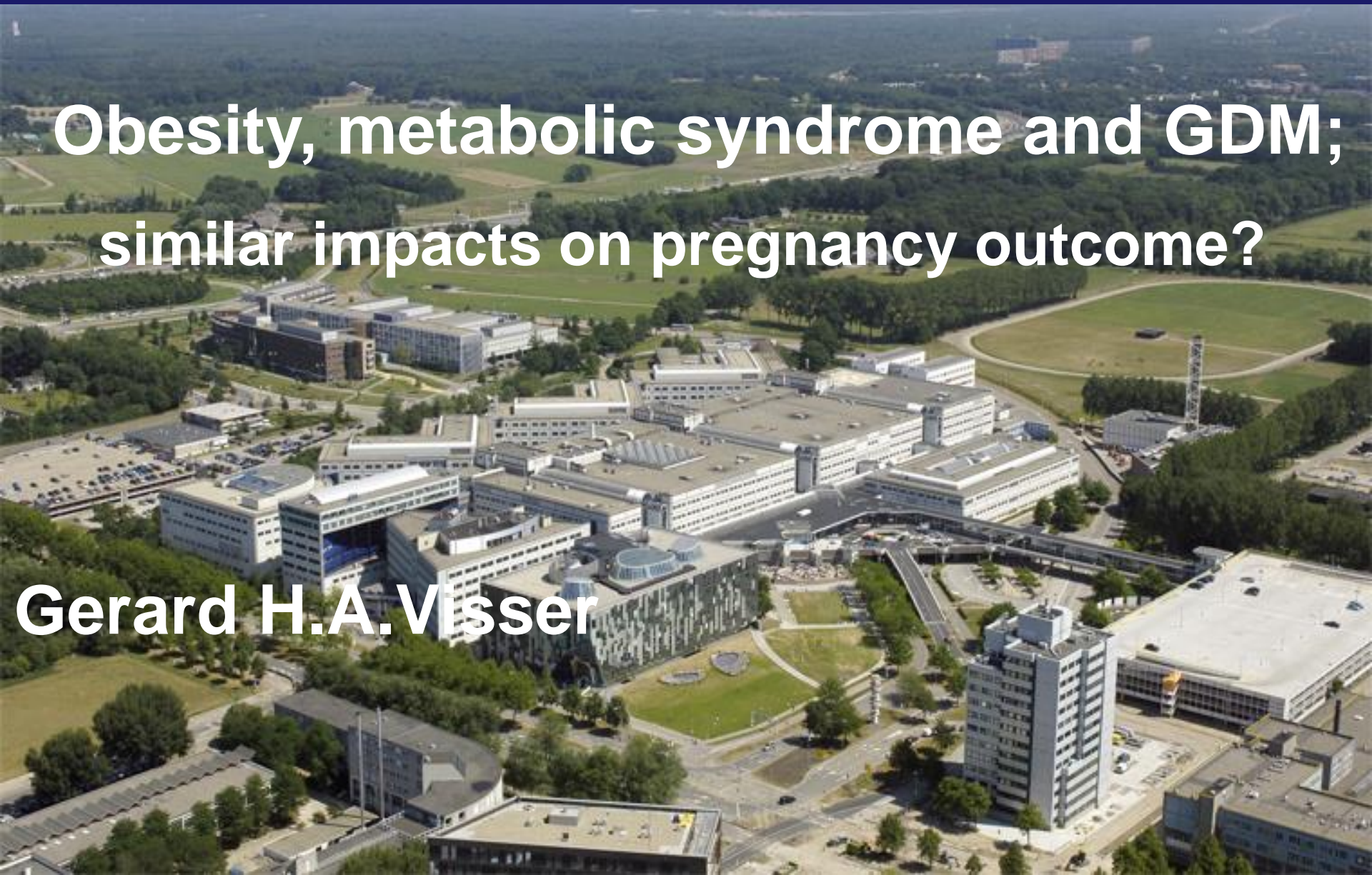


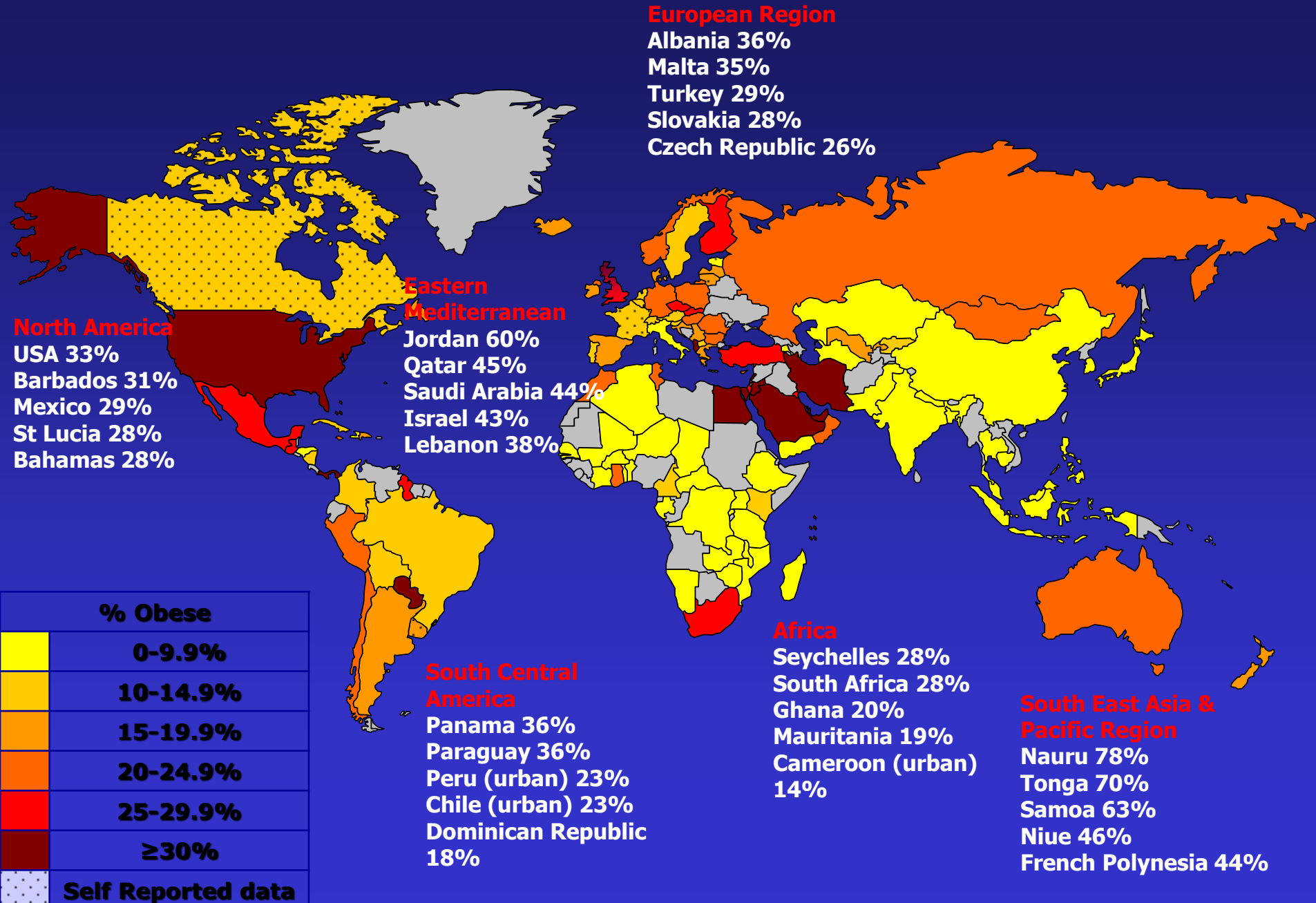
# University Medical Center, Utrecht, the NL

