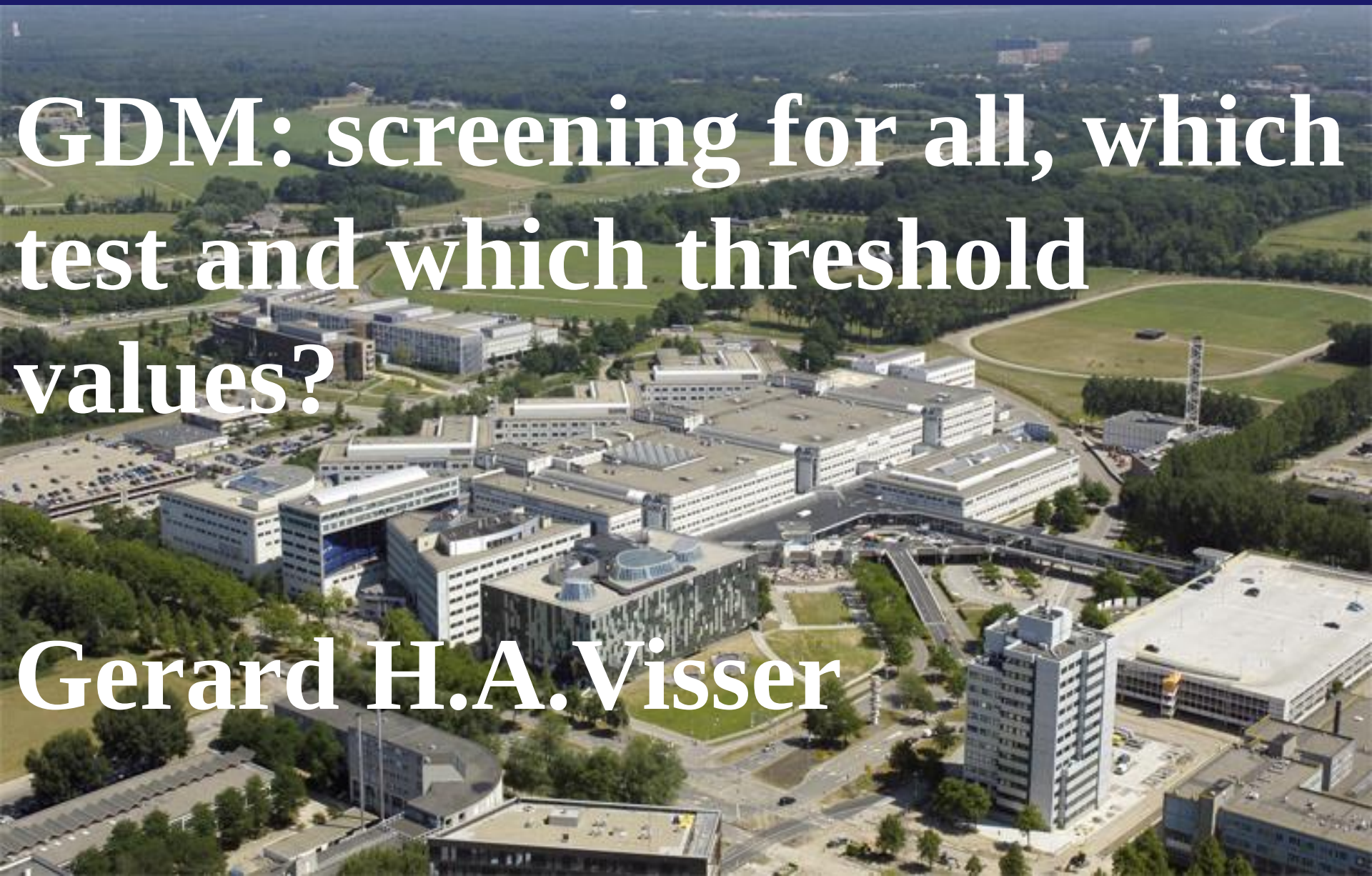
University Medical Center, Utrecht, the NL



GDM: screening for all, which test and which threshold values?

Gerard H.A.Visser

It used to be quiet on the GDM front

- GDM a diagnosis still looking for a disease
- Just another routine test to tell 2.3% of pregnant women that they have a disease
- GDM is the mere interpretation of a laboratory test
- Antenatal scare, not care

Liu et al, 2000; Odent 2008

Treatment improves outcome

- Treatment improves outcome (screening is therefore useful)

- Mortality
- Birth trauma
- LGA

} 50% reduction

- % CS (Landon et al, only)

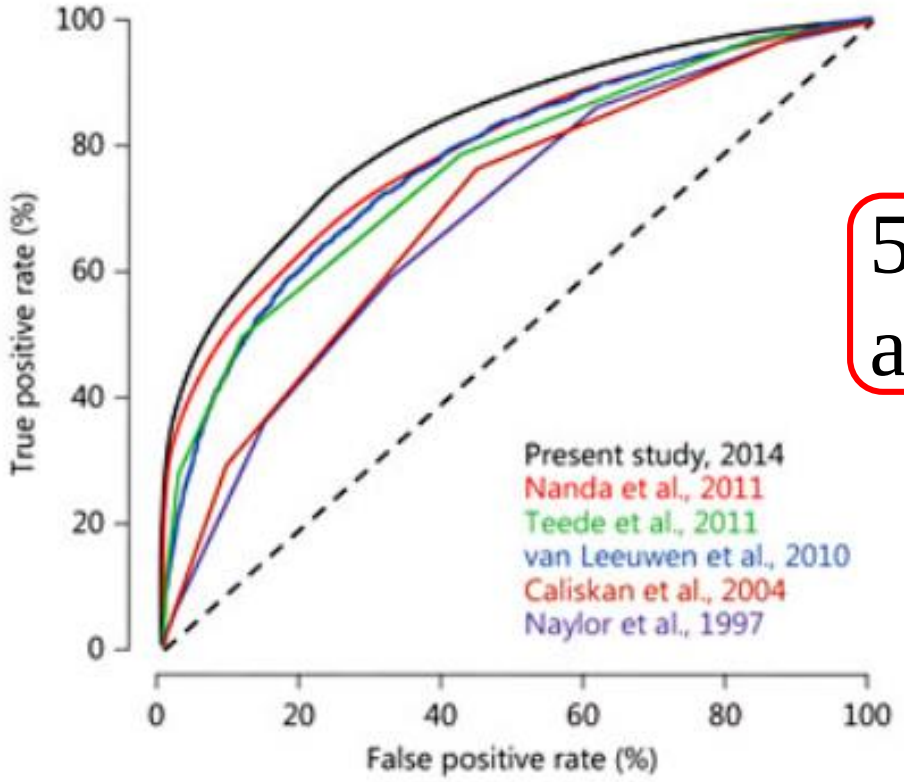
Crowther et al, 2005; n=1000; Landon et al, 2010, n=958

Treatment does improve outcome; Can we identify women who will develop GDM, or do we have to screen everyone?

