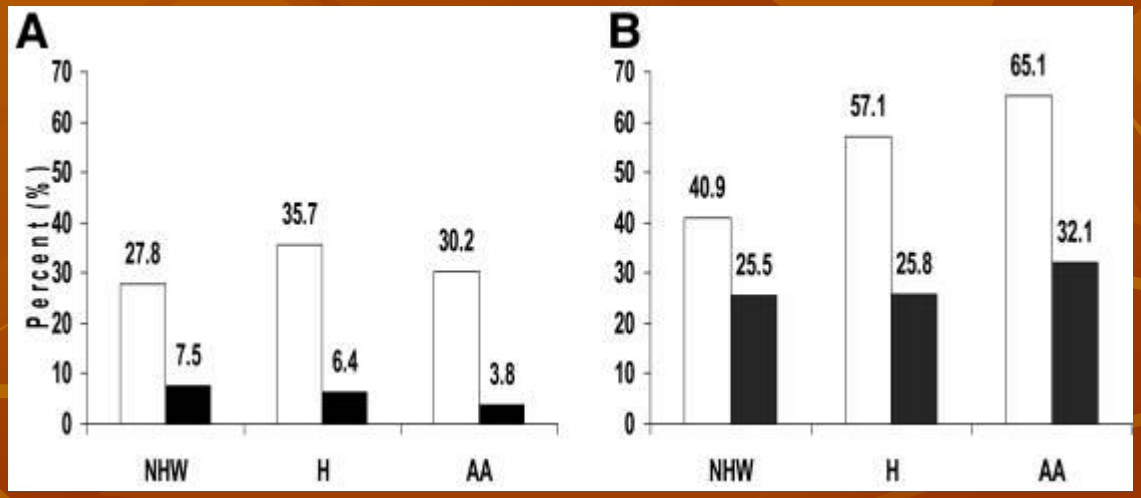
Father Mother

Dabelea et al., 2000

.Epigenetic modifications



Risk of youth diabetes and maternal diabetes/obesity- SEARCH study



Maternal diabetes (Pederson)

Maternal obesity (Freinkel)

Dabalea et al., 2008

Relative impact of maternal diabetes and obesity

Proportion of type 2 diabetes in youth attributable to intrauterine exposure to maternal diabetes and overweight/obesity

Exposure category	Case patients	Control youth	OR (95% CI)[*]	PAF[†]
Not exposed to either maternal diabetes or maternal obesity	36.7	68.9	1	Unexposed
Exposed to maternal diabetes only	6.3	3.7	3.9 (1.1–14.5)	4.7
Exposed to maternal obesity only	32.9	24.7	2.5 (1.3–5.0)	19.7
Exposed to both maternal diabetes and maternal obesity	24.1	2.6	19.2 (6.1–60.8)	22.8
Overall proportion of type 2 diabetes in youth attributable to in utero exposure to maternal diabetes and obesity		47.2 (30.9–63.5)[‡]		

Data are % unless indicated otherwise.

[*]ORs for the association between mutually exclusive exposure categories and case/control status, additionally adjusted for age, sex, and race/ethnicity.

[†]PAFs were calculated using the formula: $P_i\,[(OR_i - 1)/OR_i]$, where P_i is the proportion of case patients in each exposure category and OR_i is the adjusted OR comparing each exposed group with the unexposed reference category ($i = 0$).

[‡]Calculated using the formula: $\Sigma\,\sqrt{P_i}\,[(OR_i - 1)/OR_i]$.

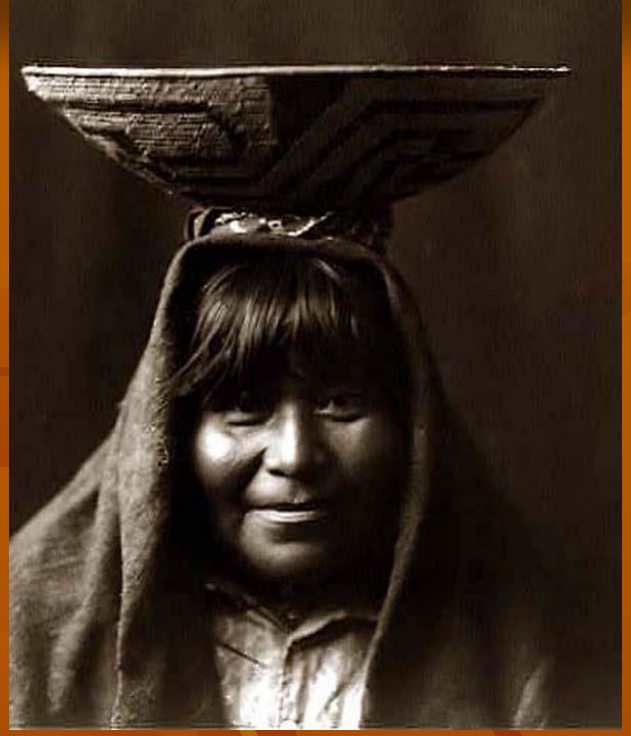
Dabalea et al.

