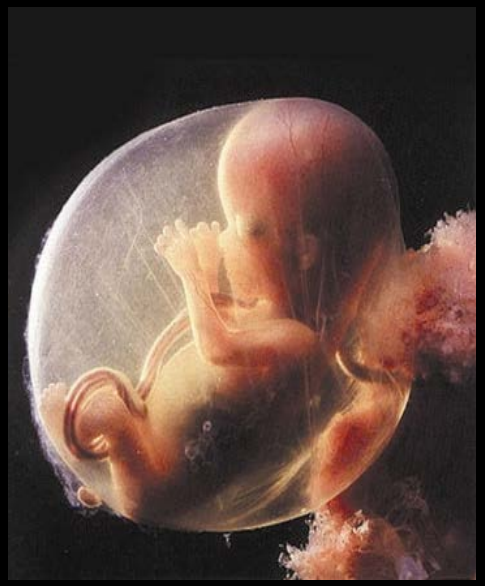
Gestational Diabetes: Epidemiology and Consequences

Dana Dabelea, MD, PhD

University of Colorado Denver



Gestational Diabetes in 7 Questions

1. What is gestational diabetes-GDM?
2. Why focus on pregnancy?
3. What are the consequences of hyperglycaemia in pregnancy?
    1. For the offspring
    2. For the mothers
4. How to diagnose GDM?
5. How to screen?
6. Is it worth treating GDM?
7. How is GDM treated?

1

WHAT IS GESTATIONAL DIABETES?

Gestational Diabetes

"Any degree of glucose intolerance with onset or first recognition during pregnancy"

2

WHY FOCUS ON PREGNANCY?

Glucose Metabolism in Pregnancy

- First Half of Pregnancy
  - Pancreatic beta-cell hyperplasia causes hyperinsulinemia
  - Increased uptake and storage of glucose
- Second Half of Pregnancy
  - Placental hormones cause insulin resistance
    - Increased lipolysis
    - Increased gluconeogenesis
    - Decreased glycogenesis
  - Increased glucose and other nutrients for the fetus
- Normal pregnancy is a “diabetogenic” state

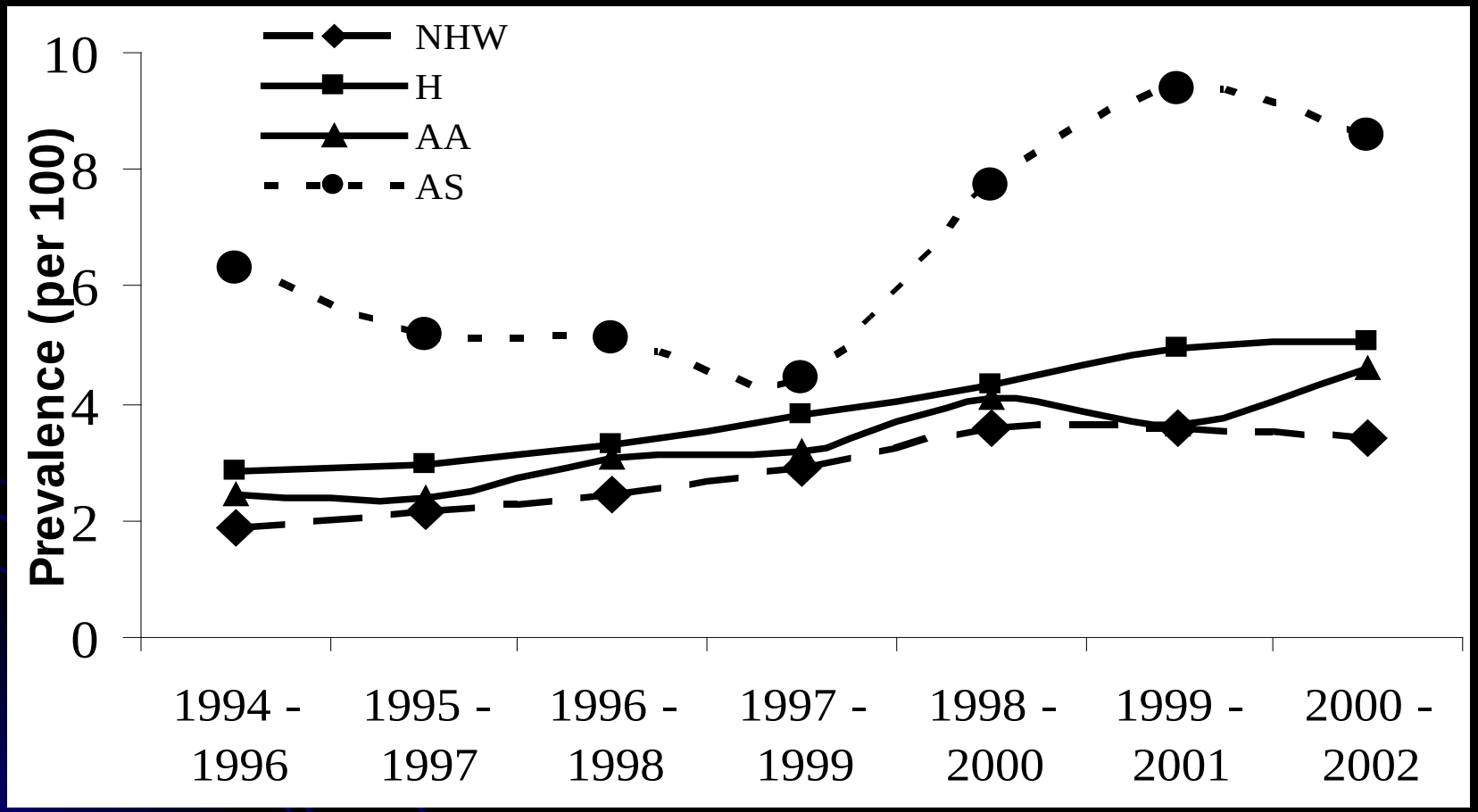
Who is at risk of GDM?

- Maternal age >25
- Family history of diabetes
- Ethnic group: non Caucasians
- Obesity
- Prior macrosomia
- Previous unexplained stillbirth

Epidemiological reasons

- Despite the young age of pregnant women, diabetes is frequent in pregnancy
- Prevalence ranges from 2-14%; higher in non Caucasians
- Increasing trends over time
- Presence of diabetes during pregnancy has short and long-term consequences for offspring and mothers