- Maternal age, weight, height, racial origin, family history of diabetes, use of ovulation drugs, obstetrical history (GDM, birth weight)
- By using a predictive logistic regression model

First trimester prediction of GDM based on maternal and family history characteristics (Syngelaki et al, Fetal Diag & Therapy, 2015)

Relationship between true and false positive rates in screening for GDM in the new model and in five previously published clinical risk prediction models.



55% prediction at a 10% FPR

Can we identify women who will develop GDM in the 1st trimester?

- Yes
- But not all
- Therefore 2nd trimester universal screening is promoted by all bodies

- And that seems good, more so since……

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

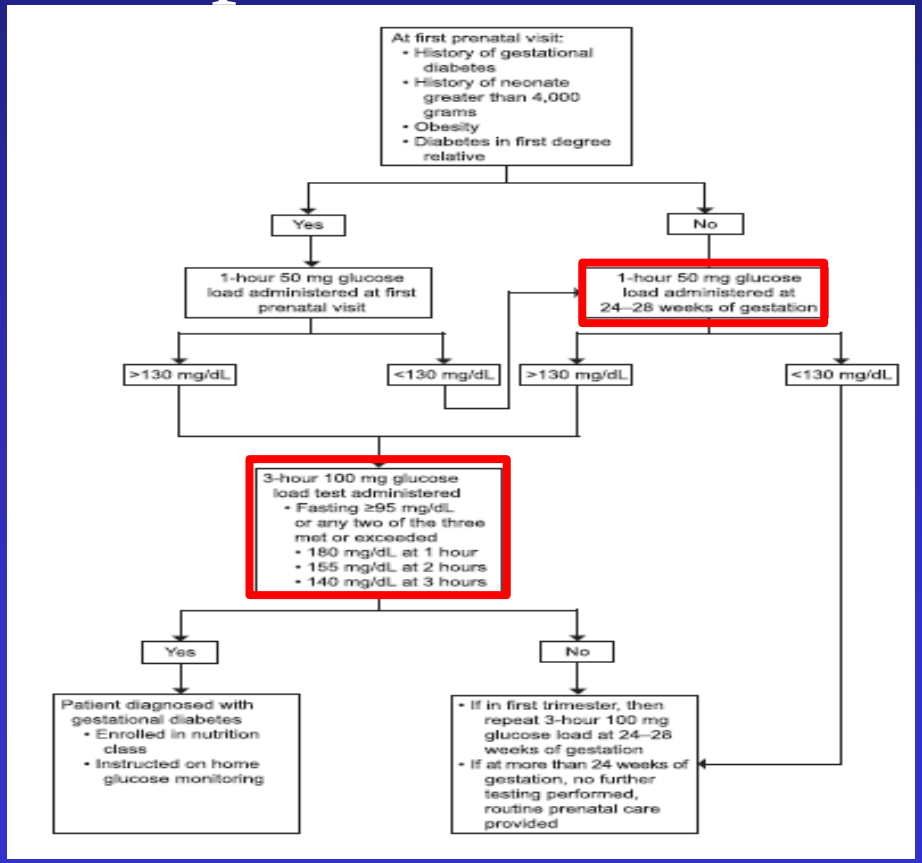
Outcome after screening is better than outcome following symptoms

