Gestational Diabetes:

The importance of making the diagnosis for mother and child.

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Objectives of the Presentation

- Understand the controversies surrounding the diagnosis of GDM comparing 100g/75g criteria

- Understand the short and long-term risks for mothers

- Understand the short and long-term risks for the offspring…

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Why Diagnose and Treat GDM?

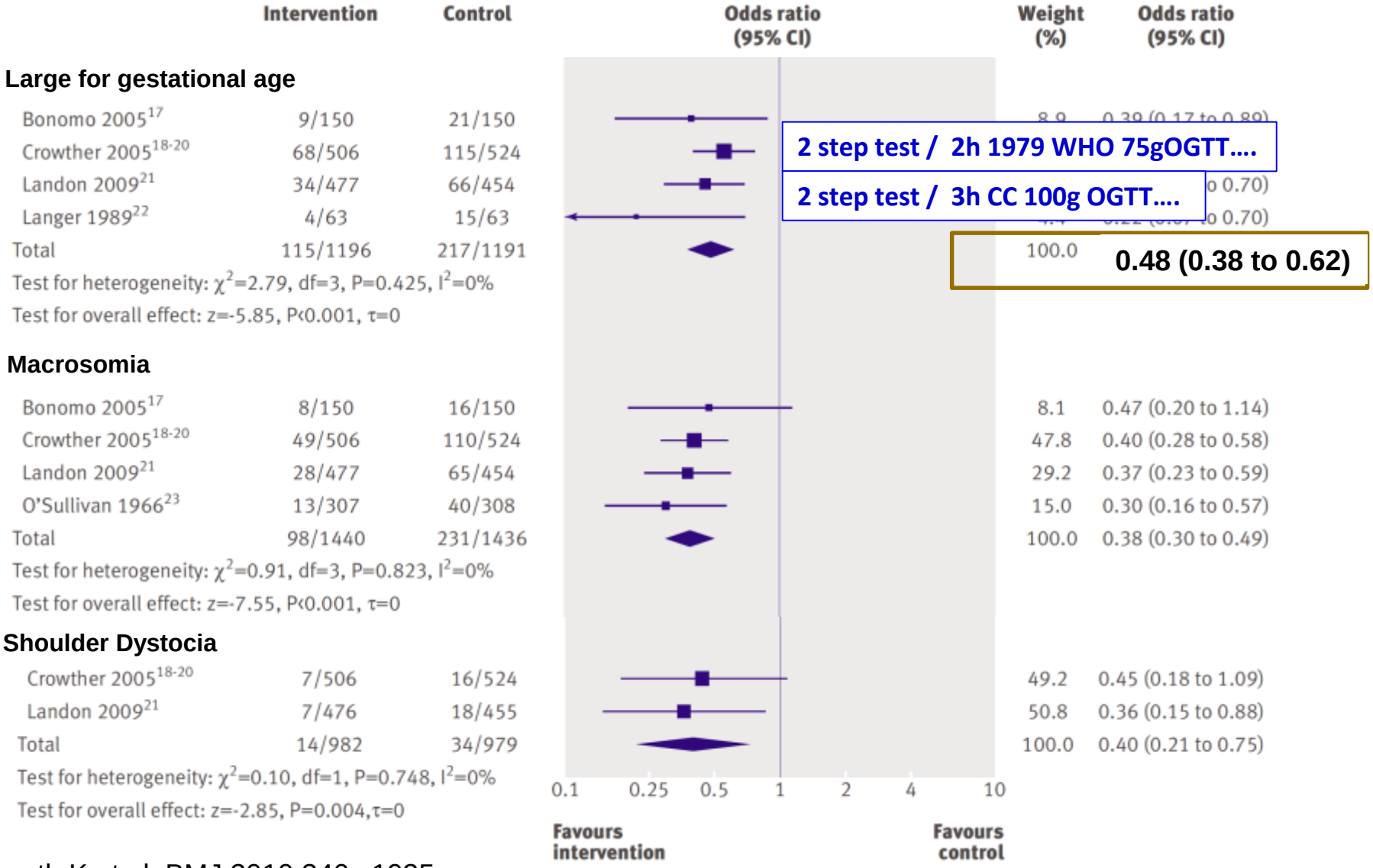
Maternal concerns:

- Preterm delivery
- Traumatic delivery due to macrosomia
- Caesarian section risk
- Pre-eclampsia risk increased
- Future T2DM and CV risks increased

Fetal / Offspring concerns:

- Macrosomia
- Shoulder dystocia and nerve injury
- Hyperbilirubinemia
- Neonatal hypoglycemia
- Offspring obesity (?)
- Offspring diabetes (?)

Benefits of Treatment of GDM



Horvath K et al. BMJ 2010;340:c1935

O'Sullivan & Mahan (1964) original diagnostic criteria defining GDM

Original normative data from 752 women in NY:

- **Threshold values were 2 SD above the mean using whole blood glucose**
- **Reapplied thresholds retrospectively to a different group of 1013 subjects tested in pregnancy & followed for 5 - 10 years PP**
- **Diabetes developed over 7 – 8 years in 22 % (17 women) in whom 2 glucose values were ≥ 2SD above the mean.**
- **Criteria were accepted as assessing risk for future maternal diabetes**

O'Sullivan and Mahan, 1964

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An Overview of some of the different diagnostic criteria for GDM