Increasing Prevalence of GDM in All Racial/Ethnic Groups in Colorado



Dabelea D, Diabetes Care 2005; 28:579

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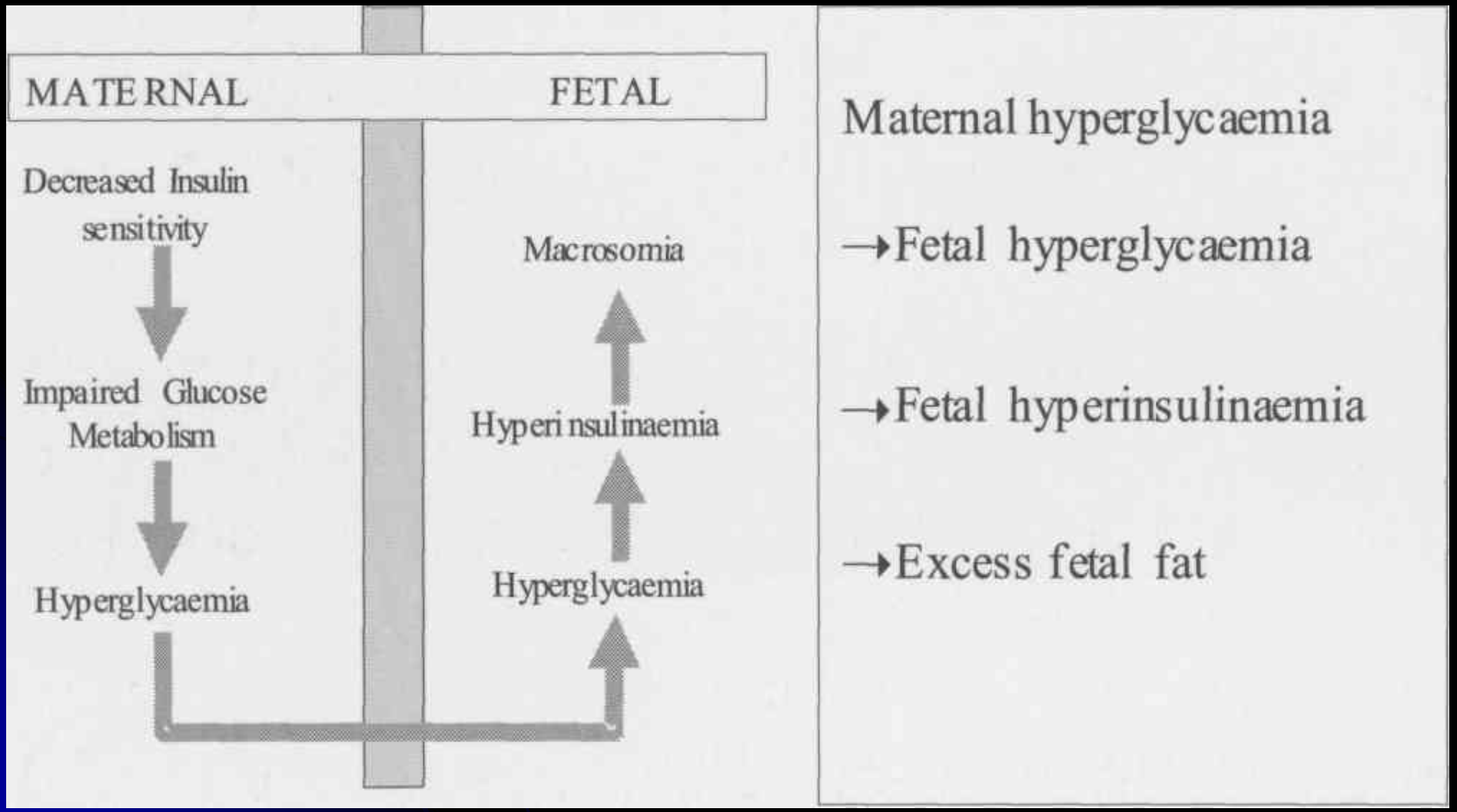
WHAT ARE THE CONSEQUENCES OF MATERNAL HYPERGLYCAEMIA DURING PREGNANCY?

Pedersen hypothesis (1952)



Short Term Consequences- The Neonate

- Increased risk of stillbirth
- Macrosomia / Shoulder dystocia
- Neonatal Hypoglycaemia; Hyperbilirubinaemia; Polycythaemia; Hypocalcaemia
- Neonatal respiratory distress syndrome
- No increase in congenital anomalies
  - Risk increased with pre-gestational diabetes

Cousan 1995, Yang 2002

Fuel-Mediated Teratogenesis

Intrauterine exposure of the fetus of women with diabetes in pregnancy to an excess of fuel (for example, glucose) causes permanent fetal change, leading to malformations, greater birth weight, and an increased risk of developing obesity and type 2 diabetes in later life

(Freinkel, Banting Lecture 1980)

Long-Term Consequences:

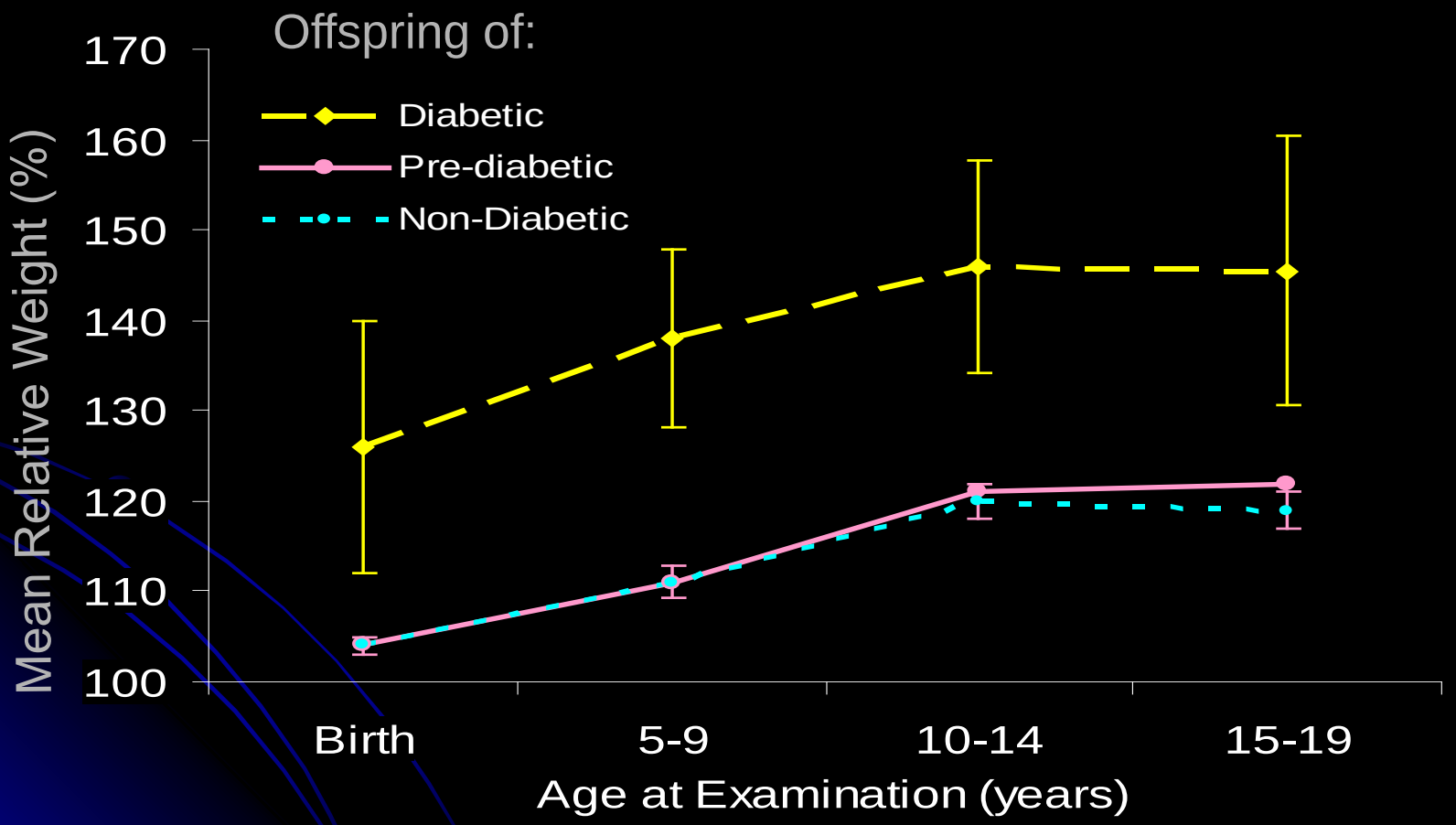
Offspring Adiposity

Exposure to Maternal Diabetes Results in Increased Neonatal Adiposity

	Offspring of GDM Mothers N=195	Offspring of NGT Mothers N=220	p
BWT (g)	3398 ± 550	3337 ± 549	0.2
Fat Mass (g)	**436 ± 206**	**362 ± 198**	**0.0002**
Body Fat (%)	**12.4 ± 4.6**	**10.4 ± 4.6**	**0.0001**
FFM (g)	2962 ± 405	2975 ±	0.7