**Obesity, metabolic syndrome and GDM;  
similar impacts on pregnancy outcome?**

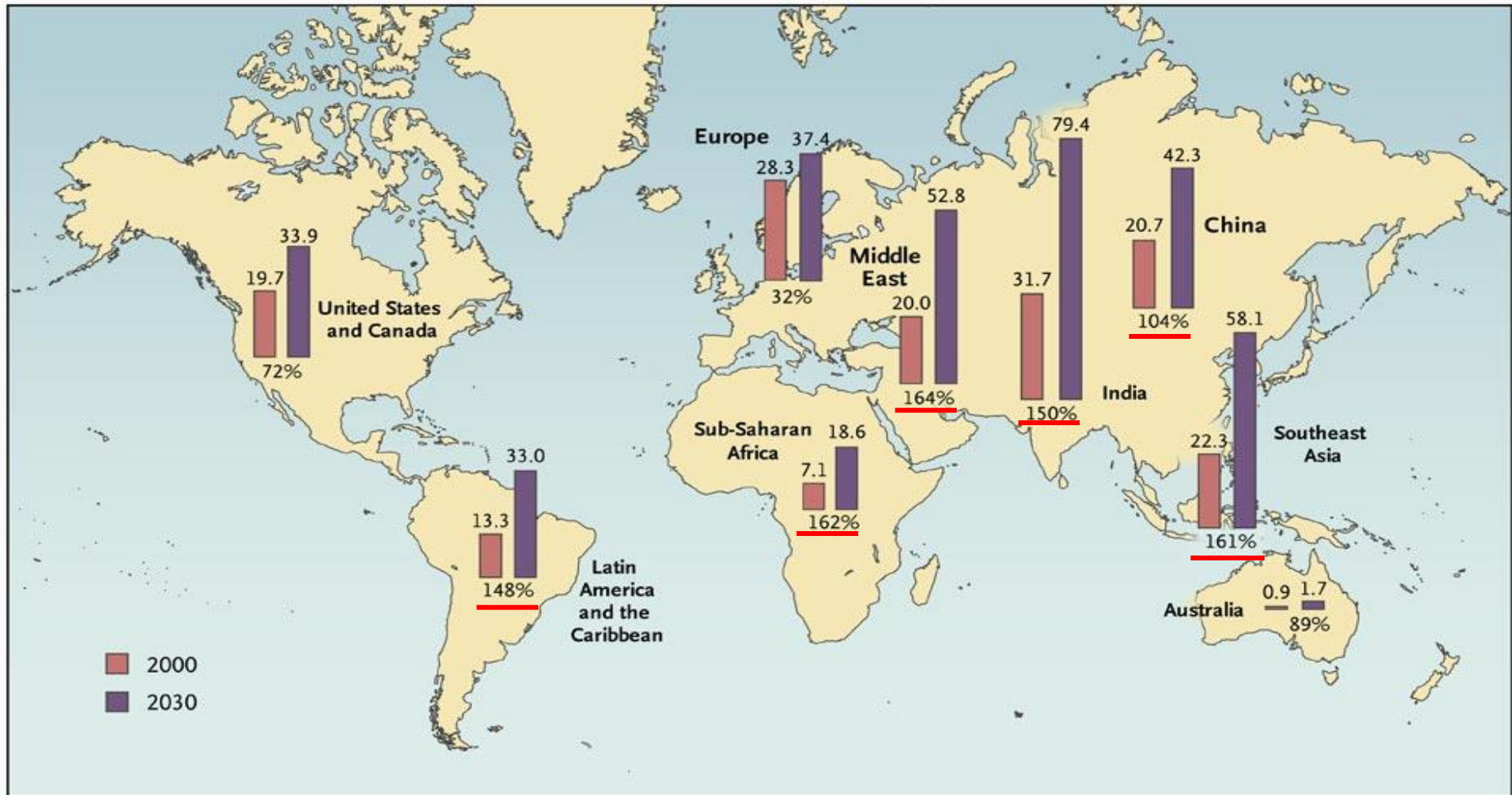
**Gerard H.A. Visser**



# Obesity – Global prevalence



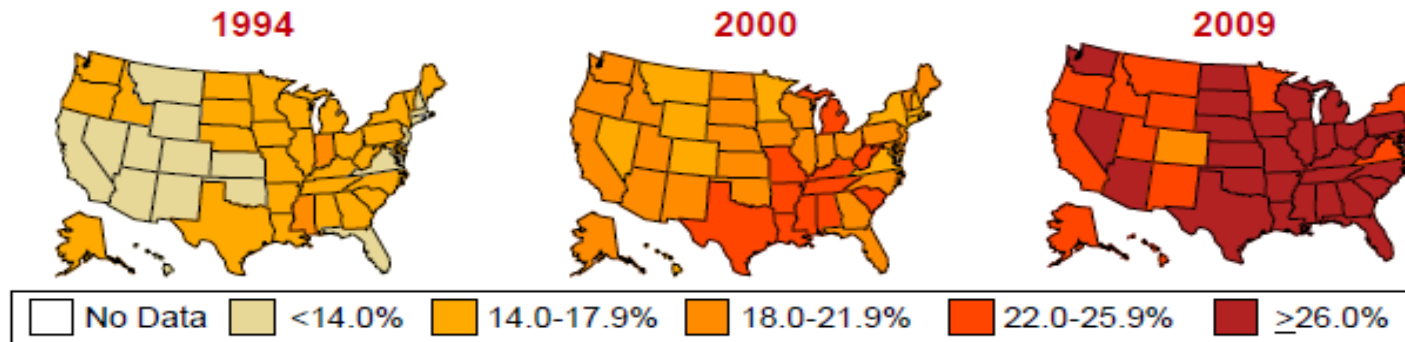
# The Epidemic of Diabetes, 2000 and 2030