Plasma glucose	NDDG 3h 100g OGTT 1979	Carpenter & Coustan 3h 100g OGTT	WHO/ IADPSG 75g OGTT	WHO 1999 75g OGTT
Fasting	≥ 5.8 (105)	≥ 5.3 (95)	≥ 5.1 (92)	≥ 6.1 (110)
1h	≥ 10.6 (190)	≥ 10.0 (180)	≥ 10.0 (180)	-
2h	≥ 9.2 (165)	≥ 8.6 (155)	≥ 8.5 (153)	≥ 7.8 (140)
3h	≥ 8.0 (145)	≥ 7.8 (140)	N/A	
Number of abnormal values needed for diagnosis	≥ 2 O'Sullivan & Mahan numbers converted to plasma glucose	≥ 2 Don Coustan & Marshall Carpenter recalculated more precisely the O'Sullivan & Mahan numbers and did not round them …	≥ 1 Based on HAPO OR of 1.75	≥ 1 Based on consensus

Acknowledged that values also indicated fetal and maternal risks in pregnancy, not only that of future maternal diabetes.

Values are presented in mmol/l. NDDG: National Diabetes Data Group; OGTT: oral glucose tolerance test; IADPSG: The International Association of Diabetes and Pregnancy Study Groups.

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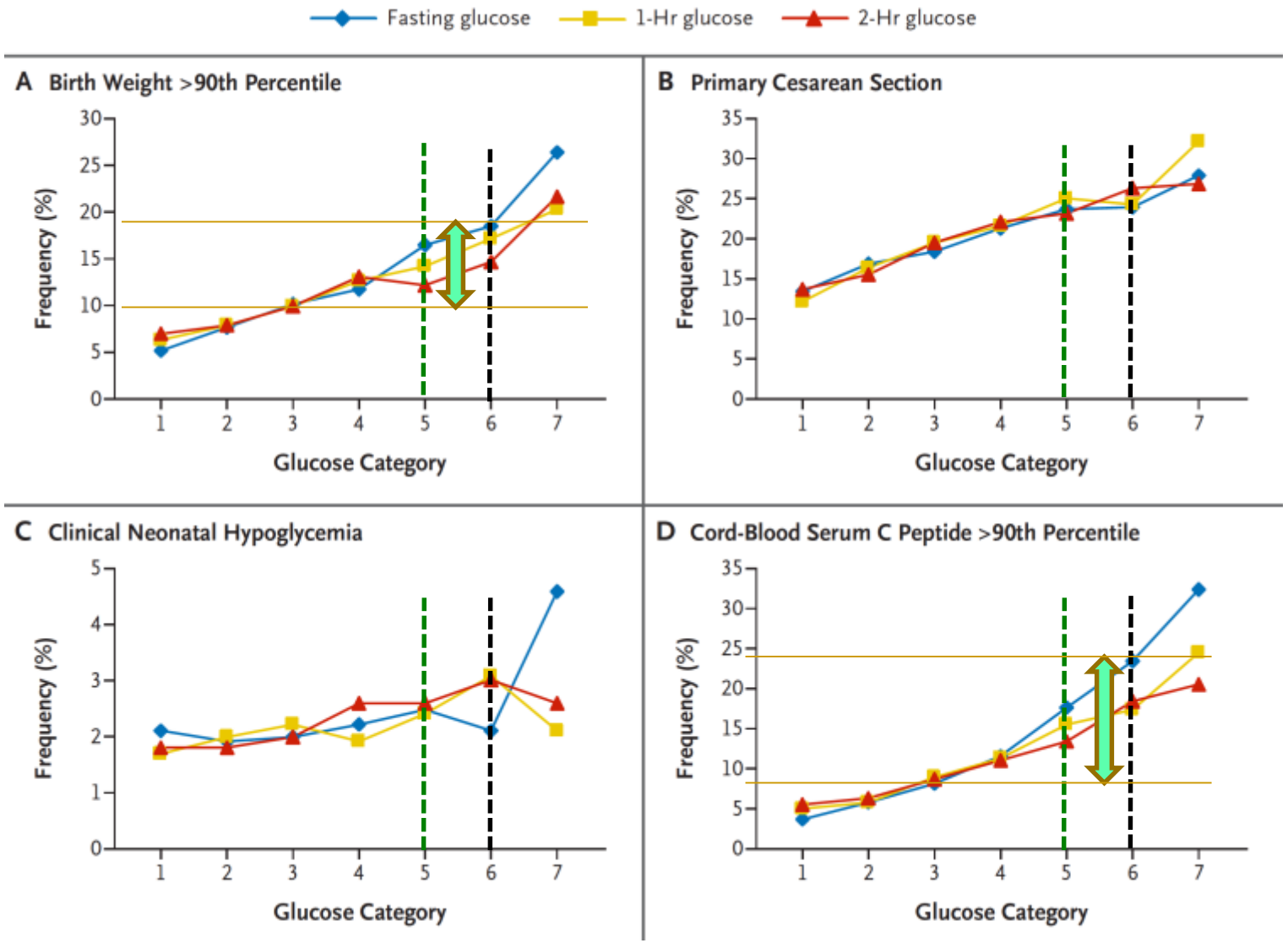
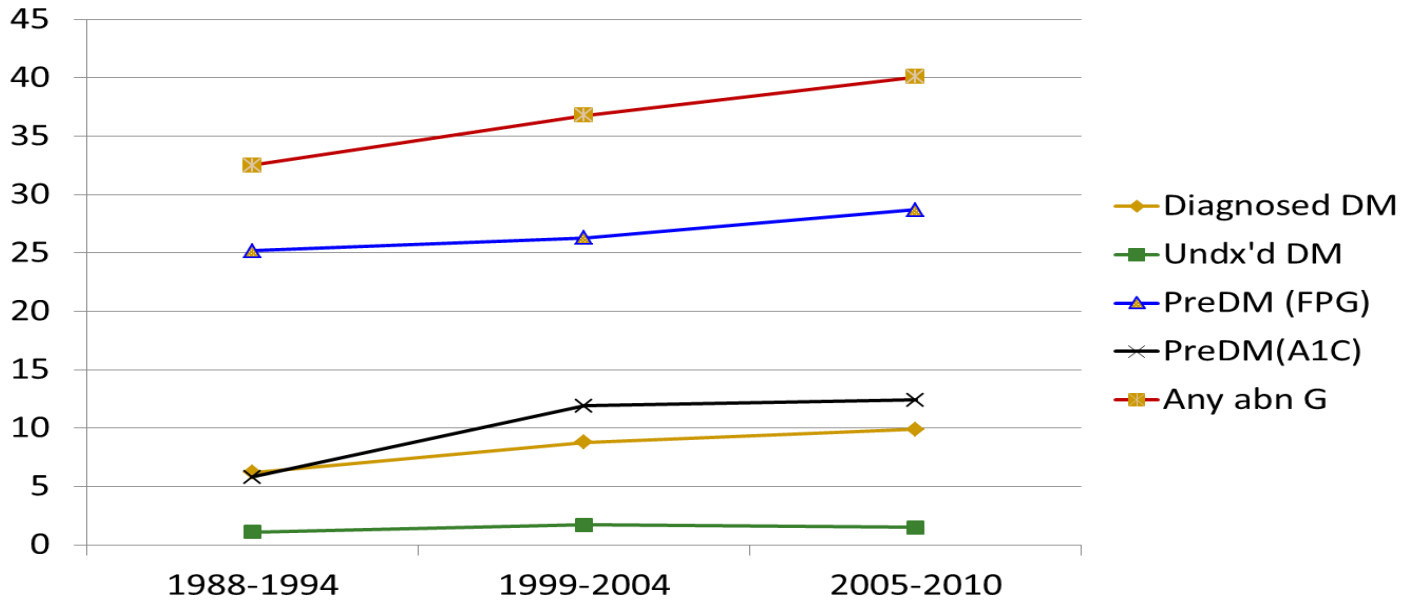
HAPO: Incidence of Adverse Outcomes for Glucose Categories (OR 1.75 or 2.0)