	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

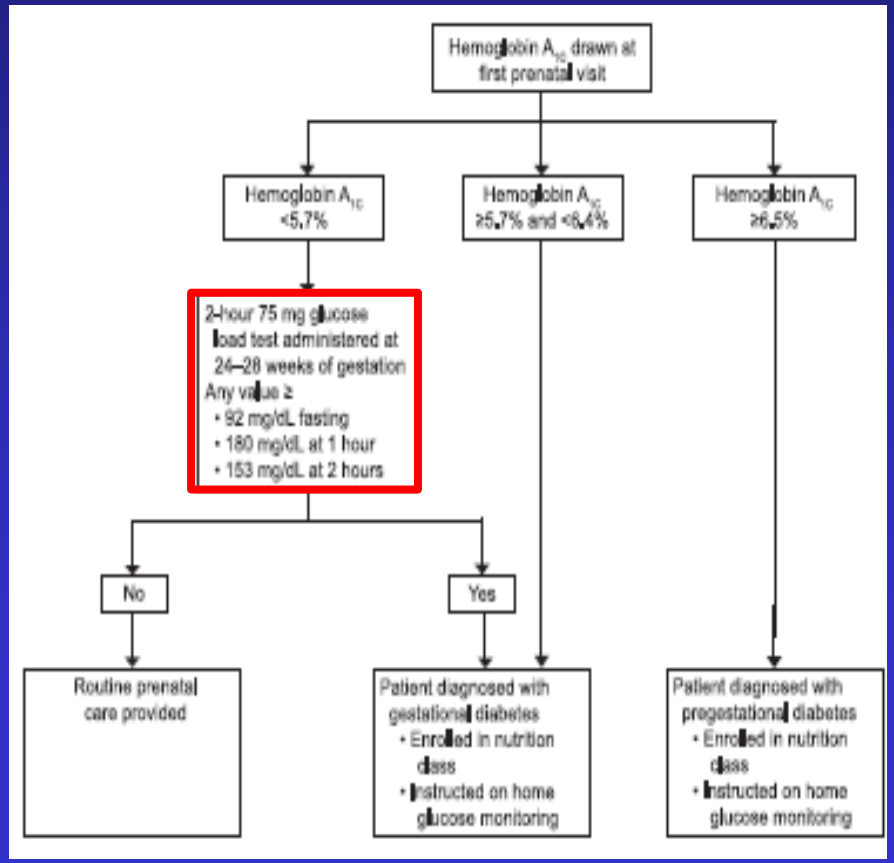
Hammoud et al, JMFNM 2012

Two-step or one-step screening

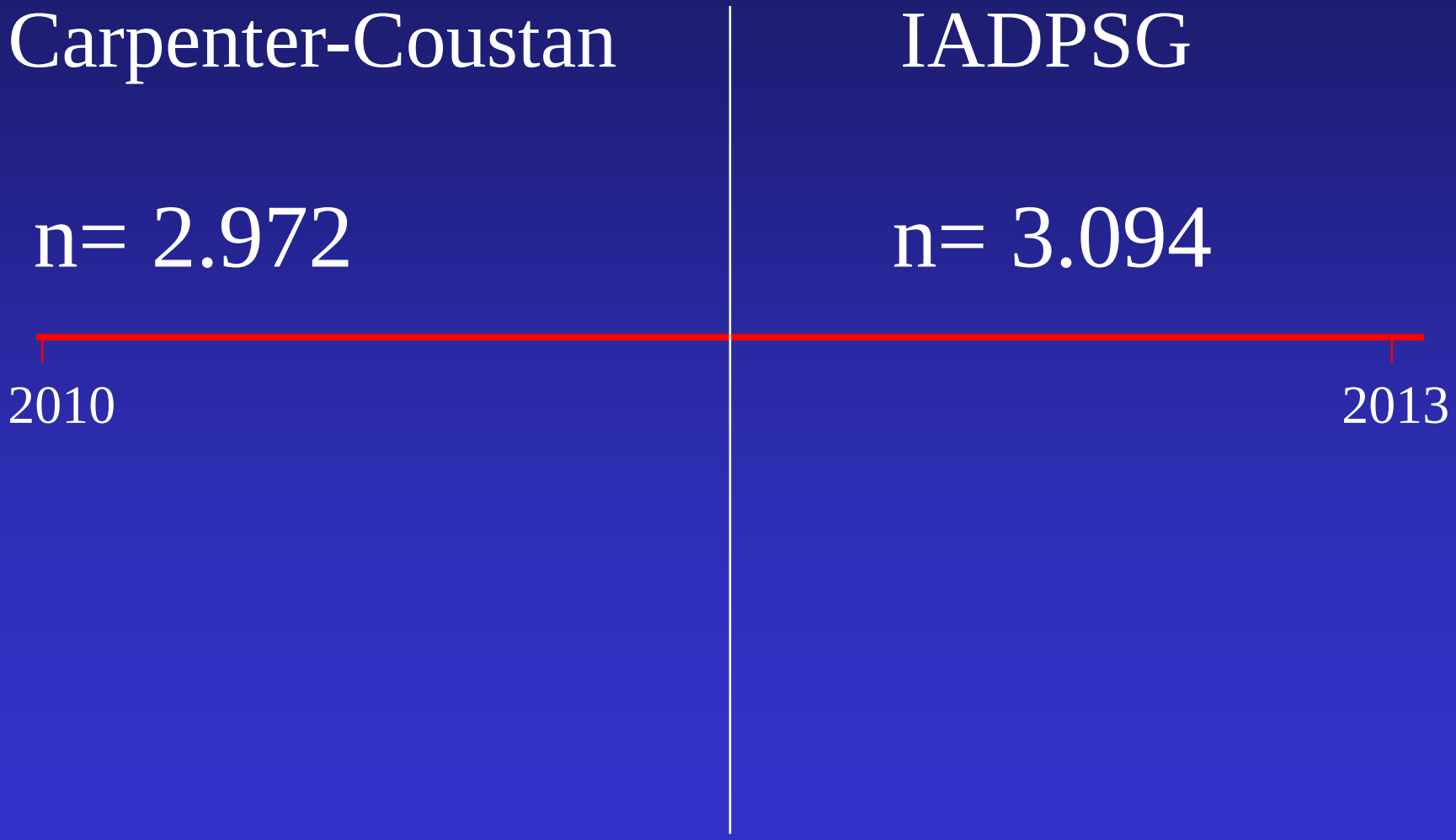
Carpenter-Coustan



IADPSG



Two-step or one-step screening



Feldman et al, O&G, 2016

Two-step or one-step screening

Carpenter-Coustan	IADPSG
n= 2.972	n= 3.094
2010	2013
GDM n=513 17%	GDM n=847 27% p<0.001
LGA 10%	LGA 9% p=0.25
Prim C.Del 16%	Prim CD 20% p<0.001

Feldman et al, O&G, 2016

Two-step or one-step screening

Carpenter-Coustan	IADPSG
n= 2.972	n= 3.094

So, more GDM, more Cesarean deliveries, no difference in LGA

Feldman et al, O&G, 2016

How to screen for GDM; at 24-28 wks as compared to oGTT

	cutoff value	ROC
• Random Glucose	(>6.8mmol/l)	0.69
• 50 g glucose load	(>7.8mmol/l)	0.88

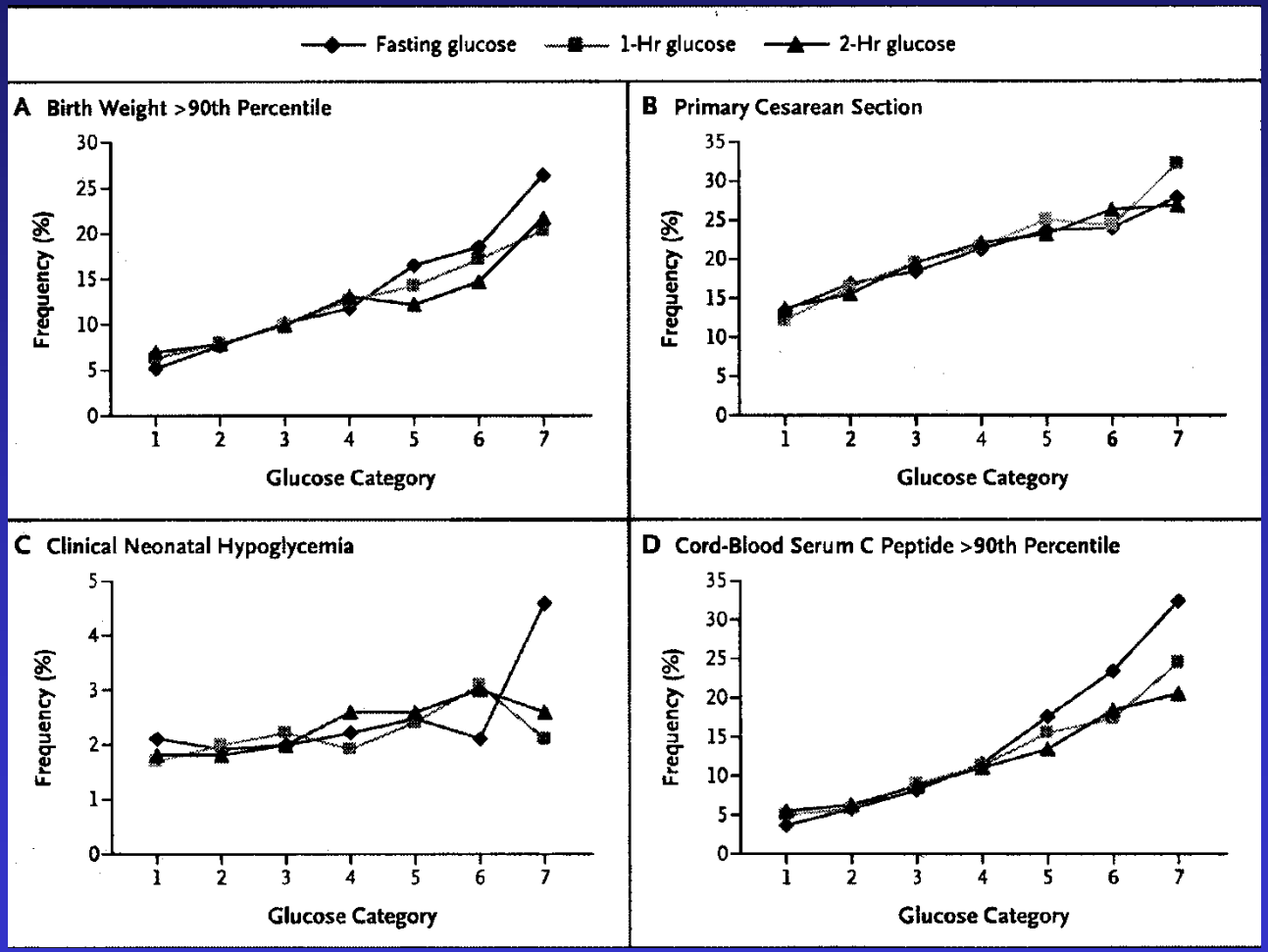
50g glucose load has a 74% detection rate for GDM and is an adequate screening tool; however, not to replace the oGTT for diagnosis

