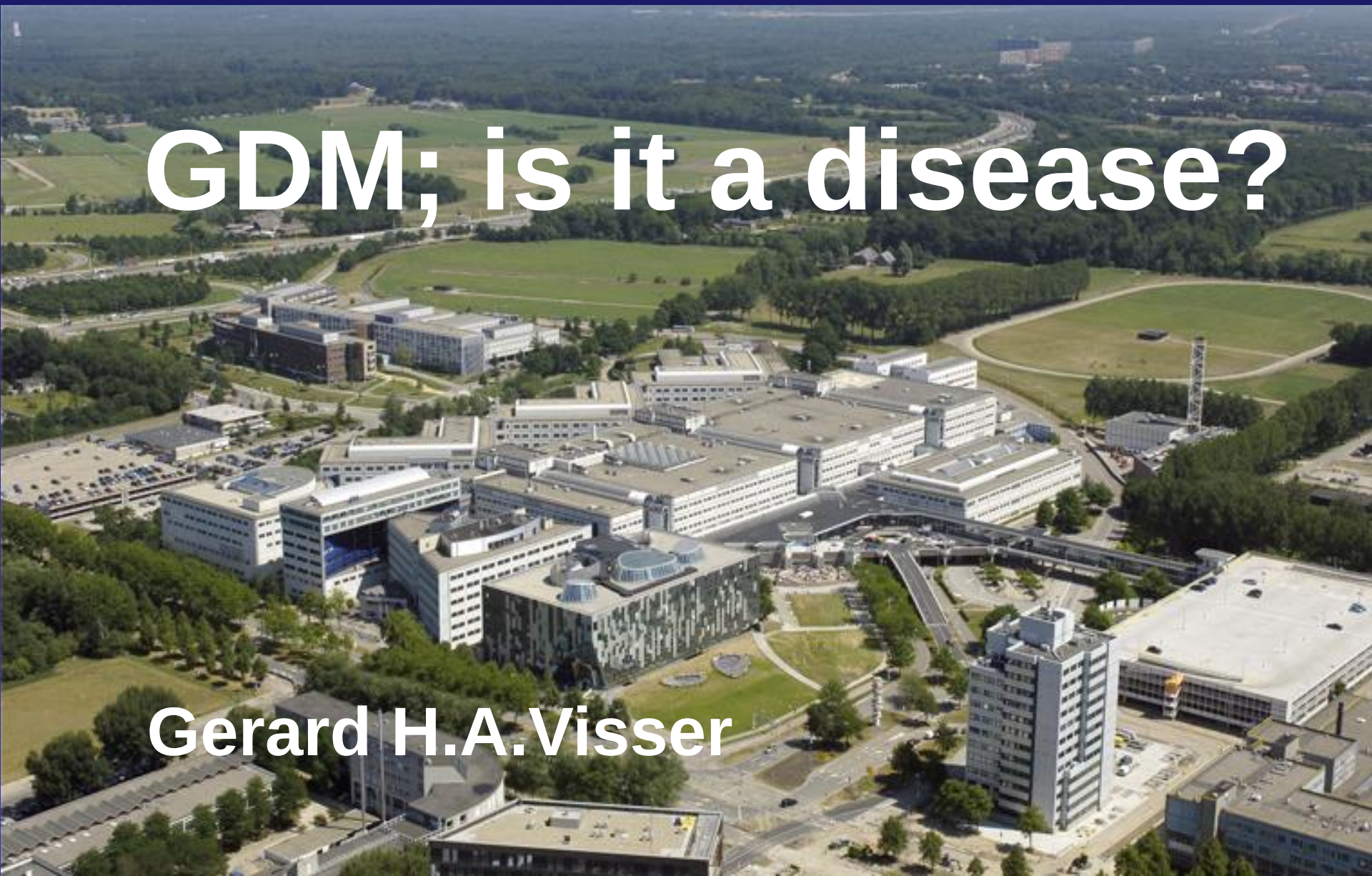
University Medical Center, Utrecht, the NL



GDM; is it a disease?

Gerard H.A.Visser

GDM; is it a disease?