Metzger BE, et al. HAPO. *NEJM* 2008;358(19):1991-2002.

DM 2 is increasing in the general population – why not in pregnancy?

- SEARCH for Diabetes Study indicated a 30.5% (95% CI, 17.3%-45.1%) overall increase in type 2 diabetes between 2000 and 2009 in US in children and adolescents.



Ann Intern Med. 2014;160(8):517-525.
doi:10.7326/M13-2411

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McGill GDM Diagnosis Study –

a prospective randomized controlled trial involving 5481 multiethnic, pregnant women in Montréal using a 75g vs 100 g OGTT

S. Meltzer, J. Snyder, L. Morin, M. Nudi, MSc

- Comparison of NDDG criteria for diagnosis and outcome with Canadian criteria using a 75g 2hOGTT either with or without glucose screen

- Canadian values of interest because they are virtually equivalent to an OR of 2.0 from HAPO study

Use of McGill trial to assess impact on a multiethnic, North America population to assess prevalence and potential outcomes

Funded by the Canadian Diabetes Association

Study Design

Visit 1: **Randomization**
(83% recruitment rate)

Group 1	Group 2	Group 3
n = 1813	n = 1839	n = 1836
1h 50g GS	1h 50g GS	2h 75g OGTT

if Glucose Screen (GS) 7.8 -10.2

Visit 2:

20.4% → **3h 100g OGTT**

3 day diet provided

21.9% → **2h 75g OGTT**

Normative ethnic values developed from this population

131/3753 (3.5%) missed second test or did wrong one

A total of 5637 women recruited; 148 withdrawn (vomited the glucose drink, did not comply with study design or had incomplete data sets) and data analysis performed on 5481 women

Evaluation of cost of screening methods between 1 and 2 steps

Cost components	GR1 50gGS +100gGTT	GR2 50gGS + 75gGTT	GR3 Only 75gGTT
Direct costs (Drink, blood test costs-$CAN)	21.77	**20.16**	36.89
Mean time in clinic (hrs)	3.48	**3.24**	3.79
Transportation costs	14.66	15.32	**11.92**
Time costs	55.18	**53.56**	59.57
Direct + Indirect costs ($CAN) per women screened	91.61	**89.03**	108.38
Average cost per case diagnosed	1145.13	**1112.88**	1354.75
Avg. cost per South Asian woman screened	**95.87**	105.24	104.15

Least expensive is GS (Dx 10.3) + 75g GTT if needed

GDM diagnostic rate = 24%

Except for highest risk group

Meltzer et al, BJOG 2010

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Prevalence (%) of GDM and IGT

ADA CC 100 g 3h test (G1)
vs IADPSG 75g 2h test (GR 2&3)

Study Group, (n=)	GDM by GS	GDM by GTT	Total GDM	IGT by GTT	GDM and IGT
CC 100g (1812)	2.2	3.9	6.1	5.2	11.3
GR2 (1839)	2.6	2.6*	5.2	5.0	10.2
GR3 (1838)	N/A	5.1	5.1	6.0	11.1

* Difference with GR1 gold standard is significant ($p<0.05$)

The 75 g GTT IADSPG criteria with or without GS give **similar** diagnostic rates of GDM/GIGT compared to ADA CC 100g GTT criteria (2014 ACOG)