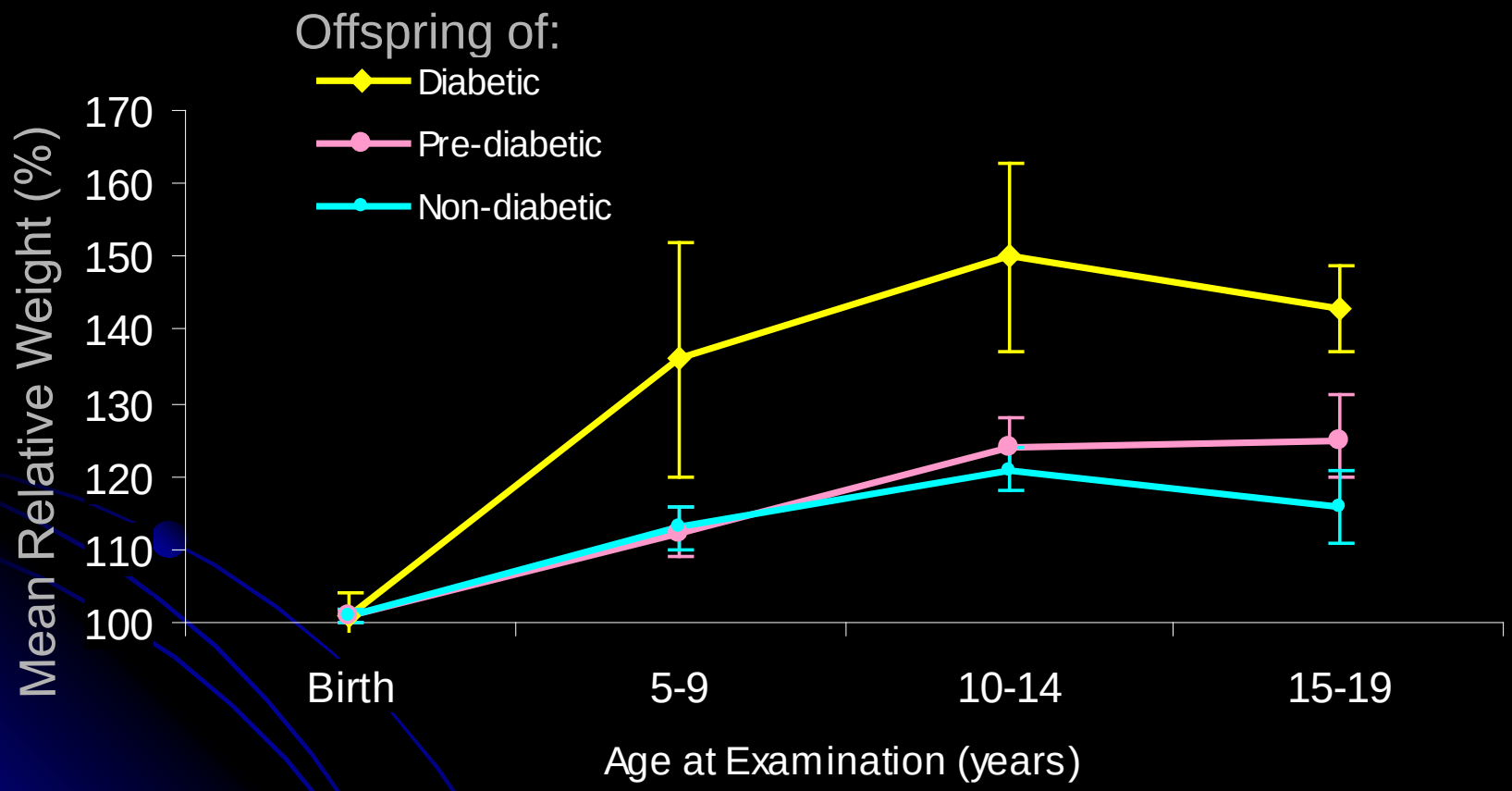
Catalano PM, Am J Obstet Gynecol, 2003; 189: 1698

Mean Relative Weight in Pima Indian Offspring by Age and Mothers Diabetes



Pettitt DJ, Diabetes Care 1987; 10:76

Mean Relative Weight in Pima Indian Offspring by Age and Mothers Diabetes in Normal Birth Weight Offspring



(birth weight = 90% to 109% of the median weight for gestational age.)

Pettitt DJ, N Engl J Med 1983; 308:242

Exposure to Maternal GDM and Childhood Adiposity: EPOCH Study

	Exposed (N=95)	Not Exposed (N=405)	Mean Difference	P
BMI (Kg/m²)	**20.2**	**18.9**	**1.3**	**0.02**
Waist (cm)	**69.6**	**65.4**	**4.2**	**0.004**
SAT (cm2)	**156.4**	**121.7**	**34.7**	**0.006**
VAT (cm2)	**27.8**	**24.2**	**3.6**	**0.04**

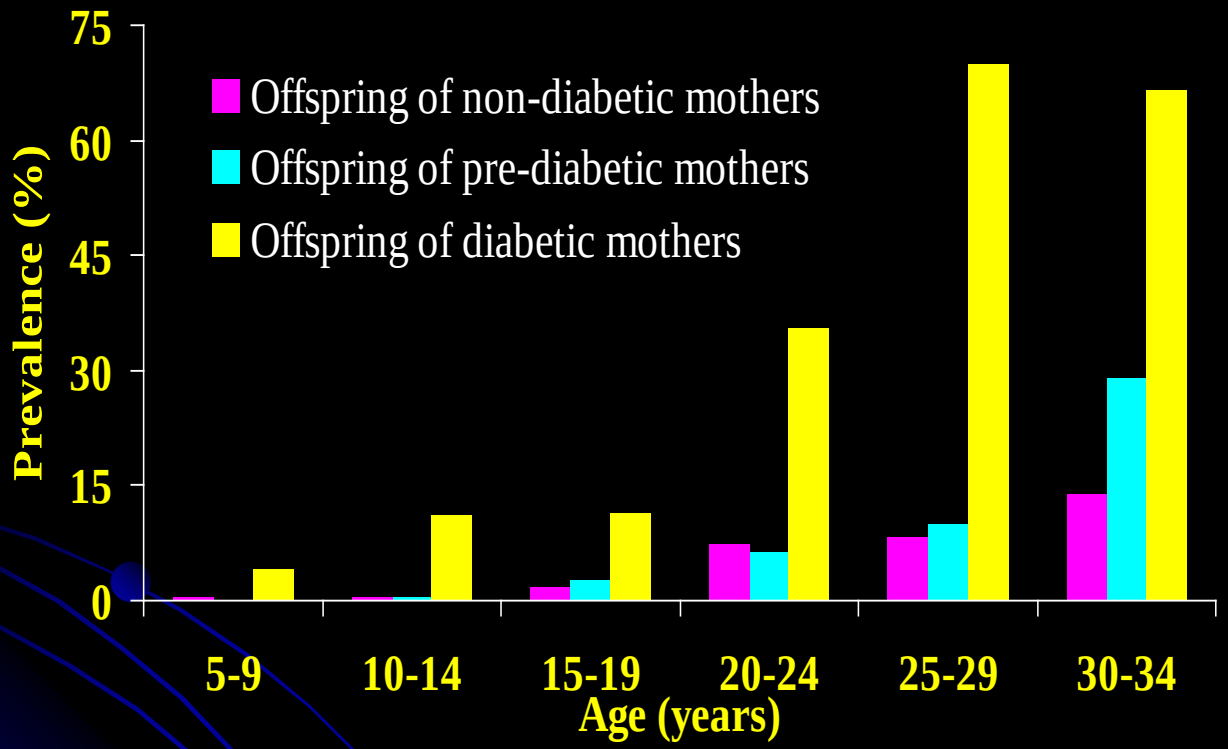
Models adjusted for age, sex, race/ethnicity, Tanner stage

Crume T; Diabetologia, 2011

Long –Term Consequences:

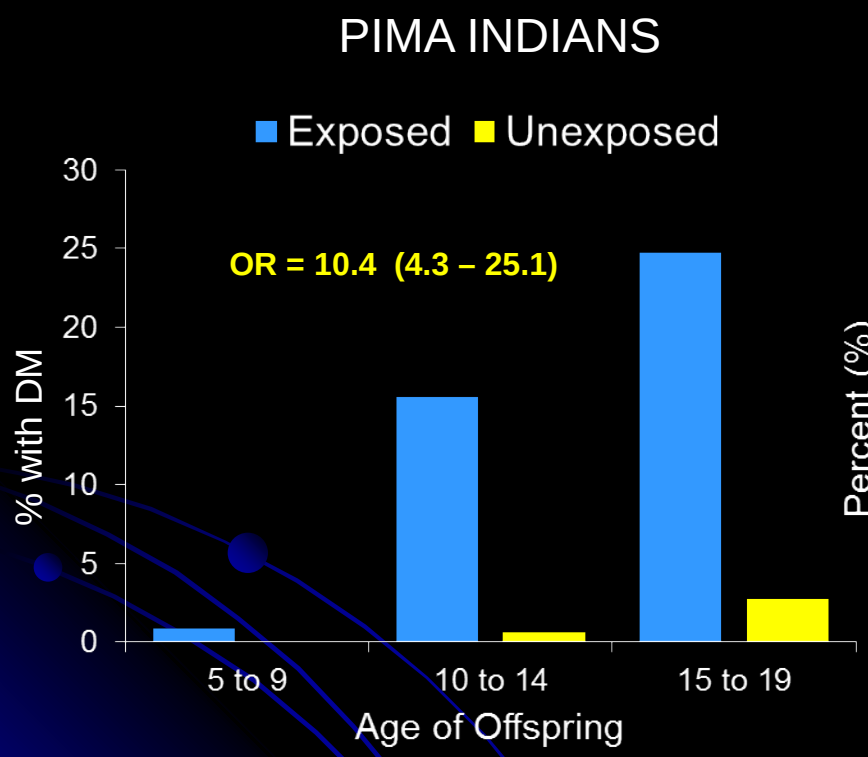
Offspring T2D

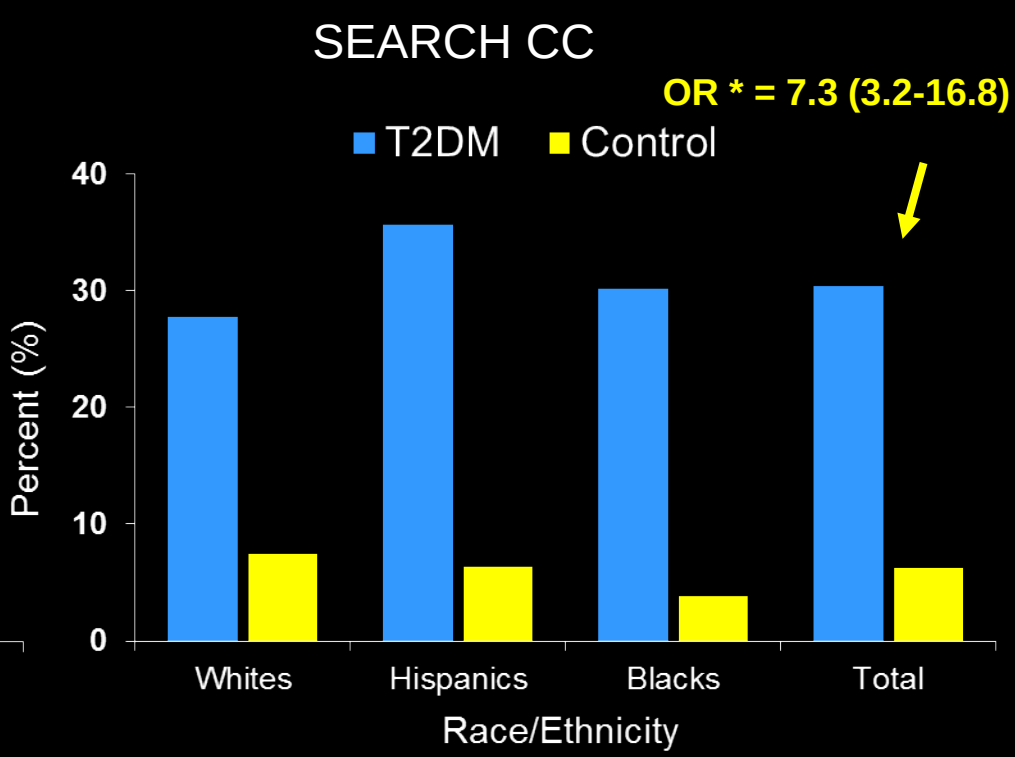
Prevalence of T2D in Pima Indians, by Mothers Diabetes in Pregnancy



Dabelea D, Pettitt DJ, J Mat. Fetal Med. 2000; 9:83.

Exposure to Diabetes In Utero- Strongest Risk Factor for T2D in Youth





*Adjusted for age, sex, race

Dabelea D, *Diabetologia*. 41:904-910, 1998

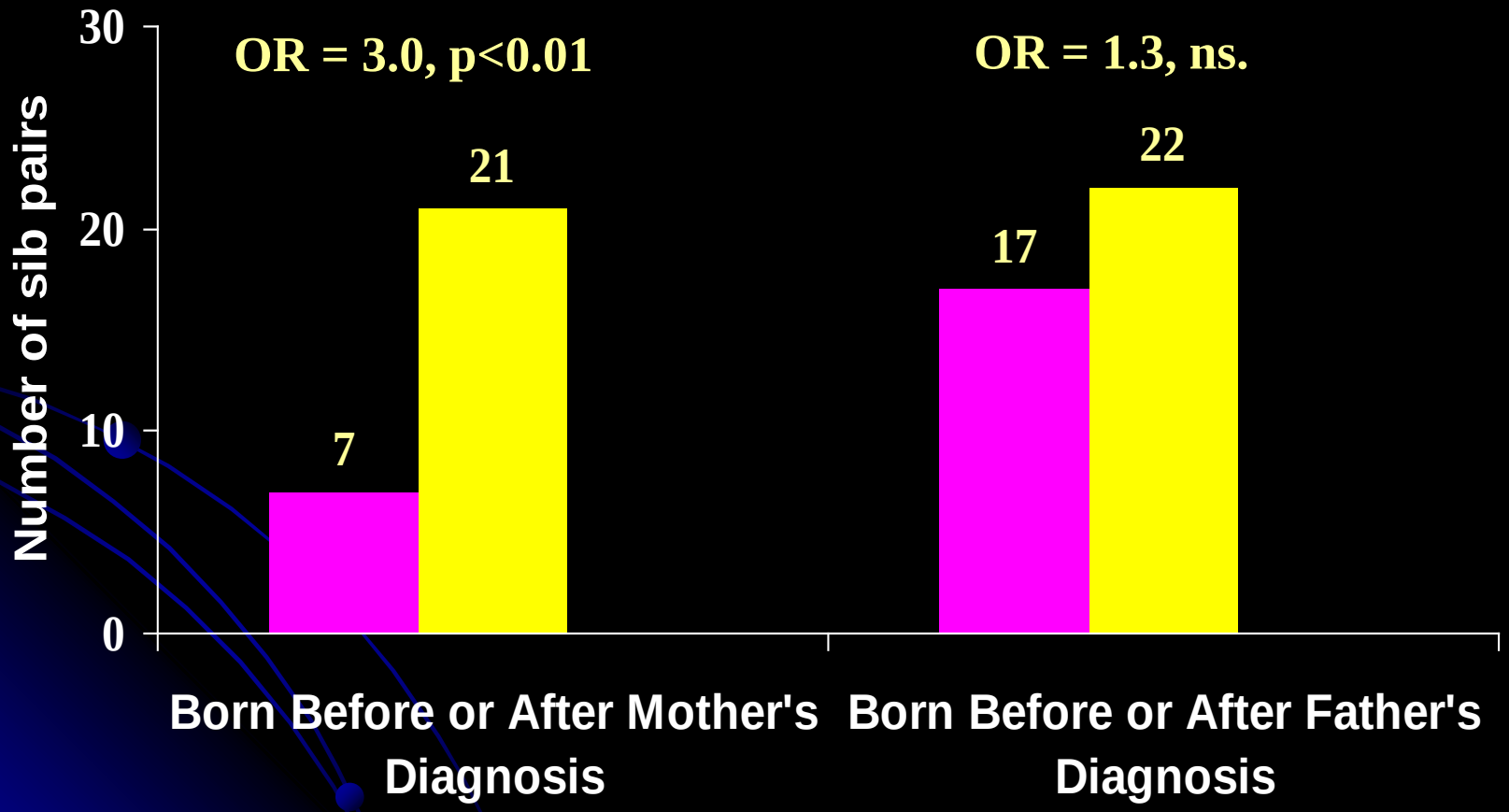
Dabelea D, *Diabetes Care*, 2008; 31: 1422

Gestational Glucose Tolerance and T2DM Risk in Pima Offspring age 5-24 years

Maternal Glucose	N Offspring	N T2DM	Incidence T2DM	Hazard Ratio (per SD maternal glucose)
Impaired Glucose Tolerance (140-200 mg/dl)	**1436**	**87**	**3.6/1000 PY**	**1.6 (1.2-2.0)**
Normal Glucose Tolerance (<140 mg/dl)	**1288**	**68**	**3.1/1000 PY**	**1.3 (1.04-1.71)**