- Yes (related to fetal macrosomia and associated complications)
- Usually mild (diet); 20% requires insulin
- May have long term consequences for the offspring (?)
- Or is it maternal obesity which is the biggest problem?
- How rigorous should we be in identifying all cases of GDM?

Treatment improves outcome

- **Screening is therefore useful**

- Mortality
- Birth trauma
- LGA

} 50% reduction

- % CS (Landon et al, only)

Crowther et al, 2005; n=1000; London 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

Hammoud et al, JMFNM 2012

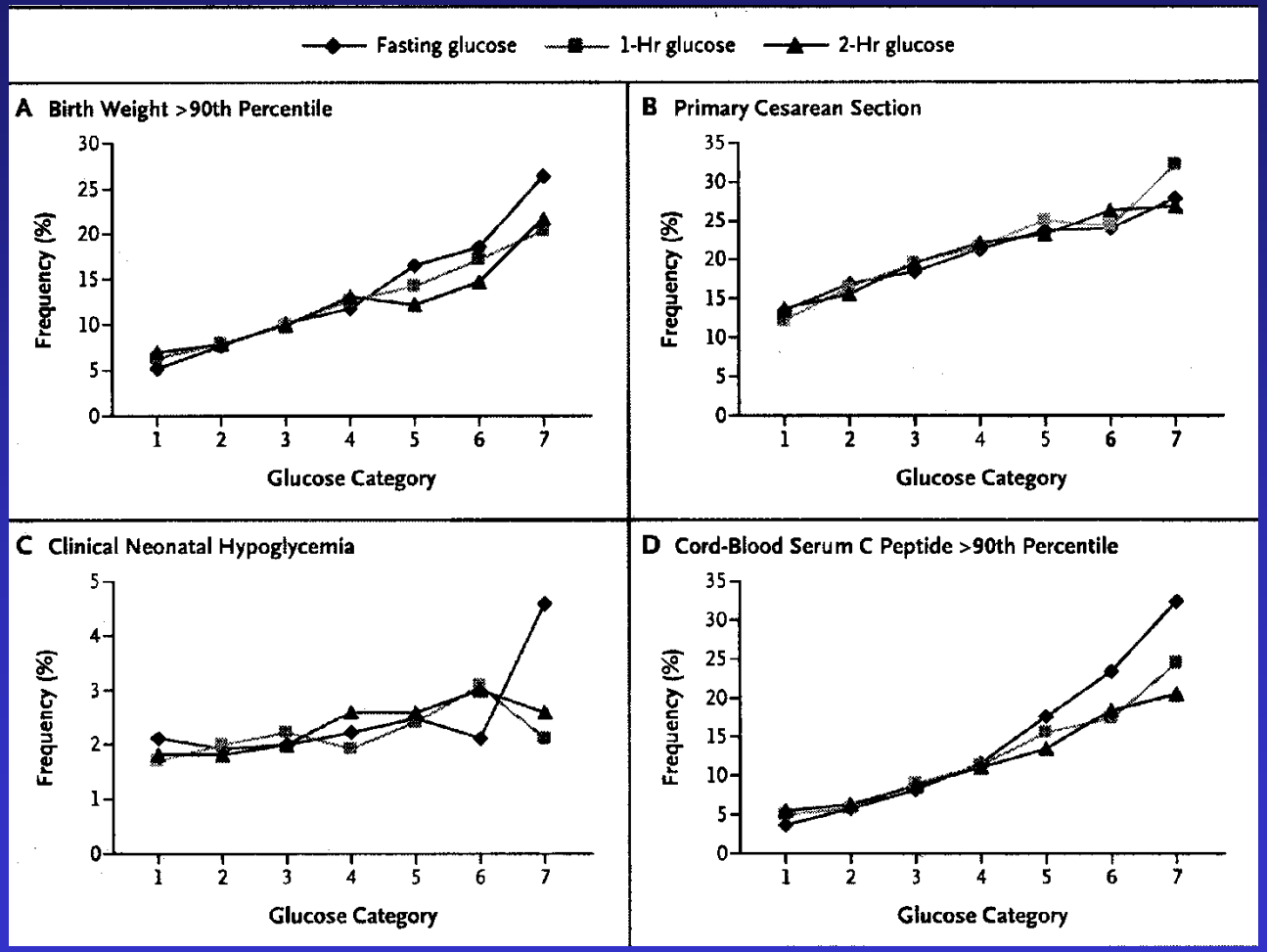
Outcome after screening is better than outcome following symptoms