Less time for the woman; easier test to tolerate

Odds Ratios of Outcomes by group vs NDDG

Corrected for age, weight, BMI, ethnicity

Comparison parameter	OR for **all women**		OR for **normal** women	
	Group 2	Group 3	Group 2	Group 3
Unplanned C/S	**1.43** [1.04-1.89]	**1.35** [1.05-1.80]	**1.35** [0.99-1.85]	**1.32** [0.97 -1.81]
Pre-eclampsia	**1.15** [0.76–1.74]	**1.33** [0.89-1.97]	**1.32** [0.84-2.05]	**1.53** [1.00-2.35]
Neonatal hypoglycemia (<2.2mmol/L)	**1.40** [0.98-2.17]	**1.21** [0.78-1.87]	**1.52** [0.92-2.44]	**1.34** [0.82-2.19]
NICU admission	**1.22** [0.89-1.68]	**1.15** [0.84-1.58]	**1.19** [0.85-1.67]	**1.16** [0.83-1.63]

Only unplanned C/S and pre-eclampsia in "normal" untreated women are significant but all trends suggest poorer outcomes with CDA criteria

Comments on "Considerations"

- **Do we have sufficient evidence with respect to treatment benefit at the various thresholds to make an informed decision….**
  - The ACHOIS data and the majority of the meta-analysis data was made based on old WHO criteria… the **2h value** was what diagnosed almost all of them and it was lower than both the OR for 1.75 (8.5) and 2 (9.0)…it was 7.8mmol/L!
  - Thus the present historical outcome data suggests even lower cutoff values would be justified…
- **What is the LONG TERM economic cost of NOT treating, thus not recognizing women and offspring with elevated risks ?**
  - Prevention of DM early rather than late is a justifiable cost
  - Prevention of obesity and potentially adolescent diabetes in the offspring also would justify costs ?

The cost-effectiveness of gestational diabetes screening including prevention of type 2 diabetes: application of a new model in India and Israel

- WHO has proposed that interventions costing less than the per capita GDP of a country be deemed "highly cost-effective", and those costing up to three times per-capita GDP "cost-effective" [37].

- Screening and treating gestational diabetes, considering adverse perinatal events and future diabetes, has an incremental cost-effectiveness of $1626 per Diability Adjusted Life Years (DALY) averted for a general hospital in India, and $1830 per DALY averted for an HMO in Israel.

- Since the 2010 per-capita GDP of India and Israel are $3500 and $29 800 [38], respectively, the interventions are **"highly cost-effective".**

Marseille et al, J. Matern Fetal Neonatal Med 2013: 26(8) p 802

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A question of balance…

Poorer pregnancy outcomes
Obese mothers with diabetes
Obese offspring ? Future patients?
Overall increased societal costs?

An overloaded medical system
Harried doctors & nurses
Exorbitant initial treatment costs

What about after the baby is born – for the Mom?

Understand the controversies surrounding the diagnosis of GDM comparing 100g/75g criteria

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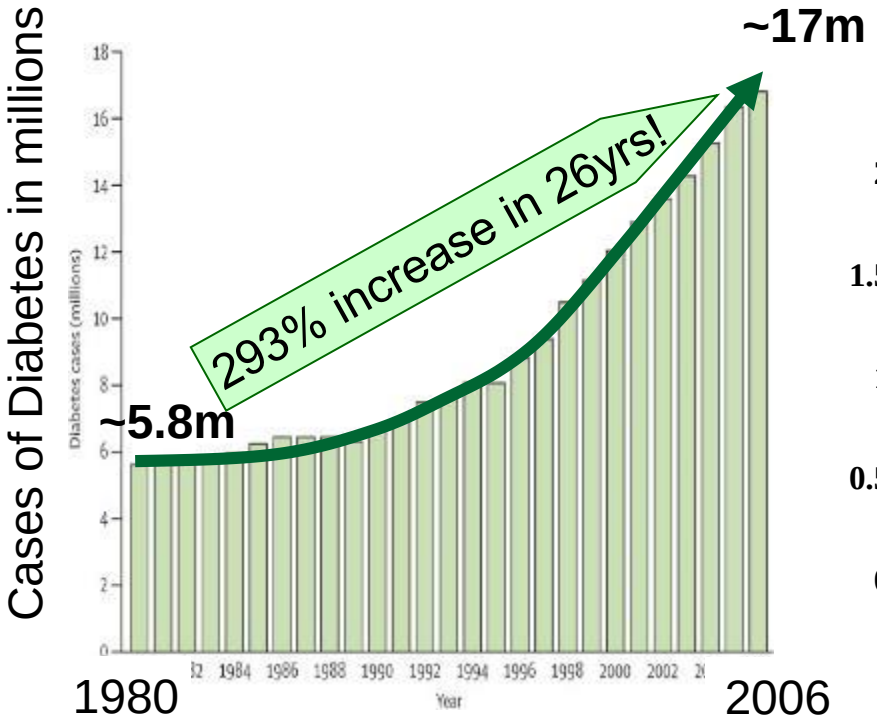
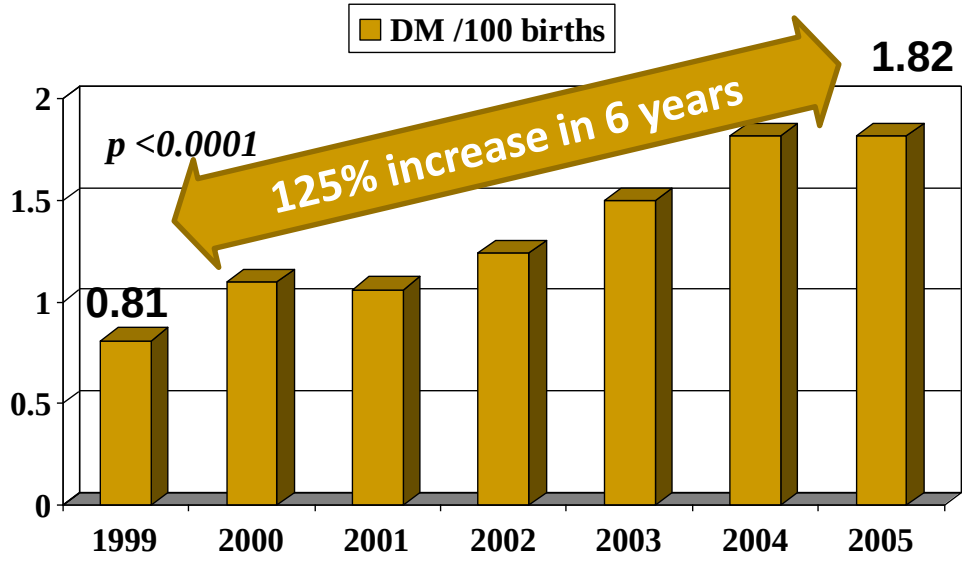
Understand the short and long-term risks for the offspring…