Maternal diabetes and fetal epigenome

- Inverse correlation between maternal 2 hour postload glucose and DNA methylation of the fetal side placental leptin gene. (*Bouchard, 2010*)

- Inverse correlation between maternal 2 hour postload glucose and DNA methylation of fetal side placental adiponectin gene (*Bouchard et al., 2012*)

Pima Indians



- 58 siblings from 19 families with at least 1 diabetic sibling
- Diabetes 3.7 times more likely if born after maternal diabetes onset cf before
- BMI of 183 offspring of 52 mothers $2.6 kg/m^2$ higher in offspring of diabetic cf nondiabetic mothers at a mean age of 13

Dabelea et al., 2000

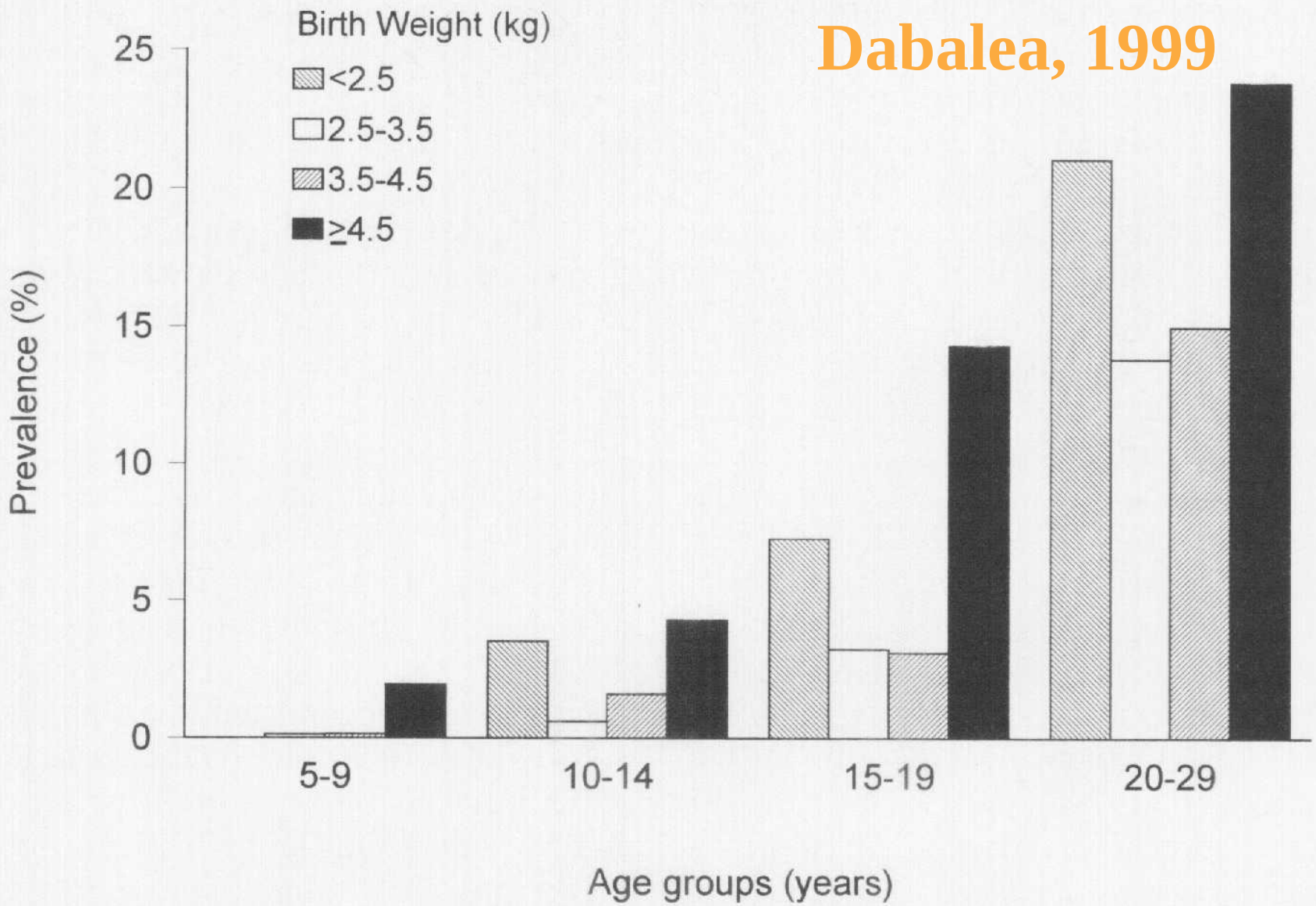


Figure 2—*Prevalence of type 2 diabetes by birth weight in age-groups 5–9, 10–14, 15–19, and 20–29 years.* P = *0.001 (Mantel-Haenszel* χ^2 *test, controlled for age and sex).*

Risk of Diabetes and intrauterine environment

	Diet controlled GDM	No GDM but risk factors	Type 1 diabetes	Background population
Offspring diabetes/IGT	21%	12%	11%	4%
BMI	23.7	23.8	23.5	22.4
Adjusted OR (maternal bmi, offspring age, FHx diabetes)	7.76	4.46	4.02	1

Clausen, 2008

Offspring adiposity and maternal diabetes

Within sibling analysis in 280,866 Swedish men found 0.94 kg/m^2 greater bmi in men whose mothers had diabetes during their pregnancy compared with brothers born before their mothers were diagnosed with diabetes. No difference after adjustment for maternal bmi.