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

Hammoud et al, JMFNM 2012

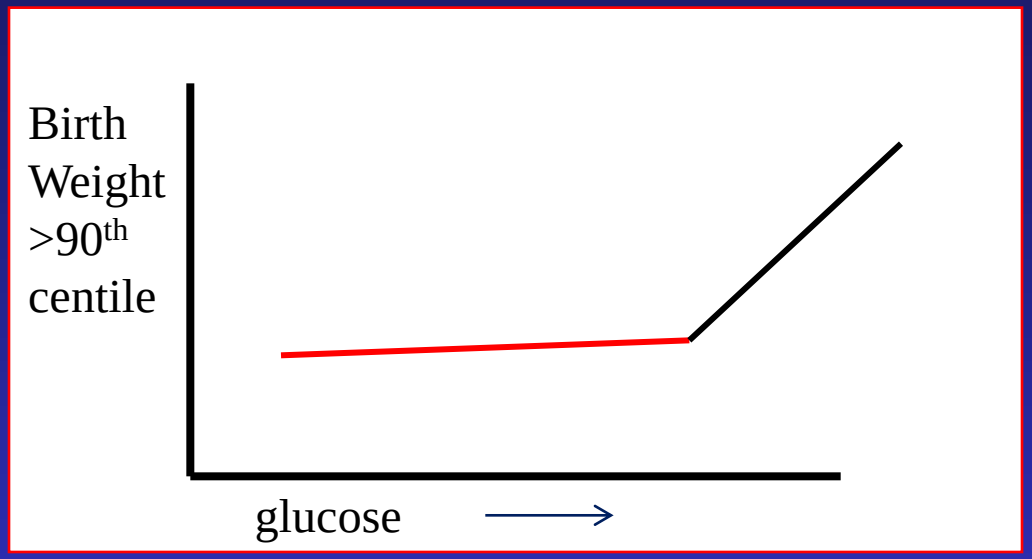
So, screen everyone, but how ?

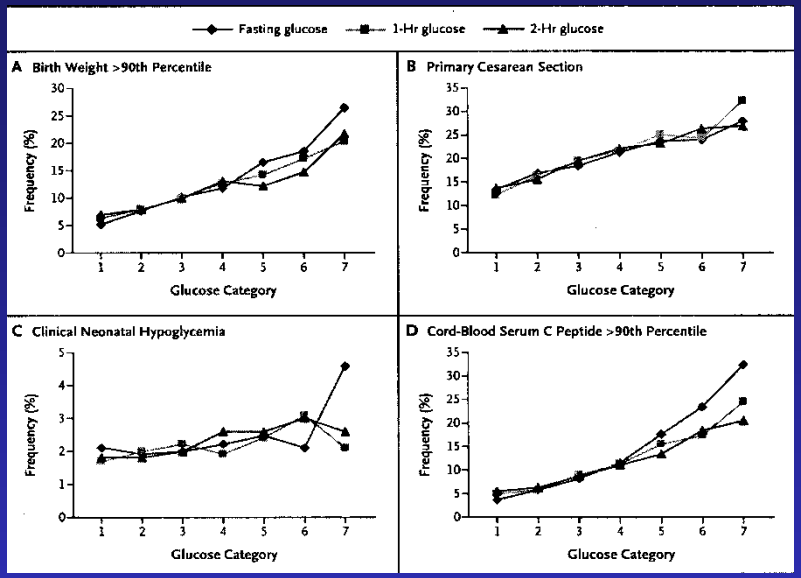
HAPO study



(NEJM, May 8, 2008)

Gestational diabetes





So we may conclude that…….