The Incidence of Diabetes (and type 2 DM in pregnancy) is Increasing

Data from Centers for Disease Control and Prevention



Pre-existing DM2 in pregnancy Kaiser-Permanente Data



Laurence DC 2009

Overall prevalence of Type 2 DM post GDM

12.66 Feig

	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)
				9.90
Total		3997/31867	6862/643588	7·43 (4·79–11·51)

Egeland & Meltzer, 2010

Test for heteroge… % (95%CI 78–90)
Test for overall ef…

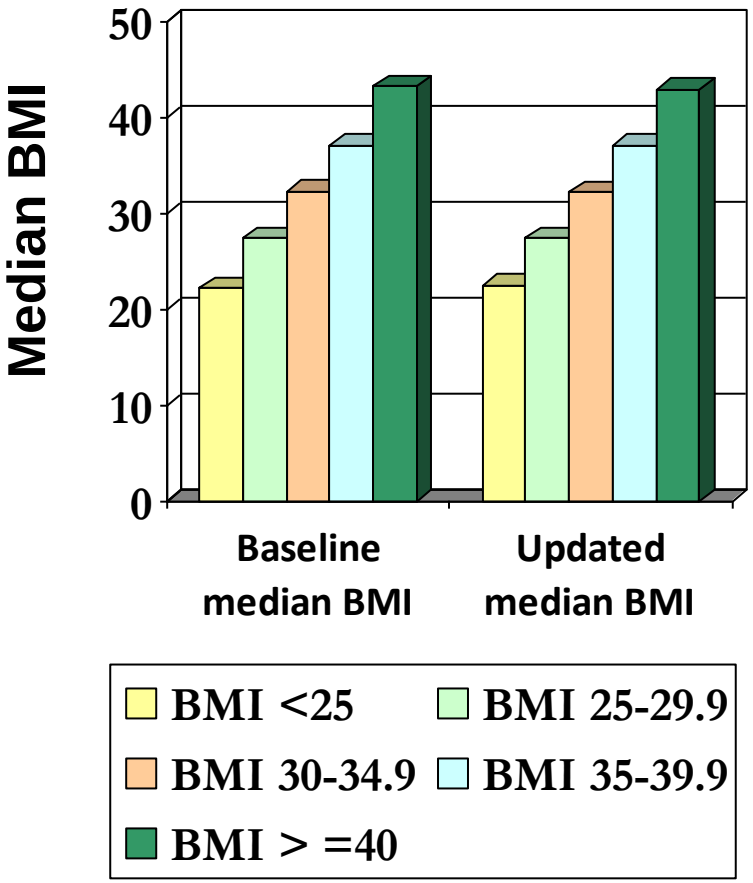
O'Sullivan 1954 to 1970
36.4% vs 5.9% prevalence