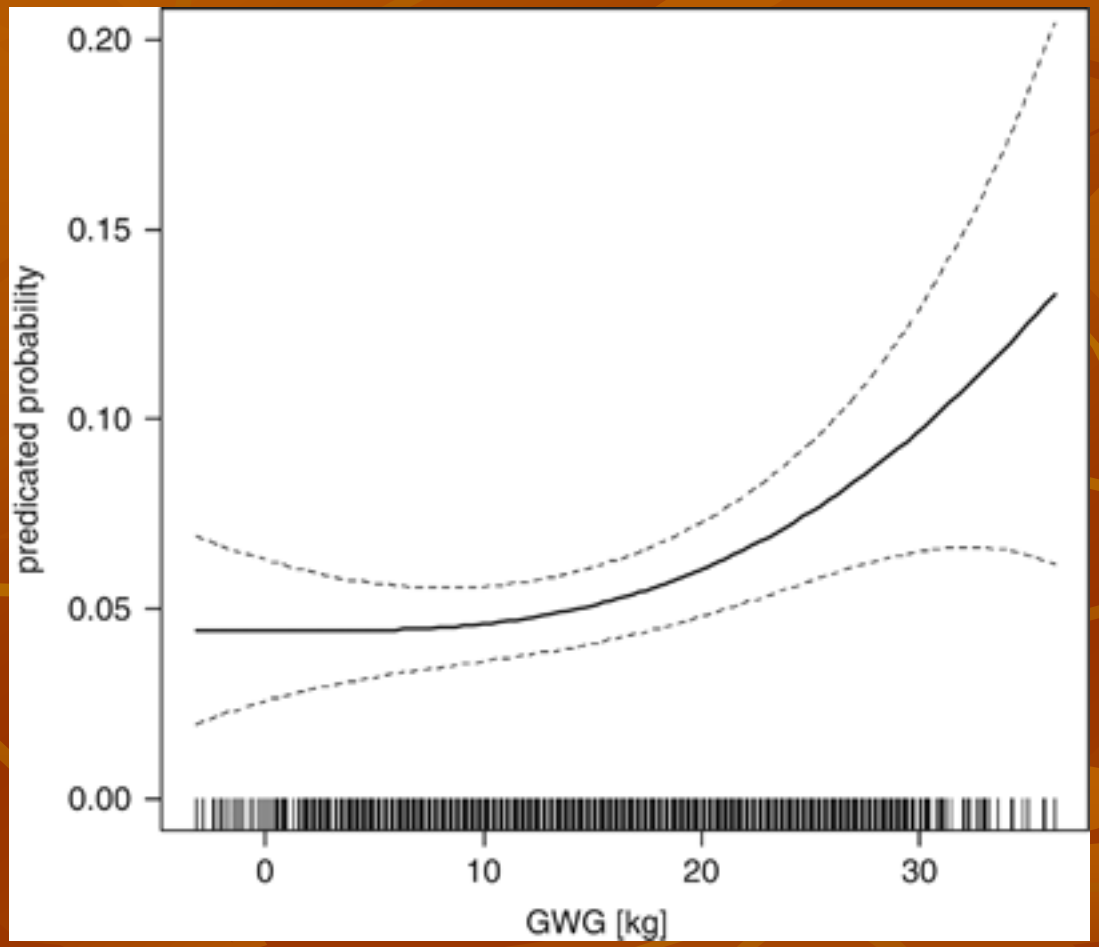
Lawlor et al., 2011

Prevention of transmission of obesity to offspring by maternal weight loss pre-pregnancy

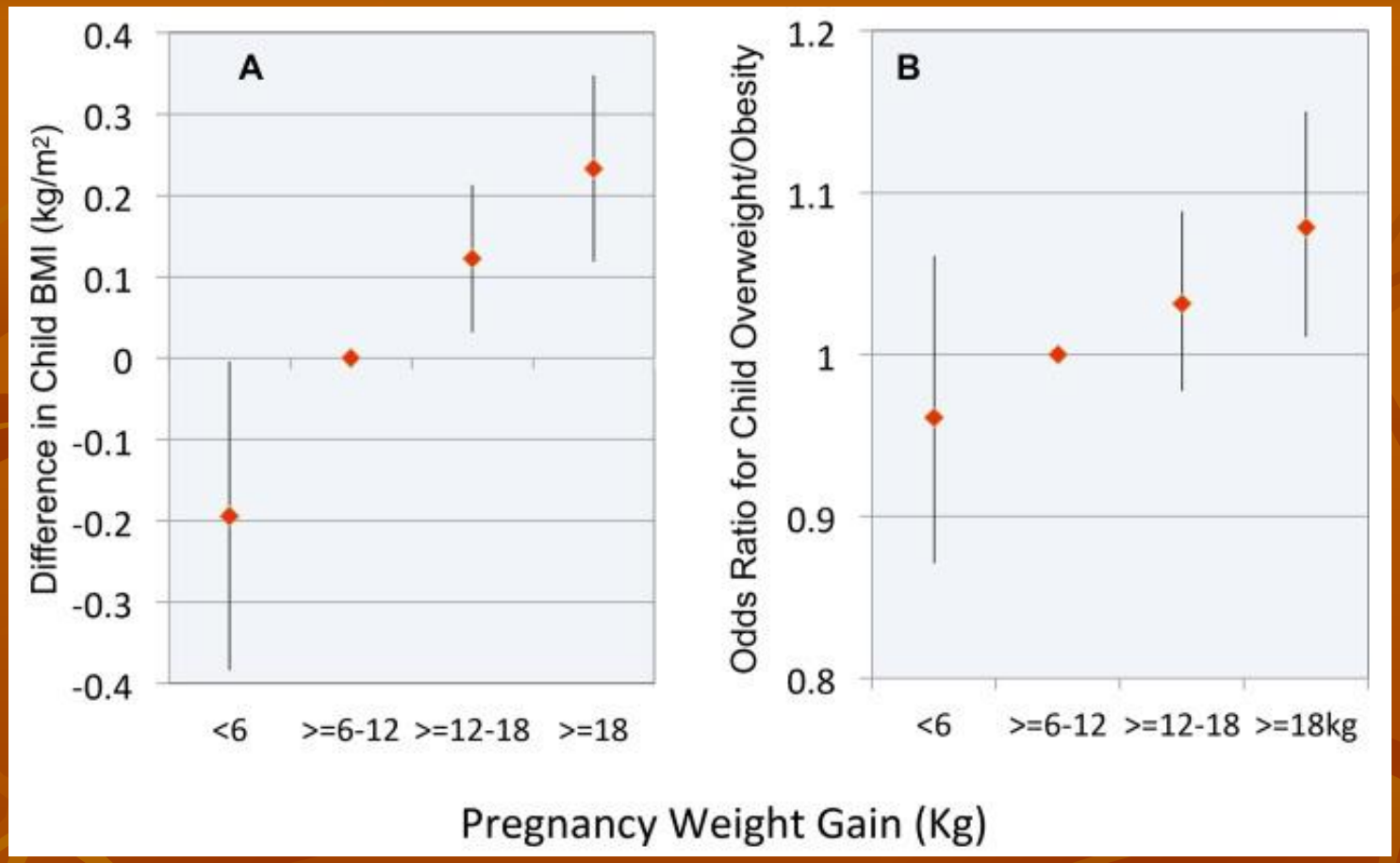
	Pre BS-bmi 48 n=45	Post BS bmi 31 n=172	P value
Normal weight	36%	57%	
Overweight	20%	16%	P=0.006
Obese	40%	19%	P=0.005
Underweight	4.4%	7.5%	

Kral et al., 2006

Probability of childhood overweight by GWG



Ensenauer et al., 2013, Int J Obesity



Relationship between pregnancy weight gain and body weight in childhood, Ludwig, DS et al., PLOS Med, 2013.