- oGTT threshold values, for normality or otherwise, are –by definition- arbitrary, given the linear relationship between glucose values and impaired outcome

University Medical Center, Utrecht, the NL

Threshold values for oGTT

tell me how many GDM you want and

I will give you the formula

Gerard H.A.Visser

Gestational diabetes according to the IADPSG

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%

It is the question if are we ready for such an increase in GDM?

- Don’t we make the healthy sick

(stop harming the healthy, Moynihan et al, BMJ 2012)

- Does outcome really improve
- Shouldn’t we look more for women with risk factors
- Etc
- And the answer is: we do not know !

‘Preventing overdiagnosis: how to stop harming the healthy’ Moynihan et al, BMJ 2012

Drivers for over-diagnosis:

- Technological changes detecting even smaller abnormalities
- Commercial and professional vested interests
- Conflicting panels producing expanded disease definitions and writing guidelines
- Legal incentives that punish under-diagnosis but not over-diagnosis
- Health system incentives favoring more tests and treatments
- Cultural belief that more is better

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 0f

10.5%

IADPSG criteria

Accepted	Rejected
ADA	ACOG
	NIH
WHO	Spain
Brasil	NZ
Italy	
Germany	
Japan	

ELSEVIER

American Journal of Obstetrics and Gynecology

Available online 24 October 2012

In Press, Uncorrected Proof — Note to users

OBSTETRICS

Is the evidence strong enough to change the diagnostic criteria for gestational diabetes now?

Gerard H. A. Visser, MD; Harold W. de Valk, MD, PhD

In 2008, the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study group published the results of a large international observational study on the relationship between second-trimester oral glucose tolerance test (oGTT) values and outcome.[1] Unfortunately, but not surprisingly, there was a linear relationship among fasting, 1-hour and 2-hour glucose values, and the frequency of primary cesarean delivery, fetal macrosomia (birth weight >90th centile), clinical neonatal hypo-

The International Association of the Diabetes and Pregnancy Study Groups has proposed new thresholds for oral glucose tolerance test that are based on the large observational Hyperglycemia and Adverse Pregnancy Outcomes study. By using these criteria about 18% of pregnant women will be diagnosed as having gestational diabetes mellitus. The question arises if we are ready for such an enormous increase in gestational diabetes mellitus patients, if outcome would really by using these criteria, and if additional studies are necessary before deciding on new diagnostic thresholds. In this clinical opinion, the pros and cons will be discussed.

Key words: adverse pregnancy outcome, diabetes mellitus, glucose intolerance, metabolic syndrome, oral glucose tolerance test

Change diagnostic criteria for GDM?

Arguments in favor

√ - Previous oGTT thresholds were set in such a way that about 2.5% of population would classify as GDM, irrespective of relationship of glucose values with prerinatal outcome

- Striking increase in obesity and type 2 diabetes in general population may well correspond to GDM incidence of about 20%