Van Leeuwen et al, Diab Care 2007 and BJOG 2012

FIGO / WHO

- Use a one-step screening/diagnostic approach
- Preferably oGTT at 24-28 wks
- Cut-off values?

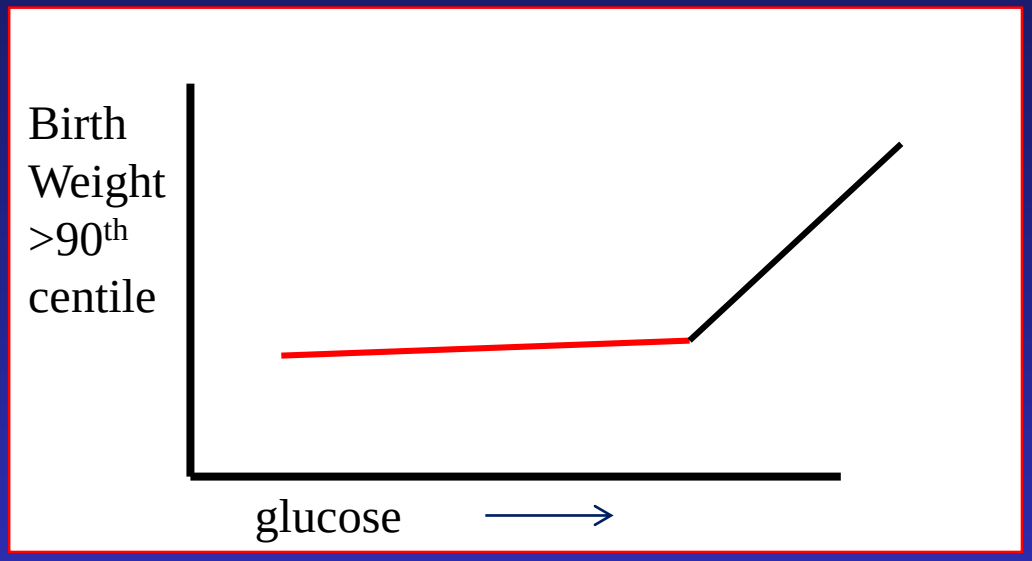
Which threshold values should be used

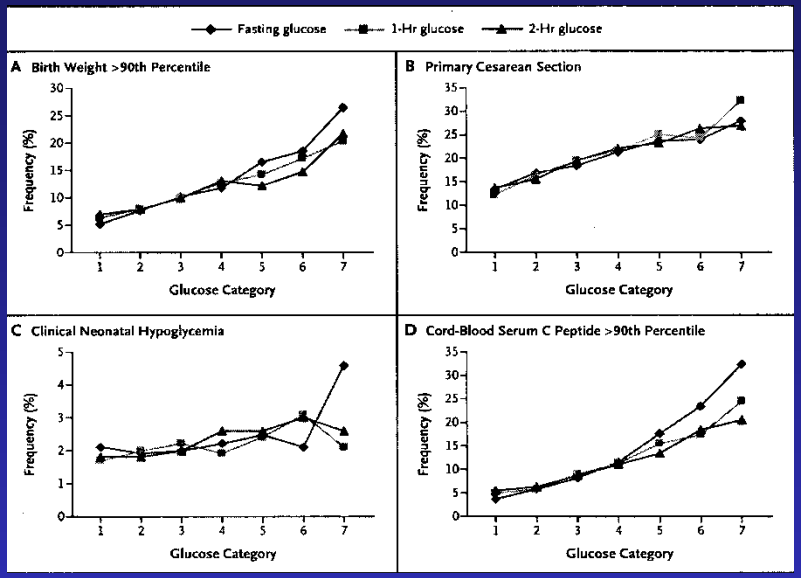


HAPO

(NEJM, May 8, 2008)

Gestational diabetes





oGTT threshold values will, by definition, be arbitrary, giving the linear relation between glucose and impaired outcome

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%

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

Drivers for overdiagnosis:

- Technological changes detecting even smaller abnormalities
- Commercial and professional vested interests
- Conflicting panels producing expanded disease definitions and writing guidelines
- Legal incentives that punish underdiagnosis but not overdiagnosis
- 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