Maternal bmi effect on adolescent offspring

- Raine study data from 1392 mother and adolescent offspring show higher maternal prepregnancy weight and early pregnancy weight gain assoc higher adolescent bmi, systolic BP and insulin levels

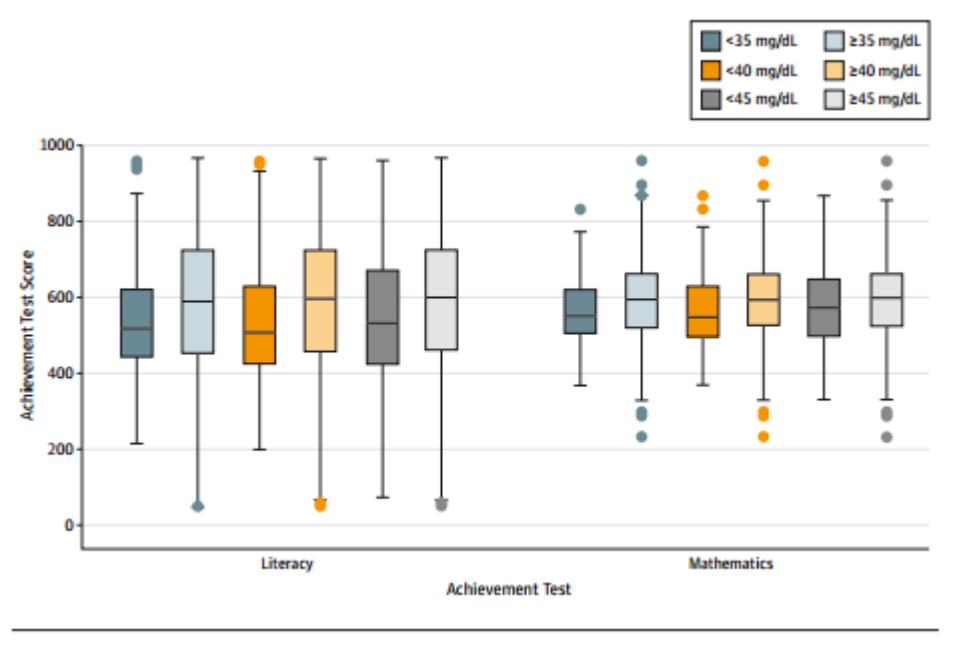
Gaillard et al., BJOG, 2015

Long-term cognitive implications of intrauterine hyperglycemia in adolescent offspring- EPICOM

	T1 diabetes (277)	Nondiabetic (301)	p
Intelligence indices			
Composite intelligence index	95.7	100	0.001
Verbal intelligence index	96.2	100	0.004
Nonverbal intelligence index	96.4	100	0.008
Composite memory index	95.7	100	0.001
Learning difficulties			
Reading problems	22.4%	18.7%	0.269
Writing problems	19.3%	16.3%	0.353
Learning diffs, Danish	23.3%	13.8%	0.003
Learning diffs, maths	16.4%	7.7%	0.001

Bytoft et al, 2016

4th grade achievement test scores for transient neonatal hypoglycemia



Kaiser et al. 2015

Breastfeeding and risk of diabetes in offspring

- Retrospective database study in Manitoba
- 334,553 deliveries with up to 24 yrs fup
- Breast feeding initiated in 83% non-First Nations mothers and 56% First Nations mothers
- Breastfeeding initiation associated with a 17% lower risk of youth-onset type 2 diabetes (HR 0.83, p=0.038)

Martens et al., Obs and Gyn, 2016

What can we do?

- Encourage weight loss prepregnancy
- Control weight gain
- Healthy diet
- Control blood glucose levels
- Support and encourage breastfeeding
- Support and encourage weight loss following pregnancy
- Consider metformin/other medications following pregnancy
- Encourage followup


THANK YOU