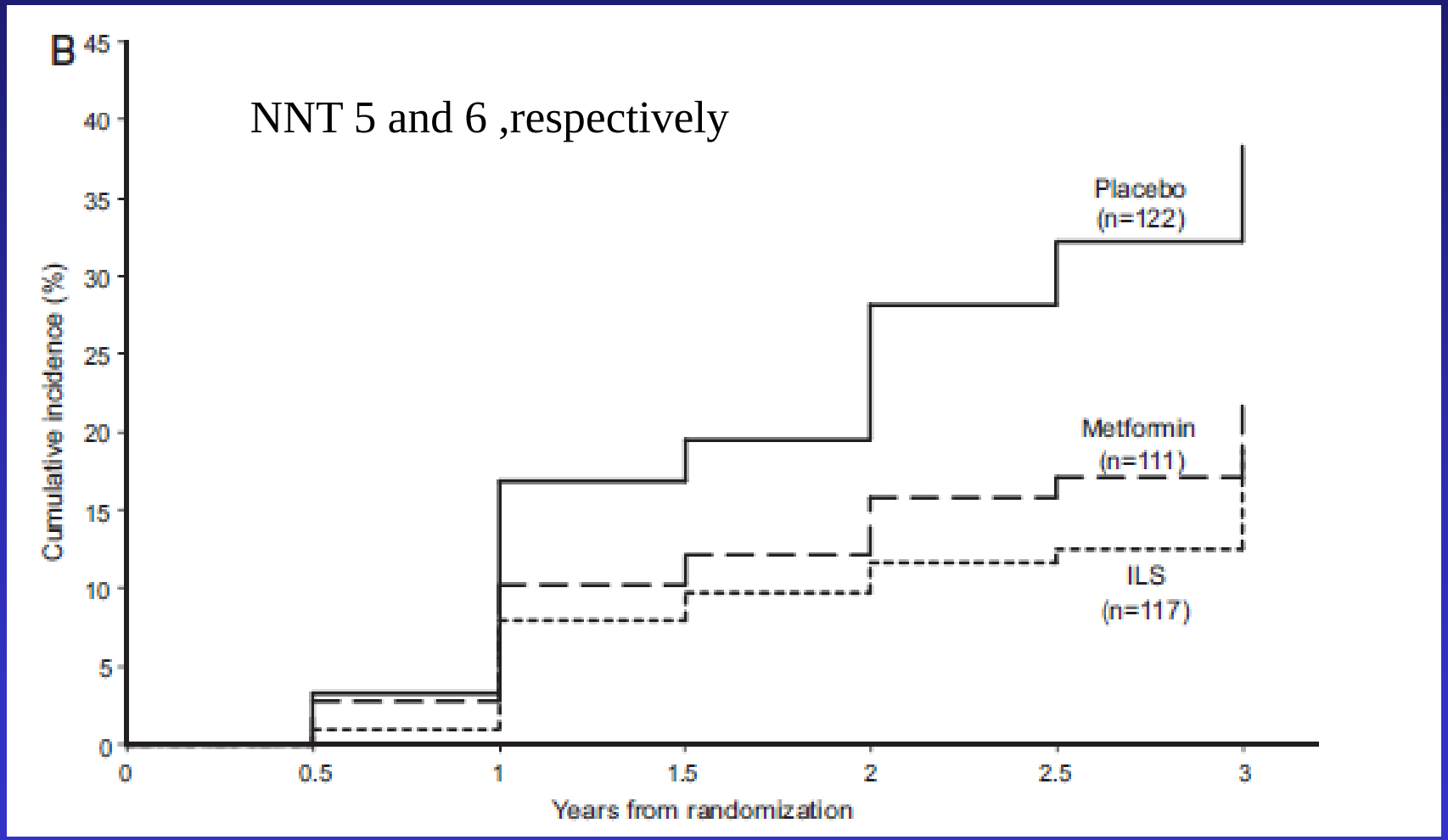
- Treatment of GDM improves perinatal outcome

√ - Treatment of GDM is generally easy with insulin treatment in only 8-20% of women

- Adequate diagnosis is cost-effective

Visser & de Valk, AJOG, 2012

Incidence of diabetes following GDM



Ratner et al, JCEM 2008

Post partum testing following GDM

- Systemic review; 54 articles

- Postpartum testing on average in 33% of patients (9-71%)
- With proactive patient contact programs: 60% (14-95%)

Carson MP et al, Prim Care Diabetes, Oct 2013

Post partum testing following GDM

- Systemic review; 54 articles
- Postpartum t
  pati
  ntact programs:

In other words, we do not seem ready for such an increase in GDM

Carson MP et al, Prim Care Diabetes, Oct 2013

Change diagnostic criteria for GDM?

Arguments against

- oGTT has poor reproducibility
- Even with very strict threshold values, only a minority of fetal macrosomia will be identified
- GDM is related to childhood obesity, but mainly in case of maternal obesity
- Overdiagnosis of GDM may well result in overtreatment
- Stricter oGTT criteria will result in increasing workload

GDM, gestational diabetes mellitus; *oGTT*, oral glucose tolerance test.

Visser. Is evidence strong enough to change diagnostic criteria for gestational diabetes now? Am J Obstet Gynecol 2012.