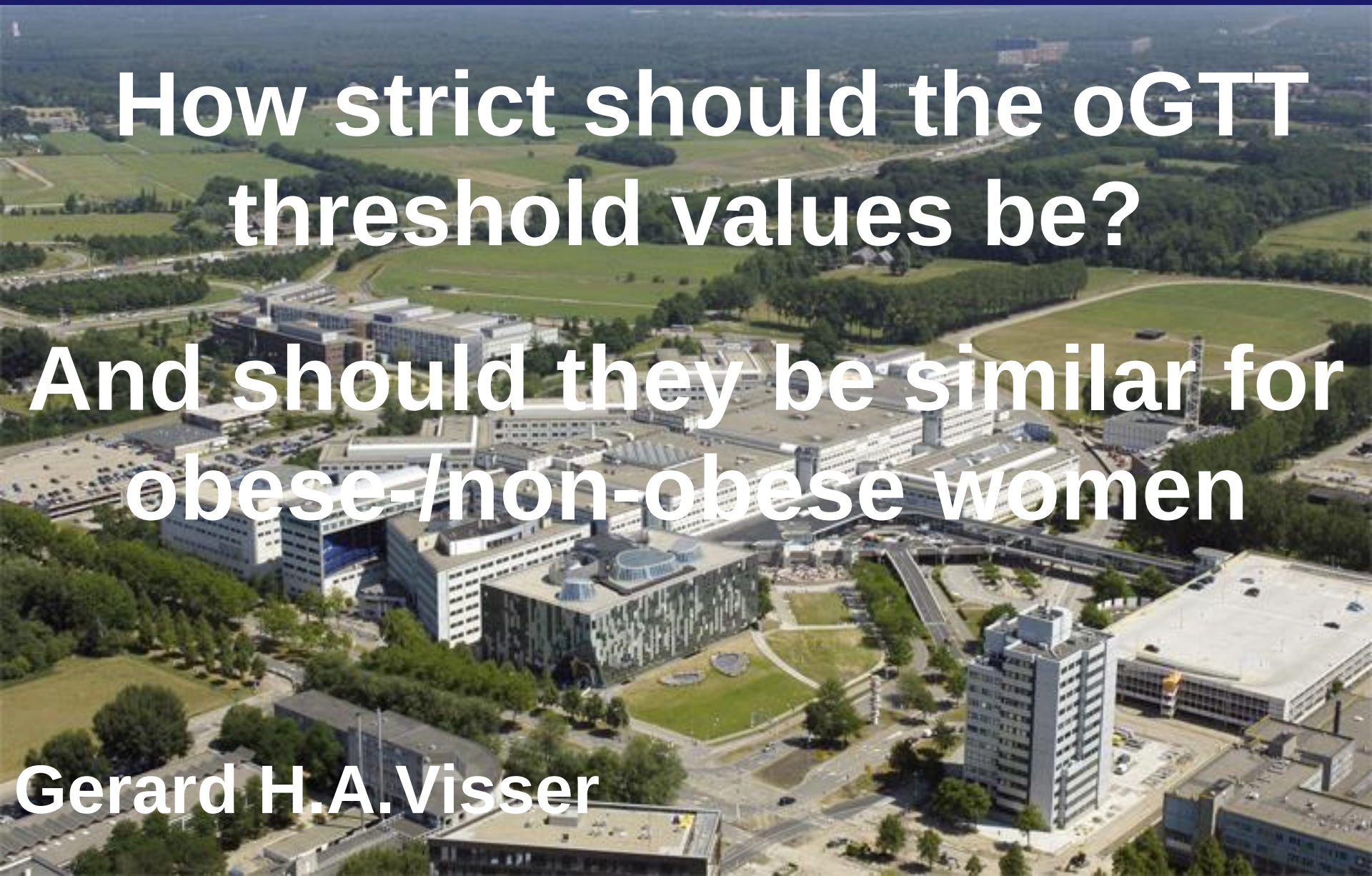
2 hour => 9.0

Diagnostic criteria based on 2 fold increase in LGA infant

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

Prevalence of GDM 0f

10.5%



How strict should the oGTT threshold values be?

And should they be similar for obese-/non-obese women

Gerard H.A.Visser

Obesity and GDM; direct perinatal 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

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)

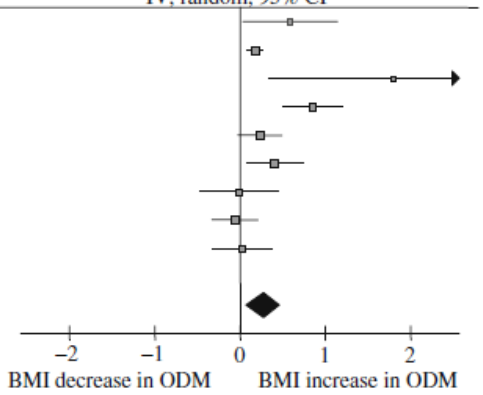


Fig. 2 Forest plot showing the unadjusted association between all types of maternal diabetes and offspring BMI *z* score. Heterogeneity: τ^2=0.05; χ^2=27.02, *df*=8 (*p*=0.0007); I^2=70%. Test for overall effect: *z*=2.90 (*p*=0.004). IV, inverse variance; ref., reference

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)

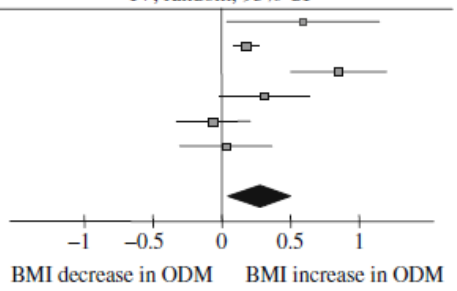


Fig. 3 Forest plot showing the unadjusted pooled analysis of offspring BMI *z* score of mothers with gestational diabetes mellitus and controls. Heterogeneity: τ^2=0.06; χ^2=25.54, *df*=5 (*p*=0.001); I^2=76%. Test for overall effect: *z*=2.39 (*p*=0.02). IV, inverse variance; ref., reference

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)

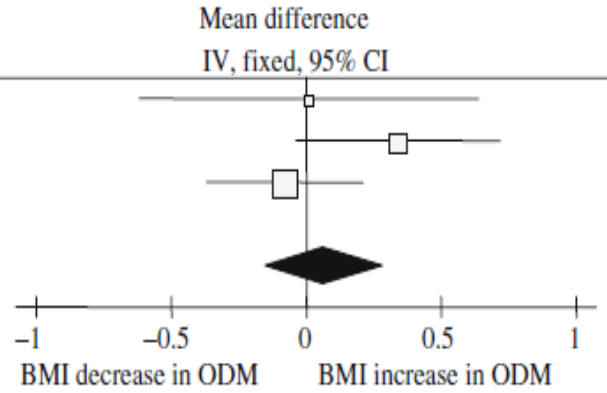


Fig. 5 Forest plot showing the adjusted association between all types of maternal diabetes and offspring BMI *z* score. Heterogeneity: χ^2= 3.02, *df*=2 (*p*=0.22); I^2=24%. Test for overall effect: *z*=0.61 (*p*=0.54). IV, inverse variance; ref., reference

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

Long term outcome in offspring: maternal overweight is the main problem and not GDM