Franks PW, Diabetes 2006; 55: 460

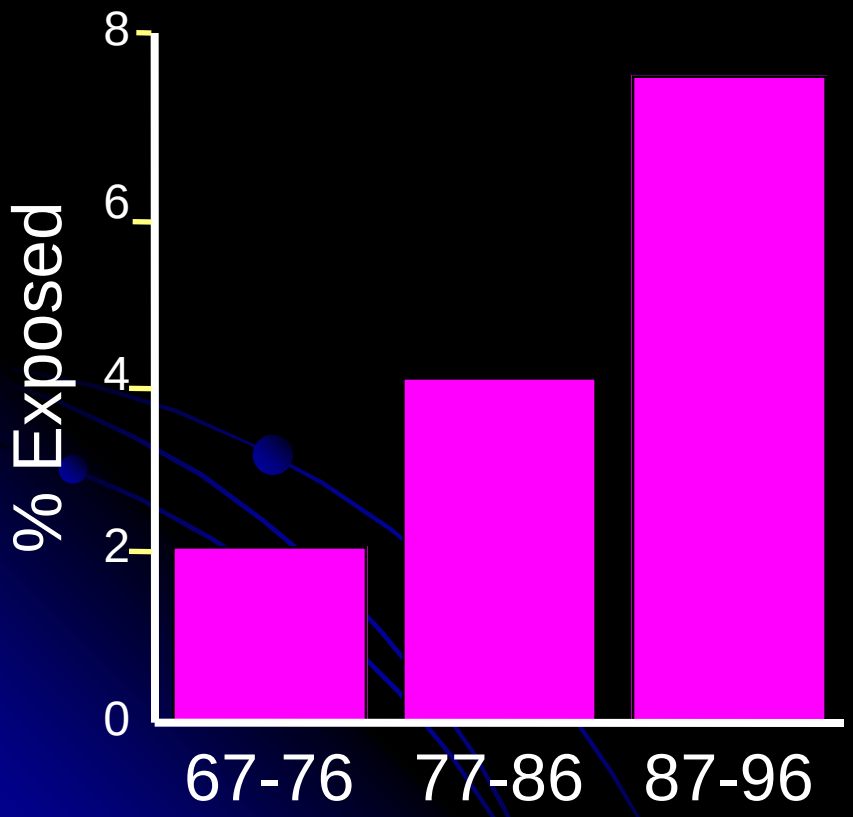
Beyond Genetics: Pima Indian Sib Pairs Discordant for Diabetes and Exposure to Diabetes in Utero

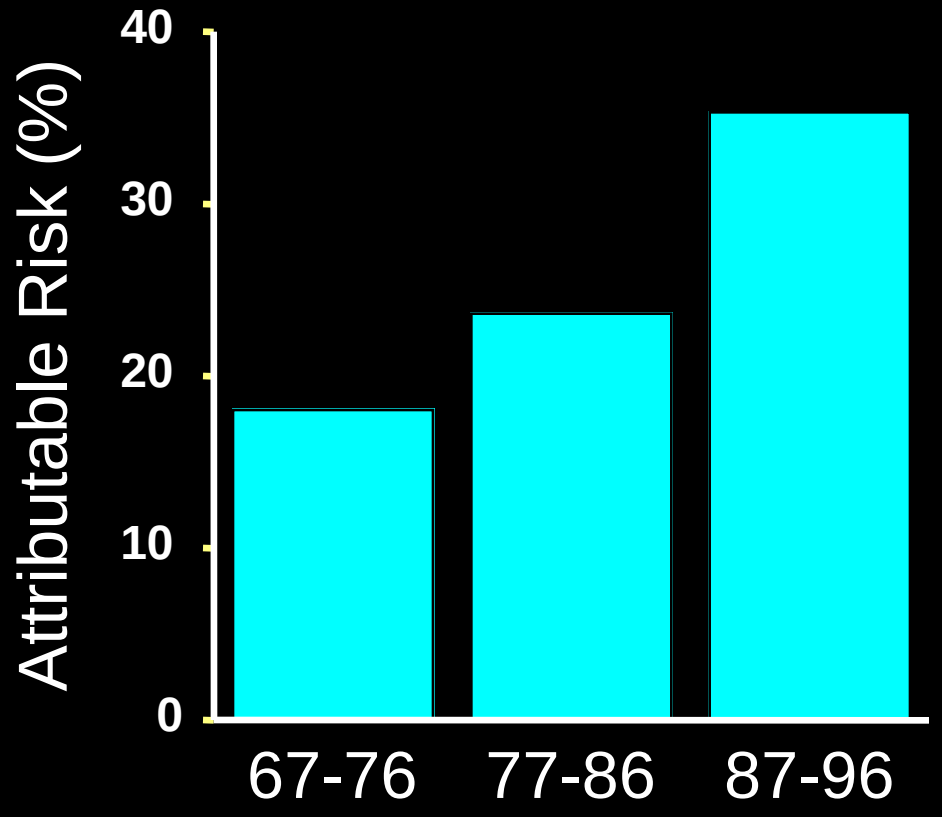


Dabelea D, Diabetes, 2000; 49:2208

Public Health Impact

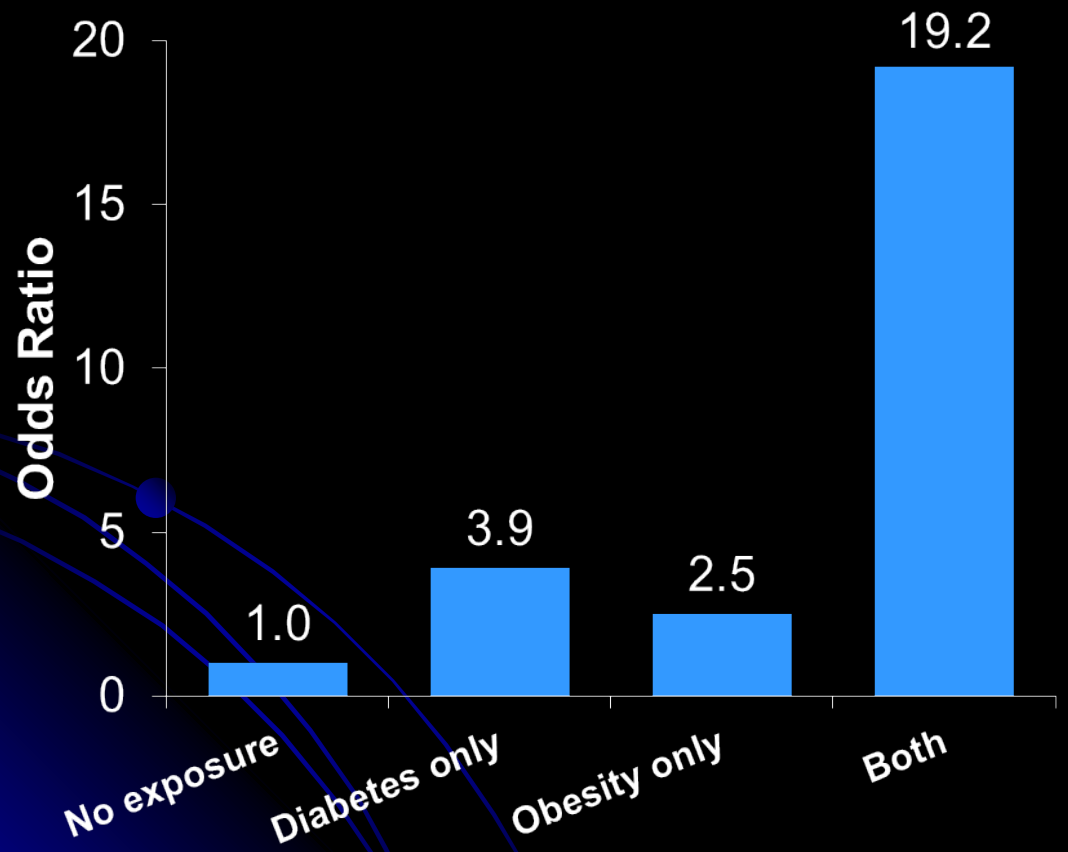
Time Trends in Maternal Diabetes and Attributable Risk for Offspring T2D – Pima Indian Study