Maternal overweight is the main problem and not GDM

overweight and abdominal obesity in 16 y old adolescents

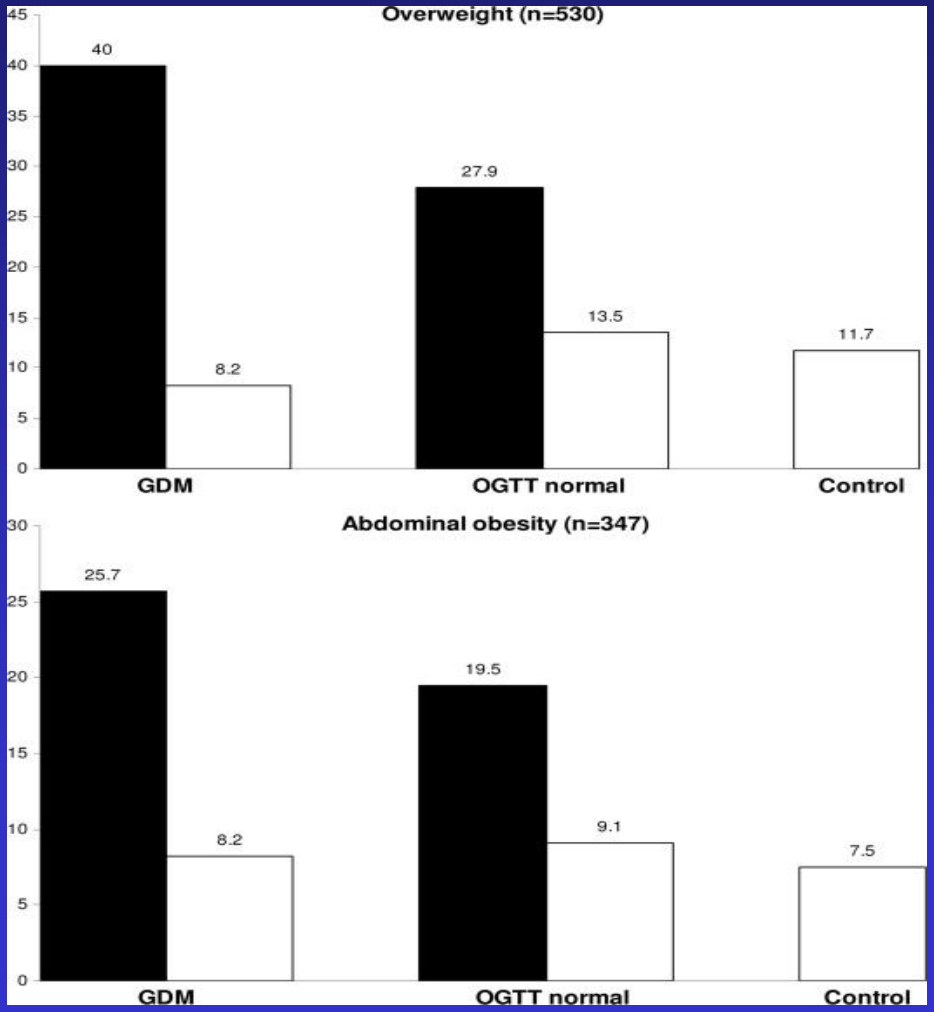
Risk population:

-GDM 84

-Normal OGTT 657

Control 3.427

■ = mat BMI> 25



Pirkola et al, Diab Care 2010

Metabolic syndrome in 175 infants age 7-11, according to birth weight and GDM

TABLE 4. Hazard Ratio for the Risk of MS (n = 175)

Variables	Hazard Ratio	P Value	95% CI for Hazard Ratio
LGA versus AGA	2.19	.006	1.25–3.82
Maternal obesity* versus nonobese	1.81	.039	1.03–3.19
GDM versus control	1.44	.191	0.83–2.50
Male versus female	1.52	.133	0.88–2.61

* Prepregnancy BMI of >27.3 kg/m^2.