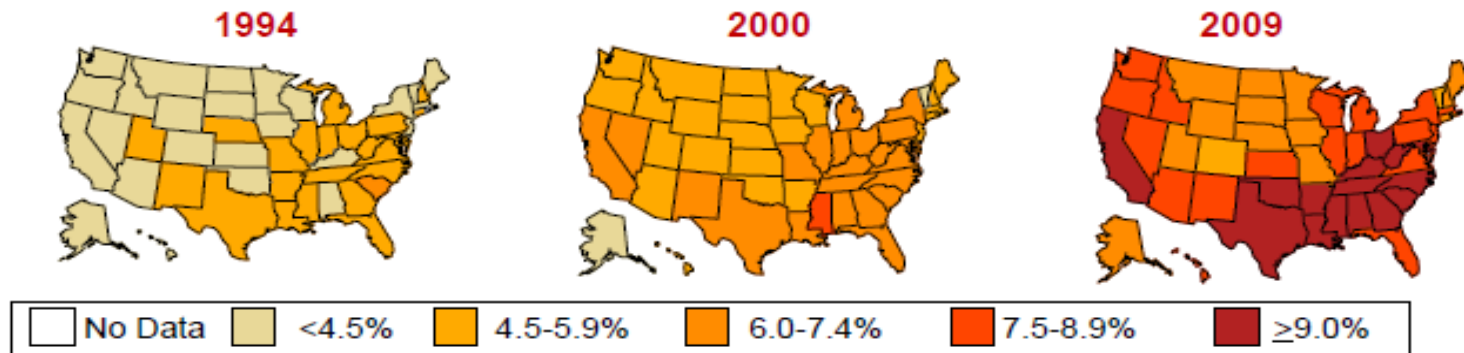
# Obesity and Diabetes in the USA

## Age-adjusted Percentage of U.S. Adults Who Were Obese or Who Had Diagnosed Diabetes

### Obesity (BMI $\geq 30$ kg/m<sup>2</sup>)



### Diabetes



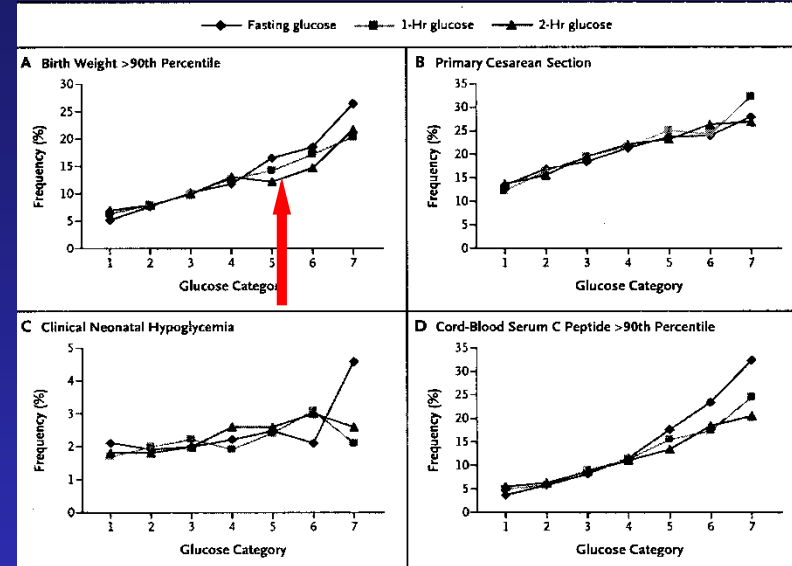
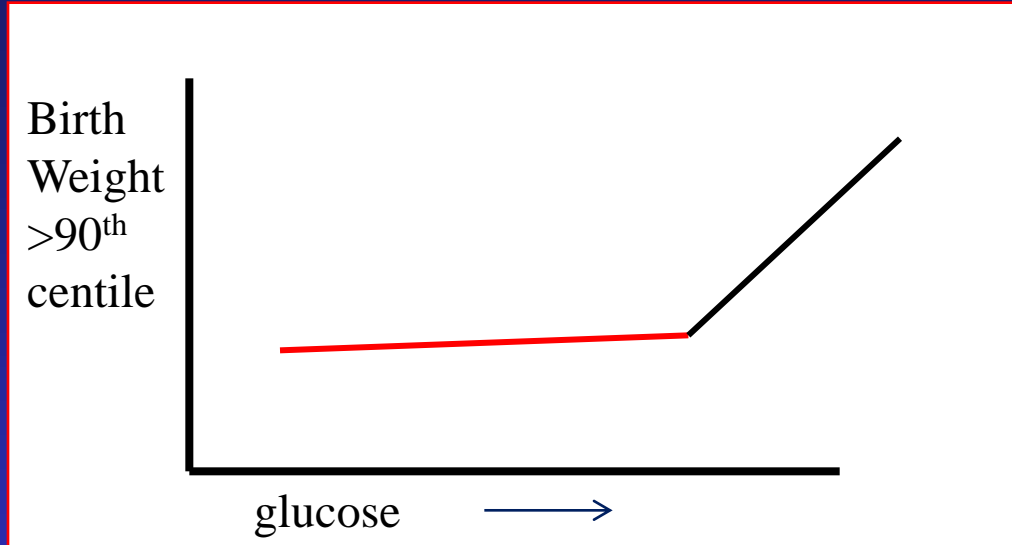
CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at <http://www.cdc.gov/diabetes/statistics>



**More diabetes, more gestational diabetes**

---

# More diabetes, more gestational diabetes

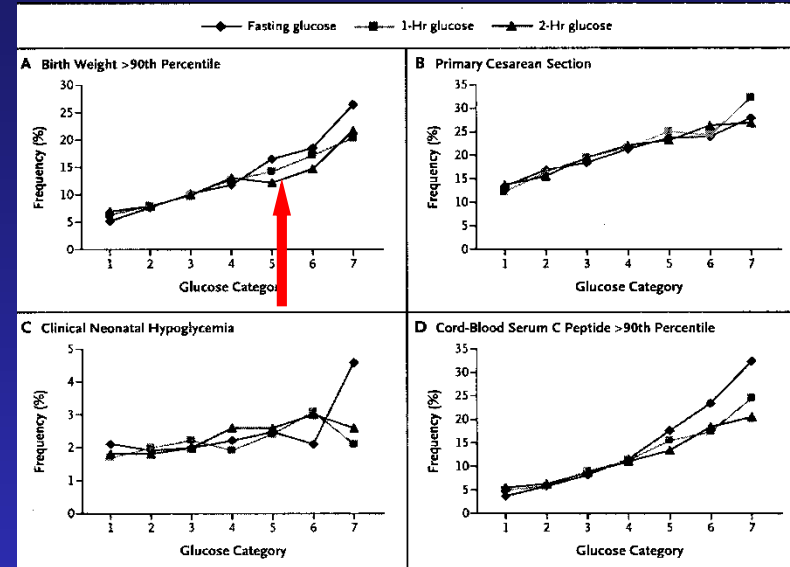


# More diabetes, more gestational diabetes

75 g OGTT:      fasting => 5.1 mmol/l  
                     1 hour => 10.0  
                     2 hour => 8.5

Diagnostic criteria based on 1.75 fold  
increase in LGA infant

(Metzger et al, Diab Care, 2010)



# More diabetes, more gestational diabetes

75 g OGTT:      fasting => 5.1 mmol/l  
                     1 hour => 10.0  
                     2 hour => 8.5

Diagnostic criteria based on 1.75 fold  
increase in LGA infant

(Metzger et al, Diab Care, 2010)

Prevalence of GDM of

17.8%

# More diabetes, more gestational diabetes

75 g OGTT:      fasting => 5.1 mmol/l  
                    1 hour => 10.0  
                    2 hour => 8.5

Diagnostic criteria based on 1.75 fold increase in LGA infant

(Metzger et al, Diab Care, 2010;33:676-682)

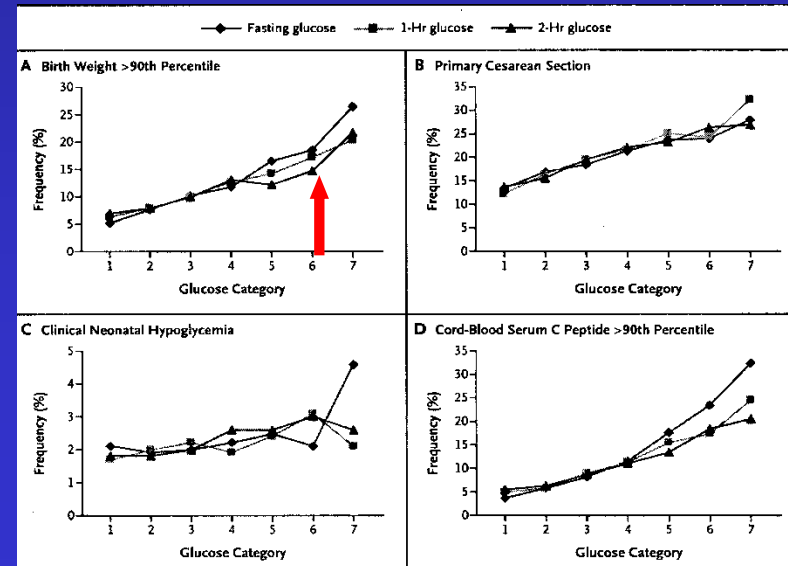
Prevalence of GDM of

17.8%

75 g OGTT:      fasting =>5.3 mmol/l  
                    1 hour => 10.6  
                    2 hour => 9.0