overweight and abdominal obesity in 16 y old adolescents

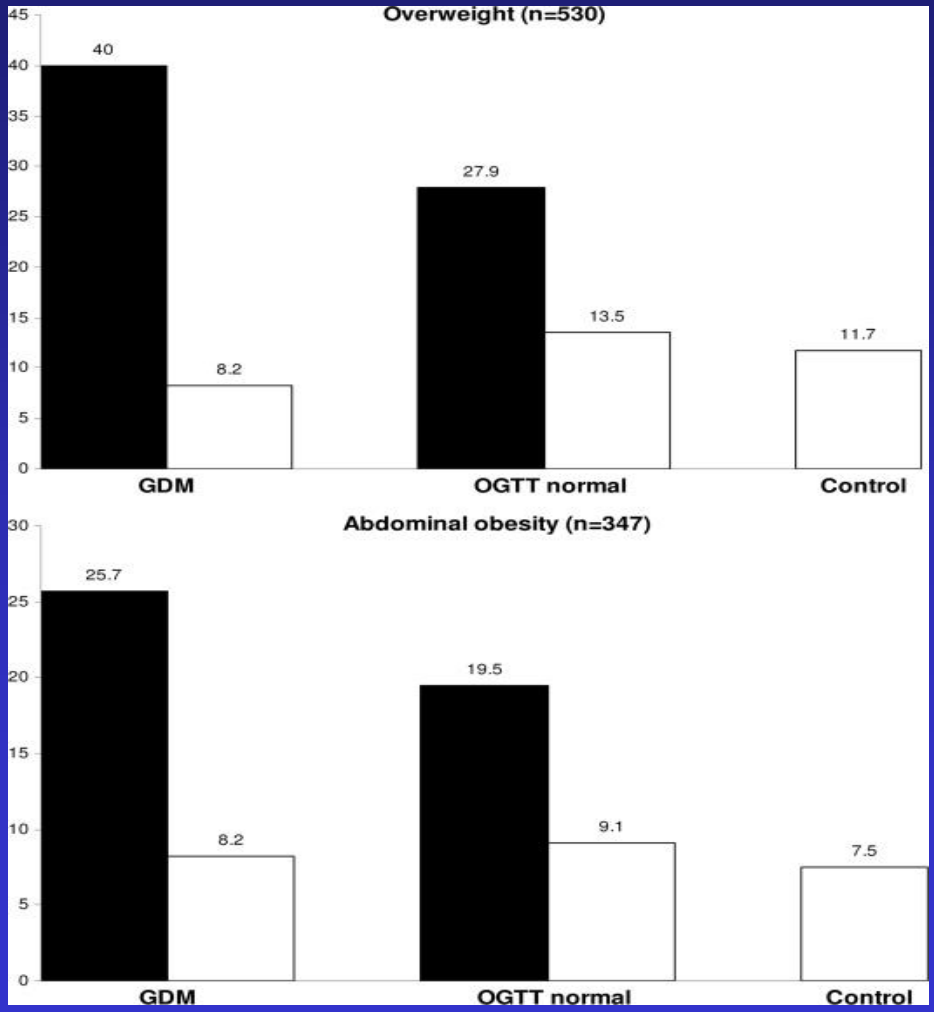
Risk population:

-GDM 84

-Normal OGTT 657

Control 3.427

■ = mat BMI> 25



Pirkola et al, Diab Care 2010

Treatment improves outcome

- Treatment improves neonatal outcome, with a 50% rduction in macrosomia at birth (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

Treatment improves outcome

- Treatment improves neonatal outcome, with a 50% reduction in macrosomia at birth (screening is therefore useful)

- However, no difference in childhood BMI at follow-up at 5y of age (Gillman et al, Diab Care 2010; n=199), or 5-10y of age (Landon et al, Diab Care 2015; n=500)

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

Review Article

Does exposure to hyperglycaemia *in utero* increase the risk of obesity and diabetes in the offspring? A critical reappraisal

L. E. Donovan[1] and T. Cundy[2]

[1]Department of Medicine, Division of Endocrinology and Metabolism and Department of Obstetrics and Gynaecology, University of Calgary, Alberta, Canada and [2]Department of Medicine, Faculty of Medical & Health Sciences, University of Auckland, New Zealand

Results Some animal studies support a relationship between exposure to hyperglycaemia *in utero* and future development of obesity and diabetes, but the results are inconsistent. Most of the human studies claiming to show a relationship have not taken into account important known confounders, such as maternal and paternal BMI. Evidence supporting a dose–response relationship between maternal hyperglycaemia exposure and obesity and diabetes in the offspring is weak, and there is no convincing evidence that treating gestational diabetes reduces the later risk of offspring obesity or glucose intolerance.

Conclusions Exposure to hyperglycaemia *in utero* has minimal direct effect on the later risk of obesity and Type 2 diabetes. The increased risk of obesity in the offspring of women with Type 2 or gestational diabetes can be explained by confounding factors, such as parental obesity.

Diabet. Med. 32, 295–304 (2015)

Type-1, type-2 diabetes and GDM

which infants have the highest risk of becoming obese during childhood?

	LGA at birth
Type-1	
Type 2	
GDM	

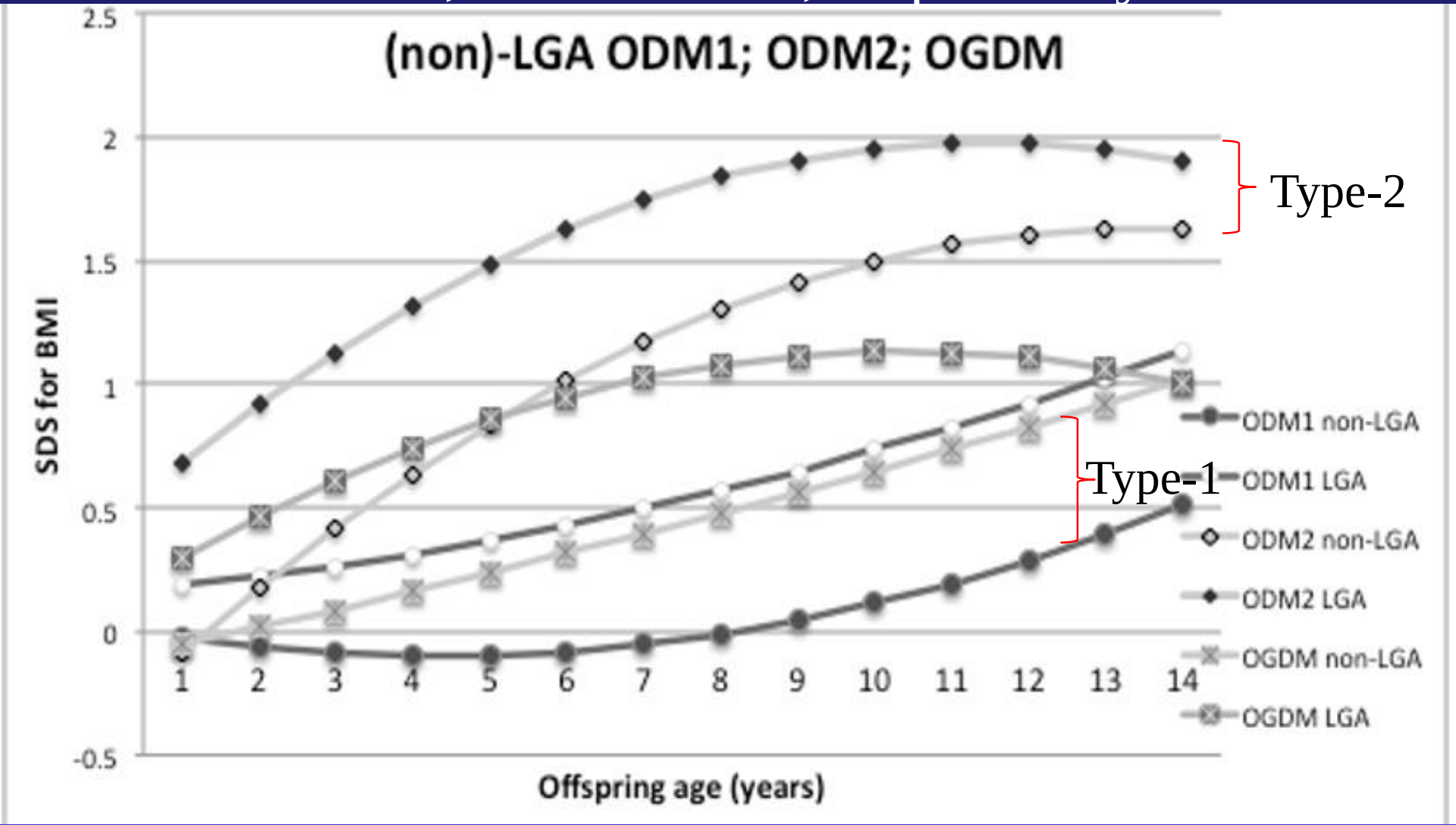
Type-1, type-2 diabetes and GDM

which infants have the highest risk of becoming obese during childhood?