Dabelea D., Diabetologia, 1998;41: 904

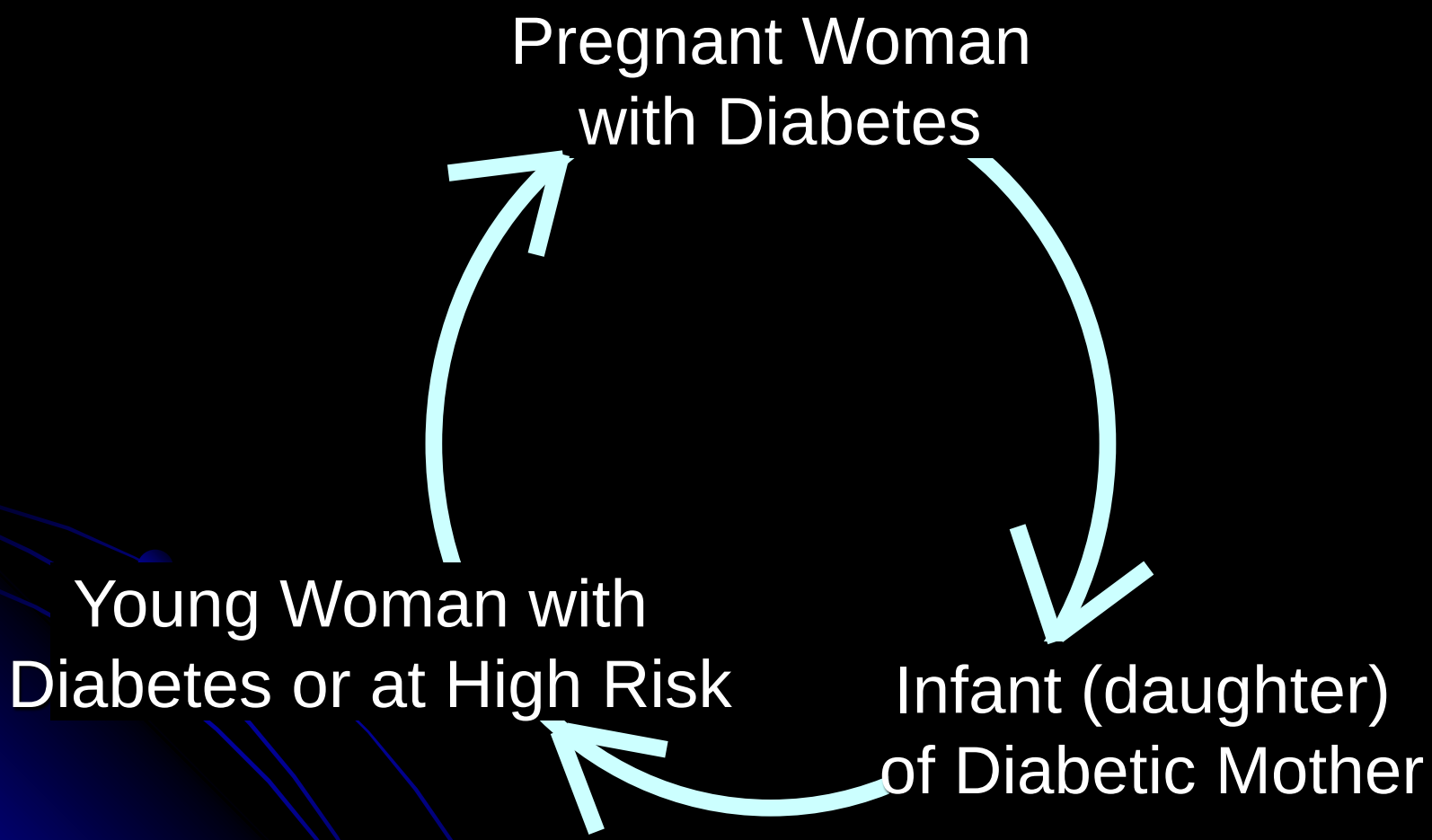
Proportion of T2D in youth Attributable to In utero Exposure to GDM and Obesity: SEARCH CC Study



Population Attributable %	
No exposure	---
Diabetes only	4.7%
Obesity only	19.7%
Both	22.8%
Overall	**47.2%**

Dabelea D, *Diabetes Care*, 31: 1422, 2008;

Diabetes & Obesity: The Vicious Cycle



Pettitt & Knowler, J Obes Wt Reg, 1988

Consequences for the mother

- Rates of GDM recurrence range between 30 and 84% *(Kim C et al. Diabetes Care 2007)*

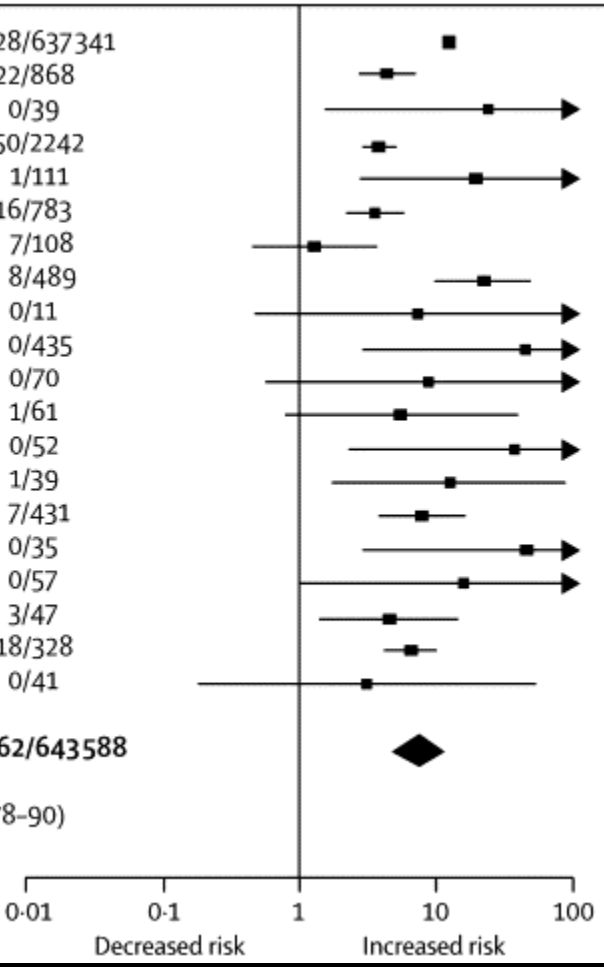
- Women with a history of GDM have a high risk of
  - Type 2 **diabetes mellitus** (x 7)
    - 40% -70% of mothers with GDM will develop T2D within 20 -30 years of their pregnancies
  - Metabolic syndrome (x 2 - 5)
  - Cardiovascular diseases (x 1.7)

Verier-Mine, Diabetes Metab 2010

Increased risk of T2D in Mothers with GDM- Meta-analysis

	Country	T2DM/GDM	T2DM/no GDM	Relative risk (95% CI)
Feig et al,[18] 1995–2002	Canada	2874/21823	6628/637341	12·66 (12·15–13·19)
Lee H et al,[15] 1995–97	Korea	71/620	22/868	4·52 (2·83–7·21)
Madarasz et al,[21] 1995	Hungary	21/68	0/39	24·93 (1·55–400·64)
Gunderson et al,[22] 1985–206	USA	43/166	150/2242	3·87 (2·87–5·22)
Vambergue et al,[23] 1992	France	53/295	1/111	19·94 (2·79–142·47)
Lee A et al,[24] 1971–2003	Australia	405/5470	16/783	3·62 (2·21–5·93)
Ferraz et al[17]*	Brazil	6/70	7/108	1·32 (0·46–3·78)
Krishnaveni et al,[25] 1997–98	India	13/35	8/489	22·70 (10·09–51·08)
Morimitsu et al,[26] 1999–2001	Brazil	7/23	0/11	7·50 (0·47–120·11)
Järvelä et al,[5] 1984–94	Finland	23/435	0/435	47·00 (2·86–771·65)
Albareda et al,[27] 1966–93	Spain	44/696	0/70	9·07 (0·56–146·25)
Åberg et al,[28] 1991–99	Sweden	21/229	1/61	5·59 (0·77–40·66)
Linné et al,[16] 1964–65	Sweden	10/28	0/52	38·38 (2·33–631·74)
Bian et al,[29] 1964–65	China	15/45	1/39	13·00 (1·80–93·93)
Ko et al,[30] 1988–95	China	105/801	7/431	8·07 (3·79–17·19)
Osei et al,[31] 1990–91	USA	10/15	0/35	47·25 (2·95–757·28)
Damm et al,[32] 1978–85	Denmark	33/241	0/57	16·06 (1·00–258·06)
Benjamin et al,[33] 1961–88	New Mexico	14/47	3/47	4·67 (1·43–15·21)
O'Sullivan,[34] 1954–60 and 1962–70	USA	224/615	18/328	6·64 (4·19–10·52)
Persson et al,[35] 1961–84	Sweden	5/145	0/41	3·16 (0·18–55·76)
Total		**3997/31867**	**6862/643588**	**7·43 (4·79–11·51)**

Test for heterogeneity: τ^2=0·50, χ^2=126·67, df=19 (p<0·0001), I^2=85·0% (95%CI 78–90)
Test for overall effect: Z=9·39 (p<0·0001)



Bellamy et al, Lancet 2009

4

HOW TO DIAGNOSE GESTATIONAL DIABETES?