Diagnostic criteria based on 2 fold increase in LGA infant

(E.A.Rian, Diabetologia 2011;54:480-486)



# More diabetes, more gestational diabetes

75 g OGTT:      fasting => 5.1 mmol/l  
                  1 hour => 10.0  
                  2 hour => 8.5

Diagnostic criteria based on 1.75 fold  
increase in LGA infant

(Metzger et al, Diab Care, 2010;33:676-682)

Prevalence of GDM of

17.8%

75 g OGTT:      fasting =>5.3 mmol/l  
                  1 hour => 10.6  
                  2 hour => 9.0

Diagnostic criteria based on 2 fold  
increase in LGA infant

(E.A.Rian, Diabetologia 2011;54:480-486)

Prevalence of GDM of

10.5%

# More diabetes, more gestational diabetes

75 g OGTT:      fasting => 5.1 mmol/l  
                  1 hour => 10.0  
                  2 hour => 8.5

Diagnostic criteria based on 1.75 fold increase in LGA infant

(Metzger et al, Diab Care, 2010;33:676-682)

75 g OGTT:      fasting =>5.3 mmol/l  
                  1 hour => 10.6  
                  2 hour => 9.0

Diagnostic criteria based on 2 fold increase in LGA infant

(E.A.Rian, Diabetologia 2011;54:480-486)

- Poor reproducibility of OGTT
- Glucose weak predictor of LGA
- Obesity is a stronger predictor

-GDM is only related to childhood obesity in case of maternal obesity (Pirkola et al, 2010)

-Economic factors

-On the other hand: treatment is relatively easy ( insulin in only 8-20 % of women)

(Rian, 2011; RCOG SACO paper 23, January 2011; Visser & de Valk AJOG, 2012)

# Maternal obesity is the main problem and not GDM

overweight and abdominal obesity in 16 y old adolescents

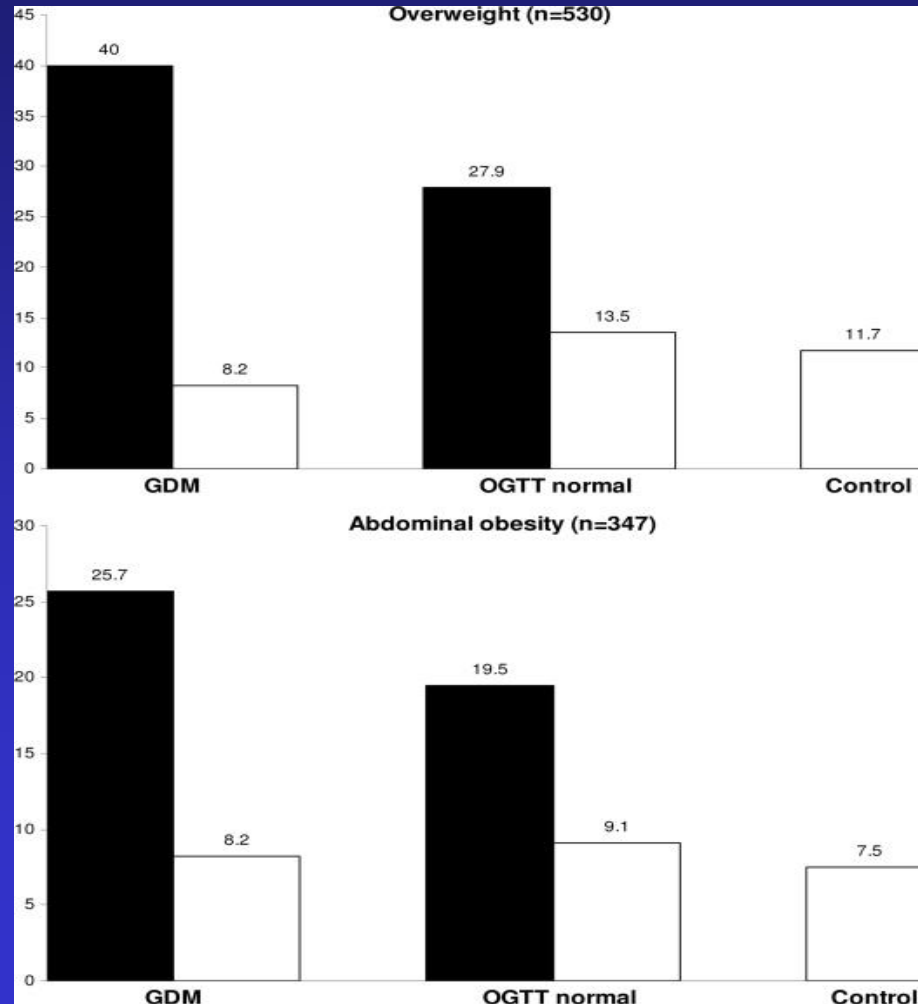
Risk population:

-GDM 84

-Normal OGTT 657

Control 3.427

 = mat BMI > 25



# Mat Diabetes and Childhood obesity meta-analysis, Philipps et al, Diabetologia 2011

All types of diabetes:

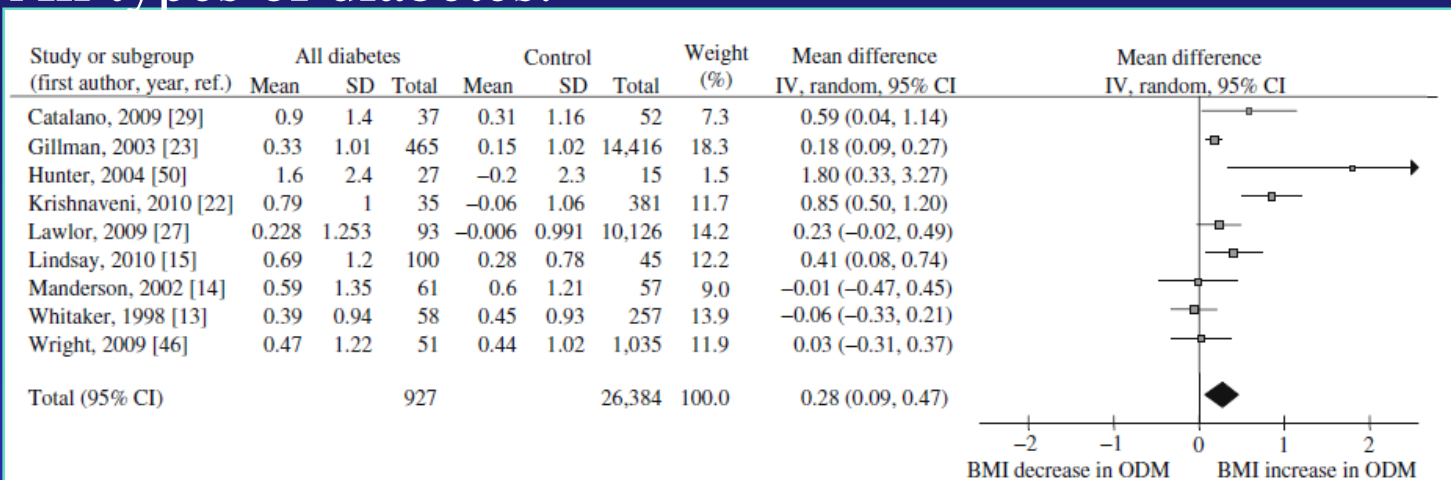


Fig. 2 Forest plot showing the unadjusted association between all types of maternal diabetes and offspring BMI z score. Heterogeneity:  $\tau^2=0.05$ ;  $\chi^2=27.02$ ,  $df=8$  ( $p=0.0007$ );  $I^2=70\%$ . Test for overall effect:  $z=2.90$  ( $p=0.004$ ). IV, inverse variance; ref., reference