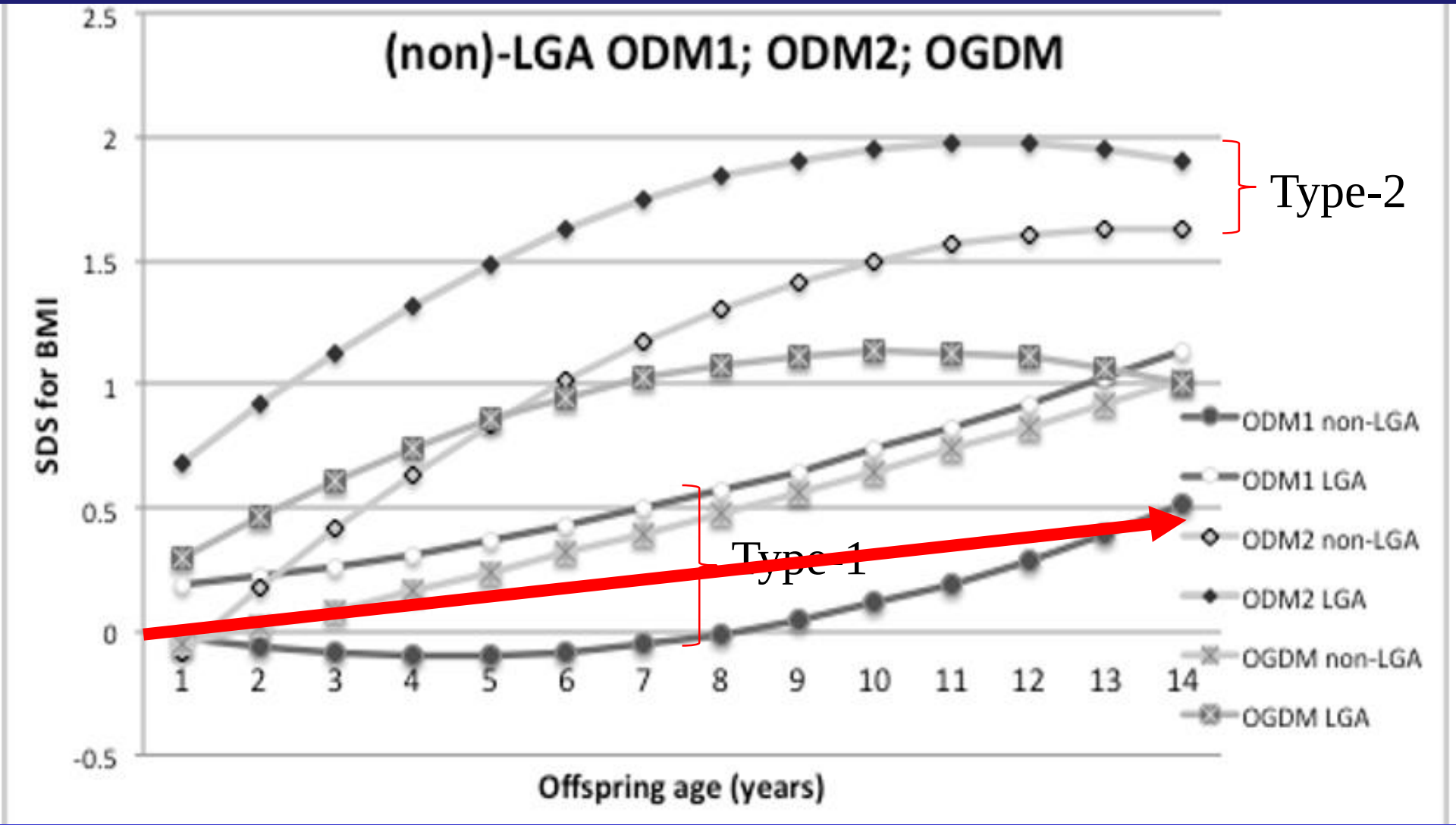
	LGA at birth
Type-1	50%
Type 2	35%
GDM	20%

Childhood growth of infants of women with type-1, type-2 and Gest diabetes(Hammoud et al, 1018)