GDM: A moving target?

Initial approach to GDM definition

- Goal: To identify women at increased risk of type 2 diabetes
- Test: OGTT in late pregnancy (24-28 weeks)
- 1964: Statistical Criteria (O'Sullivan)
  - Abnormal = 2 or more values at, or above, two standard deviations above the mean
- Differences in approach, samples, cut points

O'Sullivan J B, Mahan C M. *Diabetes 1*964

The diagnostic tests

- 3 h 100-g OGTT with samples at 0, 1, 2 and 3h
- 2 h 75-g OGTT with samples at 0 and 2 hours

Comparison of criteria

	ADA/ACOG	WHO
Load	3h 100-g glucose	2h- 75-g glucose
Samples	plasma glucose	plasma glucose
Abnormal values	2 or more time points	1 or more time points
Fasting	>5.3 mmol/l	>7.0 mmol/l;
1-hour	>10.0 mmol/l	-
2-hour	>8.6 mmol/l	> 7.8 mmol/l
3-hour	>7.8 mmol/l	

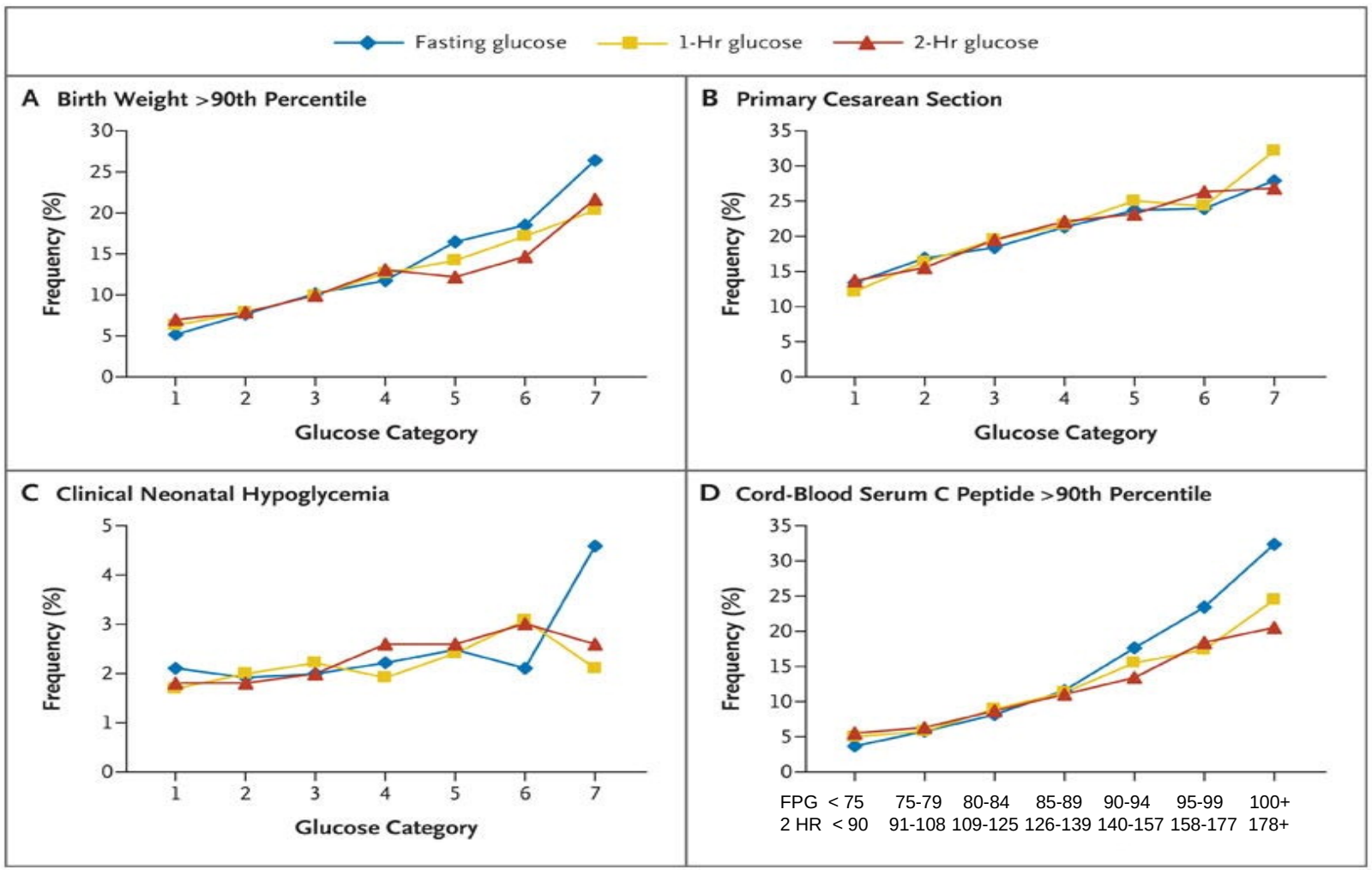
Simmons D, Diabetes Care 2010

The HAPO Study

- Attempt to define GDM based on risk of perinatal outcomes
- Attempt to standardize GDM diagnostic criteria

- HAPO design
  - 25,505 pregnant women at 15 centers in nine countries had 75-g OGTT at 24 to 32 weeks.
  - Fasting, 1-hour and 2-hour glucose levels blinded
  - Primary outcomes: BWT ≥ 90th percentile, primary C-section, neonatal hypoglycemia, cord-blood C-peptide level ≥ 90th percentile.

Frequency of Primary Outcomes across Glucose Categories



The HAPO Study Cooperative Research Group. N Engl J Med 2008;358:1991-2002.

The NEW ENGLAND JOURNAL of MEDICINE

HAPO Cut-Points?

Glucose levels associated with an OR of 1.75 for primary outcomes were chosen as threshold

Load	75-g glucose
Samples	plasma glucose
Abnormal values	1 or more time points
Fasting	>5.3 mmol/l
1-hour	>10.0 mmol/l
2-hour	>8.6 mmol/l

International Association of Diabetes and Pregnancy Study Groups, 2009

Translation of HAPO study for GDM diagnosis

- IADPSG recommendations *(Metzger BE, Diab Care 2010):*
  - **Universal screening and diagnosis of GDM** with 2 hour 75-g OGTT at 24–28 weeks
  - GDM is to be diagnosed if any one of the 3 blood glucose results (fasting, 1h, 2 h) reaches chosen cut points.

International Association of Diabetes and Pregnancy Study Groups, 2009

Proportion of HAPO participants above various glucose thresholds

Glucose measure with a 75 g OGTT	Glucose threshold (mmol/L)	Proportion of HAPO cohort above threshold (%)
Fasting plasma glucose (FPG)	**5.1**	8.3
1-h plasma glucose	**10.0**	14.0
2-h plasma glucose	**8.5**	16.1

OGTT = Oral Glucose
HAPO = Hyperglycemia
IADPSG. Diabetes Care 20

Controversies

- New ISDPSG criteria would increase GDM prevalence by 2- to 3-fold (18% in HAPO)
  - By increasing the number of women tested,
  - By lowering the diagnostic thresholds,
  - By requiring only 1 abnormal result.