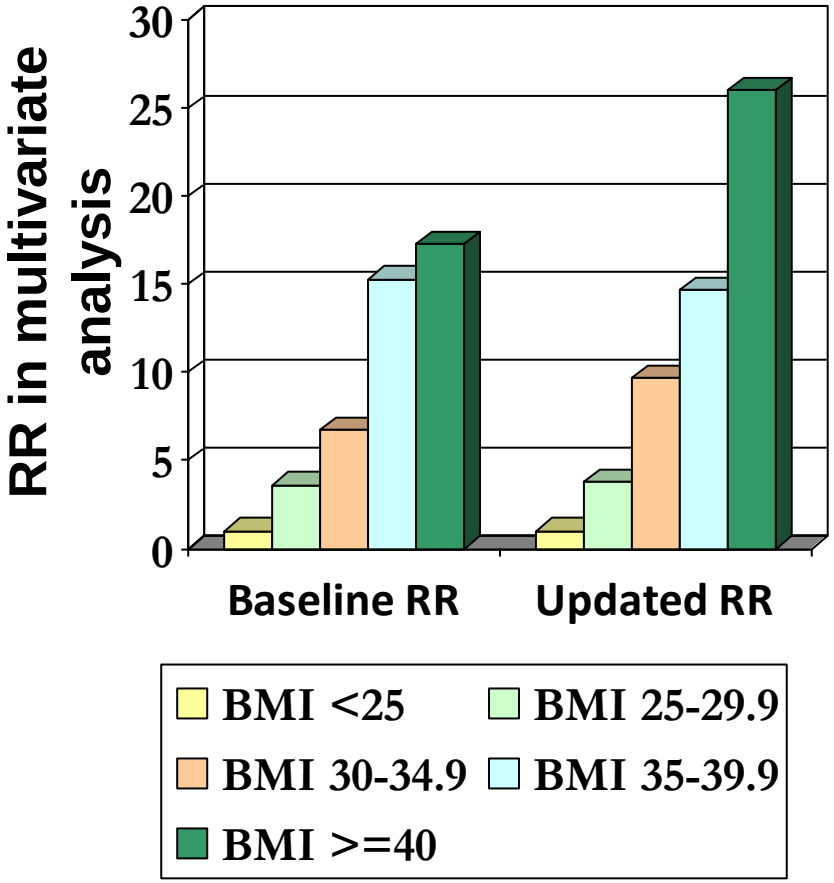
Overall 7.43

0·01 0·1 1 10 100
Decreased risk Increased risk

Bellamy et al, The Lancet, May 2009

Risk of Type 2 DM post GDM related to BMI changes over time





Bao et al, Diabetologia 2015 – Nurses' Health Study II

Postpartum GDM Management Checklist

1. Encourage **Breastfeeding**
2. **75g OGTT** between **6 weeks - 6 months** postpartum to detect prediabetes or diabetes
3. **Discuss increased long-term risk of diabetes** – Importance of returning to pre-pregnancy weight

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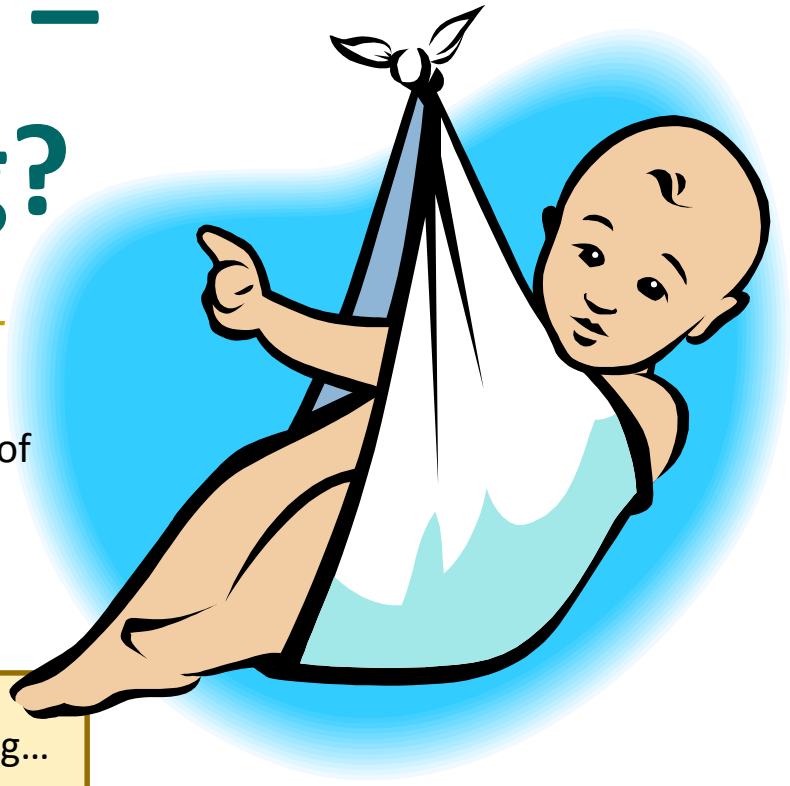
What about after the baby is born – for the offspring?



Understand the controversies surrounding the diagnosis of GDM comparing 100g/75g criteria

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Understand the short and long-term risks for the offspring…

In-Utero Fetal programming

A stimulus or an insult at a critical and sensitive period of early life which permanently alters the organism's physiology and metabolism

Low Birth-weight

Barker

High Birth-weight

Pederson/ Frienkel/ Pettit

At risk neonate

Obese adult with insulin resistance, hypertension & type 2 DM

Maternal DM leads to increased DM in offspring

- **Pima Indian Population in Southern United States** …moved from an agrarian lifestyle to almost no activity
  - NIH began studying the diabetes risks early in the 1970's
  - Treatment of DM and GDM was not well-established initially, so even if diagnosed, glucose control was relatively poor. (personal communication with Dr. Bennett)
- **Increased obesity in offspring of Pima women with DM2 than non-DM2 women** (Pettit 1983)
- **In Pima Indians aged 25-34 Exposure to DM in utero was strongest risk factor for DM (Dabalea 1999)**
  - **70% of offspring of DM2 mothers**
  - **15% of offspring of non-DM mothers**
  - **Ages 7 – 11 already see increased systolic BP in offspring**
  - **Evidence of increase MAU 4 – 6X if DM in utero**

Childhood Obesity & Metabolic Imprinting

- HMO's in Northwest USA & Hawaii with births 1995-2000.
- Offspring studied (9439) 5-7 years later
- Universal screen (> 140); NDDG criteria for treatment GDM

* sex specific weights

Mother's Glucose test result	Odds Ratio For Overweight (≥ 85%ile) child *	Odds ratio For Obese child (≥ 95%ile)*
Normal	Reference	Reference
+ GS, normal OGTT	0.98	0.97
+ GS, 1 abn (CC or NDDG)	1.37	1.30
+ GS, + CC, - NDDG	1.89	1.82
+GS, + NDDG - treated	1.29	1.38