## GDM:

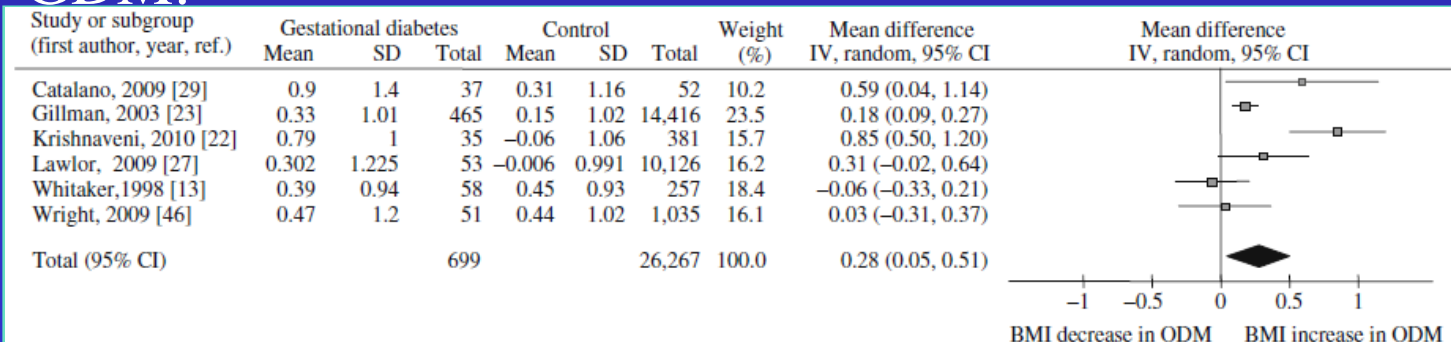


Fig. 3 Forest plot showing the unadjusted pooled analysis of offspring BMI z score of mothers with gestational diabetes mellitus and controls. Heterogeneity:  $\tau^2=0.06$ ;  $\chi^2=25.54$ ,  $df=5$  ( $p=0.001$ );  $I^2=76\%$ . Test for overall effect:  $z=2.39$  ( $p=0.02$ ). IV, inverse variance; ref., reference

# Mat Diabetes and Childhood obesity meta-analysis, Philipps et al, Diabetologia 2011

## Adjusted for maternal BMI:

All types of diabetes:

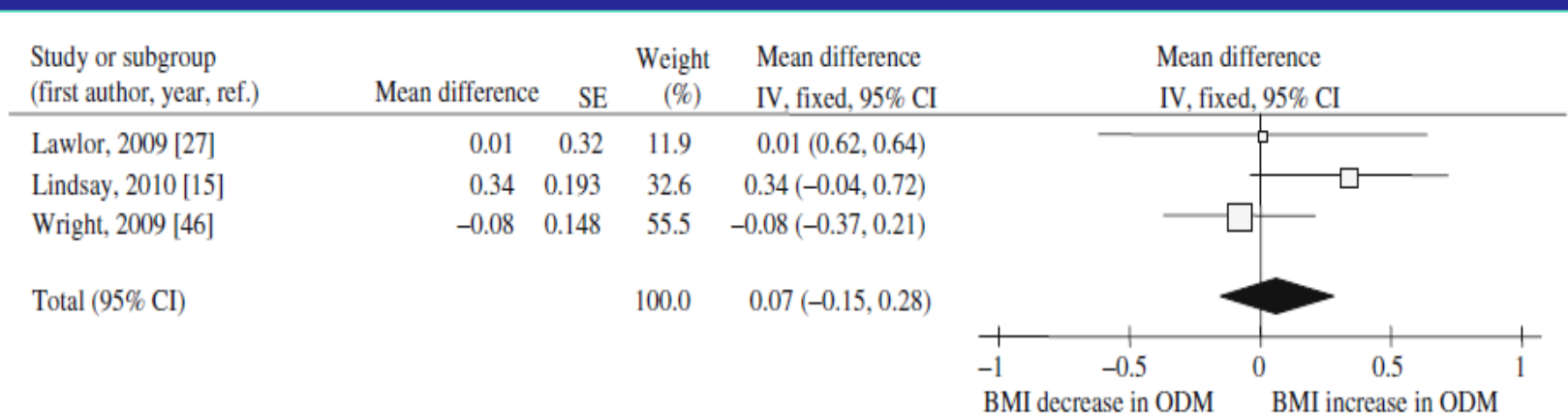


Fig. 5 Forest plot showing the adjusted association between all types of maternal diabetes and offspring BMI z score. Heterogeneity:  $\chi^2=3.02$ ,  $df=2$  ( $p=0.22$ );  $I^2=24\%$ . Test for overall effect:  $z=0.61$  ( $p=0.54$ ). IV, inverse variance; ref., reference

# Overweight and pregnancy

- GDM
- Macrosomia
- C.section
- Hypertension
- Preterm delivery
- Post operative complications
- Congenital malformations
- Fetal death
- Neonatal morbidity



Odds ratios 2-3

# Obesity without diabetes

Body Mass index	<25	25-30	>30
PIH	1	1.7	5.6
Birth weight>p90	1	1.1	2.5
CS	1	1.6	2.7
Induction of labour	1	1.5	3.2

Jensen et al, 2003. 2459 'glucose tolerant' women

Correction for 2 h glucose level, age, parity, ethnicity, smoking, gest weight gain,,gest age at delivery



# Obesity and GDM

BMI	Odds ratio
-----	------------

---

20-25

1

25-30

1.6-1.7

>30

3.6-4

>40

10

# Obesity and GDM

independent risk factors with synergistic effects

	Control	GDM	Obesity	GDM and Obesity
Birth weight>90 <sup>th</sup> centile	1	2.19	1.73	3.62
Cord C-peptide>90 <sup>th</sup> centile	1	2.49	1.77	3.61
Primary Caesarean section	1	1.25	1.51	1.71
Preeclampsia	1	1.74	3.91	5.98
Newborn % body fat>90 <sup>th</sup> centile	1	1.98	1.65	3.69
Shoulder dystocia/birth injury	1	1.14	1.03	1.8

# Obesity and GDM

- Both have a(n synergistic) effect on early perinatal outcome
- Obesity seems to have the most important effect on long term development of the offspring ( especially childhood obesity)

# Management of gestational diabetes

---

- Treatment improves outcome ( screening is therefore useful)
  - Mortality
  - Birth trauma
  - LGA
  - % CS ( Landon et al, only)
- } 50% reduction

Crowther et al, 2005; n=1000; Landon et al, 2010, n=958

# Outcome after screening is better than outcome following symptoms

	screening	symptoms
• N	175	74
• BMI	30	26
• GA at diagnosis (wks)	27	31
• HbA1c at diagnosis (%)	5.4	5.5
• FAC > 90 <sup>th</sup> centile (%)	33	68
• Birthweight > 90 <sup>th</sup> centile (%)	17	36
• Birthweight > 97.7 <sup>th</sup> centile (%)	5	16