Boney, Pediatrics 2005

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

All types of diabetes:

Study or subgroup (first author, year, ref.)	All diabetes Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Catalano, 2009 [29]	0.9	1.4	37	0.31	1.16	52	7.3	0.59 (0.04, 1.14)
Gillman, 2003 [23]	0.33	1.01	465	0.15	1.02	14,416	18.3	0.18 (0.09, 0.27)
Hunter, 2004 [50]	1.6	2.4	27	–0.2	2.3	15	1.5	1.80 (0.33, 3.27)
Krishnaveni, 2010 [22]	0.79	1	35	–0.06	1.06	381	11.7	0.85 (0.50, 1.20)
Lawlor, 2009 [27]	0.228	1.253	93	–0.006	0.991	10,126	14.2	0.23 (–0.02, 0.49)
Lindsay, 2010 [15]	0.69	1.2	100	0.28	0.78	45	12.2	0.41 (0.08, 0.74)
Manderson, 2002 [14]	0.59	1.35	61	0.6	1.21	57	9.0	–0.01 (–0.47, 0.45)
Whitaker, 1998 [13]	0.39	0.94	58	0.45	0.93	257	13.9	–0.06 (–0.33, 0.21)
Wright, 2009 [46]	0.47	1.22	51	0.44	1.02	1,035	11.9	0.03 (–0.31, 0.37)
Total (95% CI)			927			26,384	100.0	0.28 (0.09, 0.47)

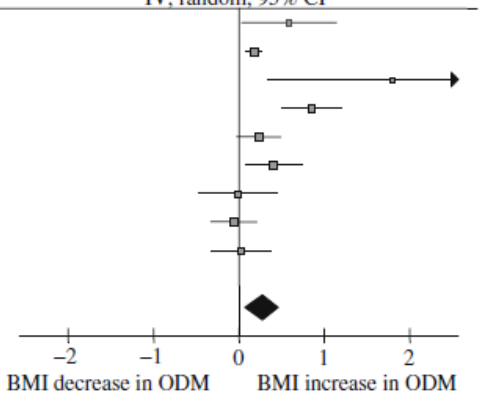


Fig. 2 Forest plot showing the unadjusted association between all types of maternal diabetes and offspring BMI *z* score. Heterogeneity: τ^2=0.05; χ^2=27.02, *df*=8 (*p*=0.0007); I^2=70%. Test for overall effect: *z*=2.90 (*p*=0.004). IV, inverse variance; ref., reference

GDM:

Study or subgroup (first author, year, ref.)	Gestational diabetes Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Catalano, 2009 [29]	0.9	1.4	37	0.31	1.16	52	10.2	0.59 (0.04, 1.14)
Gillman, 2003 [23]	0.33	1.01	465	0.15	1.02	14,416	23.5	0.18 (0.09, 0.27)
Krishnaveni, 2010 [22]	0.79	1	35	–0.06	1.06	381	15.7	0.85 (0.50, 1.20)
Lawlor, 2009 [27]	0.302	1.225	53	–0.006	0.991	10,126	16.2	0.31 (–0.02, 0.64)
Whitaker,1998 [13]	0.39	0.94	58	0.45	0.93	257	18.4	–0.06 (–0.33, 0.21)
Wright, 2009 [46]	0.47	1.2	51	0.44	1.02	1,035	16.1	0.03 (–0.31, 0.37)
Total (95% CI)			699			26,267	100.0	0.28 (0.05, 0.51)

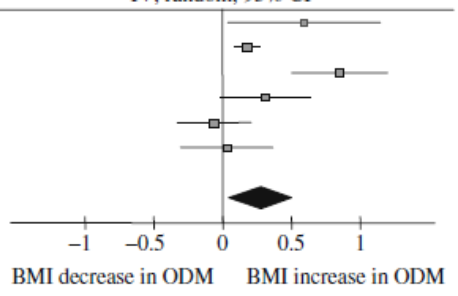


Fig. 3 Forest plot showing the unadjusted pooled analysis of offspring BMI *z* score of mothers with gestational diabetes mellitus and controls. Heterogeneity: τ^2=0.06; χ^2=25.54, *df*=5 (*p*=0.001); I^2=76%. Test for overall effect: *z*=2.39 (*p*=0.02). IV, inverse variance; ref., reference

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

Adjusted for maternal BMI:

All types of diabetes:

Study or subgroup (first author, year, ref.)	Mean difference	SE	Weight (%)	Mean difference IV, fixed, 95% CI
Lawlor, 2009 [27]	0.01	0.32	11.9	0.01 (0.62, 0.64)
Lindsay, 2010 [15]	0.34	0.193	32.6	0.34 (–0.04, 0.72)
Wright, 2009 [46]	–0.08	0.148	55.5	–0.08 (–0.37, 0.21)
Total (95% CI)			100.0	0.07 (–0.15, 0.28)

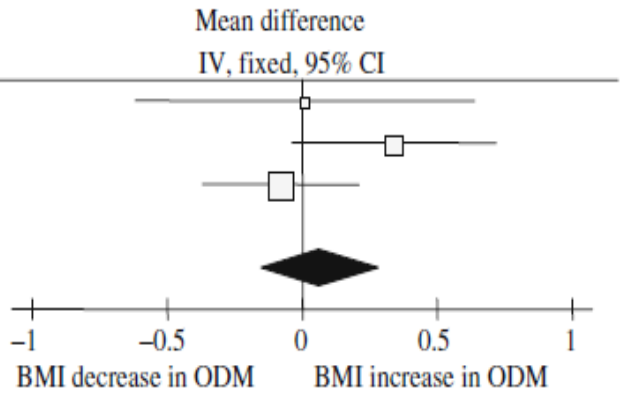


Fig. 5 Forest plot showing the adjusted association between all types of maternal diabetes and offspring BMI *z* score. Heterogeneity: χ^2= 3.02, *df*=2 (*p*=0.22); I^2=24%. Test for overall effect: *z*=0.61 (*p*=0.54). IV, inverse variance; ref., reference

Obesity and GDM; short term outcome

independent risk factors with synergistic effects

	Control	GDM	Obesity	GDM and Obesity
Birth weight>90th centile	1	2.19	1.73	3.62
Cord C-peptide>90th 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>90th centile	1	1.98	1.65	3.69
Shoulder dystocia/birth injury	1	1.14	1.03	1.8

Adapted from Catalano et al, 2012

Obesity and GDM; long term outcome

- Obesity seems to have the most important effect on long term development of the offspring (especially childhood obesity)

Screening for gestational diabetes:

- Yes, the whole population; but that does not happen yet ! (Even in countries with 'universal' screening only 10-90% of women will actually be screened; Jiwani et al JMFNM 2012). Priority!

- Tell me how many GDM you want and I will give you the formula

- Use strict criteria in obese women. Priority!

NIH Consensus Development Conference:

DIAGNOSING GESTATIONAL DIABETES MELLITUS

March 4-6, 2013
Bethesda, Maryland

- Evaluate to decrease subsequent signs of metabolic syndrome, diabetes and cardiovascular disease in women with GDM

- Too early to adopt the stringent IADPSG odiagnostic thresholds associated with an adverse outcome of 2.0 in the HAPO study as opposed to 1.75
- Determine whether women, normal in a two step strategy and

Use strict oGTT criteria in obese women

- Glucose values in obese women with a normal oGTT are higher than those in women with normal weight, and GDM is usually more severe
- Obesity by itself has a negative effect on outcome
- Obesity and GDM have a synergistic effect on outcome
- Diet, treatment and frequent visits may reduce weight gain, which by itself has a positive effect on outcome

Normal 2nd trimester oGTT and big baby in 3rd trimester…..

- Low risk, no GDM?
- Might have late onset GDM and be at high risk

Normal 2nd trimester oGTT and big baby in 3rd trimester…..

- Low risk, no GDM?
- Might have late onset GDM and be at high risk

So, repeat glucose testing !!

Conclusions 1:

- Screen all pregnant women
- Preferably oGTT 24-28 wk
- Use strict threshold values in case of maternal obesitas (IADPSG criteria)
- Less stringent criteria in the others

- PM: normal oGTT and fetal macrosomia near term (continue thinking!!!)

Conclusions 2:

- GDM is really a disease
- But, for the time being do not over-diagnose and medicalize
- Maternal obesity is a bigger problem

- If you have the money: use insulin and not oral antidiabetic medication


Thank you