Offspring risk lower in treated women than with milder GDM untreated

Hillier, T et al: Diabetes Care 2007(30)2287

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Long-term studies looking at offspring

Author, year	Pays	Patients / Controls	Age of offspring	GI %
Plagemann 1997		Offspring DM1 & DM2	Age 1 - 4	9.4% 20%
Silverman 1998	Chicago, USA	96 Offspring of DM1/DM2 & GDM	Age 8 – 17 Amnio. Ins. Lo vs hi	31.5% 17% / 63%
Dabalea 1999	Pima USA	Offspring of GDM/DM or not	Age 25 – 34 - GDM Controls: Non GDM	70% 15%
Keely 2006	Ottawa, Canada	Offspring of GDM treatment intense or not	Age 8 – 17	36%
Clausen 2007	Denmark	Offspring of + RF women + or – for GDM; O-DM1, O-Bkgd population	Age 18-27 O-GDM O-nonGDM	21%OR 12% 4%
Vaarasmaki, 2009	Finland	1986 Finnish birth cohort 95 O-GDM; 3903 Reference grp	Overweight O-GDM 18.4 vs 8.4% (P<0.001)	Not reported
Egeland, Meltzer 2010	Montreal Canada	Case-control study matched for age, social status 89 cases,99 controls	Age 14-16 girls GDM Controls	1% 0%

RR of IGT = 4.7 for ODM with elevated insulin level

OR O-GDM relative to O-Background for DM/GI was 7.76

Very low incidence of offspring GI???

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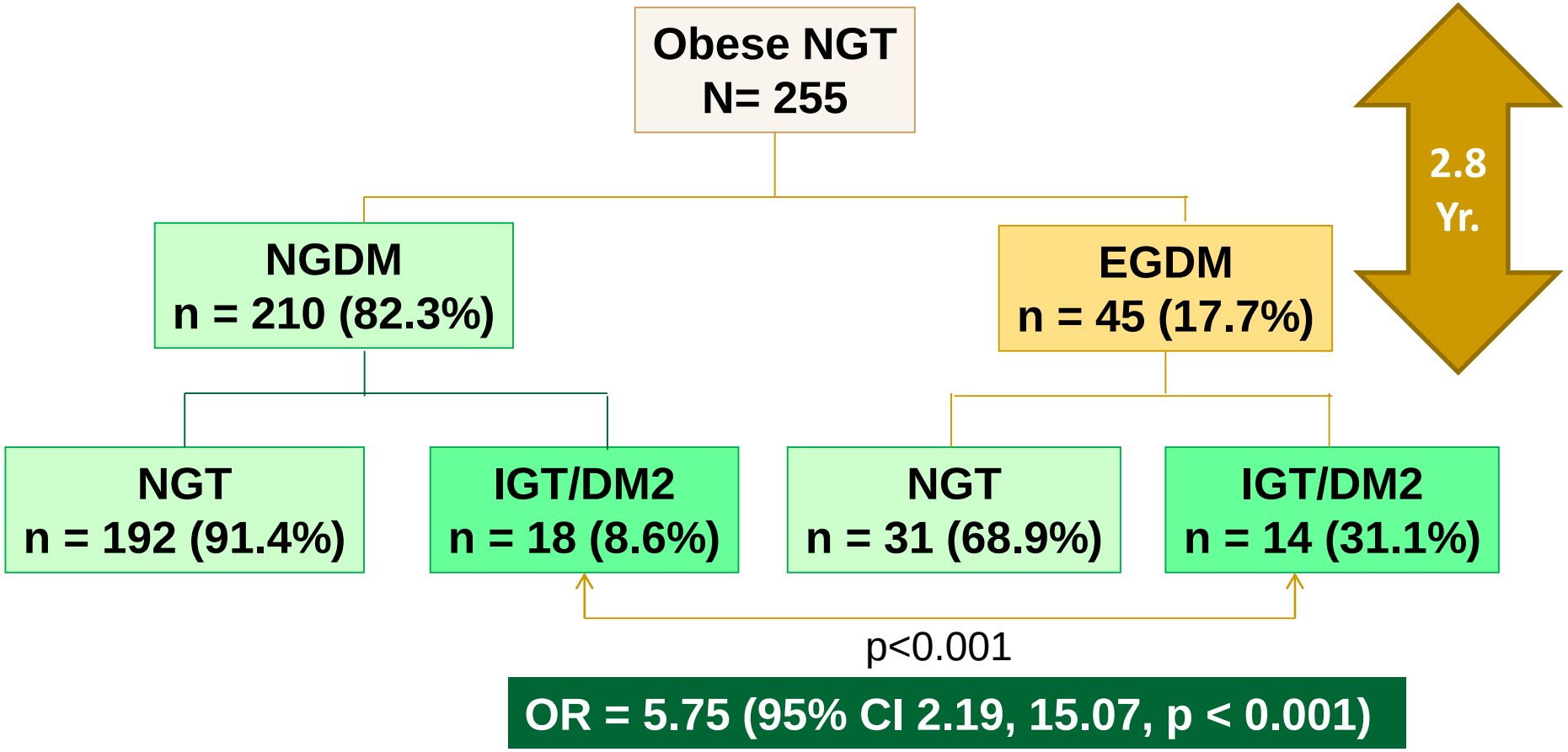
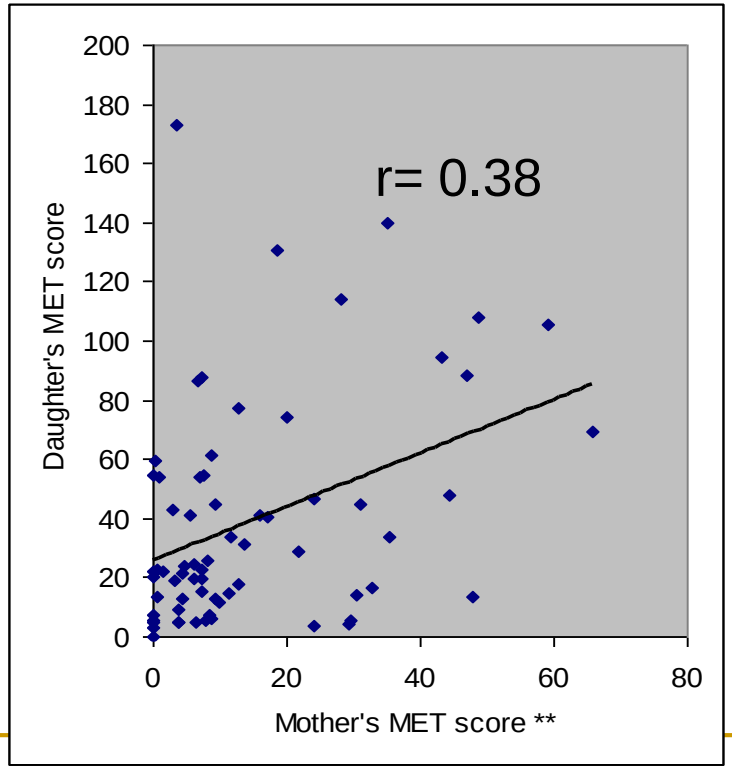
Obese adolescent offspring of GDM more at risk for DM2/IGT conversion