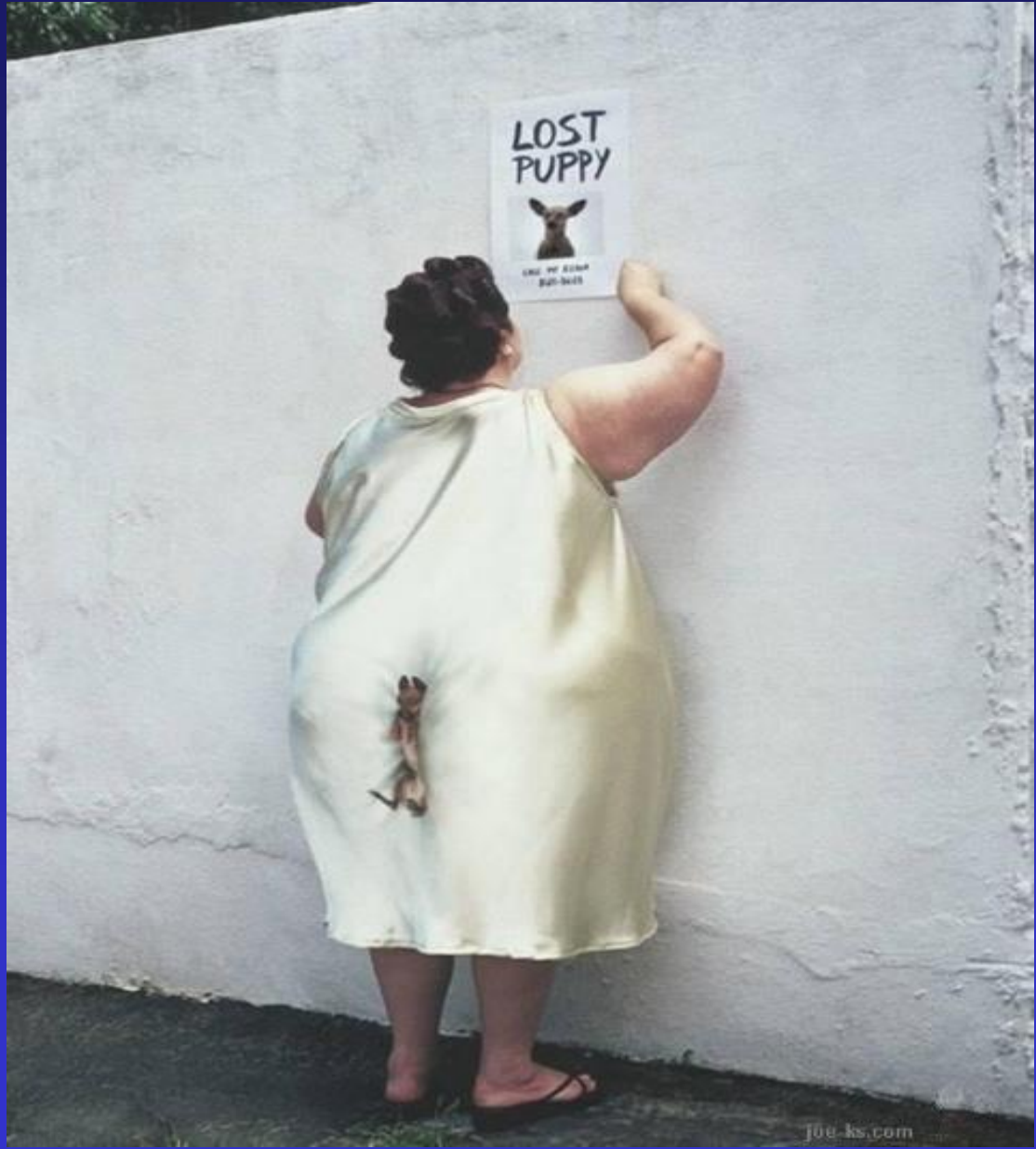
# Screening for gestational diabetes:

- Yes, the whole population; but that does not happen yet !
- Tell me how many GDM you want and I will give you the formula
- Use strict criteria in obese women

# Do you want to become pregnant?



Than first lose weight, and than we will tell you were your puppy is.....



# Management of the obese patient

- Lose weight before pregnancy
- Restrict weight gain during pregnancy
- First trimester screening for unrecognised type-2 diabetes ( OGTT or HbA1c)
- Second trimester OGTT
- Beware of large baby and 3<sup>rd</sup> trimester onset of GDM
- Metformin?

# Alternatives for insulin; type-2; gest diabetes

---

**-Glibenclamide (glyburide)** ( Langer et al, NEJM 2000)

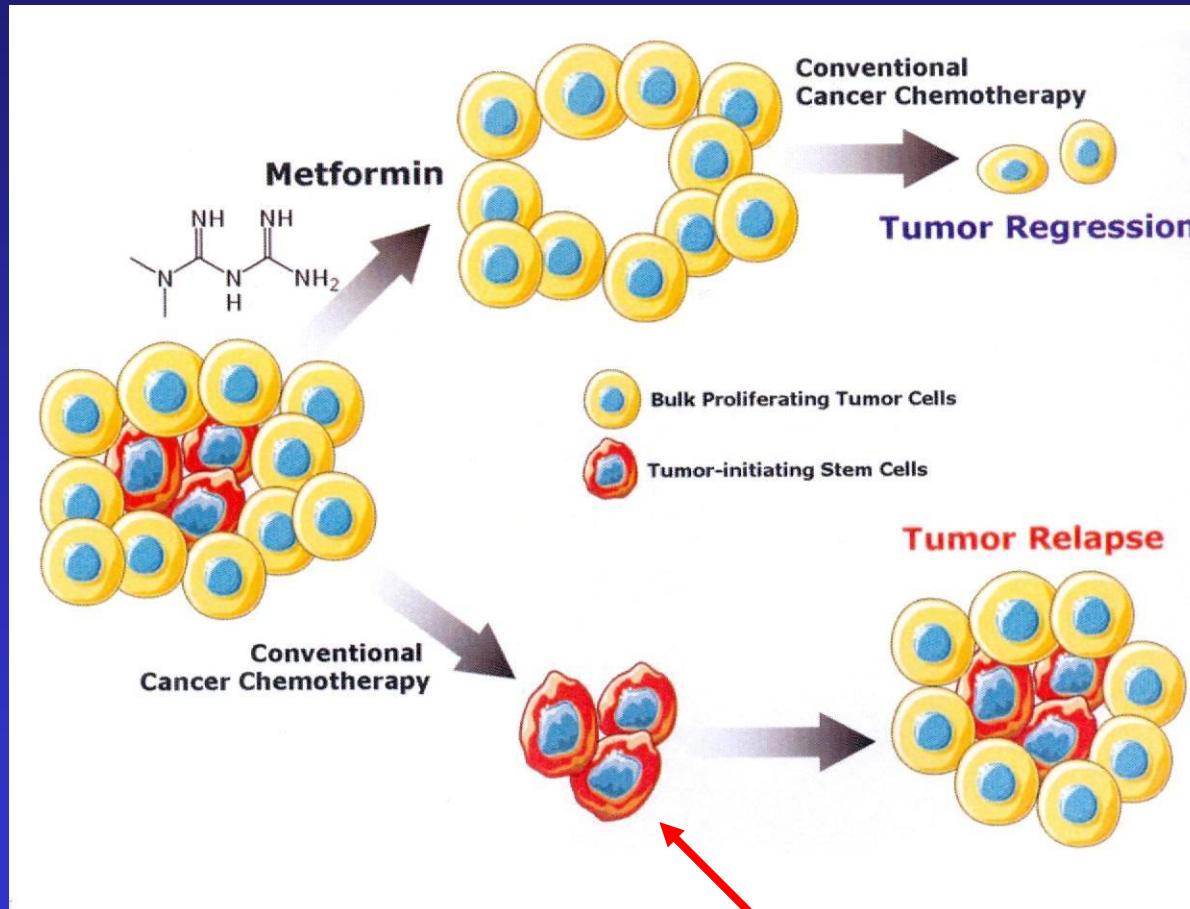
FDA Category C

**-Metformin** ( Rowan et al, NEJM 2008)

Metformin crosses the placenta ( fetal concentration 50% of maternal). It has been used in women with PCOS and/or type-2-diabetes in the first half of pregnancy and there is thus far no evidence that it may induce congenital malformations.