5

SCREENING FOR GESTATIONAL DIABETES

Why screen?

- 2-3 hour OGTT not feasible in all pregnant women worldwide
  - Capacity
  - Cost and cost effectiveness
  - Time
- Does the risk in all women make heavy diagnostic procedure worth?

Feasibility

Diabetologia
DOI 10.1007/s00125-015-3713-6

ARTICLE

Feasibility, acceptability and uptake rates of gestational diabetes mellitus screening in primary care vs secondary care: findings from a randomised controlled mixed methods trial

Marie Tierney[1] · Angela O'Dea[1] · Andriy Danyliv[2] · Liam G. Glynn[3,4] · Brian E. McGuire[4,5] · Louise A. Carmody[4] · John Newell[6] · Fidelma P. Dunne[1,4]

Conclusions/interpretation Currently, provision of GDM screening in primary care in Ireland, despite its acknowledged benefits, is unfeasible due to poor uptake rates, poor rates of primary care provider engagement and primary care provider concerns.

When and How to screen?

Depends on who you ask!!

- ADA
- ACOG
- WHO
- 4th International Workshop-Conference on GDM
- National Diabetes Data Group
- United States Preventive Services Task Force
- 5th International Workshop-Conference on GDM
- …

Strategies

- (1) step- screening/diagnosis
  - 75-g OGTT in all pregnant women - IADPSG

- 2 steps
  - Screening: Fasting blood glucose or Random blood glucose or 50-g Glucose challenge test
    - followed by
  - Diagnostic OGTT only if screening abnormal

Current recommendations for screening for GDM

- Risk assessment at first visit, with no screening for low risk
  - Low-risk ethnicity (Caucasian, European)
  - Age < 25
  - BMI $\leq$ 25
  - No known diabetes in first degree relative
  - No h/o glucose intolerance
  - No h/o obstetric complications usually associated with GDM

4th International Workshop-Conference on Gestational Diabetes Mellitus, ADA, ACOG

Screening for GDM (24 - 28 weeks)

- ACOG Recommendations (2001):
  - Risk based approach
  - States that “...since so few people have no risk factors, a universal screening program may be more practical...”
- United States (50-g OGTT – venous glucose at 1 hour
  - Levels above the threshold = 130 – 140 mg/dl – diagnostic testing with 3h 100g-OGTT
- WHO
  - Universal with 2h-75g OGTT

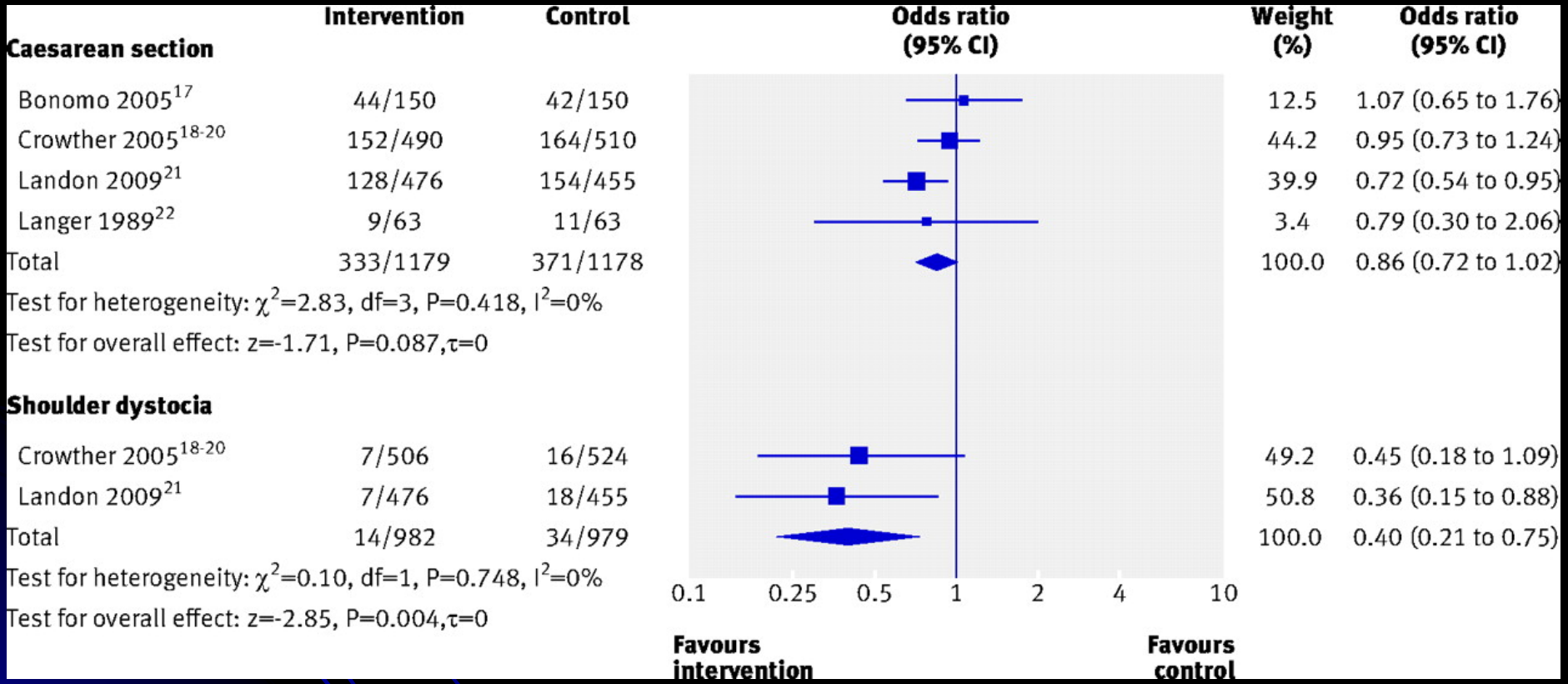
6

IS IT WORTH TREATING GESTATIONAL DIABETES?

Controversies

- Two major RCT in GDM- the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) and the Maternal Fetal Medicines Unit Network (MFMU) study- reduce perinatal outcomes
- Role of DM treatment on short term perinatal outcomes
  - Meta-analysis of all intervention trials in GDM (including major RCTs) confirmed that the main effect of treatment is lighter babies (by 2 %–3 %), which leads to a lower incidence of macrosomia and shoulder dystocia.
- Unclear if GDM treatment influences long-term effects.

Metaanalysis of effect of treatment of gestational diabetes mellitus on pregnancy outcomes



No Effect of Treatment of Mild GDM on Child BMI at age 4-5

	Intervention	Control	Adjusted Effect
Weight (kg)	19.1 (2.9)	19.4 (4.2)	-0.37 (-1.4 to 0.66)
Height (cm)	107.9 (4.6)	108.5 (5.8)	-0.66 (-2.16 to 0.85)
BMI >85th	31 (33)	29 (27.6)	1.17 (0.77 to 1.78)

Gillman MW, Diabetes Care 2010

7

THE CHOICE OF TREATMENT

Treatment options

- Nutritional intervention
- Physical activity
- Insulin therapy
- Oral hypoglycaemic agents

Recommendations of the Fifth International Workshop-Conference on Gestational Diabetes

- Oral antihyperglycemic agents
  - Metformin is thought to act by inhibiting liver's production of glucose; appears to increase insulin sensitivity/reduce insulin resistance

Diabetes Care 2007

- Randomized, prospective study comparing metformin and insulin in GDM
  - Conclusion: *In women with GDM, metformin (alone or with supplemental insulin) is not associated with increased perinatal complications as compared with insulin. The women preferred metformin to insulin treatment.*

Rowan, et al. NEJM 2008

Key messages

- Normal pregnancy is a diabetogenic state; risk factors for GDM similar to those for T2D
- Prevalence of GDM is increasing
- Hyperglycemia during pregnancy has serious short and long term consequences for offspring and mothers
  - Likely sets in motion a transgenerational vicious cycle of obesity and diabetes
- Lack of standard, uniform criteria for GDM diagnosis
- Screening strategies also vary, need to be adapted to the real world
- Treatment of GDM reduces some perinatal outcomes, but unclear if worth treating “mild” GDM
- Evidence that treating GDM reduces long-term consequences is lacking
- Oral hypoglycaemic agents may be used

Thank you !