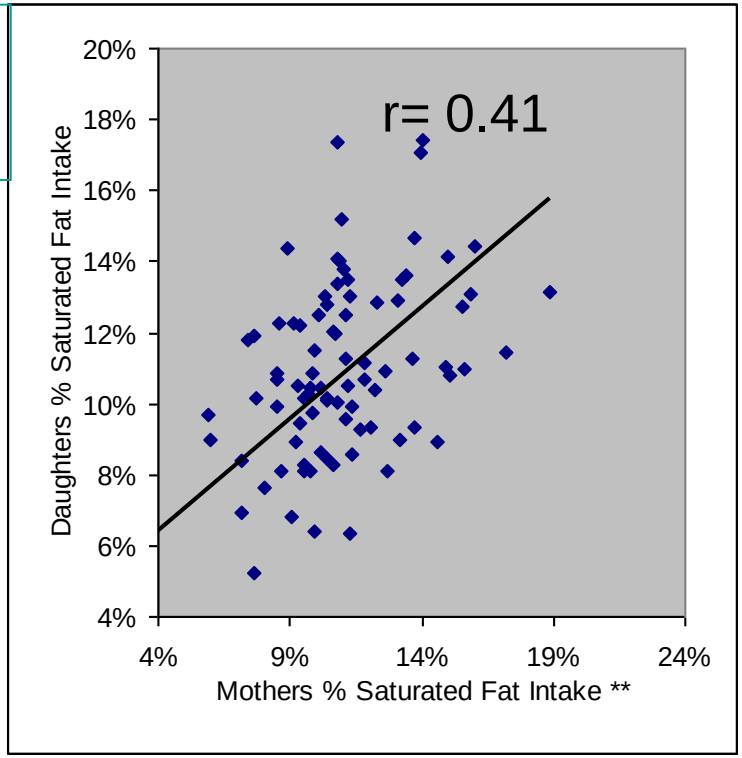


Holder et al, Diabetologia 2014; 57:2413

Like mother…
like daughter

Mothers' Saturated Fat Intake (%) ** predicts Daughters adjusted for mother's case status





Mothers' MET Score ** predicts daughters MET score adjusted for case status and daughter's age

Meltzer, Egeland, EASD abstract, 2008

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Diabetes in pregnancy begets Diabetes?

Environmental Factors

Environmental Factors

Altered fetal islet / fat cells / insulin res.

Poor Family eating & activity habits?

Childhood obesity

IGT in adolescence

Increased incidence of PreDM/DM in the adult population

Diabetes in pregnancy

Abnormal Maternal fuels

Can this circle be altered?

Lifestyle Prevention: Good Diet, Good Habits

All of these habits – less than 10% develop T2DM

- BMI < 25 (23 in Asians?)
- Diet high in cereal fiber & polyunsaturated fat and low in trans fat and glycemic load
- Exercise ≥ 150 minutes/week of moderate intensity
- No smoking
- Consumption of low amounts of alcohol (< 9 drinks a week) may reduce risk

Nurse's Health Study, NEJM 344:1343, 2001

Lifestyle Prevention: Activity

- Aerobic activity equal to brisk walking or more at least 3 times a week (≥150 min).
- Resistance exercises 3 times per week for 3 sets of 10 repetitions
- General increase in activity levels of any kind needs to be encouraged

Cost considerations

- Knowing lifetime excess medical costs attributable to diabetes provides a benchmark from which to measure the maximum future medical costs that could be avoided by preventing diabetes.

Age at diagnosis	Discounted life-time medical spending for people with vs without diabetes
40	$124, 600
50	$91,200
60	$53,800
65	$35,900

- Younger age at diagnosis and female sex were associated with higher levels of lifetime excess medical spending attributed to diabetes.

X Zhuo X, Zhang P,Barker L, et al **Lifetime Cost of Diabetes and Its Implications for Diabetes Prevention, DC 2014, August 21**

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