However, long term follow-up data are lacking, especially in IUGR infants

# Metformin a new drug to kill the 'dandelion root'



# Metformin and the risk of cancer

- Anti-angiogenetic effects, including negative effects on VEGF
- Anti-inflammatory effects
- Growth inhibitory effects
- Anti-oxidative effects
- Decreases( tumor-initiating) **stem cells**

# Metformin and the risk of cancer

- Anti-angiogenetic effects, including negative effects on VEGF
- Anti-inflammatory effects
- Growth inhibitory effects
- Anti-oxidative effects
- Decreases (tumor-initiating) stem cells

That appears to be good for the prevention and/or treatment of cancer

# Metformin and the risk of cancer

- Anti-angiogenetic effects, including negative effects on VEGF
- Anti-inflammatory effects
- Growth inhibitory effects
- Anti-oxidative effects
- Decreases (tumor-initiating) stem cells

But what about a nine months  
exposition of the fetus ??

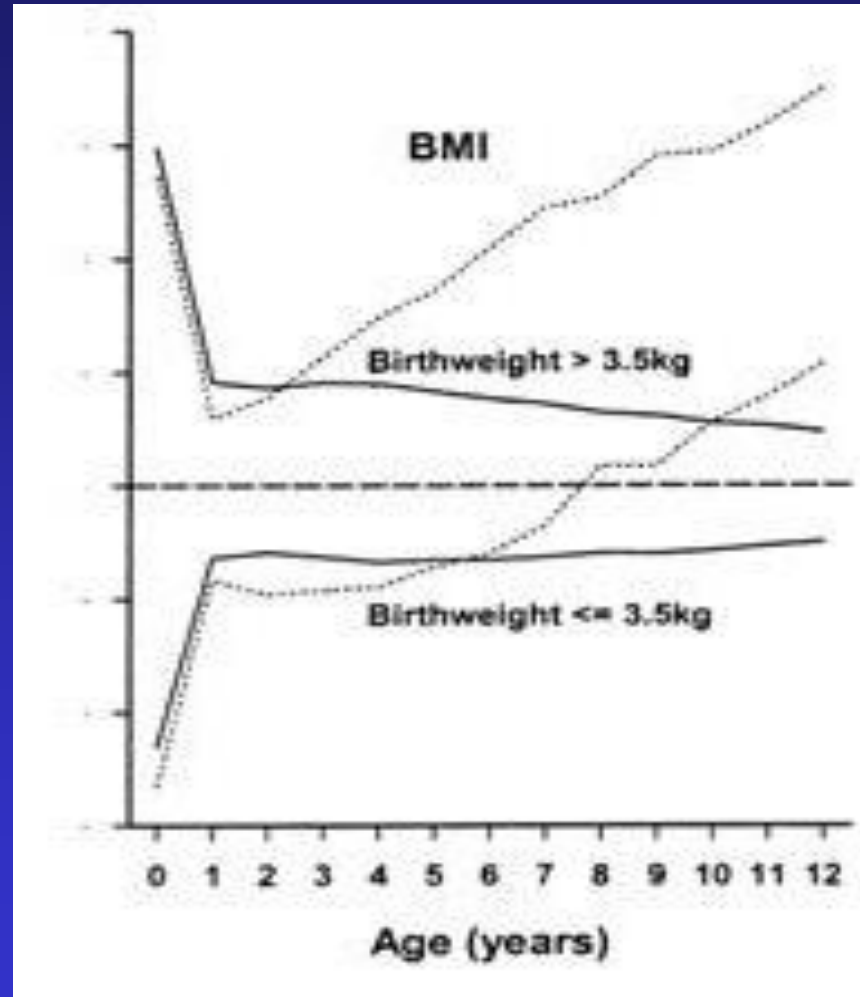
# Oral antidiabetic drugs and pregnancy

- So,....better not, for the time being ( if you can afford insulin)
- ‘The poor man’s insulin’ (Coetzee, 2011)