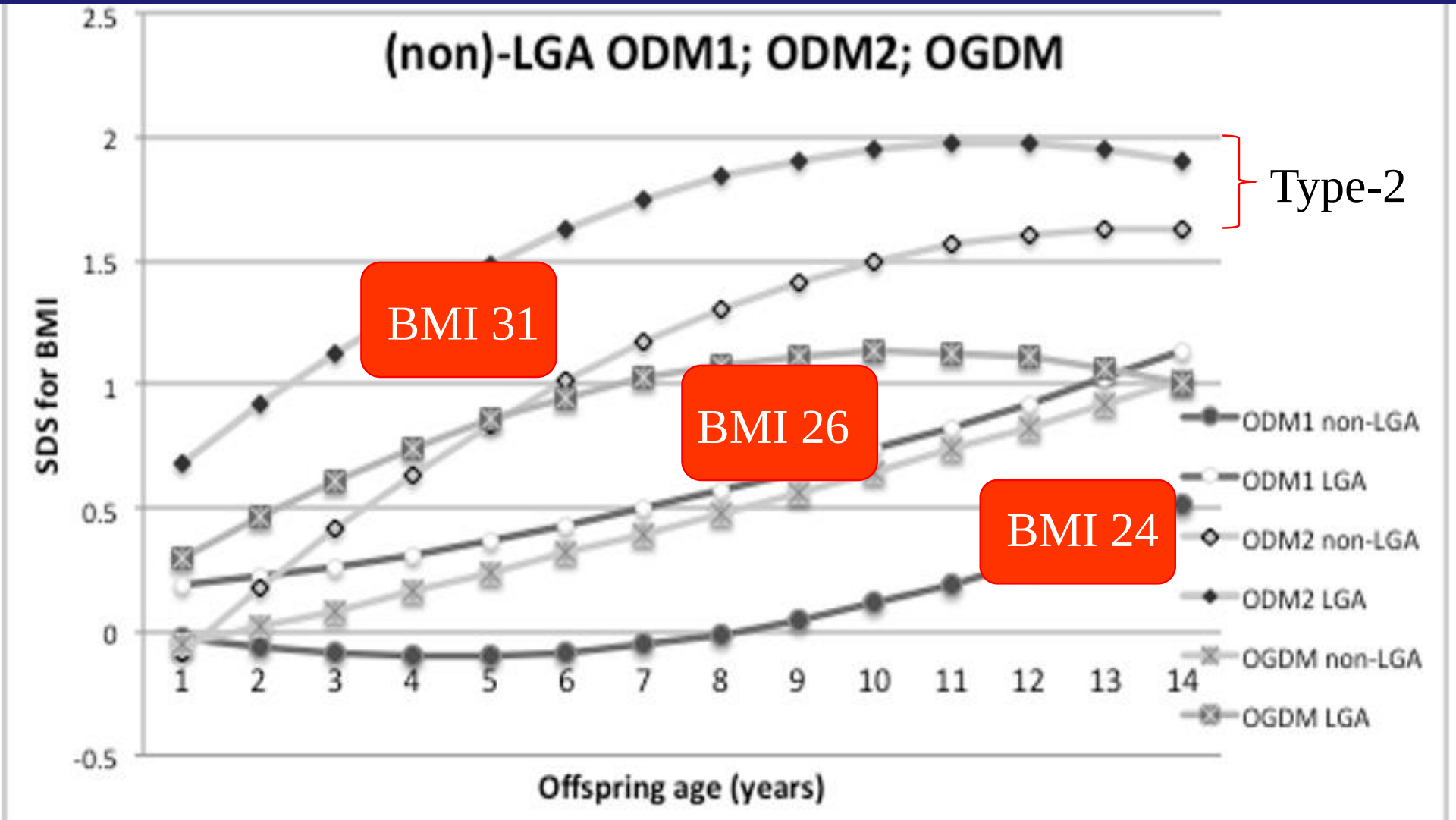
LGA at birth: 50, 35 and 20%, respectively



Childhood growth of infants of women with type-1, type-2 and Gest diabetes (Hammoud et al,Ped Res 2017, Diabetologia, 2018)



Childhood growth of infants of women with type-1, type-2 and Gest diabetes (Hammoud et al, Diab 2018)



So,

- Obesity is the driving factor for impaired offspring outcome
- With diabetes as an adjunct factor. In GDM only for obese women.

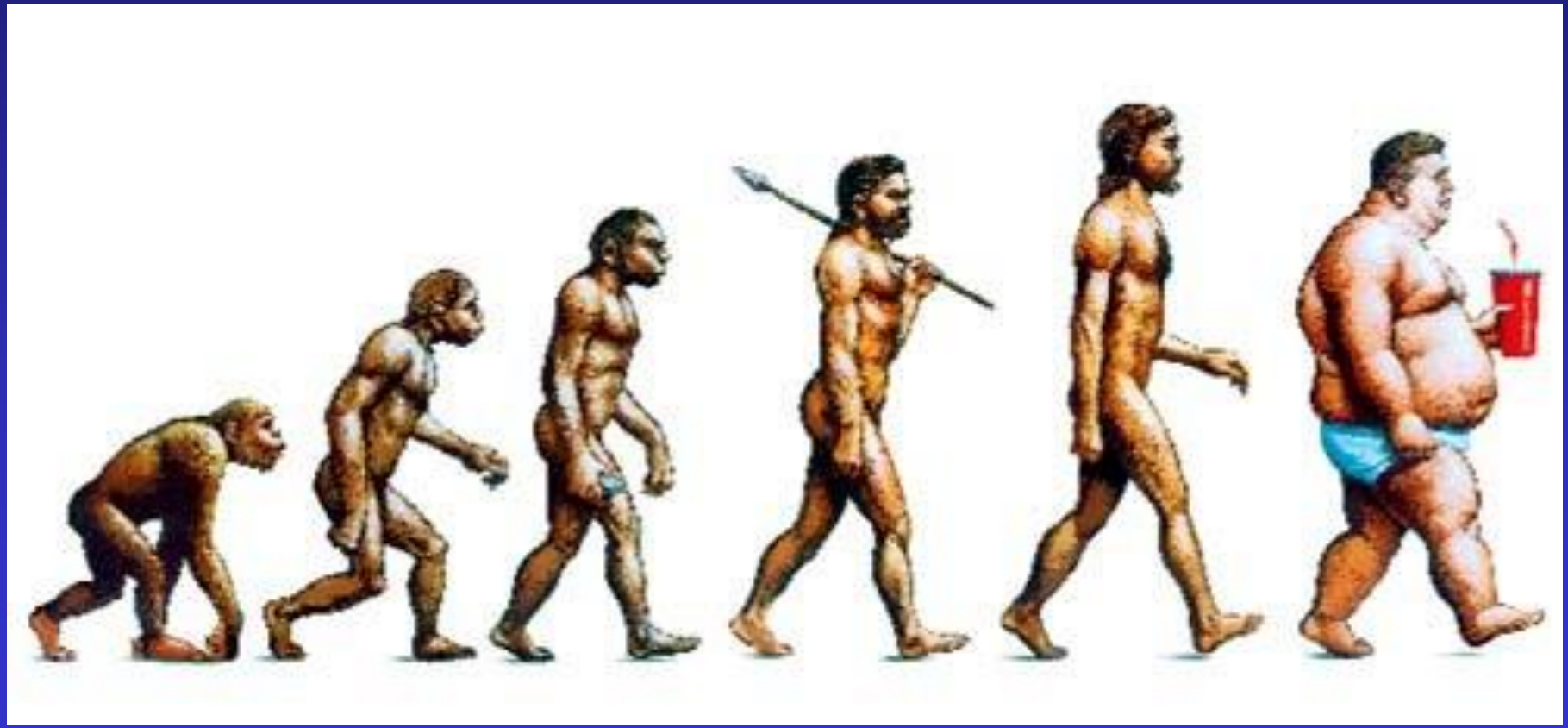
However,….

- That may not hold for infants born ‘stunted’, with a normal weight later in life, but with an abnormal fat distribution
- Which may also hold in Europe, in case of a relatively low birth weight and normal BMI but increased body fat (E.Huvinen, EBCOG Paris, 2018)

But, altogether

- Use strict threshold oGTT values in obese women
- Be less strict in lean women
- Try to prevent obesity and high weight gain in (before)pregnancy in these women.
- But prevention should already start in early childhood

The descent of Man



Thank you

And finally, do not forget…

that 3rd trimester fetal macrosomia and/or polyhydramnios may be a sign of GDM, also in women who had a normal oGTT at 24-28 weeks