**MICHELIN MAN DENIES PATERNITY SUIT..... CLAIMS CHILD IS NOT HIS**

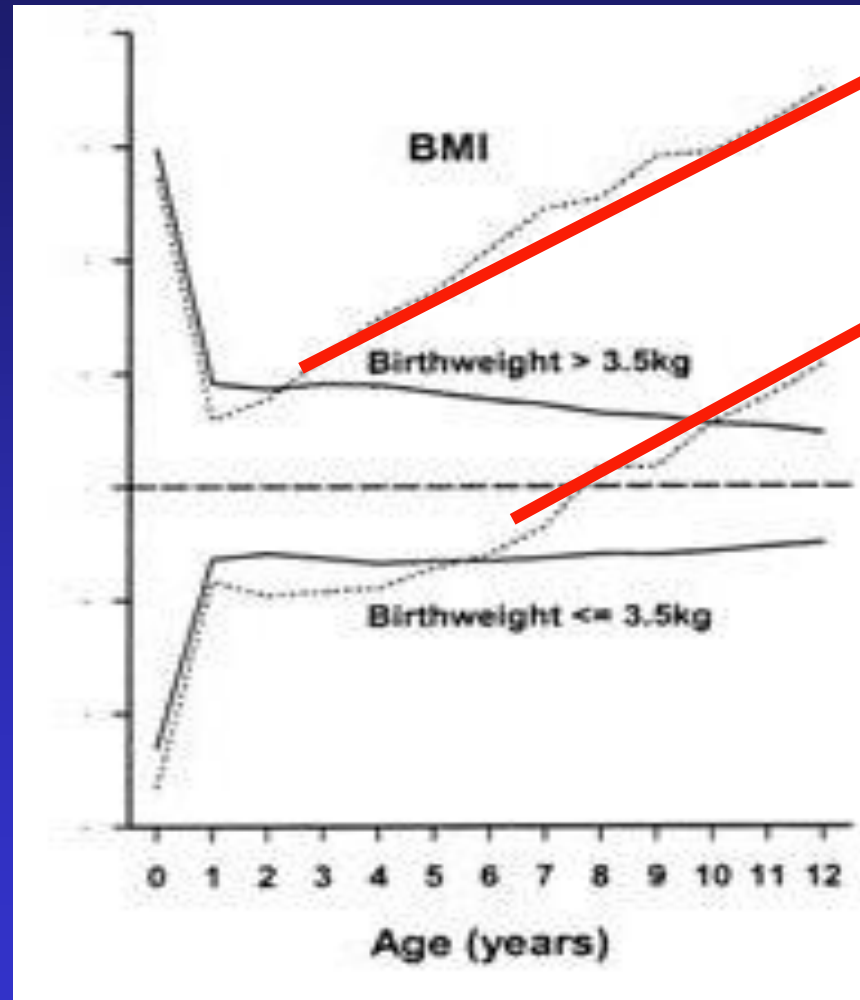


# Birthweight, Infant growth & Type-2 diabetes



Mean Z-score

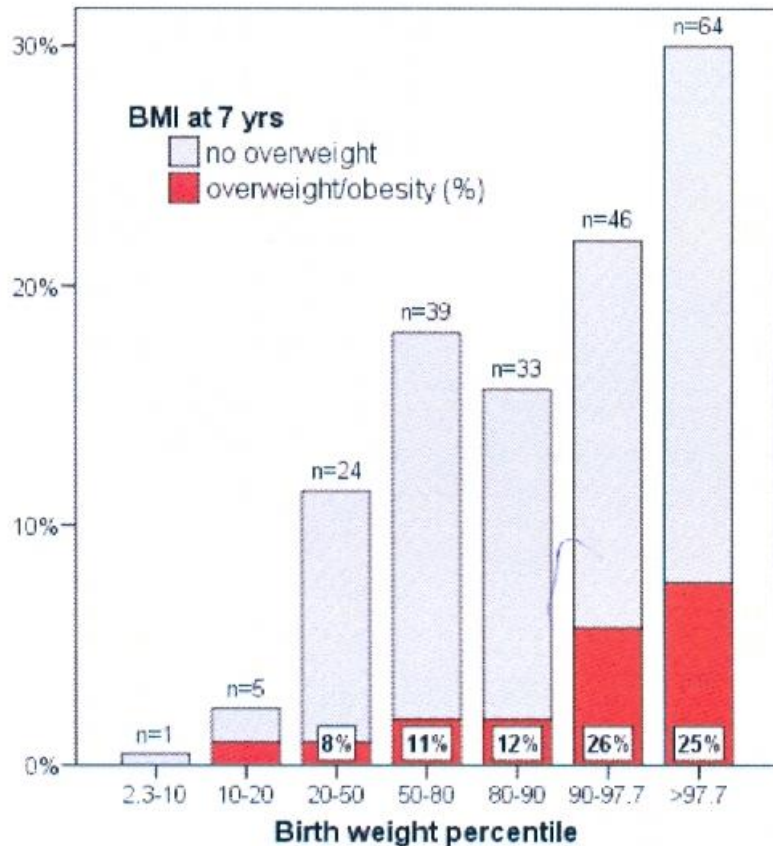
# Birthweight, Infant growth & Type-2 diabetes



Mean Z-score

diabetes

# Follow-up infants of women with type-1 diabetes



**Figure 1.** % overweight/obesity is related to birth weight percentile; data based on 212 ODM.

**Independent predictors of childhood overweight:**

**OR**

Birthweight > p90 4.4(1.6-11.8)

Maternal weight 2.8(1.2- 6.6)

# So, which infants are likely to develop diabetes

---

- High maternal BMI
- Macrosomia at birth
- And.....excessive weight gain  $> 2$  y of age

# Prevention

---

-- Healthy diet

-- Exercise

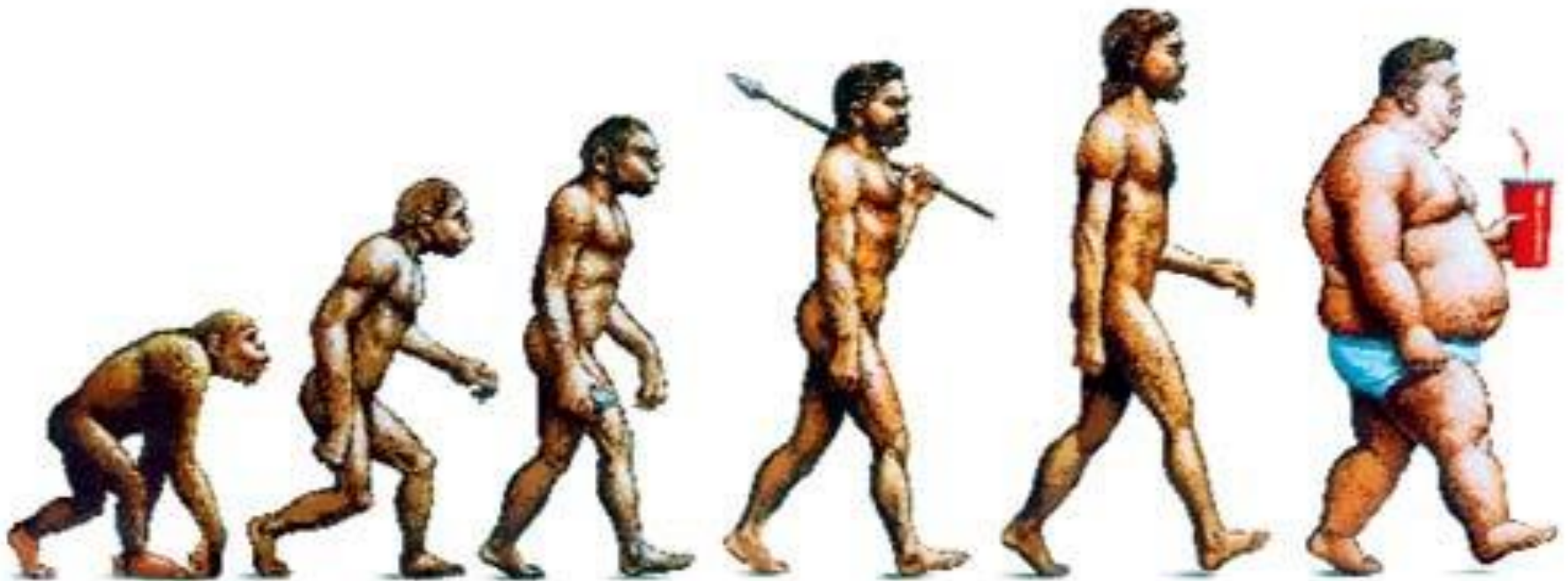
-- Folic acid

(may prevent epigenetic changes)

---

(Eriksson; Lillycrop et al, 2005)

# The descent of Man



Thank you

# Pima Indians NIDDM

Incidence of NIDDM in 20-24 y old offspring of:



- nondiabetic women 1.4 %
- women developing NIDDM after pregnancy 8.6 %
- **women with NIDDM during pregnancy 45 %**

differences persist taking into account paternal diabetes, age at onset diabetes in parents, birth weight

# Type-2 diabetes or impaired glucose intolerance in 18-27 y offspring ( total study group 597)

- Women with gest diabetes 21%
- Genet predisposed women 12%  
( but no diabetes in pregnancy)
- Women with type-1 diabetes 11%
- Control group 4%

# Type-2 diabetes or impaired glucose intolerance in 18-27 y offspring ( total study group 597)

- Women with gest diabetes 21%  9%
- Genet predisposed women 12%  
( but no diabetes in pregnancy)
- Women with type-1 diabetes 11%  7%
- Control group 4%

**So, diabetes during pregnancy results in an almost 10% incidence of diabetes in offspring**

# So,

- Abnormal intrauterine environment induces DM and obesity in offspring
- Most studies were not controlled for maternal BMI
- It remains uncertain whether GDM or Obesity is the factor most strongly related to obesity in offspring

# However,

- Given the synergistic effect of Obesity and GDM, be very strict in diagnosing and treating Obese women who have GDM



**Thank you**

# Obesity

## Prevalence - Europe

Male and female obesity levels in selected European countries

